

Perioperative management of patients who are receiving antiplatelet therapy: a case-based, evidence-informed approach

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ABSTRACT

Addressing the optimal management approach for patients who are receiving single or dual antiplatelet therapy is a common and sometimes challenging clinical problem, especially for patients with coronary stents who are receiving dual antiplatelet therapy with acetylsalicylic acid (ASA) combined with a P2Y₁₂ inhibitor. Using a case-based format, we summarize the findings of recent clinical trials and key observational studies which help inform best practices for the perioperative antiplatelet management of noncardiac surgery and coronary artery bypass graft surgery. In this review, we explore the evidence to address 3 key questions: What is the minimum duration that a surgery should be delayed after coronary stent implantation? In patients who are receiving single antiplatelet therapy with ASA, how to manage patients who require noncardiac and cardiac surgery? In patients who are receiving dual antiplatelet therapy for a coronary stent, how to manage patients who require noncardiac and cardiac surgery?

Introduction The perioperative management of patients who are receiving antiplatelet therapy is a common and challenging clinical problem, especially in patients with coronary artery stents. In the United States (US) alone, 900 000 patients have coronary stents implanted annually, and within 1 year of stent implantation, 4% to 5% (36 000–45 000) of such patients will require surgery, a number that increases to 11% (99 000) within 2 years of stent implantation.^{1,2} In addition, a higher number of such patients will require an invasive procedure such as coronary angiography or gastrointestinal endoscopy.^{3–6} Such patients are expected to be receiving treatment with single antiplatelet therapy, typically with low-dose acetylsalicylic acid (ASA; 75–100 mg/d), or dual antiplatelet therapy, typically consisting of ASA combined with a P2Y₁₂ inhibitor (clopidogrel, prasugrel, or ticagrelor). The scope and complexity of this clinical problem can be illustrated by the clinical scenarios described below.

Clinical scenarios Case 1 A 76-year-old female with hypertension, type 2 diabetes, and stable angina, with no prior coronary stents or coronary artery bypass graft (CABG) surgery, is scheduled for an elective outpatient laparoscopic hernia repair. She is receiving ASA, 81 mg/d, and is referred to the perioperative risk assessment and management clinic.

Case 2 A 59-year-old male who has smoked for 40 years suffered an anterior wall ST-segment elevation myocardial infarction (MI) that required implantation of a drug-eluting coronary stent in the left anterior descending coronary artery. He is now receiving dual antiplatelet therapy with ASA, 81 mg/d, and clopidogrel, 75 mg/d. A routine chest X-ray showed a suspicious coin lesion, which was subsequently diagnosed, 4 weeks after his MI, as squamous cell lung cancer. A lobectomy is recommended.

Case 3 A 65-year-old male presents to the emergency department just after midnight with

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4 hours of retrosternal chest pressure and is diagnosed with a non-ST-segment elevation MI. Antiplatelet therapy is initiated, consisting of ASA, 81 mg, and ticagrelor, 180-mg loading dose followed by 90 mg twice daily. The next day, coronary angiography reveals diffuse 3-vessel coronary artery disease with involvement of the left anterior descending artery. CABG surgery is recommended.

Objectives and scope Against this background, the overall objective of this review is to provide clinicians with a case-based, evidence-informed approach to the perioperative management of patients receiving antiplatelet therapy who require major surgery in which interruption of antiplatelet therapy should be considered. This review does not address procedures for which antiplatelet or anticoagulant therapy can be safely continued, as this issue is discussed elsewhere.⁷⁻¹⁰

First, we provide a general approach to risk stratification for perioperative management of patients who are receiving antiplatelet therapy. Secondly, we use the abovementioned cases to address the following clinical questions: 1) What is the minimum duration that a surgery should be delayed after coronary stent implantation?; 2) How to manage patients who require noncardiac or cardiac surgery, and are receiving single antiplatelet therapy with ASA?; and 3) How to manage patients who require noncardiac or cardiac surgery and are receiving dual antiplatelet therapy with ASA and a P2Y₁₂ inhibitor? Finally, we provide some practical clinical guidance for perioperative management. Such clinical guidance should be considered in the context of emerging clinical practice guidelines in this area, which show variability reflecting the paucity of well-designed prospective trials assessing perioperative antiplatelet management.¹¹⁻¹⁵

