

Prasugrel (Effient) for acute coronary syndrome in people undergoing percutaneous coronary intervention

(PRA-suh-grel)

Summary

- Prasugrel is a new antiplatelet drug from the same class as clopidogrel.
- Prasugrel is an alternative to clopidogrel for treating moderate to high risk acute coronary syndromes that are managed by percutaneous coronary intervention in combination with aspirin.
- Prasugrel reduces the risk of atherothrombotic events (mainly non-fatal myocardial infarction) more than clopidogrel, but at the expense of more bleeding, including life-threatening and fatal episodes.
- Avoid prasugrel in people with a previous stroke or transient ischaemic attack, active bleeding, severe hepatic impairment, or otherwise at high risk of bleeding that could outweigh the benefit.
- People aged ≥ 75 years or weighing < 60 kg experience increased incidence of bleeding with prasugrel. A lower maintenance dose (5 mg daily) is recommended to minimise their bleeding risk; however, there are currently no clinical data on the use of lower doses in these patients.
- The optimal duration of therapy and full adverse-effect profile of prasugrel are yet to be established. Clinical efficacy and safety data are currently limited to 15 months.

PBS listing

Authority required (Streamlined)

Treatment of acute coronary syndrome (myocardial infarction or unstable angina) managed by percutaneous coronary intervention in combination with aspirin.

Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended the listing of prasugrel on the basis of acceptable cost effectiveness compared with clopidogrel.¹ The PBAC accepted that prasugrel is more effective than clopidogrel but causes a higher incidence of bleeding.

Place in therapy

Prasugrel is a new oral thienopyridine antiplatelet drug from the same class as clopidogrel.² The active metabolite of prasugrel inhibits platelet activation and aggregation by irreversibly blocking P2Y₁₂ adenosine diphosphate receptors.²

Prasugrel is an alternative to clopidogrel for treating acute coronary syndrome (moderate to high risk unstable angina, ST-segment-elevation myocardial infarction [STEMI] or non-ST-segment-elevation myocardial infarction [NSTEMI]) in combination with aspirin in people who are to undergo percutaneous coronary intervention (PCI).²

Clopidogrel with aspirin is the mainstay antiplatelet therapy for people with an acute coronary syndrome not managed by PCI, and in those without an acute coronary syndrome but who require a cardiac stent insertion (see the August 2009 *NPS RADAR* In-brief item: *Clopidogrel PBS listing extended to cardiac stent insertion*).

Prasugrel has a more rapid and potent effect on platelet inhibition than does clopidogrel.^{3,4} This results in a greater reduction in the risk of atherothrombotic events, mainly non-fatal MI, but at the expense of an increased risk of bleeding (see Safety issues).

There is evidence that some groups of patients do not derive a net clinical benefit from prasugrel over that for clopidogrel, mainly because of increased bleeding (see Safety issues). Clopidogrel is an option for these people, such as those with low body weight (< 60 kg) or aged 75 years and over.

Prasugrel results in fewer non-fatal MIs, but more serious bleeds than clopidogrel

The efficacy and safety of prasugrel was investigated in the TRITON–TIMI 38 trial involving 13,608 people undergoing planned PCI for a moderate to high risk acute coronary syndrome (unstable angina, NSTEMI or STEMI).⁵ Participants received prasugrel (60 mg, then 10 mg daily) or clopidogrel (300 mg, then 75 mg daily) in combination with aspirin (75–162 mg daily).⁵

The incidence of the primary outcome (any one of: death from cardiovascular causes, non-fatal MI or non-fatal stroke) was significantly lower with prasugrel (9.9%) compared with clopidogrel (12.1%) after a median of 14.5 months (hazard ratio 0.81; 95% confidence interval: 0.73 to 0.90).⁵

Most of the benefit from prasugrel was due to a reduced incidence of non-fatal MI compared with clopidogrel (7.3% vs 9.5%).⁵ There was no significant difference in the incidence of non-fatal stroke, cardiovascular death, or death from any cause.⁵ However, prasugrel significantly increased the risk of bleeding compared with clopidogrel, including fatal events (see Safety issues).

