

# Medical management of chronic stable angina

## SUMMARY

Stable angina pectoris is characterised by typical exertional chest pain that is relieved by rest or nitrates.

Risk stratification of patients is important to define prognosis, to guide medical management and to select patients suitable for revascularisation.

Medical treatment aims to relieve angina and prevent cardiovascular events. Beta blockers and calcium channel antagonists are first-line options for treatment. Short-acting nitrates can be used for symptom relief.

Low-dose aspirin and statins are prescribed to prevent cardiovascular events.

## Introduction

Cardiovascular disease is the leading cause of death in Australia. Angina pectoris affects more than 353 000 Australians and accounts for approximately 72 000 hospital admissions annually.<sup>1</sup>

Angina is caused by myocardial ischaemia. Chronic stable angina has a consistent duration and severity, and is provoked by a predictable level of exertion. It can also be provoked by emotional stress. The pain is relieved by rest or short-acting nitrates.<sup>2</sup>

The aim of medical therapy is to minimise symptoms and retard disease progression. This requires lifestyle modification as well as drug treatment.<sup>3-6</sup>

## Diagnosis

The diagnosis of angina is usually suspected from a thorough history and examination. Patients should have an ECG and undergo assessment for cardiovascular risk factors such as diabetes<sup>7</sup> and hyperlipidaemia.<sup>4</sup> An echocardiograph can help with the assessment of left ventricular function.<sup>8</sup> Once the clinical diagnosis of stable coronary artery disease is established, the patient's risk of future cardiovascular events is evaluated.

## Risk stratification

In patients with stable coronary artery disease the risk of cardiovascular mortality may be predicted by clinical and demographic variables. These include gender,<sup>9</sup> left ventricular function,<sup>8,9</sup> the provocation of myocardial ischaemia with stress testing,<sup>10,11</sup> and the severity of coronary artery disease seen on angiography.<sup>3,5,8,12,13</sup> Patients at high risk of cardiovascular events may need revascularisation<sup>14,15</sup> as well as medical therapy.

## Clinical evaluation

The history, examination, ECG and laboratory tests provide important prognostic information. Increasing age, chronic kidney disease, diabetes, hypertension, current smoking, previous myocardial infarction, hypercholesterolaemia and heart failure are predictive of adverse outcomes.<sup>9</sup>

## Echocardiography

Echocardiography provides information about left ventricular function, and regional wall motion abnormalities that may be related to infarction or ischaemia. In patients with stable coronary artery disease, left ventricular ejection fraction is the strongest predictor of long-term survival. The 12-year survival of medically treated patients with ejection fractions greater than 50% is 73%, and 54% if the ejection fraction is between 35% and 49%. Survival is only 21% if the ejection fraction is less than 35%.<sup>8</sup>

## Stress testing

Stress testing on a treadmill or bicycle is recommended for patients with normal resting ECGs who can exercise.<sup>2,10</sup> Symptoms such as chest discomfort and dyspnoea, exercise workload, blood pressure response and ECG changes consistent with ischaemia are recorded as the patient exercises.<sup>10</sup> Abnormalities present at rest such as atrial fibrillation, left ventricular hypertrophy, intraventricular conduction abnormalities and ECG changes related to electrolyte imbalance or digoxin will result in more frequent false-positive results. Stress testing is also used to evaluate the efficacy of revascularisation and medical treatment, and to direct the prescription of exercise.<sup>2,3,16</sup>

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## Key words

beta blockers, calcium channel antagonists, glyceryl trinitrate, stable angina

*Aust Prescr* 2015;38:131-6

Exercise or pharmacological stress echocardiography may be necessary to demonstrate ischaemic changes in left ventricular systolic function in patients whose resting ECGs<sup>5</sup> are abnormal or unable to be interpreted (because of left bundle branch block, paced rhythm). Exercise echocardiography provides information about cardiac structure and function, exercise workload, heart rate and rhythm and blood pressure response. Pharmacological testing may be necessary in patients who cannot exercise.<sup>3,5</sup> Myocardial perfusion scintigraphy is an alternative for those with uninterpretable ECGs or inability to exercise.<sup>11</sup>

**Imaging of coronary arteries**

Computed tomography (CT) of the coronary arteries without contrast injection can show coronary calcification,<sup>17</sup> although correlation with the degree of luminal narrowing is poor.

