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Peri-operative dilemma of coronary stents and antiplatelet therapy

M Grobbelaar

Commentator: C Evans

Moderator: NR Rodseth

Department of Anaesthetics

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Introduction

Coronary stents are placed in up to 90% of all percutaneous coronary interventions (PCI)[1] because they increase procedural success and decrease restenosis.[2] Roughly 5% of these patients will present for non-cardiac surgery (NCS) within the first twelve months after stenting.[3] Anaesthetists are faced with the peri-operative dilemma of managing patients on dual antiplatelet therapy – stop the drugs and risk life-threatening stent thrombosis, or continue therapy and risk potentially disastrous bleeding.

Stent basics

Coronary artery stents were first used in 1987 because of high failure rates with balloon angioplasty. Bare metal stents (BMS) were used to prevent the immediate elastic recoil of the lumen and vessel occlusion.[4]

Drug eluting stents (DES) were introduced in the late 1990s in response to the high observed incidence of stent restenosis with BMS. DES were designed to prevent restenosis by coating a standard coronary stent with a thin polymer carrier containing an antiproliferative agent. It combines the advantages of a stent scaffold with controlled release of a drug which inhibits smooth muscle proliferation and neointimal hyperplasia within the stented segment. DES are currently used in 70% to 80% of PCI procedures in the U.S.[2]

The most frequently used DES from the first generation were coated with either sirolimus (CYPHER-stent) or paclitaxel (TAXUS-stent).[5] Everolimus and zotarolimus, used on second-generation DES, exert a similar inhibitory effect on vascular smooth muscle cell activation.[6]

Table 1. Comparison of Sirolimus vs. Paclitaxel [7]

	Sirolimus	Paclitaxel
Origin	Macrolide antibiotic produced by the fungus *Streptomyces hygroscopicus*	Anti-neoplastic drug derived from the Pacific yew tree, *Taxus brevifolia*
Type of agent	Antifungal and immuno-suppressive properties	Antineoplastic agent used in treatment of breast and ovarian cancer
Cellular function	Cytostatic agent which possesses antimitotic properties	Cytotoxic agent which alters intracellular microtubule function and impairs mitosis
Mechanism of action	Binds with the intracellular receptor, FKBP12, inhibits down-regulation of the cyclin-dependent kinase inhibitor, p27K1P1, thus arresting the cell cycle in the G1/S phase	Binds to the N-terminal 31 residues of the β-tubulin subunit, causing polymerization and disassembly of the microtubules, thus inhibiting cellular replication in the G0/G1 and G1/M phases
Drug kinetics	100% of the drug elutes from the polymer over 4–6 wk	10% of drug elutes from polymer in the initial 10–14 d; remaining 90% sequestered indefinitely

Stent Thrombosis

Table 2. Academic Research Consortium definitions of stent thrombosis[9]

Event	Definition
Definite	1. Angiographic confirmation: • TIMI 0 with occlusion originating in or within 5 mm of stent in the presence of a thrombus or • TIMI flow grade 1, 2, or 3 originating in or within 5 mm of stent in the presence of a thrombus 2. AND ≥1 of the following criteria <48 hours: • New acute onset of ischemic symptoms at rest (typical chest pain with duration >20 minutes) • New ischemic ECG changes suggestive of acute ischemia • Typical rise and fall in cardiac biomarkers 3. Pathologic confirmation: • Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy
Probable	1. Any unexplained death within the first 30 days 2. Myocardial infarction related to acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other cause
Possible	1. Any unexplained death >30 days after intracoronary stenting

Stent thrombosis is catastrophic complication of stent placement with high morbidity and mortality. It is classified according to the time period after stent placement[9]:

- **Acute** – within 24 hrs
- **Sub-acute** – after 24 hrs up to 30 days
- **Late** – between 30 days and 12 months
- **Very late** – after 12 months

BMS thrombosis and in-stent restenosis

BMS implantation effectively eliminates acute vessel closure following balloon angioplasty, but initial trials reported acute and subacute stent thrombosis rates of 16%–24%. The BENESTENT and STRESS studies showed subacute stent thrombosis rates of 3.5% and 3.4%, respectively, despite the use of a complex anticoagulation regimen consisting of dextran, aspirin, dipyridamole, heparin, and warfarin.[7]

Two practices led to a dramatic reduction in the incidence of stent thrombosis in BMS:

- the use of intravascular ultrasound and high balloon pressures to optimize apposition of the stent struts to the vessel wall
- replacement of anticoagulation with dual antiplatelet therapy.

These advancements effectively reduced the incidence of BMS thrombosis to the current rate of 1.2%.[7]

Restenosis is a side-effect of the normal healing process with the growth of scar tissue around the stent mesh. Although initial stent placement prevents acute recoil, the stent struts traumatize the vascular wall provoking an inflammatory reaction followed by an exaggerated proliferative response within the media and adventitia, which results in neointimal hyperplasia. This can lead to occlusion of the coronary lumen, i.e. restenosis. The process peaks at around the third month and reaches a plateau between 3 and 6 months after the procedure. 12-20% of patients with BMS develop in-stent restenosis requiring repeat intervention.[5]

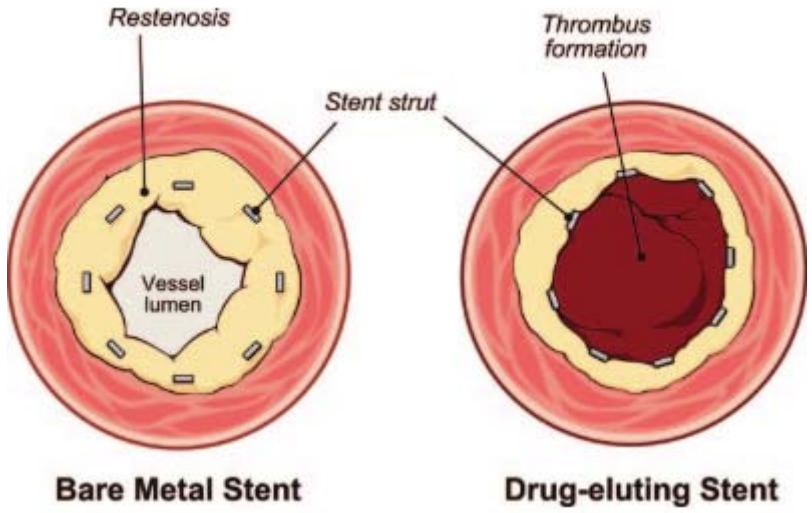

Figure 1. Complications of coronary artery stents: restenosis of bare metal stent (left) and acute stent thrombosis in drug-eluting stent (right).[7]

DES and stent thrombosis

Clinical trials reported similar early (acute and subacute) stent thrombosis rates for DES and BMS (<1%) and attributed this complication to mechanical factors.[7] In late and very late stent occlusion the mechanism of DES obstruction is different to that of BMS. In BMS, the pathophysiological mechanism of obstruction is restenosis with neointimal hyperplasia. DES

inhibit this process, but the resulting inhibition of endothelial cell proliferation causes delayed endothelial healing - i.e. the failure to form a complete neointimal layer over stent struts. Since the stent struts remain uncovered, they are prone to thrombosis. The polymer carriers can also elicit inflammation and hypersensitivity reactions, predisposing to late thrombosis.

