Australian Government
Department of Veterans' Affairs

Veterans'MATES

# Therapeutic brief 13

# Aspirin and clopidogrel in cardiovascular disease

This therapeutic brief focuses on the use of aspirin and clopidogrel in the prevention of thrombotic events. We acknowledge the role of other antiplatelet agents such as dipyridamole and ticlopidine, but their place in therapy lies outside the scope of this document.

## Clinical efficacy of aspirin vs. clopidogrel

### Key clinical points

- Aspirin is a highly cost-effective agent for primary and secondary prevention of cardiovascular and cerebrovascular thrombotic events.[1]
- Clopidogrel has been shown to be as effective as aspirin for the prevention of a composite outcome of cardiovascular/cerebrovascular events in patients with established atherosclerotic disease.[2]
- Aspirin + clopidogrel in combination is beneficial for the management of acute unstable angina and myocardial infarction, including situations where stenting or fibrinolytic therapy is employed.[1,3,4,5,6]
- Aspirin + clopidogrel in combination has not been shown to be superior to either clopidogrel or aspirin alone in the secondary prevention of ischaemic stroke.[7,8]

## Inside



www.dva.gov.au/health/veteransmates

## Key messages

- Use aspirin in preference to clopidogrel for both primary and secondary prevention of thrombotic events in cardiovascular and cerebrovascular disease unless contraindicated.
- Aspirin + clopidogrel in combination is beneficial for the management of acute coronary syndromes. Duration of therapy will vary with clinical circumstances (see below).
- If aspirin + clopidogrel in combination is ceased, monotherapy with aspirin should be continued indefinitely for secondary prevention of cardiovascular and/or cerebrovascular thrombotic events.
- There is no clear advantage (and an increased risk of bleeding) of aspirin + clopidogrel over aspirin alone for patients with stable cardiovascular or cerebrovascular disease. An important exception to this is in the longer term management following acute coronary syndromes or stenting, where continued combination therapy may be beneficial despite achievement of a stable cardiovascular state.
- Warfarin is superior to aspirin and clopidogrel in the prevention of stroke in patients with atrial fibrillation at moderate to high risk of thromboembolic stroke. Aspirin is recommended for patients with atrial fibrillation at low risk of stroke.

## 2 Clinical efficacy of aspirin vs. clopidogrel

### Summary of recommendations for aspirin and clopidogrel therapy

| | Primary prevention | Secondary prevention | | |
|---|---|---|---|---|
| | | Stable cardiovascular disease | Acute coronary syndrome | Following stent insertion |
| Aspirin monotherapy | Yes, if 5-year cardiovascular risk > 15%* | Yes, preferred option | After combination therapy completed | Indefinitely after combination therapy completed |
| Clopidogrel monotherapy | Evidence lacking | Only for aspirin intolerance | Only for aspirin intolerance | Only for aspirin intolerance |
| Aspirin - clopidogrel dual therapy | No | No | Yes, initial phase (duration variable – see below) | Yes, initial phase (duration variable – see below) |

* The cardiovascular benefits of low-dose aspirin outweigh the harm in people with a 5-year cardiovascular risk greater than 15%. However, the risk of a significant bleed or major haemorrhage with aspirin outweighs the benefit for people with a 5-year cardiovascular risk of less than 15%.[9] A commonly used cardiovascular risk calculator is the New Zealand Risk Calculator available at http://www.sld.cu/galerias/pdf/servicios/hta/ebm_cardio_new_zeland.pdf

### Aspirin alone vs. clopidogrel alone (the CAPRIE study)[2]

This large (19,185 patients) randomised controlled trial evaluated the relative efficacy of clopidogrel (75 mg once daily) vs. aspirin (325 mg once daily) in reducing the risk of a composite outcome comprising ischaemic stroke, myocardial infarction, and vascular death.

The study population comprised subgroups of patients with atherosclerotic vascular disease, as evidenced by recent ischaemic stroke, recent myocardial infarction, or symptomatic peripheral arterial disease. Patients were followed for 1 to 3 years (mean 1.9 years).

Interpreting the results of CAPRIE:

- For patients with previous ischaemic stroke or myocardial infarct, there was no significant difference in the composite outcome between those taking clopidogrel or aspirin.
- For patients with existing peripheral artery disease, there was a small benefit of clopidogrel over aspirin in reducing the composite outcome.

