



The Cardiac Society of Australia and New Zealand

Guidelines for the use of antiplatelet therapy in patients with coronary stents undergoing non-cardiac surgery

These guidelines were developed by a committee convened by the Cardiac Society of Australia and New Zealand (CSANZ) comprising representatives from the Royal Australasian College of Surgeons (RACS), the Australian and New Zealand College of Anaesthetists (ANZCA), the Royal Australasian College of Dental Surgeons (RACDS), the Australasian Society of Cardiac and Thoracic Surgeons (ASCTS) and a non-affiliated consumer.

These guidelines were ratified at the CSANZ Board meeting held on Wednesday, 12th August, 2009.

Background

Coronary stent thrombosis is an uncommon but clinically devastating complication of coronary artery stenting that usually results in significant myocardial infarction or death. The pathophysiology of stent thrombosis is related to non-endothelialisation of the stent struts, often due to inadequate deployment or delayed healing in the case of drug eluting stents (1).

Approximately 40% of reported cases have occurred in the context of non-cardiac surgery (NCS) performed in patients with coronary artery stents, in whom dual antiplatelet therapy or clopidogrel alone has been ceased (2).

In patients with coronary disease cessation of aspirin or clopidogrel is associated with an approximate 2-3 fold increase in subsequent death or myocardial infarction (3-5). This risk is further elevated in patients with intracoronary stent and is of added concern because the dramatic consequences of stent occlusion. There is uncertainty regarding the risks of stent thrombosis in individual patients, and in particular how to balance this risk against that of surgical complications if antiplatelet therapy is continued throughout the perioperative period.

This guideline provides consensus advice regarding the use of antiplatelet therapy in patients with intracoronary stents for whom non-cardiac invasive procedures are planned. It is designed for cardiologists, anaesthetists, surgeons and dentists preparing patients for these procedures.

Development of the guideline

Following representation from its members, the Cardiac Society of Australia and New Zealand (CSANZ) convened a committee composing representatives from the Royal Australasian College of Surgeons, the Australian and New Zealand College of Anaesthetists, the Royal Australasian College of Dental Surgeons, the Australasian Society of Cardiac and Thoracic Surgeons and a non-affiliated consumer.

This Committee was charged with the task of producing guidelines for the use of antiplatelet therapy in patients with coronary artery stents undergoing non-cardiac surgery. Individual surgical subspecialty subgroups were also contacted and asked to provide input and comment on the draft guideline. Details of the membership of the committee and the surgical subspecialties who contributed are included in Appendix 1.

A literature review was conducted through searching Medline Database and Cochrane Databases of systematic reviews and Cochrane Central Register of Controlled Trials. Specific MESH search terms included stents, coronary disease, surgery, thrombosis and bleeding. A series of Committee teleconferences were held during which the literature was discussed and consensus recommendations developed.

Following this, the draft guidelines were presented for pilot evaluation at clinical forums in different disciplines. The final guidelines were ratified by the professional societies cited above.

The levels of evidence used in these guidelines are adapted from the National Health and Medical Research Council (NHMRC) levels of evidence for clinical interventions (6) (Appendix 2). This has been combined with the GRADE system of recommendation (7) which incorporates the quality and consistency of evidence, the balance of benefit against harm, and the applicability of the evidence to the local context into a single recommendation term (Appendix 3).

Incidence of stent thrombosis during non-cardiac surgery

It is well established that the risk of stent thrombosis is increased in patients who undergo surgical or invasive dental procedures soon after stent implantation (8, 9). This is contributed to by cessation of antiplatelet therapy in the context of the prothrombotic milieu of the surgical procedure.

Following Percutaneous Coronary Intervention (PCI) with bare metal stenting (BMS)

Stent thrombosis following Percutaneous Coronary Intervention with bare metal stenting occurs most commonly within the first 4 weeks of the procedure. The current American College of Cardiology/American Heart Association/Society for Cardiovascular Interventions practice guidelines recommend continuing dual antiplatelet therapy (DAP) for 1 month following placement of bare metal stents (10). It is recognised that continuing DAP for up to 12 months may further reduce ischaemic events (11), and these guidelines endorse this practice in patients who are not at high risk of bleeding.

In Australia, it has not been common practice to continue DAP for beyond 1 month in patients with bare metal stents in the absence of an acute coronary syndrome presentation. This may change with the Pharmaceutical Benefit Scheme reimbursement of clopidogrel for the indication of coronary artery stenting.

With regard to the specific issue of timing of non-cardiac invasive procedures following PCI with BMS, the first published series reported a mortality rate of 32% in 25 patients having non-cardiac surgery within the first 2 weeks of the stenting procedure (8). A subsequent Mayo clinic analysis showed that of 207 patients undergoing NCS within 9 weeks of stent placement, the death/MI/stent thrombosis rate

was 4.8% (8 patients) for the 168 having surgery within 6 weeks. All ceased DAP for the procedure. None of the 39 patients undergoing surgery between 7 and 9 weeks experienced an event (9).

