Coronary stents: factors contributing to perioperative major adverse cardiovascular events

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Key points
• Patients with coronary stents are at increased risk of major perioperative cardiovascular complications.
• The major risk factor for stent thrombosis is discontinuation of dual antiplatelet therapy.
• If clopidogrel must be discontinued perioperatively, aspirin should be continued unless contraindicated.
• Myocardial ischaemia indicates stent thrombosis until proven otherwise and requires rapid triage to an interventional cardiology facility.

Summary. Patients with coronary stents undergoing non-cardiac surgery are at increased risk of major adverse cardiovascular events perioperatively. Impeccable patient care and communication between all members of the healthcare team will minimize this risk. The dominant risk factor for stent thrombosis and major adverse cardiovascular events is the interruption of dual antiplatelet therapy (e.g. aspirin and clopidogrel). If clopidogrel therapy has to be interrupted due to increased risk of bleeding, continuation of aspirin is strongly recommended to reduce the risk of stent thrombosis. The interval between percutaneous coronary interventions and operation is the next major risk factor for stent thrombosis. The incidence of major adverse cardiovascular events is inversely related to this interval, with the highest mortality rate occurring <30 days after stent implantation. Ideally, for patients with drug-eluting stents, elective surgery should be delayed for at least 1 yr and for patients with bare-metal stents, the recommended minimum period is 6 weeks. The use of a neuraxial anaesthetic technique must be carefully considered due to the risk of an epidural haemotoma. Perioperative monitoring should focus on early recognition of myocardial ischaemia, infarction, or both. If stent thrombosis is present, rapid triage to an interventional catheterization laboratory is essential for restoration of coronary blood flow.

Keywords: drug-eluting stents; perioperative care; platelet aggregation inhibitors; postoperative myocardial infarction; thrombosis

Percutaneous coronary interventions, as a mechanical means of restoring coronary blood flow, pose significant challenges to the anaesthesia care team. Patients with coronary stents undergoing non-cardiac surgery are at increased risk of major adverse cardiovascular events perioperatively. Perioperative mortality rates as high as 85% have been reported. In addition to the ‘typical patient’ with coronary artery disease, the anaesthesiologist might encounter paediatric and obstetric patients with coronary stents as well. Successful percutaneous coronary angioplasty was first reported by Gruentzig in 1977. Restenosis of the angioplasty site occurred in 15–60% of patients after percutaneous coronary angioplasty, manifesting as either death or non-fatal myocardial infarction. Subsequent improvements in technology were aimed at reducing the rate of restenosis, but each new generation of percutaneous coronary intervention technology created unanticipated problems. Bare-metal stents, introduced in 1986, were thought to be a solution to abrupt coronary vessel closure (arterial recoil and constrictive remodelling) associated with percutaneous coronary angioplasty. However, restenosis due to neointimal hyperplasia is observed in 10–30% of patients with bare-metal stents. In 2003, drug-eluting stents were introduced as a solution to this problem. Nevertheless, stent thrombosis is still seen in 5–10% of patients with drug-eluting stents. Stent implantation causes injury to the endothelial surface, which initiates interactions between the stent surface, blood, and vessel wall. This leads to neointimal hyperplasia and increased thrombogenicity. Various coatings have been applied to stents to reduce neointimal hyperplasia and subsequent stenosis. Drug-eluting stents are composed of three components: the platform (stent), a carrier (a polymer), and a drug to reduce the incidence of neointimal hyperplasia. In order to prevent stent thrombosis, patients with coronary stents also require dual antiplatelet therapy with clopidogrel and aspirin. The predominant drug-eluting stents in use today are the sirolimus and paclitaxel families of stents. Sirolimus is a naturally occurring immunosuppressive, cytostatic compound that arrests the cell cycle and reduces neointimal hyperplasia. Paclitaxel is an
antiproliferative and cytotoxic agent. Drug elution off the sirolimus platform is thought to be complete in 6 weeks; for paclitaxel, 10% of the drug is released in the first 10 days and the remainder is slowly eluted over an indefinite period.13 14 Both types of drug-eluting stents appear similar in performance and clinical profile.15 16 Newer generations of drug-eluting stents are being tested with different coatings and delivery systems, including bioabsorbable materials.11 12 Modifications of drug-eluting stent design might confer more protection against thrombosis and thus allow for a reduced duration of dual antiplatelet therapy.17 However, some consider the reports of second- and third-generation drug-eluting stents being less prone to stent thrombosis as ‘premature’.18 Their long-term safety is unknown.

