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Reducing the risk of adverse thrombotic events

The role of aspirin and clopidogrel

■ **Clopidogrel and aspirin both inhibit platelet aggregation, but have differing mechanisms of action that are additive in terms of antithrombotic function. The additive antithrombotic effect of aspirin and clopidogrel combination therapy provides additional clinical benefit compared to monotherapy in some circumstances, but the risk of major bleeding with combination therapy is greater than with either agent alone.**¹⁻³

Key clinical issues

The key clinical issues relating to the use of aspirin and clopidogrel in reducing the risk of adverse thrombotic events are summarised in *Table 1*.

Recommendations for therapy

A summary of recommendations for aspirin and clopidogrel therapy, alone or in combination, is provided in *Table 2*.

The clinical trial evidence

Stable cardiovascular disease

Two large clinical trials have compared the efficacy of aspirin and clopidogrel, alone or in combination, for the prevention of thrombotic events in stable cardiovascular disease (CVD). The patient profiles and results of these trials are summarised below.

Aspirin alone versus clopidogrel alone

The CAPRIE study was a randomised controlled trial that evaluated the relative efficacy of clopidogrel (75 mg once daily) versus aspirin (325 mg once daily) in reducing the risk of a composite outcome comprising ischaemic stroke, myocardial infarction and vascular death.⁴

The study population (N=19185) 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 1–3 years (mean 1.9 years). The main findings were:

- 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 arterial disease, there was a small benefit of clopidogrel over aspirin in reducing the composite outcome.

The overall result for all patients in all subgroups was a 0.5% absolute risk reduction in the composite outcome for clopidogrel compared to aspirin (event rate per year 5.3 vs. 5.8%; $p=0.043$). This means that you would need to treat about 200 patients with clopidogrel instead of aspirin for 2 years to prevent one adverse cardio- or cerebro-vascular outcome.

Aspirin and clopidogrel versus aspirin alone

The CHARISMA study was a randomised controlled trial that evaluated the relative efficacy of clopidogrel (75 mg/day) and low dose aspirin (75–162 mg/day) versus placebo and aspirin in reducing the risk of a composite outcome of myocardial infarction, stroke, or death from cardiovascular causes.²

The study population (N=15603) comprised patients with either clinically evident cardio- or cerebro-vascular disease, or multiple cardiovascular risk factors. Patients were followed for a median of 28 months. The main findings of the study were:

- the combination of clopidogrel and 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- or cerebro-vascular disease or multiple cardiovascular risk factors

- the risk of moderate to severe bleeding was increased with combination therapy.

The study did not support the use of combination antiplatelet therapy across a broad high cardiovascular risk population.

A subgroup analysis of the CHARISMA study examined outcomes in patients with either prior myocardial infarction, prior ischaemic stroke, or symptomatic peripheral arterial disease (N=9478).⁵ This analysis found that the rate of cardiovascular death, myocardial infarction or

stroke was significantly lower in the clopidogrel and aspirin group than in the placebo and aspirin group (7.3 vs. 8.8%, $p=0.01$). This equates to a number needed to treat of 67 patients for approximately 28 months. So, although the original CHARISMA study did not find a significant benefit of combination antiplatelet therapy across a high cardiovascular risk population comprising a mix of primary and secondary prevention, this subgroup analysis showed a benefit in terms of secondary prevention.

Table 1. Key clinical issues for aspirin and clopidogrel therapy

Monotherapy	
<ul style="list-style-type: none"> • Aspirin is a highly cost effective agent for primary and secondary prevention of cardiovascular and cerebrovascular thrombotic events¹ • Clopidogrel has been shown to be at least as effective as aspirin for the prevention of a composite outcome of cardiovascular and cerebrovascular events in patients with established atherosclerotic disease⁴ • Use aspirin in preference to clopidogrel for both primary and secondary prevention of thrombotic events in cardiovascular and cerebrovascular disease unless contraindicated • Aspirin and clopidogrel are each used for the management of arterial thrombosis, but not for venous thrombosis 	
Combination therapy	
<ul style="list-style-type: none"> • Aspirin and clopidogrel in combination are beneficial for the management of acute unstable angina and myocardial infarction, including situations where stenting or fibrinolytic therapy is employed.^{1,12–15} Duration of therapy will vary with clinical circumstances (see below) • In patients not presenting acutely, there is no significant benefit (and a significantly increased risk of bleeding) of adding clopidogrel to long term aspirin in people at high risk of atherothrombotic disease with or without established CVD. One important exception is the longer term management following acute coronary syndromes or stenting, where continued combination therapy may be beneficial despite achievement of a stable cardiovascular state • Aspirin and clopidogrel in combination have not been shown to be superior to either clopidogrel or aspirin alone in the secondary prevention of ischaemic stroke^{2,6,27} • If aspirin and clopidogrel in combination are ceased, monotherapy with aspirin should be continued indefinitely for secondary prevention of thrombotic events 	
Gastrointestinal bleeding prophylaxis	
<ul style="list-style-type: none"> • The use of a PPI decreases the rate of gastrointestinal bleeding in patients receiving either aspirin or clopidogrel²⁵ • Adding a PPI to aspirin may be more effective than changing from aspirin to clopidogrel in reducing the risk of a gastrointestinal bleed for patients with a history of aspirin induced gastrointestinal bleeding²⁶ 	
Atrial fibrillation	
<ul style="list-style-type: none"> • Warfarin should be used in preference to aspirin or 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^{19–22} 	

