

DAPT Management for Noncardiac Surgery After PCI

Strategies for treating a challenging patient population.

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The need for antithrombotic therapy after percutaneous coronary intervention (PCI) has been a troublesome issue for physicians for more than 20 years. With the advent of drug-eluting stents (DES), a minimum of 12 months of dual-antiplatelet therapy (DAPT) has become the norm. However, evolving stent and drug technologies are now set to change this dogma. In this article, we focus on the perioperative management of antiplatelet therapy after PCI in patients who require noncardiac surgery. We begin by describing the current optimal management and then consider future possible solutions to this clinical dilemma.

CASE SCENARIO

A generally healthy, 73-year-old, nondiabetic woman presented with a 6-week history of Canadian Cardiovascular Society Class III angina. She was referred for an exercise nuclear study, which showed a large area of inferior ischemia and normal ventricular function. Her symptoms were only marginally relieved after commencing aspirin, simvastatin, a beta-blocker, and isosorbide mononitrate. She was referred for coronary angiography, which revealed single-vessel coronary artery disease with an 80% to 90% stenosis in the proximal segment of a large, dominant right coronary artery. The patient received 600-mg on-table loading with clopidogrel, and the lesion was treated by the successful placement of a 3- X 23-mm everolimus-eluting stent. The patient was discharged home the next day on DAPT and her other usual medications.

At follow-up 3 weeks later, she reported complete relief of her angina symptoms. However, she noted several episodes of "at least a tablespoon" of bright blood per rectum. On further questioning, she revealed that this has actually been occurring for perhaps the last 2 to 3 months, although she did not tell anybody until now because it was only infre-

quent and in very small amounts. The patient was referred to a gastrointestinal surgeon who explained 5 days later that there was a moderate-sized abdominal mass on computed tomographic scan. Although no biopsies were taken due to DAPT, limited colonoscopy confirmed the presence of what was most likely a locally confined and potentially curable colonic tumor. A surgical colleague communicated in very clear terms that surgery should proceed as soon as possible and that deferring the operation for 3 to 4 months would pose a significant risk of malignant spread. Management of this case is discussed in the Conclusion section.

Although this appears to be a worst-case scenario, it is, in fact, a common clinical conundrum that every seasoned interventionist and cardiologist has faced. Thankfully, the need for noncardiac surgery after PCI while still receiving DAPT is not always as challenging as the presented case scenario. As a first step in considering the management of these cases, it is always of importance to bear in mind current guideline recommendations.

CURRENT GUIDELINES: WHAT IS THE MINIMUM DURATION OF DAPT AFTER PCI?

With Bare-Metal Stents

Current American Heart Association/American College of Cardiology (AHA/ACC) guidelines indicate that aspirin should be taken at 81 mg indefinitely after PCI (level of evidence B). Clopidogrel should be taken at 75 mg daily for at least 1 month and ideally for up to 1 year. However, even if the patient is at an increased risk of bleeding, clopidogrel should be taken for a minimum of 2 weeks (level of evidence, B).¹ Although the minimum suggested duration of clopidogrel treatment after placement of a bare-metal stent (BMS) is 1 month, CREDO as well as PCI-CURE results indicate that patients who are not at high risk of bleeding may benefit from taking clopidogrel for at least 12 months.^{2,3}

CHECKLIST FOR PREOPERATIVE EVALUATION AFTER STENTING

- Determine type of stent(s): BMS or DES?
- If DES, sirolimus/paclitaxel/everolimus/other?
- Determine how long ago each stent was implanted.
- Determine location of each stent in the coronary circulation.
- How complicated was the revascularization? Were there any procedural complications (eg, known under-expanded stent)?
- Is there a history of stent thrombosis (ST)?
- What antiplatelet regimen is being used?
- Determine patient comorbidities to further ascertain ST risk level (ejection fraction, diabetes, renal insufficiency).
- What is the recommended duration of antiplatelet therapy for the specific patient?

