

Perioperative management of patient with intracoronary stent presenting for noncardiac surgery

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ABSTRACT

As the number of percutaneous coronary interventions increase annually, patients with intracoronary stents (ICS) who present for noncardiac surgery (NCS) are also on the rise. ICS is associated with stent thrombosis (STH) and requires mandatory antiplatelet therapy to prevent major adverse cardiac events. The risks of bleeding and ischemia remain significant and the management of these patients, especially in the initial year of ICS is challenging. The American College of Cardiologists guidelines on the management of patients with ICS recommend dual antiplatelet therapy (DAT) for minimal 14 days after balloon angioplasty, 30 days for bare metal stents, and 365 days for drug-eluting stents. Postponement of elective surgery is advocated during this period, but guidelines concerning emergency NCS are ambiguous. The risk of STH and surgical bleeding needs to be assessed carefully and many factors which are implicated in STH, apart from the type of stent and the duration of DAT, need to be considered when decision to discontinue DAT is made. DAT management should be a multidisciplinary exercise and bridging therapy with shorter acting intravenous antiplatelet drugs should be contemplated whenever possible. Well conducted clinical trials are needed to establish guidelines as regards to the appropriate tests for platelet function monitoring in patients undergoing NCS while on DAT.

Key words: Antiplatelet therapy; Coronary stent; Noncardiac surgery

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INTRODUCTION

Percutaneous coronary intervention (PCI) has become the mainstay treatment for coronary artery disease (CAD). Percutaneous coronary balloon angioplasty (PTCA) is associated with complications such as acute closure and restenosis of the affected vessel.^[1] To reduce these complications, intracoronary stents (ICS) were introduced which are of two types: Bare metal stents (BMS) and drug-eluting stents (DES). Both types of ICS reduced the above complications but were associated with stent thrombosis (STH) and required mandatory antiplatelet therapy to prevent major adverse cardiac events (MACEs). The American College of Cardiologists (ACC) guidelines on the management of patients with ICS recommend dual antiplatelet therapy (DAT) for minimal 14 days after balloon angioplasty, 30 days for BMS and 365 days for DES. As the number of PCIs increases annually, patients with ICSs who

present for noncardiac surgery (NCS) are also on the rise. The risks of bleeding and ischemia remain significant and the management of these patients, especially in the initial year of ICS is challenging. In this review, we discuss the perioperative management of patients with ICS on antiplatelet therapy presenting for NCS and summarize the available current literature.

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METHODS

An online search was performed for literature which included original articles, reviews, case reports, and observational case series with the following keywords Percutaneous coronary intervention, percutaneous coronary angioplasty, coronary stents, BMS, DES, biodegradable stents, STH, antiplatelet therapy, DAT, platelet function tests, bleeding, myocardial infarction (MI), NCS, coronary artery bypass grafting (CABG), aspirin, clopidogrel, glycoprotein (GP) IIa/IIIb antagonists, and guidelines. The websites of a number of organizations (Cardiac Society of Australia/New Zealand, Austrian Society of Anaesthesiology, American Society of Anaesthesiology, European Society of Cardiology, ACC, Canadian Cardiovascular Society, French Task Force and Japanese Circulation Society) were searched for the guidelines.

THE EVOLUTION OF PERCUTANEOUS CORONARY INTERVENTIONS

Initial PCI involved stand-alone angioplasty. PTCA was successful in increasing the coronary blood flow, but acute closure and late restenosis remained significant risks. An acute closure which was associated with increased morbidity and mortality occurred in 3–5% of angioplasties.^[1] Restenosis, defined as greater than 50% reduction in the postprocedural luminal diameter was found to occur in 30–60% of the PTCAs performed.^[1] Restenosis was due to exaggerated inflammatory response at the site of intervention and required revascularization in nearly 20–30% of the cases.^[1] With the introduction of BMS which provides structural support to the dilated segment, the above complications decreased significantly. However, BMS was associated with increased neointimal hyperplasia and in-stent restenosis.^[2,3] Development of DES which are nothing but BMS eluting an antiproliferative drug over a period of time further reduced the incidence of stent restenosis.^[4] Currently four DES are available- the first generation sirolimus-eluting stent and paclitaxel-eluting stents and the second generation zotarolimus-eluting stent and everolimus-eluting stents (EES). Both BMS and DES delay re-endothelialization (DES for a longer time than BMS) and provide a nidus for platelet aggregation and STH.^[5-8] The second generation DES, though easier to place and reduce restenosis, still carry a significant risk associated with STH due to the durable polymer residue.^[9,10] This led to the innovation of DES with biodegradable and biocompatible

