Antiplatelet drugs, coronary stents, and non-cardiac surgery

Revalidation
FOR ANAESTHETISTS
RCA Revalidation matrix
Matrix reference CPD 2C03

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Key points

Drug-eluting stents have improved procedural success in interventional cardiology but require a longer duration of dual antiplatelet therapy (DAPT).

DAPT should be continued perioperatively wherever possible to prevent stent thrombosis.

Bridging therapy refers to the substitution of irreversible antiplatelet agents with short-acting agents to offer reversible thrombosis prophylaxis during the perioperative period.

Future developments include short-acting, reversible ADP blockers and modified thromboelastography as point-of-care platelet function monitoring.

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Antiplatelet agents used in cardiology

The main antiplatelet agents used in cardiology are salicylates, thienopyridines (e.g. clopidogrel), and glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors (such as tirofiban, abciximab, and eptifibatide). Patients with stable angina or known ischaemic heart disease are usually prescribed lifelong low-dose aspirin. For those with a recent acute coronary syndrome or percutaneous coronary intervention (PCI), additional cover with clopidogrel is indicated for a finite period of usually 3–12 months.

GPIIb/IIIa inhibitors have even greater antiplatelet activity, as these glycoproteins on the platelet surface represent the final common pathway in platelet activation, leading to platelet aggregation and subsequent thrombus formation (Fig. 1).

Both aspirin and clopidogrel inhibit platelet function irreversibly. Aspirin non-selectively acetylates the enzyme cyclooxygenase, permanently inhibiting the ability of the platelet to synthesize the pro-thrombotic eicosanoid thromboxane A_2. Endothelial cells instead synthesize the anti-thrombotic prostaglandin PGI_2, favouring a balance towards reduced platelet activation. Clopidogrel inhibits the $P2Y_{12}$ subtype of the ADP receptor, preventing ADP-mediated platelet activation. It is a prodrug that must first be metabolized to its active form by the hepatic cytochrome P450 isoenzyme CYP3A4. The lifespan of a platelet is around 10 days; hence, restoration of normal platelet function in patients taking aspirin or clopidogrel takes 5–10 days.

GPIIb/IIIa inhibitors are licensed for use in patients with unstable angina or non-ST elevation myocardial infarction (MI) and as an adjunct to PCI. In contrast to salicylates and thienopyridines, they offer reversible platelet inhibition in a dose- and concentration-dependent manner. Tirofiban and eptifibatide are the shortest acting of these agents, with half-lives of around 2–5 h. Both are cleared by the kidney largely unchanged, with normal platelet function usually returning within 6–8 h of stopping an infusion.

Progression and development of PCI

Coronary angioplasty, the original type of PCI, was first described in 1977. A catheter with a surrounding balloon was fed into the lumen of a coronary artery and passed through the diseased vessel to traverse a stenotic lesion. Subsequent balloon inflation stretched the vessel to relieve the stenosis, restoring distal flow to the myocardium. However, balloon angioplasty often required repeat procedures, as inflation of the balloon led to an inflammatory reaction within the media, causing neointimal proliferation and re-stenosis of the coronary lumen.

Coronary stents were developed to reduce re-stenosis rates. These comprise a metal cylindrical mesh that surrounds the angioplasty balloon; they are expanded under high pressure into the lumen of the vessel during balloon inflation and left in the artery to maintain its patency and prevent re-stenosis. Their increased efficacy and safety 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 stent.[1] Coronary revascularization by PCI exceeds the number of coronary artery bypass grafts (CABG) performed each year three-fold.

Types of coronary stents

There are two types of stents: bare-metal stents (BMS) and drug-eluting stents (DESs). The introduction of BMS significantly reduced the frequency of symptom recurrence and repeat procedures due to stent re-stenosis by comparison with angioplasty. However, the incidence

