VIEWPOINT

Antiplatelet Therapy in Patients With Coronary Stents Undergoing Elective Noncardiac Surgery

Continue, Stop, or Something in Between?

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Surgeons, cardiologists, primary care physicians, and anesthesiologists frequently make decisions regarding antiplatelet management for patients undergoing elective surgery. Patients with recent coronary stent implantation can be particularly challenging as clinicians balance the cardiac risks of discontinuing therapy with the bleeding risks of continuing antiplatelet agents. More than 600 000 patients receive coronary stents annually in the United States, with up to 23% of these individuals requiring noncardiac surgery within 2 years.[1] Observational evidence suggests that patients who have undergone percutaneous coronary intervention with stent implantation are at increased risk of perioperative major adverse cardiac events (MACE) and that this risk is moderated by stent type (bare metal stent [BMS] vs drug-eluting stent [DES]), operative urgency, early discontinuation of antiplatelet therapy, and time from coronary intervention.[2-4]

Early studies in the pre-DES era showed the potential for major perioperative adverse outcomes in patients undergoing noncardiac surgery shortly after stent placement. In one retrospective study, 8 of 40 patients (20%) undergoing surgery within 6 weeks of stent placement died of either myocardial infarction or procedural hemorrhage.[2] After the advent of DES, subsequent cohort studies suggested that elevated thrombosis risk persisted for 6 weeks after BMS placement and up to 1 year following DES placement.[4] Second- and third-generation DES have lower thrombogenic risk,[5] and current American College of Cardiology (ACC) and American Heart Association (AHA) guidelines[6] recommend delaying noncardiac surgery until 30 days after BMS placement and ideally 6 months after DES placement unless clinical judgment indicates that the benefits exceed the risks for earlier (3-6 months after DES placement) surgery.

While the evidence surrounding timing of surgery appears robust, the role of antiplatelet agents in mitigating this risk is unclear. Continuing antiplatelet agents through the perioperative period may increase procedural bleeding, especially among patients receiving dual antiplatelet therapy (DAPT), whereas discontinuing antiplatelet agents may increase the risk of perioperative MACE, including acute stent thrombosis. The ACC/AHA guidelines[6] recommend that patients receiving DAPT undergoing elective surgery should continue aspirin through the perioperative period and restart the $P2Y_{12}$ inhibitor as soon as possible. The level of evidence is cited as expert opinion. A recent systematic review assessed the evidence regarding perioperative antiplatelet management to help guide clinicians with this common clinical conundrum.[7]

This review included a search of PubMed, Web of Science, and Scopus (through December 17, 2015) and identified 4608 possible citations. Of these, 13 studies addressed patients after percutaneous coronary intervention with stent placement who were undergoing elective noncardiac surgery, with MACE, bleeding outcomes, or both associated with perioperative antiplatelet management strategies (**Table**). None of the included studies were randomized clinical trials. Of the 13 observational studies, 2 were prospective, 10 were retrospective, and 1 had a case-control design. Most studies were small, with 9 of 13 studies including fewer than 150 patients, limiting power to detect differences in rare events. All studies included DES and 7 of 13 studies also included BMS. Multiple antiplatelet strategies were used both across and within a given study, including numerous permutations of preoperative (single antiplatelet therapy or DAPT) and perioperative (stop all, stop one, continue both, etc) options. Bridging—the temporary administration of an antithrombotic agent (eg, intravenous heparin) to avoid prolonged cessation of antiplatelet agents—was an additional layer of complexity in some studies; however, each study used a different antithrombotic agent and algorithm.

While these studies were too heterogeneous to statistically pool, qualitatively there was no signal of an association between antiplatelet strategy and MACE or bleeding rates. For example, 4 studies reported 0% MACE rates despite 3 different antiplatelet strategies including both continuing and discontinuing DAPT. Furthermore, among the studies that used DAPT preoperatively, the study with the highest MACE event rate (21.4%) continued aspirin, whereas the studies that discontinued both agents had lower MACE event rates (11.1% and 2.3%). Three studies reported 0% bleeding rates despite 3 different antiplatelet therapy strategies including continuing DAPT, continuing single antiplatelet therapy, and discontinuing all therapy, whereas the highest bleeding rate (14.8%) was reported in a study in which both agents were discontinued. In further assessment of these 13 studies by bridging strategy, timing of discontinuation of the antiplatelet agent, and type of surgery (eg, major vs minor, neurosurgery vs orthopedics), there was no evidence of a consistent pattern. Additional factors relevant to the cardiologist (eg, location of the stent, complexity of the percutaneous coronary intervention, acuity of presentation) and the surgeon (eg, reoperative site, intricacy of the operation) were not reported.