Pathophysiological mechanisms

Several factors may contribute to stent thrombosis, including patient-, lesion-, and procedure-related factors, antiplatelet therapy and thrombogenicity of the stent.[9]

1. ***Patient related factors***
   Clinical conditions linked to an increased probability of acute and subacute stent thrombosis are acute myocardial infarction, diabetes mellitus, renal failure and low ejection fraction. This holds true for both DES and BMS.[9] Also, advanced age seems to be a risk factor for subacute stent thrombosis, whereas younger age has been associated with late stent thrombosis.[6]

2. ***Lesion related factors***
   Bifurcation lesions, lesion length and restenosis lesions also promote the occurrence of thrombotic events.[6]

3. ***Procedural related factors***
   Stent length, placement of multiple or overlapping stents, stent under-expansion, residual reference segment stenosis, bifurcation, slow coronary blood flow, positive remodelling and residual coronary artery dissections predispose to stent thrombosis. All these factors do not differ between DES and BMS.[9] Incomplete stent apposition has been observed more frequently after DES implantation as compared to BMS, which may contribute to late thrombotic events.[6] DES might also alter the normal healing process of the vessel wall and trigger positive vessel remodelling leading to acquired malapposition.[10]

4. ***Impaired re-endothelialization***
   Stent deployment causes endothelial denudation and exposes thrombogenic material to the circulating blood. Complete re-endothelialization of the stented segment is crucial for vessel healing. Drugs eluted from DES target smooth muscle cell proliferation by inhibiting the cell cycle. This process is not specific to muscle - endothelial cell proliferation and migration are also

inhibited resulting in delayed endothelial healing. Thrombogenic stent struts are left in contact with the circulating blood favouring the development of thrombosis.[6]

5. *Discontinuation of antiplatelet therapy*

Discontinuation of dual antiplatelet therapy, particularly during the first six to twelve months after stent deployment, has been shown to increase the risk of DES thrombosis. Cessation of clopidogrel has recently been associated with higher rates of death and myocardial infarction up to two years after DES deployment. Also, stent thromboses have been observed after interruption of long-term antiplatelet monotherapy. Non-responsiveness to antiplatelet therapy may also promote thrombus formation after stent implantation.[10] Impaired intimal healing extends the window during which DES are prone to thrombosis. Unfortunately at present there is no way of predicting endothelial recovery and a "safe time" to interrupt dual antiplatelet therapy.[9]

6. *Inflammatory reaction to the stent*

Stent length and strut thickness correlate with an increased risk of stent thrombosis. Eosinophilic infiltrates around struts reflect a hypersensitivity reaction to the stent, most likely the polymer. Reactions to the metal struts or the loaded drugs may also contribute.[6]

7. *Enhanced tissue factor expression*

Data suggests that both sirolimus and paclitaxel may promote thrombus formation and favour stent thrombosis in vivo by enhanced tissue factor expression and diminished fibrinolysis.[6]

8. *Vasoconstriction after DES deployment*

DES, unlike BMS, can impair the endothelial response to acetylcholine- and exercise-mediated vasodilation in vessel segments adjacent to the stent, promoting endothelial dysfunction. Vasoconstriction alters coronary flow velocity and may thereby further promote thrombotic events. Clinical consequences of these findings are still uncertain.[6]

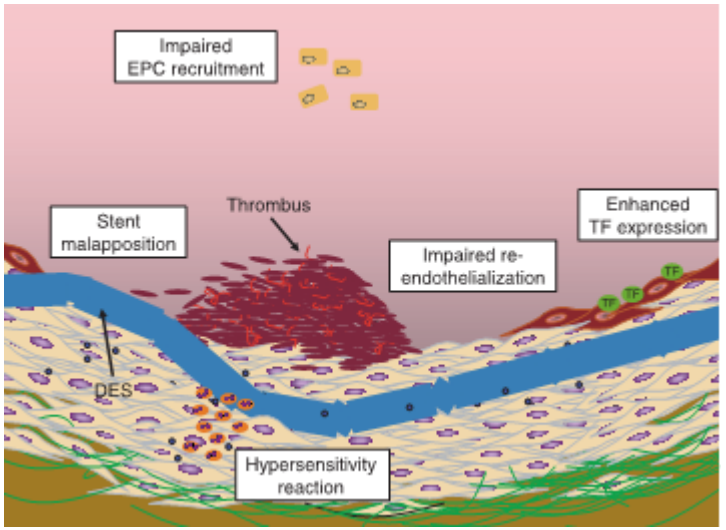

Figure 2. Pathophysiological mechanisms of stent thrombosis after drug-eluting stent (DES) deployment.[6]

Procedure-related factors such as stent malapposition predispose to stent thrombosis. Eosinophilic infiltrates around stent struts reflect a hypersensitivity reaction, probably to the polymer, which delays vascular healing. The drugs released from the stent delay re-endothelialization by inhibiting proliferation and migration of endothelial cells, impair the function of endothelial progenitor cells (EPC) and enhance expression of tissue factor (TF).

To look at it from another perspective… 3 combined factors put the patient at risk for stent thrombosis[10]:

1. A predisposing underlying anatomic substrate (abnormality), e.g. incomplete endothelialization.
2. An unfavourable thrombogenic milieu e.g. drug discontinuation.
3. Any potent trigger for platelet activation, such as surgery.

Thus, the perfect recipe for a peri-operative disaster.

Off-label indications for DES and safety concerns

Table 3. On-label (FDA-approved) use of drug-eluting stents.[7]
Single de novo lesion in a native coronary artery in patients with stable coronary artery disease
Cypher (sirolimus) 2.5–3.5 mm reference vessel diameter, ≤30 mm long
Taxus (paclitaxel) 2.5–3.75 mm reference vessel diameter, ≤28 mm long

Table 4. Off-Label (Non-FDA Approved) Uses of Drug-Eluting Stents (DES)[7]	
Advanced age	Long stent length
Acute coronary syndrome	Multiple lesions
Diabetes	Overlapping stents
Low ejection fraction	Ostial or bifurcation lesions
Prior brachytherapy	Small vessels
Renal failure	Suboptimal stent results
Resistance to aspirin/clopidogrel	Stent mal-apposition
Premature discontinuation of antiplatelet therapy	Persistent dissection
Saphenous vein graft stenting (strut penetration into a necrotic core)	Stent underexpansion/ overexpansion
Left main coronary artery stenting (discontinuation of standard antiplatelet therapy)	Multivessel stenting
Lesion with chronic total occlusion	Vessels with in-stent restenosis

Approved indications for DES include the treatment of discrete, previously untreated lesions. However, currently more than 60% of DES use is off-label in patients with complex conditions and this off-label use may be associated with an increased risk of both early and late stent thrombosis. The conclusion of recent expert discussions was that the 'on-label' use of DES is safe and efficient in terms of a highly significant reduction in target vessel revascularisation. 'Off-label use' is accompanied by higher event rates when BMS are used, with early evidence that DES show better results in certain 'off-label' indications.[1]

Peri-operative management of stent thrombosis

Post-operative management of patients with coronary stents should include admission to a high care unit/ICU with continuous ECG monitoring and cardiology surveillance. Routine monitoring of cardiac biomarkers is useful in detecting myocardial injury, recurrent ischaemia and for risk stratification.[8]

Stent thrombosis most often manifests as an STEMI and should be treated with immediate reperfusion. It results in the abrupt interruption of coronary blood flow in a myocardial region that is not preconditioned by recurrent chronic ischaemia and has no collateral flow.