polymers (BP-DES) which provide vessel patency until the lesion is healed and after that degrade into nontoxic compounds.^[11] BP-DES have been found to be as efficacious as the second generation DES in terms of late STH risk.^[12] Another exciting advancement is the drug coated balloon (DCB) that is coated with an antirestenotic drug, which is released into the vessel wall when the expanded balloon comes in contact.^[13] DCB seeks to overcome the limitations of DES such as STH and the need for prolonged DAT and may be a useful preoperative treatment strategy in patients who may require NCS in the near future. Nanoparticle and gene eluting stents are currently under research and could offer a new avenue for the improvement of current stent technology.^[14] With the changes in the technology of DES, there has also been a shift in the duration of DAT required with many studies recommending DAT for <1 year depending on the stent deployed.^[15,16]

STENT THROMBOSIS AND NONCARDIAC SURGERY

Stent thrombosis

STH is a serious complication of ICS and is seen with both BMS and DES. Even with the improvements in stent technology, STH is associated with up to 70% rate of MI and 20% mortality depending on the location of the stent and other factors.^[17] According to the time of occurrence, the Academic Research Consortium has defined STH as acute, within 24 h; early, 2–30 days; late, more than 1 month to <1 year; and very late, more than 1 year.^[18] The incidence of early and late STH is similar in BMS and DES whereas very late STH is more common with DES.^[19,20] For this reason, DAT is recommended for longer duration in DES as compared to BMS (4–6 weeks for BMS and at least for 1 year for DES).

Stent thrombosis and noncardiac surgery

NCS is a frequent occurrence following ICS. The results from the EVENT registry estimate the frequency of NCS to be around 4% in the 1st year after placement of DES, whereas a more recent study estimates it to be 9%.^[21,22] In a large cohort study describing the timing of NCS in patients with ICS, 12% of patients with BMS and 47% of patients with DESs had early surgery (defined as surgical procedures within 6 weeks in patients with BMS or within 12 months in those with DES).^[22] NCS is identified as the second most common cause of discontinuation of DAT in the 1st year after ICS.^[23] The perioperative period per se is a prothrombotic state. This hypercoagulability seems to be mainly due to platelet activity and may last for seven days.^[24] Cessation of antiplatelet agents was suspected to cause rebound

hypercoagulability. Both prothrombotic tendency and rebound hypercoagulability due to withdrawal of DAT is suspected to increase the probability of STH in a patient with poorly endothelialised stent after NCS. But recent randomized controlled studies have mentioned that it is withdrawal of protection with DAT which plays a more important role than rebound hypercoagulability.^[25,26]

Factors associated with stent thrombosis

The type of ICS and the duration of DAT have been identified as the most important factors for STH. Early reports suggested that NCS within 6 months after stent placement was safer after BMS.^[27] However, recent literature reports that the incidence of MACE after NCS within 45–180 days of stent implantation was similar to BMS and DES. There was no difference in both stents for surgery after 6 months.^[22,28] In a their meta-analysis (though not in perioperative patients), Kang *et al.* found that all DESs significantly reduced the risk of STH up to 1 year compared with BMS. In individual comparisons, EES was the safest stent. BP-DES also had significantly reduced the risk of STH compared with BMS but was inferior to EES.^[29] Zhang reported that BP-DES has increased the risk of early STH in comparison to durable polymer DES.^[12] The findings of these studies are in contrast to other studies which have shown that BP-DES is noninferior to DES.^[30,31]

The most common cause for STH is patient noncompliance with DAT. A brief interruption of DAT for NCS was earlier considered a risk factor for STH.^[32] However, Mehran *et al* reported that perioperative interruption of DAT did not increase the risk of STH. In this study, the effect of permanent discontinuation, and brief perioperative interruption and disruption of DAT on MACEs were evaluated. The former two were on the physician's advice while disruption of DAT was due to patient stopping on account of bleeding or noncompliance. Overall, DAT was stopped in 2.9 and 23.3% of the patients within 30 days and 1 year, respectively. MACE was strongly associated with the manner of termination with no increase in risk with discontinuation or interruption. Disruption, however, was associated with high risk of adverse events.^[33] Continuation of DAT also does not guarantee safety from STH. In fact, 74% of MACEs occurred in patients who continued to receive DAT. From the above reports, it is clear that factors other than the type of stent and duration of DAT are causative of STH in the perioperative period.

