Significant Gastrointestinal Bleeding in Patients at Risk of Coronary Stent Thrombosis

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The evolution of drug-eluting stents (DES), effective periprocedural antithrombotic therapy, and advanced interventional techniques have fueled the surge of percutaneous coronary interventions. Stent thrombosis remains a serious complication of coronary artery stent implantation. Long-term antiplatelet therapy is required to prevent stent thrombosis, especially following DES implantation. Discontinuation of antiplatelet therapy (particularly clopidogrel) is the strongest independent risk factor for the development of stent thrombosis. Bleeding complications, most of which arise from the upper gastrointestinal (GI) tract, are the major limiting factors for antiplatelet therapy. The association of aspirin with the increased risk of upper GI bleeding has been well established. Peptic ulcer bleeding and Helicobacter pylori *infection are the 2 most important risk factors for aspirin-associated GI bleeding complications. Endoscopy (for both surveillance and potential intervention), performed either emergently or semi-electively, is the primary tool for definitive management of GI bleeding. Considering the increase in GI bleeding risk seen with prolonged antiplatelet therapy, adjunctive proton pump inhibitor therapy and/or eradication of* H. pylori *infection might be beneficial for DES patients on long-term antiplatelet therapy.*
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In patients with coronary stents, thrombosis is a rare but potentially catastrophic complication. Premature discontinuation of antiplatelet therapy, especially the discontinuation of clopidogrel in the standard regimen, predisposes patients to a higher risk of stent thrombosis. Observational data indicating an unacceptably high incidence (> 25%)[1] of acute/subacute stent thrombosis or serious associated consequences of acute/subacute stent thrombosis following unplanned discontinuation of antiplatelet therapy in the early poststenting period argue strongly against withholding antiplatelet therapy

from patients with gastrointestinal (GI) bleeding. However, the severity of the GI bleed must be weighed against the risk of stent thrombosis in all patients who experience this clinical scenario. As the amount of patients with stents rapidly and steadily expands, an increasing number of patients are potentially at higher risk of experiencing hemorrhagic complications while taking antiplatelet agents. This article will discuss studies of patients who experience significant GI bleeding that results in the cessation of antiplatelet therapy, and the inherent risk of stent thrombosis in these patients.

Clinical Scenario

The patient was an 80-year-old white woman with a medical history of breast cancer and hypertension, a 60-pack-year history of cigarette smoking, and a strong family history of coronary artery disease. Two weeks prior to the current admission, she had undergone elective percutaneous coronary intervention (PCI) with successful implantation of paclitaxel-eluting stents in the proximal (70% stenosis) and mid (90% stenosis) segments of the left anterior descending artery, and angioplasty of an 80% stenosis in the first diagonal artery. The patient had received periprocedural eptifibatide and was taking daily aspirin ([ASA] 325 mg) and clopidogrel (75 mg). She did well until 4 days prior to admission, when she started passing black stools associated with increasing weakness and paleness, but without nausea, vomiting, or abdominal pain.

Urgent esophagogastroduodenoscopy was performed on hospital day 1 upon presentation. It revealed 2 bleeding arteriovenous malformations in the bulb region of the duodenum and multiple nonbleeding arteriovenous malformations in postbulb regions, all of which were endoscopically cauterized. Following the procedure, the antiplatelet regimen (ASA and clopidogrel) was withheld; proton pump inhibitor (PPI) infusion was initiated, and the patient was monitored hemodynamically and with serial blood counts.

From hospital day 2 (postendoscopic day 1), the patient's cardiologist repeatedly recommended resumption of the antiplatelet regimen as soon as possible, with clopidogrel at a minimum, whereas the gastroenterologist recommended that ASA and clopidogrel be withheld until cessation of active bleeding was clinically proven. After the patient's hemoglobin level had been stable for 3 days, clopidogrel was resumed (postendoscopic day 3). The patient was observed for an additional day and eventually was discharged home under close follow-up with instructions to take clopidogrel and a PPI daily. No thromboembolic events were reported at 3 months follow-up.

