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REVIEW ARTICLE

Coronary artery stents and non-cardiac surgery

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The utility of interventional cardiology has developed significantly over the last two decades with the introduction of coronary angioplasty and stenting, with the associated antiplatelet medications. Acute coronary stent occlusion carries a high morbidity and mortality, and the adoption of therapeutic strategies for prophylaxis against stent thrombosis has major implications for surgeons and anaesthetists involved in the management of these patients in the perioperative period. Currently, there is limited published information to guide the clinician in the optimal care of patients who have had coronary stents inserted when they present for non-cardiac surgery. This review examines the available literature on the perioperative management of these patients. A number of key issues are identified: the role of surgery *vs* percutaneous coronary intervention for coronary revascularization in the preoperative period; the different types of coronary stents currently available; the emerging issues related to drug-eluting stents; the pathophysiology of coronary stent occlusion; and the recommended antiplatelet regimes that the patient with a coronary stent will be receiving. The role of preoperative platelet function testing is also discussed, and the various available tests are listed.

Appropriate management by all the clinicians involved with patients with coronary stents undergoing a variety of non-cardiac surgical procedures is essential to avoid a high incidence of postoperative cardiac mortality and morbidity. The review examines the evidence available for the perioperative strategies aimed at reducing adverse outcomes in a number of different clinical scenarios.

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In the last 20 yr, there have been important developments in the field of percutaneous coronary intervention (PCI), initially with balloon angioplasty alone and now in combination with coronary stent insertion.[110] The technique was initially described in 1977 and involves advancement of a balloon-tipped catheter into an area of coronary narrowing, inflation of the balloon, and then subsequent removal of the catheter after balloon deflation.[48] Widespread use of balloon angioplasty was initially limited by two major complications: acute vessel closure during or immediately after the procedure secondary to thrombosis or vessel dissection and re-stenosis of the vessel due to a combination of elastic recoil, smooth muscle proliferation, and neointimal hyperplasia. Both of these complications were considerably reduced by the introduction of coronary stents which are deployed over a balloon at the site of an atheromatous lesion.[110] This increased safety and efficacy of PCI has led to an exponential rise in the number of procedures being performed, with currently more than 90% of all PCIs involving the placement of at least one coronary stent.[115] Consequently, an increasing sub-group of the population with coronary artery disease (CAD) has a coronary stent implanted and may subsequently require non-cardiac surgery. The aim of this review is to identify the issues surrounding the perioperative management of patients with coronary artery stents in place and summarize the current literature with particular relevance to the anaesthetist.

Search strategy

In order to assess fully the risks and outcomes associated with non-cardiac surgery in the patient with a coronary

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stent, we first searched the literature for articles giving any indication of current knowledge and clinical practice. Secondly, we examined the literature to identify appropriate case reports and observational series of such patients. Searches for information regarding the issues surrounding the management of these patients perioperatively were performed using Medline (WINSPIRS 5.0) and Pubmed (National library of Medicine; www.pubmed.gov) with keywords including: percutaneous coronary intervention, balloon angioplasty, coronary artery stents, bare metal stent, drug-eluting stent, perioperative, surgery, non-cardiac, cardiac, coronary artery bypass grafting, coronary revascularization, pathophysiology, stent occlusion, stent thrombosis, re-stenosis, coagulation, hypercoaguable state, bleeding, haemorrhage, platelet function, monitoring, tests, platelet aggregation, thrombocytopenia, platelet transfusion, antiplatelet agents, aspirin, thienopyridines, clopidogrel, ticlopidine, glycoprotein IIb/IIIa receptor inhibitors, loading dose, heparin, low molecular weight heparin, flurbiprofen, aprotinin, antifibrinolytics, recombinant factor seven, neuro-axial block, regional anaesthesia, recommendations, and guidelines. The websites of a number of organizations [The American Heart Association (AHA), The American College of Cardiology (ACC), The European Society of Cardiology (ESA), The British Cardiac Intervention Society, The Scottish Intercollegiate Guidelines Network (SIGN), The American Society of Anesthesiologists (ASA), The Association of Anaesthetists of Great Britain and Ireland (AAGBI), and The Royal College of Anaesthetists (RCOA)] were also searched for relevant guidelines.

The different types of coronary artery stents

There are two major types of coronary artery stent: bare metal stents (BMS) and drug-eluting stents (DES). DES were introduced in the late 1990s in response to the high observed incidence of late stent re-stenosis with BMS. Re-stenosis is a side-effect of the normal healing process with the growth of scar tissue around the stent mesh in a process called neointimal hyperplasia, which in some cases, can lead to occlusion of the coronary lumen. The process peaks at around the third month and reaches a plateau at between 3 and 6 months after the procedure. In patients receiving a BMS, in-stent re-stenosis requiring repeat intervention occurs in 12–20%,[36] and procedures to treat stent re-stenosis were developed including balloon angioplasty, mechanical debulking, repeat stenting, and intra-coronary irradiation (brachytherapy).[132] Late thrombosis after BMS is a well documented, although rare, complication when brachytherapy is used as an adjunct to stent placement to reduce re-stenosis after PCI, and is attributed to delayed vascular healing.[76]