Risk stratification for adverse cardiovascular and bleeding outcomes Irrespective of the clinical scenario, in patients who are receiving antiplatelet therapy and require elective surgery, clinicians should balance the estimated perioperative risks for major adverse cardiovascular events, in particular stent thrombosis associated with perioperative interruption of antiplatelet therapy, against the risk of bleeding associated with continuation of single or dual antiplatelet therapy.^{16,17}

Estimating adverse cardiovascular risk Patients without coronary stents have a 1% to 5% risk of developing adverse cardiovascular complications after elective noncardiac surgery; this risk is heightened to a range of 8% to 10% in patients with coronary stents.¹⁸ Clinically, stent thrombosis is associated with significant morbidity and mortality, with up to 40% to 60% of such events being fatal.¹⁹ The timing of antiplatelet interruption after stent implantation is an important factor in estimating the risk for perioperative stent thrombosis, with the risk being the highest during

the time interval between stent implantation and reendothelialization at the stent site. This process takes 4 to 6 weeks in patients with a bare metal stent and 6 to 12 months in patients with a drug-eluting stent. Premature interruption of dual antiplatelet therapy, most commonly in the perioperative setting, is the strongest predictor of stent thrombosis.^{20,21} Based on a prospective registry involving 432 patients with coronary stents who had surgery (urgent in 22% of cases), other predictors of major adverse cardiac events were non-specific and included recent MI, chronic kidney disease, diabetes, and no use of preoperative antiplatelet therapy.²²

Overall, there are no established risk stratification schemes that estimate the risk for adverse cardiovascular events with perioperative single or dual antiplatelet interruption. Risk prediction models, such as the CHADS₂ score (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke [double weight]), have been assessed in a perioperative setting but in patients with atrial fibrillation in whom the assessment was for stroke prediction and not acute coronary events.²³

Risk stratification should be individualized so as to consider the following factors²⁴: 1) time interval from stent implantation to surgery; 2) type of surgery (cardiovascular vs noncardiovascular site, bleeding risk); 3) stent characteristics (location, length, diameter); 4) other patient characteristics (prior acute coronary syndrome, left ventricular dysfunction, peripheral arterial disease, smoking). Of these factors, the type of surgery is an overlooked but important determinant. Thus, among patients with atrial fibrillation who required the interruption of anticoagulant therapy for surgery, the type of surgery was an important independent determinant of postoperative stroke in patients having cardiac or vascular surgery at the highest risk.²³ Similarly, a large US linked administrative database study assessed 20 590 patients, separated into 2 groups, who had surgery 1.5 to 6 months and 6 to 24 months after coronary stenting.²⁵ In these 2 groups, the 30-day postoperative risk for adverse cardiovascular events was the lowest in patients having outpatient surgery (0.1% and 0.2%, respectively), higher after inpatient surgery (1.9% and 3.7%, respectively), and the highest after complex inpatient surgery (2.4% and 5.3%, respectively). For each type of surgery, the risk was higher in the group who had surgery 1.5 to 6 months after stenting.

Estimating bleeding risk Few studies have assessed determinants of bleeding in a perioperative setting. One observational study applied the HAS-BLED score (hypertension, abnormal renal or liver function, stroke, bleeding history or predisposition, labile international normalized ratio, age >65 years, drug therapy, or alcohol consumption) to warfarin-treated patients who required elective surgery,²⁶ and

