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Abstract

Management of antiplatelet agents in the perioperative setting is a common clinical challenge. Although discontinuation of aspirin therapy in patients who are taking aspirin for primary or secondary prevention is common, premature cessation of antiplatelet therapy in a patient with a prior drug-eluting stent is the single most important predictor of stent thrombosis, which carries a high morbidity and mortality. Therefore, these patients should ideally continue their antiplatelet therapy throughout surgery. However, this approach to reducing the risk of stent thrombosis must be counterbalanced by the increased risk of surgical bleeding. Multiple factors require evaluation to appropriately balance the risk of stent thrombosis against the risk of surgical bleeding. These include the type and timing of surgery, type and location of coronary stents if present, extent of coronary artery disease, and patient-specific risk factors. In general, for patients with coronary stents, all elective surgeries should be delayed until dual antiplatelet therapy is no longer crucial. Most surgical procedures may be performed on aspirin with acceptable risk of bleeding.

Keywords

Antiplatelet agents • Perioperative • Stent thrombosis • Coronary stents • Surgical bleeding • Percutaneous coronary intervention

Management of antiplatelet agents in the perioperative setting is a challenging clinical dilemma. Antiplatelet agents are widely prescribed in primary and secondary prevention of various cardiovascular diseases such as coronary artery disease (CAD), peripheral arterial disease (PAD), and cerebrovascular disease. Antiplatelet therapy also plays a key role in the management of acute coronary syndromes (ACS).

However, their use becomes of paramount importance in patients who have undergone percutaneous coronary intervention (PCI) with stent insertion. In these patients, maintenance of dual antiplatelet therapy (DAPT) is essential for the prevention of stent thrombosis (ST), a catastrophic complication that carries a high morbidity and mortality.

It is estimated that 5 % of patients undergoing PCI will need surgery within 12 months after stent insertion, and 40 % of cases of ST occur in the perioperative setting, often when DAPT is held [1, 2]. Although antiplatelet agents are associated with an increased risk of surgical hemorrhage, the risk of preoperative cessation of antiplatelet drugs may outweigh the risk of surgical bleeding. Therefore, the routine practice of cessation of antiplatelet agents to avoid excess bleeding in patients undergoing surgical procedures should be avoided, and each patient must be managed on a case-by-case basis by balancing the risk of ST against the risk of bleeding.

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heals by neointimal formation within 2–6 weeks after placement of a bare-metal stent (BMS) [8]. This healing process may be associated with intimal hyperplasia that leads to in-stent restenosis in approximately 16–32 % of cases after BMS [9, 10]. In order to reduce the rate of restenosis, drug-eluting stents (DES) were introduced in 2002. Despite their success in reducing the rate of in-stent restenosis to less than 10 %, the recognition of late and very late ST following DES placement raised many concerns regarding their safety [11]. When a DES is used, re-endothelialization and neointimal healing are delayed resulting in prolonged exposure of thrombogenic stent struts to blood facilitating platelet adherence, aggregation, and thrombus formation within the DES [8, 12]. Complete healing of a DES may take years during which time there is an ongoing risk of late and very late ST [13]. Available data suggest about a 0.6 % incremental risk of ST with DES compared to BMS [14].

According to the 2011 American College of Cardiology Foundation/American Heart Association/Society of Cardiovascular Angiography and Interventions (ACCF/AHA/SCAI) guidelines for PCI, aspirin should be continued indefinitely, and a P2Y₁₂ inhibitor should be given for at least 1 month and up to 12 months after PCI with a BMS and for at least 12 months after PCI with DES [15]. The 2011 updated guidelines for the management of UA/NSTEMI add that in patients with clinical features associated with an increased risk of ST, such as diabetes or renal insufficiency or procedural characteristics such as multiple stents or a treated bifurcation lesion, extension of DAPT beyond 12 months may be reasonable in patients with DES [16].