The 2007 American College of Cardiology/American Heart Association practice guidelines on Perioperative Cardiovascular Evaluation and Care for Non-Cardiac Surgery recommend delaying NCS for at least 6 weeks following PCI with BMS (12). Since these guidelines have been published however, an updated analysis of the Mayo Clinic database including 899 patients undergoing PCI with BMS suggested that the frequency of major in-hospital cardiac events (MACE: death, myocardial infarction, stent thrombosis or repeat revascularisation) was 10.5% when NCS was performed within 4 weeks of stenting, 3.8% when NCS was performed between 31 and 90 days after PCI with BMS and 2.8% when NCS was performed more than 90 days after PCI with BMS. Although the difference between 31-90 and >90 days was not significant, the authors did conclude that the incidence of MACE was lowest if the surgery was performed more than 90 days following PCI with BMS (Table 1) (13).

Summary and recommendations:

Death/MI/stent thrombosis/urgent revascularisation are increased if non-cardiac surgery is performed within 6 weeks of bare metal stenting (5-30%). There would appear to be further reduction of risk if surgery is deferred for at least 3 months following PCI with BMS.

- Elective non-cardiac surgery should be deferred for at least 6 weeks and ideally 3 months following PCI with bare metal stenting (Level of Evidence III-3, GRADE of recommendation A).

Following PCI with drug eluting stenting (DES)

Late stent thrombosis (> 1 month) has been reported more frequently following placement of drug eluting stents than after BMS, in part attributable to delayed endothelialisation following DES. In view of this, the current American College of Cardiology/American Heart Association/Society for Cardiovascular Interventions practice guidelines recommend continuing DAP for 12 months following the placement of DES in patients who are not at high risk of bleeding (10).

Thrombotic events have been reported beyond this time; with a large registry analysis of 8,146 patients showing a steady incidence of 0.4-0.6% per year for 4 years following DES in patients not receiving DAP (14). An FDA advisory panel on drug eluting stents convened to address the issue of DES thrombosis endorsed the recommended duration of 12 months but suggested that large randomised trials looking at the appropriate duration of antiplatelet therapy are required.

The specific question of timing of non-cardiac surgery following PCI with DES has been addressed by several recent studies. Schouten et al reported a series of 192 patients undergoing non-cardiac surgery within 2 years of either bare metal or drug eluting stent placement (15). Early surgery was defined as <1 month post BMS, 3 months post Sirolimus eluting stents (SES), 6 months post Paclitaxel eluting stents (PES). Of the 30 patients who had early surgery, 4 had a fatal event (13.3%). All 4 patients had stopped DAP; the event rate among the early surgery group who stopped DAP was 30%. No patients who continued antiplatelet therapy had an event. Of the 162 patients who had late surgery, only 1 had a fatal event (0.6%). This patient had ceased antiplatelet therapy.

A Korean group reported on 141 patients requiring surgery with discontinuation of dual antiplatelet therapy within 12 months of PCI with DES (16). Stent thrombosis occurred in 7 cases (5%). A prolonged period of discontinuation of clopidogrel was associated with higher risk of stent thrombosis during the perioperative period.

The Mayo clinic recently reported their experience on 520 patients undergoing NCS within 2 years of PCI with DES (17). In contrast to earlier studies, 70% of patients continued aspirin within 1 week of surgery and 35% continued both aspirin and clopidogrel. The risk of MACE (death, MI, ST, urgent

revascularisation) attenuated over time: 0-3 months: 6.4%, 3-6 months: 5.7%, 6 months-1yr: 5.9%, >1yr: 3.3% (Table 1). These differences were not significant.

Low event rates were reported in a Cleveland Clinic study linking PCI and NCS databases suggested the risk of coronary events among patients with DES undergoing NCS to be small. They identified 114 patients who had undergone non-cardiac surgery following DES. 45 of these procedures were performed within 6 months, and 15 within 3 months of PCI. Most (77%) discontinued AP therapy and only 2 MIs were reported (18). All these surgical procedures were low risk.

The 2007 American College of Cardiology/American Heart Association practice guidelines on Perioperative Cardiovascular Evaluation and Care for Non-Cardiac Surgery recommend delaying NCS for at least 12 months following PCI with DES (12). This recommendation is acknowledged to be somewhat arbitrary because of lack of high quality evidence which is based on expert opinion. There has been no stronger evidence since this guideline was published, and the writing group endorses this recommendation.

Summary and recommendations:

Perioperative death/MI/stent thrombosis occurs in at least 5% of patients if dual antiplatelet therapy is ceased and non-cardiac surgery performed within 12 months of DES placement.

- Elective surgery should be deferred for 12 months following DES because of a likely increased risk of death/myocardial infarction/stent thrombosis (Level of Evidence IV, GRADE of recommendation B).

Predictors of stent thrombosis

In addition to the duration of time that has elapsed since stent placement, patients with a previous stent thrombosis have a high recurrence rate (19), and stents placed in unprotected left main coronary arteries represent particularly high risk situations because the consequences of stent occlusion can be catastrophic (20). There are a number of additional anatomic and clinical features that contribute to the risk of drug eluting stent thrombosis. These factors have been identified from individual registries and the strength of association varies (21-23). The data is not sufficiently robust to enable the development of a pooled relative risk estimate for each variable and it is likely that these factors will change as further information become available.

The clinical and stent related factors that increase the likelihood of stent thrombosis when antiplatelet therapy is reduced or stopped are included in Table 2.

