

Perioperative Management of Patients with Coronary Artery Stents

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In the United States, approximately 2000 cardiology catheterization laboratories perform an average of one million stent procedures per year with 1.5 stents per patient. The volume of stent placements increase by 5% to 8% each year. Today stents can be deployed in native coronaries, in saphenous vein grafts, or in internal mammary grafts. Since 10% of the population receives a surgical procedure each year, the anesthesiologist may frequently encounter patients with coronary stents. This issue of *Anesthesiology Rounds* discusses the management of patients with previously implanted coronary stents who present for noncardiac surgery. The balance between stent thrombosis or restenosis and increased risk of perioperative bleeding requires the comprehensive involvement of the patient, the surgeon, the cardiologist, and the anesthesiologist.

INTRODUCTION

Since the first percutaneous coronary intervention (PCI) took place in San Francisco in 1977,¹ interventional cardiology has made remarkable progress. Initially, percutaneous transluminal coronary angioplasty (PTCA) involved the placement of a balloon-tipped catheter into a narrowed coronary artery, the inflation of the balloon and a subsequent flattening of the plaque, followed by balloon deflation and catheter withdrawal. Emergent coronary artery bypass grafting (CABG) was needed in 14% of cases, as the success rate of PTCA was only slightly above 60% in the beginning.² Balloon dilation can be considered as a surgical trauma,³ since it involves the alteration of atheromatous plaque, endothelial exposure, platelet and fibrin accumulation, elastic recoil, and postinjury arterial constriction (negative remodelling).^{4,5} These mechanisms explain the 2 major limitations of PTCA: acute vessel closure and restenosis.⁶ In 6%-8% of cases, acute vessel closure occurs within 24 hours of the procedure,⁶ which exposes patients to acute myocardial infarction (MI), emergent CABG, and death. On the other hand, restenosis tends to occur in the first 6 months following the procedure; the inflammatory response generated by the initial controlled injury induces fibroblast activation and scar formation.⁷ Potential contraction of this scar may create negative remodelling and restenosis;⁷ restenosis is defined as a post-procedural decrease in luminal diameter of >50%.⁸ The occurrence of restenosis varies from 30%-50% and tends to occur more frequently following saphenous-vein graft angioplasty.⁹

BARE-METAL STENTS (BMSs)

The first human coronary stents following PTCA were used in 1986, in Toulouse and Lausanne,¹⁰ to provide mechanical support for offsetting elastic recoil during PTCA. In 1993, coronary stents were introduced in the United States (US) to treat acute and imminent vessel closure following PTCA.¹¹ With confirmation of significant improvements in clinical outcomes by randomized, controlled trials, these stents were accepted as a standard of care and also approved for elective use in the US. Several years later, 84.2% of all interventions involved stent insertion,¹² but with acute (<24 hours) and subacute (24 hours-30 days) stent thrombosis rates at 16%-24%,

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aggressive anticoagulation regimens were implemented.¹³ In 90% of patients, stent thrombosis presents as a ST-segment elevation MI (STEMI) and 20% of them die.¹⁴ Two practices helped to decrease the high incidence of thrombosis in BMSs:

- use of intravascular ultrasound to perfectly localize the lesion and high balloon pressures to improve stent placement against the vessel wall
- institution of “dual-antiplatelet” therapy with clopidogrel and acetylsalicylic acid (ASA) as the new standard of therapy.^{15,16}

The thienopyridines (clopidogrel, ticlopidine) and ASA inhibit platelet activation and aggregation by different mechanisms. Thienopyridines inhibit the adenosine diphosphate (ADP) pathway to reduce ADP-mediated activation of glycoproteins (GPs) IIb/IIIa and Ia/IIa responsible for platelet aggregation, and prevent fibrinogen binding to GPIIb/IIIa.¹⁷ On the other hand, ASA irreversibly binds the enzyme cyclooxygenase-1 to prevent the conversion of the prostaglandin intermediate, PGH₂, into thromboxane A₂ (TxA₂), which is a potent vasoconstrictor and platelet agonist.¹⁸ A single dose of 160 mg ASA completely inhibits platelet TxA₂ production.¹⁸ Dual anticoagulation with clopidogrel and ASA beyond 30 days after PCI has been shown to decrease the combined risk of death, MI, and stroke by 26.9% at 1 year as opposed to ASA alone.¹⁹ The current anticoagulation regimen for BMS implantation involves an initial dose of clopidogrel 300-600 mg and ASA 325 mg several hours before the intervention. Then, ASA 75-325 mg and clopidogrel 75 mg are prescribed daily for 4-6-weeks to allow for stent endothelialization.²⁰ Patients remain on ASA for lifelong prophylaxis.²¹