The one case-control study[1] included in the analysis reviewed 42 000 noncardiac operations within 2 years of coronary stent placement. It demonstrated an

Table. Summary of the Studies Included in the Systematic Review Including Preoperative and Perioperative Antiplatelet Strategies, Sample Size, and Event Rates

Preoperative Antiplatelet Strategy	Perioperative Antiplatelet Strategy	MACE			Bleeding		
		Studies, No.[a]	Patients, No.	Event Rate for Each Study, %	Studies, No.[a]	Patients, No.	Event Rate for Each Study, %
DAPT	Continue both	2	87	0, 0	3	108	0, 4.8, 9.5
	Continue one	1	14	21.4	1	14	0
	Stop both	2	115	2.3, 11.1	2	115	1.1, 14.8
DAPT or SAPT[b]	Continue	2	200	0.6, 4.8	2	200	9.5, 13.4
	Stop all	2	133	0, 2.7	1	22	0
Bridging[c]		5	271	Range, 0-7.8	5	271	Range, 0-22.3

Abbreviations: DAPT, dual antiplatelet therapy; MACE, major adverse cardiac events; SAPT, single antiplatelet therapy.

[a] Studies were included more than once if they calculated outcome rates for more than 1 antiplatelet strategy.

[b] Studies did not differentiate outcome rates for patients receiving DAPT vs SAPT preoperatively.

[c] Bridging studies used 1 or more of the preoperative and perioperative antiplatelet strategies listed above.

inverse relationship between time since stent implantation and risk of MACE and found that this risk returned to baseline at approximately 6 months, regardless of stent type. In a subanalysis of 284 patients with confirmed MACE matched 1:1 on multiple covariates including time from stent implantation and stent type, there was no difference in odds of MACE across 8 different preoperative and perioperative antiplatelet strategies.

Based on this available evidence, there is no clear association between antiplatelet strategy and rates of perioperative MACE and bleeding, even though physiological reasons would suggest that antiplatelet agents should be a factor in the risk of both. Any effect that does exist is likely small relative to other factors associated with MACE and bleeding, such as indication and urgency of operation, time since stent placement, invasiveness of the procedure, preoperative cardiac optimization, and underlying functional status. It is unlikely that observational studies will be able to control for these variables sufficiently to allow small effects to be detected or excluded.

Rather than continue to invest resources in observational studies, 1 or more adequately powered randomized clinical trials are needed. For example, to identify a reduction in MACE from 5% to 3%, a magnitude of difference frequently sought in cardiovascular research, approximately 1500 patients per treatment strategy would need to be studied—a sample much larger than any of the studies in the review. Conducting a study of such size would require substantial effort and administrative skill but should be within the capability of the cardiovascular community, which frequently publishes large randomized trials. Such trials would also provide the opportunity to collect data on the large number of factors—other than antiplatelet management—that potentially influence MACE and bleeding risk, such as location of the stent and details about the surgical procedure. In the meantime, the decision about perioperative antiplatelet management should remain individualized, made by an informed decision-making process involving the surgeon, anesthesiologist, cardiologist, and patient.

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REVIEW TOPIC OF THE WEEK

Use of Antiplatelet Therapy/DAPT for Post-PCI Patients Undergoing Noncardiac Surgery

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ABSTRACT

Dual antiplatelet therapy (DAPT) is prescribed to millions of patients worldwide following coronary stenting. DAPT is indicated to lower the risk of ischemic events, such as myocardial infarction, including stent thrombosis, ischemic stroke, or death from cardiovascular causes. A significant number of these patients undergo noncardiac surgery and may require DAPT interruption. This poses a significant clinical dilemma because DAPT interruption exposes patients to the potential risk of stent thrombosis, perioperative myocardial infarction, or both. Conversely, continuing DAPT may be associated with excess bleeding complications. Observational data in this area are conflicting, and there are no randomized clinical trials to guide practitioner decision making. On the basis of predominantly consensus recommendations, various strategies for managing DAPT during the perioperative period have been proposed. This review presents 3 commonly encountered clinical scenarios that lead into an evidence-based discussion of practical strategies for managing perioperative antiplatelet therapy in patients following percutaneous coronary intervention. (J Am Coll Cardiol 2017;69:1861–70) Published by Elsevier on behalf of the American College of Cardiology Foundation.

One of the most common questions that prompts cardiology consultation is management of antiplatelet therapies in patients undergoing noncardiac surgery and procedures (NCS) following percutaneous coronary intervention (PCI) (1). For cardiologists, this is an opportunity to combine interpretation of relevant clinical data with an exercise of sound clinical judgment. Decisions made under these circumstances require careful consideration of a myriad of contributing factors that often cannot be summarized into a prescriptive risk calculator. However, the expectation that we must conform diverse clinical variables and risk factors into a cohesive decision-making algorithm may often be challenging to the practicing physician. Potential limitations of guideline recommendations in this area primarily include articulation of a more generalized strategy that may not speak to the assessment of risks and benefits relevant to an individual patient.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

APT = antiplatelet therapy

BMS = bare-metal stent(s)

CABG = coronary artery bypass graft

CI = confidence interval

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

HR = hazard ratio

IV = intravenous

LAD = left anterior descending coronary artery

MACE = major adverse cardiac events

MI = myocardial infarction

NCS = noncardiac surgery and procedure

NSTE-ACS = non-ST-segment elevation-acute coronary syndrome

PCI = percutaneous coronary intervention

ST = stent thrombosis

TIMI = Thrombolysis In Myocardial Infarction

PCI with stent implants, especially drug-eluting stents (DES), is the most frequent form of coronary revascularization procedure performed in patients with both stable ischemic heart disease and an acute coronary syndrome (ACS) (2,3). Of the ~3 million individuals worldwide who undergo PCI each year, approximately 7% to 17% require a NCS within a year of stent implantation (4,5) Antiplatelet agents are prescribed following PCI to lower the risk of future ischemic and atherothrombotic events; their use over the period around NCS raises several important clinical concerns. Although antiplatelet therapy (APT) interruption may expose patients to the potential risk of stent thrombosis (ST), perioperative myocardial infarction (MI), or cardiovascular death, continuing these agents is often associated with increased bleeding. Herein, we present a case-based review of the various aspects of this clinical problem faced by a diverse group of providers on a daily basis, and also provide rational management strategies to address these therapeutic dilemmas in the absence of definitive, high-quality, trial-based evidence.