Stent Thrombosis

Stent thrombosis is a sudden and potentially catastrophic complication after PCI. It usually manifests as an acute MI, generally with ST-segment elevation, malignant arrhythmia, or death. Adding P2Y₁₂ inhibitors to aspirin is the standard of care after PCI with stent insertion as it reduces the rate of early stent thrombosis from 3.5 % with aspirin alone to 0.5 % with DAPT [17]. Although the optimal duration of DAPT is yet to be determined in patients with DES, available data suggest that long-term use of DAPT beyond 12 months may be reasonable for the prevention of very late stent thrombosis [16, 18].

Several risk factors for stent thrombosis with DES have been described (Table 37.2) [8, 19–23]. Early stent

Table 37.2 Risk factors for stent thrombosis in patients with drug-eluting stents (DES)

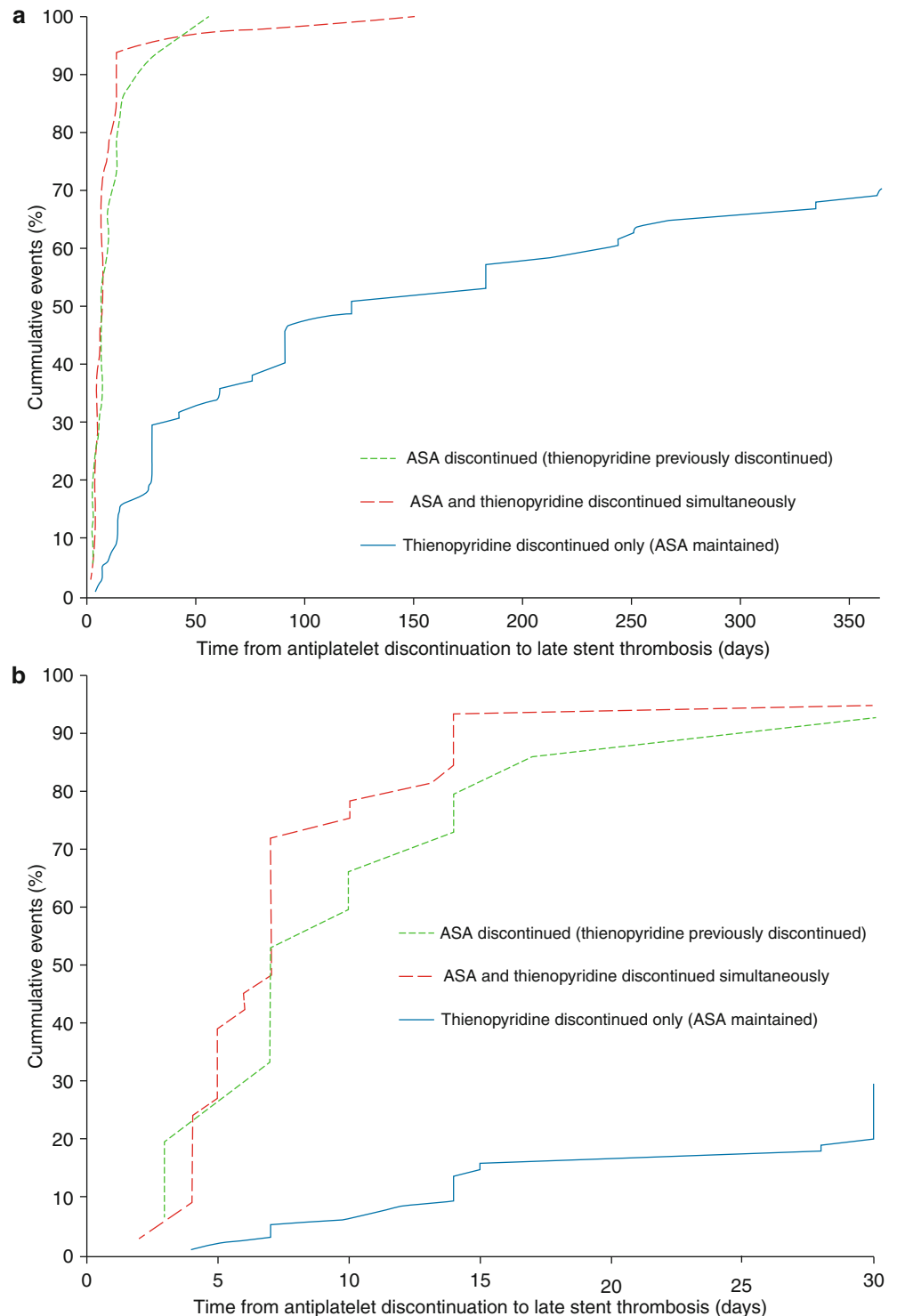
Acute coronary syndrome
Reduced left ventricular ejection fraction
Diabetes mellitus
Renal insufficiency
Hypercoagulable states (e.g., malignancy, surgery, diabetes)
Residual dissection
Incomplete stent apposition or under-expansion
Side branch occlusion
Left main coronary artery stent
Bifurcation
Long and narrow lesions
In-stent restenosis
Multivessel disease
Bypass graft
Stent surface
Hypersensitivity to polymer
Cessation of antiplatelets
Antiplatelet resistance