TABLE 1 Suggested surgery- or procedure-related bleeding risk classification

High-bleeding-risk surgery or procedure	
Any surgery requiring neuraxial anesthesia	Neuraxial anesthesia/injection
	Epidural anesthesia/injection
Major intracranial or neuraxial surgery	Brain cancer resection
	Laminectomy or neuraxial tumor resection
	Intracranial (subdural, epidural) bleed evacuation
Major thoracic surgery	Lobectomy, pneumonectomy
	Esophagectomy
Major cardiac surgery	Coronary artery bypass
	Valve replacement or repair
Major vascular surgery	Aortic aneurysm repair
	Aortobifemoral bypass, popliteal bypass
	Carotid endarterectomy
Major abdominopelvic surgery	Hepatobiliary cancer resection
	Pancreatic cancer or pseudocyst resection
	Colorectal and gastric cancer resection
	Diverticular disease resection
	Inflammatory bowel disease resection
	Renal cancer resection
	Bladder cancer resection
	Endometrial cancer resection
	Ovarian cancer resection
Major orthopedic surgery	Radical prostatectomy
	Hip arthroplasty or hip fracture repair
	Knee arthroplasty or tibial osteotomy
	Shoulder arthroplasty
	Metatarsal osteotomy
Other major cancer or reconstructive surgery	Head and neck cancer surgery
	Reconstructive facial, abdominal, limb surgery
Low-bleeding-risk surgery or procedure	
Gastrointestinal procedures	Colonoscopy
	Gastroscopy
	Sigmoidoscopy
	Endoscopic retrograde pancreaticocholangiography
	Capsule endoscopy
	Push enteroscopy
	Barrett esophagus ablation
Cardiac procedures	Permanent pacemaker implantation or battery change
	Internal cardiac defibrillator implantation or battery change
	Arterioventricular node ablation
	Coronary artery angiography (radial approach)
Dental procedures	Tooth extraction (up to two extractions)
	Endodontic (root canal) procedure
Skin procedures	Skin biopsy
Eye procedures	Phacoemulsification (cataract)

found that a score of 3 or higher was associated with a 12-fold increased risk for clinically relevant bleeding, although the overall risk was only 3.5%.²⁷ However, this score was applied to patients who were receiving anticoagulant therapy, although it is likely that some of

the determinants are sufficiently germane to be applicable for perioperative antiplatelet management. Estimates of perioperative bleeding risk are also based on the type of planned surgery, and an empiric risk classification is shown in **TABLE 1**.²⁸ Patients who are receiving neuraxial anesthesia or closed space surgery can be considered, in general, as being at high risk for bleeding because of the consequences of bleeding.^{14,29,30}

For patients who are receiving antiplatelet therapy, a basic understanding of the pharmacokinetic and pharmacodynamic properties of antiplatelet drugs informs decisions on the timing of their perioperative interruption and resumption. The antiplatelet effect of ASA occurs within a few hours of intake and is mediated by the irreversible inhibition of platelet cyclooxygenase-1, leading to a decrease in thromboxane A₂ synthesis and platelet aggregation. Clopidogrel is a thienopyridine that irreversibly inhibits platelet function through inhibition of platelet receptor P2Y₁₂, requires multistep hepatic conversion to an active metabolite, and its efficacy can be limited by genotype variants of cytochrome P450 enzymes. Prasugrel is also an irreversible inhibitor of platelet receptor P2Y₁₂ but, unlike clopidogrel, it is converted to its active form in a single-step hepatic process, rendering it with greater antiplatelet potency and less susceptibility to efficacy variability by cytochrome P450 genotype variants. Ticagrelor is also a P2Y₁₂ receptor inhibitor but, unlike clopidogrel and prasugrel, it does not require hepatic conversion to become active and is the only P2Y₁₂ inhibitor that has reversible platelet inhibition effects. As shown in **TABLE 2**, studies that have assessed the effect of antiplatelet drug interruption on platelet function indicate differences in the time required for platelet function recovery after 4- to 5-day interruption and 7- to 10-day interruption.³¹⁻³⁴