With DES

Current (2011) guideline recommendations are that aspirin should be taken at 81 mg indefinitely, regardless of the type of DES that is used. After DES placement, P2Y₁₂ inhibitor therapy should be given for at least 12 months. Options include 75 mg of clopidogrel daily, 10 mg of prasugrel daily, and 90 mg of ticagrelor twice daily (level of evidence B).^{1,4}

As all physicians are aware, these are general guidelines for DAPT—individual therapy needs to be tailored to the specific patient. As reports of very late ST began to appear in 2007, concern arose over the need to extend the duration of clopidogrel treatment.⁵ Bavry et al⁴ quantified the incidence of late and very late ST in a meta-analysis of 14 clinical trials that randomized patients to receive either DES (paclitaxel or sirolimus) or BMS.² The incidence of ST within 30 days was similar for both groups at 4.4 per 1,000 patients versus 5 per 1,000 patients ($P = .74$). However, the rate of very late ST was significantly higher in those receiving DES versus BMS (5 per 1,000 patients treated; relative risk, 5.02; 95% confidence

interval, 1.29–19.52; $P = .02$).³ The results of this and other studies, such as BASKET LATE and others,^{6,7} led the ACC and AHA to revise their joint guidelines to recommend that in patients with clinical features associated with an increased likelihood of ST (ie, renal insufficiency, diabetes, or procedural characteristics [multiple stents or treatment of a bifurcation lesion]), extending DAPT beyond 1 year might be reasonable.^{3–5}

The recently completed PRODIGY⁸ study has shed further light on the role of DAPT beyond 12 months in patients with DES. This multicenter study included 2,000 patients who were scheduled for elective or emergency PCI. They were randomized to receive one of four stent types: everolimus-eluting, paclitaxel-eluting, zotarolimus-eluting, or a thin-strut BMS. At 30 days, patients in each stent group were then further randomized to either 6 or 24 months of DAPT. There was no difference in major adverse cardiac events in the 6-month group versus the 24-month group. However, the risk of bleeding was doubled in the 24-month group, with a hazard ratio of 2.17 (95% confidence interval, 1.02–3.13; $P = .037$).

Larger, ongoing trials should provide a clear answer as to whether there is any benefit of continuing DAPT for longer than 1 year in patients who have received a DES. The largest of the studies is the DAPT study,⁹ a 20,000-patient, randomized clinical trial testing optimal DAPT duration after DES implantation. The DAPT study will compare 12 months versus 30 months of DAPT and is powered to assess the primary endpoints of differences in ST and major adverse cardiovascular and cerebrovascular events. Highlighting the uncertainties in this area and the fact that second-generation DES may have a lower risk for ST, the 6,000-patient ISAR-SAFE study¹⁰ will test a shorter duration DAPT of 6 months versus 12 months in patients who receive DES.

WHEN IS NONCARDIAC SURGERY SAFE AFTER PCI?

A not insignificant number of patients who undergo PCI require surgery while still receiving DAPT. It has been demonstrated that patients undergoing noncardiac surgery

TABLE 1. HEMORRHAGIC RISK IN NONCARDIAC SURGERY^a

Surgical Hemorrhagic Risk	Blood Transfusion Requirements	Type of Surgery
Low	Usually not required	Peripheral, plastic, general surgeries, biopsies, minor orthopedic, otolaryngology, general surgery, endoscopy, eye anterior chamber, dental extraction
Intermediate	Frequently required	Visceral surgery, cardiovascular surgery, major orthopedics, otolaryngoscopy and urological reconstructive surgery
High	Possibility of bleeding in a closed space	Intracranial neurosurgery, spinal cord surgery, and eye posterior chamber surgery

