Antiplatelet therapy after coronary occlusion

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Summary

Platelets are pivotal in the pathogenesis of acute coronary syndrome and in the complications following the implantation of coronary stents. Dual antiplatelet therapy with aspirin and clopidogrel is essential to reduce the risk of recurrent ischaemic events. The combination should be taken for up to one year following acute coronary syndrome in patients at high risk of future events. Aspirin should be continued indefinitely. The duration of treatment with clopidogrel depends on the type of stent implanted. Patients with drug-eluting stents require combination therapy for at least one year. Premature withdrawal of antiplatelet therapy carries a risk of thrombosis in the stent. In patients with drug-eluting stents, thrombosis may occur as a late complication of stent implantation. Withdrawal of antiplatelet therapy should be done in consultation with the cardiologist who implanted the drug-eluting stent.

Key words: aspirin, clopidogrel, stents.

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Introduction

The term 'acute coronary syndrome' encompasses the spectrum of unstable angina and myocardial infarction with or without elevation of the ST segment of the ECG. These conditions share a common aetiology, usually rupture of an atherosclerotic plaque, activation of the coagulation cascade with platelet thrombus formation and vessel occlusion possibly with distal embolisation.

Contemporary medical therapy in these patients includes combination antiplatelet therapy, beta blockers, angiotensin converting enzyme inhibitors and cholesterol lowering drugs. Despite optimal medical therapy a significant proportion of patients develop recurrent angina and re-infarction. An 'invasive strategy' has therefore been adopted whereby early coronary angiography is undertaken and in those with suitable coronary anatomy (namely flow limiting coronary stenoses in important sized coronary vessels) coronary revascularisation is performed. This may either be percutaneous coronary intervention (see box) or coronary artery bypass grafting surgery depending on the nature and extent of coronary disease. Such an approach reduces the rates of recurrent angina and myocardial infarction. Both acute coronary syndrome and percutaneous intervention are associated with high levels of platelet activation. Effective antiplatelet therapy is therefore essential to reduce the risk of recurrent vascular events.

Antiplatelet drugs

Platelets are activated by a number of pathways. When there is marked platelet activation, combinations of antiplatelet drugs are required to inhibit platelet function (Fig. 1).

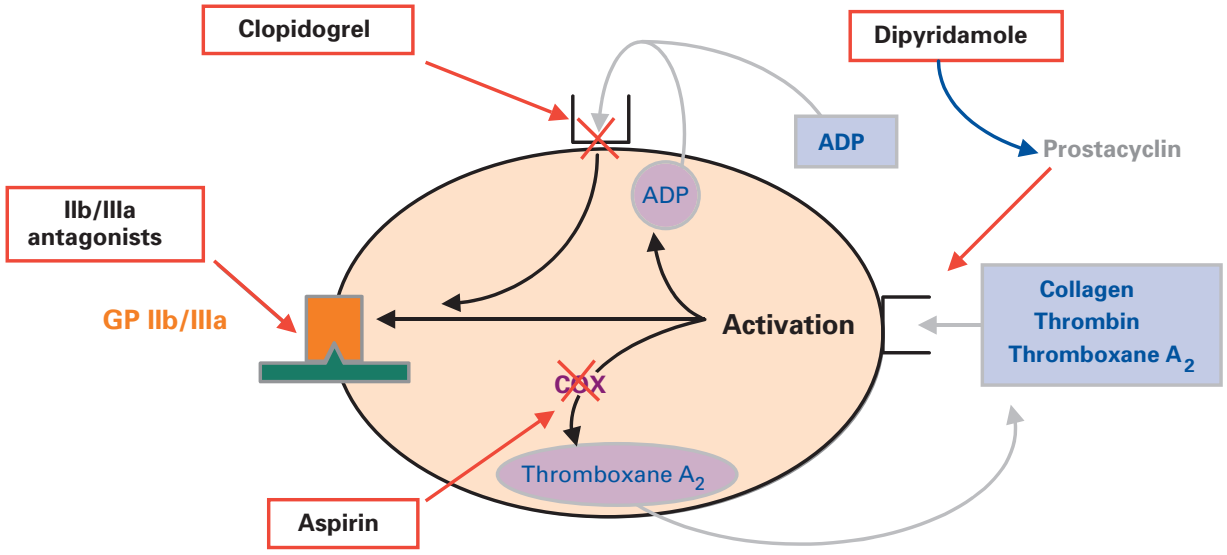
Aspirin

Aspirin acts by irreversibly inactivating platelet cyclo-oxygenase (COX)-1. This stops the synthesis of thromboxane A_2, a known vasoconstrictor and potent platelet aggregator. The antiplatelet effect is relatively weak as aspirin inhibits only one of the pathways of platelet activation. As aspirin irreversibly acetylates

