

Ischaemic heart disease

Key messages

- Inform the patient early of the need for multiple medications
- Use the simplest possible drug regimen: minimise the number of medications and daily doses
- Use low-dose aspirin in all patients with ischaemic heart disease; restrict clopidogrel to true aspirin intolerance
- Use beta blockers after myocardial infarction and in angina
- Continue ACE inhibitors after myocardial infarction in patients with left ventricular dysfunction or heart failure; consider in others at high cardiovascular risk
- Manage all cardiovascular risk factors including dyslipidaemia, hypertension and diabetes

Medication compliance is a significant issue in ischaemic heart disease because this requires management with multiple medications to reduce the risk of myocardial infarction or death.

Multiple medications are necessary in ischaemic heart disease

Inform the patient early of the benefits of multiple medications

Aspirin, HMG-CoA reductase inhibitors (statins), beta blockers and angiotensin-converting enzyme (ACE) inhibitors can prevent myocardial infarction and death. However, poor medication compliance is a problem in ischaemic heart disease; ensure the patient understands the benefits of treatments.¹⁻³

Simplify dosage regimens by limiting the number of daily doses

Limiting the number of daily doses can improve medication compliance.⁴ When possible, time doses with the patient's routine (e.g. meals) and limit the number of medications when they can treat co-existing conditions (e.g. a beta blocker can manage both angina and hypertension).



Guidance for health professionals to assist their patients with medication compliance is available in *NPS News 41* 'Targeting ischaemic heart disease: improving health outcomes with multiple medications' (www.nps.org.au/healthpro, go to 'Newsletter Index').

Manage hypertension, dyslipidaemia and diabetes to reduce the burden of ischaemic heart disease

Manage multiple risk factors concurrently to reduce total risk

Modifiable risk factors for ischaemic heart disease include smoking, elevated blood pressure and cholesterol level, physical inactivity and obesity.⁵ Managing risk factors can have additive effects in reducing myocardial infarction and death.^{6,7} Lifestyle interventions and drug treatments shown to reduce the risk of cardiovascular morbidity and mortality are also detailed in *NPS News 41*.

Depression is an independent risk factor that often coexists with ischaemic heart disease.⁷ Assess all patients for depression and manage with psychological and drug treatments when indicated.⁷

Treat all patients with ischaemic heart disease with aspirin⁶⁻⁸

Use aspirin 75–150 mg daily, unless contra-indicated or not tolerated

Low-dose aspirin is the antiplatelet drug of first choice. It is effective, has an established safety profile and is inexpensive.⁸ In a meta-analysis that included patients with ischaemic heart disease, aspirin prevented 36 serious vascular events (myocardial infarction, stroke or vascular death) per 1000 patients treated for 2 years.⁹ This outweighs the risk of major extracranial bleeding or haemorrhagic stroke (1–2 events per 1000 patients treated over 1 year).⁹

When is aspirin contra-indicated?

Aspirin is contra-indicated in patients with a history of intracranial haemorrhage, active or recent peptic ulcer disease, allergy to aspirin or bleeding disorder.¹⁰⁻¹²

Assess the signs and symptoms of aspirin allergy as reported by the patient, as they may describe intolerance that is not an allergy. Allergic reactions to aspirin include^{13,14}:

- rhinorrhoea, bronchospasm and/or laryngospasm
- urticaria, with or without angioedema
- anaphylaxis (e.g. hypotension, laryngeal oedema, pruritus).

Manage aspirin intolerance in those who should use aspirin

Severe dyspepsia, upper gastro-intestinal ulceration and/or bleeding are signs of aspirin intolerance.^{6,10,11} Advise patients with dyspepsia to take their aspirin with food and when possible avoid exacerbating medications (e.g. NSAIDs).¹⁰ Lowering the dose to 75 mg or using an enteric-coated formulation may also improve tolerance to aspirin but will not reduce the risk of gastro-intestinal bleeding.^{10,15}

Restrict clopidogrel* to patients with true aspirin intolerance^{6-8,10}

Clopidogrel (Iscover, Plavix) should not replace aspirin as the antiplatelet drug of first choice. It is as effective as aspirin in reducing serious vascular events, and as well tolerated, but is less cost effective.⁸ In the CAPRIE study, which included patients with ischaemic heart disease, the annual rate of myocardial infarction, ischaemic stroke or vascular death was 5.3% with clopidogrel and 5.8% with aspirin; there were also similar rates of gastro-intestinal bleeding (2.0% vs 2.7%) and intracranial bleeding (0.4% vs 0.5%).¹⁶

Should aspirin and clopidogrel be used together?