Thrombolytic therapy is less effective than PCI at restoring perfusion and also often contra-indicated in the post-operative period because of the bleeding risk. Primary PCI is therefore the treatment of choice for peri-operative stent thrombosis.[2] Surgical procedures in patients with coronary stents should be performed in institutions where 24hr interventional cardiology is available to provide immediate intervention.[8]

Most studies suggest that, despite early and aggressive management, episodes of stent thrombosis are associated with large Q-wave myocardial infarctions and a high mortality rate. Stent thrombosis is an independent predictor of unsuccessful attempts at repeat coronary reperfusion.[10]

Anti platelet drugs

"Dual therapy", the combination of a thienopyridine (ticlopidine or clopidogrel) with aspirin is the currently accepted and recommended drug regimen. Their combined effects result in superior antithrombotic activity when compared to conventional anticoagulation. Initially, ticlopidine was prescribed with aspirin. Clopidogrel replaced ticlopidine because of its better safety profile (including less frequent incidences of rash, neutropaenia, thrombotic thrombocytopaenic purpura and GIT symptoms[4]). The thienopyridines and aspirin selectively inhibit platelet activation by different and complementary mechanisms. [7]

Thienopyridines [7]

The thienopyridines inhibit the adenosine diphosphate (ADP) pathway. Ticlopidine and clopidogrel are prodrugs, which are oxidized via the hepatic cytochrome P450-dependent CYP3A4 pathway. The active metabolites are antagonists of the platelet ADP receptor - they irreversibly inactivate the $P2Y_{12}$ receptor subtype by covalent binding.

The $P2Y_{12}$ receptor is expressed on the platelet membrane. It is coupled to adenyl-cyclase (AC) through the Gi protein. Binding by ADP leads to downregulation of AC, which causes:

1. amplification of the response to ADP, thromboxane, thrombin, and collagen
2. enhanced platelet activation and aggregation.

The $P2Y_{12}$ receptor therefore plays a central role in thrombus formation and stabilization. Covalent binding of $P2Y_{12}$ by thienopyridines inhibits both mechanisms that are otherwise essential for platelet aggregation and stabilization:

1. ADP-mediated activation of glycoproteins IIb/IIIa and Ia/IIa
2. binding of fibrinogen to glycoprotein IIb/IIIa.

Because of the irreversible inhibition of the receptor, recovery from clopidogrel requires regeneration of platelets. Return of normal platelet function therefore relies on new platelet production (at least 7 days), not on the disappearance of the drug from plasma ($t_{½}$ 4 hrs).

Clopidogrel resistance

Because of genetic variability in the metabolic activity of the P450 CYP3A iso-enzyme and inhibitory drug interactions, there is considerable inter-individual variability of platelet inhibition. This can lead to clopidogrel resistance. Non-response to clopidogrel is classified as a relative inhibition of ADP-induced platelet aggregation of $<$10% and response as $\geq$30%, while those in-between are defined as low responders.[5] The RECLOSE trial (a prospective study of 804 consecutive patients who were treated with sirolimus- or paclitaxel-eluting stents for coronary artery disease) showed that non-responsiveness to clopidogrel was associated with a 3-fold increase in DES thrombosis.[16] In a retrospective cohort study by Ho *et al*. concomitant use of clopidogrel and PPI after hospital discharge for ACS was associated with an increased risk of adverse outcomes, suggesting that use of PPI may be associated with attenuation of benefits of clopidogrel after ACS.[17]

Aspirin[7]

Aspirin antagonises the production of thromboxane A_2 (TxA_2) by irreversibly binding the enzyme cyclooxygenase-1 (COX-1). Aspirin acetylates a serine residue on the enzyme, thereby preventing the conversion of arachidonate to the unstable prostaglandin intermediate PGH_2, which is converted to TxA_2 - a potent vasoconstrictor and platelet agonist. A single dose of 160 mg completely eliminates platelet TxA_2 production. The same effect can be progressively achieved with daily doses of 30–50mg, or maintenance doses as low as 0.5 mg/kg/day to provide more than 95% inhibition of TxA2 synthesis. High doses of aspirin may have antithrombotic effects independent of platelet COX-1 inhibition: increased fibrinolytic activity, depressed prothrombin synthesis, improved endothelial function, and anti-inflammatory effects.

Aspirin resistance[5]

Aspirin resistance has been shown to be associated with increased odds of a serious vascular event. Three distinct types of aspirin resistance have been classified:

Type 1. Pharmacokinetic resistance due to insufficient bioavailability, including poor compliance, inadequate dosing, or protection of COX-1 against acetylation by certain nonsteroidal anti-inflammatory drugs.

Type II. Pharmacodynamic ("true") resistance caused by rare genetic changes in the COX-1 protein, disabling acetylation by aspirin, or acquired, transient overexpression of less aspirin-sensitive COX isoforms .

Type III. Heightened stimulation of platelets by aspirin insensitive mechanisms.

Glycoprotein IIb/IIIa inhibitors[8]

GP IIb/IIIa inhibitors have been favoured for bridging therapy when dual therapy is stopped, since this platelet receptor is the pivotal mediator for platelet aggregation and thrombus formation. Exposure to the vascular subendothelium activates the receptor, causing a marked affinity for fibrinogen and von Willebrand factor, the principal adhesive macromolecules responsible for cross linking platelets by binding adjacent GP IIb/IIIa receptors. This facilitates platelet aggregation, the final common pathway for platelet plug and thrombus formation. The development of GP IIb/IIIa inhibitors (abciximab, eptifibatide and tirofiban) was integral in preventing thrombus formation and improving outcome in patients with ACS, particularly patients with non-STEMI. In addition to preventing platelet aggregation, these inhibitors (1) displace fibrinogen from GP IIb/IIIa receptors and (2) block signalling processes, which further prevents secretion, clot retraction, and prothrombotic activity. GP IIb/IIIa inhibitors are more potent than the combination of aspirin and a thienopyridine.