The anatomy of coronary lesion is an important contributory factor for STH. Coronary bifurcation lesions have been associated with worse in-hospital and long-term outcomes compared with nonbifurcation lesions. Implantation of double DES in both branches is associated with increased risk of MI compared with single DES and requires aggressive antiplatelet therapy.^[34] PCI has become a feasible alternative to CABG in patients with left main or proximal left anterior descending artery CAD.^[35] But when patients with prior stenting of left main coronary artery require urgent NCS, the discontinuation of DAT puts substantial myocardium at risk and has the potential for greater morbidity and mortality. ICS for acute coronary syndrome is associated with increased incidence of procedure-related angiographic events and possibly MACEs in the long-term. Acute thrombotic plaques dislodged during the procedure are associated with a 34–40% rate of acute stent malapposition and inappropriate stent selection, all of which increase the risk for STH.^[36] Stenting for multiple vessel disease and small vessels may also be more prone to thrombosis.^[37]

Other factors which predispose to STH are increased revised cardiac risk index score, emergency NCS, low ejection fraction, renal failure, and diabetes.^[38-40] A detailed history regarding the indication for PCI, coronary anatomy, urgency of NCS, and associated comorbidities are as important as the type of stent and duration after ICS before the decision to discontinue DAT is made.

ANTIPLATELET THERAPY AFTER INTRACORONARY STENTS AND THE ISSUES ASSOCIATED WITH THEIR CONTINUATION IN PERIOPERATIVE PERIOD

Dual antiplatelet therapy

DAT with aspirin and thienopyridine is found to be most efficacious in the prevention of STH. Aspirin affects the platelet aggregation by irreversible inhibition of cyclooxygenase I. Thienopyridines irreversibly bind to the platelet P2Y₁₂ receptor and inhibit adenosine diphosphate (ADP) receptor mediated platelet activation and aggregation. The three thienopyridines which are presently available include clopidogrel, prasugrel, and ticagrelor. Both clopidogrel and prasugrel are prodrugs. Clopidogrel is transformed into its active form by the hepatic CYP2C19 isoenzyme, the levels of which are variable in different subsets of the population. This variability in CYP2C19 isoenzyme renders substantial proportion

of patients nonresponsive to the action of clopidogrel and increases the risk of STH 2-fold in comparison to responders. CYP2C19 genomic typing can be done to differentiate responders from nonresponders.^[41,42] Prasugrel is also a prodrug activated by intestinal CYP3A and carboxylase 2 hydrolysis. Activation of prasugrel results in more predictable antiplatelet action than clopidogrel. The third thienopyridine, ticagrelor has direct and reversible action on P2Y12 receptor and causes more rapid inhibition of platelet function.^[43,44] The pharmacodynamic and kinetic characteristics of the antiplatelet drugs is given in Table 1.

Risk of bleeding with dual antiplatelet therapy

Several reviews regarding antiplatelet therapy in the perioperative period have been published in the last 5 years.^[45-47] Clinicians managing patients on DAT are faced with the dual problem of increased bleeding if it is continued and risk of STH if discontinued. The incidence of major spontaneous bleeding was found to be 11.6% in patients on ticagrelor and 11.2% in patients on clopidogrel.^[48] Increased bleeding was reported when procedures are performed without discontinuation of DAT. The requirement of transfusions, surgical re-exploration and length of hospital stay was significantly increased in patients on DAT undergoing CABG.^[49] In NCS, the risk of major bleeding is reported to be 21% with DAT and 4% in patients on a single antiplatelet drug.^[28] In gastrointestinal and transtracheal endoscopic procedures too, the risk of bleeding is increased by 2–3-fold in patients on DAT compared with aspirin alone.^[50,51]