^aData adapted from Chassot et al. *Br J Anaesth* (2007;99:316–328).¹¹

TABLE 2. CURRENT ACCF/AHA/SCAI GUIDELINES REGARDING REVASCULARIZATION BEFORE NONCARDIAC SURGERY¹

Recommendation	Strength of Recommendation	Level of Evidence
For patients who require PCI and are scheduled for elective noncardiac surgery in the subsequent 12 months, a strategy of balloon angioplasty or BMS implantation followed by 4–6 weeks of DAPT is reasonable.	Ila: Benefit > risk; it is reasonable to perform procedure/administer treatment	B: Limited populations evaluated and/or data derived from a single randomized trial or nonrandomized studies
For patients with DES who must undergo urgent surgical procedures that mandate the discontinuation of DAPT, it is reasonable to continue aspirin if possible and restart the P2Y ₁₂ inhibitor as soon as possible in the immediate postoperative period.	Ila	C: Very limited populations evaluated; consensus expert opinion only
Routine prophylactic coronary revascularization should not be performed in patients with stable CAD before noncardiac surgery.	III: Indicated procedure is of no benefit or has potential for harm	B
Elective noncardiac surgery should not be performed in the 4–6 weeks after balloon angioplasty or BMS implantation or the 12 months after DES implantation in patients in whom the P2Y ₁₂ inhibitor will need to be discontinued perioperatively.	III	B

have increased mortality within 6 weeks after PCI compared with patients undergoing surgery after 6 weeks.¹² Kaluza et al¹³ observed a high incidence of adverse events among 40 patients who underwent noncardiac surgery < 6 weeks after PCI with BMS. All of the deaths and myocardial infarctions and eight of the 11 bleeding episodes occurred in patients who underwent surgery < 14 days after stenting. The problem of early DAPT withdrawal in patients having surgery is compounded by other factors that predispose to thrombogenesis in this setting, such as increase in catecholamine release, increased platelet aggregability, and decreased fibrinolysis.¹⁴ Kaluza et al¹³ concluded that noncardiac surgery should be delayed for 4 weeks after BMS implantation to allow patients to complete their combination antiplatelet therapy.

After BMS placement, elective and nonurgent procedures should be delayed for at least 1 month, according to the ACC/AHA joint advisory,⁴ or for 4 to 6 weeks, according to the ACC/AHA guidelines.¹ For patients with recent (< 6 weeks) BMS placement who require urgent surgery, DAPT should be continued during the perioperative period, if possible.¹

After DES placement, elective and nonurgent procedures should be delayed for at least 12 months.¹ For patients with recent DES placement in whom surgery cannot be delayed, ideally, DAPT should be continued without interruption if the stent was placed within the previous 6 months.^{15,16} If the stent was placed more than 6 months before urgent surgery, aspirin should be continued without interruption (≥ 81 mg/d), and clopidogrel (or other P2Y₁₂ inhibitors)

should be continued until 5 days before surgery and resumed as soon as possible after surgery (for clopidogrel, at a loading dose of 600 mg followed by 75 mg/d). If the surgeon is comfortable continuing DAPT in a patient whose stent was placed 6 to 12 months earlier, that course should be considered.¹⁶

WHAT IS THE RISK OF BLEEDING WITH DAPT?

The majority of current data on the risk of bleeding pertain to aspirin and/or clopidogrel, and newer agents such as prasugrel and ticagrelor have very little information in this regard. Furthermore, for noncardiac surgery, even the data concerning the risk of surgical bleeding with aspirin and clopidogrel are limited and conflicting. Continued DAPT (aspirin and clopidogrel) during the period of noncardiac surgery results in a 30% to 50% increased need for transfusion.¹¹ Typically, however, this does not translate into severe complications or mortality (prostatectomy, intracranial surgery, spinal cord surgery, and posterior eye surgery are exceptions).¹⁷

In a meta-analysis by Burger et al¹⁸ that included a total of 49,590 patients undergoing noncardiac surgery, it was concluded that aspirin continuation led to an increase in bleeding by a factor of 1.5. However, this increase did not lead to a higher level of the severity of bleeding complications or fatal bleeding, except in intracranial surgery and possibly transurethral prostatectomy. Moreover, withdrawal of aspirin was associated with a higher incidence of cardiac, cerebral, and peripheral vascular events.¹⁸

Therefore, in many cases, the risk of withdrawing antiplatelet therapy in patients with DES might outweigh