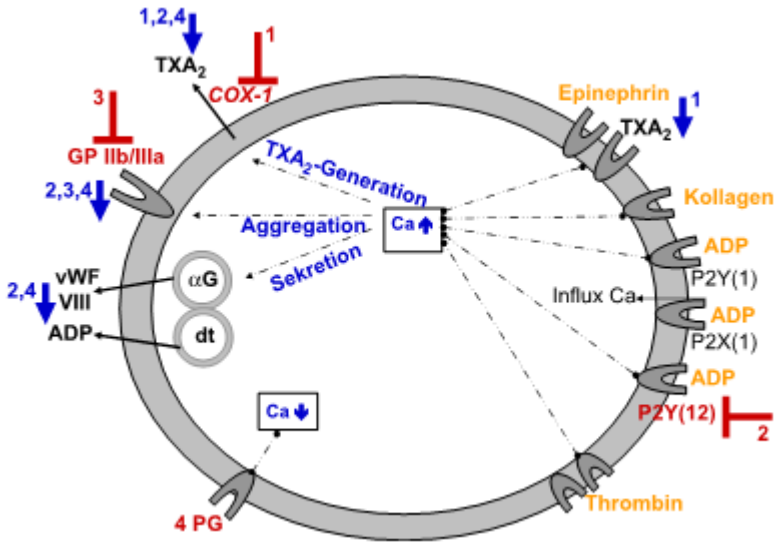

Figure 3. Modification of platelet function by antiplatelet drugs.[1]

a) Binding of agonists (adrenalin, collagen, ADP, thrombin) to their membrane-bound receptors increase the intracellular calcium concentration (Ca^{++}).

b) This subsequently leads to platelet activation

1. *TxA_2 generation from phospholipids via COX-1*
2. *Aggregation, with the expression of activated fibrinogen receptors (GP IIb/IIIa)*
3. *Secretion of von Willebrand factor (vWF), factor VIII from α-granules and ADP from dense granules.*

c) Sites of action of antiplatelet drugs and monitoring of their inhibiting effects (blue) are indicated as follows:

1. *COX-1 inhibitor*
2. *ADP receptor antagonists (blockade of P2Y12, but not P2Y1 and P2X2)*
3. *GP IIb/IIIa inhibitors*
4. *Antiaggregatory prostaglandins*

Current Guidelines

Previously, the American College of Cardiology (ACC)/ American Heart Association (AHA) recommended that, at the very least, patients should be treated with clopidogrel 75 mg and ASA 325 mg for **1 month after BMS implantation**, at least 3 months after a sirolimus DES and 6 months after paclitaxel DES, but, ideally, for up to 12 months if they are not at a high risk for bleeding.

The new AHA/ACC/ACS Science Advisory changed these recommendations in 2007, stating that the original recommendations were based on the antiplatelet regimen of trials conducted to obtain FDA approval (low risk lesions in low risk patients). As DES are now being used in high risk lesions and reports indicate that DES may be associated with delayed endothelialisation, local hypersensitivity reactions and late stent thrombosis, the advisory panel recommends **12 months of dual antiplatelet therapy after placement of a DES in patients who are not at high risk of bleeding**.[1] However, the ideal duration of dual antiplatelet therapy is not yet known, and may need to be extended beyond one-year in patients with additional risk factors for stent thrombosis.[8] Aspirin therapy should be continued life-long.[3]

Risk of non-cardiac surgery after coronary stenting

Peri-operative stent thrombosis has been studied primarily in patients with BMS. There are limited data about the risk of DES thrombosis in this setting.[2]

Bare Metal Stents[11]

The ACC/AHA practice guidelines recommend delaying non-cardiac surgery (NCS) for at least 6 weeks after PCI with BMS. This is based on the assumption that 6 weeks will allow completion of antiplatelet therapy and re-endothelialization of the BMS, thereby decreasing the likelihood of stent thrombosis.

This recommendation is based on several small studies. In a retrospective analysis of 899 patients undergoing NCS within 1 yr after PCI with BMS, Nuttal *et al*. demonstrated a clear association between the duration of time from PCI to NCS and ischaemic cardiac events. The risk of major adverse cardiac events (MACE) decreased from 10.5% to 2.8% if NCS was delayed until 90 days after PCI. NCS performed more than 90 days after PCI with BMS was associated with the lowest risk of in-hospital MACE (2.8%).

Bleeding events were not associated with duration of time between PCI and NCS.

The ACC/AHA guidelines on peri-operative cardiac risk reduction identify type of surgery as a specific risk factor for ischaemic events. Although many surgical procedures performed in a non-urgent setting may be classified as low or intermediate risk, those same procedures performed in an emergency setting are reclassified as high risk. All emergency surgical procedures performed during the study period were therefore defined as high risk in this analysis. Emergency surgery was independently associated with both MACE and bleeding events.

Drug Eluting Stents[12]

To eliminate the premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents, the recent advisory by the ACC/AHA included a recommendation to defer elective procedures with significant risk of bleeding until 12 months after DES, when patients have completed the course of clopidogrel.

In a retrospective analysis of 520 patients who underwent NCS after PCI with DES, Rabbitts *et al*. found no association between MACE (death, STEMI, non–STEMI, stent thrombosis and repeat revascularization with either CABG/PCI) and duration of time from stenting to surgery, but the observed rates of MACE were lowest after 1 year.

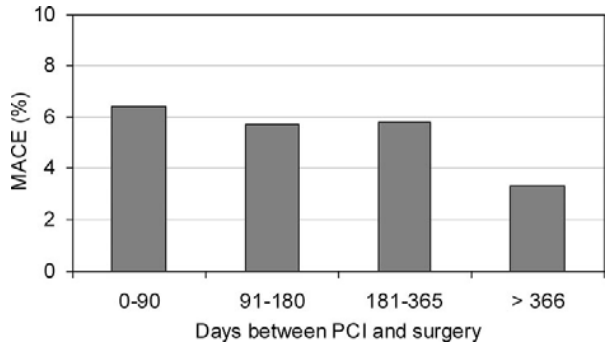

Figure 4. MACE vs. time period between PCI and surgery.[12]

The overall rate of MACE in patients with DES undergoing NCS was 5.4%. Patients presenting for emergency surgery had a much higher rate of MACE (17.9%). This group warrants aggressive preventative measures and monitoring for ischaemia, especially because peri-operative ischemia is often under diagnosed.

Patients who were no longer taking a thienopyridine had the lowest rate of MACE (3.4%), which supports the ACC/AHA recommendation of delaying NCS until completion of the thienopyridine therapy. Peri-operative continuation of clopidogrel may not be a risk factor for MACE, but rather an indicator of patients at increased risk.

An important finding of this study was the low incidence of surgical bleeding complications despite the high rate of antiplatelet therapy use. The incidence of bleeding complications and transfusion requirements did not seem to be related to the use of antiplatelet therapy. The fact that peri-operative antiplatelet therapy is not associated with bleeding events may help to provide evidence for guidelines on peri-operative antiplatelet management in certain subsets of surgical patients.