Dual antiplatelet therapy and elective surgery

A recent systematic review identified 11 practice guidelines for the management of antiplatelet therapy in patients with an ICS undergoing NCS.^[52] The ACC/American Heart Association guideline on perioperative cardiovascular evaluation and management of patients undergoing NCS, which is widely followed, recommends that elective surgery

should be postponed in patients with ICS till the completion of recommended duration of DAT.^[53] Elective NCS should be delayed for 14 days after balloon angioplasty, 30 days after BMS implantation, and 365 days after drug-eluting stent.

Dual antiplatelet therapy and nonelective surgery

However, if urgent surgery is required before this time frame, the recommendations are less clear. The available practice guidelines advise that decision to stop or replace DAT should be made on case to case basis after weighing the risks of STH and surgical bleeding. Whenever possible, efforts to continue DAT (or at least aspirin 81–150 mg) in the perioperative period should be made. The decision should be made after consultation with the treating cardiologist, anesthesiologist, and surgeon. However, it is often difficult to convince the surgeon to continue DAT perioperatively. In a 2010 survey, the risk of STH was perceived more by the cardiologists and anesthesiologists (majority of whom agreed for continuation of perioperative DAT), whereas only 64% surgeons were willing to follow the recommendation as they perceived the risk of bleeding to be greater.^[54] So how do you objectively assess the relative risks of STH and bleeding when a patient presents for urgent surgery? The guidelines are incomplete in this regard. To address this lacuna, Vetter *et al.* proposed standardized clinical assessment and management plan for perioperative DAT management which was formulated after carefully considering the existing guidelines and experts’ opinions.^[55] They prepared protocols for DAT management (one for BMS, another for DES) after weighing the risks of bleeding and STH with clear advice on when to stop, when to continue, and how much antiplatelet agent to continue perioperatively. Recommendations suggested in this study are not evidence-based and need to be evaluated. However, they provide greater clarity regarding risk assessment and management especially in urgent surgeries such as for malignancy which cannot be deferred until the completion of DAT.

Table 1: The pharmacodynamic and kinetic characteristics of the commonly used oral antiplatelet drugs

	Aspirin	Clopidogrel	Prasugrel	Ticagrelor
Mode of action	Cyclooxygenase inhibitor	ADP antagonist	ADP antagonist	ADP antagonist
Reversible	No	No	No	Yes
Loading dose (mg)	325	600	60	180
Maintenance dose	81 mg OD	75 mg OD	10 mg OD	90 mg BD
Prodrug	No	Yes	Yes	Yes
Duration of discontinuation before operation	5 days	5 days	7 days	5 days

ADP: Adenosine diphosphate

Substitutes for dual antiplatelet therapy in the perioperative period

There is no accepted therapy which can be used as an alternative to DAT in the perioperative period. Most of the guidelines do not make any statement on the bridging therapy and the ACC guidelines, in particular, do not recommend routine bridging therapy. The five practice guidelines which comment on alternate replacement suggest unfractionated heparin (UFH), low molecular weight heparin (LMWH), nonsteroidal anti-inflammatory agents, or short-acting GP IIB/IIIa receptor antagonists as substitutes.^[52] The safety of any of these substitutes is unknown. However if a bridging therapy is started, logically antiplatelet therapy should be preferred.