Adapted from references [8, 19, 21–23]

thrombosis and subacute stent thrombosis are thought to be related to procedure-related factors. In contrast, the single most important predictor of late and very late stent thrombosis is the premature cessation of DAPT [2, 19, 24, 25].

It is estimated that 5 % of patients with coronary stents will undergo a surgical procedure within the first year after PCI [1]. Furthermore, it has been reported that up to 40 % of cases of stent thrombosis with DES occur in the perioperative setting, commonly after the cessation of antiplatelet agents [2]. The increased rate of stent thrombosis in patients undergoing surgery early after PCI (<6 weeks with BMS and <12 months with DES) is likely related to the combination of a postoperative hypercoagulable state with decreased fibrinolysis, superimposed on the prothrombotic milieu of the delayed endothelialization of the stent [26]. In addition, cessation of antiplatelet agents likely triggers a rebound increase in platelet aggregation [27]. In patients with DES, discontinuation of DAPT has been associated with a 90-fold increase in ST and a mortality of 45 % [19]. A 9-fold increase in mortality has been demonstrated if thienopyridines are discontinued within the first 30 days of DES insertion [29]. ST has been shown to occur at a median of 7 days after cessation of DAPT. However, in patients maintained on aspirin with only thienopyridines discontinued, the median time to a coronary event was 122 days (Fig. 37.2) [31].

Fig. 37.2 Cumulative proportion of late stent thrombosis cases among patients who discontinued antiplatelet therapy [31]. (a) Within 1 year of discontinuing antiplatelet therapy. (b) Within 30 days of discontinuing antiplatelet therapy. Abbreviations: ASA acetylsalicylic acid



Perioperative Bleeding with Antiplatelet Therapy

Surgical Bleeding in Patients on Aspirin

A meta-analysis of 50,000 patients undergoing noncardiac surgery demonstrated that continuation of aspirin led to a 50 % increase in the risk of bleeding. However, this

increased risk did not translate to a higher level of the severity of bleeding complications except in intracranial surgery and, possibly, transurethral resection of the prostate (TURP) [30]. Moreover, withdrawal of aspirin was associated with a higher incidence of cardiac, cerebral, and peripheral vascular events. In a randomized controlled trial of 220 patients undergoing surgery, maintenance of aspirin was associated with a 7.2 % reduction of acute MI, cardiac

arrest, severe arrhythmia, or cardiovascular death within the first 30 postoperative days without an increase in bleeding complications [32].

