

New antiplatelet drugs for acute coronary syndrome

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SUMMARY

Ticagrelor and prasugrel are antiplatelet drugs that are alternatives to clopidogrel in acute coronary syndrome. Their advantages include reduced rates of ischaemia and stent thrombosis.

The risk of major bleeding is likely to be higher with prasugrel compared to clopidogrel. Intracranial haemorrhage appears to be slightly more common with ticagrelor than with clopidogrel, and it can also cause dyspnoea and ventricular pauses early in treatment.

When patients taking prasugrel or ticagrelor require surgery, perioperative management is challenging. The treating cardiologist should be consulted whenever treatment cessation is considered.

Introduction

Patients presenting with acute coronary syndromes, such as myocardial infarction, are treated with dual antiplatelet therapy to prevent recurrent ischaemia and mortality. After receiving loading doses, patients may undergo either percutaneous or surgical revascularisation. Following percutaneous revascularisation, aspirin is typically continued indefinitely, and another antiplatelet drug, most commonly clopidogrel, is continued for 12 months. While aspirin is also continued indefinitely following coronary artery bypass grafting, the role of a second antiplatelet drug remains unclear, and their use has

not been standardised. Data from recently published large randomised trials suggest that prasugrel and ticagrelor may be alternatives to clopidogrel in acute coronary syndrome.¹⁻³

Indications for use

Current guidelines published by the Cardiac Society of Australia and New Zealand (CSANZ)⁴ recommend that either ticagrelor or prasugrel should be considered as alternative drugs to clopidogrel in patients presenting with ST-elevation myocardial infarction who are at high risk of recurrent ischaemic events, such as those with:

- diabetes mellitus
- stent thrombosis
- recurrent ischaemic events despite clopidogrel therapy
- a high burden of disease on coronary angiography.

The guidelines also recommend the use of either ticagrelor or prasugrel instead of clopidogrel in all patients with high-risk non-ST-elevation acute coronary syndromes who are judged to be of low risk for haemorrhagic events. It should be noted, however, that local hospital protocols may differ from the CSANZ guidelines.

Clinical pharmacology

In acute coronary syndrome, damage to atherosclerotic plaques exposes platelet activating factors such as tissue factor, collagen and von Willebrand factor. The platelets release granules containing adenosine diphosphate. This binds to the P2Y₁₂ receptor on the surface of the platelets as the first step of the platelet aggregation pathway.⁵ Antagonism at this receptor inhibits platelet aggregation.

From the Editor



The new antiplatelet drugs help to improve the survival of patients with acute coronary syndrome. Praveen Indraratna and Christopher Cao remind us that the drugs also create problems if major surgery is needed. Austin Ng and Leonard Kritharides inform us about the other factors cardiologists consider in their preoperative assessments.

Assessing the patient is also very important when deciding whether to prescribe testosterone. Donald Perry-Keene says the hormone should not be used to manage non-specific symptoms such as reduced energy or poor concentration.

Judicious prescribing is also needed in palliative care. Debra Rowett and David Currow are concerned that adverse effects may be overlooked.

Terminal illness is likely to affect drug disposition. Bruce Charles believes that population pharmacokinetics can help us investigate drugs in patient groups that are difficult to study, including children.

While some children may be prescribed drugs such as imipramine for incontinence, Gail Nankivell and Patrina Caldwell advise that conservative treatment should be tried first.

Clopidogrel and prasugrel are thienopyridines. They bind irreversibly to the P2Y₁₂ receptor for the entire lifespan of the platelet (5–9 days). In contrast, ticagrelor binds reversibly, so platelet inhibition is not as prolonged and twice-daily dosing is required to achieve therapeutic concentrations.⁵ All three drugs require a loading dose when given in acute coronary syndrome (Table).^{6–15}

The time to onset of maximal platelet inhibition after administration of loading doses of antiplatelet drugs is an important consideration, particularly in ST-elevation myocardial infarction, as prompt revascularisation is required. Prasugrel achieves maximal platelet inhibition in approximately 30 minutes, whereas ticagrelor takes two hours. For clopidogrel, the time to maximal platelet inhibition is dose-dependent. A 600 mg dose achieves maximal platelet inhibition within two hours, whereas a dose of 300 mg takes eight hours. For this reason, loading doses of 600 mg have been used for clopidogrel in the acute management of ST-elevation myocardial infarction.

