Do percutaneous coronary interventions protect the surgical patient?

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ABSTRACT
The number of percutaneous coronary interventions (PCI) performed annually has increased rapidly over the last two decades. Coronary angioplasties are now commonly complemented with the insertion of coronary artery stents. Initially bare metal stents (BMS) were developed with drug-eluting stents (DES) subsequently being introduced. Drug-eluting stents reduce in-stent restenosis at the cost of prolonged anti-platelet therapy. While observational studies suggest that coronary artery bypass graft surgery protects against perioperative cardiac events in non-cardiac surgery, no such evidence exists for PCI. In order to prevent stent thrombosis, patients need to receive dual anti-platelet therapy (generally aspirin and clopidogrel) for four to six weeks with BMS, and at least one year with DES. Patients on dual anti-platelet therapy are at risk of severe bleeding during surgery. However, withdrawal of dual anti-platelet therapy is associated with the risk of stent thrombosis. The risk of cardiac complications seems to exceed the risk of bleeding, and maintenance of dual anti-platelet therapy is advocated whenever possible. Surgery in closed cavities (neurosurgery, intraocular surgery) necessitates the withdrawal of dual anti-platelet therapy. There is a significant risk of perioperative complications in patients who have DES, or recently inserted BMS, and consequently surgery should not be performed without a discussion involving the surgeon, cardiologist, anaesthetist, and the patient.

Introduction
Over the past thirty years there have been major advances in the management of patients with coronary artery disease. These have included life style changes, recently complemented in some countries by the ban of smoking in public places, the development of drug strategies including beta-adrenoceptor blockers, angiotensin-converting enzyme inhibitors, statins, aspirin, thrombolysis and early myocardial revascularisation. Coronary artery bypass graft (CABG) surgery has also evolved. Internal mammary arteries and subsequently radial arteries have been utilised alone or in addition to saphenous vein grafts to revascularise the coronary circulation, and CABG surgery may be performed with or without cardiopulmonary bypass. Finally, there has been the rapid development of percutaneous coronary interventions. These advances resulted in a 65% decrease in the death rate among patients below the age of 65 over the period 1970–2002.1

Percutaneous coronary interventions
The first percutaneous coronary balloon angioplasty was performed by Grüntzig in 1977.2 Though stenoses could be successfully dilated, the widespread use of balloon angioplasty was initially limited by two major complications: acute vessel closure during or immediately after the procedure secondary to elastic recoil, thrombosis or vessel dissection, and restenosis of the vessel due to a combination of smooth muscle proliferation and neointimal hyperplasia. These complications were considerably reduced by the introduction of bare metal coronary artery stents, which are deployed over a balloon at the site of an atheromatous lesion.3 The first report of successful stent implantation was published in 1987.4 The presence of a stent reduced the risk of restenosis by approximately 50% as compared to angioplasty alone.5 Still, restenosis remained an important issue. Drug-eluting stents (DESs) were designed to prevent restenosis by coating a standard bare metal stent (BMS) with a thin polymer containing an antiproliferative substance that inhibits smooth muscle proliferation and neointimal hyperplasia within the stented segment.6 DESs were first used in 1999.

The most commonly implanted DESs are coated with sirolimus or paclitaxel; however, other agents are available. These substances arrest cell division by differing mechanisms, thereby reducing cell proliferation and endothelialisation of the metal stent struts.7 DESs are highly effective at reducing late stent restenosis,8 and appear, in the short to medium term (six to twelve months), to have at least as good a safety profile as BMSs.9,10 DESs are now used in 80% of patients.11 Percutaneous coronary interventions (PCIs) are carried out for stable angina (50%), non-ST segment elevation myocardial infarction (NSTEMI; 38%), ST segment elevation myocardial infarction (STEMI; 11%) and other conditions (1%). Recent evidence suggests a mortality of 0.75% (range 0–3%) and a risk of non-fatal myocardial infarction of 0.75%.12
The increased safety and efficacy of PCI has led to an exponential increase in the number of procedures being performed, with currently more than 90% of all PCIs involving the placement of at least one coronary artery stent.12 In the UK, PCIs became more frequent than CABG surgery in 1998. Data for 2006 show 73 612 PCIs versus 23 746 CABG procedures.13 In the USA the almost exponential increase in PCIs has been associated with a decline in CABG surgery.