Bleeding risks associated with continued antiplatelet therapy in patients undergoing non-cardiac surgery.

Aspirin:

A recent literature based meta-analysis identified 41 studies of low dose aspirin, reporting on 49,590 patients (14,981 on aspirin) (24). Whilst aspirin increased the rate of bleeding complications by 50%, it did not lead to a higher level of the severity of bleeding complications except for intracranial surgery and transurethral prostatectomy (see below).

Clopidogrel:

With the exception of patients undergoing CABG, there are few studies reporting on the use of clopidogrel in addition to aspirin. In a retrospective study of major non-cardiac surgery soon after coronary stenting, stent thrombosis was implicated in 6/7 patients who died after ceasing thienopyridine

therapy, however only 1 of 20 patients who continued the thienopyridine died. Requirements for transfusion were similar whether or not the antiplatelet agent was continued (25). A recent review of non CABG surgical procedures concluded clopidogrel added to aspirin increased the risk of bleeding by a further 50% but with no increase in mortality except during intracranial surgery (26).

Most practicing surgeons regard the published literature as insufficient to guide clinical practice in the majority of circumstances. The best evidence available is therefore that provided by the limited literature interpreted through expert opinion. The following is a summary of the recommendations of the craft groups representing each of the major surgical subspecialties regarding the risk and clinical consequences of bleeding in patients undergoing procedures while receiving antiplatelet therapy.

Orthopaedic: A large haematoma following elective joint replacement surgery is a significant event which can lead to other complications such as permanent stiffness, or nerve compression or compartment syndrome or wound breakdown and infection. The principle that is followed is that any risk which can be lowered should be adjusted prior to elective surgery.

In trauma situations the situation is quite different and surgeons must often accept the reality of having to operate while antiplatelet agents are still active, as the alternative (bed rest or traction) is often more harmful. An Australian retrospective review of 181 patients with proximal femoral fracture demonstrated no significant difference in the amount of bleeding, transfusion requirement, complication rate or length of stay in 16 patients taking clopidogrel and in 48 taking aspirin (27).

Ophthalmology: The most serious bleeding complication for ophthalmology would be retro-bulbar haemorrhage with consequent pressure on the optic nerve and the risk of blindness. The frequency of retro-bulbar haemorrhage is quoted as a range from 1-3% but only a fraction of these are sight threatening. While antiplatelet agents do not cause the haemorrhages, they do compound the problem. For intraocular procedures, mainly cataract and retinal surgery, the risk of bleeding relates to the anaesthetist's technique. Intraocular surgery does not require stopping antiplatelet agents in the majority of cases. For extraocular surgery, mainly strabismus and oculo-plastic surgery, the ophthalmologist would prefer that these agents be stopped.

Dental surgery: Surgery can generally be performed on aspirin, and if necessary, clopidogrel. Several precautions should be taken. Local anaesthetic should contain adrenaline or nor-adrenaline or both. Elective cases should be performed in the mornings to minimise the likelihood of bleeding occurring after hours. Bleeding can usually be contained using local measures.

ENT surgery: Although there is some evidence that performing a tonsillectomy on a patient receiving aspirin may increase reoperation rate 7.2 times, this operation is rare in stented patients.

Urological surgery: TURP is the most widely performed urological procedure. In one series, transfusion rate increased 2.7 fold with 2 fatalities (28). This was not replicated in other studies and practices vary between urologists, with some prepared to perform TURP on patients receiving aspirin (24). Discussion with the urologist is recommended for these patients.

Intracranial neurosurgery: ASA has been implicated in increased risk of postoperative intracerebral haematoma contributing to fatal outcome in some cases. Antiplatelet therapy should be ceased in patients undergoing intracranial surgery.

Spinal surgery: The consequences of bleeding into the closed spinal canal can result in irreversible cord damage. Cessation of antiplatelet therapy recommended.

Gastrointestinal surgery: Bleeding becomes a major consideration when the area of dissection is extensive and the associated tissues are fragile. In a retrospective review of 50 patients having major abdominal surgery, patients who took clopidogrel within 6 days of surgery compared to those who

ceased clopidogrel for longer than 6 days had no difference in transfusion rate or outcome despite an observed increase in bleeding (29).

Plastic and Reconstructive surgery: Minor skin surgery (excision of skin lesions with primary closure/flaps or grafts). Review of the published literature supports the continuation of antiplatelet agents in this setting (30, 31). Major reconstructive surgery usually follows extirpative oncological excisional surgery. In many situations these patients are at high risk of bleeding related complications. In this setting the relative risk benefits of the individual procedure needs to be discussed by the multidisciplinary team.

Summary and recommendations:

Despite the observation that dual antiplatelet therapy increases the likelihood of bleeding for most surgical procedures, the consequences of bleeding are less significant than those of stent thrombosis.

- The risk benefit ratio would favour continuation of aspirin in most patients and DAP in many patients with prior coronary artery stenting undergoing non-cardiac surgery (Level of evidence IV, GRADE of recommendation: B)
- Exceptions to this include patients undergoing spinal, intracranial, extraocular TURP or major plastic reconstructive procedures. For these operations, patients at low risk of stent thrombosis should have their antiplatelet therapy routinely ceased perioperatively (Level of evidence IV, GRADE of recommendation A).

