Journal of the American College of Cardiology Vol. 54, No. 24, 2009

Published by Elsevier Inc.

ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.09.012

JACC White Paper

Management of Platelet-Directed Pharmacotherapy in Patients With Atherosclerotic Coronary Artery Disease Undergoing Elective Endoscopic Gastrointestinal Procedures

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The periprocedural management of patients with atherosclerotic coronary heart disease, including those who have heart disease and those who are undergoing percutaneous coronary intervention and stent placement who might require temporary interruption of platelet-directed pharmacotherapy for the purpose of an elective endoscopic gastrointestinal procedure, is a common clinical scenario in daily practice. Herein, we summarize the available information that can be employed for making management decisions and provide general guidance for risk assessment.

According to 2009 Heart and Stroke Statistics (1,2), an estimated 80,000,000 American adults have 1 or more types of cardiovascular (CV) disease, and nearly 17,000,000 have coronary heart disease (CHD), with 7,900,000 and 6,500,000 adults experiencing either a myocardial infarction (MI) or stroke, respectively, at some point in the past.

The estimated annual incidence of MI in men and women >20 years of age is 935,000, with 610,000 classified as new events and 325,000 as recurrent events (2). On the basis of information provided by the Framingham Heart Study (3), CHD is responsible for over 50% of all CV events in men and women <75 years of age, with an average 15 years of life lost due to an MI.

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Manuscript received June 9, 2009; revised manuscript received September 9, 2009, accepted September 15, 2009.

JACC Vol. 54, No. 24, 2009
December 8, 2009:2261–76

Abbreviations and Acronyms

ACS = acute coronary syndrome
BMS = bare-metal stent(s)
CHD = coronary heart disease
CI = confidence interval
CV = cardiovascular
DES = drug-eluting stent(s)
ECG = electrocardiogram/electrocardiographic
ERCP = endoscopic retrograde cholangiopancreatography
ESD = endoscopic submucosal dissection
FNA = fine needle aspiration
GI = gastrointestinal
MI = myocardial infarction
NSAID = nonsteroidal anti-inflammatory agent
OR = odds ratio
PCI = percutaneous coronary intervention
PPI = proton pump inhibitor
RR = relative risk
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction

The estimated annual cost of CHD approaches $170 billion. The recent and steady decrease in U.S. death rates from CHD has been attributed in large part to evidence-based medical treatments, including platelet-directed pharmacotherapies (also referred to in the document as platelet antagonists) (4).

The periprocedural management of patients who might require temporary interruption of platelet-directed pharmacotherapy because of an endoscopic gastrointestinal (GI) procedure is a common clinical consideration. The decision is challenging, because the risk of a thrombotic event during interruption of therapy must be balanced carefully against the risk for bleeding when treatment is administered in close proximity to the procedure.

There are 2 fundamental questions that each clinician must ask:

1. Is interrupting platelet-directed pharmacotherapy in the periprocedural period necessary? This question is particularly relevant when the anticipated risk for thrombosis is high and the concomitant procedure-related bleeding risk is low.
2. If platelet-directed pharmacotherapy is interrupted, what is the optimal timing and duration for temporary discontinuation?

The primary objectives of our collaborative white paper are to: 1) summarize the available data and, when available, accompanying evidence for the risk of hemorrhagic and thrombotic events associated with elective endoscopic GI procedures among patients with CHD—particularly those with coronary artery stents receiving platelet-directed pharmacotherapy; 2) summarize the available data and, when available, accompanying evidence for the risk of thrombotic and hemorrhagic events associated with elective endoscopic GI procedures among patients with CHD in whom platelet-directed pharmacotherapy is interrupted for 5 or more days before and/or after the procedure; and 3) provide direction for general risk assessment that allows practicing clinicians to better identify and, whenever possible, quantitate (as low, medium, or high) individual patient risk for either continued or interrupted platelet-directed pharmacotherapy among patients with CHD undergoing elective endoscopic procedures.

The overarching goal is to provide an informative overview for practicing clinicians that fosters a balanced approach to the care of patients with CHD undergoing elective endoscopic GI procedures. We will not craft a consensus document; however, the clinically relevant information is designed to build on the theme of reducing GI risks of platelet-directed pharmacotherapy highlighted in the 2008 ACCF/ACG/AHA Consensus Statement (5) and provide a concomitant CV risk perspective relating to withdrawing treatment in anticipation of an elective endoscopic GI procedure.

CV Risks

Dual platelet antagonists in CV disease. Aspirin and thienopyridines, such as clopidogrel, exert their platelet-inhibiting effect through distinct mechanisms that target separate pathways. Laboratory and animal studies confirm a synergistic effect of these agents on platelet activation and aggregation. In the last decade, data from large randomized clinical trials of patients with acute coronary syndrome (ACS) or those undergoing percutaneous coronary intervention (PCI) have shown a significant reduction in CV end points with dual aspirin-thienopyridine therapy compared with aspirin alone. In this section we will review and emphasize established indications (as per the ACC/AHA Management Guidelines) for a dual platelet antagonist strategy and the accompanying designated level of evidence. The anticipated safety of this strategy, particularly in relation to bleeding complications and relevant drug interactions will also be summarized.

Indications for dual platelet antagonists in CV disease.

ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION (STEMI). Clopidogrel 75 mg/day orally should be added to aspirin in patients with STEMI regardless of whether they undergo fibrinolytic therapy or do not receive reperfusion therapy (Class I, Level of Evidence: A). Treatment should continue for at least 14 days (Class I, Level of evidence: B) (6).

The CLARITY–TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis In Myocardial Infarction 28) trial compared the efficacy of clopidogrel (300 mg oral loading dose, then 75 mg/day) plus aspirin (recommended dose 150 to 325 mg on the first day and 75 to 162 mg daily thereafter) with aspirin alone in 3,491 patients ages <75 years with STEMI receiving fibrinolytic therapy (7). Patients were treated up to the time of protocol-mandated angiography (day 2 to 8); the average duration of treatment was 4 days (maximum 16 days). Dual therapy was associated with a 36% reduction in the composite end point of an

occluded infarct-related coronary artery or death or MI before angiography could be undertaken (95% confidence interval [CI]: 27% to 47%, $p < 0.001$) at 2 to 8 days. This benefit was largely due to a lower rate of occlusion of the infarct-related artery (there was no significant reduction in either death or MI). By 30 days, patients given dual therapy had 20% lower odds of CV death, MI, or urgent revascularization (14.1% vs. 11.6%, $p = 0.03$). There was no difference in Thrombolysis In Myocardial Infarction (TIMI) major bleeding through the day of coronary angiography (dual therapy 1.3% vs. aspirin alone 1.1%).

The COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction) trial, conducted in China, randomized 45,852 patients (26% of patients were older than 70 years of age) within 24 h of a suspected MI to clopidogrel 75 mg (initial loading dose) then 75 mg daily plus aspirin (162 mg daily) or aspirin and placebo (8). Approximately 93% of patients had STEMI (or a left bundle branch block pattern), and one-half received reperfusion therapy. The average duration of treatment was 15 days. The risk of death, reinfarction, or stroke was decreased from 10.1% in the placebo arm to 9.2% in the treatment arm (odds ratio [OR]: 0.91, 95% CI: 0.86 to 0.97). All cause mortality was similarly reduced in the treatment arm (8.1% vs. 7.5%, $p = 0.03$). The rate of cerebral and major bleeding did not differ between the 2 treatment groups (0.58% vs. 0.55%).