Will this trend continue? This is debatable. A recent study has shown that in patients with stable angina, optimal medical therapy is as effective as medical therapy complemented by PCI.14 Moreover, implantation of stents themselves is associated with late complications. The presence of exposed metal struts in the coronary arteries is highly thrombogenic, and the early use of stents was associated with a high risk (16–24%) of stent thrombosis.20 This potentially devastating complication is associated with a 50% incidence of acute myocardial infarction (MI) and a 20% mortality rate;21 consequently, the prevention of stent thrombosis is of paramount importance whilst the vascular endothelium regrows to cover the stent.

Whether BMSs or DESs are used, there is a need for dual antiplatelet therapy, generally with a thienopyridine (usually clopidogrel) and aspirin in order to prevent stent thrombosis. This drug combination has been shown to be more effective than aspirin and warfarin.16,17 Clopidogrel is a pro-drug that is metabolised to an active compound that inhibits the P2Y12 adenosine diphosphate (ADP) platelet receptor. Blockade of this receptor inhibits the binding of fibrinogen to the platelet glycoprotein IIb/IIIa receptor complex, preventing platelet aggregation by ADP stimulation.22

BMSs endothelialise fairly rapidly, thus dual antiplatelet therapy is started prior to implantation and continued for four to six weeks,23 while low-dose aspirin is continued for life. With this approach, the risk of stent thrombosis at 30 days is less than 1%.24 By contrast, dual antiplatelet therapy for DESs is necessary for up to a year or even for life in high-risk patients12,25 because the slow process of endothelialisation leaves metal struts exposed. It is also recommended to continue aspirin for life.26 Risk factors for stent thrombosis have been found to include early cessation of antiplatelet agents, co-existent renal failure, diabetes mellitus, or low cardiac ejection fraction, and procedures involving bifurcation lesions.27 More recently, a comparison of the incidence of adverse outcomes with on-label and off-label use of DESs has shown a higher incidence of adverse outcome, including stent thrombosis, with off-label use.28 Similarly, a further study showed that whilst absolute event rates are low, relative early safety is lower with off-label use.26 Off-label use is relatively common as the original DES studies that gained US Federal Drug Administration (FDA) approval involved stent insertion in discrete, relatively small native vessels.

Percutaneous coronary interventions and non-cardiac surgery

1. Cardiac protection

Observational studies have shown surgical coronary artery revascularisation to reduce the risk of cardiac complications after non-cardiac surgery.27,28 The evidence for protection was regarded as sufficiently convincing for patients who had CABG surgery within five years of planned non-cardiac surgery to be excluded from the PeriOperative Ischemic Evaluation (POISE) trial29 because such patients were considered to be at low risk for adverse cardiac outcome unless there had been recurrence of symptoms.

In contrast, percutaneous coronary revascularisation does not appear to protect to the same extent as CABG surgery. There have been a number of observational studies over the past ten years. Posner and colleagues carried out a case-controlled study of patients who had undergone coronary angioplasty and later underwent non-cardiac surgery. Following recent angioplasty (less than 90 days), no protection could be demonstrated. However, there were benefits where the angioplasty had preceded non-cardiac surgery by more than 90 days.30 Non-cardiac surgery carried out shortly after angioplasty is associated with considerable morbidity and mortality.31 This is also true of early surgery in patients with coronary artery stents.32 More recently, a study carried out in vascular surgical patients did not show angioplasty to have conferred any protection.33

Many observational studies have reported cardiac complications in patients with previous angioplasty ranging between 3% and 13%.34-37 For those with stents, the range is even wider as it extends from 5% to 42%.32,35,38,39

In a recent review, Howard-Alpe and colleagues found that 424 patients with mostly bare metal stents suffered 82 adverse outcomes after non-cardiac surgery. There were 28 (6.6%) cardiac deaths, 23 (5.4%) non-fatal myocardial infarctions, and a further 24 (5.4%) had evidence of myocardial damage (serum troponin elevation or myocardial ischaemia).40 It is difficult to draw firm conclusions, but the number of major complications does not suggest that stents conferred clinically significant protection.