Bridging with either UFH or LMWH is controversial and is not fail proof with STH reported with both of them leading to perioperative MACE.^[56] In fact, UFH may be potentially harmful as it is suspected to augment platelet activation by agonists such as ADP and cause thrombosis. Though platelet activation is less with LMWH, it is not the preferred substitute. The French Task Force recommends the nonsteroidal anti-inflammatory drug, flurbiprofen 50 mg twice daily in place of clopidogrel, but this is more a matter of choice than evidence-based.^[57] Broad *et al.*, reported the successful use of tirofiban, an intravenous (IV) GP IIB/IIIa in three patients undergoing NCS without increased bleeding or adverse cardiac events.^[58] Though two other larger studies confirmed the safety of substitution with GP IIB/IIIa antagonists, Alshawabkeh *et al.* reported that postoperative STH is still a potential problem.^[59-61] Another recently introduced antiplatelet agent is cangrelor, a nonthienopyridine ADP antagonist with a rapid onset and offset of effect. When compared to tirofiban, cangrelor has faster action and more specific to the P2Y12 receptor.^[62] Though still not approved for clinical use, its efficiency as bridging therapy was studied in the BRIDGE trial where patients with recently implanted ICS waiting for CABG were assigned to either cangrelor or placebo. Cangrelor consistently maintained platelet inhibition without any obvious increase in major bleeding.^[63] In all the above studies with GP IIB/IIIa antagonists and cangrelor, clopidogrel was stopped 5 days preoperatively but aspirin was continued. The infusions were started without a loading dose 48 h before and stopped 6 h before surgery. All the infusions were restarted 6 h postoperatively and continued until a loading dose of clopidogrel was given. The pharmacological characteristics and dosing of tirofiban, eptifibatide, and cangrelor are given in Table 2.

Patient on dual antiplatelet therapy presenting for emergency surgeries

Modification of DAT is possible when adequate time is available before surgery. In emergency situations, this is often not possible and patients proceed directly to surgery. In case of closed cavity emergencies (intracranial, intraspinal, and intraocular hemorrhage) and other surgeries like aortic dissection, where the sequelae of bleeding can be catastrophic, most available literature agrees that DAT should be discontinued. A recent case report highlighted the safety of continuing DAT in a patient with intracranial hemorrhage, which was managed nonsurgically.^[64] Other acute conditions such as intra-abdominal infections which require emergency procedure may be undertaken under the cover of DAT with adequate monitoring of platelet functioning and clinical assessment of bleeding. There is no literature supporting the use of prophylactic platelet transfusion or antifibrinolytic agents in these patients. An appropriate strategy is to avoid both if the risk of bleeding is less and that of STH high. In patients with excess bleeding, platelet, and antifibrinolytic therapy use may be guided by platelet function tests if available.

TESTS FOR PLATELET FUNCTION

Both quantitative and qualitative test for platelet function are available in Table 3. Quantitative analysis of platelets is of limited use as very often DAT causes a functional abnormality of platelets without a decrease in the platelet count. Although bleeding time is easy and quick to perform, there is a lack of accuracy and poor association with clinical bleeding.^[65] Moreover, till date, its use to assess bleeding after antiplatelet therapy has not been reported. Plasma drug assays of aspirin and clopidogrel do not correlate with their pharmacodynamic effect.^[66] Tests based on platelet aggregometry include light transmission aggregometry (LTA), impedance aggregometry and lumiaggregometry. LTA is considered as the gold standard for platelet function testing and many

Table 2: The pharmacological characteristics and dosing of tirofiban, eptifibatide, and cangrelor

	Tirofiban	Eptifibatide	Cangrelor
P2Y12 specific	No	No	Yes
Onset of action	Immediate	Immediate	Immediate
Offset of action (h)	4-8	4-6	1
Plasma half-life (min)	120	150	3-5
Dose (intravenous infusion) (µg/kg/min)	0.1	2.0	0.75

Table 3: Methods of platelet testing

Bleeding time
Tests for platelet aggregation
Light transmission platelet aggregometry
Impedance aggregometry
Lumiaggregometry
Tests for platelet adhesion
Platelet function analyzer
Global thrombosis test
Platelet mapping combined with viscoelastic methods
Sonoclot
TEG
ROTEM
Flow cytometry
Radio or enzyme-linked immune assays

ROTEM: Rotational thromboelastometry,
TEG: Thromboelastography

points of care tests introduced in recent times such as thromboelastography (TEG), sonoclot, and platelet function analyzer are compared against it. LTA has been used in patients on antiplatelet therapy and has been successful not only in identifying nonresponders to clopidogrel, but also in the prediction of MACE in high-risk patients.^[67,68] Impedance platelet aggregometry measures change in electrical impedance due to platelet clumping. This technique has been used to identify nonresponders to clopidogrel, patients on DAT at high risk for MACE and also patients at risk for thrombosis on heparin.^[69,70] In addition, multiple electrode aggregometer (MEA) has made it possible to detect increased risk of bleeding and is proposed as a rapid and useful tool for diagnosis of postoperative bleeding. MEA (Multiplate Function Analyzer, Roche Diagnostics, Germany) a newly introduced point of care test based on impedance aggregometry has been shown to be better predictive of perioperative bleeding than TEG in patients undergoing CABG.^[71]