In general the use of aspirin in dental surgery, anterior chamber ophthalmic surgery, dermatologic surgery, biopsies, and visceral surgery is not associated with an increased risk of bleeding complications or fatal bleeding [30]. Similarly, in patients undergoing gastrointestinal endoscopic procedures including biopsies and polypectomies, the use of aspirin alone has not been associated with an increased risk of bleeding [33]. In urologic surgery, initial reports suggested an increased risk of bleeding in patients undergoing TURP if aspirin was maintained [34]. However, more recent prospective and retrospective studies indicate that even though bleeding following TURP and transrectal prostate biopsy is increased, it is not associated with a need for blood transfusions, particularly if a laser was used [35, 36]. Studies evaluating bleeding in the setting of nephrectomy or radical prostatectomy are lacking. However, the use of robot-assisted radical prostatectomy and nephrectomy on aspirin is not associated with an increased risk of bleeding [37, 38]. In orthopedic surgery, the use of antiplatelet agents has not been associated with significant surgical morbidity or mortality except in orthopedic spinal surgery [30, 39]. In peripheral vascular surgery, aspirin use is associated with increased non-fatal bleeding but a decrease in perioperative mortality [40].

Surgical Bleeding in Patients on DAPT

The effect of DAPT on surgical bleeding has been most studied in cardiac surgery. Low-dose aspirin is associated with a low risk of excessive bleeding following coronary artery bypass surgery [41]. However, the addition of a thienopyridine to aspirin results in a significant increase in bleeding, blood product transfusion, ventilation requirements, length of hospital stay, and surgical re-exploration [42]. For this reason, the American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) guidelines recommend that in patients undergoing coronary artery bypass surgery, P2Y₁₂ inhibitors should be withheld at least 5 days and up to 7 days prior to surgery unless the urgency of revascularization outweighs the risks of excess bleeding [18, 43].

Individual reports describe significant and even fatal postoperative hemorrhage with DAPT after vascular, orthopedic, and even endoscopic procedures [44–46]. However, larger studies demonstrate that, even though there is an increase in surgical bleeding and transfusion requirements, there is no change in mortality or surgical outcome [1, 28, 39, 47]. In transbronchial biopsy, the use of DAPT has been associated with significant bleeding in all cases. However, none of these bleeding events were fatal or required transfusions [45]. The use of clopidogrel is contraindicated in regional spinal or epidural anesthesia due to the risk of significant hematomas and spinal cord compression [48]. A prospective study evaluating

patients with coronary stents undergoing noncardiac surgery demonstrated a major adverse cardiac event (MACE) rate of 10.9 % and a bleeding complication rate of 9.5 % [49]. Complete cessation of antiplatelet agents was an independent predictor of MACE, whereas the use of antiplatelet agents was not a predictor of bleeding complications.

Collectively the data suggest that most surgical procedures can be performed at low risk on aspirin and potentially on DAPT and that the increased risk of perioperative hemorrhage is not necessarily associated with worsened morbidity, mortality, or surgical outcome. Therefore, the risk of stopping antiplatelet agents in patients with coronary stents might outweigh the risk of continuing them, particularly in high-risk patients.

Strategies for Perioperative Management of Antiplatelet Agents in Patients with Coronary Stents

Any decisions regarding the perioperative management of antiplatelet agents is based on a limited body of evidence. Management of these patients requires an individualized, multidisciplinary approach by the patient's cardiologist, surgeon, and anesthesiologist. The approach should take into consideration the type of surgery and its bleeding risk, the CAD burden and ischemic risk, the timing of surgery after an event or after PCI, if a DES was used or not, and the presence of concomitant risk factors of ST. Subsequently, the risk of surgical bleeding (Table 37.3) [39] should be weighed against the estimated risk of ST (Fig. 37.3).