Despite the increased bleeding risk, the benefit–harm profile of prasugrel was favourable in the overall trial population (Table 1). This is largely because the number of non-fatal MIs that were prevented outweighed the number of excess clinically significant bleeding events.

Stent thrombosis, a serious and often fatal complication of PCI, was also less frequent with prasugrel than with clopidogrel, although the absolute risk with either treatment was small (1.1% vs 2.4%).²

The benefit–harm profile of prasugrel may improve as atherothrombotic risk increases: people in the trial with diabetes were found to gain the greatest absolute benefit from treatment.^{5,6} However, for any individual, the balance of benefits and harms may differ in clinical practice (see Safety issues).

The benefit–harm profile may change over time

The effect of prasugrel in preventing the first atherothrombotic event was greatest in the 30 days after the acute coronary syndrome compared with clopidogrel.^{6,8,9} The difference in bleeding incidence between treatments continued to diverge after this time.^{4,6,10}

Table 1: TRITON–TIMI 38 trial: primary efficacy outcome and major bleeding events with prasugrel and clopidogrel (incidence per 1000 people)⁵

Trial outcome	Prasugrel	Clopidogrel	Difference with prasugrel over clopidogrel
Death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke	99	121	22 fewer events per 1000 people
Major bleeding* (unrelated to coronary artery bypass grafting)	24	18	6 more events per 1000 people

* Major bleeding events were intracranial haemorrhage or clinically overt bleeding with a haemoglobin drop of ≥ 50 g/L.⁷

While the net clinical benefit with prasugrel over clopidogrel remained favourable for the duration of treatment^{5,9,10}, clinicians should consider the possibility of increased bleeding with longer-term use. There is no evidence as yet to support switching from prasugrel to clopidogrel at any stage of treatment.

There is no evidence to support selection of antiplatelet therapy based on platelet function or genetic testing

In pharmacodynamic studies prasugrel had a more potent and less variable effect on platelet inhibition than did clopidogrel.^{2,3} This may be partly due to individual genetic differences in the platelet response or metabolism of clopidogrel. However, evidence is still emerging on the role of testing of platelet function and the impact of genetic variations in optimising antiplatelet therapy.^{11,12} The risk of atherothrombotic events and bleeding should be the main considerations when choosing between prasugrel and clopidogrel.

Optimal duration of therapy is currently unknown

As with clopidogrel, the optimal duration of therapy with prasugrel after an acute coronary syndrome is unknown. Evidence is available for use of prasugrel in combination with aspirin for up to 15 months.⁸

Australian guidelines currently recommend clopidogrel with aspirin for up to 12 months (particularly after stent implantation)¹³, and similar recommendations have been made in Europe for prasugrel.⁴ For more information on duration of antiplatelet therapy see the March 2009 *NPS RADAR* In-brief item: *Clopidogrel PBS listing extended to include acute coronary syndrome in combination with aspirin*.

Safety issues

Bleeding is the main safety concern with prasugrel. Other than bleeding, the overall incidence of serious adverse effects appears to be similar to that for clopidogrel.⁵ There is presently no evidence that prasugrel has clinically important interactions with other drugs, including proton pump inhibitors (PPIs).^{2,6,14*} However, there is limited experience of use with prasugrel, and its full safety profile is yet to be established.

Report suspected adverse reactions to the Therapeutic Goods Administration (TGA) online (www.ebs.tga.gov.au [then click 'Adverse reaction to a medicine' at left]) or by using the 'Blue Card' distributed 3 times a year with *Australian Prescriber*. For information about reporting adverse reactions, see the TGA website (www.tga.gov.au).

Bleeding can be serious with prasugrel and is more common than for clopidogrel

In the TRITON–TIMI 38 trial, bleeding risk was consistently higher for prasugrel than clopidogrel, although the benefit–harm profile of prasugrel was generally favourable (see Place in therapy).

People at increased risk of bleeding should only use prasugrel when the expected benefits are assessed as outweighing the harm of serious bleeding.² Many people at high risk of bleeding were excluded from the trial (see Box 1), so bleeding with prasugrel could be more common in clinical practice.