Bare Metal Stents vs. Drug Eluting Stents [13]

Table 5. Cardiac risk of NCS: BMS vs. DES

	BMS	DES
MACE overall rate	5.2%	5.4%
MACE rate 1st 90 days	7.1%	6.4%
Time from PCI to NCS	MACE decrease	No significant decrease
Emergency surgery	Mace increased (11.7%)	Mace increased (17.9%)
Bleeding complications	No association with time post PCI	Few

The findings in these 2 studies by Nuttal and Rabbits form the basis for the most recent Science Advisory which recommends uninterrupted dual antiplatelet therapy for a minimum period of 1 month after BMS and 1 yr after DES implantation.[13]

For patients with both types of stents, the absolute event rates for NCS were similar during the first 90 days after stent implantation (7.1% and 6.4% for BMS and DES). Then the event rate for the BMS group dropped to 2.8% between 90 and 365 days, whereas the event rate for the DES group during the same period remained relatively constant at 5.8%. These data are possibly explained by the differential rates at which BMS and DES endothelialize. There is growing evidence to support a small (0.5%) but

persistent incidence of very late DES thrombosis, especially in patients where stents were implanted for "off-label" indications. Some cardiologists, therefore, advocate continuing dual antiplatelet therapy indefinitely in patients with DES who are at low risk of bleeding until the long-term risks of stent thrombosis are further clarified.

These two studies also convincingly demonstrated that emergency NCS was associated with a significantly higher MACE rate than non-emergency surgery, regardless of the stent type. Therefore stent patients undergoing emergency NCS are at high risk for peri-operative cardiac events and, therefore, need to be monitored closely and receive aggressive prophylactic therapy for the prevention of peri-operative ischaemia.

Pre-operative use of clopidogrel is well recognized to increase the risk of postoperative bleeding after cardiac surgery and current AHA/ACC guidelines recommend discontinuing its use if clinically feasible at least 5 days before surgery. By comparison, far less is known about the risks of peri-operative bleeding with continued dual antiplatelet therapy after noncardiac surgery. These studies suggest that for many patients with recently implanted coronary stents, the risks of significant surgical bleeding may be outweighed by the benefit of continued antiplatelet therapy.

Coronary stenting prior to NCS

The Coronary Artery Revascularization Prophylaxis (CARP) trial was the first to study prophylactic revascularisation compared with optimal medical therapy in patients with clinically stable coronary artery disease (CAD) scheduled for major non-cardiac vascular surgery. Its conclusion was that prophylactic revascularisation was safe but did not improve peri-operative or long-term outcome. The findings of both CARP and DECREASE V support the current guidelines of the ACC/AHA on peri-operative management in high-risk patients to reserve revascularisation for unstable cardiac patients only.[14]

Choosing a stent for a patient with an acute coronary syndrome, who is known to require NCS in the near future, requires careful consideration. If it is anticipated that surgery can be postponed for at least six months, DES placement might be the treatment of choice. If not, BMS should be considered. In case of anticipated urgent surgery coronary angioplasty alone with post NCS stenting might be an option.[14] The new AHA/ACC/SCAI/ACS/ADA Science Advisory states that[15]

- Elective procedures should be deferred until completion of thienopyridine therapy 12 months after DES.
- BMS should be inserted in patients likely to require surgical procedures within 12 months.

Table 6. Duration of antiplatelet therapy and timing of non-cardiac surgery[4]

	Recommended duration of antiplatelet therapy	Timing of non-cardiac surgery
Balloon dilatation only	2-4 weeks	2-4 weeks
BMS	4-6 weeks	≥ 6 weeks but before 12 weeks (as restenosis may occur)
DES	12 months	≥ 12 months

The peri-operative dilemma

Patients with coronary stents who subsequently present for NCS pose a particular challenge during the peri-operative period. For the anaesthetist the major dilemma is to balance the risk of life threatening stent thrombosis against the risk of potentially major haemorrhage.

The risk of thrombosis

Surgical intervention creates a prothrombotic and proinflammatory state contributing to the development of peri-operative stent thrombosis. The stress response to surgery results in sympathetic activation and cytokine release. These promote shear stress on arterial plaques, enhance vascular reactivity conducive to vasospasm, reduce fibrinolytic activity, increase platelet activation and hypercoagulability. While procoagulant clotting factors increase, fibrinolysis is impaired, producing a hypercoagulable state, which persists for several days post-operatively. Inflammatory activation from endothelial damage exacerbates the prothrombotic state, worsening the susceptibility for thromboembolic events.[8]

Abrupt withdrawal of dual antiplatelet therapy may cause a rebound effect and hypercoaguability. Aspirin if stopped can give rise to increased levels of both COX-1 and TxA_2, which do not return to normal for 3 or 4 days. Complete recovery of platelet function occurs in 50% of patients by day 3 and 80% by day 4. Stopping clopidogrel suddenly may also cause a proinflammatory and prothrombotic state.[4]

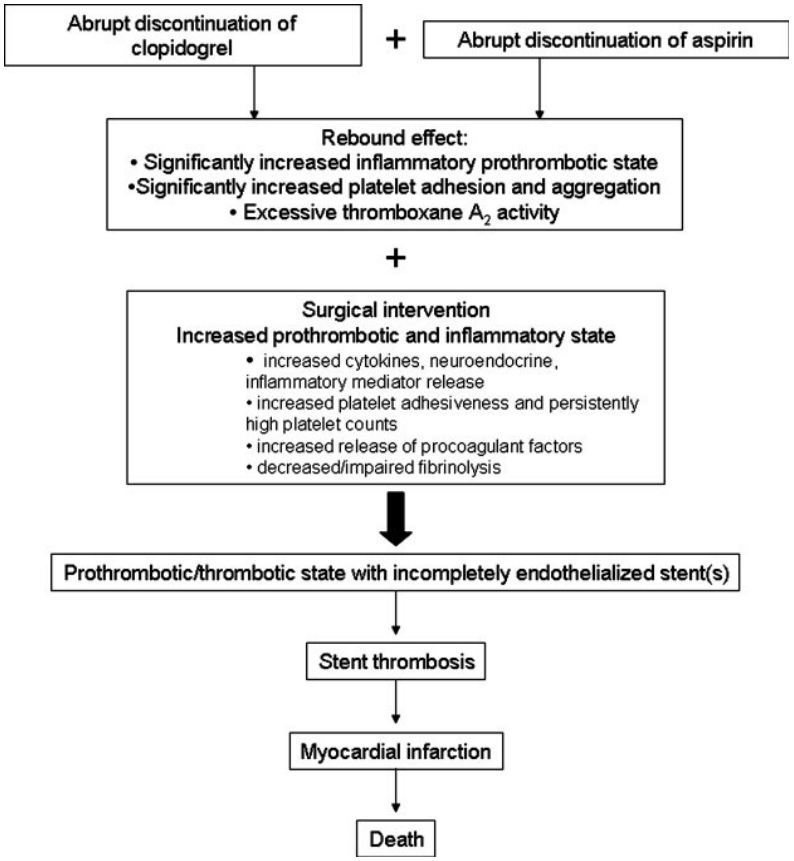

Figure 4. Diagram of the pathophysiology of acute peri-operative stent thrombosis. [8]

Table 7. Risk Factors for Peri-operative Stent Thrombosis with DES[8]