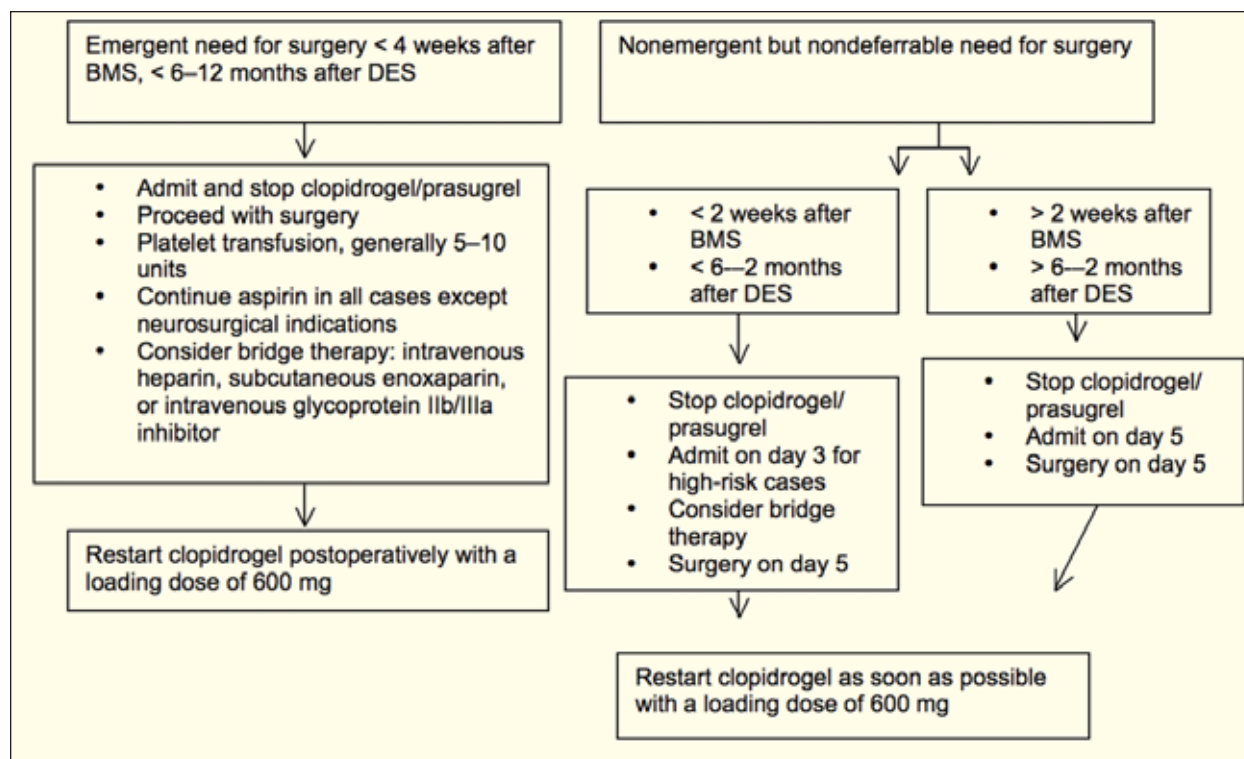


Figure 1. Proposed management of patients requiring temporary DAPT cessation. Mount Sinai Hospital protocol.

the risk of retaining them, particularly in high-risk patients. A critical factor in this consideration is that the single most important predictor of ST is the cessation of antiplatelet therapy, which may increase perioperative cardiac death rates by up to five- to 10-fold.^{19,20}

STRATEGIES

The best approach to perioperative DAPT management is to involve all members of the health care team—primary physician, surgeon, cardiologist, and anesthesiologist—together with the patient. Furthermore, it should be ensured that care is individualized and that all relevant facts are accounted for. For all patients undergoing surgery who underwent PCI in the past, a checklist before or during preoperative evaluation is advisable to determine risk of ST (see *Checklist for Preoperative Evaluation After Stenting* sidebar) and the risk of bleeding complications according to the type of surgery (Table 1).