Clopidogrel may be considered when patients have recurrent vascular events while using aspirin.^{6,7} Check first that the patient has been compliant with aspirin therapy. Adding clopidogrel to aspirin increases the risk of major bleeding^{8,17,18} but the benefits outweigh the risks in unstable angina and non-ST segment elevation myocardial infarction, and when used for up to 12 months after coronary stent implantation.^{18–20}

Ticlopidine (Ticlid, Tilodene) may be used when there is intolerance to both clopidogrel and aspirin, but it may cause more serious adverse effects (e.g. neutropenia).^{6,10} Dipyridamole (Persantin) does not reduce the risk of myocardial infarction or death compared with aspirin; combined dipyridamole and aspirin (Asasantin SR) reduces the risk of non-fatal stroke and may be used for patients at high risk of cerebral ischaemic events.^{8,21,22}

* Refer to the *Schedule of Pharmaceutical Benefits* for criteria for prescribing clopidogrel on the PBS (authority required).

Start a statin irrespective of the cholesterol level

Statins prevent serious vascular events and death from any cause in patients with ischaemic heart disease

In the Heart Protection Study²³ involving 20 536 patients at high cardiovascular risk (e.g. history of angina or myocardial infarction), treatment with simvastatin (40 mg daily for 5 years) compared with placebo reduced the absolute risk of:

- any death by 1.8% (NNT[†] = 56)
- myocardial infarction, stroke, or any revascularisation by 5.4% (NNT = 19)
- any stroke by 1.4% (NNT = 71).

Patients with ischaemic heart disease had the greatest absolute risk reductions for serious vascular events (5.7%, NNT = 18).²³ These benefits were additional to those of aspirin, beta blockers and ACE inhibitors and were irrespective of pretreatment cholesterol levels.^{‡23}

† Number needed to treat (NNT) = number of patients who need to be treated with one therapy compared to another therapy for a period of time to prevent one event.

‡ Note that total cholesterol > 4 mmol/L is required for PBS subsidy of lipid-lowering drugs for patients with existing ischaemic heart disease.

Beta blockers improve survival after myocardial infarction

Continue beta blockers indefinitely after myocardial infarction, unless contra-indicated⁵

Beta blockers after myocardial infarction reduce re-infarction, sudden death, all-cause mortality and cardiovascular mortality.⁸ In a systematic review²⁴, beta blockers given immediately after myocardial infarction and continued for 6 months to 4 years reduced the annual rate of death from any cause by 1.2% (NNT for 2 years = 42). Benefits persist for as long as treatment is taken.⁸

Beta blockers (atenolol or metoprolol) are usually begun in hospital; however, GPs may still need to adjust the dose or initiate therapy.⁶ Avoid beta blockers with intrinsic sympathomimetic activity (oxprenolol, pindolol) as they have not shown benefit after myocardial infarction.^{10,24}

Choose bisoprolol (Bicor), carvedilol (Dilatrend, Kredex) or metoprolol controlled release (Toprol-XL) for patients after myocardial infarction who have left ventricular dysfunction or chronic heart failure.^{6-8,10} These beta blockers reduce the absolute risk of all-cause mortality, cardiac death or myocardial infarction by 3–6% when used with ACE inhibitors in these patients.²⁵⁻²⁷

Start beta blockers at a low dose and slowly titrate upwards.^{6,8} If beta blockers must be stopped, reduce the dose gradually over 2 weeks, or 4–6 weeks if treatment has continued for many years.¹⁰ Abrupt withdrawal can worsen angina or cause rebound hypertension or re-infarction.¹⁰

Adverse drug reactions are common with beta blockers.⁸ Using less lipid-soluble beta blockers (e.g. atenolol, bisoprolol) may alleviate adverse effects such as insomnia and nightmares.^{8,10} Taking the dose at night may reduce postural hypotension, tiredness or lethargy.⁸ Those with beta-1-receptor selectivity (e.g. atenolol, bisoprolol, metoprolol) may cause less bronchospasm, peripheral vasoconstriction and changes in blood glucose and may be suitable for patients who experience these adverse effects with other beta blockers.¹⁰

§ Contra-indications to beta blockers include reversible airways disease (e.g. asthma, COPD), bradycardia, second- or third-degree heart block, sick sinus syndrome, cardiogenic or hypovolaemic shock, severe hypotension, uncontrolled heart failure.^{8,10}

ACE inhibitors provide additional benefit after myocardial infarction

Use an ACE inhibitor long term after myocardial infarction in patients with left ventricular dysfunction or heart failure^{6,8}

Start an ACE inhibitor within 24–48 hours of myocardial infarction in patients with^{6-8,10}:

- previous myocardial infarction
- left ventricular dysfunction or heart failure
- anterior infarction
- heart rate > 80 beats per minute
- diabetes mellitus or hypertension.

