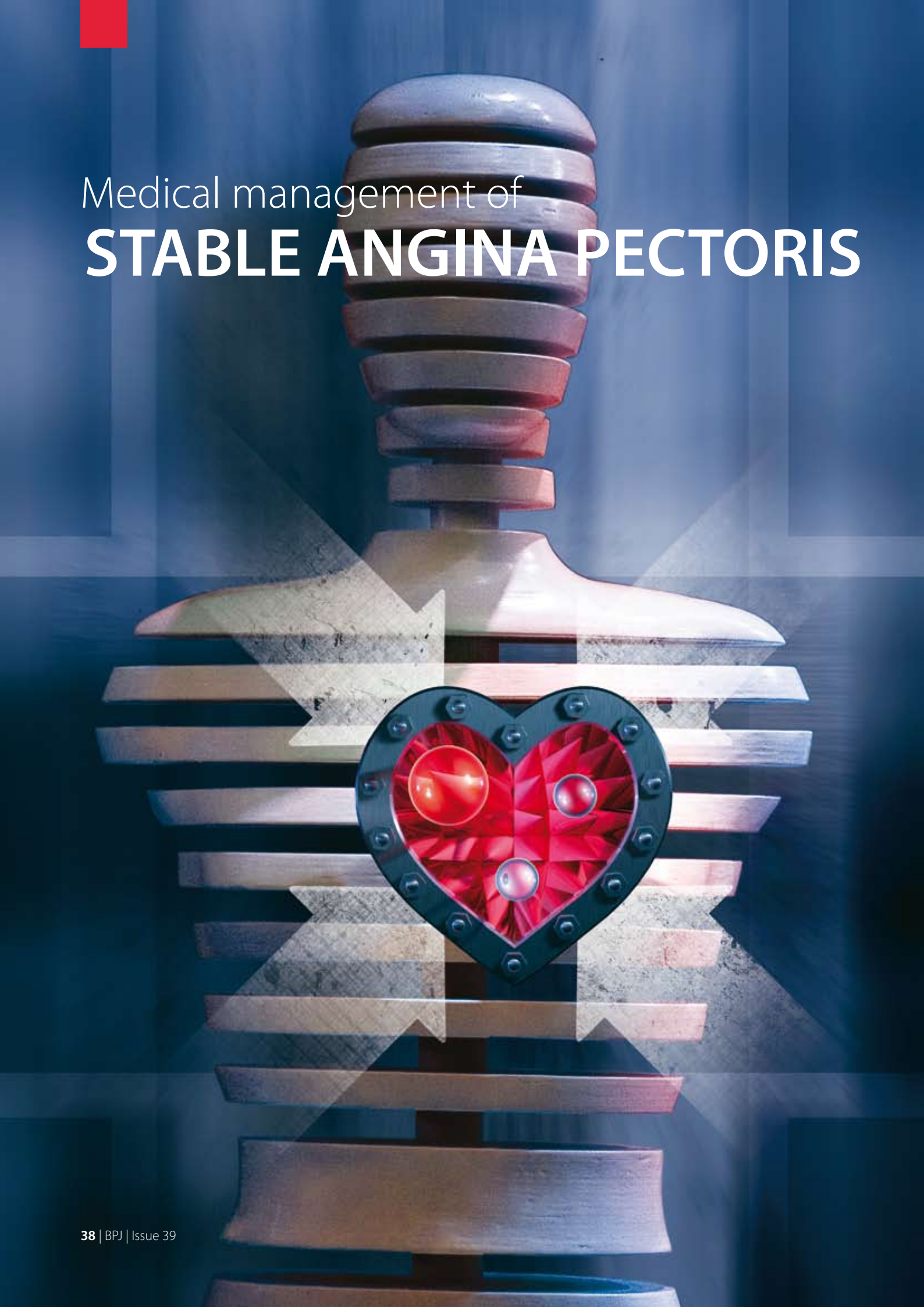
Medical management of

STABLE ANGINA PECTORIS



Defining angina

Angina is chest pain due to transient myocardial ischaemia, which usually occurs with physical activity or emotional stress, and is relieved by rest or sublingual nitroglycerin.[1,2] Angina is common, affecting 3.8% of people in New Zealand.[3] About half of patients with ischaemic heart disease initially present with symptoms consistent with a pattern of stable angina.[4]