Intravenous injection of a contrast agent allows visualisation of the vessel lumen. The severity and extent of the lesions determine the risk of a cardiovascular event (Table 1).<sup>12,16,18-20</sup> CT angiography exposes patients to radiation. It should be reserved for those who are not overweight, without excessive coronary calcium (Agatston score <400) and who are in sinus rhythm with resting heart rates of 65 beats/minute or less, with or without medication. If patients have a high risk of cardiovascular events or if their symptoms are not adequately controlled, invasive coronary angiography may be indicated. It helps define prognosis<sup>5</sup> and options for revascularisation. The 12-year survival rate in medically treated patients is 74% for single-vessel disease, 59% for two-vessel disease and 50% for three-vessel coronary disease.<sup>12</sup> Severe stenosis of the left main coronary artery or proximal left anterior descending artery has a poor prognosis if not revascularised.<sup>8</sup> Conversely, the exclusion of significant obstructive disease on angiography is reassuring.<sup>19</sup>

**Lifestyle modification**

The management of cardiovascular risk factors plays an important role in the overall care of patients with chronic stable angina (Fig.). Modifiable cardiovascular risk factors include hypertension, hypercholesterolaemia, smoking, diabetes, obesity

and sedentary lifestyle. Regular exercise, a healthy diet and maintenance of ideal weight reduce the risk of adverse cardiovascular events. Smoking is a strong and independent risk factor for coronary artery disease so efforts to quit should be encouraged and supported. Control of blood pressure and diabetes is paramount to reducing cardiovascular morbidity and mortality. Patients should be screened for sleep apnoea. Annual influenza vaccination is recommended.<sup>21,22</sup>

**Prevention of cardiovascular events**

Low-dose aspirin reduces major cardiac events by up to 30% and should be prescribed to patients with coronary artery disease.<sup>3</sup> Clopidogrel is an alternative option for patients intolerant of aspirin. Patients with established coronary artery disease should be prescribed statin therapy irrespective of their lipid profile to slow the progression or even promote regression of coronary atherosclerosis.<sup>4</sup>

Angiotensin converting enzyme (ACE) inhibitors should be prescribed for patients with stable angina, particularly those who have hypertension, left ventricular dysfunction, diabetes<sup>6</sup> or chronic kidney disease. Adverse effects include a persistent cough, hyperkalaemia and, rarely, angioedema. Angiotensin receptor antagonists may be used for those who do not tolerate ACE inhibitors.<sup>3</sup>

**Drug therapy**

The aim of drug therapy (Table 2)<sup>2,3,5,23</sup> is to minimise symptoms and prevent progression of coronary artery disease. Short-acting nitrates are prescribed to relieve acute symptoms or anticipated angina. Drug therapy aims to reduce myocardial oxygen demand or increase coronary blood supply. The choice of drugs is influenced by factors such as comorbidities, tolerance and adverse effects.