Two randomised, controlled trials of coronary revascularisation prior to non-cardiac surgery have been negative.41,42 In these studies, the majority of patients underwent percutaneous interventions (173 PCIs versus 115 CABG procedures). The cardiac complications of non-cardiac surgery were similar in the patients treated with maximal medical therapy and those who had undergone revascularisation. However, both studies have their limitations. McFalls and colleagues excluded all patients with triple vessel disease, those with aortic stenosis, and those with poor left ventricular function;41 in addition, most patients underwent revascularisation using percutaneous procedures, which do not appear to protect surgical patients. The same is true of the DECREASE-V study: there were more percutaneous interventions than CABG surgery.41,42

The absence of apparent protection by PCI as opposed to CABG surgery may reflect a number of factors. These could include a possible lesser quality of reperfusion or incomplete revascularisation by PCI, the release of inflammatory mediators and a consequent hypercoagulable state seen in the perioperative period that may predispose to stent thrombosis; and untimely interruption of antiplatelet therapy for surgery that is a risk factor for stent thrombosis.

2. Hazards in patients with coronary artery stents

Until fairly recently, excessive, life-threatening bleeding was considered to be the major risk of surgery in patients with coronary artery stents implanted taking antiplatelet therapy, and it was usual to interrupt the administration of clopidogrel and/or aspirin one week before elective surgery.43,44 However, a recent prospective study by Vicenzi and colleagues forced a rethink of this strategy.45 These authors showed that patients with coronary artery stents whose antiplatelet treatment had been maintained as long as practical before surgery and were given unfractionated heparin to cover the immediate perioperative period, suffered cardiac rather than bleeding complications (42 versus 4 respectively). An editorial accompanied this paper and
stressed that: 1) the risk of bleeding was smaller than the risk of adverse cardiac events; 2) for six to twelve weeks after PCI, only life-saving surgery should be performed; 3) it is unwise to stop all anti-platelet drugs; and 4) for operations with major risk of bleeding, there could be a switch to aspirin and low molecular weight heparin. However, more recent thinking has questioned the administration of heparin, whether unfractionated or of low molecular weight in this scenario. The problem is platelet activation, and heparin has no antiplatelet activity per se. It may be that adding heparin in the perioperative period only increases the potential for bleeding complications, with no protection against stent thrombosis. If it is absolutely necessary to stop oral antiplatelet therapy prior to surgery, the possibility of bridging to surgery with a shorter-acting antiplatelet agent is promising. This would minimise the time period that antiplatelet therapy is absent, exposing the patient to less risk of stent thrombosis. Tirofiban is a potent, intravenous, short-acting, highly specific non-peptide glycoprotein IIb/IIIa antagonist that could be utilised for this purpose. Newer shorter-acting antiplatelet agents are becoming available, such as Cangrelor, a direct-acting, reversible, P2Y 12 ADP antagonist. This drug may be potentially useful in the perioperative period.

Currently 60% to 80% of patients receive drug-eluting rather than bare metal stents. As a result of the increase in the number of percutaneous coronary interventions and the increased duration of dual antiplatelet therapy (12 months or more),47 many patients present for elective or emergency surgery while on this type of medication. There are patients in whom delaying surgery for such a long period of time is possible, though it may be inconvenient; there are others who need surgery earlier. What are the issues and options?

1. Type of surgery
Some operations can be carried out successfully in patients maintained on dual antiplatelet therapy. Haemostasis may be more difficult, but still achievable. In this situation the risk of interrupting dual antiplatelet therapy seems to exceed the risk of bleeding, as it is well documented that untimely, premature withdrawal of dual antiplatelet therapy is the strongest predictor of subsequent stent thrombosis.24,45,46 Other risk factors include renal failure, diabetes mellitus, low cardiac ejection fraction, and procedures involving bifurcation lesions.24 However, surgery in closed cavities (brain, eye) cannot be carried out under dual antiplatelet therapy, as bleeding may either negate the benefits of surgery or endanger the patient’s life, and the antiplatelet regime has to be modified.