Treating 1000 people in the trial with prasugrel instead of clopidogrel led to 12 more clinically significant bleeding events unrelated to coronary artery bypass grafting (CABG); half of these were major bleeds that included fatal events, although the incidence with either treatment was small (Table 2).⁵ Excess bleeding was worse for patients who underwent CABG.⁵

* There is some evidence that PPIs decrease clopidogrel's effect by inhibiting formation of its active metabolite.¹⁵

Box 1: Bleeding risk factors that excluded people from the TRITON–TIMI 38 trial⁷

- Active internal bleeding or history of bleeding diathesis
- Clinical findings judged by investigator to increase bleeding risk
- History of haemorrhagic stroke
- Intracranial neoplasm, arteriovenous malformation or aneurysm
- Ischaemic stroke within last 3 months
- Severe hepatic dysfunction
- International normalised ratio (INR) > 1.5
- Thrombocytopenia (platelet count < 100 000/mm³)
- Anaemia (haemoglobin < 100 g/L)
- Fibrinolytic therapy < 48 hours (< 24 hours if fibrin specific)
- Ongoing oral anticoagulation or other antiplatelet therapy
- Daily treatment with NSAIDs or COX-2 inhibitors
- Any condition associated with poor treatment compliance

Table 2: TRITON–TIMI 38 trial: clinically significant bleeding events with prasugrel and clopidogrel (incidence per 1000 people)⁵

Bleeding outcome	Prasugrel	Clopidogrel	Difference with prasugrel over clopidogrel
Major bleeding* (non-CABG)	24	18	6 more events per 1000
• Non-fatal life-threatening	11	9	2 more events per 1000
• Fatal	4	1	3 more events per 1000
Major or minor bleeding† (non-CABG)	50	38	12 more events per 1000
Major bleeding* (CABG related)	134	32	102 more events per 1000 undergoing CABG


* Major bleeding was defined as intracranial haemorrhage or clinically overt bleeding with a haemoglobin drop of ≥ 50 g/L; life-threatening events were major bleeds that were fatal, symptomatic intracranial haemorrhage, events that led to hypotension necessitating intravenous inotropic agents, or which required surgical intervention or blood transfusion (≥ 4 units over 48 hours).⁷

† Minor bleeding was defined as clinically overt bleeding with a haemoglobin drop of between 30 g/L and 50 g/L.⁷

Major bleeding with prasugrel occurred mostly from gastrointestinal or surgical sites.⁴ Intracranial haemorrhage was another important cause of fatal bleeding, but the risk did not differ significantly from that for clopidogrel.⁴

There was also an excess of 19 minimal bleeds per 1000 people treated with prasugrel (defined as clinically overt bleeding associated with a haemoglobin drop of < 30 g/L).^{6,7}

Avoid prasugrel in certain patients at higher risk of bleeding

Because of the bleeding risk, prasugrel is contraindicated in people with active bleeding, a previous stroke or transient ischaemic attack (TIA), or severe hepatic impairment (Child–Pugh Class C).² [www](#)  In people from the TRITON–TIMI 38 trial who had a previous stroke or TIA, prasugrel treatment increased harm without any benefit, increasing the rate of all strokes (6.5% vs 1.2%) and major bleeding (5.0% vs 2.9%).⁵

Carefully consider and monitor the use of prasugrel in people²:

- aged 75 years and over
- with low body weight (< 60 kg)
- undergoing or possibly requiring urgent CABG during therapy
- with renal impairment, particularly end-stage renal disease
- receiving other treatments, or with coexisting conditions, that make them more prone to bleeding (see Box 1).

In the TRITON–TIMI 38 trial there was no net benefit from prasugrel compared with clopidogrel in people aged ≥ 75 years or weighing < 60 kg, mainly because of increased bleeding in these subgroups.⁵

People aged ≥ 75 years or weighing < 60 kg may use prasugrel but at a lower maintenance dose to minimise their risk of bleeding (see Dosing issues).² However, there are currently no clinical efficacy or safety data supporting the use of lower doses in these patients.⁴

[www](#)  Refer to this review at www.npsradar.org.au for more information about Child–Pugh classification of liver disease.