Owing to the concerns related to adverse events associated with stent use, the United States Food and Drug Administration issued a policy delineating appropriate patients for stent insertion, and also caveats for techniques related to insertion.14 These ‘on label’ indications include: short lesions (28–30 mm), non-complex, and native coronary lesions in clinically stable patients without serious medical conditions. Others have appended the list to include patients with stable coronary artery disease, absence of diabetes mellitus and renal failure, and maintenance of dual antiplatelet therapy.19–21 ‘On-label’ use of drug-eluting stents decreases the need for revascularization without increasing the incidence of acute myocardial infarction or death. In this situation, the risk of stent thrombosis is reported to be <2% for the first 3 yr (0.6% per year) after implantation.12 However, ‘off label’ use of drug-eluting stents account for 60–75% of the percutaneous coronary interventions and is associated with a higher rate of adverse events, stent thrombosis, and mortality.19 Although short-term outcomes for ‘off label’ drug-eluting stents use are poorer, the absolute event rate remains low.22 23 Both paclitaxel and sirolimus drug-eluting stents do not appear to have significantly different rates of stent thrombosis.

In-stent restenosis is insidious, whereas stent thrombosis is a sudden, catastrophic complication that can lead to myocardial infarction and death.24 In 2006, the Academic Research Consortium issued a set of endpoint definitions to improve consistency in methodology of published studies and enhance clinical care.25 Acute stent thrombosis occurs within the first 24 h after percutaneous coronary intervention: sub-acute stent thrombosis occurs between 24 h and 30 days; late stent thrombosis occurs between 31 days and 1 yr; and very late stent thrombosis occurs more than 1 yr after intervention. Early stent thrombosis is usually mechanical in origin (coronary artery dissection or under expansion of the stent).9 In contrast, late stent thrombosis is related to stent malposition, abnormal re-endothelialization,10 or hypersensitivity. Incomplete intimal healing after percutaneous coronary intervention increases the period of time during which thrombosis can occur.26

Patients with a coronary stent present a significant risk regardless of the type of non-cardiac operation undertaken.10 27 In a study involving patients with either bare-metal stents or drug-eluting stents, 44.7% of the patients sustained a complication with 4.9% mortality.28 This review will focus on those factors contributing to major adverse cardiovascular events (non-fatal myocardial infarction, need for revascularization, congestive heart failure, non-fatal stroke, and mortality) in patients with coronary stent(s) undergoing a non-cardiac operation. Each study using ‘major adverse cardiovascular events’ as a composite endpoint has used different inclusion criteria to define this term. Authors use the general phrase ‘major adverse cardiovascular events’ and the reader is referred to the individual study citation for the methodological criteria used to define these events in a given investigation. For this review, we will focus solely on issues related to management of patients with coronary stents, thus excluding the subject of percutaneous transluminal coronary angioplasty. The reader is also referred to excellent general reviews on the subject of coronary stents, and also those with an overview of perioperative management.5 8 10 13 29–31

Periodic management

Background

The rates of coronary stent-related complications in patients undergoing non-cardiac surgery range from 0.6% to 45%, with a mortality rate of 2.6–4.9%.32 The adverse events rate is 2.1 times more in patients with recently implanted stents (<30 days) than in those in whom stents were inserted >90 days before operation.28 However, Sharma and colleagues1 reported an 86% mortality rate in a subset of patients with bare-metal stents undergoing non-cardiac surgery within 30 days of percutaneous coronary intervention, in whom dual antiplatelet therapy was interrupted. In those patients in whom dual antiplatelet therapy was maintained, the mortality was only 5%. Similarly, Schouten and colleagues12 reported a comparable reduction in non-fatal myocardial infarction or mortality when dual antiplatelet therapy was maintained before non-cardiac surgery (30.7% vs 0%).

In a non-surgical population, Camenzind and colleagues9 stress that discontinuing clopidogrel is the single most ‘potent correlate’ of late stent thrombosis. This observation is supported by the work of Iakovou and colleagues21 who also noted a very high hazard ratio (HR=90) for stent thrombosis in patients in whom dual antiplatelet therapy was discontinued. The incidence of stent thrombosis was 1.3% (9 months after percutaneous coronary intervention) with a mortality rate of 45%. On the basis of the hypercoagulable and inflammatory response to surgery, the predominant risk of perioperative stent thrombosis is related to discontinuing dual antiplatelet therapy for patients with incomplete endotheialisation of the stent struts.31

In an investigation from New Zealand, 26% of patients with a percutaneous coronary intervention required non-cardiac surgery in the ensuing 5 yr. Of those who required non-cardiac surgery, there was an average of 1.7 operations...
hypothesize that stent thrombosis is related to these factors on adverse outcomes (Fig. 1). Based on their interpretation of the literature, the authors, on a theoretical basis, graphically illustrate the relative impact of each of the factors on adverse outcomes (Fig. 1).