Despite the major improvements related to BMS, they are still associated with a 20%-25% stenosis rate within 6 months of implantation;²² complex lesions and certain comorbidities increase this rate to ~80%.²³ The restenotic phenomenon can be explained by an exaggerated proliferative response by the media and adventitia (neointimal formation) to the trauma created by stent deployment.²⁴ Restenosis peaks at 3 months, reaches a plateau between 3 and 6 months, but may persist beyond 1 year after stent implantation.²⁵ In patients suffering in-stent restenosis, 35% will present with an acute coronary syndrome requiring an intervention in 12%-20% of cases.²⁶

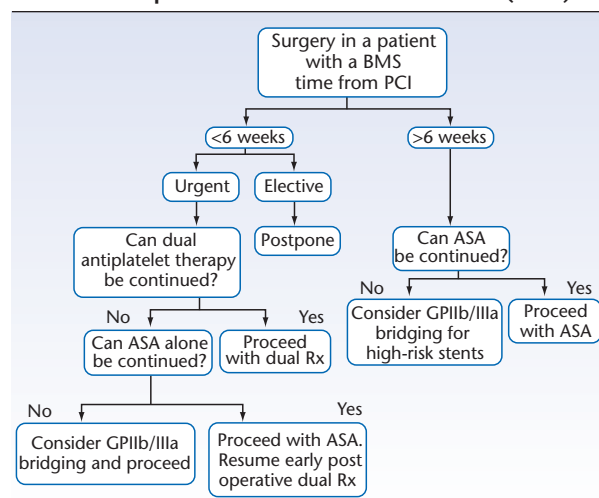
DRUG-ELUTING STENTS (DESs)

DESs were created in an attempt to prevent neointimal hyperplasia (medial hyperproliferation) and restenosis.²⁶ DESs are simply BMSs coated with an antiproliferative substance: sirolimus (macrolide antibiotic; cytostatic) or paclitaxel (antineoplastic agent; cytotoxic), which prevent vascular smooth-cell migration and proliferation.¹⁷ In comparison

with BMSs, DESs were demonstrated to effectively reduce neointimal hyperplasia, restenosis, and re-intervention at 6-12 months;²⁷ they were even shown to decrease restenosis rates by 74% at 4 years.^{28,29} By 2005, 85% of all stents implanted in Europe and the US were DESs.³⁰ Despite the advantages of DESs over BMSs concerning restenosis, concerns have been raised about stent thrombosis with DES. The overall risk of DESs thrombosis ranges from 0.5% to 3.1%,³¹ and stent thrombosis can have dramatic consequences, with very high rates of MI and death.³² DESs and BMSs have demonstrated similar acute and subacute thrombosis rates,³³ and late (30 days to 12 months) and very late (>1 year) stent thrombosis occurs with both BMSs and DESs, but the mechanisms are different.³⁴ Primary thrombosis is responsible for the occlusion of DESs, while BMS obstruction is more related to target lesion revascularization.³⁴ At 6 months, experimental models of DES revealed hypersensitivity reactions such as incomplete healing, fibrin deposition, and inflammatory cells.³⁵ Sirolimus and paclitaxel disturb endothelial function within the stent and in the distal coronary artery, delaying arterial healing and for an unknown period of time creating a pro-thrombotic environment.³⁶ Sirolimus has even been demonstrated to directly activate platelets and to induce local platelet aggregation, thus contributing to local clot formation.³⁷