An important but sometimes overlooked issue is timing and dosing of antiplatelet drug resumption after surgery. In the POISE-2 trial (Perioperative Ischemic Evaluation-2), which assessed perioperative ASA interruption or continuation in 20 010 patients, 78.3% of major bleeds occurred at the surgical site and 9.3% occurred in the gastrointestinal tract, many of which were likely due to stress ulceration.³⁵ Most postoperative bleeds occurred within 1 week after surgery; the delayed resumption of ASA for 1 week postoperatively eliminated any difference in bleeding outcomes in the ASA interruption and continuation groups. From a practical standpoint, it is reasonable to delay resumption of ASA in patients at low cardiovascular risk for 5 to 7 days after surgery, especially if they are receiving thromboprophylaxis with low-dose heparin. For clopidogrel, maximum platelet function inhibition is achieved within 5 to 10 days when starting with a 75-mg maintenance dose as opposed to 12- to 15-hour maximal antiplatelet effect when clopidogrel is started with a 300- to 600-mg loading dose; consequently, postoperative resumption of

TABLE 2 Properties of antiplatelet drugs relevant for perioperative management

Antiplatelet drug	Mode of antiplatelet action	Pharmacokinetic effect (half-life)	Pharmacodynamic effect (platelet function inhibition)	Residual platelet function 4 days after stopping drug	Residual platelet function 7 days after stopping drug
ASA	COX-1/COX-2 inhibitor	8 hours	Irreversible for lifespan of platelet (7–10 days)	20%	90%
Clopidogrel	ADP P2Y ₁₂ inhibitor	8 hours	Irreversible	30%	90%
Prasugrel	ADP P2Y ₁₂ inhibitor	8 hours	Irreversible	10–20%	80%
Ticagrelor	ADP P2Y ₁₂ inhibitor	8 hours	Reversible	70% (2 days after stopping)	90% (4–5 days after stopping)
Dipyridamole	Phospho-diesterase inhibitor	10 hours	Reversible	NA	NA
Cilostazol	Phospho-diesterase inhibitor	10 hours	Reversible	NA	NA
NSAID	COX-1/COX-2 inhibitor	4–20 hours	Reversible	NA	NA
Tirofiban	P-glycoprotein IIb/IIIa inhibitor	2 hours	Immediate onset of action, reversible	NA	NA
Eptifibatide	P-glycoprotein IIb/IIIa inhibitor	2 hours	Immediate onset of action, reversible	NA	NA
Cangrelor	P2Y ₁₂ inhibitor	<10 minutes	Immediate onset of action, reversible	NA	NA

Abbreviations: ADP, adenosine diphosphate; ASA, acetylsalicylic acid; COX, cyclooxygenase; NA, not available; NSAID, nonsteroidal anti-inflammatory drug

clopidogrel can be done earlier than with ASA or other P2Y₁₂ inhibitors.³⁶

Perioperative management of patients who are receiving acetylsalicylic acid

The perioperative milieu related to surgery is thought to confer a prothrombotic and inflammatory state characterized by a rise in circulating platelet release products and thrombin generation, which may contribute to adverse cardiovascular events.³⁷ Additionally, sudden withdrawal of antiplatelet drugs in chronic users is thought to produce a rebound prothrombotic effect due to increased thromboxane A₂ synthesis and decreased fibrinolysis. Despite these theoretical considerations regarding perioperative platelet function, the putative beneficial effects of continuing (or initiating) antiplatelet therapy in the perioperative period, typically with ASA, only can be addressed through well-designed randomized trials.

Noncardiac surgery Three randomized trials have evaluated the benefits and risks of ASA continuation or discontinuation in the perioperative setting. One trial involving 290 patients who were receiving antiplatelet agents for secondary cardiovascular prevention were allocated to ASA, 75 mg/d, or placebo, starting 10 days prior to intermediate or high-risk noncardiac surgery.³⁸ There was no difference in major thrombotic or bleeding events within the first 30 days of surgery. Another trial of 220 patients evaluated starting ASA, 75 mg/d, or placebo 7 days before surgery, and continuing treatment for 30 days postoperatively in patients at high risk for cardiovascular disease.³⁹ This study showed a significant reduction in major adverse cardiovascular events in the ASA arm (1.8% vs 9.0%;

$P = 0.02$), but it was underpowered to detect differences in bleeding outcomes.