Approach to the patient at high risk of stent thrombosis and high risk of bleeding related complications undergoing non-cardiac surgery.

Patients at high risk of perioperative stent thrombosis should have their surgical procedures performed at sites with 24/7 availability of a PCI service to ensure optimal treatment of an acute coronary occlusive event should it occur. They should be monitored in a high dependency area in the perioperative period. For patients at high risk of stent thrombosis in whom clopidogrel is ceased in the perioperative period, consideration should be given to perioperative bridging with short acting therapy, although this is an unproven concept (see below). Clopidogrel ± aspirin should be ceased 5 days prior to surgery and alternative short acting therapy commenced 3 days prior to surgery. Timing of cessation of bridging therapy will depend on drug half-life. Clopidogrel should be recommenced on the first post operative day unless this is precluded by ongoing bleeding risk. The (limited) data supporting individual bridging therapies are discussed below.

Heparins

There are two prospective studies examining the use of UFH/LMWH in patients with coronary stents in the perioperative setting. Vicenzi (32) reported 103 patients who had coronary stenting within 1 year of non-cardiac surgery. Antiplatelet therapy was either continued or discontinued for less than 3 days before operation; all patients received therapeutic doses of heparin or enoxaparin. 21% of patients suffered myocardial infarction perioperatively, 14% had emergency PCI, with an overall mortality of 4.9%, all attributed to cardiac causes. Bleeding complications were identified in 7%. Patients who underwent surgery <35 days after stenting had a 2.1 fold increase in events compared to surgery >90 days after insertion, confirming the earlier experience with bare metal stents (8). Weaknesses of this study include the failure to distinguish between patients with BMS and DES, and details on the timing and duration of anticoagulant therapy were unclear.

Godet (33) prospectively reported 96 consecutive patients with DES undergoing non-cardiac surgery. The average interval between stenting and surgery was 14 months. Clopidogrel was ceased in 35 of 72 patients, aspirin in 23 of 90. LMWH was administered to 25 patients (85-100IU antiXa/kg, twice daily in 9 patients and daily in 16). All patients received LMWH in the postoperative period until clopidogrel

was reintroduced. Two stent thromboses occurred, both in patients who had stopped DAP, and 12% of patients had a troponin rise. One stent thrombosis occurred in a BMS after withdrawal of DAP despite being given LMWH 40mg BD for 8 days to cover 3 DES and 8 BMS. The other stent thrombosis occurred in a DES 32 months after insertion after withdrawal of DAP without prophylaxis (personal communication, Godet).

Although anticoagulant therapy can impact favourably on the prothrombotic environment engendered during surgery, stent thrombosis is primarily a platelet-mediated phenomenon. This likely explains why the use of anticoagulant therapy alone has not provided comprehensive protection against stent thrombosis in the reported studies to date.

GP IIb/IIIa inhibitors

Antagonism of the platelet GIIb/IIIa receptor inhibits platelets cross-linking to fibrinogen, blocking the major pathway in platelet aggregation. As platelets are thought to play the central role in stent thrombosis, their use appears more theoretically sound than heparin anticoagulants.

There are a limited number of case reports in the literature on GP IIb/IIIa inhibitors for perioperative stent thrombosis prophylaxis. One case report describes a patient who required angioplasty and eptifibatide infusion to treat subacute thrombosis of a recently placed BMS. The patient then developed hematemesis and required major upper gastrointestinal surgery to treat a Mallory-Weiss tear. The eptifibatide infusion was continued postoperatively until recurrent hematemesis required its cessation on the 8th postoperative day, and within 4 hours the patient developed recurrent stent thrombosis (34).

A group at Geelong in Victoria have reported a case series of 3 applications of a heparin/tirofiban protocol (35) and now have an accumulated series of 15 patients without thrombotic or major bleeding complications (Myles Conroy, personal communication). The rationale for including unfractionated heparin is based on the findings of the PRISM-PLUS study (36) in acute coronary syndrome (ACS), in which one arm was terminated early because use of tirofiban without heparin was associated with an increased mortality at 7 days. Procedure types have included hip arthroplasty, arthroscopic shoulder surgery, transurethral resection of prostate and bladder tumours, hernia repair, and colonoscopy polyp resection. Bridging details are as follows: clopidogrel is ceased 5 days before surgery. Tirofiban and heparin are commenced 3 days before surgery and ceased 8 hours prior to start of surgery. Clopidogrel 300mg is given on the morning of the first post operative day.

Currently there is a prospective observational study underway at Cedars-Sinai Medical Center examining the use of tirofiban bridging therapy prior to non-cardiac surgery (37).

Evolving and future therapies

Bivalirudin

This direct antithrombin agent requires intravenous infusion but is associated with a reduction in bleeding risk relative to tirofiban and heparin (38). There is no reversal agent but its half-life is only 25 minutes, with full return of thrombin activity in 1-2 hours. Like heparin and low molecular heparin, it does not have a direct antiplatelet effect which theoretically limits its efficacy in this setting. There is one case report of the use of the direct thrombin inhibitor following drug eluting stent insertion to treat a myocardial infarction in the immediate postoperative period following TKR, without bleeding or further cardiac complication.