Several predictors of DES thrombosis have been identified: premature or standard discontinuation of antiplatelet therapy, stenosis on other coronary arteries, left-ventricular ejection fraction $\leq 30\%$, coronary bifurcation stents, renal insufficiency, and diabetes.³⁸ Premature discontinuation of clopidogrel remains the strongest independent risk factor of stent thrombosis in a multivariate analysis.³⁹ Observations indicate that continuation of clopidogrel use at 6, 12, and 24 months is associated with a significantly lower incidence of cardiac death and MI compared with patients who stopped clopidogrel at 6 or 12 months.⁴⁰ In addition, off-label indications for DES implantation – which are present in 60% of patients undergoing a DES procedure – increase the frequency of stent thrombosis.⁴¹ The current Food and Drug Administration (FDA)-approved indications for DES use are the following: single *de novo* lesion in a native coronary artery in patients with stable coronary artery disease (CAD); sirolimus 2.5-3.5 mm reference vessel diameter, ≤ 30 mm long; and paclitaxel 2.5-3.75 mm reference vessel diameter, ≤ 28 mm long.⁴² Advanced age, acute coronary syndrome, low ejection fraction, and long stent length, among others, are considered off-label indications.⁴² At 1 year, the composite of death and MI occurred in 17.5% of cases with off-label use versus 8.5% in approved use cases.⁴³

FIGURE 1: Suggested algorithm for the management of patients with a bare metal stent (BMS)⁴⁵



PCI = percutaneous coronary intervention; ASA = acetylsalicylic acid; Rx = therapy; GP = glycoprotein

The importance of 12-month dual-antiplatelet therapy and life-long ASA therapy after DES implantation has been emphasized. However, the ideal duration of dual-antiplatelet therapy remains unknown and may require prolongation in patients with additional risk factors for stent thrombosis.⁴⁴

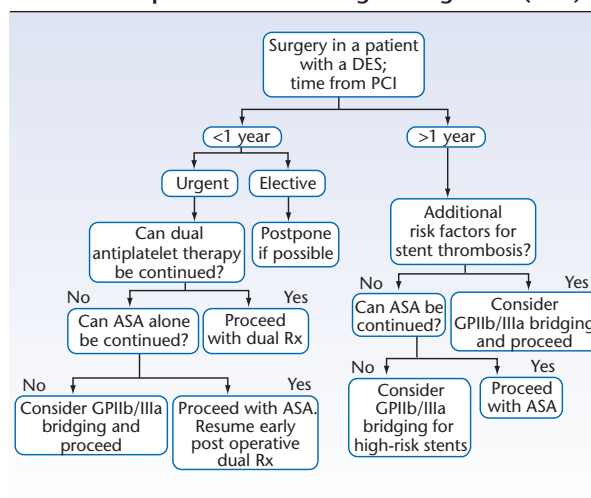
RECOMMENDATIONS FOR ANTICOAGULATION REGIMENS

In 2007, Grines et al⁴⁵ published recommendations to prevent premature discontinuation of dual antiplatelet therapy in stent recipients. For simple balloon dilation, without a stent, 2-4 weeks of dual-antiplatelet therapy is recommended and elective surgery should be postponed until after the completion of this treatment. For PCI involving a BMS, a minimum of 4–6 weeks on dual-antiplatelet therapy is recommended; elective surgery should be postponed for 6 weeks or more after the intervention, but ideally less than 12 weeks afterward, since restenosis may begin (Figure 1). For DESs, dual-antiplatelet therapy should be continued for at least 12 months after the intervention and elective surgery should ideally be postponed for that period. If a surgery mandating discontinuation of thienopyridine therapy must take place within the first year following PCI-DES, ASA should be continued, if at all feasible, and the thienopyridine restarted as soon as possible (Figure 2). For both types of stents, ASA should be a lifelong treatment.