Table 37.3 Hemorrhagic risk with noncardiac surgery

Surgical hemorrhagic risk	Type of surgery
<i>Low</i>	
Blood transfusion usually not required	Peripheral Plastic Biopsies Endoscopy Minor orthopedic Minor otolaryngologic Ophthalmic (anterior chamber) Dental
<i>Intermediate</i>	
Blood transfusion frequently required	Visceral Vascular Major orthopedic Major otolaryngologic Reconstructive Urology
<i>High</i>	
Possible bleeding in a closed space	Intracranial neurosurgery Spinal canal surgery Ophthalmic (posterior chamber)

Data adapted from Chassot et al. [39]

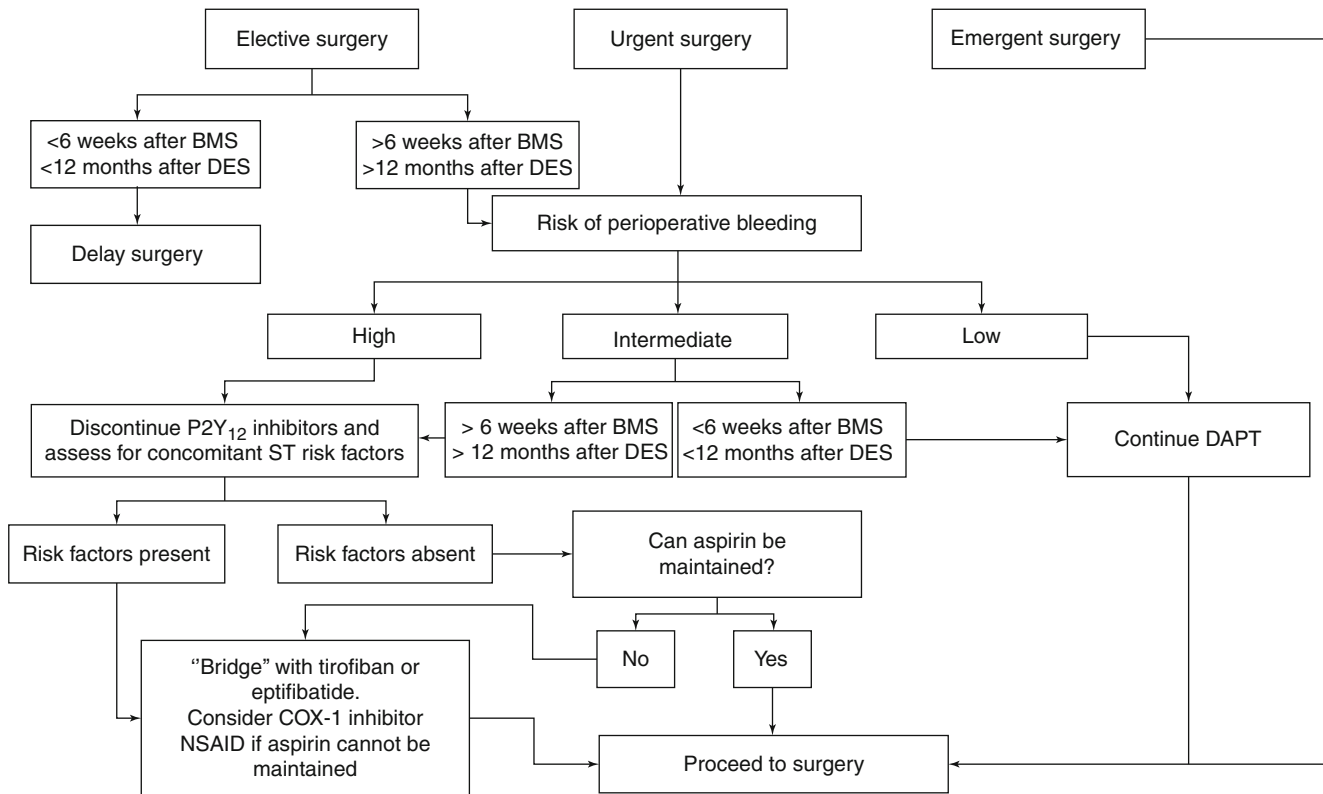


Fig. 37.3 Algorithm of perioperative management of patients with coronary stents [66]. Abbreviations: *COX* cyclooxygenase, *BMS* bare-metal stents, *DES* drug-eluting stent(s), *NSAID* nonsteroidal