Three methods of global assessment of hemostasis including platelet function, clotting, and fibrinolysis are available. These are TEG, rotational thromboelastometry (ROTEM), and sonoclot. Whole blood TEG has not been found useful in detecting platelet dysfunction in patients on clopidogrel and aspirin.^[72] Waters *et al.* reported a patient on eptifibatid in whom sonoclot predicted bleeding better than TEG.^[73] Newer modifications to TEG and ROTEM include addition of platelet mapping with similar characteristics as MEA. As these modifications are recent, their utility in the management of DAT is still to be established assessed. There are many other tests of

platelet function, the discussion of which is beyond the scope of this review and interested readers are referred to a recent comprehensive review on the subject.^[74] The number of patients on DAT are only going to increase and with the plethora of tests available, establishing clear-cut recommendations as regards platelet function tests and tailoring perioperative antiplatelet therapy accordingly has become the need of the hour.

Regional anesthesia in patients on dual antiplatelet therapy

The major concern with the use of central neuraxial blockade (CNB) in patients on antiplatelet agents is the risk of spinal epidural hematoma. The American Society of Regional Anesthesia and Pain Medicine Evidence-based Guidelines recommend that platelet function be allowed to recover before administering regional anesthesia.^[75] However, safe CNB does not mandate complete recovery of platelet function. In fact, several studies have established that CNB is not associated with increased risk of spinal hematoma in these patients.^[76,77] The risk is amplified when patients are on additional antithrombotics such as heparin. The role of platelet function tests in the assessment of the safety of CNB has not been studied. and the value of ADP aggregation at which CNB may be safely administered is not known. As the normal value of ADP aggregation is around 60-90%, it is probably safe to wait till this is achieved before CNB is attempted. After 10 days of therapy, inhibition of platelet aggregation was greater with 10 mg prasugrel than with clopidogrel 75 mg (70% vs 36%) and bleeding time was significantly prolonged only with prasugrel^[78] Obviously, more caution needs to be exercised when drugs with potent inhibition of platelet function like prasugrel are used.

MONITORING FOR MYOCARDIAL ISCHEMIA

All the preoperative cardiac medications such as antihypertensives, beta blockers, and statins should be continued in the perioperative period in patients with ICS presenting for NCS. The need for invasive monitoring such as invasive arterial blood pressure, central and pulmonary arterial pressures, cardiac output monitoring, and transesophageal echocardiography depend on the risk of STH as assessed preoperatively and on the magnitude of the planned procedure and its potential for bleeding. Postoperatively, the patient is shifted to high dependency unit and subjected to continuous hemodynamic monitoring. The antiplatelet therapy should be restarted as soon

as possible. Postoperative STH may present with symptoms of chest pain or shortness of breath or more often be asymptomatic manifesting with sudden hypotension, arrhythmia, or even cardiac arrest. Electrocardiography may provide evidence of typical ischemic changes accompanied by elevated cardiac enzymes. If STH is suspected, an urgent angiography and balloon angioplasty should be performed. Use of IV anticoagulants and GP IIb/IIIa inhibitors should be cautiously done in a postoperative setting as bleeding risk is substantial. The patient should be on the long-term follow-up as STH may present even after discharge from the hospital.

SUMMARY

As the incidence of PCIs increases, patients on DAT presenting for NCS are also on the rise. Guidelines for the management of DAT in emergency NCS are ambiguous. Many factors which are implicated in STH, apart from the type of stent and the duration of DAT, need to be considered when the decision to discontinue DAT is made. DAT management should be a multidisciplinary exercise and bridging therapy with shorter acting IV antiplatelet drugs should be contemplated whenever possible. There is a lot of scope for investigation regarding the optimal substitutes for DAT. Literature as concerning platelet function testing is rapidly emerging and this is an area which needs well-conducted research to establish guidelines as regards to the appropriate platelet function test in patients on DAT.

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