DES were designed to prevent re-stenosis by coating a standard coronary stent with a thin polymer containing an antiproliferative substance that inhibits smooth muscle proliferation and neointimal hyperplasia within the stented segment,[24] and reduces the need for repeat intervention to approximately 5%.[22 81] Currently, there are two major types of DES being inserted, releasing either sirolimus ('Cypher' stent) or paclitaxel ('Taxus' stent). Sirolimus (rapamycin) is a macrolide antibiotic with potent immunosuppressive and antimitotic properties, which binds to its cytosolic receptor, FKBP12, and inhibits down-regulation of the cyclin-dependent kinase inhibitor $p27^{kip1}$. This blocks transition from G_1 to S phase in the cell cycle and so inhibits vascular smooth muscle cell proliferation and migration.[105] The majority of sirolimus is eluted from the polymer coating of the Cypher stent by 28 days,[64] and is fully eluted at 60 days,[125] leaving a polymer BMS. Paclitaxel is a potent anti-tumour drug which inhibits microtubule formation during cell division.[24 73] About 10% of the drug is released from the polymer coating of the Taxus stent by 10 days, with the rest of the drug remaining within the polymer indefinitely.[76] DES have been widely used and are highly effective at reducing late stent re-stenosis.[80 117] They have been shown, in the short to medium term (6–12 months), to have at least as good a safety profile as BMS.[9 84] However, the mechanism of obstruction of DES is different from that of BMS. In BMS, the pathophysiological mechanism of obstruction is re-stenosis with neointimal hyperplasia and DES inhibit this process, but since the stent struts remain uncovered, they are prone to thrombosis. Currently, there is increasing concern and controversy over the safety profile of DES, with the Food and Drug Administration (FDA) responding by issuing a statement that DES are 'safe and effective when used for FDA-approved indications'. These indications involve discrete and relatively short lesions (up to 28 mm in the case of one approved stent and up to 30 mm in the case of the other) in relatively small native vessels (2.5–3.5 or 3.75 mm in diameter). However, DES are widely used on an off-label basis for longer lesions, larger vessels, and multi-vessel lesions.[107] There are concerns that DES may cause endothelial dysfunction, a phenomenon which may persist long after the drug is supposed to have fully eluted from the stent.[122] The longer term safety of DES is certainly being debated with possibly an increase in the occurrence of acute infarctions and late mortality.[13] The low incidence of re-stenosis seen with DES has allowed the PCI treatment of patients with more complex and extensive lesions who had previously only been candidates for coronary artery bypass graft (CABG) surgery. The use of DES has expanded rapidly, with one study showing that by June 2004, 80% of stents implanted in patients undergoing urgent PCI in the USA were drug eluting,[63] and nearly 6 million patients worldwide have had a DES implanted.[107]

Coronary stents and antiplatelet therapy

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.[23] This potentially devastating complication is associated with a 50% incidence of acute myocardial infarction (MI) and a 20% mortality rate,[27] and consequently, the prevention of stent thrombosis is of paramount importance. Initially, it was tackled by the use of complex anticoagulation regimes using aspirin, heparin, and warfarin, but in turn this led to high rates of major bleeding, vascular complications, and long hospital stays. The development of new antiplatelet agents (Table 1) led to a breakthrough in the use of coronary stents with the adoption of dual antiplatelet regimes combining aspirin with a thienopyridine.[68 102] Initially, ticlopidine was prescribed with aspirin, but now this has largely been replaced by clopidogrel which is better tolerated and has reduced risk of severe adverse events.[12] Clopidogrel is a pro-drug which is metabolized to an active compound that inhibits the P2Y 12 adenosine diphosphate (ADP) platelet receptor. Blockade of this receptor inhibits the binding of fibrinogen to the platelet glycoprotein IIb/IIIa receptor complex, and so prevents platelet aggregation by ADP stimulation.[92]

The most widely used antithrombotic strategy involves the administration of a loading dose of 300–600 mg of clopidogrel before implantation of a BMS, with the continued administration of both aspirin and clopidogrel for a minimum of 4–6 weeks after the procedure. Low dose aspirin therapy is then continued for life. If the above recommendations are followed, stent thrombosis within 30 days of implantation occurs in less than 1% of patients who have uncomplicated PCI.[27] In contrast, DES require a more prolonged period of dual antiplatelet therapy. In addition to inhibiting neointimal hyperplasia, the drug coating the stent also delays re-endothelialization of the stent struts, leaving bare metal exposed in the circulation for a longer period of time. Antiplatelet therapy should be continued until the stent is fully re-endothelialized. There is currently no routinely available test to show when sufficient re-endothelialization has occurred and consequently when it is safe to withdraw antiplatelet therapy. Hence, based on the initial clinical trials, stent manufacturers recommended that clopidogrel should be continued for a minimum of 3 months after implantation of a sirolimus-eluting stent and 6 months after a paclitaxel-eluting stent. However, more recent guidelines suggest that dual antiplatelet therapy should be continued for at least a year.[86108 110 116 134] Using this approach, the insertion of DES appears to pose no greater risk than BMS,[9] although the requirement for prolonged antiplatelet treatment has the potential to create problems.

Premature cessation of antiplatelet therapy has been shown to be the strongest predictor of subsequent stent thrombosis.[61 87] Other risk factors include renal failure, diabetes mellitus, low cardiac ejection fraction, and procedures involving bifurcation lesions.[61] A significant number of patients receiving DES now have a much greater risk of stent thrombosis than those recruited for the initial trials, as they have a higher incidence of diabetes, multi-vessel disease, small coronary vessels, and complex lesions.[61] Consequently, there is some debate as to whether antiplatelet therapy for DES should be continued indefinitely beyond the first year after insertion in high-risk patients. There are significant risks associated with lifelong antiplatelet therapy, especially during any future perioperative period, and consequently, the potential implications to the patient of such therapy need to be carefully considered.

The risk of an adverse cardiovascular event if clopidogrel is stopped in the perioperative period is unknown but is likely to be considerable, particularly in patients with recently implanted poorly endothelialized stents or recent acute coronary syndromes (ACS).[3576]

Table 1 The different types of antiplatelet agents

Types of antiplatelet agents
Acetylsalicyclic acid derivatives
Aspirin
Diflunisal
Thienopyridines
Clopidogrel
Ticlopidine
Glycoprotein IIb/IIIa inhibitors
Tirofiban
Abciximab
Eptifibatide
Pyrimidopyrimidine derivative
Dipyridamole

Coronary revascularization before non-cardiac surgery

Prophylactic coronary revascularization in patients with asymptomatic CAD before major non-cardiac surgery has no benefit, whether by PCI or CABG.[74 77] However, patients with indications for coronary revascularization irrespective of the non-cardiac surgery should be treated appropriately.[11 30 31] The recent SIGN 96 document reviewing the management of stable angina confirms that CABG is not recommended before major or intermediate risk non-cardiac surgery unless cardiac symptoms are unstable and CABG would be justified on the basis of long-term outcome.[11] When indicated (Table 2), PCI, in the form of angioplasty often with stent insertion, appears to be as effective as CABG, with a similar mortality rate.[30] Although PCI has the benefit of being less invasive, is economically advantageous,[104] and consequently, tends to be performed in preference to CABG where there is amenable disease and favourable coronary anatomy,[94 118] there is a significantly increased incidence of repeat revascularization.[1 47 79 104 113] There is some evidence that under specific conditions CABG may be superior to PCI, with a potential long-term advantage among patients with diabetes and multi-vessel disease.[10 127]