Short acting P2Y₁₂ antagonists

ADP receptor blockers have a similar mechanism of action to clopidogrel and two are undergoing phase 3 evaluation at present (39). The intravenous reversible ADP inhibitor Cangrelor is being evaluated as short term bridging therapy in 200 patients undergoing non-cardiac surgery (40). The orally administered short-acting reversible antiplatelet agents Ticagrelor (AZD6140) has the advantage of allowing home-based therapy. However, in preoperative use reliable offset is also required – a phase I

study showed 57% inhibition of platelet aggregation persisted at 24h (41) suggesting that a period of greater than 24h off therapy may be required if bleeding risk is high.

Summary and recommendations:

Perioperative anticoagulation with heparin or LMW heparin provides incomplete protection against stent related complications. Tirofiban/heparin or eptifibatid/heparin therapy have the theoretical advantages of providing antiplatelet cover, and allowing use of existing protocols familiar to interventional cardiology units. The current data however is not sufficient to merit unequivocal recommendation for this strategy in patients at high risk for stent thrombosis undergoing non-cardiac surgery.

- Patients at high risk of perioperative stent thrombosis should have their surgical procedures performed at sites with 24/7 availability of a PCI service. They should be monitored in a high dependency area in the perioperative period. (Level of evidence IV, GRADE of recommendation B)
- Patients at higher risk of stent thrombosis should have antiplatelet therapy continued where possible. (Level of evidence III-3, GRADE of recommendation B.)
- If clopidogrel ± aspirin must be ceased in patients receiving DAP, bridging strategies could be considered. (Level of evidence IV, GRADE of recommendation B.)
- Of currently available bridging strategies, heparin/tirofiban or heparin/eptifibatid have theoretical advantages over heparin/LMW heparin alone, although there are limited data in support of these treatments (Level of evidence IV, GRADE of recommendation B)

Guidelines for the use of antiplatelet therapy in patients with coronary stents undergoing non-cardiac surgery

Final summary and recommendations

Summary:

- Death/MI/stent thrombosis/urgent revascularisation are increased if non-cardiac surgery is performed within 6 weeks of bare metal stenting (5-30%). There would appear to be further reduction of risk if surgery is deferred for at least 3 months following PCI with BMS.
- Perioperative death/MI/stent thrombosis occurs in at least 5% of patients if dual antiplatelet therapy is ceased and non-cardiac surgery performed within 12 months of DES placement.
- Despite the observation that dual antiplatelet therapy increases the likelihood of bleeding for most surgical procedures, the consequences of this bleeding are generally less significant than those of stent thrombosis.
- Perioperative anticoagulation with heparin or LMW heparin provides incomplete protection against stent related complications. Tirofiban/heparin or eptifibatid/heparin therapy have theoretical advantages however the current data are not sufficient to merit unequivocal recommendation for this strategy in patients at higher risk for stent thrombosis undergoing non-cardiac surgery.

Recommendations:

- Elective non-cardiac surgery should be deferred for at least 6 weeks and ideally 3 months following PCI with bare metal stenting (Level of evidence III-3, GRADE of recommendation A).
- Elective non-cardiac surgery should be deferred for 12 months following DES (Level of evidence IV, GRADE of recommendation B).
- Wherever possible, continuation of antiplatelet therapy is recommended in patients with prior coronary artery stenting undergoing non-cardiac surgery (Level of evidence III-3, GRADE of recommendation B).
- Exceptions to this include patients undergoing spinal, intracranial, extraocular, TURP or major plastic reconstructive procedures. For these patients antiplatelet therapy should be ceased perioperatively (Level of evidence IV, GRADE of recommendation A).
- Patients at high risk of stent thrombosis in whom antiplatelet therapy is ceased perioperatively should have their procedures performed at facilities with capacity for 24/7 PCI, and should be monitored in a high dependency area in the peri-operative period (Level of evidence IV, GRADE of recommendation B).
- In selected cases, in patients receiving DAP prior to surgery, consideration may be given to receive bridging therapy with heparin/tirofiban or heparin/eptifibatid although there are limited data in support of such treatments (Level of evidence IV, GRADE of recommendation B).

**General approach to patients with prior coronary artery stents
undergoing non-cardiac surgery**

- Surgeons must contact the patient's cardiologist prior to surgery if a stent has been implanted
- Evaluate the risk for stent thrombosis (Table 2)
- If possible, defer surgery until 'course' of dual antiplatelet therapy complete (6 weeks to 3 months following BMS and 12 months following DES)
- If surgery is required for a patient at high risk of stent thrombosis ensure a multidisciplinary consultation with the patient's cardiologist and anaesthetist
- Ensure the patient is informed of the relative risks and consequences of both stent thrombosis and bleeding complications
- Ensure the surgical procedure is performed at a facility equipped to adequately monitor for and rapidly treat perioperative stent thrombosis
- Tailor antiplatelet therapy according to risk (Table 3)
- Recommence oral antiplatelet therapy as soon as possible following the procedure