anti-inflammatory drug, *ST* stent thrombosis, *DAPT* dual antiplatelet therapy

Aspirin and P2Y₁₂ Inhibitor Throughout Surgery

American and European Cardiology Society guidelines recommend delaying all elective surgical procedures until the duration of DAPT is completed (Table 37.4) [18, 50–56]. Therefore, as a general approach, all elective procedures should be delayed at least 4–6 weeks after PCI with BMS and 12 months after PCI with DES. According to the 2009 ESC guidelines for preoperative cardiac risk assessment and perioperative cardiac management in noncardiac surgery, elective surgery should be delayed for a minimum of 6 weeks and optimally 3 months after a BMS [52]. However, if surgery cannot be delayed due to urgency, then maintenance of DAPT is of paramount importance as the risk of ST is significantly increased. The 2011 ESC guidelines on the management of non-ST elevation acute coronary syndrome (NSTEMACS) state that most surgical procedures can be performed under DAPT or at least aspirin alone with acceptable rates of bleeding and that surgeons should be encouraged to operate under DAPT if bleeding risk is low or moderate [18]. This applies to most surgical procedures, except those in cases in which bleeding can occur in a

closed space and could be catastrophic, such as intracranial, spinal, and posterior-chamber ophthalmic surgeries (see Table 37.3).

Discontinue P2Y₁₂ Inhibitor and Maintain Aspirin

The 2011 ESC guidelines for the management of NSTEMACS state that interruption of DAPT for urgent surgical procedures 1 month after ACS while continuing aspirin in patients *without* a DES may be reasonable [18]. Similarly, in patients *with* a DES without concomitant risk factors of ST undergoing surgery more than 12 months after PCI, P2Y₁₂ inhibitors may be safely discontinued 5–7 days prior to surgery while maintaining aspirin. If risk factors of ST are present and the risk of perioperative bleeding is significantly high, then P2Y₁₂ inhibitors may be discontinued while aspirin is maintained, understanding that the patient is at increased risk of postoperative ST. Following surgery, P2Y₁₂ inhibitors should be started once the risk of bleeding is felt to be sufficiently low (ideally within the first 24 h) with a loading dose of either clopidogrel 300–600 mg,

Table 37.4 Summary of guidelines for perioperative management of antiplatelet agents in patients with coronary stents