As mentioned, as a general approach, all elective surgical procedures should be delayed by at least 1 month for BMS and ideally by 12 months after DES placement. Many of the previously mentioned issues have been adopted and simplified in the current ACCF/AHA/SCAI guidelines for revascularization before noncardiac surgery (Table 2).¹ An algorithm for patients requiring temporary DAPT cessation according to our hospital protocol is provided in Figure 1.

Other Alternatives

Complete discontinuation of DAPT (both aspirin and P2Y₁₂ inhibitor) may be required in extreme cases if the risk of surgical bleeding is potentially catastrophic or fatal, such as in intracranial, medullary, and posterior eye chamber surgeries. In these cases, all antiplatelet therapy should be discontinued 5 days before surgery (7 days for prasugrel), and the patient should be hospitalized for bridge therapy with intravenous heparin, intravenous glycoprotein IIb/IIIa inhibitor, or subcutaneous enoxaparin (Figure 1). The French Society of Anesthesiology and Intensive Care recommends substitution of a nonsteroidal anti-inflammatory drug such as flurbiprofen (50 mg, withdrawn 24 h before surgery) or low-molecular-weight heparin (85–100 IU/kg for 12 h), although it is noted that the use of nonsteroidal anti-inflammatory drugs is not indicated for this purpose in the United States.

ALLIED SPECIALTIES PERSPECTIVE

We mention several examples of specific guidelines issued by certain subspecialty societies regarding DAPT at the time of noncardiac surgery. Because many physicians may not be familiar with the specifics of the required operation and the risk of bleeding it may entail, seeking these specific guideline recommendations from the relevant subspecialty fields can be of great assistance in balancing DAPT management and

the risk of ST (DAPT cessation) versus surgical bleeding (DAPT continuation) at the time of noncardiac surgery.

Urology

According to Gupta et al in the *British Journal of Urology*,²¹ there is considerable risk associated with stopping both aspirin and clopidogrel, which is maximal soon after treatment withdrawal. Also, if antiplatelet agents are to be stopped, this should be for the minimum time and preferably covered with alternative agents or surgery should be delayed when possible. Depending on the type of urological procedure, early initiation of aspirin (24 h after stopping bladder irrigation) has no increased risk compared to initiation after 3 weeks. Finally, alternative surgical strategies (eg, photoselective vaporization of the prostate) should be considered in high-risk patients who need to continue therapy.

Anesthesia

The American Society of Regional Anesthesia has issued guidelines regarding perioperative management of patients receiving DAPT, which are in agreement with the other recommendations presented previously (see *American Society of Regional Anesthesia Guidelines for Perioperative Management of Patients on Antiplatelet Therapy* sidebar).

College of Chest Physicians

The American College of Chest Physicians has also issued guidelines. In simplified form, these guidelines (2008) on perioperative management of patients receiving antiplatelet therapy are as follows²²:

- In patients who are not at high risk of cardiac events (eg, primary preventive setting), interruption of antiplatelet agents for 7 to 10 days is appropriate.
- Patients who had aspirin/clopidogrel interruption should have this therapy restarted within 24 hours.
- For dental, dermatology, or cataract surgery, if the patient on aspirin, continue aspirin up to and beyond surgery.

NOVEL ANTIPLATELET AGENTS

Prasugrel has a much more rapid, potent, and consistent platelet inhibition effect when given at a loading dose of 60 mg as compared with the standard 300 mg of clopidogrel. It has been shown to inhibit adenosine-diphosphate-induced platelet activation in a more consistent and effective manner than clopidogrel.^{23,24} Even though prasugrel seems to be effective in patients with acute coronary syndromes undergoing PCI, its perioperative use might be limited given the increased risk of bleeding and its irreversible antiplatelet inhibition.²⁵

Compared with clopidogrel, prasugrel is associated with lower rates of myocardial infarction, urgent target vessel

AMERICAN SOCIETY OF REGIONAL ANESTHESIA GUIDELINES FOR PERIOPERATIVE MANAGEMENT OF PATIENTS ON ANTIPLATELET THERAPY¹⁵

Patients with coronary stents

- Elective surgery must be postponed for the following durations if aspirin and thienopyridine (eg, clopidogrel) therapy must be discontinued:
BMS: 4–6 weeks
DES: 12 months
- If surgery cannot be postponed, continue aspirin throughout postoperative period

