Optimal medical management of coronary artery disease

Coronary artery disease is the largest single cause of death in Australia. GPs have a key role in providing long term management and support to patients who have the disease and to those who are at risk of developing it.

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Coronary artery disease is the leading cause of morbidity and mortality in the developed world.[1] It is the largest single cause of death in Australia (Figure 1)[2] and, although the incidence and case mortality are declining,[3] the overall prevalence is rising because the population is ageing.[4]

The optimal management of coronary artery disease has two complementary objectives:

- to reduce the risk of death and myocardial infarction, and
- to reduce symptoms of angina and the occurrence of ischaemia.

A strategy for achieving these objectives is shown in the flowchart on page 19. For most patients, the goal should be the complete or near-complete elimination of angina and a return to normal activities with minimal adverse effects from medications.

The role of the GP

GPs have a critical role in providing long term management and support to patients who either have coronary artery disease or are at risk of developing it. Specialist involvement decreases as time passes after a cardiac event, and it is important that GPs become involved early to reinforce a strategy of global risk reduction and secondary prevention. GPs are also in the best position to identify individuals who are at risk of coronary artery disease and implement primary prevention.

The five components of management

There are five components of managing coronary artery disease:

- global risk reduction
- education
- pharmacotherapy
- treatment of associated diseases that may precipitate or worsen angina
- revascularisation.

These components are discussed in more detail in the following sections.

IN SUMMARY

- **The goals of management for coronary artery disease are two-fold: to reduce the risk of death and myocardial infarction, and to reduce symptoms of angina and the occurrence of ischaemia.**
- **All patients with coronary artery disease should be screened for diabetes, which is often unmasked during a presentation with an acute coronary syndrome. All diabetic patients with proteinuria should be treated with an ACE inhibitor.**
- **Antiplatelet agents have unequivocal benefits in coronary artery disease. Unless contraindicated, aspirin should be used indefinitely by most patients who have known cardiovascular disease.**
- **ACE inhibition should be considered in all coronary artery disease patients.**
- **Patient education is often neglected in the management of patients with coronary artery disease. Explanations about recognising symptoms that can be suggestive of acute myocardial infarction are particularly important.**

Global risk reduction

An individual's global risk for coronary artery disease reflects the sum of all his or her factors that are associated with increased risk – these include medical factors (such as hypertension, dyslipid - aemia and diabetes) as well as lifestyle factors (such as smoking, physical inactivity, obesity and excessive alcohol intake). These are discussed in more detail in the box on page 20.[5-33] Interventions for risk factors have been shown to reduce the incidence of coronary artery disease and prevent adverse cardiac outcomes, so it is imperative that these are identified and treated.

Education

Doctors tend to concentrate on diagnostic and therapeutic interventions in the management of coronary artery disease, and patient education is often neglected. However, effective education is valuable, and likely to lead to patients who are not only better informed about their disease, but who are able to achieve a better quality of life and feel more satisfied with their care. Explaining to patients and their families how to recognise symptoms that are suggestive of possible acute myocardial infarction is particularly important.