Off-label use (currently only 40% are 'on-label')[4]	Increased platelet activity (surgery, malignancies, diabetes)
Stent(s) implanted in the left main coronary artery	Renal failure/insufficiency
Stent(s) implanted in bifurcations or crossing arterial branch points	Diabetes
Greater total stent length (multiple stents and/or overlapping stents)	Left ventricular dysfunction (<30% EF)[4]
In-stent restenosis	Resistance to antiplatelet medications
Previous in-stent thrombosis[4]	**Inappropriate discontinuation of antiplatelet therapy (This was found to be the strongest independent predictor of stent thrombosis[4])**
Localized hypersensitivity vasculitis (possibly to the stent polymer or antiproliferative drug)	
Penetration by stent into necrotic core	

The risk of bleeding with dual antiplatelet therapy

Most research regarding bleeding with continued antiplatelet therapy has been done in cardiac and vascular surgery. In cardiac surgery patients undergoing ''off-pump'' CABG there were no differences in blood loss between aspirin users and non-users. In ''on-pump'' CABG those patients on dual antiplatelet therapy did have a higher incidence of peri-operative bleeding, re-exploration, transfusion rate and longer ICU and hospital stays.[4]

A meta-analysis by Burger *et al*. looking at the impact of aspirin on surgical blood loss showed an increase of bleeding by a factor of 1.5, without an increase in morbidity or mortality in most specialities except for neurosurgery and possibly transurethral prostate surgery. In orthopaedic surgery there have been conflicting results after finding that there is an increased rate of bleeding in hip arthroplasty, but not in femoral neck fractures.[4]

The CURE Trial (one of the first large, prospective, randomised trials demonstrating the beneficial effect of clopidogrel in addition to ASA on outcome) showed that there were significantly more patients with major bleeding in the clopidogrel group than in the placebo group (3.7% vs. 2.7%; relative risk = 1.38; $p < 0.01$).[1]

Chassot et al., in a recent review[3], estimated that surgical blood loss increases between 2.5–20% for aspirin and 30–50% for clopidogrel used peri-operatively. They found that the need for transfusion was increased by 30%, but mortality was not increased except in intracranial and possibly TURP surgery. Furthermore, the complication rate of red blood cell transfusion was only 0.4%, and mortality due to massive surgical blood loss $\leq$ 3%. This review recommended that patients should continue their dual antiplatelet therapy if possible except if there is a risk of bleeding into a closed space. Then aspirin should be maintained and clopidogrel stopped 7 days before surgery and bridging therapy with shorter acting antiplatelet agents considered. In procedures where blood loss can be controlled easily, there may be no indication to stop antiplatelet drugs.[8]

Assessing thrombotic vs. bleeding risk

At the moment there are no definitive randomised control trials on the peri-operative management of patients with coronary artery stents. This is partly because the optimum duration of dual AP therapy is yet to be established, especially in patients with DES. So, although case reports and series have

been published on the management of these patients, there are no universally agreed guidelines.[4]

Cardiologists, anaesthetists and surgeons together have to plot the risk of thrombosis against the risk of bleeding. Three factors influence the positioning in one of the four "risk fields" (which other experts categorize as low, intermediate and high risk).[15]

1. Surgical procedure-related factors, high bleeding risk procedures – intracranial and spine surgery, urological surgery, abdominal aortic aneurysm, surgery of the retina.
2. Patient-related factors – diabetes mellitus, renal insufficiency, low ejection fraction, discontinuation of AP drugs.
3. Lesion and stent procedure-related factors – type of stent (BMS, DES), time of implantation, number, location and length of stents.

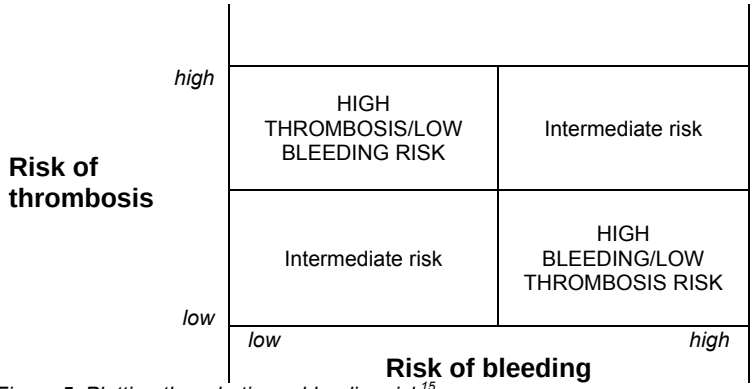

Figure 5. Plotting thrombotic vs. bleeding risk[15]

Table 8. Risk of bleeding vs. risk of thrombosis [1]

Risk of bleeding complications	Peri-operative risk of thrombosis
Time of discontinuation of antiplatelet agents	**Time of discontinuation of antiplatelet agents**
Type of surgery	**Stent associated**
Urological surgery	Type (DES, BMS)
Parenchymatous organ surgery (liver, lung, etc)	Time of implantation
	Number, location and length of stents
Intracranial and spinal surgery	**Other variables**
Abdominal aortic aneurysm	Diabetes mellitus
Surgery of the retina	Renal insufficiency
	Low ejection fraction
	Tumour

Antiplatelet treatment strategies in the peri-operative period[2]

Continue dual antiplatelet therapy during and after surgery. This option would likely be associated with the lowest frequency of stent thrombosis, especially in patients undergoing surgery early after stent implantation. In some procedures, such as dental extractions, cataract surgery or routine dermatologic surgery, bleeding almost always can be controlled with local measures and discontinuation of antiplatelet therapy is not necessary. Even in procedures with a higher bleeding risk, the risk of thrombosis might still outweigh that of bleeding. This strategy would not be appropriate for patients in whom any excess bleeding could have catastrophic consequences, such as neurosurgery patients.

Discontinue clopidogrel but "bridge" the patient to surgery using a short-acting antiplatelet agent with a glycoprotein IIb/IIIa or an antithrombin. Restart clopidogrel as soon as possible after surgery. Thienopyridines cause irreversible platelet inhibition and need to be discontinued for 5 to 10 days to allow the production and release of new platelets into the circulation to replace the inhibited platelets and restore normal haemostasis. If surgery is needed early after stent placement and clopidogrel must be stopped, some clinicians "bridge" the patient to surgery using a short-acting antiplatelet agent or anticoagulant. Because stent thrombosis is primarily a platelet-mediated phenomenon, platelet inhibitors might be a more logical choice if such a strategy is pursued. Furthermore, the cessation of heparin in a patient not on aspirin or other antiplatelet agents has been shown to cause platelet activation and a rebound phenomenon which may actually increase the likelihood of peri-operative stent thrombosis. Admitting a patient to hospital before surgery to bridge them to surgery does not offer complete protection since the greatest risk of stent thrombosis is actually during or after surgery. More data are needed that indicate that such a strategy improves outcome because this is expensive, logistically difficult and exposes the patient to the risks associated with prolonged hospitalization.