Current Recommendations for Antithrombotic Therapy in the Peri- and Post-PCI Stenting Period

Restenosis (renarrowing of vessel lumen by neointimal growth within the stent) and stent thrombosis (sudden occlusion of the vessel due to thrombus formation on the stent) are the twin limitations of PCI stent revascularization of coronary stenosis. Elastic recoil, negative arterial remodeling, and neointimal hyperplasia are major pathophysiologic components involved in restenosis after balloon angioplasty. Although stents eliminate the first 2 components, they cause deeper vessel wall injury that subsequently stimulates a higher degree of neointimal hyperplasia. Intracoronary brachytherapy inhibits smooth muscle cell proliferation and reduces about 60% of restenosis. However, the edge effect of intracoronary brachytherapy (restenosis occurring at the edges of radiated segments) has hampered its use in routine practice. The advent of drug-eluting stents (DES) generated excitement because they dramatically reduced the risk of restenosis by as much as 74%,[1] by locally introducing antiproliferative agents (paclitaxel and sirolimus are 2 examples of agents approved by the US Food and Drug Administration [FDA]). However, sufficient endothelial cell proliferation and re-endothelialization of the intrastent surface are critical for reducing the thrombogenic effect of stents. Nonselective antiproliferative effects of DES, on the other hand, inhibit endothelial cell proliferation, and therefore delay the re-endothelialization of the device. The prolonged thrombogenic status of DES has raised increasing concern of subacute and late in-stent thrombosis. The prevention of thrombosis is largely dependent on antiplatelet therapy. The most recent recommendations from the American College of Cardiology/American Heart Association (ACC/AHA) for antithrombotic therapy in the patient who has undergone coronary stenting are summarized below.[2,3]

The prevention of thrombosis is largely dependent on antiplatelet therapy.

In the pre-PCI period, all patients without known resistance or allergy to ASA should receive ASA before the procedure. Patients who are already taking daily ASA should take 75 mg to 325 mg of ASA prior to PCI. In patients not previously taking ASA, a 300-mg to 325-mg dose of ASA is recommended at least 2 hours (and

preferably 1 to 7 days) before PCI. In addition, a loading dose of clopidogrel should be administered before PCI. Although 300 mg of clopidogrel orally administered at least 6 hours before the procedure has the best established efficacy, a 600-mg loading dose administered 2 hours before PCI has shown comparable or improved efficacy in reducing major adverse coronary events,[4,5] and this dose given 6 hours prior to PCI results in even better overall outcomes.[6] No additional efficacy has been achieved with a loading dose greater than 600 mg.[7]

According to current recommendations for therapy after PCI stenting, a daily 325-mg dose of ASA should be given for at least 1 month after implantation of a bare-metal stent (BMS), for 3 months after implantation of a sirolimus-eluting stent, and for 6 months after implantation of a paclitaxel-eluting stent, after which daily ASA therapy should be continued indefinitely at a dose of 75 mg to 162 mg. Additionally, a daily 75-mg dose of clopidogrel should be given to patients with BMS for at least 1 month, to patients with sirolimus-eluting stents for 3 months, and to patients with paclitaxel-eluting stents for 6 months. Ideally, patients who are not at high risk for bleeding should receive a daily 75-mg dose of clopidogrel for up to 12 months.

Apart from these general guidelines, additional recommendations are in place to prevent negative outcomes in other subsets of patients undergoing PCI. For example, subacute and late stent thromboses have been observed in patients undergoing brachytherapy. Therefore, for patients undergoing brachytherapy, a daily 75-mg dose of clopidogrel and 75 mg to 325 mg of ASA should be given indefinitely unless there is a significant risk of bleeding. Another subset of potentially high-risk patients consists of those individuals resistant to ASA and clopidogrel. Resistance to therapies given after PCI has been a significant problem in the era of coronary stenting. Among patients in whom subacute thrombosis may be catastrophic or fatal (those who have an unprotected left main, bifurcating left main, or last patent coronary vessel), platelet aggregation studies should be considered, and if less than 50% inhibition of platelet aggregation is demonstrated on routine doses of clopidogrel, then the dose should be increased or the addition of alternative antithrombotic therapy should be considered. Therefore, except when contraindicated, dual antiplatelet therapy with ASA and a thienopyridine (clopidogrel or ticlopidine in patients allergic to clopidogrel) has been the standard of care in post–PCI-stent patients.