2. Type of stents
a. BMSs: As dual antiplatelet therapy is necessary for only four to six weeks, elective surgery should be delayed for this period of time.47 As the effects of clopidogrel last for several days after the treatment has stopped, a further week is necessary in case of closed cavity surgery to minimise the risk of bleeding. It may be sensible to continue with aspirin.
b. DESs: As dual antiplatelet therapy is recommended for 12 months,47 there are patients for whom this delay is unacceptable, and surgery cannot safely be carried out with dual antiplatelet therapy for the reasons mentioned above (closed cavity surgery). The management of these patients must be discussed by the surgeon, cardiologist, anaesthetist and patient as the risk of cardiac events is high and bleeding complications could be serious. There is no room for unilateral decisions.47 If the consensus is that dual antiplatelet therapy should be withdrawn before surgery, the question of measures to minimise the risk of stent thrombosis arises. It has been proposed to use low molecular weight heparin48,49 and/or introduce a short-acting antiplatelet agent such as tirofiban.48 It is also generally recommended that aspirin should be continued.47
c. Future stent technology: Research is ongoing on new stent technology, including polymer coatings and altered metallic stent design, with the aim of altering the drug-eluting characteristics and endothelialisation rate of stents. Other researchers are investigating bioabsorbable magnesium stents,49,50 a biodissolvable stent coating,51 endothelial progenitor cell capture by stents coated with antibody against CD34,52 and even gene-eluting stents.53

3. Perioperative implications
a. Regional anaesthesia: Dual anti-platelet therapy is generally regarded as an absolute contraindication to spinal or epidural anaesthesia because of the risk of epidural or intra-dural haematoma.46 Nevertheless, as recently as 2004 a survey of UK thoracic epidural anaesthetic practice revealed that despite the American Society of Regional Anesthesia (ASRA) guidelines,53 many respondents did not regard aspirin combined with clopidogrel to be an absolute contraindication to thoracic epidural anaesthesia.55 The use of regional neuraxial blockade should be discouraged.
b. By analogy, dual antiplatelet therapy may impose extra care in the siting of intravascular catheters. Placement of central venous catheters should be in areas where compression is possible in case of haemorrhage. This excludes the subclavian approach for central venous access. Ultrasound guided central venous cannulation should probably be the rule in such patients, irrespective of the site.
c. Nerve blocks should also be used with considerable caution, particularly in the vicinity of major vessels. Again, ultrasound guidance has potential benefits.

4. Monitoring of antiplatelet activity
It would be beneficial, both pre-operatively and postoperatively, to have the facilities to routinely and simply test platelet function in any patient presenting for surgery who has been exposed to antiplatelet therapy. However, there are no simple routine tests for evaluating platelet function and its inhibition by antiplatelet agents.46 The standard tests of coagulation, the prothrombin time (PT) and activated partial thrombin time (APTT), do not allow assessment of platelet function. The ‘bleeding time’ is probably the most accurate test of platelet function and the effect of anti-platelet agents; but in reality it is not the most practical of tests and has not been shown to correlate well with peri-operative bleeding. Plasma drug concentrations of both aspirin and clopidogrel do not correlate with their pharmacodynamic effects, as both drugs have a short plasma half-life but a long duration of action due to the irreversible nature of their antiplatelet effect.56 Evaluation of platelet function is also possible with modified assay (rotational) thromboelastography (the standard TEG cannot monitor platelet function), Plateletworks Analyzer (PWA), VerifyNow (formerly known as Ultegra Rapid Platelet Function Analyzer/RPFA), Multiple Platelet Function Analyzer (or Multiplate), Plateletworks aggregation kits, Impact cone and plate analyser, Platelet Function Analyzer (PFA-100) and the Hemostatus Device.57 However, there remains
considerable result discordance between these individual point-of-care tests and the laboratory-based tests. Further research is needed to elucidate the most accurate and reliable system.

The lack of a widely available simple test is problematic for two reasons: 1) patients on dual antiplatelet therapy may not have an acceptable reduction of platelet activity and could therefore still be at a high risk of stent thrombosis; and 2) prior to surgery, where antiplatelet therapy needs to be discontinued, it would be extremely useful to know how much recovery of platelet function has occurred, and on restarting treatment, how effective the reinitiation of antiplatelet agents has been.

5. Postoperative care
Stent thrombosis occurs most commonly during the first 48 hours after surgery. Ideally patients should be admitted to an area where continuous electrocardiographic monitoring and close clinical observation is available, which may be a high dependency unit (HDU) or intensive therapy unit (ITU) environment. Percutaneous coronary intervention and cardiac surgical services should also be available, as emergency revascularisation is essential should a stent thrombosis occur. There is no place for improvisation or delay.