**Table 1** Perioperative risk factors for stent thrombosis. Based on references 14 21 36 37 90

<table>
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<th>Risk Factor</th>
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<tr>
<td>Acute coronary syndrome</td>
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<td>Congestive heart failure (low ejection fraction)</td>
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<td>Diabetes</td>
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<td>Renal impairment</td>
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<td>Coronary anatomy (total stent length, multiple stents, bifurcation-lesion)</td>
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<td>Advanced age</td>
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<td>Prior brachytherapy</td>
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<td>Cancer</td>
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<td>Elective surgery</td>
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<td>Emergency surgery</td>
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per patient. At least one episode of major bleeding occurred in 8.6% of patients. It is projected that approximately 5% of stented patients will require a surgical procedure within 12 months of a percutaneous coronary intervention. Extrapolating these data to the estimated 6 million patients who have had stents inserted, at least 300 000 patients will present for non-cardiac operations within 1 yr of stent placement. Risk factors for perioperative stent thrombosis during this time period parallel the United States Food and Drug Administration and American Heart Association/American College of Cardiology contraindications for coronary stents 14 36 37 (Table 1). Camenzind and colleagues hypothesize that stent thrombosis is related to the classic Virchow triad: alterations in blood constituents (increased thrombogenicity), flow pattern (reduced flow), and injured endothelial lining (incomplete endothelialization). Both cancer and surgery are associated with an increased inflammatory response and a prothrombotic state.

For the anaesthesiologist, five issues must be addressed in the management of the patient with coronary stents undergoing non-cardiac surgery (Table 2). On the basis of their interpretation of the literature, the authors, on a theoretical basis, graphically illustrate the relative impact of each of these factors on adverse outcomes (Fig. 1).

**Table 2** Perioperative management issues for patients with a coronary stent

<table>
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<th>Management of anticoagulation</th>
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<td>Appropriate duration from percutaneous coronary intervention to surgical procedure</td>
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<td>Choice of anaesthetic technique</td>
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<td>Perioperative monitoring</td>
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<td>Immediate access to a cardiac catheterization laboratory</td>
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occurs in three stages: (i) conformational change in the surface area of the platelet; (ii) expression of prothrombotic substances; and (iii) activation of glycoprotein IIb/IIIa (GP IIb/IIIa) receptors that facilitates binding of fibrinogen to platelets and platelet–platelet interaction. There is significant redundancy and ‘cross-talk’ between these pathways, and platelet activation can be caused by many activators. Multiple pathways have to be blocked in order to achieve clinically effective platelet dysfunction.

Three classes of antiplatelet drugs are available and used to prevent stent thrombosis: aspirin, thienopyridines (clopidogrel and prasugrel), and the platelet GP IIb/IIIa inhibitors (eptifibatide, tirofiban, and abciximab). The latter group of drugs is used for acute coronary syndromes and percutaneous coronary intervention procedures and is not routinely used perioperatively. A fourth class of antiplatelet drugs increases levels of intraplatelet cAMP (dipyridamole), but is not widely used to prevent stent thrombosis.

After stent placement, platelet activation is usually reduced by the use of two platelet inhibitors with differing modes of action (aspirin and clopidogrel). As a consequence, thrombotic events have been significantly reduced. Aspirin irreversibly binds to cyclo-oxygenase and impairs thromboxane A2 and prostacyclin (PGI2) synthesis, disrupting platelet aggregation. Clopidogrel also inhibits platelet aggregation and platelet–leucocyte aggregation. As an irreversible inhibitor of the adenosine diphosphate receptor, P2Y12, clopidogrel prevents activation of the GP IIb/IIIa receptor.