Risk Factors for Stent Thrombosis

Incidence rates of acute and subacute stent thrombosis (occurring < 30 days following stent implantation) have been significantly reduced from higher than 20% initially to less than 2% over the last decade, largely due to efforts to improve technical consistency and proficiency, recognition and minimization of predisposing risk factors, and optimization of antiplatelet regimens as preventive measures. Table 1 lists the recognized predisposing risk factors for acute/subacute stent thrombosis.[8] In particular, the use of optimized stent size, high balloon-pressure deployment techniques, and standard intraprocedural and postprocedural antithrombotic therapy decreased the incidence of acute and subacute stent thrombosis with BMS down to 1.2% in studies involving 22,763 patients,[9-16] according to analysis from Kereiakes and colleagues.[17] Because BMS become endothelialized within a few weeks of implantation, dual antiplatelet therapy is only recommended for 4 weeks, followed by an ASA-only antiplatelet regimen. Rapid endothelialization of BMS makes late thrombosis (> 30 days after stent implantation) exceedingly rare, with a reported incidence rate of 0.7%.[18] In the BMS era, late stent thrombosis almost exclusively occurs in patients who receive adjunctive radiation brachytherapy (which delays endothelialization[19]), with a reported incidence of 2.5% in such patients.[20] Prolonged administration of dual antiplatelet therapy with clopidogrel and ASA is a proven method of prevention.[21] With DES, however, increasing concerns of late stent thrombosis have been raised recently, mostly in postmarketing case reports and clinical studies of late stent thrombosis.

Although paclitaxel and sirolimus inhibit vascular smooth muscle cell proliferation via different mechanisms, they both retard endothelial cell regeneration as well and, thus, negatively affect the restoration of the morphologic and functional integrity of the endothelium. Theoretically, it is reasonable to expect that DES have an increased thrombogenicity that may contribute to the development of late stent thrombosis.[22] In the premarketing phase of DES, however, large, randomized controlled trials revealed that these stents had a similar incidence of acute/subacute thrombosis (1%-2%) in comparison with BMS.[23-26] Shortly after FDA approval of the sirolimus-eluting stent Cypher® (Cordis Corp./Johnson & Johnson, Inc., Miami Lakes, FL), data in the FDA's Medical Device Reporting System initially raised great concern of a higher incidence of subacute thromboses. However, further analysis of postapproval registry data by the

Table 1
Predisposing Factors for Acute/Subacute Stent Thrombosis

Mechanic/Procedure-Related Risk Factors
Undersized stent
Underexpansion of stent
Asymmetry of stent
Stent overlap
Incomplete apposition
Dissection of coronary lesion
Tissue protrusion
Long stent length
Multiple stents
Combination of multiple stent types
Bifurcation stents
Unplanned procedure
Patient Factors
Acute coronary syndrome, unstable angina
Lesion characteristics (size, plaque state, etc)
Low left ventricular ejection fraction
Diabetes mellitus
Renal failure
Hypercoagulative status (protein C, protein S deficiency, etc)
Aspirin resistance
Clopidogrel resistance
Adjunctive Therapy
Brachytherapy
Inadequacy of periprocedural antithrombotic therapy
Premature discontinuation of antiplatelet therapy

FDA resulted in the conclusion that the Cypher stent is not associated with an excess rate of subacute thrombosis compared with BMS.[27] Subsequent observational clinical studies, meta-analyses, and "real world" consecutive patient analyses also repeatedly showed a comparable incidence of acute/subacute stent thrombosis within the first 30 days of DES implantation,[28-31] and even during the first 12 months in patients who received appropriate antiplatelet therapy.[32-34] A common concern cited about these studies is that they were not initially powered to detect or exclude the effect of DES on the relatively rare occurrence of stent thrombosis. In addition, patients with DES usually receive dual antiplatelet therapy for a much longer period of time than patients with BMS.

Safety concerns have been raised by case reports[35-37] and noncontrolled clinical studies of late and very late (> 6 months after implantation) stent thrombosis in DES—in particular, studies examining the impact of the discontinuation of clopidogrel on late stent thrombosis. Much attention has been devoted to determining the optimal duration of adequate antiplatelet therapy for patients with DES. Late stent thrombosis is often associated with:

- Premature discontinuation of antiplatelet therapy (clopidogrel in particular).
- Resistance to clopidogrel and/or ASA.
- Hypersensitivity to the polymer coating of the stent.
- Longer stent length.
- Smaller stent diameter.
- Stent underexpansion or the presence of residual reference segment stenosis.
- Stents used for bifurcation lesions.
- Postprocedure renal failure and chronic renal failure.
- Presence of diabetes.