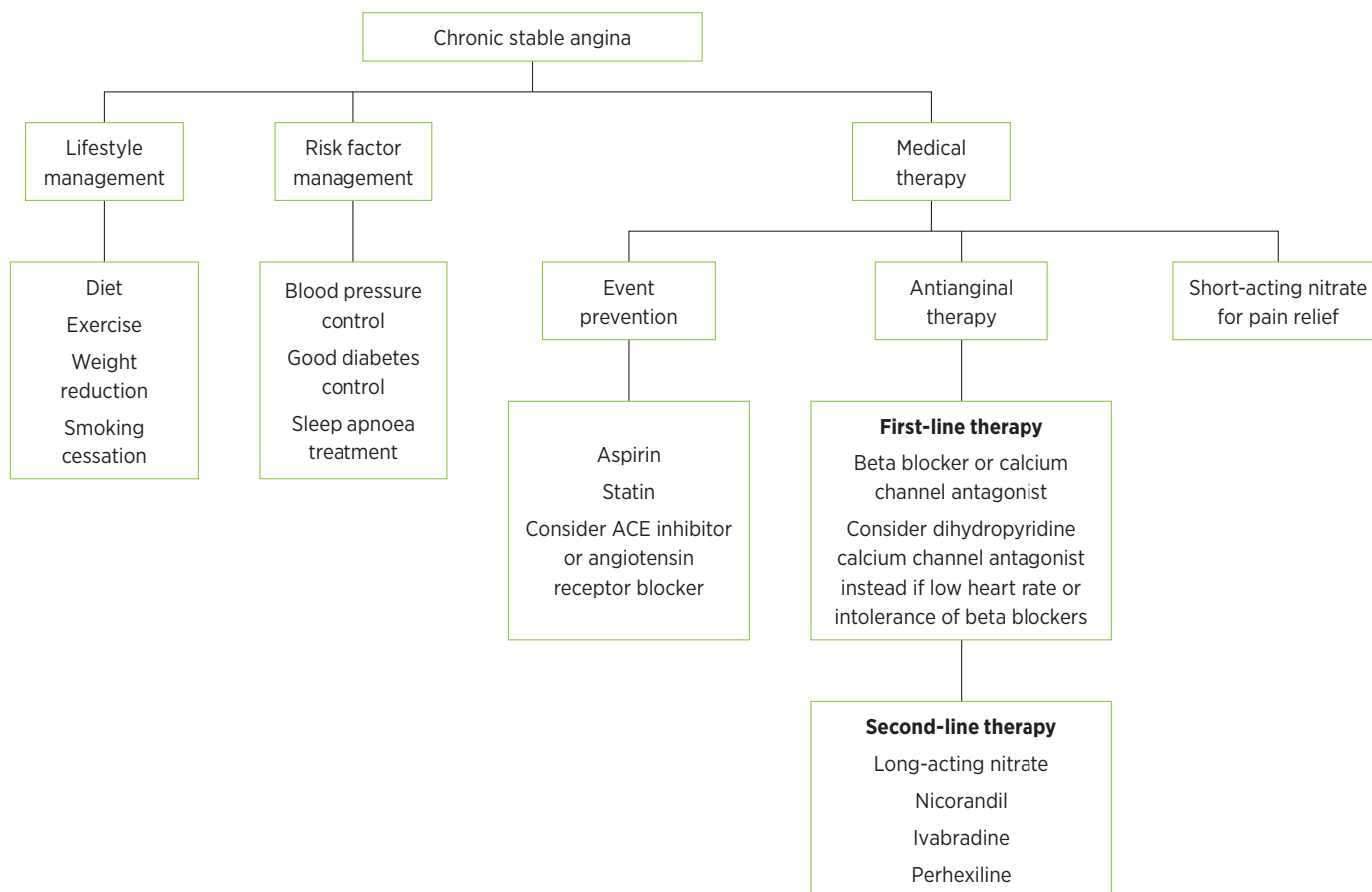
**Beta blockers**

Beta blockers are first-line therapy to reduce angina and improve exercise tolerance by limiting the heart rate response to exercise.<sup>3,5</sup> Although they reduce the risk of cardiovascular death and myocardial infarction by 30% in post-infarct patients, their benefits in those with stable coronary artery disease are less certain.<sup>3,24</sup>

Table 1 Risk stratification by CT coronary angiography<sup>12,16,18-20</sup>

Risk of cardiovascular event	Angiographic findings
High	Disease of left main or left anterior descending coronary artery, three-vessel disease with proximal stenoses
Intermediate	Significant lesion in large and proximal coronary artery, but no high-risk features
Low	Normal coronary artery or non-obstructive plaques

Fig. Management of chronic stable angina



The drugs most widely used for angina in the context of normal left ventricular function are the beta<sub>1</sub>-selective drugs such as metoprolol and atenolol. Adverse effects include fatigue, altered glucose, bronchospasm, bradycardia, impotence and postural hypotension. Switching to a less lipophilic beta blocker such as atenolol may alleviate symptoms such as insomnia or nightmares. They are usually well tolerated in patients with emphysema who have predominantly fixed airways disease. Beta blockers should not be stopped abruptly due to the risk of rebound hypertension or ischaemia.