Table 2 Typical indications for coronary artery revascularization

Indications for coronary artery revascularization[11 39]
Poorly controlled angina despite maximal medical therapy
High-risk coronary anatomy including significant (>50%) left main coronary artery stenosis
Severe two- or three-vessel CAD (>70% stenosis) with involvement of the left anterior descending (LAD) artery
Easily induced myocardial ischaemia on stress testing
Left ventricular systolic dysfunction at rest

After CABG, non-cardiac surgery should be delayed by at least 30 days,[11 14] and there is good observational evidence that successful CABG significantly reduces the risk of adverse cardiac events after subsequent non-cardiac surgery in those patients who remain symptom free with good left ventricular function.[32 42] Whether PCI affords the same degree of protection as CABG during future non-cardiac surgery remains unanswered, partly because it is not possible to compare the two types of revascularization directly as they have different indications, and the available literature is often difficult to interpret because of the range of PCI available. The protection provided by balloon angioplasty alone, without stent insertion, may be superior to that provided by stent insertion before early non-cardiac surgery.[15 59] Current evidence indicates a lack of protection before 90 days post-PCI,[91] with some reports indicating complication rates close to those observed in patients who are offered no prophylactic protection by either revascularization or medical therapy.[5 44 96] Two retrospective studies of patients undergoing non-cardiac surgery after PCI showed fairly convincing evidence of increased perioperative cardiac adverse outcome in those operated on within 6 weeks of stent insertion (Table 3). [62 131] There is also a high incidence of ischaemic complications in those undergoing non-cardiac surgery in the year following coronary stent insertion (Table 3).[123] Guidelines state that if a coronary stent is inserted, a delay of at least 2 weeks and ideally 4–6 weeks should occur before non-cardiac surgery to allow 4 full weeks of dual antiplatelet therapy and re-endothelialization of the stent to be completed.[29] This guideline refers to the management of a BMS and offers no guidance regarding the appropriate management of DES. At present, PCI is more commonly performed than CABG but given the current controversy with DES, and the problems with re-stenosis in BMS, the future preference for coronary revascularization is unclear.

Perioperative antiplatelet therapy: bleeding or thrombosis?

The protective effect of dual antiplatelet therapy in patients with coronary stents in place has to be balanced against the risk of increased bleeding. It is this balance of risk in the perioperative period that gives rise to a major clinical dilemma in patients presenting for surgery after the implantation of coronary stents. The intraoperative haemostatic reaction is well known and, after major surgery, many patients develop a hypercoagulable state. The advent of thromboelastography has shown evidence of a hypercoagulability lasting for at least 7 days after major surgery. The hypercoagulability comprises accelerated clot formation, with an early decrease in reaction time (r-time) and an increase in the clot strength, with continuous postoperative increase in the maximum amplitude (MA).[71] A raised MA (>68 mm) within 2 h of the completion of surgery has been shown to predict thrombotic postoperative complications, including MI, with a sensitivity and specificity of 80% and 62%, respectively.[75] It is unclear when coagulation returns to normal baseline values with evidence that the hypercoagulability persists beyond the duration of the surgical stress response. Despite a significant increase in fibrinogen, this hypercoagulability seems to be caused predominantly by platelet activity, which is not identified by standard coagulation monitoring.[71] There is a significant increase in ADP-induced platelet aggregation at 24 and 48 h after surgery, not associated with a change in the flow cytometry profile, indicating that platelets are not activated after operation. A high concentration of fibrinogen is seen at 48 h and is still present on the seventh postoperative day. An initial peak in the concentration of plasminogen activator inhibitor-1 soon after the cessation of surgery occurs, and this raised level is still present at 24 h after operation. No increase in thrombin–antithrombin complex concentration has been observed; in fact, a significant decrease has been documented, which occurs intraoperatively. Consequently, thrombin generation is limited and fibrinolysis is impaired after operation.[97] Although platelets are not activated in the postoperative period, they are more prone to being activated as demonstrated by aggregation studies, and the platelet count is significantly increased when measured on the seventh postoperative day.[101] The combination of stopping protective antiplatelet therapy along with the hypercoagulable perioperative state and a poorly endothelialized stent leads to a high risk of acute stent thrombosis which is associated with considerable morbidity and mortality.[61 76]

In contrast, patients taking dual antiplatelet therapy may be at increased risk of major bleeding complications. Combined therapy with clopidogrel and aspirin increases the bleeding time through a synergistic antiplatelet action,[88] and it has been shown that clopidogrel plus aspirin before operation in patients undergoing CABG results in more postoperative bleeding and increased blood product transfusion.[95 133] A recent meta-analysis of 4002 patients undergoing cardiac surgery (605 taking clopidogrel) showed a significant increase in blood loss, transfusion and ventilation requirements, length of hospital stay, and surgical re-exploration in those on clopidogrel.[93] Patients presenting with ACS who were referred for CABG showed a 37% increased blood loss and a

significantly increased re-operation rate for bleeding complications if they received clopidogrel before operation.[7] Clopidogrel within 4 days of CABG has been shown to be an independent risk factor for prolonged ICU and hospital length of stay.[20] The use of off-pump techniques may reduce the risk of bleeding,[69] as the detrimental effects of clopidogrel and cardiopulmonary bypass on platelet and clotting function may be synergistic.

There is little evidence of increased surgical bleeding in non-cardiac studies. One retrospective study of patients undergoing non-cardiac surgery after coronary stenting found no difference in the transfusion frequency regardless of the use of antiplatelet agents.[106] A further study showed that in patients who underwent non-cardiac surgery while administered heparin and aspirin plus or minus clopidogrel within a year of coronary stent insertion, there was no major morbidity from bleeding.[123]

The effect of antiplatelet agents on platelet function

Unfortunately, there is significant variation between patients with respect to their platelet function after thienopyridine and aspirin therapy.

