

Access to clopidogrel now widened

On September 1 2010 the Special Authority for clopidogrel was removed. Now that access to clopidogrel has widened it is helpful to revise its appropriate use.

Clopidogrel is an antiplatelet agent (from a group known as the thienopyridines) used for the prevention of certain cardiovascular and cerebrovascular conditions. Depending on the indication, it is used either instead of, or in combination with, low-dose aspirin.

Indications for clopidogrel

There is insufficient evidence to support the use of clopidogrel for primary prevention of cardiovascular disease (CVD), and it is not licensed for this indication.

Clopidogrel is currently recommended for secondary prevention of CVD in the following situations:

1. People with established CVD
First choice – aspirin
Second choice – clopidogrel, continued indefinitely
2. Secondary stroke prevention
First choice – aspirin + dipyridamole combination
Second choice – clopidogrel, continued indefinitely
3. Acute coronary syndrome without ST-segment elevation (non-STEMI)
First choice – aspirin + clopidogrel combination
Second choice – clopidogrel
4. Post-revascularisation procedures e.g. cardiac stenting and angioplasty
First choice – aspirin + clopidogrel combination
Second choice – clopidogrel

N.B. for acute coronary syndrome without ST-segment elevation and post-revascularisation procedures there is currently no evidence to support the use of clopidogrel beyond 12 months.

1. Established CVD

Clopidogrel alone: Patients with established CVD, e.g. angina, post-myocardial infarction or peripheral arterial disease, are normally advised to take low-dose aspirin, long-term. Clopidogrel is recommended as an alternative to aspirin if aspirin is contraindicated or not tolerated.

Aspirin intolerance is best defined as a proven hypersensitivity to aspirin-containing medicines or a history of severe dyspepsia caused by low-dose aspirin (despite concomitant use of a proton pump inhibitor). There is no evidence to support switching to clopidogrel for patients who are well managed on aspirin.

Aspirin and clopidogrel in combination is not advised: The combination of aspirin and clopidogrel does not offer additional benefit for patients with established CVD.

2. Secondary stroke prevention

Clopidogrel alone: The ProFESS trial has shown that clopidogrel is equally as effective as the combination of aspirin plus dipyridamole in secondary prevention of ischaemic stroke/TIA.¹ The use of clopidogrel alone or the combination of aspirin/dipyridamole was superior to the use of aspirin alone. Now that clopidogrel can be more easily accessed in New Zealand, it is reasonable to regard it as an alternative first-line treatment for secondary stroke prevention.

3. Acute coronary syndrome without ST-segment elevation

Aspirin and clopidogrel in combination: In acute coronary syndrome without ST-segment elevation, the CURE trial found the combination of clopidogrel and aspirin to be superior to aspirin alone in reducing the risk of death from cardiovascular causes, nonfatal myocardial infarction or stroke.² The evidence seems to indicate that the benefit is the greatest when clopidogrel is used for up to one year. In the CURE trial there was no significant excess of late, life-threatening bleeding, but there was a small excess of

major bleeds (5 per 1000 people treated) that was much smaller than the total cardiovascular benefit at one year (22 per 1000 people treated).²

Clopidogrel alone: For patients who are intolerant to aspirin or when there is a contraindication to the use of aspirin, clopidogrel can be used alone as an effective alternative.³

4. Post-revascularisation procedures

Aspirin and clopidogrel in combination: For patients who have been treated with angioplasty or with bare metal stent implantation, clopidogrel and aspirin should be used in combination for at least one month, but ideally for up to 12 months.^{4,5} For patients who have been treated with drug-eluting stents, clopidogrel and aspirin should be used in combination for up to 12 months.^{4,5}

After 12 months of combination therapy, clopidogrel is usually stopped and aspirin continued alone. There is limited evidence for use of clopidogrel beyond 12 months, but this may change with the outcomes of trials that are currently underway.

Clopidogrel alone: For patients who are intolerant to aspirin or when there is a contraindication to the use of aspirin, clopidogrel can be used alone as an effective alternative.²

Dosage and administration of clopidogrel

In primary care the maintenance dose of clopidogrel is a single daily dose of 75 mg. Clopidogrel can be taken with or without food and no dose adjustments are necessary for elderly patients or patients with renal impairment.⁸ Like aspirin, the effects of clopidogrel are irreversible and it takes seven to ten days for full recovery of platelet function following the last dose.

A loading dose of clopidogrel (of 300 mg or more) is used in secondary care for patients with a non-ST elevation acute coronary syndrome and prior to revascularisation procedures.

Safety considerations with clopidogrel use

A meta-analysis of randomised controlled trials indicated that the risk of major gastro-intestinal (GI) bleeding is very similar for clopidogrel and low dose aspirin. It has been estimated that for every 800 people treated with clopidogrel, instead of low dose aspirin, there will be one less major GI bleed (number needed to harm = 800).⁶

Do not prescribe clopidogrel for:⁷

- People with active pathological bleeding, such as peptic ulcer or intracranial haemorrhage
- People with severe hepatic impairment
- Women who are pregnant or breastfeeding (without specialist advice)
- People taking anticoagulants (without specialist advice)

Caution is recommended for those people who may be at high risk of increased bleeding, e.g. taking non-steroidal anti-inflammatory drugs (NSAIDs).⁷ If the risk of morbidity due to bleeding outweighs the anticipated benefit of anti-platelet therapy, then consider discontinuing earlier than the recommended duration of use.

Adverse effects

In addition to the increased risk of bleeding, other adverse effects of clopidogrel include:⁸

- Commonly – diarrhoea, abdominal pain and dyspepsia
- Less commonly – nausea, vomiting, constipation, pruritis, urticaria, rash, headache, dizziness, leucopenia
- Rarely – thrombocytopenia, vertigo, colitis, pancreatitis, hepatitis

Interactions

The risk of bleeding is increased when clopidogrel is co-prescribed with:

- NSAIDs – consider gastro-protection with ranitidine

- Anticoagulants – prescribe only under specialist advice and as with NSAIDs, consider gastro-protection if this combination is used
- Selective serotonin reuptake inhibitors (SSRIs), venlafaxine – consider alternatives
- Corticosteroids



For further information about interactions, refer to the Medicine Safety Datasheet, available from: www.medsafe.govt.nz

CYP2C19 inhibitors

Clopidogrel is converted from an inactive pro-drug to an active metabolite by the liver enzyme CYP2C19. Therefore other medicines that are CYP2C19 inhibitors can reduce the therapeutic effect of clopidogrel.

CYP2C19 inhibitors commonly prescribed in New Zealand include: omeprazole, cimetidine, fluoxetine, moclobemide, fluconazole, ketoconazole, ciprofloxacin, carbamazepine and chloramphenicol.

Medsafe currently advises to avoid the concomitant use of clopidogrel with omeprazole and other CYP2C19 inhibitors.⁹

Advice to patients prescribed clopidogrel

The following points may be discussed with patients prescribed clopidogrel:⁷

- Bleeding may take longer than usual to stop when taking clopidogrel (alone or in combination with aspirin)
- Report any unusual bleeding (site or duration)
- Inform healthcare professionals that they are using clopidogrel if any surgical procedure is planned
- Seek advice from a pharmacist or other healthcare professional before buying over-the-counter medicines, as these may contain ingredients which can increase the risk of adverse effects

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