**Calcium channel antagonists**

Calcium channel antagonists improve symptoms of angina via coronary and peripheral vasodilation. They are indicated for those who cannot tolerate or have insufficient control of ischaemic symptoms on beta blockers alone.

Non-dihydropyridine drugs such as verapamil and diltiazem also reduce heart rate and contractility. Verapamil has comparable antianginal activity to metoprolol and can be useful for treatment of supraventricular arrhythmias and hypertension.

However, verapamil should be avoided in patients taking beta blockers owing to the risk of heart block, and in those with heart failure because of its negative inotropic effect. Diltiazem has a low adverse effect profile with a modest negative inotropic effect. Care should be taken when prescribing in combination with a beta blocker and in patients with left ventricular dysfunction.

The dihydropyridines such as amlodipine, felodipine and lercanidipine have greater vascular selectivity and minimal negative inotropic properties. They are therefore safer in patients with left ventricular dysfunction. Amlodipine is an effective once-daily antianginal drug that can be used in combination with a beta blocker. Long-acting nifedipine is a proven antianginal drug and is most effective when used in conjunction with a beta blocker.<sup>25</sup>

Contraindications to nifedipine use include severe aortic stenosis, obstructive cardiomyopathy and heart failure. Short-acting nifedipine is rarely used as monotherapy due to reflex tachycardia, which can worsen ischaemia and has been associated with a dose-related increase in mortality. It should therefore be avoided.

Table 2 Drugs for angina<sup>2,3,5,23</sup>

Drug	Indications	Mechanism	Adverse effects	Precautions
Nitrates (short- and long-acting)	Relief of acute or anticipated pain (short-acting)  Prevention of angina (long-acting)	Systemic and coronary vasodilation	Headache Hypotension Syncope Reflex tachycardia	Avoid sildenafil and similar drugs  Tolerance with long-acting nitrates
Beta blockers	First-line therapy for exertional angina and after myocardial infarction	Reduce blood pressure, heart rate and contractility  Prolongs diastolic filling time	Fatigue Altered glucose Bradycardia Heart block Impotence Bronchospasm Peripheral vasoconstriction Hypotension Insomnia or nightmares	Avoid with verapamil because of risk of bradycardia  Avoid in asthma, 2nd and 3rd degree heart block and acute heart failure
Dihydropyridine calcium channel antagonists (e.g. amlodipine, felodipine, nifedipine)	Alternative, or in addition, to a beta blocker  Coronary spasm	Systemic and coronary vasodilator	Hypotension Peripheral oedema Headache Palpitations Flushing	Avoid short-acting nifedipine because of reflex tachycardia and increased mortality in ischaemia
Non-dihydropyridine calcium channel antagonists (e.g. verapamil, diltiazem)	Alternative, or in addition, to a beta blocker	Arteriolar vasodilator  Centrally acting drugs reduce heart rate, blood pressure, contractility, and prolong diastole	Negative inotropic effect Bradycardia Heart block Constipation Hypotension Headache	Avoid verapamil in heart failure and in combination with a beta blocker
Nicorandil	Angina	Systemic and coronary vasodilator	Headache Dizziness Nausea Hypotension Gastrointestinal ulceration	Avoid sildenafil and similar drugs  Metformin may reduce efficacy
Ivabradine	Angina  Chronic heart failure	Reduces heart rate	Visual disturbances Headache Dizziness Bradycardia Atrial fibrillation Heart block	Caution with drugs that induce or inhibit cytochrome P450 3A4  Avoid in renal or hepatic failure
Perhexiline	Refractory angina	Favours anaerobic metabolism in active myocytes	Headache Dizziness Nausea, vomiting Visual change Peripheral neuropathy	Narrow therapeutic range  Need to monitor adverse effects and drug concentrations