Check adherence with prasugrel regularly

Bleeding episodes while taking prasugrel are likely to cause significant concern for patients. For some, a minor bleed may be enough to affect adherence to treatment. Patients who prematurely stop their antiplatelet therapy may consequently be at greater risk of thrombosis, MI or death.²

More people in the TRITON–TIMI 38 trial stopped prasugrel (7.2%) than they did clopidogrel (6.3%) because of adverse effects, with the difference being mostly due to bleeding (2.5% vs 1.4%).^{5,6} Epistaxis and gastrointestinal bleeding were the main reasons people stopped prasugrel more often than clopidogrel.⁴

Long-term safety profile is yet to be established

Clinical safety data for prasugrel are currently limited to the TRITON–TIMI 38 trial. Other than bleeding, the overall incidence of serious adverse events did not differ significantly between prasugrel and clopidogrel after 15 months of treatment (22.5% vs 22.8%).⁵ However, the full adverse-effect profile of prasugrel has not been established in the broader population.


Common non-haemorrhagic adverse events that were reported in at least 1% of patients in the trial included rash, anaemia and neoplasms.² Although the incidence of colonic neoplasms with prasugrel (0.2%) was significantly higher than with clopidogrel (0.1%), half of these were discovered as a result of a gastrointestinal bleed caused by treatment.⁵

Less common adverse effects that were significantly more frequent with prasugrel than for clopidogrel, but possibly related to bleeding, were respiratory failure, hypotension, atrial flutter, pyrexia and bruising.⁶

Dosing issues

The recommended dosage of prasugrel is a single 60 mg loading dose (6 × 10 mg tablets) followed by a maintenance dose of 10 mg once daily.² Prasugrel may be taken with or without food.²

Prasugrel should be taken with aspirin as its effect has only been studied in this combination.² An aspirin dose of 75–150 mg daily is recommended long-term.¹⁵

No dosage adjustment is required in people with renal impairment, including end-stage renal failure, or in mild to moderate hepatic impairment (Child–Pugh Class A and B).² [www](#) 

No specific recommendations exist for the timing of the loading dose

In the TRITON–TIMI 38 trial, almost all patients (99%) had their planned PCI at the time of randomisation: 74% of them were given the loading dose of prasugrel or clopidogrel during or within 1 hour of the procedure.⁵ The remainder of patients either received the study drug before placing the first coronary guidewire (25%) or more than 1 hour after PCI (1%).⁵

However, because of the increased risk of bleeding, prasugrel should be carefully considered in people who have not had their coronary anatomy defined and thus may require urgent CABG after treatment has started (see Safety issues).²

Use a lower maintenance dose for people < 60 kg or aged ≥ 75 years

If a decision is made to use prasugrel in a patient weighing < 60 kg or aged ≥ 75 years, use a maintenance dose of 5 mg once daily.² The usual maintenance dose of 10 mg once daily should be avoided in these patients because of the potential

for increased bleeding. It is important to note that the evidence for using lower doses in these patients is currently limited to pharmacokinetic or pharmacodynamic studies only.⁴

Information for patients

Inform patients and their carers of the risk of bleeding with prasugrel and the signs and symptoms to look out for. Advise them that bleeding may take longer to stop during therapy, and to report any site or duration of bleeding that does not seem normal.²

The effect of prasugrel has only been studied in combination with aspirin. Inform about the importance of taking these medicines together for as long as directed, and of the risks associated with abruptly stopping therapy.

Advise patients and carers to notify physicians, dentists, pharmacists and nurses about them taking prasugrel and aspirin before any planned surgery or new treatment.² This includes when using over-the-counter and complementary medicines. When patients are undergoing elective surgery for which antiplatelet effects are to be avoided, prasugrel should be stopped at least 7 days before surgery.²

Discuss the prasugrel (Effient) consumer medicine information (CMI) leaflet with the patient.

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