Clopidogrel is a pro-drug that requires activation by the cytochrome P450 isoenzyme CYP3A4.[66 67] Because of genetic variability in the metabolic activity of this enzyme and inhibitory drug interactions, there is considerable inter-individual variability of platelet inhibition. This can lead to clopidogrel resistance.[66] Non-response to clopidogrel has been classified as a relative inhibition of ADP-induced platelet aggregation of $<10\%$ and response as $\geq 30\%$, whereas those in-between are defined as low responders. One study of clopidogrel platelet inhibition response in 32 patients undergoing coronary stent insertion and 35 healthy volunteers found 22% non-responders and 47% responders in the patient group and 16% non-responders and 72% responders in the volunteers. Percentage platelet aggregation after clopidogrel has been shown to be inversely correlated with CYP3A4 activity.[66] A recent study of platelet function using optical light aggregometry found that only 50% had a definitive response.[2] At a median of 5 days after initiation of treatment with a 300 mg loading dose, only 17.5% of patients receiving daily clopidogrel had an inadequate response to therapy.[49] Drugs known to inhibit the CYP3A4 isoenzyme include itraconazole, ketoconazole, clarithromycin, erythromycin, and ritonavir, and grapefruit juice also has an inhibitory effect. The statin group of compounds are largely metabolized by this isoenzyme and has the theoretical potential to influence clopidogrel activation but does not appear to have a clinically significant effect on the antiplatelet action of clopidogrel.[46 111]

A similar resistance to aspirin has been described, with a failure of aspirin to reduce platelet production of thromboxane A_2 by irreversible acetylation of cyclooxygenase-1 (COX-1) and thus failing to prevent platelet activation and aggregation.[51] It can be detected by tests that either measure platelet thromboxane A_2 production or assess thromboxane-dependent platelet function. Aspirin failure may be due to reduced bioavailability of the drug by poor compliance, inadequate dose, reduced absorption or increased metabolism, drug interactions, genetic polymorphisms of COX-1 and other genes involved in thromboxane production, increased platelet turnover, alternate pathways of platelet activation, and up-regulation of non-platelet sources of thromboxane synthesis.[51] Aspirin resistance, as indicated by high urinary concentrations of 11-dehydrothromboxane $B_{2,}$ has been shown to be associated with an increased odds of a serious vascular event.[34] Aspirin and clopidogrel resistance is a potentially severe clinical problem,[126] and an impaired response to antiplatelet therapy has been shown to be associated with stent thrombosis.[129] A higher dose may be needed in those patients exhibiting resistance to achieve a therapeutic clinical effect.[50]

Monitoring the effect of antiplatelet agents on platelet function

It would be beneficial in perioperative management to have a routine and simple test of platelet function in patients exposed to antiplatelet therapy presenting for surgery in order to exclude lack of clinical effect and consequently a reduced risk of bleeding, and higher risk of thrombotic complications or to have a quantifiable assessment of platelet function before neuro-axial blockade after drug cessation. A recent case report highlighted the problems of assessing and monitoring the effects of antiplatelet agents and the coagulation process.[54] The standard tests of coagulation, the prothrombin time (PT) and activated partial thromboplastin time (APTT), do not allow assessment of platelet function. The 'bleeding time' is the most accurate test of platelet function and the effect of antiplatelet agents, but in reality is not the most practical of tests and has not been shown to correlate well with perioperative bleeding. Plasma drug concentrations for both aspirin and clopidogrel do not closely correlate with their pharmacodynamic effects due to irreversible binding of the drugs to the target.[52]

A variety of tests are currently being assessed for measurement of platelet function. Optical light transmission platelet aggregometry is the most widely accepted technique of assessing platelet function being considered the 'gold standard'. Unfortunately, the method is laboratory-based and time consuming. Point-of-care techniques for assessing platelet function are now available but appear to have varying accuracy. They include the following:

Table 3 Summary of studies illustrating outcome after non-cardiac surgery in patients with coronary stents implanted. CS, case series; CR, case report; R, retrospective; L, letter; P, prospective; O, observational; av, average; BMS, bare metal stent; DES, drug eluting stent; GI, gastrointestinal; GU, genito-urinary; gynae, gynaecological; wks, weeks; mths, months; APA, antiplatelet agent; MI, myocardial infarction; postop, postoperative; preop, preoperative; periop, perioperative

Study author (year)	Type of study	Number of patients and date	Type of surgery	Type of coronary stent	Time from coronary stent insertion to surgery	Antiplatelet therapy	Perioperative management	Outcome and time to adverse cardiac event
Kaluza and colleagues (2000)[62]	CS	40 (1996–1998)	General, thoracic, urological, vascular	BMS	1–39 days (av 13 days)	All patients $\geq$1 dose of ticlopidine after stenting All received dual APA after stenting for a variable length of time Nine patients administered abciximab during stenting	Only cases that expired had their periop APA management mentioned Only one did not have aspirin withheld All, except three, had ticlopidine withheld The exact duration APAs withheld only mentioned in three patients	Death (n=8; 20%) MI (n=7; 6 fatal and 1 non-fatal). 4 out of 7 MIs within 24 h postop All patients who had MI and expired underwent surgery less than 6 days after stent insertion. Eleven bleeding episodes (6 in patients who died, cited as cause of death in 2)
Vicenzi and colleagues (2001)	CR	1 (2000)	Urological	BMS	32 days	Aspirin only	Aspirin stopped 5 days preop and LMWH administered	MI 2 h postop PCI performed with recanalization of stent
Wilson and colleagues (2003)[131]	R	207 (1990–2000)	Breast, general, head and neck, GU, orthopaedic, thoracic, vascular	BMS	1–60 days	Aspirin and heparin at time of stenting, some received GP IIb/IIIa inhibitor in addition From 1995, all patients received ticlopidine before stent insertion and for 2–4 wks after From 1998, clopidogrel substituted for ticlopidine	Aspirin and thienopyridine at time of surgery (n=54, 27%) Aspirin and last dose of thienopyridine $\leq$10 days before surgery (n=29, 14%) Aspirin and warfarin (n=4, 2%) Aspirin alone (n=104, 51%) No anticoagulant therapy for >10 days (n=13, 6%)	Cardiac death (n=6; 2.9%) Major adverse cardiac events; MI, or stent thrombosis (n=8; 6 fatal) Time to cardiac event not stated All events occurred in those undergoing surgery less than 6 wks after stent insertion. Two episodes of excessive bleeding
Auer and colleagues (2004)[8]	CR: L	1 (2003)	Orthopaedic	1×BMS and 2×DES (paclitaxel)	12 wks	6 mth course of dual APAs; aspirin and clopidogrel	APAs discontinued for surgery, length of cessation of therapy not mentioned	MI; 2 h postop PCI performed, both DES occluded, recanalization performed BMS patent
Marcucci and colleagues (2004)[72]	CR	1 (2003)	Thoracic	BMS	6 wks	Dual APA; aspirin and clopidogrel for 4 wks after stenting followed by aspirin alone for further 2 wks	Aspirin continued perioperatively No other antiplatelet, anticoagulant, or antithrombotic therapy given	Cardiac death In-stent thrombosis 1 h postop, PCI performed with recanalization of stent Further MI second night after surgery
McFadden and colleagues (2004)[76]	CS: L	3 (2004)	Urological, general, GI (endoscopic procedure)	3×DES (paclitaxel and sirolimus) and 1×BMS	331–442 days	Two patients with DES alone on aspirin only. One patient with both DES and BMS on dual APAs; aspirin and clopidogrel	APAs stopped preop	MI (n=3); day of surgery, 4 and 5 days postop. All successfully treated with PCI and recanalization of stent Patient with DES and BMS; DES occluded but BMS patent