Although empiric and without evidence-based data supporting its efficacy, multiple institutions use bridging therapy to prevent peri-operative stent thrombosis. GP IIb/IIIa inhibitors have been favoured since this platelet receptor is the pivotal mediator for platelet aggregation and thrombus formation.[8]

Discontinue clopidogrel before surgery and restart it as soon as possible after surgery. This strategy may be sufficient when the stent is believed to be fully endothelialized and the risk of stent thrombosis is very low. It should also be used whenever clopidogrel cannot be continued throughout the peri-operative period, such as in patients undergoing neurosurgery, in whom bleeding could be catastrophic. Clopidogrel should be restarted with a 600mg loading dose, which reduces the time required to achieve maximal inhibition of platelet aggregation (2-4 hrs) and the frequency of hypo-responsiveness to clopidogrel, particularly among patients with activated platelets as is the case post surgery.

Decision time

The cardiologist, the surgeon and the anaesthetist have to balance the overall peri-operative risk of stent thrombosis vs. surgical bleeding. Based on the available data, treatment of the patient can be guided at an acceptable risk level following the decision tree:

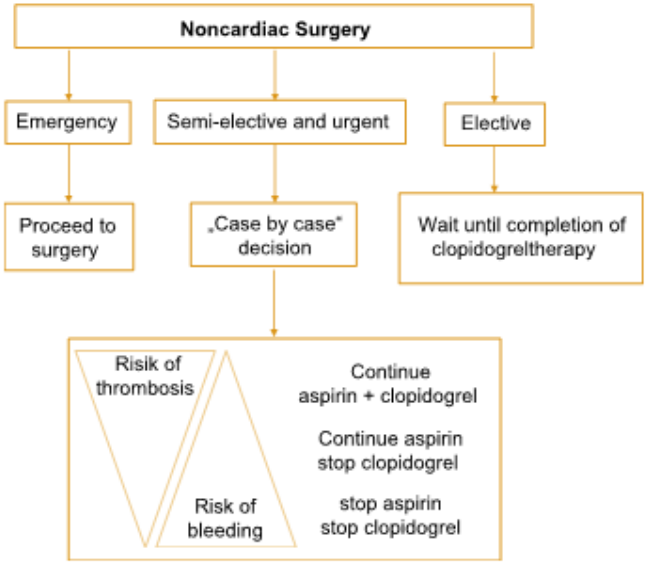

Figure 6. Pre-operative decision tree for a patient with recent stent implantation on dual antiplatelet therapy.[1]

1. Elective surgery should be postponed until the end of mandated clopidogrel therapy.

2. In emergency cases all peri-operative caregivers should be aware of the increased risk of intra- and postoperative bleeding.
3. In semi-elective or urgent cases, management should be tailored to the thrombosis/bleeding tolerance, thus:
   a. In high bleeding/low thrombosis risk scenarios it has to be accepted that the surgeon will insist on discontinuation of clopidogrel and aspirin.
   b. In high thrombosis/low bleeding risk scenarios it may be recommended that dual antiplatelet drug therapy continues until the day or the day before non-cardiac surgery.
   c. In most intermediate cases aspirin, at least, should be continued.

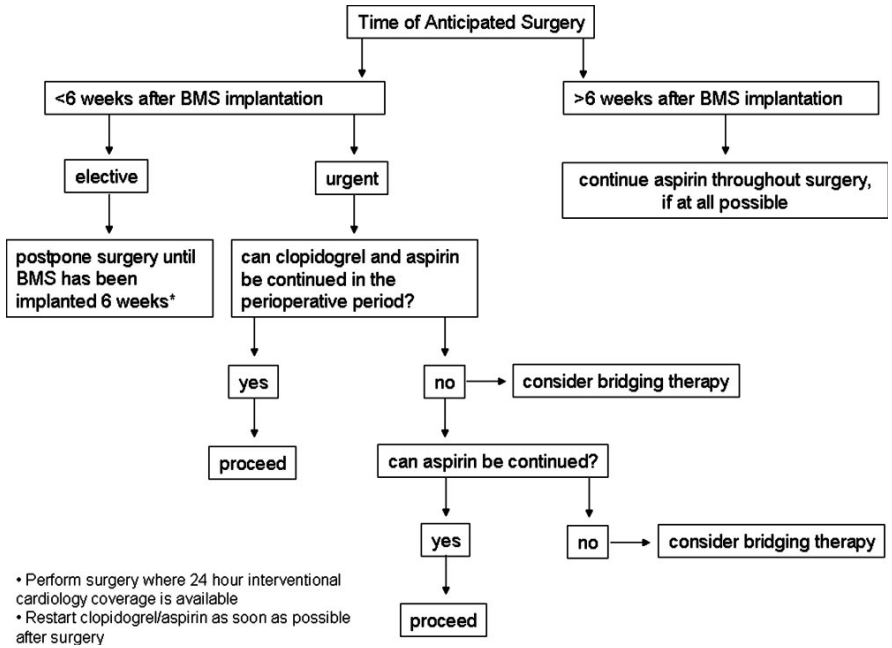

*Figure 7. Proposed algorithm for perioperative management of patients with **bare-metal stents** based on current literature. *The 2007 ACC/AHA perioperative guidelines state, "it appears reasonable to delay elective noncardiac surgery for 4–6 wk to allow for at least partial endothelialization of the stent, but not for more than 12 wk, when restenosis may occur.*[8]

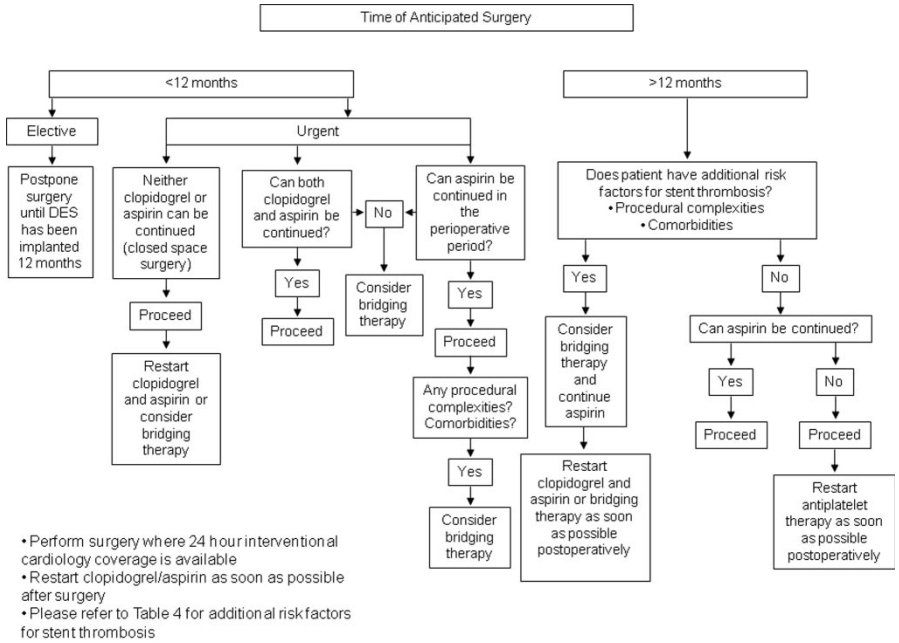

*Figure 8. Proposed algorithm for peri-operative management of patients with **drug-eluting stents** based on current literature.*[8]

Regional anaesthesia (RA)

It is generally interpreted from the 2003 American Society of Regional Anesthesia (ASRA) guidelines that the thienopyridines and dual-antiplatelet therapy are contraindications to neuraxial anaesthesia or peripheral nerve blockade in noncompressible regions that cannot be observed for bleeding. Aspirin alone does not appear to increase the risk of neuraxial haematoma. For patients receiving bridging therapy with eptifibatide or tirofiban, 8 h must elapse before a neuraxial blockade can be performed. Although perioperative platelet transfusions have been suggested in patients on dual AP therapy when RA is considered safest, this practice cannot be justified as the transfusion itself has complications. The appropriate time delay between catheter removal and clopidogrel administration remains undefined. There are also no guidelines for catheter removal preceding GPIIb/IIIa inhibitor administration.[8]

Performance of a neuraxial block, whether a single-shot technique or involving catheter insertion, significantly increases the risk of a spinal haematoma in patients who might subsequently receive antithrombotic

therapy with or without GP IIb/IIIa inhibitors during PCI in case of acute stent thrombosis.