CASE PRESENTATIONS AND DISCUSSION

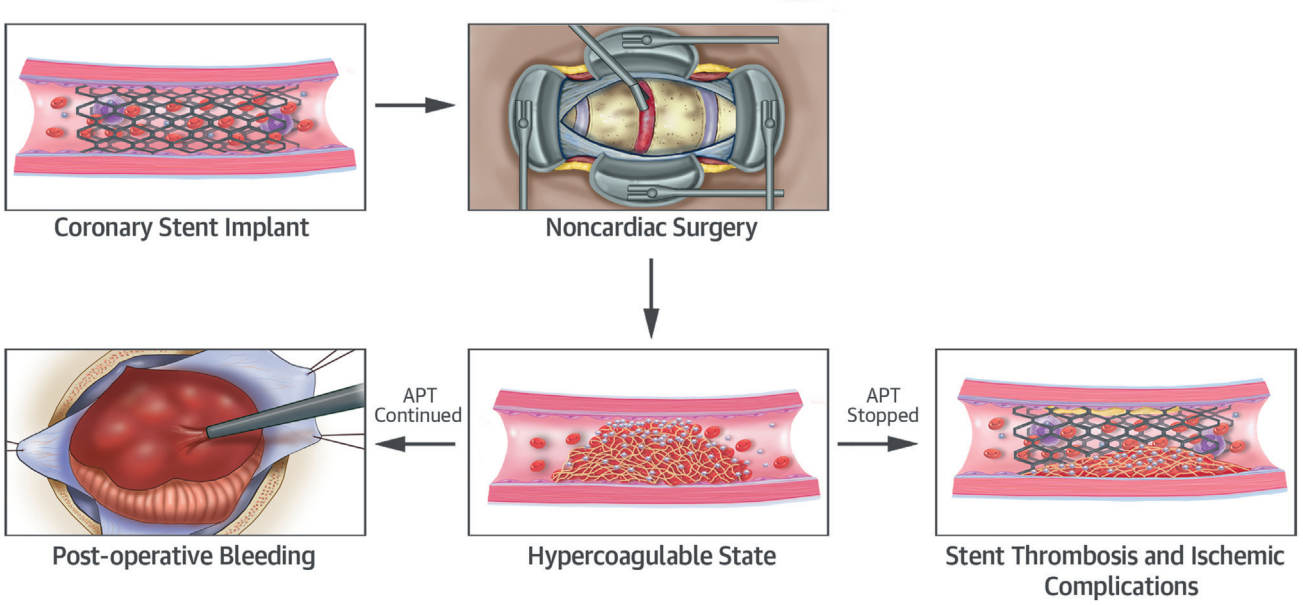
CASE 1. A 52-year-old man with no significant past medical history is admitted for evaluation of painless rectal bleeding. Colonoscopy shows stage I transverse colon carcinoma with near lumen obstruction. The patient experiences retrosternal chest discomfort while in recovery, relieved partially with sublingual nitroglycerin, accompanied by 2 mm of ST-segment depression in leads V_{1-3}, an elevated troponin I level consistent with the diagnosis of non-ST-segment elevation acute coronary syndrome (NSTE-ACS), and a stable hemoglobin value. The cardiology consult team recommends coronary angiography, which is performed the following day. It reveals preserved left ventricular systolic function and a severe proximal left anterior descending coronary artery (LAD) stenosis. Your interventionalist reaches out to you for guidance on how to best address this "on-table" coronary revascularization dilemma and ensuing questions surrounding dual antiplatelet therapy (DAPT) recommendations preceding the patient's colon surgery, which, by all measures, cannot be postponed indefinitely.

You are asked to carefully consider and select 1 of the following treatment options: 1) medical management of NSTE-ACS with intravenous (IV) nitroglycerin, aspirin, and beta-blockers, as tolerated, and recommend urgent colectomy during this hospital admission; 2) perform LAD PCI with a bare-metal stent (BMS), followed by treatment with daily low-dose aspirin (81 mg) and clopidogrel (75 mg) after a loading dose, and a recommendation for colectomy in 6 weeks; 3) perform LAD PCI with DES, prescribe daily low-dose aspirin (81 mg) and clopidogrel (75 mg) after a loading dose, and recommend colectomy after 6 months; 4) perform balloon angioplasty of the proximal LAD lesion, followed by treatment with daily low-dose aspirin (81 mg) and clopidogrel (75 mg) after a loading dose, and defer colectomy for at least 2 weeks; or 5) consider off-pump coronary artery bypass graft (CABG) surgery with planned left internal mammary artery graft to the LAD, followed by colectomy in 6 weeks.