Acute coronary syndrome	A collective term to describe unstable angina, non-ST elevation myocardial infarction, and ST elevation myocardial infarction.
Percutaneous coronary intervention	A collective term for balloon angioplasty, atherectomy and coronary stenting. Nowadays it is usually synonymous with coronary stenting.
Restenosis	Gradual renarrowing within the stent or at the site of angioplasty secondary to neointimal hyperplasia and smooth muscle proliferation. Usually occurs within 2–8 months following stent implantation. Reduced with drug-eluting stents.
Stent thrombosis	Occlusion of the stent with thrombus usually within the first 24–48 hours following stent implantation, but rarely occurring late after stent implantation. There may be higher rates of late thrombosis with drug-eluting stents.
Drug-eluting stent	A tube coated with an antiproliferative drug to prevent restenosis.

Fig. 1

Mechanism of action of antiplatelet drugs



Key

ADP	adenosine diphosphate
GP IIb/IIIa	glycoprotein IIb/IIIa complex
COX	cyclo-oxygenase

Aspirin stops platelet activation by inhibiting the enzyme cyclo-oxygenase 1. This prevents the synthesis of thromboxane A_2 which normally causes platelet aggregation.

Clopidogrel inhibits the activation of the glycoprotein IIb/IIIa complex by preventing adenosine diphosphate binding to a platelet receptor. This inhibits platelet aggregation. Antagonists of the glycoprotein IIb/IIIa receptor stop platelet aggregation by blocking the binding of fibrinogen to the receptor.

Dipyridamole increases the production of prostacyclin, a potent inhibitor of platelet aggregation.

COX-1, full recovery of platelet function requires regeneration of new platelets. This typically occurs about 7–10 days from the last dose.

Clinical data

The Antithrombotic Trialists' Collaboration showed that in patients with acute coronary syndrome aspirin is associated with a relative reduction of recurrent vascular events by about 25%. In patients with unstable angina, without myocardial infarction, the benefit is even greater.[1]

Dose and duration

A dose of 300 mg of soluble aspirin should be given immediately to any patient with suspected acute coronary syndrome. If only enteric-coated aspirin is available then this should be chewed or crushed to ensure rapid absorption.

After the acute event, long-term therapy is with aspirin 75–150 mg/day. Low doses (75–100 mg/day) are just as effective as higher doses and may confer less risk of gastrointestinal bleeding although this remains contentious. Therapy with aspirin should be continued indefinitely following acute coronary syndrome events, percutaneous coronary interventions and coronary artery bypass surgery.

Adverse effects

These include gastrointestinal adverse effects (nausea, dyspepsia, peptic ulcer, bleeding), easy bruising and hypersensitivity reactions (such as exacerbation of asthma in 10% of the population and urticaria in 0.2%). Enteric-coated aspirin may be better tolerated in the event of nausea or dyspepsia but does not confer a lower risk of gastrointestinal bleeding. The absolute increase in risk of gastrointestinal bleeding with low-dose aspirin is less than 1% per year compared with placebo (2.3% vs 1.45% per year in a meta-analysis).[2] In patients with a history of complicated peptic ulcer disease the combination of low-dose aspirin plus a proton pump inhibitor is more effective in reducing a patient's risk of gastrointestinal bleeding than switching the patient to clopidogrel.[3]

Thienopyridines

The thienopyridines (clopidogrel and ticlopidine) prevent adenosine diphosphate from binding to its receptor on platelets. This stops activation of the glycoprotein IIb/IIIa complex and thereby inhibits platelet activation. Both drugs are prodrugs which require metabolism by the cytochrome P450 enzyme system to become active.

Clopidogrel

The maximum effect of clopidogrel occurs within approximately six hours of a loading dose of 300 mg and within approximately two hours of a 600 mg loading dose. Higher loading doses have not conclusively been shown to be of further benefit. Like aspirin the effects are irreversible and full recovery of platelet function takes up to 7–10 days from the last dose.

Clinical data

The combination of clopidogrel with aspirin is synergistic providing more complete platelet inhibition than with either drug alone. After nine months of treatment in patients with non ST elevation acute coronary syndrome, the combination of clopidogrel plus aspirin provided a 20% relative risk reduction in death, myocardial infarction or stroke compared to aspirin alone.[4] The combination was of benefit regardless of whether or not a stent was implanted. In patients with ST elevation myocardial infarction receiving thrombolytic therapy, the combination of clopidogrel and aspirin provided superior outcomes compared with aspirin alone.[5] The optimal duration of combination therapy in this setting is unknown.

Adverse effects

Clopidogrel can cause gastrointestinal symptoms and skin rash. The combination of aspirin and clopidogrel is associated with a 1% absolute increase in major, non-life-threatening bleeding per year compared to aspirin alone.