Both aspirin and clopidogrel are associated with ‘resistance’, which is another predisposing factor to stent thrombosis. Faxon and Friedman define ‘resistance’ as the failure of a therapy to prevent vascular thrombotic events despite fully compliant intake of appropriate doses of the medication. Resistance to the effects of aspirin or clopidogrel is observed in 10–20% of patients and an equal number of patients are actually super-responsive. Resistance is detected by evaluating the level of platelet inhibition for a given dose of drug. In patients with drug-eluting stents, who have angiographically proven stent thrombosis, aspirin resistance was observed in 23% vs 5% of controls; clopidogrel resistance was seen in 40% of patients vs 14% of controls.
Pharmacogenomics and pharmacokinetics play a major role in clopidogrel resistance. Clopidogrel is a prodrug, a biologically inactive parent compound that requires metabolism to the active drug. Prodrugs solve problems related to drug toxicity, instability, and solubility and improve a drug’s ‘targeting’ capabilities. Clopidogrel requires biotransformation in the liver by cytochrome P450 (CYP450) to an active metabolite (15% of dose) (Fig. 2). Clopidogrel (prodrug) has a half-life of 6 h, whereas the half-life of the active metabolite is only 0.5 h. Clopidogrel requires two CYP450-dependent oxidative steps before it interrupts platelet function. Variable patient responses to clopidogrel are in part governed by genetic polymorphisms in CYP450 metabolism of clopidogrel to the active form. The CYP2C19*1 isoform has normal function, whereas the CYP2C19*2 and *3 isoforms have reduced function. Poor metabolizers have loss of two normal function alleles, whereas those with intermediate function have loss of function of only one allele. Although there are a number of alleles at the CYP2C19 site that can effect clopidogrel metabolism, the variation at *2 and *3 alleles loci is responsible for the major differences in clopidogrel metabolism in Europeans (85%) and Asians (99%). In a non-surgical setting, the presence of reduced function allele (CYP2C19) is associated with 53% higher composite major adverse cardiovascular events. Variations in the CYP2C19 gene and other genes that modulate drug activity were related to long-term major adverse cardiovascular events by a factor of 3.6. Furthermore, other drugs metabolized by CYP2C19, for example, proton pump inhibitors, can reduce the effectiveness of clopidogrel. The study of these factors is a new area of research in pharmacology, called high-risk pharmacogenomics, that evaluates the interplay of genomics and adverse effects of drugs (Fig. 3).

Prasugrel, a third-generation thienopyridine recently introduced to clinical practice, is more potent than clopidogrel with less variability in patient response. In contrast to clopidogrel, CYP genetic variants do not influence active drug metabolite levels or platelet inhibition. Major adverse cardiac events were reduced in patients treated with prasugrel (9.4%) compared with clopidogrel (11.5%). The same study reported a 50% reduction in stent thrombosis in prasugrel-treated patients; however, there was a relative increase in the risk of bleeding (30%). Of interest in the perioperative period, patients in this study who subsequently underwent coronary artery bypass grafting had more than four times the rate of major bleeding compared with the clopidogrel group (13.4% vs 3.2%). Early expectations of widespread cardiologist acceptance of this drug are currently unmet.

In the opinion of the authors, the major factors for the inability to achieve adequate therapeutic levels of clopidogrel perioperatively are premature discontinuation of clopidogrel before non-cardiac surgery and patient non-compliance (Table 3). In a study of non-surgical patients with myocardial infarction, 13.6% of patients who discontinued thienopyridine therapy within 30 days had a 10-fold greater mortality rate at 11 months than those who continued treatment (7.5% vs 0.7%). Superficial or nuisance bleeding is a significant reason (11%) for discontinuing clopidogrel by patients. In a non-surgical population, the incidence of superficial bleeding (bruising, bleeding from small cuts, etc.) in patients receiving dual antiplatelet therapy was 86%, while internal bleeding (haematoma, epistaxis, haematuria, etc.) was 14% and ‘alarming bleeding’ (life-threatening, blood transfusion administered, etc.) was 0.7%.

There is an unmet need for drugs that can be used as ‘bridge therapy’ to prevent stent thrombosis after percutaneous coronary intervention to non-cardiac surgery interval.
interruption of dual antiplatelet therapy. This is analogous to discontinuing warfarin before surgery and instituting a heparin infusion to prevent thrombo-embolic events.61 62 Unfortunately, heparins possess minimal antiplatelet effect and are thus theoretically unsuitable as ‘bridge’ treatment when dual antiplatelet therapy is discontinued. However, Savonitto and colleagues,63 Godet and colleagues,64 and Broad and colleagues65 have independently reported the

Fig 2 The metabolic pathways involved in generating the active metabolite of clopidogrel from the parent or prodrug. The dependence on the hepatic cytochrome system contributes to the genetically based bioavailability of the active compound. Reproduced with permission, copyright ©2009 Massachusetts Medical Society. All rights reserved.53
use of heparin (with tirofiban) in their bridge protocols with success. Tirofiban has a short half-life (2 h) and has been suggested to meet the ‘bridge therapy’ requirement. Four hours after tirofiban infusion is stopped, bleeding time returns to normal and platelet aggregation increases to 50% of normal function. The pharmacologic profile of cangrelor and ticagrelor (reversible, rapid onset, and short half-life) might also be attractive for perioperative use; these drugs are in various phases of pre-market testing.