Discussion. The core question here is regarding the best revascularization strategy for a patient who needs an urgent NCS. An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) is not recommended in patients with extensive comorbidities (e.g., cancer, hepatic, renal, pulmonary failure), in whom the risks of revascularization and comorbid conditions are likely to outweigh the benefits of revascularization (6). The early-stage colon cancer in this patient is potentially curable with partial colectomy, and is not consistent with an extensive comorbidity that would preclude coronary revascularization. Early CABG is performed in a minority of patients hospitalized with NSTE-ACS, and may be associated with a relatively high in-hospital mortality of ~5% (7). Therefore, CABG may not be the preferred approach in this patient with colon cancer anticipating colectomy. An early invasive approach with intent to revascularize the severe proximal LAD stenosis in the setting of rest angina, new ST-segment depression, and elevated biomarker evidence of myonecrosis may be the most reasonable approach (6).

Discontinuation of DAPT after stent implantation is one of the strongest predictors of ST, and the magnitude of risk is inversely proportional to the timing of NCS after PCI (8). Data from more recent observational studies suggest that the time frame for stent-related thrombotic complications in the perioperative period is approximately 6 months, irrespective of stent type (BMS or DES) (9). However, a meta-analysis of 51 comparative trials has demonstrated that second-generation DES exhibit better safety and efficacy compared with either first-generation DES or BMS after a median follow-up of 3.8 years (10). A recent observational study from

CENTRAL ILLUSTRATION **Antiplatelet Therapy Considerations in Post-PCI Patients During Noncardiac Surgery**



Banerjee, S. et al. J Am Coll Cardiol. 2017;69(14):1861-70.

The figure provides an overview of clinical factors and events that need to be carefully assessed prior to making antiplatelet therapy recommendations for post-PCI patients scheduled to undergo noncardiac surgery or procedures. APT = antiplatelet therapy; PCI = percutaneous coronary intervention.

Denmark reported that only patients requiring NCS within 1 month after DES-PCI had an increased risk of MI and cardiac death compared with patients without ischemic heart disease, suggesting that NCS might be undertaken earlier than currently recommended (11).

PCI for an ACS indication is an independent predictor of perioperative ischemic complications (9). The requirement for ≥6 months of DAPT following a DES or BMS implant in the setting of an ACS, along with an elevated risk of bleeding and impending colectomy, makes stenting a less viable option in this setting. Moreover, even for elective surgery, the guidelines recommend that it should not be performed within 30 days after BMS implantation or within 3 months after DES in patients who will need DAPT discontinuation perioperatively (Online Figure 1) (12).

In this situation, the clinical care team elected to use balloon angioplasty as the favored initial PCI strategy, with the option for bailout stenting to mitigate any acute complications, such as a major coronary artery dissection or an abrupt vessel closure (Online Table 1) (13). Following successful angioplasty of the LAD (residual stenosis <50% with Thrombolysis In Myocardial Infarction [TIMI] flow grade 3, and no dissection or thrombus), the patient was placed on low-dose aspirin and clopidogrel for at least 2 weeks, and referred for NCS after withholding only the $P2Y_{12}$ blocker (clopidogrel) for at least 5 days before surgery (14). DAPT would need to be started as soon as feasible following NCS. Any perioperative ischemic complications should be managed first with guideline-directed medical therapy, and PCI reserved for ST-segment elevation myocardial infarction (STEMI) and other high-risk ACS indications (15).

Implied in the selection of the revascularization strategy described in the preceding text is an assessment of thrombotic risk following PCI and hemorrhagic risk associated with planned NCS (**Central Illustration**). The genesis of thrombotic and hemorrhagic risk algorithms can be ascribed to Rossini et al. (14) who proposed such an algorithm in a European consensus document on perioperative management of APT. The prospective SAS (Stenting and Surgery) registry later validated this approach (16). Thrombotic risk was defined on the basis of: 1) type of implanted stent (BMS vs. DES); 2) timing of NCS from PCI; 3) angiographic features of coronary lesions and complexity of PCI; and 4) clinical presentation and characteristics. Determination of hemorrhagic risk

TABLE 1 Determination of Thrombotic Risk

Low Risk (<1%)*	Intermediate Risk (1%–5%)*	High Risk (>5%)*
>4 weeks after PCI with POBA	>2 weeks and ≤4 weeks after PCI with POBA	≤2 weeks after PCI with POBA
>6 months after PCI with BMS	>1 month and ≤6 months after PCI with BMS	≤1 month after PCI with BMS
>12 months after PCI with DES	>6 months and ≤12 months after PCI with DES	≤6 months after PCI with DES
	>12 months after complex PCI with DES (long stents, multiple stents, overlapping, small vessels, bifurcations, left main, last remaining vessel)	≤12 months after complex PCI with DES
		≤6 months after PCI for MI Previous ST

*30-day ischemic event rates of cardiovascular death and MI (20).