Table 2. Summary of recommendations for aspirin and clopidogrel therapy

	Primary prevention	Secondary prevention		
		Stable cardiovascular disease	Acute coronary syndrome	Coronary artery stent insertion
Aspirin monotherapy	If 5 year cardiovascular risk >15%*	Preferred option	Indefinitely 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 and clopidogrel combination therapy	No	No	Commence during initial phase; duration of combination therapy variable	Commence during initial phase; duration of combination therapy variable

*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%.²⁸ A commonly used cardiovascular risk calculator is the New Zealand Risk Calculator www.nzgg.org.nz/guidelines/0035/CVD_Risk_Full.pdf. Some guidelines suggest aspirin for primary prevention in people with a 5 year cardiovascular risk lower than 15%. For example, the US Preventive Services Task Force recommends use of aspirin in persons with a 5 year risk of greater than or equal to 3% (see [www.ahrq.gov/clinic/uspstf/uspstf.htm](http://www.ahrq.gov/clinic/uspstf/uspstf/uspstf.htm))

The authors are careful to acknowledge that any benefit from intensification of antithrombotic therapy beyond aspirin alone for the secondary prevention of adverse thrombotic events will need to be validated in future trials.⁵ The results of this subgroup analysis have been criticised on the basis that positive subgroups within negative trials such as CHARISMA are most commonly as a result of confounding or bias.⁶

A further subgroup analysis of CHARISMA did not support the use of clopidogrel and aspirin in a primary prevention population.⁷

A recent Cochrane systematic review, which included the CHARISMA trial, found that in patients at high risk of CVD but not presenting acutely, there is only weak evidence of benefit with aspirin and clopidogrel combination therapy.⁸ The review concluded that there is no statistically significant benefit of adding clopidogrel to long term administration of aspirin, but a significantly increased risk of bleeding, in people at high risk of atherothrombotic disease with or without evidence of established CVD.⁸ Therefore, clopidogrel should not be added to standard long term aspirin therapy for preventing thrombotic events in people at high risk of CVD and in those with established CVD.⁸

Acute coronary syndromes and stent implantation

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

Aspirin and clopidogrel in combination have a favourable benefit-risk ratio in acute coronary syndromes, particularly during the early phase.^{3,8–11} Benefit is in relation to reduced nonfatal myocardial infarction, not reduced stroke or death.^{1,12–15} Aspirin and clopidogrel in combination are clearly beneficial in preventing stent thrombosis.^{12–15}

The use of aspirin and 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, and, if used, the type of stent chosen. Whatever approach is taken, all patients should take low dose aspirin (100 mg daily) indefinitely if possible following acute coronary syndromes, stenting or coronary artery bypass surgery.

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.^{13,15}

For patients with STEMI use aspirin in combination with clopidogrel (optimal duration of clopidogrel therapy is unclear).¹⁵ Current Australian guidelines recommend clopidogrel therapy (75 mg daily) for at least 1 month after fibrinolytic therapy.¹²

Patients with coronary artery stenting

There are two types of stents used to keep coronary arteries patent, bare metal stents and drug eluting stents. Drug eluting stents contain an agent such as sirolimus, paclitaxel or zotarolimus and are designed to reduce the risk of early restenosis. However, drug eluting stents may carry a higher risk of late thrombosis than bare metal stents.^{1,13,14} The

optimal duration of aspirin and clopidogrel combination therapy after stent implantation is uncertain and continues to be debated in the biomedical literature.^{1,14,16–18}

One approach to clopidogrel therapy (300–600 mg loading dose peri-operatively then 75 mg daily) in combination with indefinite aspirin (100 mg daily) following stenting is illustrated in *Table 3*.^{13,15}

Discontinuation of any antiplatelet agent following acute coronary syndrome or stenting, including discontinuation for any form of surgery (cardiac, dental, other), 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.