NON-ST-SEGMENT ELEVATION ACS. For patients with unstable angina/non-STEMI in whom an initial invasive strategy is planned, antiplatelet therapy in addition to aspirin should be initiated before diagnostic angiography with either clopidogrel (loading dose followed by daily maintenance dose) or intravenous glycoprotein (IIb/IIIa inhibitor therapy (Class I, Level of Evidence: B) (4). For patients undergoing PCI, clopidogrel in addition to aspirin should be continued for up to 1 year (at least 1 year in those receiving drug-eluting stents [DES]).

For patients with unstable angina/non-STEMI in whom an initial conservative strategy is selected, clopidogrel (loading dose followed by daily maintenance dose) should be added to aspirin and anticoagulant therapy as soon as possible after admission and administered for at least 1 month (Class I, Level of Evidence: A) and ideally up to 1 year (Class I, Level of Evidence: B) (9).

The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial randomized 12,562 patients with clopidogrel (300 mg oral load followed by 75 mg/day) and aspirin versus aspirin and placebo and followed them for 3 to 12 months (10). The composite end point of CV death, MI, or stroke occurred in 11.5% of patients receiving placebo vs. 9.3% of those receiving clopidogrel (relative risk [RR]: 0.80, 95% CI: 0.72 to 0.90). The observed difference was largely due to a significant 23% reduction in recurrent MI, with weak trends for reductions in death (RR: 0.93, 95% CI: 0.79 to 1.08) and stroke (RR: 0.86, 95% CI: 0.63 to 1.18). These reductions were consistent across all prespecified patient subgroups (positive and negative biomarkers, positive and negative electrocardiographic [ECG] changes, and TIMI risk score categories). In addition, there was a 20% risk reduction in the composite end point in the first 30 days and beyond 30 days.

Major bleeding—defined as disabling bleeding, intraocular bleeding with visual loss, and/or bleeding prompting the transfusion of 2 or more units of blood—was more frequent in clopidogrel-treated patients (3.7% vs. 2.7%, $p = 0.001$). The rate of major bleeding, predominantly GI or at the femoral access site, was higher both in the first 30 days and after 30 days. The risk of bleeding was particularly high in patients who underwent coronary artery bypass grafting within 5 days of clopidogrel therapy compared with those in whom clopidogrel was held for at least 5 days (9.6% vs. 6.3%, $p = 0.06$).

In an observational study of CURE (PCI-CURE) (1), data from 2,658 patients who subsequently underwent PCI were analyzed. Patients were pretreated with aspirin and study drug for a median of 6 days before PCI. After PCI most patients received open label thienopyridine for 4 weeks, and then blinded study drug was restarted for a mean period of 8 weeks. At 30 days there was a significant reduction (4.5% vs. 6.4%, $p = 0.03$) in CV death, MI, or urgent target vessel revascularization. Over long-term follow-up there was a 30% reduction in the composite end point in patients undergoing PCI who received clopidogrel compared with those receiving placebo. Increases in minor but not major bleeding were observed in patients receiving clopidogrel.

PCI AND STENTING. A loading dose of clopidogrel (in addition to aspirin) should be administered before PCI is performed (Class I, Level of Evidence: A) (11).

In patients who have undergone PCI, clopidogrel (in addition to aspirin) should be given for a minimum of 1 month and ideally for up to 12 months after bare-metal stent (BMS) implantation (unless the patient is at increased risk for bleeding; then it should be given for a minimum of 2 weeks) (Class I, Level of Evidence: B) (11).

For all post-PCI patients receiving a DES, clopidogrel 75 mg daily (in addition to aspirin) should be given for at least 12 months if patients are not at high risk of bleeding. (Class I, Level of Evidence: B) (11). Continuation of clopidogrel therapy (in addition to aspirin) beyond 1 year may be considered in patients undergoing DES placement (Class IIa, Level of Evidence: C).

Early trials with the first-generation thienopyridine, ticlopidine, established the superiority of combined anti-

platelet therapy initiated before PCI and continued for 30 days over aspirin alone or aspirin plus warfarin, a vitamin K antagonist, to prevent early and late stent thrombosis after PCI (12–15). By virtue of a superior safety profile, similar efficacy, and once/day dosing clopidogrel subsequently became the thienopyridine of choice for this indication (16–18).

Subsequent trials have shown that extended treatment with aspirin and clopidogrel after PCI with stenting for ACS or after an elective procedure reduces CV events. The results of the PCI-CURE study have been reviewed previously. In the CREDO (Clopidogrel for the Reduction of Events During Observation) trial, 2,116 patients undergoing elective PCI were randomly assigned to receive 300 mg clopidogrel versus placebo, followed by clopidogrel 75 mg daily for 30 days (19). The initial loading-dose group received clopidogrel 75 mg/day, and the control group were given placebo for the subsequent 12 months. All patients received aspirin therapy. The composite end point of death, MI, or stroke at 12 months was decreased from 11.5% to 8.5% ($p < 0.05$) among patients receiving clopidogrel. There was a trend toward an increased rate of major bleeding in the clopidogrel arm (8.8% vs. 6.7%, $p = 0.07$).

CHRONIC STABLE CORONARY ARTERY DISEASE. The current American College of Cardiology/American Heart Association guidelines do not recommend dual antiplatelet therapy in patients with documented coronary artery disease unless there is a recent ACS (<12 months) or PCI with DES. In the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemia Stabilization, Management, and Avoidance) study (20), clopidogrel (75 mg/day) plus aspirin was compared with placebo and aspirin in 15,603 patients at high risk for CV events. Median follow-up was 28 months. Patients treated with clopidogrel had a similar rate of the combined end point (MI, stroke, or CV death) as patients in the placebo (aspirin alone) arm (6.8% vs. 7.3%, RR: 0.93, 95% CI: 0.83 to 1.05). Patients receiving dual antiplatelet therapy experienced higher rates of moderate (2.1% vs. 1.3%, $p < 0.001$) and severe bleeding (1.7% vs. 1.3%, $p = 0.09$). In a subset of patients ($n = 9,478$) with prior MI, ischemic stroke, or symptomatic peripheral vascular disease, dual antiplatelet therapy was associated with a lower risk of the combined end point compared with aspirin alone (hazard ratio: 0.83, 95% CI: 0.72 to 0.96) but with an increased risk of bleeding.

Potential drug interactions. Drug interactions between aspirin and clopidogrel are largely limited to the enhanced potential for bleeding associated with each drug's distinct mechanism of achieving platelet inhibition. In noninstrumented patients, most bleeding events are GI in origin. Aspirin is ulcerogenic by virtue of local injury to the GI mucosa and systemic depletion of prostaglandins. Although not directly ulcerogenic, clopidogrel—by virtue of its ability to inhibit platelet activation and aggregation—might impair healing of small developing ulcers (5). The combined use of clopidogrel and nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, has been associated with impaired healing of asymptomatic ulcers and with an increase in serious upper GI bleeding (21).