doi:10.1093/bjaceaccp/mkq038 Advance Access publication 30 September, 2010

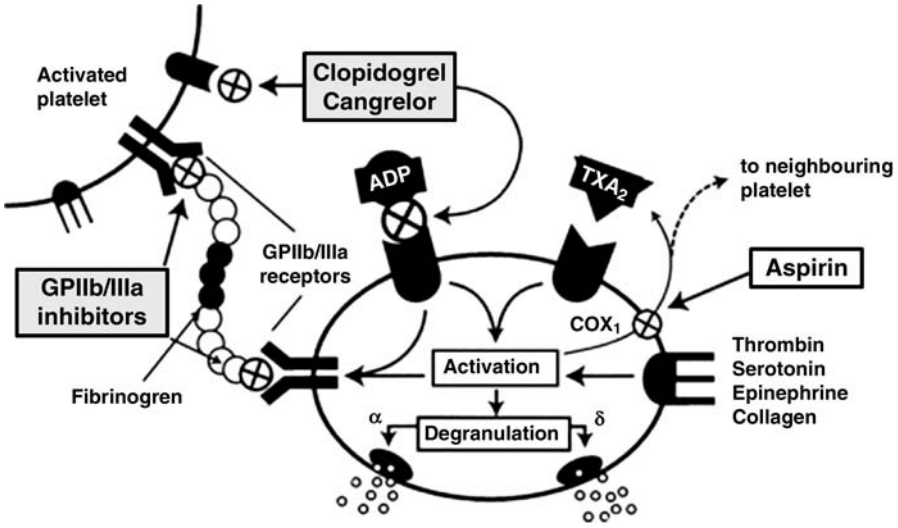

Fig 1 Mechanism of action of antiplatelet agents. (Reproduced and modified from Kereiakes and Gurbel[13] with permission from Elsevier Ltd.)

of re-stenosis was still unacceptably high. This led to the development of DESs during the 1990s.

The metal mesh of a DES is coated with a polymer that contains a potent anti-proliferative drug slowly released into the vessel wall over several weeks. Two main types exist: Taxus® stents release paclitaxel, an anti-tumour drug that inhibits microtubule formation during cell division. Cypher® stents elute sirolimus (rapamycin), a macrolide antibiotic that blocks progression from G1 to S phase of the cell cycle. Both DESs inhibit smooth muscle cell proliferation and migration of cells of the vessel media, preventing the formation of a neointima that commonly leads to stent re-stenosis. Overall re-stenosis rates for DESs are <2% compared with ~15% for BMS and 30–40% for balloon angioplasty.

The need for dual antiplatelet therapy

During normal stent deployment, significant trauma and damage to the endothelium occur. Initially, thrombogenic struts of the stent are exposed to passing coronary blood, creating the risk of early stent thrombosis until the endothelium can re-grow. During this period of re-endothelialization, dual antiplatelet therapy (DAPT) in the form of aspirin and clopidogrel is needed. Patients with BMS are typically recommended to usually continue clopidogrel for a minimum of 6 weeks to allow for complete endothelial re-growth. Beyond this period, antiplatelet cover with aspirin is all that is usually necessary. In contrast, the anti-proliferative drugs released by DESs delay endothelial growth, requiring patients with DES insertion to take clopidogrel for a minimum of 12 months and sometimes longer for more complicated lesions. All patients with stents should continue to take aspirin for life.

Stent thrombosis

The rare (~1%) but devastating complication of stent thrombosis carries a significant morbidity, with the majority of cases leading to acute MI or death.[1] Stent thrombosis most commonly occurs in the first month after insertion before re-endothelialization is complete and when the stent struts are still exposed. The most important risk factors for stent thrombosis are suboptimal flow on coronary angiography and premature cessation of antiplatelet therapy (Table 1). Stopping clopidogrel during this high-risk period (6 weeks for BMS and at least 12 months for DESs) carries an estimated 30-fold increased risk of stent thrombosis. In one study, >25% of the patients who discontinued clopidogrel therapy within the first month suffered stent thrombosis.[2] Withdrawal of all antiplatelet agents increases the relative risk of coronary thrombosis 90-fold.[3]

Stent thrombosis associated with DESs

Late (1–12 months) and very late (>12 months) stent thromboses are rare events with BMS, yet have occurred with increasing frequency after the development of DESs, especially when treating complicated, off-label disease patterns (overlapping, multiple stents, and bifurcating lesions). Their success in preventing stent re-stenosis has led to PCI treatment of more complex patients previously only suitable for CABG surgery. However, concerns have arisen that DESs may cause persistent endothelial dysfunction even after the drug has eluted from the stent, requiring long-term

Table 1 Off-label indications for DES insertion and additional risk factors for stent thrombosis, with consideration for extended DAPT. (Source: American Heart Association, Inc.[14])

Clinical	Procedural
Premature cessation of DAPT	Long stents
Prior brachytherapy	Multiple lesions
Low ejection fraction	Overlapping stents
Acute coronary syndrome	Ostial or bifurcation lesions
Renal failure	Small vessels
Diabetes	Suboptimal angiographic results

treatment with clopidogrel due to a lifelong risk of thrombosis. This has led to follow-up of greater patient numbers using very late stent thrombosis as a study endpoint to answer ongoing questions about long-term safety.