Ticlopidine

This drug is now rarely used given its adverse effect profile of gastrointestinal upset, neutropenia (in 2.4% of cases) and rare cases of thrombotic thrombocytopenic purpura. It is an alternative in the rare situation of intolerance to clopidogrel. Haematological monitoring should be undertaken every two weeks during the first four months of therapy to watch for neutropenia.

Glycoprotein IIb/IIIa receptor antagonists

The glycoprotein IIb/IIIa receptor located on the platelet surface plays a pivotal role in platelet thrombus formation by binding to fibrinogen thereby facilitating cross linkage of platelets. Tirofiban and abciximab are intravenous drugs used in patients with high risk acute coronary syndromes and patients undergoing high risk percutaneous coronary interventions. Oral glycoprotein IIb/IIIa antagonists have not shown benefit.

Other antiplatelet drugs

Dipyridamole and sulfinpyrazone confer no additional benefit in acute coronary syndrome and are not recommended.

Antiplatelet therapy following acute coronary syndrome (without coronary stent implantation)

In patients with non ST elevation acute coronary syndrome, 12 months of clopidogrel is recommended. In patients with ST elevation myocardial infarction who are not undergoing coronary stenting the optimal duration is unclear.

Antiplatelet therapy after coronary stenting

Coronary stent implantation is associated with two potentially adverse sequelae. The first is stent thrombosis. Coronary stents are inherently thrombogenic and dual antiplatelet therapy is essential to reduce the risk of thrombosis in the stent. This risk is greatest early after implantation when platelet activity is maximal and diminishes once endothelialisation of the stent occurs. The second adverse consequence of stent implantation is restenosis. Restenosis is defined as gradual renarrowing within the stent secondary to neointimal proliferation and usually occurring within 2–8 months of stent implantation. It has been dramatically reduced with the introduction of drug-eluting stents. These stents elute antiproliferative drugs such as sirolimus and paclitaxel which suppress the growth of neointimal tissue (Table 1). As a consequence adequate endothelialisation may be delayed thus the duration of dual antiplatelet therapy needs to be longer than with bare metal stents.

The usual antiplatelet regimen consists of aspirin (at least 75 mg/day) indefinitely and clopidogrel (75 mg/day). If stent implantation was for non ST elevation acute coronary syndrome then combination therapy is beneficial for at least one year.[4] If implantation was elective the duration of clopidogrel therapy depends on the stent type.

Non-drug-eluting stents

Bare metal stents require a shorter duration of combination therapy than drug-eluting stents. Initial data suggested that clopidogrel be prescribed in conjunction with aspirin for a minimum duration of one month. However, data from the

Table 1
Available drug-eluting stents

Stent name	Antiproliferative drug
Cypher	sirolimus
Taxus	paclitaxel
Endeavor	zotarolimus
Xience V	everolimus

CREDO study show a small but definite benefit from one year of dual antiplatelet therapy following elective bare metal stent implantation.[6] One year of therapy may therefore be considered in patients with more extensive vascular disease.

Drug-eluting stents

A longer duration of combination antiplatelet therapy is required because the drug in the stent delays endothelialisation. Initial data from trials suggested clopidogrel be continued for a minimum of 3–6 months following implantation of a stent. However, data are emerging that drug-eluting stents are associated with a slightly increased risk of late stent thrombosis (1 in 500 patient-years increased risk).[7] Incomplete or delayed stent endothelialisation due to drug inhibition of neointimal growth is at least partly responsible for this phenomenon.

Late stent thrombosis is serious and usually presents as myocardial infarction or sudden death with published case fatality rates in the order of 20–45%. Many cases have been associated with the withdrawal of antiplatelet therapy (for example for surgery), or with aspirin monotherapy. The risk is also higher with longer total stent lengths, multiple stents and in patients with diabetes, renal impairment and left ventricular dysfunction. An increasing number of cardiologists therefore recommend at least one year of combination therapy and in some instances indefinite combination therapy for patients with drug-eluting stents.

Recommendations

All patients should take low-dose aspirin indefinitely if possible. The duration of clopidogrel depends on the clinical situation.

One approach to therapy with clopidogrel is:

- minimum of one month of clopidogrel therapy following elective implantation of a bare metal stent. If the bleeding risk is low, consider up to 12 months in patients with more extensive vascular disease or patients with a high risk of coronary artery thrombosis.
- 12 months following implantation of a bare metal stent for acute coronary syndrome
- at least 12 months following implantation of a drug-eluting stent regardless of the clinical context
- indefinite combination therapy if possible following implantation of drug-eluting stents in high-risk patients (for example, left main coronary artery stenting, long total stent length, multivessel stenting or in patients with other risk factors for late stent thrombosis such as diabetes, renal failure, or left ventricular dysfunction).