Patients at high risk for cardiac events (exclusive of coronary stents)

- Continue aspirin throughout the perioperative period
- Discontinue clopidogrel at least 5 days (preferably 10 days) before surgery
- Resume clopidogrel 24 hours postoperatively

revascularization, and in-stent thrombosis but at the cost of a higher risk of major bleeding.²⁵ Of note, due to the fact that the pivotal trial comparing clopidogrel versus prasugrel (TRITON-TIMI 38) defined bleeding complications as events occurring within 7 days after the study drug was discontinued, and also because in that study, the bleeding risk was higher with prasugrel than clopidogrel, if discontinuation of prasugrel is required for surgical reasons, then 7 days should be allowed for the effects of this agent to have sufficiently worn off.²⁵

Ticagrelor is also a novel oral adenosine diphosphate P2Y₁₂ receptor antagonist. Unlike clopidogrel and prasugrel, ticagrelor is a nonthienopyridine adenosine triphosphate analog that binds directly and reversibly to P2Y₁₂ without any metabolic activation. Peak inhibition is observed 2 to 4 hours after a dose of ticagrelor. The recent phase 3 clinical PLATO (Platelet Inhibition and Patient Outcomes) trial demonstrated a significant reduction in major adverse cardiac events with ticagrelor compared with clopidogrel.²⁴ Furthermore, there was no significant difference in the rates of major bleeding. The main advantage of using ticagrelor perioperatively may be its reversibility, with a relatively short half-life (6–13 h), and also its rapid onset of action. However, at the current time according to recommendations arising from the PLATO study, like clopidogrel, ticagrelor should also be stopped 5 days before surgery.

Cangrelor is yet another novel reversible P2Y₁₂ receptor antagonist that is administered intravenously. Similar to ticagrelor, cangrelor does not require metabolic activation. Potentially, cangrelor may find a niche role as a bridge thera-

py for patients requiring withdrawal from antiplatelet therapy for surgical or other reasons. This is based on its unique pharmacokinetic properties, which include an intravenous route of administration, rapid onset, and a 3-minute half-life. The BRIDGE trial recently reported on 210 patients who received a “bridge” of cangrelor or placebo infusion for at least 48 hours, which was stopped 1 to 6 hours prior to coronary bypass graft surgery. Despite significant inhibition of platelet function during the period of cangrelor infusion, rates of surgical bleeding did not differ from placebo. However, this study was underpowered to assess ischemic events and ST, and a larger study will now be required to assess therapeutic utility.²⁶ However, similar to bridging with glycoprotein IIb/IIIa inhibitors, patients would require hospital admission for initiation of intravenous infusion. In this case, cangrelor would be stopped minutes before the surgical procedure and resumed sooner than oral antiplatelet agents.

CONCLUSION

The case scenario presented at the beginning of this article is best managed as per Figure 1, by continuing aspirin but stopping clopidogrel as an outpatient and then admitting the patient 3 days later. Given that there is a proximal, 1-month-old DES in a large, dominant right coronary artery, the overall risk of ST is high. In the absence of major clinical trials that have studied this scenario, we would recommend bridge therapy to be commenced on admission with intravenous heparin, subcutaneous enoxaparin, or intravenous tirofiban. Surgery should proceed on day 5 after clopidogrel cessation, with bridge therapy (and then oral loading with clopidogrel) commenced as soon as possible after surgery. Although currently not recommended, we suspect that this algorithm will soon change to incorporate the use of newer, shorter-acting agents, such as ticagrelor or cangrelor.

The management of antiplatelet therapy after PCI in patients requiring noncardiac surgery continues to pose a challenge. We have outlined some of the common pitfalls and most helpful management strategies for those patients requiring suspension of DAPT for whatever noncardiac surgical reason. In the future, newer-generation bioabsorbable stents, rapidly acting antiplatelet agents, and other advances will hopefully make this field increasingly easy to navigate. ■

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