A new class of treatment, triple therapy, has evolved to manage patients with a coronary stent and atrial fibrillation, prosthetic cardiac valve, or deep venous thrombosis where warfarin is added to the dual antiplatelet therapy. In an article summarizing the results of an observational study, Kaluza and colleagues vividly described the perturbations in this balance as ‘Catastrophic outcomes...’. Although some experts question the long-term efficacy of aspirin to reduce cardiovascular risk, it is considered an important agent in the management of ischaemic heart disease. Aspirin is 100 times more effective in preventing major adverse cardiovascular events than causing a gastrointestinal bleed (2 per 1000 patients per year). Similar risk reductions are seen for unstable angina (46%), percutaneous transluminal coronary angioplasty (53%), and prior stroke or transient ischaemic attack (22%). In a meta-analysis of 50 279 patients receiving aspirin for secondary prevention of coronary artery disease, cessation of aspirin therapy

Risk of bleeding with dual antiplatelet therapy

To understand the risk of bleeding with dual antiplatelet therapy, we will first review its effects in a non-surgical, ambulatory population. Successful management of dual antiplatelet therapy must weigh the risk of bleeding against the benefit of a decreased rate of thrombosis. In an article summarizing the results of an observational study, Kaluza and colleagues vividly described the perturbations in this balance as ‘Catastrophic outcomes...’.

Monitoring platelet function in an outpatient setting is an integral part of management of patients who are receiving dual antiplatelet therapy. Optical platelet aggregometry, the gold standard for monitoring platelet function, is a cumbersome test that cannot be easily performed in the operating theatre. Several point-of-care tests of platelet function are available for clinical use. Unfortunately, there appears to be little agreement between these tests, with varying definitions of platelet inhibition and ease of use in the operating theatre.

Table 3 Inadequate response to clopidogrel: maintenance or perioperative interruption

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<th>Pharmacology</th>
<th>Genetics</th>
<th>Physician unfamiliar with appropriate guidelines</th>
<th>Poor communication: physician to patient</th>
<th>Poor communication: physician to patient</th>
<th>Patient non-compliance</th>
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<tr>
<td>Failure of efficacy</td>
<td>CYP2C19*2</td>
<td>CYP2D6*4</td>
<td>CYP2C9*3</td>
<td>CYP3A4</td>
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<td>Clopidogrel</td>
<td>Tamoxifen</td>
<td>Codeine</td>
<td>Warfarin and bleeding</td>
<td>Terfenadine and QT</td>
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Fig 3 The concept of high-risk pharmacokinetics is the study of drug toxicity when the concentrations of a drug are dependent on the variable activity of a single metabolic pathway. Reproduced with permission. Roden and Stein.56
increased the risk of cardiac complications three-fold (odds ratio 3.1), while those with a coronary stent had a 90 times increase in the complication rate.40 In an ambulatory population, acute withdrawal of aspirin is associated with very rapid appearance of cardiovascular complications (coronary complications [8.5 (3.6) days [mean (standard deviation)], neurologic complications [14 (11) days], and peripheral arterial complications [26 (18) days]).80 Clopidogrel is added to enhance the antiplatelet effect of aspirin (20% further reduction in major adverse cardiovascular events vs aspirin alone), while increasing bleeding events by only 1–2% per year, compared with aspirin alone.49

Both patient factors and drug factors contribute to the risk of bleeding in an additive manner.63 In a large study of acute myocardial infarction, patients were classified before initiation of antithrombotic therapy into five subgroups, from very low to very high risk of bleeding.81 In the low-risk group, the use of <2 anti-thrombotic drugs was associated with 1.9% incidence of major bleeding and the use of >2 anti-thrombotic drugs increased the incidence to 3.1%. In the highest risk group, with <2 anti-thrombotic drugs, the incidence of a major bleed was 13.5% and with >2 anti-thrombotic drugs, it increased to 19.9%.81 In a meta-analysis, Eisenberg and colleagues82 evaluated the relationship of late and very late stent thrombosis to a short duration interruption of dual antiplatelet therapy. In patients in whom dual antiplatelet therapy was discontinued, the median interval to a thrombotic event was 7 days. In patients in whom aspirin was discontinued (after a thienopyridine had been discontinued safely), the median interval to a thrombotic event was also 7 days. However, for patients who continued to receive aspirin after discontinuing a thienopyridine, the median interval to a thrombotic event was 122 days.82 Discontinuation of clopidogrel also causes a rebound thrombogenic effect, further increasing the risk of stent thrombosis.83 The rate of major adverse cardiovascular events can double compared with the patients who are maintained on clopidogrel.