Atrial fibrillation

For patients with atrial fibrillation (AF) at low risk of thromboembolic stroke (no other risk factors), aspirin (75–300 mg daily) is recommended.¹⁹ Aspirin provides less benefit than warfarin for patients with AF at moderate to high risk of stroke.²⁰ Clopidogrel is not recommended for the management of AF other than in patients undergoing stenting or revascularisation surgery.¹⁹

Warfarin substantially reduces the risk of stroke in AF, and warfarin should be considered for both primary and secondary prevention of stroke in all patients with AF at moderate to high risk of thromboembolic stroke, ie. AF and one or more of the following risk factors: age ≥ 65 years, hypertension, left ventricular dysfunction, heart failure, diabetes, previous stroke, previous transient ischaemic attack, previous thromboembolic event, mitral stenosis or prosthetic heart valve.¹⁹ Target INR is 2.0–3.0. Review ongoing indication for antiplatelet therapy when initiating warfarin.

Warfarin is superior to aspirin and clopidogrel combination therapy for the prevention of vascular events (including stroke) in patients with AF at high risk of stroke. A study of warfarin versus aspirin and clopidogrel in AF was stopped early due to clear superiority of warfarin.^{21,22}

There is no evidence supporting the use of warfarin-aspirin-clopidogrel triple therapy in AF.

Risks and harms

The adverse effects judged to be severe from the CAPRIE trial in the clopidogrel and aspirin groups are listed in *Table 4*.⁴

There was a significantly increased incidence of severe rash with clopidogrel compared to aspirin in the CAPRIE study.⁴ 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, agranulocytosis, thrombocytopenia, and neutropenia.^{1,23,24}

The CAPRIE study showed a significantly increased incidence of a severe gastrointestinal bleed with aspirin (0.72%) compared to clopidogrel (0.52%).⁴ This means that 500 patients would need to be treated with clopidogrel instead of aspirin for approximately 2 years to prevent one severe aspirin induced gastrointestinal bleed.⁴

Reducing the risk of gastrointestinal bleeding

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.⁴ The use of a proton pump inhibitor (PPI) decreases the rate of gastrointestinal bleeding in patients receiving aspirin or clopidogrel.²⁵

Treat with a PPI when starting or continuing aspirin or clopidogrel in patients with a recent history of upper gastrointestinal ulceration

Table 3. Duration of clopidogrel therapy after coronary artery stenting

Type of stent	Duration of clopidogrel therapy in combination with indefinite aspirin
Bare metal stent (elective)	Clopidogrel and aspirin for at least 1 month, then indefinite aspirin Clopidogrel and aspirin for up to 12 months in patients with low bleeding risk and extensive vascular disease or high risk of coronary artery thrombosis, then indefinite aspirin
Bare metal stent (acute coronary syndrome, ie. myocardial infarction or unstable angina)	Clopidogrel and aspirin for 12 months, then indefinite aspirin
Drug eluting stent	Clopidogrel and aspirin for at least 12 months irrespective of clinical context, then indefinite aspirin Indefinite clopidogrel and aspirin in high risk patients, eg: <ul style="list-style-type: none"> • left main artery stenting • multiple stents • long stent length • left ventricle dysfunction • diabetes • renal failure

Table 4. Severe[†] adverse effects – the 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%

[†] Defined as those adverse effects judged by the investigator to be clinically severe and which may have resulted in early permanent discontinuation of study drug

* Statistically significant ($p < 0.05$)

or bleeding (after ulcer healing and eradication of *Helicobacter pylori* infection).²⁵

A recent study found that *H. pylori* negative patients with a history of aspirin induced upper gastrointestinal bleeding (N=320) had a significantly lower incidence of recurrent bleeding when treated with aspirin and esomeprazole (incidence = 0.7%) than those swapped from aspirin to clopidogrel (incidence = 8.6%).²⁶

The combination of aspirin and clopidogrel increases the risk of upper gastrointestinal bleeding compared to monotherapy. However, there are no data on the effect of PPI prophylaxis in aspirin and clopidogrel combination therapy.²⁵

Future developments

Further studies are needed before firm recommendations can be made in regard to: clopidogrel monotherapy for the primary prevention of cardiovascular and cerebrovascular thrombotic events; and the optimal duration of aspirin and clopidogrel combination therapy following acute coronary syndromes and coronary artery stenting.

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