**The overall result for all patients was a 0.5% absolute risk reduction for clopidogrel compared to aspirin. This means that you would need to treat about 200 patients with clopidogrel instead of aspirin for 2 years to prevent one adverse cardio/cerebro-vascular outcome.**

### Aspirin + clopidogrel vs. aspirin alone (the CHARISMA study)[7]

This randomised controlled trial evaluated the relative efficacy of clopidogrel (75 mg per day) plus low-dose aspirin (75 to 162 mg per day) vs. placebo plus aspirin in reducing the risk of a composite outcome of myocardial infarction, stroke, or death from cardiovascular causes. The study population comprised 15,603 patients with either clinically evident cardio/cerebro-vascular disease, or multiple cardiovascular risk factors. Patients were followed for a median of 28 months.

The combination of clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes among patients with stable cardio/cerebro-vascular disease or multiple cardiovascular risk factors. The risk of moderate-to-severe bleeding was increased. **The study did not support the use of combination anti-platelet therapy across a broad high-cardiovascular-risk population.**

## Pharmaceutical Benefits Scheme subsidy for clopidogrel

Clopidogrel is listed for the following circumstances:

1. General Schedule; Secondary prevention of ischaemic stroke, transient cerebral ischaemic events, myocardial infarction, or unstable angina, in patients:
   - with a history of cerebrovascular ischaemic episodes or cardiac ischaemic events while on therapy with low dose aspirin or
   - where low dose aspirin poses an unacceptable risk of gastrointestinal bleeding or
   - where there is a history of anaphylaxis, urticaria or asthma within 4 hours of ingestion of aspirin, other salicylates, or NSAIDs.
2. RPBS; For use in patients pre- and post-angioplasty.

## Adverse effects

The adverse effects reported, judged to be severe, from the CAPRIE trial in the clopidogrel and aspirin groups were as follows:[2]

### Adverse effects judged as severe (CAPRIE study)

| Adverse effect | Clopidogrel group | Aspirin group |
|---|---|---|
| rash | 0.26% | 0.10%* |
| diarrhoea | 0.23% | 0.11% |
| upper gastrointestinal discomfort | 0.97% | 1.22% |
| intracranial haemorrhage | 0.33% | 0.47% |
| gastrointestinal haemorrhage | 0.52% | 0.72%* |
| significant reduction in neutrophil count | 0.10% | 0.17% |

* Statistically significant ($P < 0.05$)

The study showed a significantly increased incidence of a severe gastrointestinal bleed with aspirin (0.72%) compared to clopidogrel (0.52%). **This means that 500 patients would need to be treated with clopidogrel instead of aspirin for 2 years to prevent one severe aspirin-induced gastrointestinal bleed.** There was a significantly increased incidence of severe rash with clopidogrel compared to aspirin. Other studies have reported that clopidogrel has improved gastrointestinal tolerance compared to aspirin but causes an excess of rash, diarrhoea, and adverse haematological outcomes (including thrombotic thrombocytopenic purpura, aplastic anaemia, thrombocytopenia, and neutropenia).[1,10]

## Acute coronary syndromes and stent implantation

The term 'acute coronary syndrome' encompasses unstable angina and myocardial infarction with or without ST segment elevation of the electrocardiogram (STEMI and NSTEMI respectively).

### Key clinical points

- Aspirin + clopidogrel in combination has a favourable benefit/risk ratio in acute coronary syndromes, particularly during the early phase. Benefit is in relation to reduced nonfatal myocardial infarction, not reduced stroke or death.[1,3,4,5,6]
- Aspirin + clopidogrel in combination is clearly beneficial in preventing stent thrombosis.[3,4,5,6]

**All patients should take low-dose aspirin (100 mg daily) indefinitely if possible following acute coronary syndromes, stenting, or coronary artery bypass surgery.**

The use of aspirin + clopidogrel combination therapy in acute coronary syndromes and duration of therapy may be influenced by:

- the medical condition(s) in question
- patient-specific risk factors for thrombotic events
- if used, the type of stent chosen.

There is no consensus in the biomedical literature with regard to the use of clopidogrel in acute coronary syndromes. One approach is outlined below.