In a surgical population, low-dose aspirin increases the risk of bleeding by a factor of 1.5 but not the severity of the event.42 44 80 84 In a large non-cardiac surgery study, Oscarsson and colleagues85 compared the effects of aspirin (75 mg per day) vs placebo administered 7 days before and 3 days after operation. Aspirin reduced the rate of major adverse cardiovascular events (7.2%) with no significant difference in bleeding complications between the groups. Sharma and colleagues1 reported that non-cardiac surgery patients with bare-metal stents, for whom dual antiplatelet therapy was discontinued prematurely, had 85% mortality compared with those in whom it was continued (5%). Conversely, in patients undergoing low-risk non-cardiac surgery (<90 days after percutaneous coronary intervention), only two acute myocardial infarctions occurred that were not related to stent thrombosis.86

The addition of clopidogrel to aspirin raises the relative risk of bleeding by 50%, but this represents an increase of only 0.4–1% absolute risk of bleeding.16 Chassot and colleagues67 calculated the rate of increased risk of bleeding with aspirin to be 2.5–20%, and with aspirin plus clopidogrel to be 30–50% (30% of patients requiring a blood transfusion). However, Vicenzi and colleagues28 noted only two of 103 patients with severe blood loss when antiplatelet therapy was continued. Nuttall and colleagues47 reported no difference in blood loss whether dual antiplatelet therapy was stopped <7 or >7 days in patients with bare-metal stents. Rabbitts and colleagues88 noted the low incidence of surgical bleeding complications in drug-eluting stent patients (one of 175) despite being maintained on thienopyridine therapy within 7 days of surgery. However, 20% of these patients received blood products. Three studies evaluating bleeding for urological procedures (prostate biopsy, transurethral resection of prostate, and ureteroscopy) failed to reveal any major increase in bleeding complications.10 40 However, Thurston and Briant89 reported a 50% rate of bleeding (with two deaths) in a subset of seven of 14 patients in a series of transurethral resection of the prostate procedures in which patients received aspirin before operation. From the preceding discussion, it is apparent that in a surgical population, the risk of thrombotic complications of discontinuing dual antiplatelet therapy far outweighs the risk of bleeding with dual antiplatelet therapy.24 67 88 90

Metzler and colleagues50 suggest the use of a four-quadrant approach to assist the clinician in perioperative anticoagulation decision-making. The risk of thrombosis is plotted against the risk of bleeding. In patients with high risk of bleeding and high risk of stent thrombosis, discontinuation of dual antiplatelet therapy with ‘bridge’ therapy is a plausible strategy. In patients with low risk of stent thrombosis and low risk of bleeding, continuation of dual antiplatelet therapy, though desirable, is still debated.36 39 91 92 To use this system effectively, surgical, patient, and percutaneous coronary intervention procedural factors must be considered. Operations with a high risk of bleeding (and significant consequence of bleeding) include repair of abdominal aortic aneurysm, prostatectomy, intracranial and spinal operations, and ophthalmologic procedures. Patient factors that contribute to stent thrombosis are discontinuation of dual antiplatelet therapy, diabetes mellitus, renal failure, and low ejection fraction. Percutaneous coronary intervention procedural factors include type of stent(s) deployed, the interval from implantation, etc.

Others have suggested an algorithm approach using a slightly different format.39 91 92 van Kuijk and colleagues,93 in a study of 550 stent patients, emphasized the interplay between percutaneous coronary intervention and operation interval coupled with the interruption of dual antiplatelet therapy. They reported that major adverse cardiovascular events occurred in 45% of those continuing single antiplatelet therapy and 55% of those continuing dual antiplatelet therapy (not statistically different). A 4% and 21% risk of severe bleeding was observed in these groups, respectively.