**Table 1: MACE* rates according to days from stent to non-cardiac surgery for
bare metal and drug eluting stents**

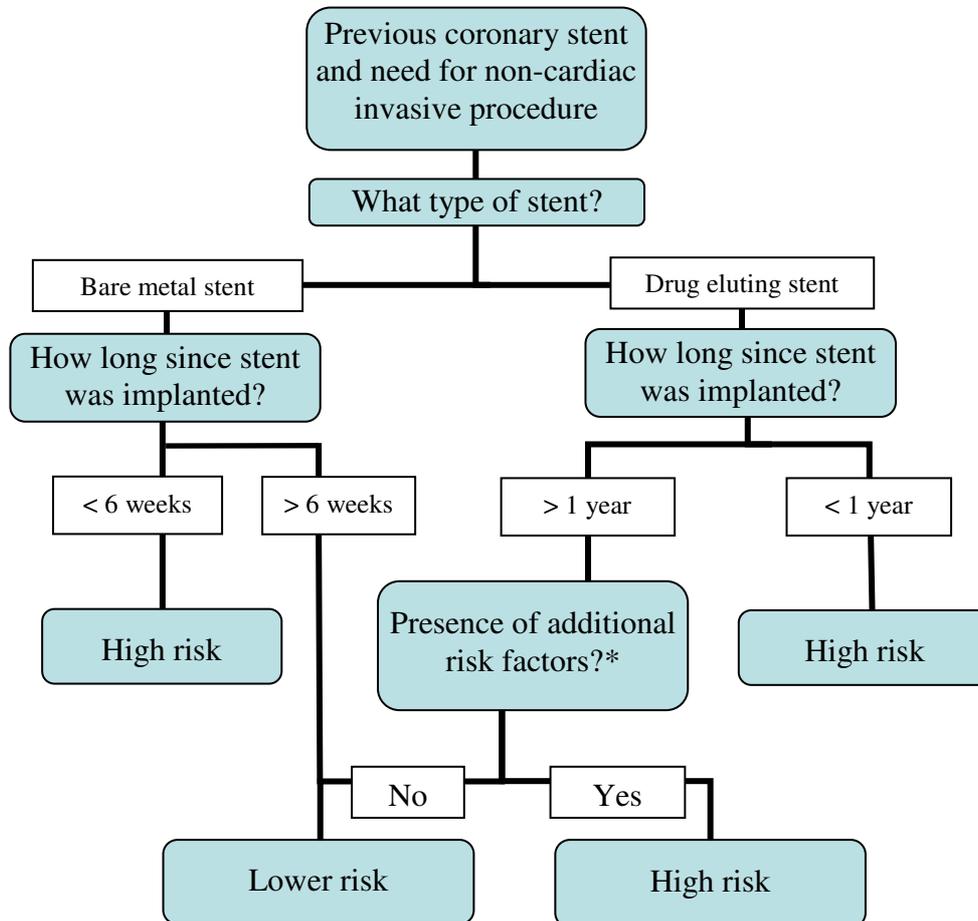
<u>BMS (n=899)</u>		<u>DES (n=520)</u>	
<u>Time (days)</u>	<u>MACE (%)</u>	<u>Time (days)</u>	<u>MACE (%)</u>
<u>≤ 30</u>	<u>10.5</u>		
<u>31-90</u>	<u>3.8</u>	<u>≤ 90</u>	<u>6.4</u>
<u>≥ 91</u>	<u>2.8</u>	<u>91-180</u>	<u>5.7</u>
		<u>181-365</u>	<u>5.9</u>
		<u>366-730</u>	<u>3.3</u>

***MACE**: death, myocardial infarction, stent thrombosis or repeat revascularisation

BMS: bare metal stent, **DES**: drug eluting stent

Data from Mayo Clinic, adapted from (13, 17)

Table 2: Evaluating risk for stent thrombosis



Additional risk factors for stent thrombosis	
Clinical factors: <ul style="list-style-type: none"> • Previous stent thrombosis • Advanced age (>80 years) • ACS indication for stent • Diabetes • Renal impairment • Low ejection fraction 	Anatomic factors <ul style="list-style-type: none"> • Left main stenting • Bifurcation stenting • Ostial stenting • Small (<3mm) stent • Long (>18mm) stent • Multiple stents

***There is insufficient published data to quantify additional risk associated with each identified risk factor and clinical judgement is required. Each factor contributes independently; the greater the number of risk factors, the greater the perioperative risk of stent thrombosis.**

Adapted from (42)

Table 3: Perioperative antiplatelet therapy tailored to risk

	ST risk high	ST risk lower
Bleeding complication risk high: <ul style="list-style-type: none"> • <i>Intracranial</i> • <i>Spinal</i> • <i>Extraocular</i> • <i>TURP</i> 	Stop antiplatelet therapy* and if on DAP, consider bridging therapy	Stop antiplatelet therapy*
Bleeding complication risk not high	Continue antiplatelet therapy	Continue antiplatelet therapy

* Stopping DAP 5 days before surgery is adequate to prevent bleeding complications (43). Antiplatelet therapy should be recommenced as soon as possible after the procedure.