### Patients without coronary artery stenting

- For patients with UA/NSTEMI, use aspirin in combination with clopidogrel for at least 1 month and ideally up to 12 months.[4,6]
- For patients with STEMI use aspirin in combination with clopidogrel (optimal duration of clopidogrel therapy is unclear).[6] Current Australian guidelines recommend clopidogrel therapy (75 mg daily) for at least 1 month after fibrinolytic therapy.[3]

### Patients with coronary artery stenting

There are 2 types of stents used to keep coronary arteries patent – bare metal stents and drug-eluting stents. Drug eluting stents contain a pharmaceutical agent which reduces the risk of early restenosis. However, drug eluting stents carry a higher risk of late thrombosis than bare metal stents.[1,4,5] The optimal duration of aspirin + clopidogrel combination therapy after drug-eluting stent implantation is uncertain.[1,5]

One approach to clopidogrel therapy (600 mg loading dose, then 75 mg daily) in combination with indefinite aspirin (100 mg daily) following stenting is as follows:[4,6]

| Stent | Suggested therapy |
|---|---|
| Bare metal stent (elective) | **Clopidogrel for at least 1 month**<br>Up to 12 months in patients with low bleeding risk and extensive vascular disease or high risk of coronary artery thrombosis |
| Bare metal stent (acute coronary syndrome) | **Clopidogrel for 12 months** |
| Drug eluting stent | **Clopidogrel for at least 12 months, irrespective of clinical context**<br>Indefinite clopidogrel in high-risk patients e.g.<br>• Left main artery stenting<br>• Multiple stents<br>• Long stent length<br>• LV dysfunction<br>• Diabetes<br>• Renal failure |

**Discontinuation of any antiplatelet agent following acute coronary syndrome or stenting, including discontinuation for any form of surgery, should be done in consultation with the patient's cardiologist.** The risk of bleeding during surgery needs to be balanced against the risk of stent thrombosis and assessed case by case.

4

## Gastrointestinal bleeding and Proton Pump Inhibitor prophylaxis[10,11]

A history of previous upper gastrointestinal bleeding is a major risk factor for clopidogrel associated bleeding, but clopidogrel appears to be associated with fewer upper gastrointestinal bleeds than aspirin.[2] The use of a proton pump inhibitor decreases the rate of gastrointestinal bleeding in patients receiving aspirin or clopidogrel.

Treat with a proton pump inhibitor when starting or continuing aspirin or clopidogrel in patients with a recent history of upper gastrointestinal ulceration or bleeding (after ulcer healing and eradication of H. pylori infection).

The combination of aspirin + clopidogrel increases the risk of upper gastrointestinal bleeding compared to monotherapy. However, there are no data on the effect of proton pump inhibitor prophylaxis in aspirin + clopidogrel combination therapy.

A recent study found that patients with a history of aspirin-induced upper gastrointestinal bleeding had a significantly lower incidence of recurrent bleeding when treated with aspirin plus esomeprazole than those treated with clopidogrel alone.[12]

## Atrial fibrillation

Warfarin substantially reduces the risk of stroke in atrial fibrillation (primary and secondary prevention). Aspirin provides less benefit than warfarin for patients with atrial fibrillation at moderate-high risk of stroke.[13]

Consider warfarin therapy for both primary and secondary prevention of stroke in all patients with atrial fibrillation at moderate to high risk of thromboembolic stroke (i.e. atrial fibrillation plus ≥ 1 of the following risk factors: age ≥ 75 years, hypertension, left ventricular dysfunction, heart failure, diabetes, previous stroke, previous transient ischaemic attack, previous thromboembolic event, mitral stenosis, or prosthetic heart valve).[14] Target INR is 2.0 to 3.0. Review ongoing indication for antiplatelet therapy when initiating warfarin.

For patients with atrial fibrillation at low risk of thromboembolic stroke (no other risk factors), aspirin (75-300 mg daily) is recommended.[14]

Warfarin is superior to aspirin + clopidogrel combination therapy for the prevention of vascular events (including stroke) in patients with atrial fibrillation. A study of warfarin versus aspirin + clopidogrel in atrial fibrillation was stopped early due to clear superiority of warfarin.[15,16]

There is no evidence supporting the use of warfarin-aspirin-clopidogrel triple therapy, but there is an increased risk of bleeding compared to warfarin or aspirin alone.

