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 intra-coronary 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 Guidelines

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 A.

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 B). 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 C).

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 four 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 one 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 one 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 to the local context into a single recommendation term (Appendix C).

Table 1. MACE* Rates According to Days from Stent to Non-Cardiac Surgery for Bare Metal and Drug-Eluting Stents.

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>MACE (%) BMS (n=899)</th>
<th>MACE (%) DES (n=726)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤30</td>
<td>10.5</td>
<td></td>
</tr>
<tr>
<td>31–90</td>
<td>5.8</td>
<td>2-90</td>
</tr>
<tr>
<td>≥91</td>
<td>2.8</td>
<td>91–180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>181–365</td>
</tr>
<tr>
<td></td>
<td></td>
<td>366–730</td>
</tr>
</tbody>
</table>

Data from Mayo Clinic, adapted from [13,17].

Table 1. MACE* Rates According to Days from Stent to Non-Cardiac Surgery for Bare Metal and Drug-Eluting Stents.

MACE: death, myocardial infarction, stent thrombosis or repeat revascularisation; BMS: bare metal stent; DES: drug-eluting stent.

Summary and Recommendations

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

• Elective non-cardiac surgery should be deferred for at least six weeks and ideally three 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 8146 patients showing a steady incidence of 0.4–0.6% per year for four 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
Elective surgery should be deferred for 12 months post-PCI. Non-cardiac surgery performed within 12 months of PCI with DES was associated with a 5% risk of dual antiplatelet therapy discontinuation and a higher risk of stent thrombosis [16]. Stent thrombosis occurred in seven cases (5%). A prolonged period of discontinuation of clopidogrel was associated with higher risk of stent thrombosis during the perioperative period.

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 post-DES because of a likely increased risk of death/myocardial infarction/stent thrombosis. (Level of evidence IV, GRADE of recommendation B.)

Table 2. Evaluating Risk for Stent Thrombosis.

<table>
<thead>
<tr>
<th>Clinical Factors</th>
<th>Academic Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous stent thrombosis</td>
<td>Left main stenting</td>
</tr>
<tr>
<td>Advanced age (&gt;80 years)</td>
<td>Bifurcation stenting</td>
</tr>
<tr>
<td>ACS indication for stent</td>
<td>Ostial stenting</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Small (&lt;3 mm) stent</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>Long (&gt;18 mm) stent</td>
</tr>
<tr>
<td>Low ejection fraction</td>
<td>Multiple stents</td>
</tr>
</tbody>
</table>

Adapted from [42]. *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.

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 [23–25]. 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...
Agents do not cause the haemorrhages, they do fraction of these are sight threatening. While antiplatelet and the risk of blindness. The frequency of retro-bulbar haemorrhage with consequent pressure on the optic nerve (below).

Intracranial surgery and transurethral prostatectomy (see below).

Antiplatelet agents are still active, as the alternative procedure needs to be discussed by the multidisciplinary team.

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.

Intraocular surgery: 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.

Urological surgery: TURP is the most widely performed urological procedure. In one series, transfusion rate increased 2.7-fold with two 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.

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 56 patients having major abdominal surgery, patients who took clopidogrel within six days of surgery compared to those who ceased clopidogrel for longer than six 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.

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.
surgery. (Level of evidence IV, GRADE of recommendation B.)

- Exceptions to this include patients undergoing spinal, intracranial, extracranial 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 periprocedural 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 is aspirin should be ceased five days prior to surgery and alternative short-acting therapy commenced three days prior to surgery. Timing of cessation of bridging therapy will depend on drug half-life. Clopidogrel should be recommenced on the first postoperative 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. Vicenzì et al. [32] reported 103 patients who had coronary stenting within one year of non-cardiac surgery. Antiplatelet therapy was either continued or discontinued for less than three 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 2.3-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 et al. [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 (85-100 IU 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 40 mg BD for eight 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 periprocedural 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 haematomatis and required major upper gastrointestinal surgery to treat a Mallory-Weiss tear. The eptifibatide infusion was continued postoperatively until recurrent haematomatis required its cessation on the 8th postoperative day, and within 4 h the patient developed recurrent stent thrombosis [34].

A group at Geelong in Victoria have reported a case series of three 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 seven 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 five days before surgery. Tirofiban and heparin are commenced three days before surgery and ceased 8 h prior to start of surgery. Clopidogrel 300 mg is given on the morning of the first postoperative 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].
Summary and Recommendations

Perioperative anticoagulation with heparin or LMW heparin provides incomplete protection against stent related complications. Tirofiban/heparin or epifibatide/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.

The 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.)

**Final Summary and Recommendations**

Summary

- Death/MI/stent thrombosis/urgent revascularisation are increased if non-cardiac surgery is performed within six weeks of bare metal stenting (5–30%). There would appear to be further reduction of risk if surgery is deferred for at least three 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 epifibatide/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 six weeks and ideally three 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, extracranial, 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 perioperative 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/epifibatide although there are limited data in support of such treatments. (Level of evidence IV, GRADE of recommendation B.)
**Table 3. Perioperative Antiplatelet Therapy Tailored to Risk.**

<table>
<thead>
<tr>
<th>Risk category</th>
<th>ST risk high</th>
<th>ST risk lower</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding complication risk high:</td>
<td>Stop antiplatelet therapy* and if on DAPT, consider bridging therapy</td>
<td>Stop antiplatelet therapy*</td>
</tr>
<tr>
<td>Intracranial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extracardiac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>URF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding complication risk not high</td>
<td>Continue antiplatelet therapy</td>
<td>Continue antiplatelet therapy</td>
</tr>
</tbody>
</table>

*Stopping DAPT five days before surgery is adequate to prevent bleeding complications [43]. Antiplatelet therapy should be recommenced as soon as possible after the procedure.

**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 (six weeks to three 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).
- Recomence oral antiplatelet therapy as soon as possible following the procedure.

**Appendix A.**

Writing Committee:

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- Cardiac Society of Australia and New Zealand (CSANZ)
- 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)

**Appendix B.**

**NHMRC Levels of Evidence**

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

**Appendix C.**

*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

A

Interpretation: Indicating a judgment that most well-informed people would make.

B

Interpretation: Indicating a judgment that a majority of well-informed people would make but a substantial minority would not.

References

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

Heart, Lung and Circulation 2010;28:10-12


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

Heart, Lung and Circulation 2010;28:10-12