Appendix 1

Writing Committee:

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Royal Australasian College of Surgeons (RACS)
Australasian Society of Cardiac and Thoracic Surgeons (ASCTS)
Australian and New Zealand College of Anaesthetists (ANZCA)
Royal Australasian College of Dental Surgeons (RACDS)

Australian and New Zealand Society for Vascular Surgery
Australian Orthopaedic Association
Australian Society of Otolaryngology Head and Neck Surgery
Australian Society of Plastic Surgeons
General Surgeons Australia
Neurosurgical Society of Australia
Royal Australian and New Zealand College of Ophthalmologists
Urological Society of Australia and New Zealand

Appendix 2

NHMRC levels of evidence

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly designed randomised controlled trial
III-1	Evidence obtained from well designed pseudo-randomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series with a parallel control group
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series with a parallel control group.
IV	Evidence obtained from case series, either post-test or pre-test and post-test

Appendix 3

The GRADE approach to evaluating quality of evidence and strength of recommendations (7)

The GRADE system is a systematic and explicit approach to making judgements about the quality of evidence and the strength of recommendations.

The approach takes into account study design, study quality, consistency and directness in judging the quality of evidence for each important outcome.

The balance between benefits and harms, quality of evidence, applicability, and the certainty of the baseline risk are all considered in judgements about the strength of the recommendation.

GRADE of Recommendation	Interpretation
A	indicating a judgment that most well informed people would make
B	indicating a judgment that a majority of well informed people would make but a substantial minority would not.

References

1. Bavry AA, Bhatt DL. Appropriate use of drug-eluting stents: balancing the reduction in restenosis with the concern of late thrombosis. *Lancet*. 2008 Jun 21;371(9630):2134-43.
2. Artang R, Dieter RS. Analysis of 36 reported cases of late thrombosis in drug-eluting stents placed in coronary arteries. *Am J Cardiol*. 2007 Apr 15;99(8):1039-43.
3. Biondi-Zoccai GGL, Lotrionte M, Agostoni P, Abbate A, Fusaro M, Burzotta F, et al. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. *Eur Heart J*. 2006 Nov;27(22):2667-74.
4. Collet JP, Montalescot G, Blanchet B, Tanguy ML, Golmard JL, Choussat R, et al. Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndromes. *Circulation*. 2004 Oct 19;110(16):2361-7.
5. Ho PM, Peterson ED, Wang L, Magid DJ, Fihn SD, Larsen GC, et al. Incidence of death and acute myocardial infarction associated with stopping clopidogrel after acute coronary syndrome. *Jama*. 2008 Feb 6;299(5):532-9.
6. National Health and Medical Research Council. A guide to the development, implementation and evaluation of clinical practice guidelines. 1999.
7. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. *BMJ*. 2004 Jun 19;328(7454):1490.
8. Kaluza GL, Joseph J, Lee JR, Raizner ME, Raizner AE. Catastrophic outcomes of noncardiac surgery soon after coronary stenting.[see comment]. *J Am Coll Cardiol*. 2000 Apr;35(5):1288-94.
9. Wilson SH, Fasseas P, Orford JL, Lennon RJ, Horlocker T, Charnoff NE, et al. Clinical outcome of patients undergoing non-cardiac surgery in the two months following coronary stenting.[see comment]. *J Am Coll Cardiol*. 2003 Jul 16;42(2):234-40.
10. King SB, 3rd, Smith SC, Jr., Hirshfeld JW, Jr., Jacobs AK, Morrison DA, Williams DO, et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. *J Am Coll Cardiol*. 2008 Jan 15;51(2):172-209.
11. Steinhubl SR, Berger PB, Mann JT, 3rd, Fry ET, DeLago A, Wilmer C, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *Jama*. 2002 Nov 20;288(19):2411-20.
12. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof EL, Fleischmann KE, et al. ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *J Am Coll Cardiol*. 2007 Oct 23;50(17):1707-32.
13. Nuttall GA, Brown MJ, Stombaugh JW, Michon PB, Hathaway MF, Lindeen KC, et al. Time and cardiac risk of surgery after bare-metal stent percutaneous coronary intervention. *Anesthesiology*. 2008 Oct;109(4):588-95.
14. Wenaweser P, Daemen J, Zwahlen M, van Domburg R, Juni P, Vaina S, et al. Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice. 4-year results from a large 2-institutional cohort study. *J Am Coll Cardiol*. 2008 Sep 30;52(14):1134-40.
15. Schouten O, van Domburg RT, Bax JJ, de Jaegere PJ, Dunkelgrun M, Feringa HH, et al. Noncardiac surgery after coronary stenting: early surgery and interruption of antiplatelet therapy are associated with an increase in major adverse cardiac events. *J Am Coll Cardiol*. 2007 Jan 2;49(1):122-4.
16. Rhee SJ, Yun KH, Lee SR, Chae J-K, Nam C-W, Jun D-H, et al. Drug-eluting stent thrombosis during perioperative period. *Int Heart J*. 2008 Mar;49(2):135-42.
17. Rabbitts JA, Nuttall GA, Brown MJ, Hanson AC, Oliver WC, Holmes DR, et al. Cardiac risk of noncardiac surgery after percutaneous coronary intervention with drug-eluting stents. *Anesthesiology*. 2008 Oct;109(4):596-604.