In summary, if a non-cardiac operation is contemplated during the vulnerable period of diminished stent endothelialization, the risk of bleeding from the operation must be weighed
against the risk of stent thrombosis96 (Table 1). Authors recommend maintaining dual antiplatelet therapy if the risk of bleeding from minor surgical procedures (dental extraction, cystoscopy, and colonoscopy) is small. If clopidogrel cannot be continued, all efforts should be made to continue aspirin. If aspirin is contraindicated, as in surgical procedures in a closed space, for example, intracranial, middle ear, ophthalmologic, etc., or if there is a high risk of bleeding from the surgical site, antiplatelet agents might have to be stopped.95

In either event, dual antiplatelet therapy should be re-instituted as soon as possible after operation. Cardiology consultation can be invaluable in this decision. If a platelet transfusion is required, the short half-life of clopidogrel and its active metabolite will not interfere with the function of transfused platelets. Platelet transfusions can be administered 4 h after discontinuation of clopidogrel.40 54 77

Timing of operation after percutaneous coronary intervention

The risk of stent thrombosis is inversely related to the interval between percutaneous coronary intervention and operation96 (Fig. 4). For drug-eluting stents, delay elective operations for 12 months from the date of the percutaneous coronary intervention and maintain dual antiplatelet therapy during this period.36 84 For bare-metal stents, delay elective surgery for at least 6 weeks after percutaneous coronary intervention and maintain dual antiplatelet therapy. The period of highest risk, with either bare-metal or drug-eluting stents, is operation within 30 days of implantation. Vicenzi and colleagues28 reported a higher complication rate (2.11-fold increased major adverse cardiovascular events) in the <35 day stent group vs the >90 day group. Evaluating data from two Mayo Clinic studies (bare-metal and drug-eluting stent patients), the rate of major adverse cardiovascular events was similar (7.1% bare-metal stents vs 6.4% drug-eluting stents).87 88 After 90 days, the event rate for bare-metal stents continued to decrease to 2.8% at 365 days. In contrast, in the drug-eluting stent group, the adverse event rate remained higher at 5.8%.90

Nuttall and colleagues87 observed that a decreased time to operation (<8 weeks) for bare-metal stent patients increases the risk for major adverse cardiovascular events 3.2-fold. Rabbitts and colleagues, using similar methodology with drug-eluting stent patients, reported no statistically significant difference between the groups that required surgery <1 vs >1 yr after percutaneous coronary intervention. However, the rate of adverse events was lowest >1 yr after intervention, with the highest complication rate <90 days after intervention.88

Emergency operation is associated with a higher incidence of adverse events than elective procedures. Rade and Hogue, in an editorial summarizing data related to perioperative cardiovascular events, noted that for patients with bare-metal stents, emergency surgery increased the event rate by three-fold (12% vs 4.4% for elective operation). For drug-eluting stent patients, comparable data indicated a 3.5-fold increase (18% vs 4.7%).90

Anaesthesia technique

Both regional and general anaesthetic techniques have been used to manage patients with coronary stents,27 77 97 but the use of neuraxial techniques (continuous or single injection) has come into question.13 In a survey of thoracic epidural anaesthesia practice in the UK, Pennefather and colleagues98 reported that 49% of respondents would use epidural anaesthesia in a patient receiving clopidogrel and 34% would use the technique in dual antiplatelet therapy patients. In a study of 306 patients who received clopidogrel and underwent elective vascular surgery with a continuous epidural, no new neurological symptoms were seen after operation; no data related to major adverse cardiovascular events were reported.97 Various national organizations have published guidelines on neuraxial techniques in the anticoagulated patient with both similarities and differences in approach. The nuances of decision-making in this area are beyond the scope of this review. Consequently, the reader is referred to recently published guidelines on this subject.99 –101

Equally important for continuous neuraxial techniques is the question of the optimal time of catheter removal when an emergent, postoperative percutaneous coronary intervention is required for acute myocardial infarction. The intense anticoagulation and platelet inhibition associated with percutaneous coronary intervention complicates epidural catheter removal. The most recent version of the American Society of Regional Anesthesia Guidelines briefly addresses this issue.92 A reasonable approach is to avoid a continuous epidural catheter in a patient with a coronary stent unless perceived benefits significantly outweigh risk.102
Perioperative monitoring strategies