BMS = bare-metal stent(s); DES = drug-eluting stent(s); MI = myocardial infarction; PCI = percutaneous coronary intervention; POBA = plain old balloon angioplasty; ST = stent thrombosis.

focused mainly on perioperative bleeding risk related to NCS, and not on an individual patient's hemorrhagic profile. Surgical interventions were classified as either high, medium, or low risk for bleeding complications. Assignment of NCS to each of these groups was largely on the basis of published studies and expert opinion. These concepts will be applied in the following clinical cases.

CASE 2. A 72-year-old obese woman, with a history of type 2 diabetes mellitus, prior MI, and 4-vessel CABG 5 years ago, presents for pre-operative evaluation before an elective right knee replacement surgery to treat her longstanding disabling osteoarthritis. Since CABG, she has undergone 3 PCI procedures and received 12 coronary DES implants, the latest approximately 14 months ago (3 DES to the right coronary artery). She is currently on low-dose aspirin and ticagrelor.

Which of the following options is the preferred perioperative antiplatelet management strategy: 1) advise against knee surgery; 2) perform myocardial perfusion imaging with pharmacological stress and, if low to intermediate risk, stop ticagrelor, proceed with surgery on aspirin, and resume clopidogrel soon after NCS; 3) stop aspirin and ticagrelor, and restart both agents as soon as feasible post-operatively; or 4) continue DAPT during scheduled NCS?

Discussion. This case is emblematic of a commonly encountered clinical scenario. Although elective NCS scheduled early (≤6 months) after coronary DES implantation could be postponed, it hardly seems to be the best option for a patient with disabling knee pain who is over a year from her last PCI. Knee replacement surgery is associated with an intermediate risk of hemorrhagic complications, whereas the thrombotic risk in this patient is high, given her complex PCI with multiple DES implants (17–19). Complex PCI is defined by inclusion of at least 1 of the following angiographic features: 3-vessel PCI; ≥3 stents implanted; ≥3 lesions treated; bifurcation PCI with ≥2 stents; total stent length ≥60 mm; or PCI of chronic total occlusion (19). In addition to angiographic features, PCI for treatment of MI and previous ST increase the thrombotic risk.

A published consensus document (14) provides the basis for a proposed scheme to assess thrombotic risk of PCI, as depicted in **Table 1**. It should be interpreted in light of findings regarding new-generation DES (20,21), Similar to the assessment of thrombotic risk following PCI, this document also provides an interdisciplinary assessment of bleeding risk associated with noncardiac and cardiac surgical procedures (**Table 2**) (14). Each of these risk assessment schemes are intended to provide practitioners with a standard frame of reference that needs to be adapted on the basis of individual patient characteristics. Once the thrombotic and hemorrhagic risks have been defined, it is advisable to carefully evaluate the composite risk of an individual patient and adopt a perioperative antiplatelet management strategy, as shown in **Table 3**.

The strategy to withhold a potent $P2Y_{12}$ agent 5 days before scheduled NCS, while continuing low-dose aspirin during surgery following a low- to intermediate-risk stress test, appears to be an acceptable option (22). Such testing could be justified, especially in the setting of an elevated surgical risk and unknown functional capacity, provided it would change management.

Discontinuation of aspirin in patients with stents undergoing NCS is associated with a significant increase in major adverse cardiac events (MACE) (23). In a descriptive study highlighting catastrophic outcomes of patients undergoing NCS following stenting and aspirin discontinuation, the time between stenting and surgery was also a major determinant of outcome (24). The evidence from the POISE-2 (Aspirin in Patients Undergoing Noncardiac Surgery) study demonstrating the lack of benefit from aspirin use before surgery and throughout the early post-surgical period may be less relevant to this discussion in light of the fact that <5% of patients with prior PCI were included in the study (25). The POISE-2 study, however, is the largest study to test the question of perioperative aspirin use.

Although there is no reliable evidence for a rebound increase in platelet aggregation with an abrupt discontinuation of aspirin or other $P2Y_{12}$ agents, surgical interventions have consistently been associated with a hypercoagulable and proinflammatory state (26–29). Surgical stress results in

TABLE 2 Determination of Hemorrhagic Risk of Noncardiac and Cardiac Surgeries

Low Risk	Intermediate Risk	High Risk
General, orthopedic, and urologic surgeries		
Hernioplasty, plastic surgery of incisional hernias, cholecystectomy, appendectomy, colectomy, gastric resection, intestinal resection, breast surgery, hand surgery, arthroscopy, cystoscopy and ureteroscopy	Hemorrhoidectomy, splenectomy, gastrectomy, bariatric surgery, rectal resection, thyroidectomy, prosthetic shoulder, knee, foot and major spine surgery, prostate biopsy, orchiectomy	Hepatic resection, duodenocefalopancreasectomy, hip, major pelvic and proximal femur fracture surgery, nephrectomy, cystectomy, TURP, TURBT, prostatectomy
Vascular surgery		
Carotid endarterectomy, bypass or endarterectomy of lower extremity, EVAR, TEVAR, limb amputations	Open abdominal aorta surgery	Open thoracic and thoracoabdominal surgery
Cardiac surgery		
	Mini-thoracotomy, TAVR (apical approach), OPCAB, CABG, valve replacement	Reintervention, endocarditis, CABG in PCI failure, aortic dissections