In a systematic review, these patients had the greatest reductions in mortality when an ACE inhibitor was started early after myocardial infarction together with conventional treatment (e.g. beta blockers).²⁸ Consider starting an ACE inhibitor in other patients after myocardial infarction, as this review showed the absolute risk of mortality at 30 days was reduced by 0.5%.²⁸

In patients with left ventricular dysfunction or heart failure, long-term treatment reduces the absolute risk of death, myocardial infarction or re-admission for heart failure by 7.2% (NNT for 3 years = 14).²⁹

Consider long-term ACE inhibitors in patients with normal ventricular function but at greatest risk

Patients with ischaemic heart disease with normal ventricular function but at greatest cardiovascular risk (e.g. elevated total cholesterol, coexisting diabetes or hypertension) achieve the greatest absolute benefits from ACE inhibitors.^{30–32} In the HOPE study³⁰, ramipril reduced the absolute risk of cardiovascular mortality, myocardial infarction or stroke by 3.8% (NNT for 5 years = 26) in high-risk patients \geq 55 years of age.

Start ACE inhibitors at a low dose and titrate slowly according to blood pressure; hypotension can be significant, especially for patients \geq 75 years of age.^{6,10,28} Check serum creatinine and electrolytes at baseline and 1–2 weeks later.^{6,10} Renal dysfunction is uncommon but can occur in the presence of existing renal disease.^{6,29}

Angiotensin II receptor antagonists may be used when patients cannot tolerate ACE inhibitors.⁷

Prevent the symptoms of angina and relieve acute attacks

Beta blockers are first line for stable angina

Start a beta blocker (atenolol or metoprolol).⁶ Use short-acting nitrate preparations, such as glyceryl trinitrate spray, for acute anginal attacks or before any exertion likely to cause chest pain.⁶

Other drugs used for angina are as effective as beta blockers for symptom control.¹⁰ However, there is no evidence that nitrates or calcium-channel blockers (other than verapamil) prevent cardiovascular events.^{7,8,10}

Use calcium-channel blockers, nitrates and/or nicorandil when beta blockers are contra-indicated or do not control angina

When a beta blocker is contra-indicated, use a long-acting calcium-channel blocker that reduces heart rate (diltiazem or verapamil).⁶ Isosorbide mononitrate sustained-release tablets, glyceryl trinitrate patches or nicorandil (Ikorel) may also be substituted for a beta blocker.⁶

When a beta blocker alone does not control angina, add a long-acting dihydropyridine calcium-channel blocker (amlodipine or controlled-release nifedipine), a nitrate or nicorandil.⁶ Avoid using verapamil (use diltiazem with caution) with a beta blocker due to the risk of severe bradycardia and heart block.^{6,10}

Use combinations of a calcium-channel blocker, nitrate and/or nicorandil when these drugs alone do not control symptoms.⁶ Perhexiline (Pexsig) is used when angina is refractory to drug treatment or surgery (e.g. revascularisation) but can cause serious adverse effects such as peripheral neuropathy.^{6,10}

Observe a 10–12 hour nitrate-free interval with all regular nitrate preparations

To avoid the development of tolerance to the anti-anginal effects of nitrates, ensure a daily nitrate-free interval of 10–12 hours when symptoms are less likely (e.g. overnight).^{6,10} The formulation of sustained-release isosorbide mononitrate tablets allows for this interval.¹⁰ When using glyceryl trinitrate patches or isosorbide dinitrate tablets, dosing must be timed to incorporate a nitrate-free interval.¹⁰ Do not combine long-acting nitrate preparations as this leads to the rapid development of tolerance.⁶

Questions to review medication use in ischaemic heart disease

- Are all patients using aspirin (or an alternative if aspirin is contra-indicated or not tolerated)?
- Are all patients using a beta blocker (unless contra-indicated)?
- Are all patients using a statin (unless contra-indicated)?
- Have all patients with angina been prescribed a rapid-onset short-acting nitrate (sublingual glyceryl trinitrate, sublingual isosorbide dinitrate) for relief or prevention of acute angina attacks?
- Are target levels for blood pressure and lipids being achieved, and is blood glucose controlled?
- Is the interval between prescription renewals consistent with good compliance?

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.



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