Risk of non-cardiac surgery after stent insertion

Non-cardiac surgery and most invasive procedures increase the risk of stent thrombosis, especially when the procedure is performed before endothelial re-growth is established. This occurs primarily because antiplatelet therapy is often discontinued in the perioperative period and because surgery creates a pro-thrombotic state, leading to most cases of stent thrombosis occurring in the immediate or early postoperative period.[4]

Delay between stent(s) insertion and surgery

The risk of stent thrombosis is drastically reduced for BMS if surgery is performed >6 weeks after insertion. The optimal delay after DES implantation is less clear, but is likely to be at least 12 months during which DAPT must be maintained. Even beyond this period of high thrombotic risk, patients with DESs still have a greater likelihood of perioperative stent thrombosis, especially if PCI was complex, with numerous reports of very late thrombosis occurring after non-cardiac surgery.

Awareness of risk

Anaesthetists and surgeons should be aware of the high risk of stent thrombosis in patients with coronary stents undergoing surgery. However, a Canadian survey of anaesthetists revealed that 63% were not aware of recommendations about the appropriate duration between stent placement and subsequent surgical procedures. In addition, one-third suggested no delay or a delay of only 1–2 weeks which is insufficient for BMS, and even more so for DESs.[5]

Perioperative management

Balance between risk of bleeding *vs* stent thrombosis

If surgery cannot be delayed beyond a stent's high-risk period, a difficult balance must be struck between thrombosis prophylaxis and surgical bleeding. In situations of catastrophic haemorrhage requiring emergency surgery, only a platelet transfusion will reverse the actions of aspirin and clopidogrel. However, for semi-elective and urgent surgery, there is minimal evidence on how best to pharmacologically manage such patients through the perioperative period. An interdisciplinary discussion between surgeon, anaesthetist, intensivist, and cardiologist for each individual case is essential. Risk factors of stent thrombosis associated with stopping antiplatelet agents are listed in Table 1. Additional consideration should also be given to the relative consequences of thrombosis within an individual stent. For example, thrombotic stent occlusion of the left main or proximal left anterior descending coronary artery carries a much greater morbidity and mortality than a more distally placed stent in a smaller vessel.[4]

Risk of surgical bleeding

The risks of surgical bleeding associated with continuing DAPT perioperatively depend on the likelihood of major haemorrhage and the potential morbidity of excessive postoperative bleeding, as a function of the site of surgery. Except for intracranial surgery and prostatectomy, low-dose aspirin increases neither the severity nor the mortality of bleeding complications.[6] The effects of clopidogrel on bleeding in non-cardiac surgery cause greater concern: because thienopyridines have greater antiplatelet activity than salicylates, coupled with firm evidence of enhanced bleeding in post-CABG patients, the general opinion is that clopidogrel will markedly increase surgical bleeding and most practitioners recommend stopping it before elective surgery. There is, however, contrasting evidence to support this view: one large study reported severe bleeding in up to a fifth of patients taking DAPT,[7] whereas another suggested only a modest increase in postoperative bleeding.[8] It is well established, however, that epidural and spinal anaesthesia is not recommended in patients taking clopidogrel.

Surgeons who are concerned about the risk of perioperative bleeding may need help balancing risks of haemorrhage against the benefits of continuing DAPT. Even for procedures with higher bleeding risk, if surgeons are informed that stent thrombosis leads to MI or death if DAPT is stopped, they can often be persuaded that the risks of thrombosis outweigh those of bleeding. This strategy, however, is not appropriate for patients in whom excess bleeding would be catastrophic, for example, bleeding in a closed cavity such as spinal or neurosurgery, surgery on the posterior segment of the eye, or transurethral prostatectomy. In this situation, antiplatelet agents such as clopidogrel should be stopped before surgery. Aspirin, however, should be continued wherever possible.