Antiplatelet therapy and non-cardiac surgery after coronary stenting

Patients taking antiplatelet drugs may need surgery. Unfortunately, some patients may be routinely instructed to stop 'blood thinners' prior to surgery without proper assessment of the risk involved in terms of stent thrombosis (and therefore myocardial infarction or death). The risk of bleeding during surgery needs to be balanced against the risk of stent thrombosis and assessed case by case. The consequences of bleeding are more critical, for example, in neurosurgical cases than in diagnostic endoscopy or following dental procedures. The risk of stent thrombosis is higher soon after implantation but may still occur late (beyond one year) particularly if it is a drug-eluting stent. Certain procedural characteristics (for example, multivessel stenting, longer total stent length, smaller stent diameter) and patient-related characteristics (for example, presence of diabetes, renal failure and left ventricular dysfunction) predispose to a higher likelihood of stent thrombosis. This needs to be factored into the decision-making process.

Elective procedures may be deferred to a period where dual antiplatelet therapy is no longer required. Alternatively, it may be an option to perform the procedure during antiplatelet therapy. For instance, patients undergoing tooth extractions may be able to continue antiplatelet therapy given that local measures during surgery (gelatin sponge and sutures) are often sufficient to control bleeding and the risk of subsequent re-bleeding is low.[8,9]

If clopidogrel must be stopped before major surgery, consider continuing to give aspirin throughout the operation and restarting clopidogrel as soon as possible.

Recommendations

Important questions to ask when a patient who has a stent needs surgery:

- Is the procedure necessary?
- Can the procedure be performed if dual antiplatelet therapy is continued?
- Can the procedure be performed on aspirin monotherapy?
- Can the procedure be delayed to minimise the risk of stent thrombosis?

In the patient who has a bare metal stent implanted, there is an appreciable risk of stent thrombosis if antiplatelet therapy is ceased before six weeks (incidence 3%). Antiplatelet therapy should therefore not be ceased for minor bleeding and elective procedures should be deferred for at least six weeks.

In the patient with a drug-eluting stent, given the concerns regarding late stent thrombosis, we recommend that elective surgery should be delayed for 12 months if possible. As isolated cases of thrombosis following antiplatelet withdrawal have occurred beyond 12 months, we recommend discussion with the cardiologist in all situations requiring cessation of antiplatelet therapy in patients with drug-eluting stents.

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Further reading

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 111)

3. Patients with drug-eluting stents only need one antiplatelet drug to prevent stent thrombosis.
4. Dual antiplatelet therapy has to be continued longer in patients with drug-eluting stents than in patients with bare metal stents.

Medicinal mishap

Bisphosphonates and osteonecrosis of the jaws

Prepared by Alastair Goss, Oral and Maxillofacial Surgeon, and Patricia Backhouse, General Practitioner, Adelaide

Case

An otherwise well 66-year-old woman was referred with pain, swelling and numbness of the left mandible with pus discharging from around a dental implant. Her problems had developed over the previous six months.

The patient had undergone dental reconstruction 15–20 years previously. This involved eight titanium implants in both jaws with extensive crown and bridge work. (This work involved a personal cost of approximately $25 000 above insurance benefits.)

The woman had been diagnosed with 'borderline osteoporosis'. Her bone mineral density was –2.42 standard deviations below normal (consistent with a diagnosis of osteopenia). She was prescribed 70 mg alendronate weekly but later developed stress fractures. Over three years she took a total dose of 11.2 g.

A clinical diagnosis of bisphosphonate-associated osteonecrosis of the left mandible was made. A CT scan showed extensive involvement around the infected implant. The right mandible and maxilla were not involved.

Alendronate was ceased and non-surgical treatment commenced with 0.12% chlorhexidine mouth washes, intermittent short courses of cephalosporins for the soft tissue infection, and tramadol or paracetamol with codeine for the pain. This controlled the acute symptoms.

One year after stopping alendronate the symptoms recurred. A repeat CT scan showed extension of the necrosis without bone reformation. The involved implant and soft tissue were curetted under general anaesthesia. The wound healed slowly (see Fig. 1).

Comment

In this case alendronate was commenced before bisphosphonate-associated osteonecrosis of the jaw had been described.[1] Osteonecrosis associated with a previously stable implant was one of the first such presentations in Australia.

Bisphosphonate-associated osteonecrosis of the jaws is now defined as an area of exposed bone in the jaws which persists for more than eight weeks. Other conditions, including osteoradionecrosis and the presence of tumour, need to be excluded. The first described cases were in older, medically compromised patients treated with intravenous infusions