Guidelines	BMS	DES	Bleeding risk necessitating AP cessation
2007 ACC/AHA guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery [50]	Delay elective surgery for at least 4–6 weeks After 6 weeks proceed on aspirin	Delay elective surgery for at least 12 months After 12 months proceed on aspirin	Aspirin should be maintained if thienopyridines are discontinued and should be restarted as soon as possible Resuming DAPT perioperatively 12 m after PCI should be considered if risk factors of ST are present No evidence for use of warfarin, antithrombotics, or GP IIb/IIIa inhibitors
2007 ACC/AHA/SCAI/ACS/ADA Science advisory on prevention of premature discontinuation of DAPT in patients with coronary stents [51]	Delay elective procedures at least 1 month	Delay elective procedures at least 12 months	Aspirin should be maintained if thienopyridines are discontinued and should be restarted as soon as possible
2009 ESC guidelines for preoperative cardiac risk assessment and perioperative cardiac management in noncardiac surgery [52]	Delay elective surgery for at least 6 weeks and optimally for 3 months (Class I) After 3 months proceed on aspirin (Class I)	Delay elective surgery for at least 12 months After 12 months proceed on aspirin	Discontinue AP 5 days and optimally 10 days prior to surgery If surgery is urgent, transfusion of platelets or pro-hemostatic agents is recommended Resume AP within 24 h
2011 ESC guidelines for the management of ACS without persistent ST-segment elevation [18]	Interruption of DAPT after 1 month may be reasonable	If bleeding risk is low or moderate, surgeons should be encouraged to operate on DAPT	Discontinue clopidogrel or ticagrelor 5 days prior to surgery Discontinue prasugrel 7 days prior to surgery Bridging with GP IIb/IIIa inhibitors is not considered evidence-based yet
2011 Canadian Cardiovascular Society guidelines on the use of antiplatelet therapy [53]	Delay elective surgery for at least 6 weeks (Class I) If urgent surgery continue DAPT (Class I)	Delay elective surgery for at least 12 months (Class I) If urgent surgery continue DAPT (Class I)	Discontinue clopidogrel 7–10 days prior to surgery
2012 ACCP Perioperative management of antithrombotic therapy [55]	Delay elective surgery for 6 weeks If within 6 weeks continue DAPT	Delay elective surgery for 6 months (12 months in 2008 guidelines [54]) If within 6 months continue DAPT	Use of bridging with GP IIb/IIIa inhibitors is inadvisable due to lack of evidence
2010 Cardiac Society of Australia and New Zealand guidelines for the management of antiplatelet therapy in patients with coronary stents undergoing noncardiac surgery [63]	Delay elective surgery for at least 6 weeks and ideally for 3 months	Delay elective surgery for at least 12 months	Patient with high risk of ST requires monitored clinical setting in a facility with 24/7 PCI capacity Bridging with GP IIb/IIIa and heparin should be considered in high-risk patients
2006 Perioperative management of antiplatelet agents in patients with coronary stents: recommendations of a French Task Force [56]	Delay elective surgery for at least 4–6 weeks	Delay elective surgery for at least 6–12 months If within 6–12 months, continue DAPT	Discontinue DAPT 5–10 days before surgery Consider using another NSAID such as flurbiprofen (50 mg × 2, withdrawn 24 h before surgery) or LMWH (85–100 IU aXa per KG for 12 h)

Abbreviations: *BMS* bare-metal stent, *DES* drug-eluting stent, *DAPT* dual antiplatelet therapy, *ACC* American College of Cardiology, *AHA* American Heart Association, *ESC* European Society of Cardiology, *SCAI* Society of Cardiovascular Angiography and Interventions, *ACS* American College of Surgeons, *ADA* American Dental Association, *ACCP* American College of Chest Physicians, *PCI* percutaneous coronary intervention, *NSAID* nonsteroidal anti-inflammatory drug, *AP* antiplatelet, *LMWH* low-molecular-weight heparin

prasugrel 60 mg, or ticagrelor 180 mg. Short-term discontinuation of thienopyridines has been shown to be relatively safe if aspirin is maintained; however, the risk of ST remains elevated [31].

“Bridging Therapy” with Glycoprotein IIb/IIIa Inhibitors

Glycoprotein (GP) IIb/IIIa inhibitors act by blocking fibrinogen-mediated cross-linking of platelets, thereby inhibiting platelet aggregation [57]. Abciximab causes a prolonged irreversible antagonism of GP IIb/IIIa leading to platelet aggregation inhibition that lasts for at least 48 h and up to 7 days and therefore should not be used perioperatively [58]. The synthetic peptides eptifibatid and tirofiban are competitive, reversible binders to GP IIb/IIIa receptors and dissociate rapidly. Their half-life is quite short, and platelet function is completely restored 2–4 h after stopping the infusion, making them potentially suitable for perioperative use [59].

Even though GP IIb/IIIa inhibitors have not been studied extensively in the perioperative setting, their successful use as a “bridge” when P2Y₁₂ inhibitors are stopped before surgery has been reported [60–62]. Two small series of patients, at high risk of both ST and surgical bleeding, demonstrated that bridging with eptifibatid was associated with a favorable postoperative outcome without increased perioperative hemorrhage [61, 62]. Perioperative bridging with tirofiban was evaluated in another prospective study of 30 patients undergoing high bleeding risk surgery within 1–12 months after PCI with DES. There were no MACE, and major bleeding was observed in two patients who did not require surgical re-exploration [60].