THE PERIOPERATIVE CONFLICT

Cessation of antiplatelet therapy soon after PCI and before noncardiac surgery significantly increases morbidity and mortality.⁴⁶ Since stent endothelialization may be incomplete at the time of surgery, sudden discontinuation of dual-antiplatelet ther-

FIGURE 2: Suggested algorithm for the management of patients with a drug-eluting stent (DES)⁴⁵



apy combined with the prothrombotic and hypercoagulable state of the surgical procedure may place the patient at risk of an abrupt vessel closure and stent thrombosis.⁴² Sudden discontinuation of dual-antiplatelet therapy creates a rebound phenomenon and significantly increases inflammatory and prothrombotic states.⁴² Acute stent thrombosis, MI, and death appear more frequent with a DES than with a BMS, especially when dual-antiplatelet therapy is discontinued perioperatively.⁴⁷ No effective test exists to determine when endothelialization is complete; perioperative stent thrombosis can occur as late as 4 years after DES implantation, despite prolonged periods of dual-antiplatelet therapy.⁴⁷ Clinicians must evaluate and balance the risks of discontinuing antiplatelet therapy – exposing the patient to stent thrombosis and its potential devastating consequences – versus continuing the therapy and increasing the risk of surgical bleeding that may be life-threatening in certain situations.

PERIOPERATIVE BLEEDING

In a meta-analysis, Burger et al⁴⁸ demonstrated that ASA withdrawal preceded 10.2% of acute perioperative vascular syndromes, such as MI, stroke, and cardiac death. ASA appears to increase the incidence of bleeding by a factor of 1.5, but it does not affect perioperative morbidity and mortality, except in intracranial surgery and transurethral prostatectomy (TURP) where increased bleeding may be life threatening. Burger et al recommended withholding ASA only if the risk of bleeding complications exceeds the cardiovascular risk of ASA withdrawal; ideally, ASA monotherapy should be continued in elective surgery except for brain and TURP surgery.

For thienopyridines, little evidence exists to determine the real effect of their discontinuation on bleeding in noncardiac surgery; thus, the risk of bleeding in noncardiac surgery is mostly inferred from the

cardiac surgical literature.⁴⁹ Compared with ASA alone, the combination of ASA and clopidogrel increases the absolute risk of major bleeding by 0.4%-1.0%.⁵⁰ Chassot et al⁵¹ reported that the continuation of clopidogrel use during the perioperative period increased surgical bleeding and transfusion rates by 50%, without a concomitant increase in mortality and morbidity, except in intracranial surgery. Therefore, in procedures where blood loss can be controlled easily, there may be no indication to hold antiplatelet therapy.⁵¹ Ongoing or recently stopped (<7 days) clopidogrel is a contraindication to locoregional anesthesia/analgesia techniques. The lack of epidural analgesia may increase postoperative morbidity after major thoracoabdominal surgery. The risk of clopidogrel withdrawal must be weighed against the benefits of locoregional techniques on a case to case basis.

STENT THROMBOSIS

Acute manifestations of stent thrombosis include STEMI or sudden malignant dysrhythmias. Treatment consists of immediate reperfusion to avoid a transmural MI, since continuing myocardial necrosis may lead to hemodynamic instability, cardiogenic shock, and/or cardiac arrest.⁵² Primary PCI is the definitive treatment for perioperative stent thrombosis and restoration of coronary flow, whereas thrombolytic therapy is significantly less effective and contraindicated in the perioperative setting.⁵² Surgeries should take place in hospitals where 24-hour interventional cardiology care can be provided quickly.⁵¹ PCI carries an increased risk of bleeding when performed early after surgery because antiplatelet and antithrombin medications must be administered during the procedure.⁵² However, recent data⁵³ suggests that aspirin alone plus a single dose of heparin provide acceptable PCI conditions in patients with an acute coronary stent occlusion who are at risk of bleeding. Postprocedural surveillance should take place in a high-care unit with continuous cardiac monitoring.⁵³