Continued

Table 3. *Continued*

Study author (year)	Type of study	Number of patients and date	Type of surgery	Type of coronary stent	Time from coronary stent insertion to surgery	Antiplatelet therapy	Perioperative management	Outcome and time to adverse cardiac event
Sharma and colleagues (2004)[106]	R	47 (1995–2000)	GI, oncological, orthopaedic, urological, vascular	BMS	All <90 days (<3 wks [27] >3 wks [20])	All patients on dual APA; aspirin and ticlopidine, after stent placement for 2–4 wks NB From 1998, ticlopidine replaced by clopidogrel	13 had thienopyridine stopped for at least 5 days preop	Death (n=7) MI (n=4, fatal=3) Stent thrombosis proven at angiography in two Cardiogenic shock (n=1, fatal) All patients who had cardiac event were not on thienopyridine Majority of events occurred early postop, all occurred <17 days postop Rate of bleeding similar whether on thienopyridine or not
Murphy and colleagues (2005)[83]	CR	1 (2005)	Gynae	DES (sirolimus)	2 wks	Dual APAs; aspirin and clopidogrel	APAs withheld for one dose preop	MI with stent thrombosis 20 min postop PCI performed with, thrombectomy and further stent insertion APAs administered including GP IIb/IIIa inhibitor, aspirin, and clopidogrel
Herbstreit and colleagues (2005)[54]	CR	1 (2004)	General	Not specified.	1 mth	Dual APAs; aspirin and clopidogrel	Platelet transfusion administered (2 pools)	Uneventful procedure including regional blockade
Brown and colleagues (2006)[17]	CR	1 (2005)	Orthopaedic	DES (sirolimus)	7 wks	Dual APAs; aspirin and clopidogrel, plus warfarin	Dual APA continued but warfarin stopped preop	MI; 12 h postop, treated with i.v. heparin
Charbucinska and colleagues (2006)[19]	CS: L	15 (but 18 procedures) (2006)	Vascular	19×DES (12 patients), 13 stents unspecified (3 patients)	1–12 mths	All taking aspirin preop; 14 taking clopidogrel preop	Aspirin withdrawn before three procedures (7–10 days) Clopidogrel withdrawn before 10 procedures (3–28 days), and 8 started LMWH 5 days preop LMWH given to further 5 patients	Cardiac death (n=1); fatal MI occurred post D/C (DES implanted for 6 mths, patient not on clopidogrel, but aspirin maintained) Myocardial ischaemia (n=2), both had clopidogrel but not aspirin withdrawn and received LMWH No excessive bleeding No complications (n=11)
Vicenzi and colleagues (2006)[123]	P. O.	103	ENT, general, neurological, orthopaedic, re-constructive, thoracic, urological, vascular	25 BMS and 5 DES (however, 79 cases stent type not identified)	Within 1 yr	Aspirin ± clopidogrel	APAs, aspirin ± clopidogrel, continued throughout the periop period or discontinued <3 days before operation. All patients received either UFH or LMWH in therapeutic dose	Cardiac death (n=5; 4.9%) MI (n=12) Myocardial cell injury (n=22) Bleeding (n=4) Some kind of event (n=46) Majority of cardiac events occurred early postop
Broad and colleagues (2007)[16]	CS	3	ENT, general, orthopaedic	BMS and DES (paclitaxel). Two patients had only DES and one patient had both types	49 days, ~1 yr, 33 mths	Dual APAs, aspirin, and clopidogrel	Clopidogrel stopped 5 days preop Commenced on a GP IIb/IIIa inhibitor (tirofiban) infusion 3 days preop 6 h preop tirofiban and heparin infusions ceased Loading dose of clopidogrel given on first postop day, followed by maintenance dose thereafter Aspirin continued throughout	Minimal surgical bleeding and no stent thrombosis observed NB Patient 2 (with DES) previously presented for surgery 18 months after DES insertion and had clopidogrel withdrawn for 1 wk. MI occurred preop on day 7 after stopping clopidogrel

Thromboelastography

This whole blood coagulation monitor can demonstrate certain platelet aggregation defects but is unable to detect the platelet adhesion and endothelial defects that occur with aspirin therapy, or demonstrate the ADP receptor blockade caused by clopidogrel. Patients taking clopidogrel who demonstrate platelet inhibition on aggregometry are found to have normal MA.[121] A recent modification of the assay, which generates a clot without thrombin generation using reptilase and factor XIIIa, should overcome this problem.[25] Platelet agonists, arachidonic acid (for aspirin), and ADP (for clopidogrel) are added enabling measurement of the degree of platelet inhibition resulting from the antiplatelet agent. A recent study compared this modification with aggregometry and demonstrated that it detected 90% of the platelet inhibition seen on aggregometry for aspirin therapy and 70% of the platelet inhibition seen on aggregometry for clopidogrel.[2]

Plateletworks analyser

This whole blood assay measures percentage aggregation using a single-platelet counting Coulter technology before and after exposure to ADP to calculate aggregation. A recent comparison between plateletworks analyser (PWA) and optical aggregometry showed good correlation between the two tests with regard to clopidogrel inhibition.[25]