For patients with coronary stents who are at an increased risk of perioperative bleeding and a significant risk of ST (e.g., early after PCI) but who require surgery, bridging therapy with aspirin and a GP IIb/IIIa inhibitor could be considered, although limited data exist in support of this strategy. This entails stopping P2Y₁₂ inhibitors 5–7 days before surgery and admitting the patient to the hospital 2–4 days before surgery to begin tirofiban or eptifibatid which is discontinued 6 h before surgery. Importantly, the increased bleeding risk associated with GP IIb/IIIa inhibitor treatment also has to be considered.

Even though this strategy is not practical in most cases and is not considered evidence-based yet, it might be worthwhile in patients at extremely high risk of stent thrombosis. According to the 2010 Cardiac Society of Australia and New Zealand guidelines for the management of antiplatelet therapy in patients with coronary stents undergoing noncardiac surgery, bridging with GP IIb/IIIa inhibitors and heparin can be considered in high-risk patients [63].

Discontinue Aspirin and P2Y₁₂ Inhibitors and Consider Alternatives

If the risk of surgical bleeding is potentially catastrophic or fatal, such as in intracranial, spinal, and posterior-chamber ophthalmic surgeries, aspirin cessation might be necessary. In these cases aspirin and P2Y₁₂ inhibitors should be discontinued 5–7 days before surgery. Given the increased risk of ST with cessation of antiplatelet agents, intensive perioperative monitoring and early interventions are of paramount importance. Moreover, dual antiplatelet therapy should be reintroduced once the risk of hemorrhage is diminished.

Heparin has been considered as a substitute to aspirin or P2Y₁₂ inhibitors. However, heparin is an antithrombin agent, rather than an antiplatelet agent. The use of unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) has been proposed in the perioperative management of patients with coronary stents [64]. However, data on perioperative heparin use suggest increased mortality [1]. In addition, abrupt cessation of UFH may be associated with a rebound hypercoagulable state [65]. Finally, since ST is a platelet-mediated process, it is expected that antithrombin agents such as UFH and LMWH would not be ideal agents.

Management of Postoperative Stent Thrombosis

Given that ST most often presents as an STEMI, the most appropriate management is early reperfusion therapy. Since thrombolytic therapy is contraindicated postoperatively, due to the excessive bleeding risk, primary PCI is the treatment of choice for perioperative ST.

Conclusion

Management of antiplatelet agents in the perioperative setting remains a common clinical challenge. Premature cessation of antiplatelet therapy is the single most important predictor of ST, which carries a high morbidity and mortality, particularly in the perioperative setting. Therefore, patients ideally should continue their antiplatelet medications throughout surgery to reduce the risk of ST. However, this reduction is accompanied by an increased risk of surgical bleeding. All elective surgeries should be delayed until DAPT is no longer crucial. Most surgical procedures may be performed on aspirin with an acceptable risk of bleeding. However, if the bleeding risk is unacceptable on oral antiplatelets, then bridging with a GP IIb/IIIa inhibitor could be considered.

Key Points

- All patients with CAD should receive aspirin indefinitely, and a P2Y₁₂ inhibitor (clopidogrel, prasugrel, or ticagrelor) should be added and maintained for at least 1 month and up to 12 months after BMS insertion and for at least 12 months after DES insertion that may be extended beyond 12 months in patients with increased risk of ST.
- All elective surgical procedures should be delayed until the duration of DAPT is completed (at least 1 month after PCI with BMS and 12 months after PCI with DES).
- If surgery cannot be delayed due to urgency, then maintenance of DAPT is of paramount importance for the prevention of ST.
- Most surgical procedures can be performed under DAPT or at least aspirin alone with acceptable rates of bleeding.
- Interruption of DAPT for necessary surgical procedures 1 month after ACS in patients without a DES may be reasonable.
- In patients with DES without concomitant risk factors of ST undergoing surgery more than 12 months after PCI, P2Y₁₂ inhibitors may be safely discontinued 5–7 days prior to surgery while maintaining aspirin.

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