‘Clopidogrel resistance’ is a poorly defined phenomenon that may affect 4–30% of the

population.^{7,16} It may be related to a genetic variation of the cytochrome P450 2C19 enzymes that does not appear to affect either prasugrel or ticagrelor.

Prasugrel: safety and efficacy

Prasugrel has been compared to clopidogrel in two separate phase III randomised trials. It has not yet been directly compared to ticagrelor in a randomised clinical trial.

The TRITON-TIMI-38 study randomised patients (n=16 843) undergoing percutaneous coronary intervention to either prasugrel or clopidogrel, in combination with aspirin (75 to 162 mg daily).¹ The efficacy end point (a composite of death due to cardiovascular causes, non-fatal myocardial infarction and non-fatal stroke) was reached by 12.1% of the patients randomised to clopidogrel, compared with 9.9% of the patients taking prasugrel. This significant difference (p<0.001) was offset by an increase in major bleeding in the prasugrel group (2.4% vs 1.8%, p<0.001) which was sometimes fatal (0.4% vs 0.1%, p=0.002). The overall mortality rates for clopidogrel and prasugrel were similar

Table Pharmacological summary of P2Y₁₂ inhibitors

| | Clopidogrel | Prasugrel | Ticagrelor |
|--|--|---|--|
| Loading dose | 300 mg or 600 mg | 60 mg | 180 mg |
| Maintenance dose | 75 mg daily | 10 mg daily | 90 mg twice daily |
| P2Y ₁₂ receptor binding | Irreversible | Irreversible | Reversible |
| Hepatic metabolism | Two-step metabolism involving CYP2C19 to convert it to an active metabolite ⁶ Dysfunction of this enzyme may be the cause of clopidogrel resistance ⁷ | Rapidly hydrolysed to an intermediate metabolite, and then further metabolised by CYP3A and CYP2B63 | Metabolised by CYP3A4 ⁸ |
| Examples of drug interactions affecting P2Y ₁₂ inhibitors | CYP2C19 inhibitors will decrease efficacy e.g. clarithromycin, fluconazole, omeprazole | No significant CYP interactions, however data are limited | CYP3A4 inhibitors will increase adverse effects e.g. clarithromycin CYP3A4 inducers will decrease efficacy e.g. carbamazepine, dexamethasone, rifampicin |
| Examples of P2Y ₁₂ inhibitors affecting other drugs | - | - | Inhibits CYP3A4 so may increase concentrations of substrates such as simvastatin ⁹ * Ticagrelor is also a weak P-glycoprotein inhibitor ¹⁰ so digoxin concentrations increase and need monitoring ¹¹ |
| Time to onset of maximal platelet inhibition | 8 hours (300 mg) ¹² 2 hours (600 mg) ¹³ | 30 minutes ¹⁴ | 2 hours ¹² |
| Time to recover platelet function after ceasing medication | 5 days ¹⁵ | 7 days ¹⁵ | 2–3 days ¹² |

* simvastatin doses of 40 mg or more may be associated with an increased risk of myopathy and other adverse effects
CYP cytochrome

(3.0% vs 3.2%, $p=0.64$).¹ Subgroup analysis revealed that patients with a history of stroke or transient ischaemic attack experienced poorer outcomes with prasugrel. In patients over 75 years of age or weighing less than 60 kg treated with prasugrel, there was no benefit in relation to the composite end point.

The TRILOGY-ACS study included 7243 patients who did not undergo revascularisation.² There was no difference in the combined end point in the prasugrel and clopidogrel groups (13.9% vs 16%, $p=0.21$) and the risk of haemorrhage was similar.

Prasugrel may be of overall benefit to patients undergoing percutaneous coronary intervention, but it has a higher risk of haemorrhage. It would be better to use clopidogrel for patients with:

- a history of stroke or transient ischaemic attack
- age more than 75 years
- body weight less than 60 kg.

Ticagrelor: safety and efficacy

The PLATO trial compared ticagrelor with clopidogrel, both in combination with aspirin, in 18 624 patients with acute coronary syndrome.³ Ticagrelor significantly reduced the occurrence of the 12-month composite end point (consisting of death from cardiovascular causes, stroke and myocardial infarction) compared to clopidogrel (9.8% vs 11.7%, $p<0.001$). The dose of aspirin used in the study was 75–100 mg.