Proton pump inhibitors (PPIs) have been shown to decrease the risk of gastroduodenal ulcers and upper GI bleeding in patients taking aspirin or NSAIDs (22,23). Proton pump inhibitors also decrease the risk of GI bleeding associated with the combination of clopidogrel and aspirin. In a matched case-control study of 2,777 consecutive patients with upper GI bleeding and 5,532 control subjects, use of PPIs was associated with an 87%, 68%, and 81% reduction in risk of upper GI bleeding associated with users of NSAIDs, low-dose aspirin, and clopidogrel, respectively. Accordingly, recommendations from an expert consensus document supported the use of a gastroprotective agent, preferably a PPI, for the prophylaxis of NSAID- and aspirin-associated GI injury (5). Proton-pump inhibitors are now commonly administered to patients at increased risk for GI bleeding who require dual antiplatelet therapy after coronary stent placement.

There is increasing interest surrounding potentially important interactions between PPIs and clopidogrel. These medications share common metabolic pathways involving hepatic P450 isoenzymes, specifically 2C19. At least 1 study suggested decreased platelet inhibition after coronary stent implantation among patients receiving PPIs in addition to aspirin and clopidogrel (24). In a retrospective cohort study of 8,205 patients with ACS taking clopidogrel, the use of PPIs was associated with an increased risk of death or repeat hospital stay for ACS (adjusted OR: 1.25, 95% CI: 1.11 to 1.41) (25). Although observations from population-based registries and cohort studies are best interpreted as "hypothesis generating," further investigation must be undertaken to provide clarity around this very important area.

In the PRINCIPLE–TIMI 44 (Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation–Thrombolysis In Myocardial Infarction 44) trial (26), mean inhibition of platelet aggregation among patients assigned to clopidogrel (600-mg oral loading dose) was significantly lower ($23.2 \pm 19\%$ vs. $35.2 \pm 20\%$, $p = 0.02$). There was a much more modest difference in patients assigned to prasugrel. The observations made in PRINCIPLE–TIMI 44 did not translate to differences in clinical end points for patients participating in the TRITON–TIMI 38 (TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibitioN with prasugrel–Thrombolysis In Myocardial Infarction 38) trial. Accordingly, when clinically indicated, PPIs should not be withheld.

Safety of discontinuing single agent and dual platelet antagonists. The risk of thrombotic events for patients with atherosclerotic disease is generally low after brief cessation of platelet antagonists. In contrast, the risk for CV events might be markedly increased among patients with an inherent predisposition to thrombosis. The section will focus primarily on the patient group at greatest potential risk for thrombotic events upon cessation of antiplatelet therapy—those having undergone prior coronary stenting.

SUBSTRATES FOR STENT THROMBOSIS. The efficacy and safety of DES are well-documented in clinical trials; however, animal studies and human autopsy data clearly show a persistence of prothrombotic substrate for prolonged periods of time. Histopathological evaluation of the vessel wall after DES implantation consistently reveals circumferential granulomatous inflammation consisting of macrophages, multinucleated giant cells, lymphocytes, and eosinophils adjacent to stent struts (27). Fibrin deposition within neointima and smooth muscle cell apoptosis are frequently identified beyond 6 months of implantation. The inflammatory response after BMS implantation is minimal and relatively brief in duration. Endothelial cell injury and delayed and/or incomplete endothelialization of the stent struts are also important determinants of thrombogenicity.

DEFINITION OF STENT THROMBOSIS. The Academic Research Consortium, in response to a request from the U.S. Food and Drug Administration Circulatory System Device panel's recommendation to implement consensus definitions for stent thrombosis in clinical trials, offered the following definitions (28):

Stent thrombosis may be classified as definite, probable, or possible and as early (0 to 30 days), late (31 to 360 days), or very late (>360 days).

Definite stent thrombosis requires the presence of an ACS with either angiographic or autopsy evidence of either occlusion or thrombus.

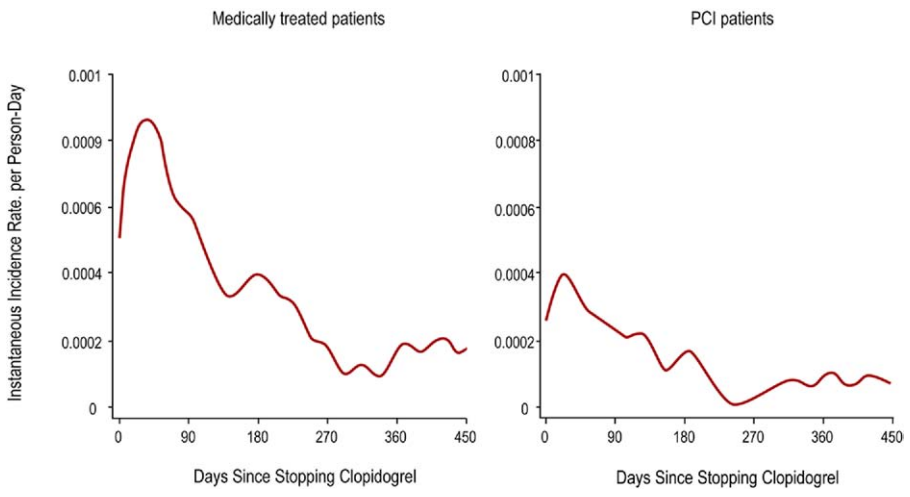
Probable stent thrombosis includes unexplained deaths within 30 days after implantation or acute MI involving the original target vessel distribution.

Possible stent thrombosis includes all unexplained deaths at least 30 days after the procedure.

Beyond its well-known initial and potentially catastrophic features, coronary stent thrombosis has long-term clinical implications as well. The Dutch Stent Thrombosis Registry (29) reported recently on long-term clinical outcomes after a first angiographically confirmed stent thrombosis in 43 consecutive patients. Cardiac death and/or definite recurrent stent thrombosis at 30 days, and 1, 2, and 3 years were 18%, 23.6%, 25.3%, and 27.9%, respectively (Fig. 1). The timing of the first definite recurrent stent thrombosis among 75 patients with this complication was early in 54 patients, late in 15 patients, and very late in 6 patients, suggesting that a wide temporal range of stent thrombosis (and its risk) applies in multiple clinical settings.

Figure 1

Risk of Clinical Events After Clopidogrel Cessation



Risk-adjusted instantaneous incidence rates of death or acute myocardial infarction over time after stopping treatment with clopidogrel among medically treated and percutaneous coronary intervention (PCI)-treated patients with acute coronary syndrome. Reprinted with permission from Ho PM, Peterson ED, Wang L, et al. Incidence of death and acute myocardial infarction associated with stopping clopidogrel after acute coronary syndrome. JAMA 2008;299:532–9.

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Table 1

Risk Stratifcation for Early and Late Stent Thrombosis

Variables	Low Risk	Moderate Risk	High Risk
Cumulative absolute rate*	1%	2%–5%	>6%
Absence of variables below	x		
Clinical risk factors			
Prior stent thrombosis			x
Presentation with ACS or STEMI		x	
Multivessel PCI		x	
Diabetes		x	
Renal failure		x	
Depressed ejection fraction		x	
Procedural risk factors			
Diffuse coronary disease		x	
Smaller post-PCI diameter		x	
Multiple stents		x	
Residual dissection		x	
Bifurcation stenting		x	
Large thrombus burden		x	
First generation drug-eluting stents		x	
Drug-resistance factors			
Cytochrome P450 variant		x	
Increased platelet reactivity		x	
Dual aspirin and clopidogrel nonresponsiveness			x
Time-related factors			
<4 weeks of DPA		x	
Aspirin alone for 30 days		x	
Noncardiac surgery early after PCI			x

*With platelet antagonist therapy.
ACS = acute coronary syndrome; DPA = dual platelet antagonists; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

THROMBOTIC EVENTS IN THE FIRST MONTH AFTER STENTING. What is the anticipated clinical impact of stopping aspirin or clopidogrel or both in the first 30 days after stenting? Although one can generally estimate the early (within 30 days of PCI) risk of stent thrombosis at 1% for both BMS and DES, there is a marked variation in risk, depending upon clinical, procedural, treatment, and genetic risk factors (Table 1) (28,30–33). The STARS (STent Anti-thrombotic Regimen Study) reported 30-day stent thrombosis incidence rates of 3.6% and 0.5%, respectively, for patients with BMS receiving aspirin alone versus those given dual antiplatelet therapy (15). In contrast, several trials and registries have demonstrated an increased risk of 30-day stent thrombosis solely in high-risk patient groups. Noncompliance with dual antiplatelet therapy is a consistent risk factor for early stent thrombosis (31,32).