Ultegra rapid platelet-function assay

This test is similar to aggregometry, measuring the rate and extent of platelet aggregation with the change in optical transmittance but uses fibrinogen-coated beads, thus allowing the use of whole blood and eliminating the need for sample preparation.[109] When compared with aggregometry in the assessment of platelet function after glycoprotein IIb/IIIa inhibitors, it had equivalent accuracy and precision.[130] However, a recent comparison of whole blood impedance aggregometry with the Ultegra assay in patients given a loading dose of clopidogrel after PCI found that the Ultegra assay showed only slight changes.[57]

Platelet function analyser

This measures the time taken for a platelet plug to occlude an aperture (closure time) in a membrane that is impregnated with collagen and either epinephrine or ADP. Aspirin has been shown to increase the epinephrine closure time, and in some studies clopidogrel has been shown to increase the ADP closure time. However, the accuracy of detecting inhibition of platelet function by clopidogrel is variable. A recent study showed that the platelet function analyser (PFA-100) did not detect any of the platelet inhibition caused by clopidogrel seen with optical aggregometry.[2]

Current practice in the management of the patient with a coronary stent and antiplatelet therapy

A recent questionnaire of current anaesthetic and surgical practice in hospitals in the Oxford region[60] found that 77% of respondents had treated patients taking clopidogrel and 57% had experienced bleeding complications in these patients, of which 15% were regarded as life-threatening, although no deaths were reported. Eighty percent of the anaesthetists would not perform spinal anaesthesia in these patients. With regard to the period of time clopidogrel should be stopped before operation, there was a wide range (0–28 days, median 7). There was no consensus on when to restart clopidogrel after operation and there appeared to be uncertainty about the increased thrombotic risk of different types of stents. In 2004, a survey of UK thoracic epidural anaesthetic practice revealed that despite the American Society of Regional Anesthesia and Pain Medicine (ASRA) guidelines,[58] 49% of respondents did not regard clopidogrel as an absolute contraindication to thoracic epidural anaesthesia and furthermore only 66% considered the combination of aspirin and clopidogrel an absolute contraindication.[90] A Royal College of Surgeons of England survey of UK vascular surgical practice showed that there was a wide diversity of practice with regard to stopping antiplatelet agents in the perioperative period with no consensus with regard to thienopyridines and major vascular surgery.[112] Only three of the 88 surgeons who completed the questionnaire stated that they would stop clopidogrel before operation but not aspirin, and 77% would not routinely stop antiplatelet agents before abdominal aortic aneurysm repair and of the 23% that would stop antiplatelet therapy, the mean time was 7 days before operation (range 2–14 days). Eighty-eight per cent would restart these drugs as soon as the patient was able to eat and drink.

The management of antiplatelet therapy in the perioperative period in patients with coronary stents?

Currently, there is little evidence from randomized controlled trials to guide the perioperative management of patients on antiplatelet agents with coronary stents. However, as larger numbers of patients are implanted with DES requiring longer-term dual antiplatelet therapy, the question of how to manage these patients needs addressing. The majority of published material on this topic is based on expert opinion with broad agreement on the principles of stent management in the perioperative period.[4 114]

The patient requiring elective non-cardiac surgery

When faced with a patient who requires non-cardiac elective surgery and has a coronary stent, the risk of stent

Table 4 Assessing surgical and haemorrhagic risk

Assessment of the patient's surgical and haemorrhagic risk
What is the precise nature of the planned operation and anaesthetic, and the possible complications?
How high is the perceived haemorrhagic risk?
Are there any other individual haemorrhagic risk factors?
What are the consequences of excessive bleeding?
How necessary is the surgery?
What is the urgency of the surgery—can the surgery be delayed?
Are there any possible alternatives to surgical treatment?

Table 5 Assessing thrombotic risk

Assessment of the patient's thrombotic risk
When was the stent inserted?
What type of stent does the patient have?
How many stents were inserted and where are they located?
Was the revascularization complete?
Is there a history of stent thrombosis previously?
What antiplatelet regimen is being followed and what duration of therapy has been recommended?
Does the patient suffer from other associated risk factors for stent thrombosis including:
Diabetes?
Renal impairment?
Low cardiac ejection fraction?
Are there any other individual thrombotic risk factors?

thrombosis needs to be assessed and balanced against both the potential risk of haemorrhage and the adverse consequences of any such bleeding. Management depends upon numerous factors that are summarized in Tables 4 and 5. Surgery can be classified according to the risk of major bleeding and the adverse effects of excessive bleeding. Management decisions must be based on each individual case after consultation between the patient, cardiologist, surgeon, haematologist, and anaesthetist. The risk of stent thrombosis associated with stopping antiplatelet agents is influenced by factors such as the nature of the lesion and the timing of the procedure.[43] The risk of stent thrombosis is likely to be highest where multiple recently implanted DES are present, particularly where they involve arterial bifurcations in patients with renal impairment, diabetes, or dehydration. It is also important to assess the consequences of thrombosis within an individual stent, as thrombosis in a stent in the proximal left anterior descending artery or the left main coronary artery carries a potentially greater morbidity and mortality than in a more distally placed stent in a smaller vessel.

The risk of haemorrhage is of major importance in the decision to stop antiplatelet agents. If the risk is small and the consequences relatively minor, then it may be possible to continue dual antiplatelet therapy. If the patient is to undergo surgery associated with a major haemorrhagic risk, then the consequences of excessive blood loss may outweigh the risks of possible stent thrombosis and antiplatelet agents such as clopidogrel should be stopped before surgery. If it is deemed necessary to stop a thienopyridine, then it is recommended that clopidogrel be stopped 7 days before operation[78] and ticlopidine 14 days before.[65] These recommendations are based on the half-life of a platelet, which is approximately 10 days, and the pharmacokinetics of the individual agent. A French working party, in 2006, recommended stopping clopidogrel between 5 and 10 days before operation dependent on the balance between haemorrhagic and thrombotic risk.[4] Whenever possible, with surgical consent, aspirin should be continued perioperatively in both the elective and emergency situation as withdrawal of aspirin is a risk factor for ACS and stent thrombosis.[18 21 37] The only types of surgery where perioperative aspirin therapy has been shown to lead to a higher severity of bleeding complications are intra-cranial surgery, and possibly transurethral prostatectomy.[18]