The current recommendation of indefinite ASA and at least 12 months of clopidogrel might have contributed to a stabilization in the incidence of late stent thrombosis. Table 2 lists published cases reporting the occurrence of late thrombosis in patients with DES. Another worrisome phenomenon reported by both McFadden and colleagues[35] and Stabile and coworkers[38] is that in patients who have both DES and BMS, angiographically confirmed stent thrombosis is often found only in the DES, whereas the BMS remains patent (Table 2).

Discontinuation of Antiplatelet Therapy and Late Thrombosis Following DES Implantation

It would be ethically unacceptable to prospectively study the contributing effects of the discontinuation of antiplatelet therapy in late stent thrombosis. However, available published

Table 2
Late Stent Thrombosis Associated With Discontinuation of Antiplatelet Therapy

Patient Cases		Types	Post-PCI	ASA	Clopidogrel	Reason for Discontinuation of Antiplatelet Therapy	Intervention/Outcome
1[37]		SES × 1	31 mo	On	28 mo	Scheduled d/c after 3 mo	STEMI—PCI Survived
1[36]		SES × 1	105 d	100 d	15 d	Scheduled d/c after 3 mo	STEMI—PCI Survived
4[35]	# 1	PES × 1	343 d	5 d	ND	Elective resection of bladder polyps	STEMI—PCI Survived
	# 2	PES × 1	442 d	7 d	ND	Resection of colon for cancer	STEMI—PCI Survived
	# 3	BMS × 2 SES × 1	375 d	14 d	ND	ND	STEMI—PCI Survived SES—Thrombosis BMS—Patent
	# 4	SES × 2 BMS × 1	335 d	4 d	4 d	Colonoscopy, polypectomy	STEMI—PCI Survived SES—Thrombosis BMS—Patent
8[41]	# 1	SES	2 mo	5 d	5 d	ND	STEMI—PCI Survived
	# 2	PES	7 mo	On	28 d	Scheduled	STEMI—PCI Survived
	# 3	PES	6 mo	On	21 d	Scheduled	STEMI—PCI Survived
	# 4	PES	11 mo	5 d	d/c ? d	Surgery	STEMI—PCI Survived
	# 5	PES	14.5 mo	7 d	d/c ? d	Surgery	STEMI—PCI Survived
	# 6	PES	8 mo	On	2 mo	Scheduled	STEMI—PCI Survived
	# 7	SES	25 mo	On	19 mo	Scheduled	STEMI/Shock—PCI Dead
	# 8	SES	26 mo	On	23 mo	Scheduled	STEMI/Shock—PCI Dead
1[73]		SES	8 mo	ND	On	NA	STEMI—Dead Autopsy—ST
1[74]		SES × 2	17 mo	On	8 mo	Scheduled	STEMI—PCI Survived
1[75]		ND	19 mo	On	On ticlopidine	NA	STEMI—PCI Survived
2[38]	# 1	BMS × 2 SES × 1	12 mo	14 d	6 mo	Scheduled d/c after stress test	STEMI—PCI Survived BMS—Patent SES—Thrombosis
	# 2	BMS × 1 SES × 1	9 mo	4 d	4 d	Colonoscopy	STEMI—PCI Survived SES—Thrombosis BMS—Patent
3[42]	# 1	SES	193 d	On	2 wk	Scheduled	STEMI—PCI Survived
	# 2	SES	244 d	7 d	7 d	Urological procedure	STEMI—PCI Dead
	# 3	SES × 1 BMS × 1	535 d	13 d	13 d	Colonoscopy	STEMI—PCI Survived
4[43]	# 1	PES	204 d	7 d	7 d	Surgery	STEMI—PCI Survived
	# 2	PES	49 d	4 d	4 d	Bleeding, surgery	STEMI—PCI Survived
	# 3	SES	927 d	45 d	45 d	GI bleeding	STEMI—PCI Survived
	# 4	SES	227 d	7 d	7 d	ND	STEMI—PCI Dead
29[39]		20 PES	14 subacute	4 cases	5 cases	Surgery, intolerance/ bleeding, poor adherence	MI—PCI in all cases 1 Dead
		9 SES	15 late	d/c	d/c		28 Survived