A large European registry identified bifurcation lesions, renal failure, diabetes, lower ejection fraction, and longer stent length (31) as predictors of early DES thrombosis but did not identify factors such as diffuse coronary artery disease, higher hemoglobin levels (32), or initial thrombus burden (34). Each risk factor would potentially increase the STARS trial estimate (3.6%) for stent thrombosis in the first 30 days after BMS with aspirin therapy alone.

Aspirin withdrawal might be associated with an increased risk of ACS, especially STEMI (35,36). In addition, surgical procedures (with aspirin or clopidogrel or both discontinued) performed in the first 2 to 4 weeks after stenting have reported up to a 30% rate of major adverse CV events (37–40). The early risk is similar for both BMS and DES (37). Thus, stopping both aspirin and clopidogrel for even a brief period of time among patients within 30 days of stent placement is accompanied by risk.

RISK FOR LATE AND VERY LATE STENT THROMBOSIS. Histological studies have demonstrated uniform and complete endothelial coverage of BMS >30 days after stent implantation. Conversely, a higher stent thrombosis risk is maintained during the 3-month to 3-year period of follow-up with DES as compared with BMS, potentially related to delayed endothelialization of DES (41). Thus, there might be an advantage to prolonged dual antiplatelet therapy for at least 1 year after DES. In an observational study of over 4,000 patients, continued use of clopidogrel beyond 6 months did not influence death or MI rates from 6 to 24 months after BMS placement. In contrast, continued use of clopidogrel reduced death or MI rates between 6 and 24 months after insertion of a DES (42). Randomized data are required to provide clarity for practicing clinicians.

THROMBOTIC EVENTS IN THE ABSENCE OF PRIOR PCI. The CHARISMA trial randomized stable patients with known atherosclerosis or multiple coronary risk factors to aspirin/clopidogrel versus aspirin alone (1). Among patients with documented prior MI, ischemic events were 23% higher with aspirin alone as compared with dual antiplatelet therapy (8.3% vs. 6.6%, $p = 0.01$). These events accrued over 2.5 years, yet there seemed to be a small but significant hazard for thrombotic events even 30 days after randomization among patients receiving single antiplatelet therapy. The Kaplan-Meier curves from the CHARISMA trial demonstrate confirmed thrombotic events in <1% of patients managed with aspirin alone in the first month after randomization. Accordingly, the overall risk of spontaneous thrombotic events in patients with established coronary

artery disease receiving aspirin alone is low. In contrast, the risk of withdrawing all antiplatelet therapy might not be equally low, because "aspirin withdrawal" has been associated with acute coronary events clustered soon after aspirin discontinuation (average time from aspirin cessation to event = 10 days) (35,36).

CESSATION OF PLATELET ANTAGONISTS: WHEN IS IT SAFE? Among patients receiving DES, discontinuing clopidogrel within the first 6 months after PCI is associated with a heightened risk of stent thrombosis. In addition, stent thrombosis tends to occur shortly after discontinuing any antiplatelet agent, with a median interval of 7 to 14 days (interquartile range 5.2 to 25.7 days) (43). The discontinuation of both aspirin and a thienopyridine is associated with a particularly high risk for stent thrombosis. In the C-Cypher Registry (44), patients who discontinued both aspirin and either ticlopidine or clopidogrel had a significantly higher rate of stent thrombosis than those who continued dual platelet-directed therapy between 31 and 180 days, 181 and 365 days, and 366 and 548 days (1.76% vs. 0.1%, $p < 0.001$; 0.72% vs. 0.07%, $p = 0.02$; and 2.1 vs. 0.14%, $p = 0.004$), respectively.

Eisenberg et al. (45) performed a systematic overview of reported cases of late stent thrombosis and very late stent thrombosis (Academic Research Consortium defined "definite" cases). A total of 161 cases were identified. Patients who discontinued both aspirin and a thienopyridine had a median time to an event of 7 days. In those who discontinued a thienopyridine but remained on aspirin, the median time to an event was 122 days. There were a total of 6 cases (6%) of stent thrombosis within 10 days of thienopyridine cessation, suggesting that short-term discontinuation between 30 days and 1 year from DES placement might be relatively safe but by no means risk free.

A practical approach to minimizing CV risk can be summarized as follows:

- Cessation of all antiplatelet therapies after PCI, at any time, for any stent, is associated with an increased risk of thrombotic events, including late stent thrombosis. These events are likely to occur within 7 to 30 days of drug discontinuation.
- Cessation of clopidogrel (alone) during the early period after PCI (within 30 days of either DES or BMS placement) is associated with an increased risk of thrombotic events.
- Cessation of clopidogrel (alone) beyond 30 days from the time of BMS placement is common in clinical practice and does not confer increased risk of thrombosis over a brief period of time. There is likely benefit from more prolonged dual platelet antagonists among patients with ACS undergoing PCI.
- Cessation of clopidogrel (alone) upon completion of 6 months of treatment after DES placement is controversial (in terms of long-term risk) but does not seem to confer a significant short-term risk (within the subsequent 30 days) in a majority of patients if aspirin is continued.

The potential importance of continued aspirin therapy is supported by a recent structured overview of all reported cases of late stent thrombosis: the median time to an event was 7 days if both platelet antagonists were discontinued and 122 days if only the thienopyridine was stopped (34).

INTERRUPTION OF PLATELET ANTAGONIST THERAPY: PHARMACODYNAMIC CONSIDERATIONS. For patients who are receiving aspirin, clinicians intending no antiplatelet effect at the time of a procedure should interrupt therapy for 7 to 10 days. Although aspirin has a plasma half-life of 15 to 20 min, it irreversibly and near-completely inhibits platelet cyclooxygenase-1 activity, and therefore, the pharmacodynamic effect persists for 7 to 9 days. Consequently, 4 to 5 days after cessation of aspirin, 50% of circulating platelets will have normal cyclooxygenase-1 activity, whereas after 7 to 10 days >90 of platelets exhibit normal thromboxane A_2 synthesis and aggregation response. Santilli et al. (46), in a study of 48 healthy volunteers randomized to receive aspirin 100 mg daily for 1 to 8 weeks, highlighted a nonlinear relationship between inhibition of thromboxane production and inhibition as gauged by platelet function assays. This observation offers clinical relevance to recovery kinetics after aspirin cessation, wherein platelet function measurements might return to normal in several days, whereas serum thromboxane B_2 levels do not recover until 7 days.

In patients who are receiving clopidogrel or ticlopidine, a thienopyridine derivative that causes noncompetitive platelet $P2Y_{12}$ receptor inhibition, similar pharmacodynamic principles to those of aspirin apply—with up to 10 days being required to replenish a normal platelet pool (47).