The most compelling findings are derived from the POISE-2 trial. In this study, 10 010 patients at risk for cardiovascular disease who were scheduled to have noncardiac surgery were randomized to perioperative aspirin ($n = 4998$) vs placebo ($n = 5012$).³⁵ Patients were stratified according to baseline ASA use as either initiation stratum (not taking ASA at baseline) or continuation stratum (taking ASA at baseline). In both strata, ASA, 200 mg, or placebo was administered just before surgery. Among those who had not been on aspirin previously, the study drug of ASA, 100 mg/d or placebo, was continued for 30 days after surgery (initiation stratum). Among those who were on aspirin previously, aspirin was stopped 1 week before surgery, the study drug was continued for 7 days after surgery, and then their usual aspirin therapy was resumed (continuation stratum). The perioperative use of ASA did not reduce the incidence of the composite primary outcome of nonfatal MI or death (7.0% vs 7.1%; hazard ratio [HR], 0.99; 95% CI, 0.86–1.2) but was associated with a statistically significant increased risk for major bleeding (4.6% vs 3.8%; HR, 1.2; 95% CI, 1.01–1.5). There was no effect on the outcomes of MI, life-threatening bleeding, stroke or mortality. The overall risk for bleeding was increased in patients who were receiving postoperative low-dose heparin prophylaxis, and it appeared to be correlated with the timing of postoperative ASA initiation, with the suggestion that delaying resumption for 7 to 8 days would allow the risk to diminish to that of ASA nonusers. It is noteworthy that only 4% of patients enrolled in POISE-2 had a coronary stent, an issue that is discussed below.

TABLE 3 Suggested perioperative management of antiplatelet therapy

Clinical situation	Suggested management
Patient on ASA alone having noncardiac surgery	• Interrupt ASA ~7 days before surgery in most patients; resume 5–7 days after surgery. • Continue ASA perioperatively in patients with coronary stents, while monitoring for bleeding.
Patient on ASA alone having CABG surgery	• Continue ASA around the time of CABG (withholding on day of surgery and 1–2 days postoperatively).
Patient with coronary stent on ASA + clopidogrel having noncardiac surgery	• Continue ASA around the time of surgery (withholding on day of surgery and 1–2 days postoperatively). • Hold clopidogrel for 5–6 days preoperatively and resume 1–2 days after surgery. • If recent coronary stent, continue both antiplatelet drugs and transfuse platelets if excessive bleeding.
Patient on ASA + clopidogrel having CABG surgery	• Continue ASA around the time of surgery (withholding on day of surgery and 1–2 days postoperatively). • Hold clopidogrel 5–6 days before surgery. • Resume ASA and clopidogrel 1–2 days after surgery.
Patient on ASA + ticagrelor and having noncardiac or CABG surgery	• Continue ASA around the time of surgery (withholding on day of surgery and 1–2 days postoperatively). • Hold ticagrelor for 2–3 days before surgery. • Resume ASA and ticagrelor 1–2 days after surgery.
Patient on ASA + prasugrel having noncardiac or CABG surgery	• Continue ASA around the time of surgery (withholding on day of surgery and 1–2 days postoperatively). • Hold prasugrel for 7–10 days before surgery. • Resume ASA and prasugrel 1–2 days after surgery.

Abbreviations: CABG, coronary artery bypass graft; others, see [TABLE 2](#)

Clinical guidance In patients who are receiving ASA and are at risk for cardiovascular events, we suggest interrupting ASA for ~7 days before noncardiac surgery and to resume ASA with caution postoperatively, especially if patients are receiving thromboprophylaxis with low-dose heparin. In patients not at risk for cardiovascular events, we suggest not initiating ASA in the perioperative period.