Because of the high risk of stent thrombosis, patients who have stopped clopidogrel should be managed in an HDU or ITU with continuous ECG monitoring and regular review by a cardiologist. Close monitoring until full antiplatelet therapy has been re-established is essential. This applies not only to patients in whom clopidogrel has been stopped for a week, but also to patients in whom it has been stopped for a shorter period in view of the adverse cardiac outcome reported by Vicenzi and colleagues.

The signs and symptoms of stent thrombosis are as varied as those of myocardial infarction in the absence of stents. If stent thrombosis is likely to have occurred, coronary angiography and intervention to reopen the occluded vessel is essential. For this reason high-risk patients should undergo surgery in hospitals where interventional cardiology is available. Aggressive use of antiplatelet agents may be necessary, and consequently the use of a glycoprotein IIb/IIIa inhibitor, such as tirofiban, may be indicated. Its effects will be short lasting should massive bleeding occur.

6. Resumption of antiplatelet therapy
Thienopyridines should be restarted as soon as possible following surgery. The precise timing of reinstatement of therapy should be actively discussed between the surgeon, anaesthetist and cardiologist. The risk of bleeding should have diminished and any neuro-axial catheters should preferably have been removed prior to restarting therapy, otherwise platelet transfusion cover may be needed for their removal. Some cardiologists advocate restarting clopidogrel with a loading dose as is routine in interventional cardiology. The licensed loading dose of clopidogrel following PCI is 300 mg, but cardiologists are increasingly using a loading dose of 600 mg with the aim of shortening the time to maximal platelet inhibition. Following the 600 mg loading dose, the full antiplatelet effect of the drug can be seen after two hours, compared to six hours with the 300 mg loading dose. A similar loading dose could be considered in postoperative patients to ensure a rapid return of antiplatelet activity.

7. Treatment of the possible complication of excessive bleeding: the only way in which the effects of dual antiplatelet therapy can be reversed is by transfusion of platelets. In the absence of active platelets, agents such as aprotinin (UK license now suspended) and recombinant Factor VII are of no proven value.

8. Emergency surgery
For many types of procedures platelet transfusion should bring the platelet to a count above 50 000 μL; for neurosurgery and ophthalmic surgery involving the posterior segment of the eye, the platelet count should be above 100 000 μL. However, in the majority of patients who take antiplatelet agents, the platelet count is normal, but the functioning of the platelet is abnormal. The effects of clopidogrel and aspirin are irreversible and new platelets have to be generated to reverse the effects of these drugs. Consequently in the emergency situation, where it is necessary to rapidly correct platelet function, the only solution is to administer platelet transfusion. A recent study has shown that two to three pools of platelets are needed to correct platelet function following treatment with aspirin and clopidogrel.

The latest guideline on the management of patients with angioplasty and stents who are to undergo non-cardiac surgery proposes the following strategy: After angioplasty, BMS and DES insertion, surgery should be delayed by respectively more than 14, more than 35, and more than 365 days, as after these delays, dual antiplatelet therapy can usually be reduced or discontinued, while aspirin is continued.

Conclusions
Currently there is little evidence from observational studies that percutaneous interventions, with or without insertion of coronary stents, result in the protection of patients with coronary artery disease who undergo non-cardiac surgery. The only two randomised, controlled trials of preoperative coronary revascularisation did not show any protection. However, as they included both CABG surgery and stent insertion, they did not specifically address the question of protection by coronary stenting. What is clear, however, is that the need for dual antiplatelet therapy for shorter or longer periods, depending on the type of stent implanted, can cause major problems. Untimely interruption of antiplatelet therapy can be responsible for stent thrombosis, and its maintenance is not possible in the case of closed cavity surgery. The strategy for such patients includes discussion between the surgeon, cardiologist and anaesthetist involved in the patient’s peroperative care, along with a thorough briefing of the patient. It is also important for surgery to ideally take place in a centre where emergency interventional cardiological services are available in case of stent thrombosis. It is generally agreed that regional anaesthesia carries excessive risk if dual antiplatelet therapy is continued. For emergency surgery, excessive bleeding requires the administration of platelets.

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