Unlike aspirin, clopidogrel and ticlopidine are pro-drugs that require a 2-step conversion to an active metabolite, which subsequently inhibits the $P2Y_{12}$ receptor. The relative plasma concentrations of the active metabolite are low, permitting some receptors to remain unoccupied. Considered collectively, 5 days might be a sufficient amount of time for the restoration of an adenosine diphosphate-mediated platelet response. In contrast, the plasma concentration of prasugrel's active metabolite is high, suggesting that a complete turnover of the circulating platelet pool, approximately 7 to 9 days, would be required to restore functionality (this distinction is the basis for differing recommendations for withholding treatment in proximity to coronary bypass grafting). An abbreviated course of drug interruption (3 days) might be sufficient with the reversible, non-

thienopyridine, platelet $P2Y_{12}$ receptor antagonist, ticagrelor (48). Cilostazol is a phosphodiesterase inhibitor with antiplatelet and vasodilatory properties that reversibly affects platelet function through cyclic adenosine monophosphate-mediated inhibition of platelet activation and aggregation. Cilostazol may be used in patients with CHD, particularly those with coronary arterial stents, or peripheral arterial disease. The pharmacokinetics of cilostazol are dose-dependent, with an elimination half-life of approximately 10 h. Consequently, this drug would need to be interrupted for approximately 3 days (corresponding to 5 elimination half-lives) before a procedure is performed that poses a risk for hemorrhage.

Additional investigations of the temporal sequence of platelet-mediated biological events—including onset, offset, duration of effects, and mechanism of action for all platelet antagonists, to include newly developed agents such as ticagrelor—will ultimately prove useful for clinicians worldwide.

Strategies for bridging and restarting platelet antagonist therapy. BRIDGING THERAPY. Although the interruption of platelet antagonists for elective GI procedures—particularly among individuals at risk for stent thrombosis—should not be a common occurrence, management options are important for practicing clinicians.

As summarized in prior sections, interruption of oral platelet antagonists for scheduled procedures has been associated with increased 30-day mortality (36). The potential risk, on the basis of observational studies and registries, has not been influenced favorably or lessened by heparin bridging (36,49).

The periprocedural administration of glycoprotein IIb/IIIa receptor antagonists, although representing a more biologically sound approach than anticoagulant therapy (50), lacks randomized effectiveness and safety data. Short-acting platelet $P2Y_{12}$ inhibition with reversible agents like cangrelor or ticagrelor (not available for clinical use at the present time) or an alternative compound with similar properties of target selectivity and a very short biological half-life represents the most attractive platform for bridging therapy. The BRIDGE (Maintenance of Platelet inihiBition With cangRelor After dIscontinuation of ThienopyriDines in Patients Undergoing surgery) trial (ClinicalTrials identifier: NCT00767507) will compare cangrelor and placebo among 200 patients in whom a thienopyridine drug is discontinued before coronary artery bypass grafting.

RESTARTING PLATELET ANTAGONISTS. In patients who have temporary interruption of platelet antagonists before elective endoscopic procedures, treatment should be resumed as soon as possible afterward. A common question is whether resumption of treatment should be with a maintenance dose, which achieves maximal effect in several days, or with a loading dose that more rapidly produces platelet inhibition. The choice of loading dose might not be a major determinant of major bleeding risk (51). The dose of clopidogrel (300 mg or 600 mg) should be gauged by individual patient risk, to include the presence of a coronary stent, the type of stent (BMS or DES), and how recently the stent was placed.

POTENTIAL ROLE FOR POINT-OF-CARE PLATELET FUNCTION TESTING. In addition to traditional laboratory-based platelet aggregation tests, several point-of-care (whole-blood) platelet-monitoring devices are available for clinical use (52). An ongoing clinical trial, the GRAVITAS (Gauging Responsiveness with A VerifyNow Assay-Impact on Thrombosis and Safety) trial (53) is testing whether platelet-function guided clopidogrel therapy can reduce major adverse cardiac events after DES placement. In contrast, the use of either laboratory-based or point-of-care platelet aggregation measurement platforms to gauge bleeding risk associated with surgical (or endoscopic) procedures remains poorly defined. Accordingly, neither is recommended as a routine "screening test" before elective endoscopy.

GI Risks

Cardiopulmonary complications of elective GI endoscopy. The potential for cardiopulmonary complications inherent to endoscopy must be considered when assessing the relative risk of discontinuing platelet antagonists in preparation for the procedure. These risks, although generally low, might be related to anxiety/stress generated by the procedure itself, the effects of medications used to achieve sedation, or the preparation (in particular for colonic purgatives). The importance of individual patient risk assessment must be emphasized, as illustrated by reports of renal dysfunction with phosphate containing cathartics, leading to their recent removal from the U.S. market (Table 2).

There is significant variation in the reported rates of cardiopulmonary complications associated with endoscopy. Most of the reports have focused on the consequences of sedation and analgesia. In a retrospective review of 21,011 procedures, the complication rate was reported as 5.4 of 1,000 procedures, with a death rate of 3 of 10,000 (54). In a prospective survey of 14,149 gastroscopies, the calculated rate of complications including the 30-day post-procedure period was 2 of 1,000. There were 11 patients (8 deaths) with pneumonia (presumed to be related to aspiration), 3 patients (3 deaths) with pulmonary emboli, and 19 patients (14 deaths) with acute MI. The overall death rate was 1 of 2,000 (55).

In a survey of 25,298 colonoscopies, MI was reported in 0.012% of patients (56). In studies specifically involving colonoscopy, ECG changes have been reported in 41% to 65% of patients (57). A study of ECG changes during assessment of 100 patients undergoing rigid sigmoidoscopy reported premature ventricular complexes in 40% of patients with cardiac disease and in 17% of patients without a cardiac history (58).

Table 2

Gastrointestinal Procedures Considered High and Low Risk for Bleeding

High Risk	Low Risk
Polypectomy	Diagnostic esophagogastroduodenoscopy with or without biopsy
Biliary sphincterotomy	Flexible sphincterotomy with or without biopsy
Pneumatic or bougie dilation	Colonoscopy with or without biopsy
PEG placement	ERCP without endoscopic sphincterotomy
Endoscopic ultrasound-guided fine needle aspiration	Biliary/pancreatic stent without sphincterotomy
Laser ablation and coagulation	Endoscopic ultrasound without fine needle aspiration
Treatment of varices	Enteroscopy

Adapted from Zuckerman MJ, et al. (84).
ERCP = endoscopic retrograde cholangiopancreatography; PEG = percutaneous endoscopic gastrostomy.

Cardiopulmonary complications associated with GI endoscopy, as mentioned previously, have several possible contributing factors. Sedative medications, in particular the narcotics, exert dose-related and inhibitory effects on respirations and blood pressure. Air insufflation can cause bradycardia and hypotension from vagally mediated effects. In patients with coronary artery disease, hypoperfusion might occur due to endoscopy or medication-related changes in blood pressure, heart rate, and oxygenation saturation. Oxygen desaturation is a well-recognized risk factor for cardiac arrhythmias (59,60). In addition, catecholamine release secondary to dehydration, anxiety, and pain are possible mechanisms. Vagal stimulation, generated through a stretching of the hollow viscus (through air insufflation or mechanical distention related to the endoscope) might also be a plausible explanation in some patients.