Angina symptoms occur when there is insufficient blood supply to the heart at times of increased oxygen demand, e.g. exercise. This is most often due to coronary artery disease where atherosclerotic plaques in the coronary arteries cause narrowing of the lumen, reducing blood flow to the myocardium.[1]

Diagnosis of stable angina

Angina should be suspected in people presenting with tight, dull or heavy chest discomfort which is retrosternal or left-sided and may be radiating to the left arm, neck, jaw or back. The chest discomfort may also be associated with exertion or emotional stress and relieved within several minutes by rest. Women and older people are more likely to present with atypical symptoms of angina which include; breathlessness, nausea or belching.[1,2] Angina pain is not usually sharp or stabbing or influenced by respiration. Antacids and simple analgesia do not usually relieve the pain (also see "Other possible causes of chest pain", over page).[1,2]

A comprehensive history is required when angina is suspected as findings on physical examination and ECG are invariably normal even in patients presenting with acute coronary syndromes.

Key concepts

- All patients with suspected angina should be referred appropriately for diagnostic assessment including stress testing or similar further risk stratification, unless significant co-morbidities would preclude this.
- Results of this assessment will guide management, which may include revascularisation and pharmacological treatment, or pharmacological treatment alone
- While awaiting assessment, patients with suspected stable angina should be prescribed a sublingual nitrate and provided with an action plan for acute episodes of angina.
- Minimising the risk of future cardiovascular events is one of the most important aspects of the treatment of stable angina. This includes lifestyle modification and good control of other cardiovascular risk factors.
- An antiplatelet medicine, usually aspirin and a statin are appropriate for all patients with stable angina to prevent adverse cardiovascular events
- ACE inhibitors are appropriate for patients with co-existing conditions that would benefit from their use
- Beta-blockers are an appropriate first-line medical treatment to relieve the symptoms of angina. Calcium channel blockers or long-acting nitrates may be appropriate for those who do not tolerate or who have contraindications to beta-blockers.

All patients with suspected angina should be considered for referral for diagnostic assessment including stress testing or similar further risk stratification, unless significant co-morbidities preclude this.

Patients with pain at rest or on minimal exertion, or angina which seems to be progressing rapidly despite treatment, should be considered for referral to hospital as they may have unstable angina.[1]

Management of stable angina

The medical management of angina has two purposes; to prevent future myocardial infarction and death with vasculoprotective medicines and to reduce symptoms of angina with anti-ischaemic medicines. Further risk stratification is required with exercise tolerance testing or similar to identify patients who require angiography and possible revascularisation. Revascularisation is usually undertaken for symptomatic management of angina but also for prognostic benefit in a small subset of patients (e.g. those with left main coronary artery disease) identified at angiography (see Page 45 for further discussion of revascularisation).

Sublingual glyceryl trinitrate relieves acute anginal symptoms

Patients with newly diagnosed angina, or those with suspected angina waiting for further assessment, should be given a sublingual nitrate (either a spray or tablet) to use at the onset of angina. An angina action plan should be discussed with patients so they are aware of the appropriate actions to take if they experience chest pain.

Sublingual nitrates may also be used before activities that are known to bring on episodes of angina. Check first if a patient uses a phosphodiesterase (PDE5) inhibitor, e.g. sildenafil, as the concomitant use of this type of medicine with any form of nitrate is contraindicated.[5] If this combination cannot be avoided, most recommendations suggest withholding nitrate treatment for 24 hours after use of sildenafil and vardenafil and 48 hours after use of tadalafil.[6]

An example of an angina action plan can be found on the National Heart Foundation website (**www.heartfoundation.org.nz**). The plan contains the following instructions:

Other possible causes of chest pain[1]

Cardiac causes:	Non-cardiac causes:
Myocardial infarction – constant pain usually lasting more than 20 minutes. Nausea and vomiting may also be present	Oesophageal disorders, e.g. gastro-oesophageal reflux
Prinzmetal's angina – due to vasospasm. Pain is not precipitated by cardiac work and is associated with an unusual ECG	Musculoskeletal pain, e.g. costochondritis (swelling of a rib)
Unstable angina – increasingly frequent angina, angina at rest or prolonged episodes of severe angina	Psychological causes, e.g. panic attack, anxiety
Pericardial pain, e.g. pericarditis – pain influenced by breathing and change in posture	Pleural pain, e.g. infection, pulmonary embolism, tumour

- When an episode occurs, stop what you are doing and rest
- Use your glyceryl trinitrate spray (one puff) or one tablet (or as directed)
- Take a second dose five minutes after the first dose if the pain has not eased
- Call an ambulance if the pain has still not eased five minutes after the second dose or earlier if the pain is intensifying