BMS, bare-metal stent; d/c, discontinued; GI, gastrointestinal; MI, myocardial infarction; NA, not applicable; ND, not described; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; STEMI, ST-elevation myocardial infarction.

data clearly show that discontinuation of antiplatelet therapy (particularly clopidogrel) is the strongest independent risk factor for the development of stent thrombosis.[35-39] The discontinuation of antiplatelet therapy is a significant risk factor for both acute and subacute stent thrombosis, regardless of whether the patient has a BMS or DES. This association is also true for late stent thrombosis following DES implantation.[35,39] The magnitude of this problem is demonstrated by the fact that interruption of antiplatelet therapy following PCI has been identified in 4.1% to 5.4% of all patients admitted for acute coronary syndrome.[40]

The contribution of the discontinuation of antiplatelet therapy to the subsequent risk of developing stent thrombosis cannot be overemphasized. Jeremias and colleagues[28] found that premature discontinuation of clopidogrel was associated with an approximately 30-fold increase in the risk of developing stent thrombosis. In fact, more than 25% of patients who discontinued clopidogrel within the first month experienced stent thrombosis.[28] Ong and coworkers[41] followed 2006 patients treated with DES for longer than 1 year. Stent thrombosis did not occur in patients who continued dual antiplatelet therapy throughout the follow-up period. Discontinuation of clopidogrel or of both antiplatelet agents, however, resulted in 8 cases of angiographically confirmed stent thrombosis (Table 2).[41] Waters and colleagues[42] reported 3 cases of late stent thrombosis (at 193 days, 237 days, and 535 days after stent insertion) in patients who received a DES to address restenosis of a previously implanted BMS. Thrombosis in all cases occurred within 2 weeks of the discontinuation of clopidogrel as scheduled; 1 patient was still taking ASA, and the other 2 patients had discontinued both clopidogrel and ASA (1 for an anticipated urological procedure and the other for a colonoscopy with biopsy).

Iakovou and colleagues[39] reported data from a 9-month follow-up prospective observational cohort study that included 2229 consecutive patients who underwent successful implantation of a sirolimus-eluting stent (1062 patients, 1996 lesions, and 2272 stents) or a paclitaxel-eluting stent (1167 patients, 1801 lesions, and 2223 stents). They found that 29 patients (1.3%) had stent thrombosis, with 14 subacute and 15 late thromboses. They concluded, once again, that independent predictors of stent thrombosis were premature discontinuation of antiplatelet therapy together with renal failure, bifurcation lesions, diabetes, and a low ejection fraction.

Further evidence supporting the role of post-PCI antiplatelet therapy can be found throughout the literature. For example, Kuchulakanti and colleagues[30] reported that 14 out of 38 patients who developed stent thrombosis were found to have discontinued clopidogrel. Among these patients, 3 had acute thrombosis (2 due to an allergy to clopidogrel), 7 had subacute thrombosis, and 4 developed late thrombosis. The mean duration between cessation of clopidogrel and presentation of thrombosis among patients with subacute thrombosis was 6.2 $\pm$ 4.9 days; among those with late thrombosis, it was 55.5 $\pm$ 34.5 days (range, 21-90 days).[30] Iakovou and colleagues[39] studied 2229 consecutive patients who underwent successful implantation of sirolimus-eluting stents (1062 patients with a total of 1996 lesions and 2272 stents) or paclitaxel-eluting stents (1167 patients with 1801 lesions and 2223 stents). At 9-month follow-up, 29 patients had angiographically confirmed stent thrombosis, for a total incidence of 1.3%. In this particular patient pool, 17 patients discontinued either clopidogrel or both clopidogrel and ASA for various reasons, such as surgery (7 patients, 41%), intolerance or bleeding (6 patients, 35%), and poor adherence (4 patients, 24%). Five of these 17 patients (29.4%) experienced acute stent thrombosis within 30 days after discontinuation of antiplatelet therapy. Interestingly, in the Argentine Randomized Trial of Coronary Stents versus Bypass Surgery (ERACI) III trial, stent thrombosis was found only in DES in those patients who had received both BMS and DES in different coronary artery branches.[43,44] In addition, this study indicated that patients who discontinue clopidogrel while maintaining low-dose ASA therapy may also be at increased risk of late stent thrombosis.[41] Such data argue strongly in favor of ensuring proper post-PCI antiplatelet therapy administration.