Oral colonic purgative lavage solutions are widely used to prepare patients for colonoscopy. Cardiac arrhythmias have been reported in patients undergoing continuous ECG monitoring during both the preparation and procedure phases of colonoscopy. In 1 small study, 12 of 24 patients who were hospitalized for other reasons, demonstrated an increase in ventricular premature contractions during the preparation phase compared with the control period ($p = 0.01$). Two patients demonstrated ventricular tachycardia, 4 patients manifested complex ventricular ectopy without ventricular tachycardia, and 6 patients demonstrated an increase in simple premature ventricular contractions. The authors concluded that peroral colonic lavage was associated with increased ventricular ectopy (61). Administration of sodium phosphate products is an alternative for catharsis before colonoscopy. Changes in serum sodium, potassium, chloride, calcium, ionized calcium, and inorganic phosphorous levels have been noted in some patients after sodium phosphate preparation when compared with values before the preparation. Fatalities due to significant fluid shifts, severe electrolyte abnormalities, and cardiac arrhythmias have been rarely reported (62). To minimize risk, patients with underlying CV and renal disease are prescribed polyethylene glycol colonic lavage solution for preparation and instructed to avoid dehydration by ingestion of additional fluids to maintain appropriate volume status.

Endoscopy-related GI bleeding. In assessing the risks of temporary discontinuation of platelet antagonists for a patient with CV disease who is undergoing elective endoscopy, it is important to assess the inherent risk of bleeding associated with the procedure. Although generally considered overall low-risk, GI endoscopy does increase the risk of bleeding. The risk varies with procedure type and whether or not associated therapeutic interventions are performed. The published reports assessing this risk have significant methodological limitations, being composed almost entirely of surveys and small case series, as recently reviewed (63). It is generally accepted that all diagnostic procedures with or without mucosal biopsy as well as endoscopic retrograde cholangiopancreatography (ERCP) without sphincterotomy, diagnostic balloon-assisted enteroscopy, and endosonography without tissue sampling are low-risk. High-risk procedures with an increased risk of bleeding include endoscopic polypectomy or endoscopic mucosal resection, laser ablation, therapeutic balloon-assisted enteroscopy, and endoscopic sphincterotomy. Those therapeutic procedures with the potential to produce bleeding that is inaccessible or uncontrollable by endoscopic means, such as dilation of benign or malignant strictures, percutaneous endoscopic gastrostomy, endosonography-guided fine needle aspiration (FNA) or tru-cut biopsy are considered high-risk (64).

Colonoscopy is the most commonly performed diagnostic and therapeutic procedure in current clinical practice, and large cohort studies provide valuable information for determining procedure-related risks. A recent population-based study in Canada of 97,091 patients undergoing outpatient

colonoscopy reported the occurrence of bleeding in 1.64 of 1,000 procedures. Older age, male sex, performance of a polypectomy, and the procedure being performed by a low-volume endoscopist were factors associated with an increased risk of a complication (65).

Colonoscopic polypectomy carries a low bleeding risk, in the range of 0.4% to 3.4%, but the risk increases with polyp size >10 mm (adjusted OR: 4.5; 95% CI: 2.0 to 10.3) (66) and might be influenced by technique, polyp morphology, and location. Endoscopic biopsy or polypectomy can induce 2 types of bleeding: immediate, which can usually be controlled during the procedure; and delayed, occurring up to 30 days later (67). Considered collectively, the rate for both types of bleeding associated with colonoscopic polypectomy has been reported to be <1% (68).

Some patients are at higher risk of bleeding; these include elderly persons and patients with chronic comorbid conditions such as hypertension, diabetes, coronary artery disease, and chronic obstructive pulmonary disease. Advancing age increases the likelihood of a requirement for blood-transfusion after post-polypectomy bleed (69), and patients with systemic hypertension experience a 5-fold increased risk of delayed post-polypectomy bleed (66). In a recent post hoc analysis of a case-control study, diabetes (OR: 2.5; 95% CI: 1.2 to 5.1), coronary artery disease (OR: 3.0; 95% CI: 1.5 to 6.2), and chronic obstructive pulmonary disease (OR: 2.2; 95% CI: 1.1 to 4.8) were associated with delayed post-polypectomy bleeding, but the risk was attenuated after adjusting for anticoagulant use (70).

Immediate post-polypectomy bleeding is more common with cutting or blended current, and delayed bleeding is more common with coagulation current, which might create a deeper ulcer at the polypectomy site and is particularly relevant to the risk associated with the use of a hot biopsy forceps. Immediate hemorrhage may be treated with injection of epinephrine followed by multipolar cautery or clipping, and the endoscopist can almost invariably achieve hemostasis. Delayed bleeding classically presents as passage of large-volume bloody bowel movements and can occur up to 21 days after polypectomy. Risk factors for hemorrhage include large polyp size and location in the proximal colon (70). Immediate bleeding after cold forceps or cold snare removal of small polyps is nearly always capillary in nature and clinically insignificant. Because this approach successfully achieves polyp removal and is associated with a lower risk of bleeding than hot biopsy forceps, it is the recommended strategy to minimize complications (71).

Bleeding from diagnostic esophagogastroduodenoscopy is uncommon and estimated to occur in 1 of 1,000 procedures or less according to publications from the 1970s and 1980s. Diagnostic endoscopy occasionally causes bleeding from iatrogenic Mallory-Weiss tears or endoscopic biopsies. Therapeutic procedures, such as sclerotherapy or gastroduodenal polypectomy, are associated with much higher bleeding complication rates. For example, bleeding complications from gastroduodenal polypectomies have been reported in 0.2% to 8% of procedures—a rate that is similar to colonoscopic polypectomy (63).

Esophageal dilation can be performed in the upper GI tract with tapered "over the wire" dilators or through the endoscope balloon dilation, which can also be employed at any site within reach of an endoscope. The risk of bleeding after dilation is <1%—typically at the site of mucosal tears or abrasions at site of dilation. The risk of bleeding is increased when dilations are performed for malignant stenoses. Overall, the bleeding is typically self-limited, and the type of dilator used is probably less important than the experience of the primary endoscopist in using a given device (71).

Treatment of esophageal varices with banding and/or sclerotherapy can initiate bleeding, but this is usually managed at the time of the therapeutic procedure. The placement of a percutaneous gastrostomy has been associated with rates of bleeding in the range of 0.2% to 2.5% and is generally related to the initial skin puncture for tube passage or as a result of delayed ulceration at the stoma site (72).

Endoscopic sphincterotomy at ERCP can cause bleeding. The overall risk has been estimated at <5% and can be delayed as well as life-threatening (73). Endoscopic ultrasound without FNA has a risk of bleeding similar to esophagogastroduodenoscopy, whereas FNA has a risk of bleeding estimated in the range of 2% (74). Endoscopic mucosal resection, where large areas of tissue are removed with a variety of techniques, is increasingly used in the U.S. for removal of Barrett's esophagus with high-grade dysplasia or early cancer. It can be used in other parts of the GI tract as well. Bleeding is the most common complication of this procedure, generally in the range of 10% in large series (74).

Characterization of bleeding risk associated with platelet antagonists. The attributable risk of post-endoscopic bleeding among patients taking platelet antagonists remains poorly characterized. Although it is assumed that these agents increase the risk of post-procedure bleeding, few confirmatory studies have been undertaken.

Bleeding risk associated with a single platelet antagonist.