## Surgery

Cessation of antiplatelet therapy before surgery (cardiac or other) or dental procedures should be done in consultation with the treating cardiologist.

## What to tell my veteran patient

- Aspirin is as good as clopidogrel in most situations.
- Aspirin and clopidogrel are sometimes used together, especially for heart attack, unstable angina or when a stent is implanted. The combination may not be needed indefinitely.
- Both aspirin and clopidogrel can slightly increase the risk of bleeding in the stomach or brain. A proton pump inhibitor can be added to reduce the risk of a stomach bleed.
- The risk of a major bleed in the stomach or brain is greater when aspirin and clopidogrel are used together.

For drug information, including interactions and contraindications, refer to the Australian Medicines Handbook 2007[10] and approved product information.

## References


1. Eshaghian S, Kaul S, Amin S, Shah PK, Diamond GA. Role of Clopidogrel in Managing Atherothrombotic Cardiovascular Disease. Annals of Internal Medicine 2007;146(6):434-441.
2. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet. 1996;348:1329-1339.
3. Acute Coronary Syndromes Working Group, National Heart Foundation of Australia and The Cardiac Society of Australia and New Zealand. Guidelines of the management of acute coronary syndromes 2006. MJA 2006;184(8) Supplement:S1-S30.
4. ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non–ST-Elevation Myocardial Infarction. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction). Journal of the American College of Cardiology 2007;50(7):e1-e158.
5. Plosker GL, Lyseng-Williamson KA. Clopidogrel: A Review of its Use in the Prevention of Thrombosis. Drugs 2007; 67 (4): 613-646.
6. McCann A. Antiplatelet therapy after coronary occlusion. Australian Prescriber 2007,30(4):92-96.
7. Bhatt DL et al for the CHARISMA Investigators. Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events. NEJM 2006;354(16):1706-1717.
8. MATCH Investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet 2004;364:331-337.
9. New Zealand Guidelines Group (NZGG). A Best Practice Evidence-Based Guideline. The Assessment and Management of Cardiovascular Risk. Available at: http://www.nzgg.org.nz/guidelines/0035/CVD_Risk_Full.pdf
10. Rossi S, et al, editors. Australian Medicines Handbook. January 2007 online edition. Adelaide: Australian Medicines Handbook Pty Ltd, 2007.
11. Liberopoulos EN, Elisaf MS, Tselepis AD, Archimandritis A, Kiskinis D, Cokkinos D, Mikhailidis DP. Upper gastrointestinal haemorrhage complicating antiplatelet treatment with aspirin and/or clopidogrel: Where we are now? Platelets 2006;17(1): 1–6.
12. Chan FKL, Ching JYL, Hung LCT, Wong VWS, Leung VKS, Kung NNS, Hui AJ, Wu JCY, Leung WK, Lee VWY, Lee KKC, Yuk TL, Lau JYW, To KF, Chan HLY, Chung SCS, Sung JJY. Clopidogrel versus Aspirin and Esomeprazole to Prevent Recurrent Ulcer Bleeding. NEJM 2005;352(3):238-244.
13. National Prescribing service. Prescribing Practice Review (PPR): using antithrombotics: maximising benefits; minimising risks. December 2003. Available at www.nps.org.au
14. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). European Heart Journal 2006;27:1979-2030.
15. Cleland JGF, Coletta AP, Lammiman M, Witte KK, Loh H, Nasir M, Clark AL. Clinical trials update from the European Society of Cardiology meeting 2005: CARE-HF extension study, ESSENTIAL, CIBIS-III, S-ICD, ISSUE-2, STRIDE-2, SOFA, IMAGINE, PREAMI, SIRIUS-II and ACTIVE. The European Journal of Heart Failure 7 2005;1070-1075.
16. The ACTIVE Writing Group on behalf of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet 2006; 367:1903-12.



UniSA

Veterans'MATES

Provided by: University of South Australia | Quality Use of Medicines and Pharmacy Research Centre

In association with: Department of General Practice, University of Adelaide | Department of Public Health, University of Adelaide | Repatriation General Hospital, Daw Park National Prescribing Service | Australian Medicines Handbook | Drug and Therapeutics Information Service