Preventing future myocardial infarction and death

Reducing the risk of future cardiovascular events is the most important aspect of the treatment of stable angina. This is achieved by lifestyle modification, e.g. eating a healthy diet, smoking cessation and exercising regularly and good control of other cardiovascular risk factors, e.g. diabetes and hypertension – target blood pressure: <130/80 and target HbA_{1c}: 53 mmol/mol (see Page 54 for information on change of units).[7]

All patients with stable angina should be treated with aspirin and a statin, unless contraindicated.[1] ACE inhibitors are recommended for patients with co-existing conditions that would benefit from this treatment (Table 2).

All patients with stable angina should be taking aspirin or another antiplatelet medicine

All patients with stable angina should be taking aspirin 100 mg unless contraindicated, not tolerated or there is an indication for anticoagulation (e.g. patient also has atrial fibrillation). Evidence has shown that in people with cardiovascular disease, including those with stable angina, antiplatelet treatment leads to a significant reduction in serious vascular events, non-fatal myocardial infarction, non-fatal stroke and vascular mortality.[8]

Clopidogrel is an option for people who are intolerant of, or have contraindications to, aspirin. It is also used for 12 months in combination with aspirin for patients who have had percutaneous coronary intervention (PCI).[2]

See consensus statement on antithrombotic medicines (Page 10)

Table 2: Medicines to improve prognosis for stable angina (adapted from Abrams, 2005)[2]

Medicine	Indications	Comment
Aspirin	All patients, except those with aspirin allergy or intolerance. Clopidogrel may be considered as an alternative.	Dose: 100 mg daily
Statin	All patients, aiming to achieve LDL cholesterol of < 2 mmol/L and total cholesterol < 4 mmol/L	Dose: 40 mg simvastatin initially or switch to atorvastatin 40mg if targets not achieved.
ACE inhibitor	Patients with co-existing indications for ACE inhibitors; hypertension, diabetes, heart failure, asymptomatic left ventricular dysfunction or previous myocardial infarction	Uncertain usefulness in patients without co-existing indications for ACE inhibitors

All patients with stable angina should be taking a statin

All patients with stable angina should be taking a statin, unless contraindicated or not tolerated. Simvastatin 40 mg is recommended initially. If the treatment target is not achieved with this dose, switch to atorvastatin in preference to uptitrating simvastatin. High dose (80 mg) simvastatin has been associated with an increased incidence of rhabodomyolysis (see "Precautions with high-dose simvastatin" below).[9, 10] In clinical trials, statins reduced all-cause and coronary mortality, myocardial infarction, the need for coronary revascularisation and fatal or non-fatal stroke in patients with stable angina.[8]

ACE inhibitors are recommended for patients with coexisting indications for their use

There is conflicting evidence as to whether ACE inhibitors are of benefit in the treatment of stable angina. ACE inhibitors may not improve symptoms or long-term prognosis in people with stable angina, therefore they are only recommended for patients with co-existing conditions that would benefit from their use, e.g. hypertension, diabetes, heart failure, asymptomatic left ventricular dysfunction or previous myocardial infarction.[2]

Management of symptoms – beta-blockers, calcium channel blockers and nitrates

Beta blockers, calcium channel blockers and nitrates are used to manage the symptoms of angina (Table 3). While these medicines have been shown to reduce anginal symptoms, i.e. prolong the duration of exercise before the onset of angina and reduce the frequency of angina, none have been shown to prevent myocardial infarction or death in people being treated for chronic stable angina.[2, 12]

These medicines prevent attacks of angina by doing one or both of the following:[12]

- Decreasing myocardial oxygen consumption (by lowering heart rate, blood pressure, myocardial loading, or myocardial contractility)
- Increasing myocardial oxygen supply (by increasing coronary blood flow)

A beta-blocker is a suitable first-line regular treatment to reduce the symptoms of stable angina

Beta-blockers lessen anginal symptoms by reducing heart rate and myocardial contractility and decreasing

Precautions with high-dose simvastatin

Recently the United States Food and Drug Administration (FDA) recommended restricting the use of high-dose simvastatin (80 mg) because of the increased risk of myopathy. They advised that simvastatin 80 mg should only be prescribed for those already taking this dose for longer than 12 months with no signs of myopathy and that simvastatin 80 mg should not be started in newly diagnosed patients or in those already taking lower doses of simvastatin. Medsafe advises that high dose simvastatin should only be prescribed for patients who have not reached their target cholesterol level with a lower dose or with alternative medicines.[11]