Early recognition of myocardial ischaemia, infarction, or both and immediate transfer to an interventional cardiac catheterization laboratory are essential for optimal management of a stent-related adverse cardiovascular event. Therefore, in addition to basic monitors required for intraoperative monitoring, the clinical focus of monitoring is on rapid detection of acute pathological changes in cardiac function. Although most perioperative myocardial infarctions are ‘silent’, anginal symptoms in a patient with a coronary stent strongly suggest an acute myocardial infarction or ischaemia and, until proven otherwise, represent stent thrombosis, a true medical emergency. Further, new onset of irregular rhythm or pulmonary rales suggests a diagnosis of myocardial ischaemia/infarction. Electrocardiography is the most cost-effective means of detecting myocardial ischaemia. Meticulous technique is required for lead placement and minimization of artifact. The presence of angina plus objective signs of myocardial ischaemia or infarction mandates immediate triage to the cardiac catheterization laboratory to rule out and/or manage stent thrombosis. Elevated biomarkers (troponins) should be used to confirm the diagnosis of a perioperative myocardial infarction, but the clinician should not wait for laboratory results if stent thrombosis is the probable diagnosis.

If a pulmonary artery catheter is inserted for management, certain haemodynamic changes are highly suggestive of myocardial ischaemia including new onset ‘v’ waves and clinically significant increases in pulmonary artery pressure with either no change or decrease in cardiac output. These signs are consistent with decreased left ventricular compliance due to myocardial ischaemia. However, the pulmonary artery catheter is a poor and unreliable indicator of myocardial ischaemia, and its use to monitor myocardial ischaemia is not accepted. Transoesophageal echocardiography is currently considered the de facto standard for early recognition of intraoperative myocardial ischaemia. However, there is a high false-positive rate in the diagnosis of myocardial ischaemia based on new onset regional wall motion abnormalities. These abnormalities are among the earliest signs of myocardial ischaemia, and coupled with other objective signs of myocardial ischaemia (e.g. electrocardiography), increase suspicion of stent thrombosis in a patient with a coronary stent.

Immediate availability of the interventional cardiac catheterization laboratory

Once the diagnosis of an acute myocardial infarction due to possible stent thrombosis is made (or considered), triage to the interventional cardiology suite within 90 min is critical. Mortality increases by nearly 50% with delayed re-perfusion (3% at 30 min to 4.3% at 90 min). Prompt transfer to a cardiac catheterization laboratory can be lifesaving. Incremental delay in further diagnostic manoeuvres only increases the risk for death or significant increase in major adverse cardiovascular events. Terkelsen and colleagues reported that healthcare system delays in triage of patients for emergency percutaneous coronary intervention results in a mortality of 28% when the delay is 121–180 min from the onset of anginal symptoms. Any facility caring for surgical patients with coronary stents that does not have in-house interventional cardiology capabilities should have a protocol in place for patient transfer to the nearest catheterization laboratory. This means that ambulatory surgical facilities, endoscopy suites, etc. without these resources on site should develop a relationship with interventional cardiologists that will facilitate prompt transfer if needed.

Conclusions

Impeccable patient care and communication minimizes the risk of major adverse cardiovascular events to the patient with a coronary stent undergoing non-cardiac surgery. Although time-consuming, perioperative management must be tailored to each patient. The dominant risk factor for stent thrombosis and poor outcome is the interruption of dual antiplatelet therapy for the operative procedure. If continuing clopidogrel is contraindicated, then continuation of aspirin is essential unless contraindicated by the site of the surgical procedure. The next major risk factor is the interval between stent placement and the operation. For patients with drug-eluting stents, this interval should be at least 1 yr, and for patients with bare-metal stent, at least 6 weeks. The use of neuraxial anaesthetic techniques must be carefully considered due to risk of epidural haematoma. Perioperative monitoring should focus on early recognition of myocardial ischaemia/infarction with electrocardiography, echocardiography, and troponin assay. If stent thrombosis is present, rapid triage to an interventional catheterization laboratory is critical to reduce morbidity and mortality.

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Conflict of interest

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References

2. Rocchini AP. Pediatric cardiac catheterization. Curr Opin Cardiol 2002; 17: 283–8


96 Schouten O, Bax J, Damen J, Poldermans D. Coronary artery stent placement immediately before noncardiac surgery: a potential risk? Anesthesiology 2007; 106: 1067–9
106 de Souza DG, Baum VC, Ballent NM. Late thrombosis of a drug-eluting stent presenting in the perioperative period. Anesthesiology 2007; 106: 1057–9
111 Adesanya AO, de Lemos JA, Greilich NB, Whitten CW. Management of perioperative myocardial infarction in noncardiac surgical patients. Chest 2006; 130: 584–96
112 Archan S, Fleisher LA. From creatine kinase-MB to troponin: the adoption of a new standard. Anesthesiology 2010; 112: 1005–12