It is clear that premature discontinuation of antiplatelet therapy is one of the strongest independent risk factors for the development of stent thrombosis. Given the increasing rate of late thrombosis for DES, the duration of dual antiplatelet therapy should most likely be longer. However, questions as to exactly how long would be adequate and how soon thrombosis would occur following the interruption of therapy are yet to be answered. Furthermore, there is evidence suggesting that the rate of stent thrombosis may be higher in the general population than in patients enrolled in controlled studies. As a result of the increasing amount of data, patients are now often advised to stay on prolonged antithrombotic therapy, especially when they are considered to be at increased risk for late stent

thrombosis, in particular with DES implantation.

Consequences of Stent Thrombosis

Stent thrombosis remains a serious complication of coronary artery stent implantation. Whether it occurs early (< 30 days after stent implantation) or late (> 30 days), stent thrombosis is often associated with death or nonfatal myocardial infarction (MI) requiring emergency PCI.[15,45] Ong and colleagues[41] reported a total of 38 incidents of stent thrombosis that occurred within 30 days of stenting. In that study, 77% of patients suffered an acute MI, with a mortality rate of 12%.[41] Jeremias and coworkers[28] reported 7 cases of angiographically confirmed stent thrombosis (1 at 39 days following stent placement, and the rest at 2 to 13 days following stent placement). One patient died after repeated PCI, 5 sustained an MI (4 had an ST-elevation MI [STEMI], 1 had a non-STEMI), 3 patients developed cardiac arrest, and 5 presented in cardiogenic shock. Of the 29 stent thrombosis patients in the study by Iakovou and colleagues,[39] 13 patients died (for a case fatality rate of 45%), and the rest required emergent PCI. In the ERACI III trial, 3 out of the 7 patients who developed stent thrombosis died despite aggressive intervention, and all the others developed STEMI requiring emergent intervention.[43] Given such data, the problem of stent thrombosis must be approached aggressively from both the prevention and treatment perspectives.

Risk of GI Bleeding Associated With Antiplatelet Therapy

Bleeding complications, most of which arise from the upper GI tract, are the major limiting factors for antiplatelet therapy. A recent case-control study by Ibanez and colleagues[46] showed that antiplatelet drugs as a group account for 14.5% of all cases of upper GI bleeding, which translates to about 58 cases per million per year (334 cases per million per year among those older than 70 years).[46]

The association of ASA with the increased risk of upper GI bleeding has been well established. The mechanisms underlying this association include: 1) its antiplatelet activity; 2) ASA-related impairment of prostaglandin E_2-mediated cytoprotection in the GI mucosa; and 3) the direct ulcerogenic effect of the contact between ASA and the GI mucosa. No dose of ASA is free of bleeding risk. The inhibition of thromboxane A_2-mediated antiplatelet function with a dose of ASA greater than 30 mg is considered dose-independent, but the other 2 mechanisms of ASA-associated GI bleeding are dose-dependent, with the risk of bleeding amplified at higher doses (resulting in a relative risk that is 4-6 times higher at the analgesic/anti-inflammatory doses). ASA at a dose as low as 75 mg/d is associated with a risk of upper GI bleeding that is 2 times higher than in patients not taking ASA.[47] It was estimated that about 1 in 248 subjects who used long-term low-dose ASA (75-160 mg/d) would develop GI bleeding each year.[48] A recent post hoc analysis by Peters and colleagues[49] of published observational studies examined the effect of ASA on GI bleeding by grouping patients based upon the dose of ASA received (< 100 mg/d, 101-199 mg/d, and ≥ 200 mg/d). The study revealed that among the 12,562 ASA users randomized to receive clopidogrel or placebo, the lower dose was safer than the higher doses. As a result, a 75 mg/d to 81 mg/d dose was recommended. In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study, the rate of potentially life-threatening bleeding events associated with ASA was 1.9 per 100 patient-years with a dose below 100 mg/d, as compared with 3.9 per 100 patient-years with a dose of 200 mg/d to 365 mg/d.[49]