See: "High dose simvastatin increases myopathy risk". Prescriber Update, Sept 2011. Available from: www.medsafe.govt.nz/profs/PUarticles.asp

See: "Simvastatin: risk associated with higher doses" BPJ 38 (Sept, 2011)

Table 3: Anti-anginal medicines (adapted from Abrams, 2005)[2]

Medicine	Dose	Adverse effects	Cautions
Beta-blockers			
Metoprolol tartrate	50–100 mg twice daily	Fatigue, shortness of breath, wheezing, weakness, dizziness, cold extremities	Caution with use in people with chronic obstructive pulmonary disease, diabetes, depression. Avoid in those with heart block
Metoprolol succinate	95–190 mg once daily		
Atenolol	25–100 mg once daily		
Calcium channel blockers			
Amlodipine	5–10 mg once daily	Headache, flushing, dizziness, oedema Verapamil may cause constipation	Verapamil and diltiazem should be used with caution in patients with low ejection fraction (< 30%) or with sinus or atrioventricular nodal dysfunction
Felodipine, sustained release	5–10 mg once daily		
Nifedipine, sustained release	30–90 mg once daily		
Verapamil, sustained release	120–240 mg once or twice daily		
Diltiazem, sustained release	120–360 mg once daily		
Nitrates			
Isosorbide mononitrate, long-acting formulations	40–120 mg once daily	Headache, dizziness, nausea, palpitations Tolerance is a major limiting factor	Contraindicated with phosphodiesterase (PDE5) inhibitors e.g. sildenafil
Nitroglycerin, patch	Initially one (5 mg/24 hour) patch daily. Maintenance: usually one (10 mg/24 hour) patch daily; may increase to two (10 mg/24 hour) patches daily. Used for no more than 12–14 hours per 24 hours		

Notes:

There is some evidence that the sudden withdrawal of a beta-blocker or a calcium channel blocker may cause an exacerbation of angina and therefore a gradual reduction of dose is preferable when either medicine needs to be stopped.[17]

Long-acting isosorbide mononitrate can be taken either in the morning or the evening, depending of the time of day that angina attacks usually occur.[18] Twice daily dosing of long-acting isosorbide mononitrate is not appropriate.[19]

blood pressure. This results in decreased myocardial oxygen demand.[12] They can be considered as the first-line treatment for reducing the symptoms of stable angina.

Beta-blockers have not specifically been shown to reduce the rate of coronary events or mortality in patients with stable angina, but there is evidence that they improve prognosis in those who have previously had a myocardial infarction or have heart failure.[2]

All beta-blockers appear to be equally effective in treating stable angina, however, cardioselective beta-blockers, such as metoprolol and atenolol, are preferred because they have advantages in terms of their adverse effect profile and precautions when compared with non-selective beta-blockers.[12, 13]

Calcium channel blockers are appropriate if beta-blockers are contraindicated or not tolerated

Calcium channel blockers can be considered second-line for treating the symptoms of angina if a beta-blocker is contraindicated or not tolerated. Calcium channel blockers have been shown to be equally effective as beta-blockers in the management of stable angina, i.e. studies have shown no difference in nitroglycerin use or exercise time and no evidence of a difference in total or cardiovascular mortality, or in risk of myocardial infarction or stroke.[13] The recently updated National Institute for Health and Clinical Excellence (NICE) guideline for the management of stable angina considers either a beta-blocker or a calcium channel blocker as appropriate first-line treatment.[14]

Calcium channel blockers minimise symptoms of angina by dilating coronary and other arteries and increasing coronary blood flow. Non-dihydropyridine calcium channel blockers (verapamil and diltiazem) also reduce myocardial contractility and heart rate and decrease myocardial oxygen demand.[12]

All calcium channel blockers are effective in the treatment of stable angina. Long-acting calcium channel blockers, e.g. amlodipine, or sustained released formulations of short-acting calcium channel blockers, e.g. felodipine, nifedipine, verapamil and diltiazem, are preferred.[12] Short-acting calcium channel blockers, particularly nifedipine, are not recommended because they cause reflex tachycardia which may exacerbate ischaemia and have been associated with an increased risk of cardiovascular events.[15]

A rate limiting calcium channel blocker such as verapamil or diltiazem is a suitable alternative for patients who have had a previous MI who do not tolerate beta-blockers or have a contraindication to their use.[12] However, verapamil is not suitable in patients with heart failure.