The overall incidence of major bleeding for ticagrelor and clopidogrel was similar (11.6% vs 11.2%, $p=0.43$), as was the rate of fatal bleeding (0.3% vs 0.3%, $p=0.66$). Ticagrelor, however, had a higher propensity to cause intracranial haemorrhage (0.3% vs 0.2%, $p=0.06$). The rate of bleeding related to urgent coronary artery bypass grafting was 7.4% with ticagrelor and 7.9% with clopidogrel.³

Dyspnoea was more common with ticagrelor (13.8% vs 7.8%, $p<0.001$), however this adverse effect was not related to any drug-induced cardiac, metabolic or respiratory dysfunction. The cause of this dyspnoea remains unknown, but ticagrelor inhibits cellular uptake of endogenous adenosine, and dyspnoea is a common adverse effect of adenosine administration.¹⁷ Further studies have found the dyspnoea to be transient,¹⁸ but ticagrelor should be avoided in patients who have chronic shortness of breath, such as those with chronic lung disease or symptomatic left ventricular failure.

In the PLATO study, ventricular pauses longer than three seconds were more common in the first week of therapy with ticagrelor (5.8% vs 3.6%, $p=0.01$), but

this difference resolved after one month of treatment. Uric acid and creatinine also increased slightly in patients taking ticagrelor.

Compliance with ticagrelor has been a concern, given its twice-daily dosing requirement, and more rapid offset time. In the PLATO study, the rates of adherence between clopidogrel and ticagrelor were equal (82.8% in each group), however this may not reflect clinical practice.

Overall, ticagrelor appears to be more effective in preventing ischaemic events, with a similar rate of major bleeding. However, clopidogrel should be preferred over ticagrelor in patients with:

- chronic dyspnoea
- increased risk of intracranial haemorrhage
- bradycardia or a history of ventricular pauses
- a risk of non-compliance due to the twice-daily dosing requirement of ticagrelor.

Prevention of stent thrombosis

In TRITON-TIMI-38, prasugrel was more effective in preventing stent thrombosis than clopidogrel (1.1% vs 2.4%, $p<0.001$).¹ A post hoc analysis of PLATO found that the rates of stent thrombosis were lower with ticagrelor than with clopidogrel over a period of up to 12 months (2.9% vs 3.8%).¹⁹ Higher rates of stent thrombosis could be expected in patients who do not adhere to the twice-daily regimen of ticagrelor.

Optimum duration and withdrawal of treatment

Current Australian guidelines suggest that following acute coronary syndrome treated with any form of stenting, dual antiplatelet therapy, including aspirin, should be continued for 12 months.⁴ After 12 months, the risk of haemorrhage may outweigh potential cardiovascular benefits. Dual antiplatelet therapy may be prescribed for longer than 12 months in patients with drug-eluting stents.

In cases of acute coronary syndrome treated with coronary artery bypass grafting, the data are currently inadequate to make a recommendation for or against dual antiplatelet therapy after surgery.

Opinion is divided as to whether abrupt clopidogrel cessation results in a 'platelet rebound' effect causing thrombotic events. Studies have demonstrated mixed results.^{20–22} Clopidogrel tapering has been proposed as a strategy to minimise the risk, but the benefits of this are unclear. The decision to cease or taper antiplatelet therapy should be made at the discretion of the treating cardiologist. Aspirin should be continued indefinitely if tolerated.

Management of bleeding

There are no formal guidelines for the management of bleeding related to P2Y₁₂ inhibitors. The most common approach is platelet transfusion, but there are no clinical trials of its efficacy and the number of units required has not been standardised. There are no drugs to reverse the effect. The treating cardiologist should be contacted about the bleeding for advice on whether or not to stop the antiplatelet drug. Given the lack of data and standardised protocols on platelet transfusion, consultation with a haematologist may also be required.

Perioperative management

The antiplatelet drugs prescribed to prevent coronary occlusion also increase the risk of bleeding during surgery. Aspirin should be continued, with the exception of certain high-risk procedures such as neurosurgical, ophthalmological or prostate surgery, which cannot be delayed.²³ P2Y₁₂ inhibitors are more difficult to manage.