An appropriate alternative antithrombotic strategy is a controversial issue, with no consensus of opinion for any particular regimen. Heparin therapy, either unfractionated heparin (UFH) by i.v. infusion or low molecular weight heparin (LMWH) by s.c. injection, has been proposed during the period of time that the thienopyridine is stopped, but efficacy has not been proven.[119 123] There is no consensus on the target APTT ratio for UFH infusion, or whether a prophylactic or treatment dose of LMWH is indicated. If LMWH is compared with UFH, LMWH displays a reduced antifactor IIa activity relative to antifactor Xa activity, a more favourable benefit–risk ratio in experimental animals, and superior pharmacokinetic properties,[55] which allow once daily dosing and avoids the need for plasma monitoring. Of these potential advantages, only the pharmacokinetics have clear clinical importance. However, it is unknown whether UFH displays any added protection against stent thrombosis through its increased range of activity. In the setting of ACS, a treatment dose of LMWH (enoxaparin 1 mg kg^{-1} s.c. twice daily) has been shown in the INTERACT trial to be associated with early outcome benefits that are sustained over a two and a half year follow-up period.[38 45] The French working party[4] felt that if total withdrawal of antiplatelet therapy is necessary before non-cardiac surgery, consideration can be given to drug substitution with either a non-steroidal anti-inflammatory agent (NSAID), for example, flurbiprofen 50 mg×2, withdrawn 24 h before surgery, or LMWH (s.c. dose of 85–100 IU aXa per kg for 12 h). They did acknowledge that heparin exposes the patient to a substantial perioperative risk of bleeding, but concerns over an increased incidence of thrombotic complications with NSAIDs were not mentioned. However, heparin therapy is unlikely to protect against stent thrombosis as it has no antiplatelet properties. A strategy of perioperative heparin therapy was still associated with a high risk of cardiac morbidity and mortality in the study by Vicenzi and colleagues (Table 3),[123] and the possibility of 'heparin rebound', a period of hypercoagulability after abrupt cessation of an infusion of UFH, should be considered.[28]

A recently proposed perioperative strategy involves stopping clopidogrel 5 days before any major surgical procedure, admitting the patient to hospital 3 days before operation, and commencing a tirofiban and UFH infusion (target APTT not stated). Six hours before the surgery these infusions are stopped. Clopidogrel is then restarted on the first postoperative day with an initial loading dose of 300 mg followed by the usual maintenance dose thereafter. Aspirin is continued throughout.[16] There is no evidence to recommend stopping clopidogrel 5 days before non-cardiac surgery. The CURE trial[40] advocated stopping clopidogrel 5 days before CABG to decrease postoperative bleeding, but this is not the cessation period recommended by the British National Formulary before surgery,[78] or what ASRA recommend if regional anaesthesia is planned.[58] The pharmacokinetic profile of clopidogrel shows that after discontinuation of the drug, platelet function gradually increases and complete recovery is seen 7 days after the last clopidogrel dose,[128] with half the platelet pool expected to be replaced at 5 days. Glycoprotein IIb/IIIa inhibitors are licensed for use in patients with unstable angina or non-ST elevation MI, and as an adjunct to percutaneous transluminal coronary angioplasty. Unlike clopidogrel, they are not licensed for the prevention of ischaemic events in patients with a history of symptomatic CAD.

Dual antiplatelet therapy also presents problems for regional anaesthesia. The placement of neuro-axial blocks in patients taking dual antiplatelet therapy cannot be recommended unless a platelet transfusion is given before the procedure and platelet function is within acceptable limits on testing. The guidelines produced in 2003 by ASRA suggest that without prior platelet transfusion, clopidogrel should be stopped for a minimum of 7 days and ticlopidine for a minimum of 14 days.[58] Under these circumstances, normal platelet function on platelet function testing is reassuring. The timing of removal of an epidural catheter and early reinstatement of the antiplatelet therapy must be considered. Delaying restarting dual antiplatelet therapy in a patient for neuro-axial catheter removal may expose the patient to an unacceptable risk of stent thrombosis. Aspirin and NSAIDs do not represent an added risk for the development of spinal haematoma in patients receiving epidural or spinal anaesthesia.[58] Information on anaesthetic complications related to antiplatelet agents is limited to case reports. Complications have occurred after neuro-axial blockade in patients receiving clopidogrel therapy, despite adherence to recommended guidelines for cessation of therapy before the procedure. Epidural haematoma has been reported after both spinal[70] and combined spinal and epidural anaesthesia;[120] in both cases, the clopidogrel was stopped 7 days before the regional technique.

Similar caution is required for the placement and removal of central venous lines, particularly using the subclavian route, in patients on dual antiplatelet therapy.

The patient requiring emergency surgery with a coronary stent and antiplatelet therapy

The recent SIGN 96 document[11] includes guidelines on the management of these patients stating that if emergency or urgent non-cardiac surgery is required after PCI, dual antiplatelet therapy should be continued whenever possible, but if the bleeding risk is unacceptable and antiplatelet therapy withdrawn, it should be reintroduced as soon as possible after surgery.[11] There should be close liaison between the surgeon, cardiologist, anaesthetist, and haematologist on a case by case basis. Like elective surgery, it is important to assess both the risk of haemorrhage and the risk of stent thrombosis (Tables 4 and 5).

If the surgery involves a high risk of haemorrhage, or if regional neuro-axial blockade is thought to be essential, it may be necessary to give a platelet transfusion before surgery. The French Health Products Safety Agency reviewed the issue of perioperative platelet transfusion in 2003 and made the following recommendations:[99 100] for commonly practised invasive procedures transfuse to achieve a platelet count of $>50\,000\ \mu l^{-1}$, in the absence of platelet dysfunction, for surgery with a standard haemorrhagic risk ensure a platelet count $>50\,000\ \mu l^{-1}$, for neurosurgery and ophthalmic surgery involving the posterior segment of the eye a platelet count of $>100\,000\ \mu l^{-1}$ is required, for axial regional anaesthesia a platelet count of $50\,000\ \mu l^{-1}$ is sufficient for spinal anaesthesia, with $80\,000\ \mu l^{-1}$ proposed for epidurals. The plasma half-life of clopidogrel is short, so inhibition of transfused platelets should not be a clinically relevant issue and clopidogrel therapy only results in a maximum of 40–60% inhibition of aggregation.[52] Each unit of platelet concentrate is known to raise the platelet count by a minimum of $5000\ \mu l^{-1}$ under normal circumstances. However, some experts believe the above transfusion thresholds to be too high.[53] There is a case report of uneventful spinal anaesthesia after a two unit platelet transfusion in a patient taking clopidogrel and aspirin who required urgent surgery, with the rise in the platelet count documented as $24\,000\ \mu l^{-1}$.[54] An appropriate strategy may be to use the information provided by modified thromboelastography (TEG) test results to guide the quantity of platelet transfusion administered. If the risk of haemorrhage is lower, and the risk of stent thrombosis significant, then it may be advisable to continue antiplatelet therapy perioperatively and not administer platelets before operation. In this circumstance, it is important to have a valid blood sample for crossmatch with the haematology/transfusion laboratory and it is advisable to liaise with the haematology department about the potential need for platelets in the event of bleeding.