If combining beta-blockers and calcium channel blockers, it is appropriate to use a non-rate limiting (dihydropyridine) calcium channel blocker such as felodipine or amlodipine. Diltiazem may be cautiously used in combination with a beta-blocker when heart rate remains above 60 beats per minute despite maximum tolerated doses of beta-blocker. Verapamil is not suitable in combination with beta-blockers because severe bradycardia and heart failure can occur.[1]

A long-acting nitrate can be used if a beta-blocker or calcium channel blocker are not tolerated or contraindicated

Long acting nitrates, e.g. isosorbide mononitrate, are a suitable choice as monotherapy for people who are intolerant of beta-blockers or calcium channel blockers or if those medicines are contraindicated. They may also be used in combination with a beta-blocker or calcium channel blocker. Nitrates produce venous and arterial dilatation, reducing ventricular pre-load and after-load which lowers myocardial oxygen demand and improves subendocardial blood flow.[8]

Nitrate tolerance is a major problem with long-term use, and needs to be avoided because it diminishes the response to short acting nitrates.[16] A "nitrate-free" interval of 12–14 hours each day is required to avoid nitrate tolerance. This is achieved with once daily dosing of modified release tablets, e.g. Corangin, Duride.

Other medicines used to treat angina

Nicorandil is an option if other treatments have failed, are not tolerated or are contraindicated, however, it is not funded in New Zealand. Nicorandil is a potassium channel activator with nitrate like effects. Tolerance to its effects may occur with chronic dosing, however, cross tolerance with nitrates does not appear to be a problem.[12] Nicorandil can be used as monotherapy or in combination with a beta-blocker or calcium channel blocker if symptoms are not controlled.[14]

Perhexiline may be used when angina is unable to be managed with pharmacological treatment or surgery, but it can cause serious adverse effects such as peripheral neuropathy.[20] It is only available in New Zealand under Special Authority.

Revascularisation to treat symptoms of angina

Revascularisation involves either percutaneous coronary intervention (PCI) or coronary-artery bypass surgery (CABG). Revascularisation is most frequently performed for symptom relief but a small percentage of patients also have a prognostic benefit (usually those who are at high risk). Stress testing or similar further risk stratification is required in all patients with stable angina unless co-morbidities would prohibit revascularisation.

Patients who may benefit from revascularisation include:

- Those at high-risk, e.g. patients with symptomatic multi-vessel disease, proximal left anterior descending or left main artery disease, left ventricular systolic dysfunction, diabetes or a large ischaemic burden (referring to all angina episodes, including silent angina).[2]
- Those who have failed to respond to pharmacological treatment, i.e. patient is still experiencing symptoms while on two anti-anginal drugs.

Secondary prevention measures are still important because PCI does not change the natural history of coronary artery disease where non-obstructive plaques may suddenly progress to high grade stenosis or even total vessel occlusion.[21] Repeat revascularisation may be necessary after PCI or CABG, but is more common after PCI.[21]

Optimal medical treatment or revascularisation?

Clinical trial evidence suggests that revascularisation initially provides better symptom control than pharmacological treatment,[21] but in the long-term, it appears that there is little difference between the two approaches to angina symptom control.

Two large, recent clinical trials have compared the effectiveness of pharmacological treatment to revascularisation in the management of chronic stable angina. Earlier trials may no longer be relevant to modern clinical practice due to advances in PCI techniques (e.g. the use of stents) and improvements in the optimal use of medicines for both symptom control and risk factor reduction.

The Clinical Outcomes Utilising Revascularisation and Aggressive Drug Evaluation (COURAGE) trial was a randomised controlled trial (RCT) which randomly assigned 2287 patients with angina and significant coronary artery disease to either optimal medical treatment alone or PCI and optimal medical treatment.[22] High-risk patients who were likely to have a survival benefit from revascularisation (usually CABG) were excluded from the trial. Optimal medical treatment included medicines to prevent angina; beta blockers, calcium channel blockers, nitrates individually or in combination and an ACE inhibitor or angiotensin receptor blocker (ARB), as well as an antiplatelet medicine and a statin. The results showed no significant difference in the risk of death, myocardial infarction, or rates of hospitalisation between the two groups. Significantly more patients in the PCI group were free of angina at one and three year follow-up, however, by five years there was no significant difference between the groups.[22]