Peptic ulcer bleeding and *Helicobacter pylori* infection[44] are the 2 most important risk factors for ASA-associated GI bleeding complications. Patients who continued to take ASA following ulcer healing and eradication of *H. pylori* infection had a 15% recurrent bleeding rate within a year.[50] No good evidence supports the routine use of proton-pump inhibitors or cytoprotective agents in patients taking daily ASA in the range of 75 mg to 100 mg. However, long-term daily use of low-dose ASA was associated with a significant reduction in the recurrence of ulcer complications in patients with a history of ulcer bleeding who were taking PPIs and in whom *H. pylori* was eradicated.[50,51]

Clopidogrel has a low potential for inducing peptic ulcers[52] and a GI safety profile superior to that of ASA alone.[53-56] In a double-blind, double-dummy, parallel-designed study of healthy volunteers, 75 mg of clopidogrel monotherapy for 8 days did not induce any gastroscopically detectable macroscopic changes in the gastroduodenal mucosa, whereas 325 mg of ASA did.[54] The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study showed that the overall frequency of bleeding disorders was similar between the clopidogrel and ASA groups (9.27% for clopidogrel vs 9.28% for ASA; difference not statistically significant), but the incidence of GI tract hemorrhages was significantly lower in the clopidogrel group (1.99%) than in the ASA group (2.66%).[53,57] A previous history of GI bleeding (due to either *H. pylori*

infection or ASA use) also correlated with increased clopidogrel-associated GI bleeding as an independent risk factor that can be minimized by coadministration of PPIs.[58] Among patients with a history of ulcer bleeding, after ulcers were healed and *H. pylori* was eradicated, clopidogrel (75 mg/d) alone was found to be associated with a higher rate of recurrent ulcer bleeding in comparison with the coadministration of low-dose ASA (80 mg/d) and maximum-dose esomeprazole (20 mg twice a day).[59] Concomitant use of a PPI with clopidogrel to reduce the incidence of clopidogrel-associated upper GI bleeding in patients at risk may be justifiable based upon these data.[60]

In the CURE study of patients with unstable angina, combination therapy with clopidogrel and ASA provided a 20% relative risk reduction compared with ASA alone in the composite endpoint of cardiovascular death, nonfatal MI, or stroke.[61] Patients taking combination therapy also had a greater long-term life expectancy.[62] The reduction in relative risk, however, was accompanied by a significant increase in the risk of major bleeding, which was 3.7% in the combination group and 2.7% in the ASA-alone group (relative risk, 1.38; 95% confidence interval [CI], 1.13-1.67; P = .001). Most of the major bleeding episodes were due to GI hemorrhage and bleeding at the sites of arterial punctures. An increase in bleeding associated with concurrent administration of clopidogrel and ASA was also noticed in the Clopidogrel for the Reduction of Events During Observation (CREDO) trial[63] and the Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH) trial.[64] Interestingly, adding ASA to clopidogrel may result in a higher risk of GI bleeding than adding clopidogrel to an existing ASA regimen, as revealed by a comparison of the findings of the MATCH trial with those from the CURE and CREDO trials.[65]

There has been no systematic study of how different patient populations are affected by the GI bleeding risk associated with ASA and clopidogrel for the prevention of stent thrombosis. Although direct data support is lacking, it is reasonable to assume that previous GI bleeding history and *H. pylori* infection would influence the risk of GI bleeding in patients on clopidogrel and ASA combination therapy. However, the effect of PPI prophylaxis on the risk of GI hemorrhage in patients taking a combination of ASA and clopidogrel must be assessed in future clinical trials before specific recommendations can be formalized.

Management of GI Bleeding in Patients Receiving Antiplatelet Therapy

After the general initial assessment and resuscitation of patients diagnosed with GI bleeding, other essential aspects of the initial management include the withholding of exacerbating medications—such as nonsteroidal anti-inflammatory drugs, heparin, warfarin, and antiplatelet agents—and reversal of anticoagulative states. Endoscopy (for both surveillance and potential intervention), performed either emergently or semielectively, is the primary tool for definitive management of GI bleeding.[66,67] However, in the case of patients with well-known high thromboembolic risk conditions, such as mechanic valves, atrial fibrillation, recent or recurrent venous or arterial thromboembolism, or who are in a hypercoagulable state with recent thromboembolic events, clinicians often face the difficult situation of weighing the risk of continued bleeding against the risk of thrombosis. Some safety issues surrounding endoscopic procedures in patients taking heparin, warfarin, ASA, or non-ASA antiplatelet agents, such as clopidogrel, have been addressed by guidelines from the American Society for Gastrointestinal Endoscopy (ASGE) that are based on expert consensus and available studies.[68,69] Limited data[70,71] suggest that ASA administered at standard doses does not increase the risk of significant bleeding after high-risk endoscopic procedures. These agents may be continued in patients undergoing endoscopy in the absence of a preexisting bleeding disorder.[68]