BRIDGING THERAPY

In 2006, a group of cardiologists, anesthesiologists, and hematologists published perioperative management guidelines for the use of antiplatelet agents in stent patients.⁵⁴ They emphasized that withdrawal of dual-antiplatelet therapy during the perioperative period places patients at significant risk of stent thrombosis, and they recommended the continuation of ASA. However, in surgeries where bleeding risk is excessive, they recommended the institution of a bridging therapy:

the combination of flurbiprofen (nonsteroidal anti-inflammatory drug) and low-molecular-weight heparin (LMWH).^{54,55} There is no scientific evidence to support this idea and an acute coronary syndrome has been reported with this practice.⁵⁶

Other bridging regimens have been suggested. The use of LMWH alone is controversial. Some studies concluded that it is associated with significantly increased postoperative bleeding and reexploration in cardiac surgery,⁵⁷ while another found that enoxaparin, in comparison with unfractionated heparin (UFH), reduced perioperative blood loss in CABG and reduced the incidence of death and MI by 39% over a 2.5-year period.⁵⁸ Although often used perioperatively for thromboembolic prophylaxis, UFH is not protective against stent thrombosis because it does not have antiplatelet properties.²¹ In addition, there is a rebound phenomenon after abrupt heparin discontinuation; after an infusion, platelet and thrombin activity increase and persist for many hours after cessation, whereas the protective anticoagulant effect of UFH decreases rapidly due to its short half-life.⁵⁹

GPIIb/IIIa inhibitors (abciximab, eptifibatid, tirofiban) have been favoured for bridging, since they target one of the family of adhesion receptors (integrins) that are crucial for platelet aggregation and thrombus formation.⁶⁰ These drugs also displace fibrinogen from GPIIb/IIIa receptors and block signalling processes, which further prevents prothrombotic activity.⁶¹ GPIIb/IIIa inhibitors demonstrate more potency than ASA and a thienopyridine;⁶² therefore, they can provide a bridge in unstable situations such as perioperative stent thrombosis.⁶³ Recent protocols suggest their use for patients who have not completed dual-antiplatelet therapy or in patients where stent complexities and comorbidities place them at an increased risk of perioperative stent thrombosis.⁶⁴ Reversible direct inhibitors of the platelet adenosine 5'-diphosphate P2Y₁₂ receptor (cangrelor, AZD6140) are undergoing clinical trials. Cangrelor, given parenterally, has a much shorter half-life and recovery time than GPIIb/IIIa inhibitors and full platelet inhibition can be achieved within minutes.⁶⁵

Prospective studies are necessary to demonstrate bridging therapy as an effective and durable management strategy. Although successful cases have been reported with bridging therapy, opponents argue that it does not confer additive protection against stent thrombosis, that it exposes patients to more risks, and that it is logistically difficult.^{52,63} The pharma-

TABLE 1: Some GPIIb/IIIa antagonists for bridging therapy

	Abciximab	Eptifibatide	Tirofiban
Main elimination route	Rapid plasma elimination for free drug and platelet/receptor turnover for bound abciximab	Mainly renal	Mainly renal
Recommended dosage*	250 µg/kg followed by 10 µg/min	180 µg/kg bolus × 2, followed by 2 µg/kg/min	0.4 µg/kg/min for 30 minutes, followed by 0.1 µg/kg/min
Plasma half-life	20 – 30 minutes	2–3 hours	90 – 120 minutes
Platelet half-life	4 hours [†]		
Time to restoration of normal platelet aggregation after infusion stopped	72 hours	4 hours	3–4 hours

* Recommended dosage is based on primary PCI studies since no stent thrombosis prevention with antiplatelet withdrawal studies were available.

[†] Abciximab remains in circulation in a platelet-bound state for up to 15 days, with 25% of GPIIb/IIIa receptor being blocked after 1 week.

Adequate platelet function is usually restored in 48-72 hours.

cokinetics and dosages for GPIIb/IIIa inhibitors are presented in Table 1.^{66,67}

CONCLUSION

Stent thrombosis is a potential catastrophe for patients with previous PCI undergoing non-cardiac surgery, especially if the PCI is recent. Some recommendations have been formulated to manage these cases, but there is yet no definitive standard of care. Early identification and a multidisciplinary approach to preoperative assessment and management are essential to maximize chances of success.

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