CABG = coronary artery bypass graft; EVAR = endovascular aortic aneurysm repair; OPCAB = off-pump coronary artery bypass; PCI = percutaneous coronary intervention; TAVR = transcatheter aortic valve replacement; TEVAR = thoracic endovascular aortic aneurysm repair; TURBT = transurethral resection of bladder tumor; TURP = transurethral resection of prostate.

sympathetic activation, vasospasm, and higher shear stress on arterial plaques. It down-regulates fibrinolysis and activates platelets, contributing to an overall hypercoagulable milieu during the perioperative period (27). These factors contribute to higher perioperative MACE following APT discontinuation. Conversely, this risk is mitigated with aspirin maintenance. In an observational study performed by Schouten et al. (30), in which 192 patients underwent surgery within 2 years after the initial PCI procedure, APT interruption was associated with a significantly higher incidence of MACE versus those who continued (5.5% vs. 0%; p = 0.023). There was no difference in the incidence of MACE between DES and BMS recipients (2.2% vs. 3.0%; p = 0.70). The reason for DAPT cessation may also be relevant, as demonstrated by the data from the PARIS (Patterns of Non-Adherence to Anti-Platelet Regimens in Stented Patients) registry (31). This prospective registry included >5,000 patients and classified DAPT cessation as: 1) physician-recommended discontinuation; 2) brief interruption for surgery; and 3) disruption due to patient noncompliance or bleeding. Adjusted hazard ratios (HRs) for MACE were 1.41 (95% confidence interval [CI]: 0.94 to 2.12) and 1.50 (95% CI: 1.14 to 1.97) for DAPT interruption and disruption, respectively, compared with those on DAPT. Although these data suggest an overall lowering of perioperative ischemic complications in patients with stents who continued APT, it is invariably associated with an increased risk of bleeding and transfusion.

TABLE 3 Perioperative Management of DAPT

	Thrombotic Risk		
Hemorrhagic Risk	**Low Risk**	**Intermediate Risk**	**High Risk**
Low risk	Continue ASA; discontinue $P2Y_{12}$ receptor inhibitor; resume within 24–72 h with a loading dose	Postpone elective surgery. If surgery nondeferrable: continue ASA; discontinue $P2Y_{12}$ receptor inhibitor; resume within 24–72 h with a loading dose	Postpone elective surgery. If surgery nondeferrable: continue ASA and $P2Y_{12}$ receptor inhibitor perioperatively
Intermediate risk	Continue ASA; discontinue $P2Y_{12}$ receptor inhibitor; resume within 24–72 h with a loading dose	Postpone elective surgery. If surgery nondeferrable: continue ASA; discontinue $P2Y_{12}$ receptor inhibitor; resume within 24–72 h with a loading dose	Postpone elective surgery; if surgery nondeferrable: continue ASA; discontinue $P2Y_{12}$ receptor inhibitor; resume within 24–72 h with a loading dose; consider bridging with short-acting IV APT
High risk	Continue ASA; discontinue $P2Y_{12}$ receptor inhibitor; resume within 24–72 h with a loading dose	Postpone elective surgery. If surgery nondeferrable: continue ASA; discontinue $P2Y_{12}$ receptor inhibitor; resume within 24–72 h with a loading dose	Postpone elective surgery. If surgery nondeferrable: continue ASA; discontinue $P2Y_{12}$ receptor inhibitor; resume within 24–72 h with a loading dose; consider bridging with short-acting IV APT

APT = antiplatelet therapy; ASA = aspirin; IV = intravenous.