Elective major surgery

Surgery produces a prothrombotic state where myocardial ischaemia may develop if the P2Y₁₂ inhibitor has been ceased, even if aspirin is continued. Current guidelines recommend delaying elective surgery until after the 12-month course of dual antiplatelet therapy is complete.⁴

In some cases, P2Y₁₂ inhibitors may be temporarily withheld one month after bare metal stenting or six months after insertion of a drug-eluting stent at the discretion of the treating cardiologist. This period of time correlates to complete re-endothelialisation of the stents in animal models.

While it is generally accepted that clopidogrel should be ceased five days before elective surgery, the timing of discontinuation of prasugrel and ticagrelor is uncertain. There are no randomised trials to guide management, so recommendations have been based

on pharmacokinetic data. If appropriate, prasugrel should be ceased seven days before elective surgery, and ticagrelor between 3 and 5 days, depending on the patient's thrombotic risk.²³⁻²⁵ In light of the lack of conclusive data, the treating cardiologist should be consulted about stopping P2Y₁₂ inhibitors before elective surgery.

Emergency surgery

There are no formal guidelines for the management of patients on dual antiplatelet therapy who need emergency surgery. One strategy is perioperative platelet transfusion.

Spinal or epidural anaesthesia

The risk of epidural haematoma following neuraxial blockade is believed to be increased in patients taking dual antiplatelet therapy, although further studies are required. Precautions regarding antiplatelet therapy should be similar to those observed for surgery. In elective circumstances, P2Y₁₂ inhibitors should be stopped before the procedure and in the case of an emergency lumbar puncture or neuraxial blockade, platelet transfusion is recommended beforehand to minimise the risk of severe haemorrhage.²⁶

Conclusion

Ticagrelor and prasugrel have some advantages over clopidogrel in selected patients. Platelet inhibition is more rapid with prasugrel, and for both drugs the rates of ischaemic events and stent thrombosis are statistically lower. However, the risk of haemorrhage is higher than with clopidogrel.

Perioperative management of patients on dual antiplatelet therapy is a controversial area. The risks of myocardial ischaemia and haemorrhage need to be balanced judiciously for each individual patient. ◀

Conflict of interest: none declared

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SELF-TEST QUESTIONS

True or false?

1. Aspirin should not be used at the same time as prasugrel or ticagrelor.
2. Antiplatelet therapy is not required by patients with drug-eluting stents.

Answers on page 219

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Dental note

New antiplatelet drugs

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Dentists should be familiar with clopidogrel, which is commonly used in combination with aspirin following placement of coronary stents to prevent coronary stent thrombosis. Clopidogrel may also be used in patients who are unable to take aspirin. Ticagrelor and prasugrel are new antiplatelet drugs that may be used as alternatives to clopidogrel.

All antiplatelet drugs place patients at an increased risk of bleeding following invasive dental procedures, especially dental extractions or dentoalveolar surgery. In patients who are receiving dual antiplatelet therapy following coronary artery stenting, premature discontinuation of the drugs can increase the risk of stent thrombosis, which may lead to acute myocardial infarction and death.¹

Australian guidelines² recommend that patients requiring dental extractions or dentoalveolar surgery should not cease antiplatelet therapy, either monotherapy with aspirin, or dual therapy where aspirin is combined with other antiplatelet drugs. Patients should be warned of the increased risk of prolonged bleeding and also bruising.

Local measures such as placement of haemostatic materials into sockets and suturing should be used. If patients stop these medicines without substitute anticoagulants or monitoring, there is a risk of significant cardiac events or cerebrovascular accident. Elective extractions or surgery are best delayed if possible, especially in patients taking dual antiplatelet therapy temporarily (usually 12 months following stent placement).

It is important that a thorough medical history, including a medication history, is obtained for all patients. This should be updated at each visit. For patients requiring dental extractions or dentoalveolar surgery, their antiplatelet medication should not be ceased.² However, their treating physician should be made aware of the planned procedures. When a dentist lacks experience in the oral surgical management of patients on antiplatelet therapy, the patient should be referred to an oral and maxillofacial surgeon for specialist management.

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