In patients at high risk of catastrophic bleeding, potential possible strategies may include the prophylactic use of agents such as aprotinin or recombinant factor VII. The experience of prophylactic aprotinin in patients taking

clopidogrel is limited to cardiac surgery where it has been shown significantly to reduce bleeding, transfusion requirements, and complications.[3] Aprotinin has not been shown to increase the risk of perioperative MI in patients undergoing CABG,[98] but its effect on coronary stent thrombosis in non-cardiac surgery has not been studied. In orthopaedic surgery, antifibrinolytics have been shown to reduce allogenic blood transfusion but the data were too limited to draw conclusions about safety.[135] The use of recombinant factor VII in uncontrolled haemorrhage is controversial, with some retrospective data suggesting some efficacy but with a possible high mortality from non-haemorrhagic causes.[33 85 89] There is only one double-blind randomized controlled trial examining its use prophylactically in retropubic prostactectomy which showed a reduction in perioperative blood loss.[41] However, it seems unlikely that in the absence of normal platelet function, any pharmacological agent will have a high level of efficacy. The cause of bleeding in patients on antiplatelet therapy is usually dysfunctional platelet action and, consequently, the logical treatment of choice is platelet transfusion.

Restarting clopidogrel after operation

Thienopyridines should be restarted as soon as is practicable and safe after surgery. The precise timing should be discussed between the surgeon, anaesthetist, and cardiologist. If there is a high risk of postoperative bleeding, restarting antiplatelet agents should be delayed until this risk has diminished, and removal of any indwelling catheters should have occurred or platelet transfusion may be indicated before their removal if antiplatelet therapy has been restarted. Patients unable to take oral medication after their surgery will be unable to restart their antiplatelet drugs and consideration should be given to an alternative antiplatelet strategy. Following initiation of therapy, clopidogrel reaches its maximum platelet aggregation inhibition after 3–5 days, with the bleeding time reaching a maximum of 1.5–3 fold of baseline at 3–7 days.[52] Restarting clopidogrel with a loading dose is routine in interventional cardiology, and the licensed loading dose after 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.[26 56] After the 600 mg loading dose, the full antiplatelet effect of the drug can be seen after 2 h,[57] compared with after 6 h with the 300 mg loading dose.[6 82] When stent thrombosis occurs it appears to present early in the postoperative period.[8 62 72 83 124] Therefore, it may be advantageous to administer a loading dose in the postoperative period to ensure a rapid return of antiplatelet activity and protection against stent thrombosis. However, whether a loading dose is beneficial in preventing perioperative thrombotic events or is accompanied by an unacceptably greater potential for bleeding complications is currently not known. The patients at highest risk of perioperative thrombosis,[61] and those who exhibit a prolonged MA on TEG,[75] may benefit from a loading dose of clopidogrel.

Postoperative monitoring

In patients at high risk of stent thrombosis in the perioperative period, who have stopped clopidogrel prematurely, the risk of an ischaemic event may be as high as 45%.[123] Consequently, these patients should be managed in a high dependency unit (HDU) setting with continuous ECG monitoring and regular review by cardiologists. The optimum duration of HDU stay is not known, as, although stent thrombosis appears to occur in the early postoperative period, there are reported cases of later presentation (Table 3). The perioperative hypercoagulable state lasts for several days and it is probably appropriate to monitor these patients intensively until antiplatelet therapy has been reinstated and the antiplatelet action confirmed. The most appropriate length of stay may vary according to the individual patient risk of complications.

Recommended action if stent thrombosis is suspected perioperatively

The signs of stent thrombosis can be non-specific but may include chest pain, shortness of breath, hypotension, arrhythmia, or even cardiac arrest. If stent thrombosis is suspected, appropriate measures and investigations should be instigated immediately and a cardiologist contacted urgently. If stent thrombosis is likely, the patient will need to be transferred to an interventional cardiology unit. Urgent angiography is necessary and the priority is reopening of the occluded stent and target vessel. Aggressive use of anticoagulants and antiplatelet agents including heparin, clopidogrel, aspirin, and GpIIb/IIIa inhibitors may be required. However, their use may be limited if the patient has just undergone major surgery and has a high risk of life-threatening haemorrhage, as spontaneous bleeding is a possibility in a surgical patient on antiplatelet therapy even at a site unrelated to the surgery.[124] If aggressive antiplatelet therapy is necessary in the postoperative period, consideration should be given to the use of shorter acting small molecule GpIIb/IIIa inhibitors such as eptifibatide or tirofiban rather than the monoclonal antibody inhibitor abciximab, as the small molecule inhibitors have a much shorter half-life and therefore the antiplatelet effect will abate more quickly once the drug is stopped, which may be important if catastrophic bleeding were to occur.[103]

Conclusions

The management of patients with a coronary stent presenting for both elective and emergency non-cardiac surgery

is an increasing clinical problem. These patients may be at high risk of stent thrombosis and, consequently, their management should involve careful discussion between the surgeons, anaesthetists, cardiologists, and haematologists. Anaesthetists play a vital role in balancing the surgeons concerns of increased bleeding against the cardiologists' fear of acute stent thrombosis. Cardiologists need to recognize the potential need in their patients for future non-cardiac surgery and if non-cardiac surgery is known to be necessary within a year of PCI and stent insertion, BMS should be used in preference to DES.[4] In patients who have had stents placed recently, elective non-cardiac surgery should be avoided until clopidogrel can be safely stopped. There are few data to guide the most appropriate management, and this is an area that urgently needs well-conducted clinical trials and peer-reviewed guidelines.

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