Most of the evidence for higher bleeding rates with aspirin continued perioperatively comes from meta-analyses (32). These analyses include a limited number of randomized studies. The only double-blind, placebo-controlled, randomized clinical study of perioperative low-dose aspirin was conducted by Oscarsson et al. (23). Nearly 70% of patients had ischemic heart disease, and ~30% had prior coronary revascularization (20% PCI) (23). Thirty-day MACE was 1.8% in the aspirin arm and 9.0% in the placebo arm ($p = 0.02$). There was no excess bleeding observed in the aspirin group. Therefore, continuing low-dose aspirin perioperatively in patients with prior coronary stenting is advised, with the possible exception of intracranial and intraspinal neurosurgery, and transurethral prostatectomy, all of which associated with an unacceptably high bleeding-related fatality rate (33,34). The best contemporary evidence for NCS on perioperative DAPT or triple APT comes from analysis of the TRACER (Thrombin-Receptor Antagonist Vorapaxar in Acute Coronary Syndromes) trial, a global double-blind, placebo-controlled, randomized clinical trial of vorapaxar in 12,944 NSTE-ACS patients (5). Nearly 17% of patients (2,202) underwent NCS during a median follow-up period of 1.5 years; 64.3% were treated with coronary stent implants (~60% DES). Fifty percent of patients underwent NCS ≤6 months after NSTE-ACS, and 79% of surgeries were classified as minor. Median time to NCS was 180 days (interquartile range: 51 to 341 days). Vorapaxar or placebo was continued perioperatively in 89% and 86% with additional aspirin and thienopyridine (predominantly clopidogrel) in 97% and 98%, respectively. Pre-specified 30-day ischemic and bleeding endpoints were similar in both the vorapaxar and placebo groups. Primary ischemic events, comprising cardiovascular death, MI, ST, or urgent coronary revascularization, occurred in 3.4% and 3.9% of the vorapaxar and placebo groups, respectively ($p = 0.41$). Over the same period, no differences in rates of NCS-related bleeding (3.9% and 3.4%; $p = 0.17$) or moderate/severe bleeding (4.2% and 3.7%; $p = 0.55$) were observed between the vorapaxar and placebo groups, respectively. Importantly, the use of background thienopyridine was significantly greater in the vorapaxar group. As observed in prior studies of NCS post-PCI, perioperative ischemic complications peaked within 30 days of NSTE-ACS- and NCS-related bleeding events within 6 months. The use of BMS, DES, or medical management of the index NSTE-ACS did not affect perioperative outcomes. The study also highlighted the significantly greater comorbidity of ACS patients referred for NCS and their higher long-term risk of ischemic (adjusted HR: 1.62; 95% CI: 1.33 to 1.97) and bleeding (adjusted HR: 5.63; 95% CI: 3.98 to 7.97) complications. These data support the continued use of DAPT in patients at a high thrombotic risk undergoing surgical procedures that are minor or low risk for bleeding (**Table 3**). However, it is important to point out that none of the randomized trials of long-term DAPT therapy have shown "net benefit" of extended therapy. The PEGASUS (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on the Background of Aspirin) trial showed a reduction in MI that was balanced by an increase in bleeding and no overall mortality benefit (35).

Careful consideration of the data presented in the preceding text indicates that the strategy of withholding ticagrelor 5 days before NCS and continuing low-dose aspirin perioperatively following low- or intermediate-risk stress myocardial perfusion imaging may be the best course of action (Online Table 1) (14). Substituting clopidogrel for ticagrelor postoperatively is reasonable: first, to avoid a more potent $P2Y_{12}$ agent soon after NCS, and secondly, given the likely addition of an oral anticoagulant for prophylaxis against deep vein thrombosis following knee replacement surgery (36–38).

CASE 3. A 62-year-old morbidly obese man is advised cholecystectomy for frequent bouts of right upper-quadrant abdominal pain secondary to long-standing cholelithiasis. His past medical history is significant for an inferior STEMI 7 months ago, which was treated with 2 overlapping (3.0 mm in diameter) second-generation DES to the proximal segment of a diffusely diseased dominant right coronary artery. No other obstructive coronary lesions were reported. Approximately 2 months following his PCI, the patient presented acutely with rest angina associated with nonspecific ST-segment and T-wave electrocardiographic abnormalities, and during urgent coronary angiography, was noted to have a partial occlusion of the proximal right coronary artery stents consistent with ST. Successful thrombectomy and balloon angioplasty were performed, and intravascular ultrasound revealed well-expanded prior stents. The episode of ST was attributed to possible clopidogrel interruption for a period of approximately 3 days due to business travel. The patient was discharged home on low-dose aspirin and prasugrel.

You are asked to see the patient in the hospital, where he has been admitted for another bout of cholecystitis. The surgeons advise laparoscopic

cholecystectomy, but with an intermediate risk of open conversion and bleeding complication, given the patient's morbid obesity and multiple prior bouts of cholecystitis. After a review of the clinical findings and coronary angiograms, you are considering the following management options: 1) stop prasugrel and advise urgent cholecystectomy; 2) perform endoscopic sphincterotomy and delay cholecystectomy by at least a month; 3) continue prasugrel and proceed with cholecystectomy; or 4) perform cholecystectomy after withholding prasugrel for 7 days, while continuing low-dose aspirin and instituting IV bridging therapy with a short-acting antiplatelet agent.

Discussion. This scenario calls for a careful selection of a treatment strategy to mitigate the potential perioperative risk of ST associated with $P2Y_{12}$ interruption. Continuation of DAPT during the perioperative period is likely to increase the risk of hemorrhage and transfusion, particularly for intermediate- or high-risk surgical procedures (39). Thus, continuing prasugrel, a potent $P2Y_{12}$ agent, perioperatively may not be reasonable. Current recommendations suggest at least a 7-day period of prasugrel discontinuation before NCS to limit bleeding complications; however, this strategy may be associated with an increased risk of perioperative ischemic complications in this patient (14).