Cardiac surgery In a meta-analysis of 13 trials (2399 patients) assessing the continuation of ASA, preoperative ASA reduced the risk of MI (odds ratio [OR], 0.56; 95% CI, 0.33–0.96) without a reduction in mortality, but its use increased postoperative chest tube drainage, red cell transfusion, and need for surgical reexploration (OR, 1.85; 95% CI, 1.1–3.0).⁴⁰ The ATACAS trial (Aspirin and Tranexamic Acid for Coronary Artery Surgery) involved 2100 patients scheduled for elective CABG surgery who interrupted ASA 4 days before surgery and then were randomly allocated to receive ASA, 100 mg, or placebo, 1 to 2 hours preoperatively, with continuation within 24 hours postoperatively.⁴¹ ASA use had no significant effect on the incidence of MI (13.8% vs 15.8%; HR, 0.87; 95% CI, 0.71–1.1), bleeding requiring reoperation (1.8% vs 2.1%; HR, 0.87; 95% CI, 0.46–1.6),

or need for transfusion (43.9% vs 42.6%; HR, 1.0; 95% CI, 0.93–1.1).

One concern with this trial relates to the generalizability of findings since the approach used to stop ASA at least 4 days before CABG and administer a single dose just before surgery is not widely used. It is possible that a beneficial effect of ASA may have been shown, as in other non-randomized studies, by allowing a simpler ASA interruption for 7 to 10 days vs ASA continued (uninterrupted) design.^{2,10,42} Moreover, the close proximity of ASA administration to the surgery may not have been sufficient to allow a full antiplatelet effect.⁴³

Clinical guidance Until there is compelling evidence that perioperative continuation of ASA causes harm in patients having CABG surgery, it is reasonable to continue ASA without interruption in patients having elective CABG surgery.

Management of patients with a coronary stent who need elective surgery

The perioperative management of patients with a coronary stent typically centers around patients who are receiving dual antiplatelet therapy with ASA in combination with a P2Y₁₂ inhibitor, either clopidogrel, prasugrel, or ticagrelor. In terms of available evidence, there are no randomized control trials to compare different perioperative management strategies for patients with coronary stents who require elective surgery. Consequently, current management recommendations are weakened as they rely on observational studies or post hoc subanalyses of randomized trials.

Noncardiac surgery In general, the time interval between stent placement and noncardiac surgery appears to be a key determinant of perioperative risk for adverse cardiovascular events. Thus, in a retrospective single-center study of 1120 patients with coronary stents who had noncardiac surgery, the risk for major cardiac events was increased in the first year after stenting (OR, 2.6; 95% CI, 1.4–4.9) but not after 1 year had elapsed (OR, 0.89; 95% CI, 0.6–1.4).⁴⁴ In a linked administrative database study encompassing 20 590 patients with coronary stents and 41 180 controls without stents who underwent noncardiac surgery, the incidence of major adverse cardiovascular events was the highest in the initial 6 weeks after surgery but remained significantly higher than in the control group until 6 months postsurgery.²⁵ These results are expanded by those of a Danish study of 22 590 patients with drug-eluting coronary stents. In this study, 4303 patients with surgery within 1 year were frequency-matched by surgery type with 20 232 controls. It confirmed a higher rate of MI among patients who underwent surgery within 1 month (OR, 14.3; 95% CI, 7.5–27.4), but there was a strong effect modification if the surgery was emergent rather than elective (OR, 26.6; 95% CI, 11.2–62.8).⁴⁵ Together, these

studies suggest waiting at least 6 weeks and preferably 6 months after stent implantation before noncardiac surgery, and such guidance is consistent with clinical practice guidelines. A registry studied 880 patients who had percutaneous coronary intervention and subsequently underwent noncardiac surgery, in whom ASA and dual antiplatelet therapy were continued in approximately 70% and 10% of patients, respectively. In this study, 30-day rates of perioperative adverse cardiac and major bleeding events were 3.5% and 5.6%, respectively.