There are no guidelines regarding peripheral nerve blockade and catheters.[8] Nerve blocks causing haemorrhagic complications that are easily treatable (e.g. peripheral nerve blocks), may be performed as atraumatically as possible in these patients without drug discontinuation if their standardised bleeding history is normal.[1]

Based on the current information available, the decision to perform RA should be made case-by-case, with consideration given to all potential complications. The anaesthetist has to choose between keeping the protective effect of clopidogrel and proceeding with general anaesthesia, or stopping clopidogrel for at least 7 days before the operation to perform a neuraxial block and benefit from its sympatholytic and analgesic effects. To the best of our knowledge, the protection of antiplatelet drugs is far more efficient than the effects of regional anaesthesia on arterial thrombosis and on the reduction of MI and cardiac death rates. Also, the intra-operative sympatholysis of epidural anaesthesia can be achieved with intravenous drugs such as β-blockers, α_2-agonists and high dosages of opioids. The only real disadvantage is potentially less post-operative analgesia. In conclusion, the risk/benefit ratio for patients on dual AP therapy is in favour of continuing ASA and clopidogrel and thus renouncing neuraxial blocks.[3]

Table 9. Recommended drug-free intervals prior to regional anaesthesia[1]

Active substance	Time stopped before intervention	Restart after intervention
Clopidogrel	7 days	No interval
Ticlopidine	10 days	No interval
Aspirin	72 hours	No interval

Avoiding peri-operative stent thrombosis[2]

Avoiding preoperative revascularization. The CARP study results suggest that revascularization may not be necessary for a large number of patients without an unstable coronary syndrome or other very high-risk features.

Revascularization without stents (balloon angioplasty only). Revascularization with balloon angioplasty may be safer than stent placement before planned non-cardiac surgery, particularly if it is planned early (within 4 to 6 weeks) after revascularization.

Stent selection before surgery. If stenting cannot be avoided, choosing the stent type should be influenced by the timing of planned surgery. If surgery needs to be performed within 12 months from revascularization, then BMS implantation is likely preferable to DES, because BMS endothelialize more rapidly and may therefore carry a lower risk of stent thrombosis. This is particularly likely if dual antiplatelet therapy cannot be continued through the peri-operative period. If restenosis, which is more likely to occur after BMS than DES, does develop, it almost always does so more than 2 to 3 months after stent placement, at which point the patient already will have undergone the surgical procedure. At that time, a DES could be used to treat the in-stent restenosis.

Delay of surgery. The earlier the surgery is performed after stenting, the higher the risk for stent thrombosis.

Antiplatelet therapy in the peri-operative period. As discussed previously, interruption of dual AP therapy should be minimized as this is the cornerstone of stent thrombosis prevention.

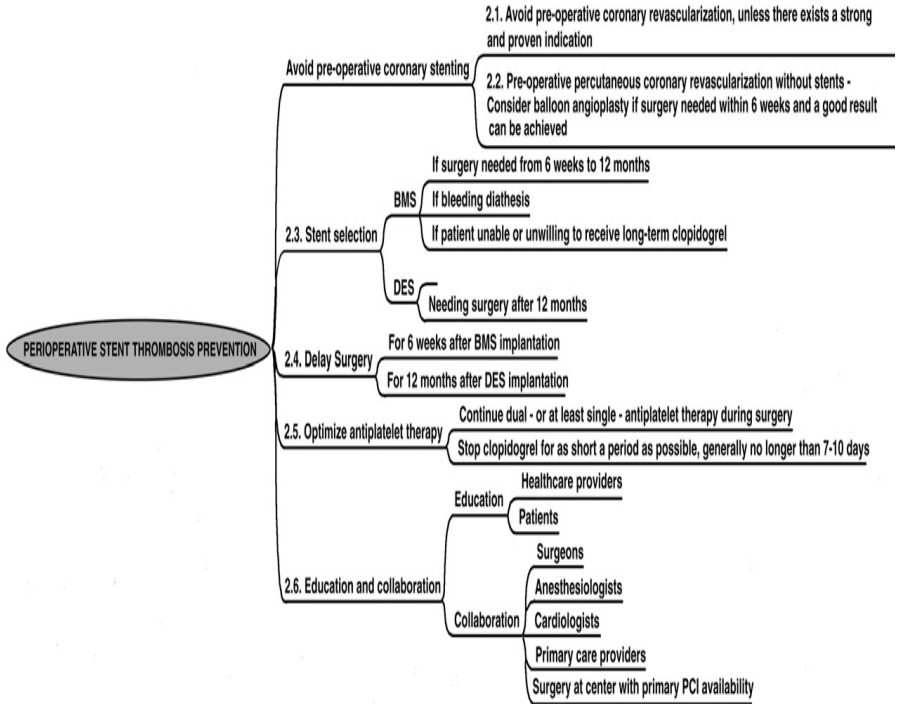

Figure 9. Outline of different strategies to prevent peri-operative stent thrombosis.[2]

Conclusion

The problem with bare metal stents is restenosis. They require a minimum of 4-6 weeks of dual antiplatelet therapy to endothelialize. Drug eluting stents develop late in-stent thrombosis and patients should be on dual antiplatelet therapy for at least 12 months.

The management of patients with coronary stents in the peri-operative period mandates an interdisciplinary approach between cardiologist, anaesthetist and surgeon. The following factors should be considered:

1. Timing of surgery: elective vs. urgent
2. Stent
   a. Type
   b. When placed?
   c. Complications during revascularization
   d. Location in coronary circulation
3. Patient co-morbidities
4. Assessing thrombotic vs. bleeding risk
5. Antiplatelet therapy
   a. Current regimen for patient
   b. When or if to stop
   c. Is there a need for bridging therapy?
   d. When to restart therapy?

The risk/benefit ratio for patients on dual antiplatelet therapy is in favour of continuing aspirin and clopidogrel and thus avoiding neuraxial blocks, despite its potential advantages.[3] Interruption of dual antiplatelet therapy should be minimized as this is the cornerstone of stent thrombosis prevention.[2] Surgical procedures should be performed where 24hr interventional cardiology services are available in case of stent thrombosis requiring emergency PCI.

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