18. Brotman DJ, Bakhru M, Saber W, Aneja A, Bhatt DL, Tillan-Martinez K, et al. Discontinuation of antiplatelet therapy prior to low-risk noncardiac surgery in patients with drug-eluting stents: a retrospective cohort study. *J Hosp Med.* 2007 Nov;2(6):378-84.
19. van Werkum JW, Heestermaans AA, de Korte FI, Kelder JC, Suttorp MJ, Rensing BJ, et al. Long-term clinical outcome after a first angiographically confirmed coronary stent thrombosis: an analysis of 431 cases. *Circulation.* 2009 Feb 17;119(6):828-34.
20. Goldberg RJ, Gore JM, Alpert JS, Osganian V, de Groot J, Bade J, et al. Cardiogenic shock after acute myocardial infarction. Incidence and mortality from a community-wide perspective, 1975 to 1988. *N Engl J Med.* 1991 Oct 17;325(16):1117-22.
21. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents.[see comment]. *Jama.* 2005 May 4;293(17):2126-30.
22. Airolidi F, Colombo A, Morici N, Latib A, Cosgrave J, Buellfeld L, et al. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment.[see comment]. *Circulation.* 2007 Aug 14;116(7):745-54.
23. Daemen J, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study.[see comment]. *Lancet.* 2007 Feb 24;369(9562):667-78.
24. Burger W, Chemnitius JM, Kneissl GD, Rucker G. Low-dose aspirin for secondary cardiovascular prevention - cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation - review and meta-analysis.[see comment]. *J Intern Med.* 2005 May;257(5):399-414.
25. Sharma AK, Ajani AE, Hamwi SM, Maniar P, Lakhani SV, Waksman R, et al. Major noncardiac surgery following coronary stenting: when is it safe to operate?[see comment]. *Catheter Cardiovasc Interv.* 2004 Oct;63(2):141-5.
26. Chassot PG, Delabays A, Spahn DR. Perioperative antiplatelet therapy: the case for continuing therapy in patients at risk of myocardial infarction. *Br J Anaesth.* 2007 Sep;99(3):316-28.
27. Walsh NA, Khatib Y, Molnar R. Perioperative complications associated with clopidogrel in patients presenting with a proximal femoral fracture. *Australian Orthopaedic Association Scientific Meeting 2007.* p. 27.
28. Thurston AV, Briant SL. Aspirin and post-prostatectomy haemorrhage. *Br J Urol.* 1993 May;71(5):574-6.
29. Ozao-Choy J, Tammaro Y, Fradis M, Weber K, Divino CM. Clopidogrel and bleeding after general surgery procedures. *Am Surg.* 2008 Aug;74(8):721-5.
30. Khalifeh MR, Redett RJ. The management of patients on anticoagulants prior to cutaneous surgery: case report of a thromboembolic complication, review of the literature, and evidence-based recommendations. *Plast Reconstr Surg.* 2006 Oct;118(5):110e-7e.
31. Muskett A, Barber WHt, Lineaweaver WC. The plastic surgeon's guide to drugs affecting hemostasis. *Ann Plast Surg.* 2005 May;54(5):570-6.
32. Vicenzi MN, Meislitzer T, Heitzinger B, Halaj M, Fleisher LA, Metzler H. Coronary artery stenting and non-cardiac surgery--a prospective outcome study.[see comment]. *Br J Anaesth.* 2006 Jun;96(6):686-93.
33. Godet G, Le Manach Y, Lesache F, Perbet S, Coriat P. Drug-eluting stent thrombosis in patients undergoing non-cardiac surgery: is it always a problem? *Br J Anaesth.* 2008 Apr;100(4):472-7.
34. Jaffe R, Halon DA, Carmeli J, Lewis BS. Prolonged intravenous eptifibatid infusion for prevention of coronary stent thrombosis. *Int J Cardiol.* 2007 Jan 18;114(3):409-11.
35. Broad L, Lee T, Conroy M, Bolsin S, Orford N, Black A, et al. Successful management of patients with a drug-eluting coronary stent presenting for elective, non-cardiac surgery. *Br J Anaesth.* 2007 Jan;98(1):19-22.
36. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. *N Engl J Med.* 1998 May 21;338(21):1488-97.

37. ClinicalTrials.gov identifier NCT00653601 [cited; Available from: <http://clinicaltrials.gov/ct2/show/NCT00653601>
38. Stone GW, Ware JH, Bertrand ME, Lincoff AM, Moses JW, Ohman EM, et al. Antithrombotic strategies in patients with acute coronary syndromes undergoing early invasive management: one-year results from the ACUTY trial. *Jama*. 2007 Dec 5;298(21):2497-506.
39. James S, Akerblom A, Cannon CP, Emanuelsson H, Husted S, Katus H, et al. Comparison of ticagrelor, the first reversible oral P2Y₁₂ receptor antagonist, with clopidogrel in patients with acute coronary syndromes: Rationale, design, and baseline characteristics of the PLATElet inhibition and patient Outcomes (PLATO) trial. *Am Heart J*. 2009 Apr;157(4):599-605.
40. The Medicines Company. [cited 2009 16/5/09]; Available from: <http://ir.themedicinescompany.com>
41. van Geizen J. Optimising platelet inhibition. . *Eur Heart J* 2008. 2008;10(Suppl D):D23-D9.
42. Riddell JW, Chiche L, Plaud B, Hamon M. Coronary stents and noncardiac surgery. *Circulation*. 2007 Oct 16;116(16):e378-82.
43. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001 Aug 16;345(7):494-502.