A key limitation of all these observational studies was that perioperative antiplatelet management was not defined, and a comparison between different management strategies was not feasible. The only data from a randomized trial that assessed perioperative antiplatelet drug management in stented patients is a post hoc subanalysis of POISE-2. In this study of 470 patients (4.7% of the entire study population) with a prior coronary stent implantation, perioperative ASA continuation reduced the absolute risk for the combined primary outcome of MI and death by 5.5% (HR, 0.50; 95% CI, 0.26–0.95), and reduced the absolute risk for MI by 5.9% (HR, 0.44; 95% CI, 0.22–0.87). Continuing ASA was associated with a 1.3% absolute risk in major and life-threatening bleeding, as in the overall study population, but the small sample studied was associated with wide confidence limits around this point estimate (ie, –2.6% to 5.2%).⁴⁶ Overall, in stented patients who are receiving dual antiplatelet therapy and are having noncardiac surgery, the perioperative increase in the risk of bleeding with ASA continuation appears to be modest and outweighed by the putative benefits of ASA continuation.

As for the management of the P2Y₁₂ inhibitor, there are no studies in a perioperative setting to inform whether it should be continued or interrupted, but there is evidence from nonperioperative settings that dual antiplatelet therapy confers a significant risk for bleeding, similar to that of anticoagulant therapy with warfarin, and this bleeding risk is likely to be magnified in a perioperative setting.

Clinical guidance In patients with coronary stents who require elective noncardiac surgery, we suggest delaying surgery for at least 3 months after stenting (at least 1 month after bare metal stent implantation). We suggest continuing ASA perioperatively, without interruption, and withholding ticagrelor for 2 to 3 days, clopidogrel for 5 to 6 days preoperatively, and prasugrel for 7 to 10 days preoperatively. After surgery, we suggest restarting the P2Y₁₂ inhibitor when surgical site hemostasis is secured.

Cardiac surgery Patients who are receiving dual antiplatelet therapy and require elective or semi-urgent CABG surgery pose a considerable challenge, especially after an acute coronary

syndrome, because of the high bleeding risk associated with CABG and the potentially serious consequences of bleeding (ie, pericardial tamponade). The ATACAS trial did not include patients who were receiving dual antiplatelet therapy and required urgent CABG, and the relevant available evidence is derived from observational studies. One registry study assessed 786 patients who required CABG surgery after an acute coronary syndrome and were receiving ASA and ticagrelor.⁴⁷ This study found that, compared with patients receiving only ASA, continuing ticagrelor up to the time of surgery or discontinuing its use <2 days before surgery conferred a higher risk of platelet transfusion (22.7% vs 6.4%) and bleeding (18.2% vs 5.9%), based on the E-CABG bleeding classification used in this study.⁴⁷ A retrospective cohort study assessed patients who, following an acute coronary syndrome, were receiving ASA and ticagrelor (n = 1266) or clopidogrel (n = 978) and required CABG surgery. Perioperative bleeding was decreased if either ticagrelor or clopidogrel were interrupted at least 3 days before surgery compared with a shorter interruption interval.⁴⁸ For ticagrelor, there was no increase in bleeding with an interruption lasting 3 to 5 days vs lasting more than 5 days (OR, 0.93; 95% CI, 0.53–1.6), whereas for clopidogrel an interruption interval lasting 3 to 5 days was associated with an increased risk for bleeding compared with an interruption lasting more than 5 days (OR, 1.7; 95% CI, 1.1–2.8). There are no studies assessing the optimal timing of prasugrel interruption before CABG surgery, but it is known to be more potent than ticagrelor and clopidogrel.

Clinical guidance We suggest continuation of ASA in all patients with a coronary stent who require CABG surgery. In patients with a coronary stent who are receiving a P2Y₁₂ inhibitor, we suggest interrupting ticagrelor for 2 to 3 days, interrupting clopidogrel for 5 to 6 days, and interrupting prasugrel for 7 to 10 days before CABG surgery.