Does the withholding of antiplatelet agents benefit the clinical outcome of acute GI bleeding management? Surprisingly, there have not been, to our knowledge, any published studies designed to answer this question. Due to the irreversible nature of the antiplatelet effects of ASA and the thienopyridines, short-term withholding should not be expected to achieve a beneficial effect in the cessation of acute GI bleeding. There appear to be no published data regarding the safety of thienopyridines during endoscopic procedures. Based upon their pharmacology and known clinical effects, the ASGE recommends that "with acute GI hemorrhage in the patients taking clopidogrel or ticlopidine, these agents should be discontinued. The decision to reverse the antiplatelet effect, risking ischemic consequences, must be weighed against the risk of continued bleeding by maintaining the state of impaired platelet aggregation. If quick reversal is required, platelet transfusion may be appropriate."[69]

For high-risk elective endoscopic procedures, the need to discontinue these agents has not been definitively determined. If deemed necessary, these antiplatelet agents should

be stopped 7 to 10 days prior to the procedure. It is appropriate to restart the drug(s) the day following the procedure.[69,72]

Conclusion

Hemorrhage is a well-known complication of antiplatelet therapy, and upper GI bleeding is the most common origin. ASA and clopidogrel therapy are associated with an increased risk of GI bleeding. A history of GI bleeding, gastric ulcer disease, or infection with *H. pylori* are major risk factors for GI bleeding associated with antiplatelet therapy. Endoscopy with possible intervention is the most reliable tool to diagnose and stop active GI bleeding. Withholding of antiplatelet therapy is the recommended course of action in the management of a patient with active life-threatening bleeding. However, no published data are currently available to justify the necessity or benefit of withholding antiplatelet agents in management of GI bleeding.

In patients with coronary stents, thrombosis is a rare but potentially catastrophic complication. Premature discontinuation of antiplatelet therapy, especially the discontinuation of clopidogrel, predisposes patients to a higher risk of stent thrombosis. Dual antiplatelet therapy is absolutely required for the first 30 days following stenting (with both BMS and DES), and a longer duration than is currently recommended is likely desirable given the increasing concerns regarding late stent thrombosis. Two factors argue strongly against the withholding of antiplatelet therapy in patients with GI bleeding: observational data indicating an unacceptably high incidence of thrombosis (> 25%) and the serious associated consequences of acute/subacute stent thrombosis following unplanned discontinuation of antiplatelet therapy in the early poststenting period. Considering the increase in GI bleeding risk seen with prolonged antiplatelet therapy, adjunctive PPI therapy and/or eradication of *H. pylori* infection might be beneficial for DES patients on long-term antiplatelet therapy. More studies to determine long-term outcomes are necessary to allow for standardization of treatment guidelines. ■

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Main Points

- As the amount of patients with stents rapidly and steadily expands, an increasing number of patients are potentially at higher risk of experiencing hemorrhagic complications while taking antiplatelet agents.
- Restenosis (renarrowing of vessel lumen by neointimal growth within the stent) and stent thrombosis (sudden occlusion of the vessel due to thrombus formation on the stent) are the twin limitations of percutaneous coronary intervention (PCI) stent revascularization of coronary stenosis.
- Except when contraindicated, dual antiplatelet therapy with aspirin and a thienopyridine (clopidogrel or ticlopidine in patients allergic to clopidogrel) has been the standard of care in post–PCI-stent patients.
- Available published data clearly show that discontinuation of antiplatelet therapy (particularly clopidogrel) is the strongest independent risk factor for the development of stent thrombosis.
- Peptic ulcer bleeding and *Helicobacter pylori* infection are the 2 most important risk factors for aspirin-associated gastrointestinal bleeding complications.
- Endoscopy with possible intervention is the most reliable tool to diagnose and stop active gastrointestinal bleeding.

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