ASPIRIN. Several studies have assessed the risk of post-procedure bleeding attributable to aspirin. In the absence of a pre-existing bleeding disorder, it is reasonable to perform elective endoscopic procedures in patients taking aspirin or other NSAIDs. Two studies have demonstrated that aspirin is not associated with an increased risk of post-procedure bleeding (75,76). Furthermore, the current published data support the safety of continued aspirin administration in the periendoscopic period, even after high-risk endoscopic procedures such as polypectomy (70,75,77) or sphincterotomy (78,79). That said, the available data are limited to retrospective observational

studies demonstrating trends toward increased post-polypectomy bleeding that fails to reach statistical significance (75). Yousfi et al. (77) observed higher rates of post-polypectomy bleeding among patients who ingested aspirin within 3 days of colonoscopic polypectomy when compared with control subjects (40% vs. 33%); however, they failed to demonstrate a statistically significant association between aspirin and post-endoscopic bleeding complications (OR: 1.4; 95% CI: 0.6 to 3.0). In a large retrospective study of 4,592 patients who underwent colonoscopic polypectomy, aspirin use (defined as at least 1 dose within 1 week before and 1 week after polypectomy) was not found to be a clinically significant predictor of post-polypectomy bleeding (OR: 1.1; 95% CI: 0.5 to 2.2, $p = 0.8$) (70).

Two small-scale, retrospective studies assessed the risk of bleeding after endoscopic sphincterotomy in patients receiving platelet antagonists, with mixed results. Among 40 patients exposed to a platelet antagonist, including aspirin, clopidogrel, or ticlopidine, 16% had been exposed before the endoscopic sphincterotomy (13% taking aspirin, and 3% taking clopidogrel). After adjusting for possible confounders (i.e., presence of coagulopathy and cholangitis), exposure to a platelet antagonist did not significantly increase the risk of clinically important procedure-related bleeding after endoscopic sphincterotomy (OR: 0.41; 95% CI: 0.13 to 1.31) (78). In contrast, a second retrospective study reported an increased risk of bleeding after endoscopic sphincterotomy in patients taking aspirin up to the day of the procedure versus those who did not take aspirin (9.7% vs. 3.9%, OR: 2.1; 95% CI: 1.1 to 4.0; $p = 0.01$) (73). However, in addition to the case-control design, limitations of these studies include an unclear definition of bleeding, a statistical analysis that did not adequately adjust for possible cofounders, and lack of statistical power (79).

CLOPIDOGREL. Clopidogrel causes irreversible platelet inhibition, and upon drug cessation, a return of platelet aggregation to at least 50% of normal requires a minimum of 5 days (80,81). Although it is uncertain whether clopidogrel causes direct mucosal injury (82), it is associated with an increased risk of GI bleeding.

The published data do not provide an accurate gauge for determining the risk of bleeding associated with clopidogrel (or ticlopidine) after an endoscopic procedure. Although 1 retrospective study attempted to discern the effects of clopidogrel, only 3% of patients received the agent (vs. 13% receiving aspirin), limiting conclusions for its safe use before endoscopic sphincterotomy (79). Clopidogrel has been associated with an increased risk of bleeding in non-GI invasive procedures. For example, moderate or severe bleeding after trans-bronchial lung biopsy occurred in 61% of clopidogrel-treated patients compared with 1.8% among control subjects (83). Current guidelines recommend withholding clopidogrel for at least 7 days for patients with a planned high-risk endoscopic procedure (64,84).

Patients in whom the risk of a CV event, particularly stent thrombosis, is high should have elective endoscopic procedures deferred until clopidogrel can be safely discontinued. Emergent procedures should be undertaken as the clinical circumstances dictate. Strategies to reduce the risk while receiving antiplatelet therapy are discussed in the following text.

There is currently no experience with prasugrel or ticagrelor.

Bleeding risk associated with dual platelet antagonists. Although the risk of bleeding after an endoscopic procedure in patients prescribed dual platelet antagonists with aspirin and clopidogrel is unknown, their effects on the GI tract have been studied. Dual platelet antagonists significantly increase the risk of GI bleeding when compared with monotherapy (10,21,85) and also impair the healing of ulcers (23). The addition of clopidogrel to aspirin increases the relative risk of GI bleeding by up to 70% (86). Therefore, in patients prescribed clopidogrel plus aspirin, stopping clopidogrel (and continuing aspirin) before performing a high-risk elective endoscopy likely reduces bleeding risk (discussed in the next section).

Strategies to reduce the risk of endoscopic procedures for patients receiving platelet antagonists. Although current American Society for Gastrointestinal Endoscopy guidelines recommend withholding non-aspirin platelet antagonists and anticoagulants for 7 to 10 days before elective high-risk endoscopic procedures (84), the potential impact of this strategy on reducing the risk of bleeding is uncertain. In a case series of 408 patients who underwent endoscopic submucosal dissection (ESD) for early gastric cancer, postoperative bleeding that required endoscopic treatment occurred in 10.7% of patients in whom platelet antagonists or anticoagulant therapy had been withheld for 1 week before and 1 week after tumor removal. In contrast, only 5.2% of patients without prior exposure to platelet antagonists or anticoagulant therapy had postoperative bleeding (although the difference did not reach statistical significance) (87).

Limited data have suggested that prophylactic PPI therapy reduces the risk of delayed hemorrhage after endoscopic removal of large gastric mucosal lesions. A randomized trial of ESD of early gastric cancer reported that oral PPI given 1 day before and for 8 weeks after ESD significantly reduced the risk of bleeding complications (88).

Although data are lacking, patients receiving dual platelet antagonists are probably at higher risk of bleeding after an endoscopic procedure. If long-term dual platelet antagonist therapy is anticipated (e.g., placement of a DES), physicians should advise these patients to consider elective endoscopic procedures before the cardiac intervention—provided that they are clinically stable.

The bleeding risk after polypectomy of small polyps (<1 cm) in anticoagulated patients might potentially be reduced by the application of prophylactic clips (89–91). However, no

randomized controlled trials have been performed in patients being actively treated with antithrombotic agents (platelet antagonists or anticoagulants). One randomized, controlled study of 413 average risk patients did not show a decrease in delayed bleeding, although the mean polyp size in this study was 7.8 mm (89). Similar studies evaluating the efficacy of detachable snare devices (e.g., Endoloop, Olympus, Tokyo, Japan) as well as clips for the prevention of post-polypectomy bleeding have been done in average-risk patients but not in patients using antithrombotics (89,90–94). Because of the absence of strong clinical data, routine application of prophylactic mechanical clips or detachable snares in anticoagulated patients or those receiving antiplatelet agents cannot be recommended at this time. The studies reported to date have been underpowered to assess the risk–benefit relationship of these interventions and their overall cost-effectiveness, but they should be considered on a case-by-case basis for high-risk patients. The use of "state-of-the-art" techniques for management of large polyps, including injection with saline with or without dilute epinephrine—particularly for large polyps or piecemeal removal of polyps (and endoscopic mucosal resection as well)—seems to enhance the safety of these advanced techniques for neoplasm resection.