Management of patients with a coronary stent who need urgent surgery

The management of patients who are receiving dual antiplatelet therapy and are undergoing urgent noncardiac surgery after recent (within 6 to 12 weeks) stent implantation is an infrequent but challenging clinical scenario. Related literature is limited to mainly retrospective case series.⁴⁹ A summation of this clinical experience encompasses 280 patients, in whom the mean time interval between stenting and surgery (cardiac, 50%; urgent, 40%) was 5.1 months. A mean duration of 5 days of bridging therapy was administered, mainly with a glycoprotein IIb/IIIa inhibitor (eptifibatide, 64%; tirofiban, 35%). Rates of adverse events were high for cardiovascular outcomes (4.6%; 95% CI, 2.5–7.3), stent thrombosis (1.3%; 95% CI, 0.3–3.0), major bleeding (7.4%; 95% CI, 2.8–14.1), and death (3.5%; 90% CI, 1.7–5.9). The management options for such patients are empiric and include

interrupting both antiplatelet drugs and administering an antiplatelet bridging agent. Antiplatelet bridging can be considered with cangrelor, an intravenous P2Y₁₂ inhibitor with a very short half-life (<10 minutes), which has been assessed in the setting of urgent CABG surgery as an antiplatelet bridging agent and can effectively maintain platelet inhibition during interruption of antiplatelet therapy.⁵⁰ Another management option, especially for selected high-bleeding-risk surgery types (eg, intracranial, spinal), may involve continuing dual antiplatelet therapy and administering a platelet transfusion just before the surgery to provide fully functional, uninhibited platelets to optimize hemostasis. One retrospective study assessed 181 patients managed using this approach, of whom 72 were receiving dual antiplatelet therapy; this study reported relatively high rates of perioperative adverse cardiac events (5.5%; 95% CI, 3.0–9.9), major bleeding (12.2%; 95% CI, 8.2–17.7%), and bleeding leading to reoperation (6.6%; 95% CI, 3.8–11.2%), but there were no episodes of stent thrombosis.^{51,52} Additional studies are needed to explore this and other bridging-related management options.

Return to the clinical scenarios **Case 1** This patient is undergoing a low-bleeding-risk surgery but is not at high risk for coronary ischemia. An approach based on the POISE-2 trial where ASA is interrupted for 5 to 7 days before surgery and resumed 2 to 3 days after surgery, when hemostasis is secured, is reasonable. Low-dose heparin thromboprophylaxis is not administered as the patient is ambulatory and, otherwise, is at low risk for venous thromboembolism.

Case 2 In this clinical setting, surgical resection of the lung cancer can be life-saving and should be performed as soon as possible. Given the patient has a single stent and no prior coronary events, a 4-week interval between stenting and surgery appears sufficient to mitigate the risk for recurrent coronary events. The suggested management is to continue ASA uninterrupted (including on the day of surgery) and interrupt clopidogrel 4 to 5 days before surgery. In patients with a higher-risk stent status (eg, multiple recent stents, ostial location), an alternative approach would be to interrupt clopidogrel 5 days before surgery and administer intravenous bridging with intravenous glycoprotein IIb/IIIa inhibitor (or intravenous unfractionated heparin if inexperienced with IIb/IIIa inhibitors) until 3 to 4 hours before the time of surgery. Postoperatively, the high bleeding risk precludes the resumption of the glycoprotein IIb/IIIa inhibitor. Clopidogrel is resumed on the second postoperative day when hemostasis is secured. Low-dose heparin is also started on the first postoperative day, administered for at least 7 to 10 days and possibly for 30 days given the thrombosis risk associated with such cancer surgery.

Case 3 Assuming the patient is clinically stable, with no further acute coronary events, CABG surgery is delayed for 3 days to allow the effect of ticagrelor to recede and the patient proceeds to surgery. Ticagrelor is resumed 2 days after surgery when hemostasis is secured. The patient also receives postoperative low-dose heparin, starting on the first postoperative day until discharge from hospital.

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