Bridging therapy

In situations where clopidogrel must be stopped, bridging therapy may be used. This refers to the substitution of an irreversible antiplatelet agent with a reversible and short-acting anti-coagulant and/or antiplatelet drug to offer thrombosis prophylaxis during the perioperative period. Many bridging regimes have been suggested, with little definitive evidence for one over another. Examples include unfractionated heparin (UFH), subcutaneous injection of low-molecular-weight heparin, non-steroidal anti-inflammatory drugs, and GPIIb/IIIa inhibitors.

Heparin therapy alone is unlikely to protect against stent thrombosis, as it has no antiplatelet properties.[4] It makes more pharmacological sense to replace the thienopyridine with a short-acting, reversible antiplatelet agent. One possibility reported by Savonitto

and colleagues is to start an infusion of tirofiban 4 days before operation (having discontinued clopidogrel the day before), maintained until 4 h before surgery. The patient is then re-loaded with clopidogrel on the first postoperative day; aspirin is continued throughout.[9] If there is bleeding concern in the immediate postoperative period, tirofiban can be resumed and clopidogrel loading delayed until deemed safe to do so. Although there is limited evidence and no licence for GPIIb/IIIa inhibitors in this setting, at present, these are the only reversible inhibitors of platelet activity that offer a logical short-acting substitute for the prevention of stent thrombosis. However, admitting patients well before surgery is expensive and often logistically difficult. Furthermore, this strategy may not offer complete protection, since the greatest risk of stent thrombosis is actually during or soon after surgery. More data are therefore needed.

A summary of suggested pharmacological management[10] of antiplatelet agents during the perioperative period is shown below.

(i) *Low bleeding risk*. Maintain DAPT.
(ii) *Moderate bleeding risk*. Maintain DAPT if possible, unless surgical bleeding risk outweighs thrombosis risk. Consider bridging therapy if clopidogrel must be stopped.
(iii) *High bleeding risk*. Stop clopidogrel 5 days before surgery, and start bridging therapy 4 days before operation. Maintain aspirin wherever possible.

Use of thromboelastography as an adjunct to bridging therapy

This whole-blood coagulation monitor is used increasingly as a point-of-care dynamic test of haemostasis. The maximum amplitude (MA) of conventional thromboelastography (TEG®) is not sensitive enough to detect the presence of thienopyridines or salicylates. However, it may be used to monitor the antiplatelet effects of GPIIb/IIIa inhibitors.[11] One possible strategy is the titration of a tirofiban infusion against a pre-determined target MA, agreed upon by considering a patient's relative risk of stent thrombosis *vs* surgical bleeding, similar to titrating the APTT in UFH infusions.

Future developments

New antiplatelet agents

Cangrelor is a new, rapidly acting, reversible ADP blocker currently undergoing phase III trials. It binds selectively and specifically to the $P2Y_{12}$ receptor on the platelet surface. Unlike thienopyridines, the drug offers reversible antiplatelet activity with a rapid onset and offset of action, and does not need activation or conversion by the liver to an active metabolite. It is administered by i.v. infusion, with a plasma half life of 3–5 min, resulting in full recovery of platelet activity within 60 min.[12] Such a drug would offer useful short term control of platelet function and may be more suitable as bridging therapy during the perioperative period.

Modified TEG

Modified TEG (mTEG®) is a modification of the conventional TEG assay that uses reptilase (a proteolytic enzyme from snake venom) and Factor XIII to produce a cross-linked clot through which platelets can interact. Reptilase generates fibrin, reinforced by Factor XIII, creating a limited platelet interaction in the absence of thrombin generation. The resulting thromboelastogram produces an MA that is sensitive to the presence of thienopyridines and salicylates. Early results suggest good correlation with gold standard laboratory-based tests, such as optical platelet aggregometry.[11] This novel assay could be very useful in monitoring the antiplatelet effects of cangrelor during bridging therapy, allowing its rate of infusion to be titrated against a pre-determined mTEG MA during the perioperative period.

Future stents

New DESs are under development, the safety of which has become of major clinical importance. Strategies include coating of the stents with antiplatelet drugs, enhancement of their drug-eluting profile leading to improved endothelial function, and the development of fully bio-resorbable stents made from magnesium alloys or poly-L-lactic acid.

Conflict of interest

None declared.

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Please see multiple choice questions 17–20.