Currently, there are limited data for the management of bleeding complications after elective endoscopic procedures in patients receiving platelet antagonists. The choice of endoscopic hemostatic therapy for bleeding complications and the nature of the post-endoscopy care provided can only be inferred from indirect evidence. A single study reported an increase in serum epinephrine concentration 4- to 5-fold, with normalization in 20 min after endoscopic injection of epinephrine for bleeding peptic ulcers (95). Although CV complications were not reported, the study design did not permit a comprehensive safety evaluation of epinephrine injections in patients at high CV risk. Continuous ECG monitoring is advisable if a large volume of epinephrine injection is deemed necessary in patients with known CHD. Alternatively, use of a more diluted epinephrine solution or substitution of epinephrine by other endoscopic hemostatic methods (e.g., clips) should be considered. After achieving endoscopic hemostasis, a decision that considers the continuation or reintroduction of platelet-directed pharmacotherapy must be made. In a double-blind, randomized, placebo-controlled trial of aspirin therapy in patients with CHD complicated by bleeding peptic ulcers, all patients underwent endoscopic therapy followed by high-dose proton-pump inhibitor infusion. The group receiving continuous low-dose aspirin had a 2-fold increase in 30-day risk of rebleeding compared with the group without aspirin therapy for the entire study period (96). In this study, however, aspirin cessation was associated with a significant increase in all-cause mortality and a trend toward a greater occurrence of adverse CV outcomes. Thus, prolonged cessation of platelet antagonists in patients with known CHD and bleeding complications after an elective endoscopic procedure is not recommended. Although it remains to be proven, withholding aspirin for 3 to 5 days might reduce the likelihood of early rebleeding after initial hemostasis (e.g., post-polypectomy bleeding), whereas the residual antiplatelet effects might continue to provide CV protection.

Management of bleeding complications after endoscopic procedures in patients receiving dual platelet antagonists is a major challenge, because it requires careful assessment of both bleeding and thrombotic risks. The decision often needs to be individualized. If there is a major bleeding complication (i.e., hypotension or requirement for transfusion) and endoscopic hemostasis is difficult to achieve, all platelet antagonists should be withheld for 3 to 5 days to reduce the likelihood of early rebleeding. If complete cessation is not advisable, temporary transition to a single agent might attenuate the risk of rebleeding. Although some cardiologists prefer clopidogrel over aspirin as a temporary monotherapy, the only available head-to-head comparison of aspirin versus clopidogrel monotherapy revealed only a modest benefit for the latter (97).

Endoscopist experience has been shown to lessen bleeding complications associated with colonoscopy, and this is likely true for other procedures as well. There are few strategies, from the technical standpoint, that reduce bleeding risk, other than avoiding excessive tissue injury during the diagnostic or therapeutic intervention. Nevertheless, experience and skill across a wide range of endoscopic therapies likely offers real benefit that is difficult to quantify by outcome studies. Thus, the sickest patients will benefit most from the wisdom and skill of an experienced endoscopist who balances successfully both the GI and CV risks.

Summary. Platelet-directed pharmacotherapy with aspirin and, among patients experiencing ACS and/or those undergoing PCI and stent placement, a thienopyridine represents the current standard of care. Existing guidelines provided by the American College of Cardiology/American Heart Association, European Society of Cardiology, and American College of Chest Physicians underscore the benefit of dual platelet antagonists in patients at high risk for thrombotic events and the potential detrimental effects of sudden drug cessation—particularly within the first 6 months after PCI with DES insertion. Accordingly, elective endoscopic procedures should be deferred during this time period and possibly up to 12 months, if clinically acceptable. Procedures scheduled beyond 6 months, particularly those associated with heightened bleeding risk, could be undertaken 5 to 7 days after thienopyridine drug cessation. If possible, aspirin should be continued.

Whether a modified approach will be needed for patients receiving prasugrel, a thienopyridine platelet antagonist

Table 3

A Practical Approach to Managing Cardiovascular Risk and Bleeding Complications

Avoid cessation of all antiplatelet therapies after PCI with stent placement when possible.
Avoid cessation of clopidogrel (even when aspirin is continued) within the first 30 days after PCI and either DES or BMS placement when possible.
Defer elective endoscopic procedures, possibly up to 12 months, if clinically acceptable from the time of PCI and DES placement.
Perform endoscopic procedures, particularly those associated with bleeding risk, 5–7 days after thienopyridine drug cessation. Aspirin should be continued when possible.
Resume thienopyridine and aspirin drug therapy after the procedure once hemostasis is achieved. A loading dose of the former should be considered among patients at risk for thrombosis.
Continue platelet-directed therapy in patients undergoing elective endoscopy procedures associated with a low risk for bleeding.

BMS = bare-metal stent(s); DES = drug-eluting stent(s); PCI = percutaneous coronary intervention.

capable of achieving a greater degree of platelet inhibition than clopidogrel and ticlopidine, is currently unknown.

After the procedure, and once hemostasis has been achieved, a thienopyridine can be resumed either with or without an initial oral loading dose, depending on the anticipated risk for thrombosis and delayed bleeding. Platelet-directed pharmacotherapy should be continued for patients undergoing elective endoscopic procedures known to pose a low risk for bleeding (Table 3).

There are few strong indications for platelet bridging therapy among patients undergoing elective endoscopic procedures. Bridging with anticoagulants (as a substitute for platelet antagonists), given the absence of supportive data, does not have a place in periprocedural patient management. The only currently available platelet antagonist that could be used for this specific purpose is eptifibatide, an intravenously administered glycoprotein IIb/IIIa receptor inhibitor. Evidence-based recommendations are not available.

Endoscopist experience is known to lessen bleeding complications related to colonoscopy and potentially for other elective GI procedures as well. The potential for complications associated with high-risk endoscopic procedures can be reduced by avoiding excessive tissue injury during the procedure, sound technical skills, and good clinical judgment.

Author Disclosures

Dr. Scheiman is a consultant for AstraZeneca, Novartis, Pfizer, Bayer, Takeda, Pozen, and NiCox, and has received speaker's honoraria from Takeda and AstraZeneca. Dr. Dauerman has received research grants and/or consulting fees from Abbott Vascular, Boston Scientific, Medtronic, The Medicines Company, and Bristol-Myers Squibb. Dr. Spencer is on the advisory board of GRACE (Global Registry of Acute Coronary Events), which is funded by Sanofi-Aventis; is on the Drug Safety Monitoring Board for Apixiban CAD studies, which is funded by Sanofi-Aventis; and is on the Drug Safety Monitoring Board for E5555 201 and 202 CAD studies, which is funded by EISAI. Dr. Rao is a consultant for and/or received honoraria from Sanofi-Aventis, Bristol-Myers Squibb, The Medicines Company, AstraZeneca, and received research funding from Momenta, Portola, and Cardis. Dr. Sabatine received research grant support and served on the advisory board for AstraZeneca; has received honoraria for education presentations and served on the Speaker's Bureau for Bristol-Myers Squibb; has received honoraria for educational presentations from Eli Lilly; has received research grant support, served on the scientific advisory boards, and received honoraria for education presentations from Sanofi-Aventis; and received research grant support from Schering-Plough. Dr. Johnson has received consulting fees/honoraria and research grant support from AstraZeneca, Novartis Pharmaceuticals Corp., and TAP Pharmaceuticals, and is on the Speakers' Bureau of AstraZeneca. Dr. Chan is the Chairman of the Steering Committee of the CONDOR study, which is a Pfizer-sponsored multicenter trial; receives consulting fees from Pfizer, Otsuka, and Takeda; received speaker's honoraria from Pfizer, AstraZeneca, and Takeda; and has received an investigator-initiated independent research grant from Pfizer.

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Key Words: coronary heart disease ■ periprocedural risk assessment ■ platelet antagonists.