## Nitrates

Sublingual glyceryl trinitrate tablets or nitroglycerin spray remain the treatment of choice for rapid relief of acute symptoms and anticipated angina. Sublingual glyceryl trinitrate tablets are absorbed in the sublingual mucosa and take effect within a couple of minutes. The tablet can be discarded with resolution of chest pain to minimise adverse effects such as headache. Glyceryl trinitrate spray is equally effective and, due to its longer shelf-life, is more convenient for those with infrequent symptoms of angina.

Isosorbide dinitrate undergoes hepatic conversion to mononitrate, resulting in an onset of action of 3–4 minutes. It can provide an antianginal effect for up to one hour. Less commonly it is used as a chronic antianginal drug but requires multiple dosing, and tolerance limits its usefulness. It is often used up to three times per day with a nitrate-free period of up to 14 hours to minimise tolerance.

Long-acting nitrates such as oral isosorbide mononitrate or transdermal patches are effective in relieving angina and can improve exercise tolerance. Chronic nitrate therapy is limited by the development of nitrate tolerance. A nitrate-free period of at least eight hours may reduce this problem. The mechanism of nitrate tolerance is not well established but involves attenuation of the vascular effect of the drug rather than altered pharmacokinetics.<sup>26</sup> A nitrate-free period restores the vascular reactivity of the vessel. Transdermal patches are generally used for 12 consecutive hours with a 12-hour nitrate-free period. There is no evidence that nitrates improve survival.

Common adverse effects include headache, hypotension and light-headedness. Nitrates should not be prescribed for patients taking phosphodiesterase-5 inhibitors such as sildenafil due to the risk of profound hypotension. Other contraindications include severe aortic stenosis and hypertrophic cardiomyopathy.

## Nicorandil

Nicorandil is a potassium channel activator that improves coronary flow as a result of both arterial and venous dilation. It may be used in addition to beta blockers and calcium channel antagonists to control angina or in patients who are intolerant of nitrates. Nicorandil has been shown to reduce

cardiovascular events by 14% in patients with chronic stable angina.<sup>27</sup> Its use has been associated with headaches, hypotension, painful ulcers and genital and gastrointestinal fistulae.<sup>28</sup>

## Ivabradine

Ivabradine can be considered for patients intolerant of, or insufficiently responsive to, other drugs. It acts on I<sub>f</sub> channels in the sinus node to lower the heart rate of patients in sinus rhythm without affecting blood pressure, conduction or myocardial contractility.<sup>29</sup> Ivabradine has been shown to reduce a composite primary end point of cardiovascular death and hospitalisation with myocardial infarction or heart failure. However, a recent placebo-controlled trial involving 19 102 patients with stable coronary artery disease found that adding ivabradine to standard therapy did not improve a composite outcome of death from cardiovascular causes, or non-fatal myocardial infarction.<sup>30</sup> Ivabradine has been used in combination with beta blockers.<sup>31</sup>

## Perhexiline

Perhexiline promotes anaerobic metabolism of glucose in active myocytes. Its use is limited by a narrow therapeutic window and high pharmacokinetic variability.<sup>23</sup> Given its potential for toxic effects such as peripheral neuropathy and hepatic damage, it is usually reserved for patients whose angina is refractory to other therapies. It may be used safely with conscientious monitoring of clinical effects and regular measurement of plasma drug concentrations.<sup>32</sup>

## Conclusion

Stable angina is typically provoked by exertion and relieved by rest or nitrate therapy.<sup>2</sup> Risk stratification should be done to define prognosis, guide management and select appropriate patients for revascularisation.<sup>3,5,19</sup> The aims of medical therapy are to control symptoms, improve quality of life and prevent cardiovascular events.<sup>2,5</sup> Beta blockers and calcium channel antagonists remain first-line options for treatment. Short-acting nitrates can be used for symptoms. ◀

*Conflict of interest: none declared*

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