A follow-up study using an angina specific health questionnaire compared the quality of life for patients in each group and found marked improvement in the health status of patients in both groups.[23] Although patients in the PCI group initially reported greater benefit, by three years there was no significant difference in health status between the two groups. The most benefit with PCI, as indicated by quality of life measures, was in a subgroup of patients who, at baseline, had the most severe angina.[23]

The Bypass Angioplasty Revascularisation Investigation 2 Diabetes (BARI) trial, also a RCT involving 2368 patients randomised to PCI and intensive medical treatment or intensive medical treatment alone, reported similar results to those reported for the COURAGE trial, with no significant difference in the primary outcome of death from any cause or in the rate of major cardiovascular events.[24]

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References

1. Clinical Knowledge Summaries (CKS). Stable Angina. CKS, 2009. Available from: www.cks.nhs.uk/angina (Accessed Sep, 2011).
2. Abrams J. Chronic stable angina. N Engl J Med 2005;352(24):2524-33.
3. Ministry of Health. Ischaemic heart disease. Potrait of Health. Wellington: Ministry of Health, 2006/2007.
4. Marzelli M, Affinito S, Focardi M. Changing scenario in chronic ischemic heart disease: Therapeutic implications. Am J Cardiol 2006;98(5A).
5. Douglas Pharmaceuticals Ltd. Nitrolingual Pumpspray. Medicine Data sheet. 2003. Available from: www.medsafe.govt.nz (Accessed Sep, 2011).
6. Beckman T, Abu-Lebdeh H, Mynderse L. Evaluation and medical management of erectile dysfunction. Mayo Clin Proc 2006;81(3):385-90.
7. Yusuf S, Natarajan M, Karthikeyan G, Taggart D. Management of stable angina. Brit Med J 2009;339(7719):470-1.
8. Scottish Intercollegiate Guidelines Network (SIGN). Management of stable angina. Edinburgh: SIGN, 2007. Available from: www.sign.ac.uk (Accessed Sep, 2011).
9. New Zealand Guidelines Group. New Zealand Cardiovascular Guidelines Handbook: A summary resource for primary care practitioners. 2nd ed. Wellington: NZGG, 2009.
10. National Institute for Health and Clinical Excellence (NICE). Lipid modification. London: NICE, 2008. Available from: www.nice.org.uk (Accessed Sep, 2011).
11. Medsafe. High dose simvastatin increases myopathy risk. Prescriber Update Sept 2011;32(3):23.
12. Fox K, Garcia M, Ardissino D, et al. Guidelines on the management of stable angina pectoris: executive summary. Eur Heart J 2006;27(11):1341-81.
13. Kannam J, Aroesty J, Gersh B. Overview of the management of stable angina pectoris. UpToDate, 2010. Available from: www.uptodate.com (Accessed Sep, 2011).
14. National Institute for Health and Clinical Excellence (NICE). Management of stable angina London: NICE, 2011. Available from: www.nice.org.uk (Accessed Sep, 2011).
15. Kannam J, Aroesty J, Gersh B. Calcium channel blockers in the management of stable angina pectoris. UpToDate, 2010. Available from: www.uptodate.com (Accessed Sep, 2011).
16. Kannam J, Aroesty J, Gersh B. Nitrates in the management of stable angina pectoris. UpToDate, 2010. Available from: www.uptodate.com (Accessed Sep, 2011).
17. British National Formulary (BNF). BNF 60. London: BMJ Publishing Group and Royal Pharmaceutical Society of Great Britain, 2010.
18. Novartis New Zealand Ltd. Corangin. Medicine Data sheet. 2009. Available from: www.medsafe.govt.nz (Accessed Sep, 2011).
19. Mylan New Zealand Ltd. Duride. Medicine Data sheet. 2009. Available from: www.medsafe.govt.nz (Accessed Sep, 2011).
20. National Prescribing Service (NPS) Australia. Ischaemic heart disease. Prescribing Practice Review 31. NPS, 2005.
21. Pfisterer M, Zellweger M, Gersh B. Management of stable coronary artery disease. Lancet 2010;375:763-72.
22. Boden W, O'Rourke R, Teo K, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356(15):1503-16.
23. Weintraub W, Spertus J, Kolm P, et al. Effect of PCI on quality of life in patients with stable coronary disease. N Engl J Med 2008;358(7):677-87.
24. The BARI 2D Study Group. A randomised trial of therapies for Type 2 diabetes and coronary artery disease. N Engl J Med 2009;360(24):2503-15.