The clinical approach of performing an endoscopic sphincterotomy as an interim procedure for providing symptom relief in this patient with acute cholecystitis, followed by a planned elective cholecystectomy, is an attractive one. However, the risk of recurrent ST remains high, and the reported cumulative HR is 16% (95% CI: 4% to 20%) at 1 year and 24% (95% CI: 16% to 36%) at 5 years, whereas postponing NCS may not substantially alter this risk (40). On the basis of consensus recommendations, long-term DAPT should either be interrupted, or a bridging treatment with short-acting IV APT should be additionally instituted to mitigate the potential risk of ST, perioperative MI, and other ischemic events (16). The use of anticoagulant agents such as unfractionated or low molecular weight heparin is not recommended for bridging (41). Heparin paradoxically potentiates platelet aggregation, and therefore may exacerbate platelet-mediated vessel thrombosis and ensuing ischemic complications, while adding to the risk of hemorrhage (41). However, short-acting small-molecule IV platelet glycoprotein (GP) IIb/IIIa receptor-blocking agents tirofiban and eptifibatide, or the more recently approved non-thienopyridine, reversible, ultra-short-acting platelet $P2Y_{12}$ receptor antagonist, cangrelor, can be used for perioperative bridging (42). **Table 4** summarizes the profiles of short-acting IV APT agents. It is important to note that the maintenance dose regimens of GP IIb/IIIa inhibitors being used for bridging are the same as for PCI, whereas cangrelor has been subject to dedicated dose-finding studies specifically for bridging (43). In this study, cangrelor was used for bridging therapy before cardiac surgery off DAPT and provided optimal platelet inhibition without excess bleeding. The different pharmacology of oral $P2Y_{12}$ receptor inhibitors is important to consider when defining timing of drug discontinuation before NCS and initiation of bridging therapy (**Figure 1**). In place of a "one-size-fits-all" concept of perioperative APT management, a personalized approach on the basis of platelet function testing has been proposed, which, however feasible, requires further clinical validation (44).

TABLE 4 Short-Acting IV Antiplatelet Bridging Agents

	Tirofiban	Eptifibatide	Cangrelor
Onset of action	Immediate	Immediate	Immediate
Potent platelet inhibition	Yes	Yes	Yes
Plasma half-life	2 h	2.5 h	3–5 min
Offset of action	4–6 h	4–6 h	1 h
$P2Y_{12}$ specific	No	No	Yes
Dose (no bolus)	0.1 μg/kg/min (0.05 μg/kg/min for creatinine clearance <50 ml/min)	2.0 μg/kg/min (1.0 μg/kg/min for creatinine clearance <50 ml/min)	0.75 μg/kg/min (does not require dose adjustment with impaired renal function)

IV = intravenous.

In a recent multicenter prospective study of perioperative management of APT post-PCI, 19% of patients undergoing NCS received IV APT bridging within 6 months of coronary stenting (16). Despite the reported frequency of perioperative bridging, high-quality evidence to support this strategy is lacking. Most recommendations regarding bridging are on the basis of limited prospective data, retrospective studies, meta-analyses, and expert opinion. A prospective study of consecutive patients referred for urgent surgery after a median of 4 months (range 1 to 12 months) following PCI with DES reported favorable clinical outcomes with temporary withdrawal of oral clopidogrel and IV tirofiban bridging (45). There was no death, MI, ST, or surgical re-exploration due to bleeding reported during the index hospitalization. There was 1 case of perioperative TIMI major bleeding and 1 case of TIMI minor bleeding.

FIGURE 1 Proposed Perioperative IV Antiplatelet Bridging Strategies

Description of short-acting intravenous antiplatelet drug regimen that could be used for perioperative bridging. GP = glycoprotein; IV = intravenous.

A more recent weighted meta-analysis of 8 perioperative IV APT bridging studies involving 280 patients arrived at the following pooled estimates of outcomes: in-hospital mortality 3.5% (95% CI: 1.7% to 5.9%); ST 1.3% (95% CI: 0.3% to 3.0%); MI 1.6% (95% CI: 0.3% to 3.6%); and major bleeding 7.4% (95% CI: 2.8% to 14.1%) (46). Despite this limited evidence, in a national survey of 374 interventional cardiologists, 50% of respondents opted for perioperative IV APT bridging, and 49% opted for identifying a surgeon who would operate on DAPT in clinical situations when a surgical intervention is more urgent and cannot be postponed (47).

On the basis of the previously discussed considerations, the option of withholding prasugrel for 7 days while continuing low-dose aspirin and instituting IV APT bridging with a short-acting antiplatelet agent may be reasonable if longer-term postponement is not feasible (Online Table 1).

CONCLUSIONS

The case presentations presented earlier highlight the need to carefully consider the risk of ischemic complications, consequences of delayed surgery, and perioperative bleeding in post-PCI patients on DAPT undergoing NCS, and to individualize treatment decisions on the basis of the particular clinical risks and benefits of the strategy selected. The accumulating evidence for improved DES safety (particularly with newer-generation stent platforms) derived from several studies of DAPT duration, along with a patient-level analysis of trials involving newer-generation DES with 3- or 6-month duration of DAPT, have led to modifications of guideline recommendations (10,48). The prior Class I recommendation that elective NCS in DES recipients be delayed for 1 year has been modified and reduced to at least 6 months; the prior Class IIb recommendation to

consider NCS after 180 days has been modified and reduced to 3 months (12).

The clinical decisions regarding management of APT in post-PCI patients scheduled for NCS are complex, and cannot be addressed via guidelines that are primarily on the basis of consensus recommendations. These decisions require an astute clinician, a highly individualized and collaborative approach to patient care, and team-based decision making. The paucity of high-quality evidence in this important therapeutic area also underscores an important unmet need for well-designed and adequately powered clinical studies to guide and inform physician practice.

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APPENDIX For a supplemental figure and table, please see the online version of this paper.