Pharmacotherapy

Antiplatelet agents

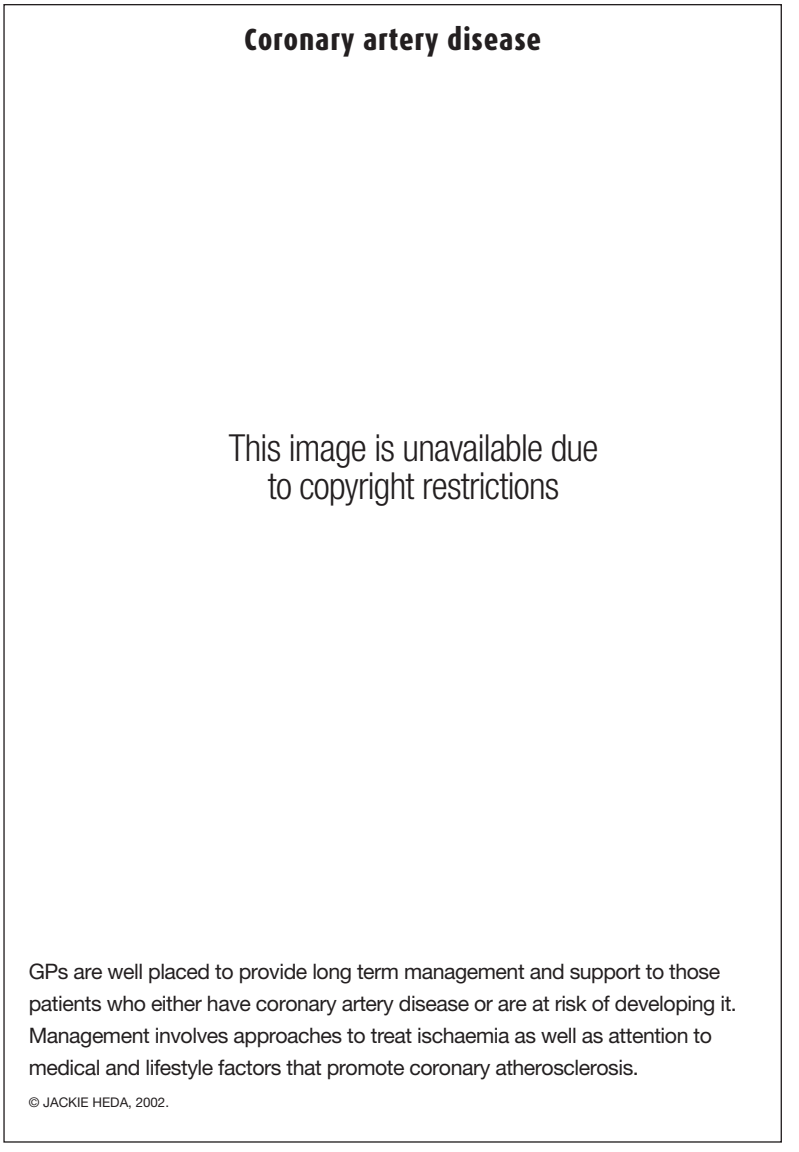
Antiplatelet agents have unequivocal benefits in patients with coronary artery disease, significantly reducing mortality and subsequent cardiac events by 25%.[34] Unless contraindicated, aspirin (75 to 150 mg/day) should be used indefinitely by most patients with known cardiovascular disease;[35] clopidogrel ([Iscover, Plavix], 75 mg/day) should be used when aspirin is contraindicated and in patients who are intolerant of aspirin. Combined aspirin and clopidogrel therapy should be considered for patients who have recurrent ischaemic events on aspirin – the CURE trial has shown additional benefits in those with unstable angina.[36]

Clopidogrel should be prescribed after stent implantation for between one and 12 months. The duration of therapy will depend on the type of stent and clinical situation.[37]

Beta blockers

In the absence of contraindications, beta blockers are the preferred initial therapy for angina pectoris.

Coronary artery disease



GPs are well placed to provide long term management and support to those patients who either have coronary artery disease or are at risk of developing it. Management involves approaches to treat ischaemia as well as attention to medical and lifestyle factors that promote coronary atherosclerosis.

All agents appear to be equally effective. The dosage should target a resting heart rate of around 60 beats per minute – examples include either metoprolol or atenolol.

Beta blockade after myocardial infarction reduces the long term risk of recurrent cardiovascular events by 18%.[38] Carvedilol (Dilatrend, Kredex), bisoprolol (Bicor) and metoprolol have shown additional survival benefit in patients with heart failure.[39-41]

Absolute contraindications to beta blockade are reversible bronchospasm (i.e. asthma) and symptomatic bradycardia. Selective beta blockers like metoprolol and atenolol are well tolerated in

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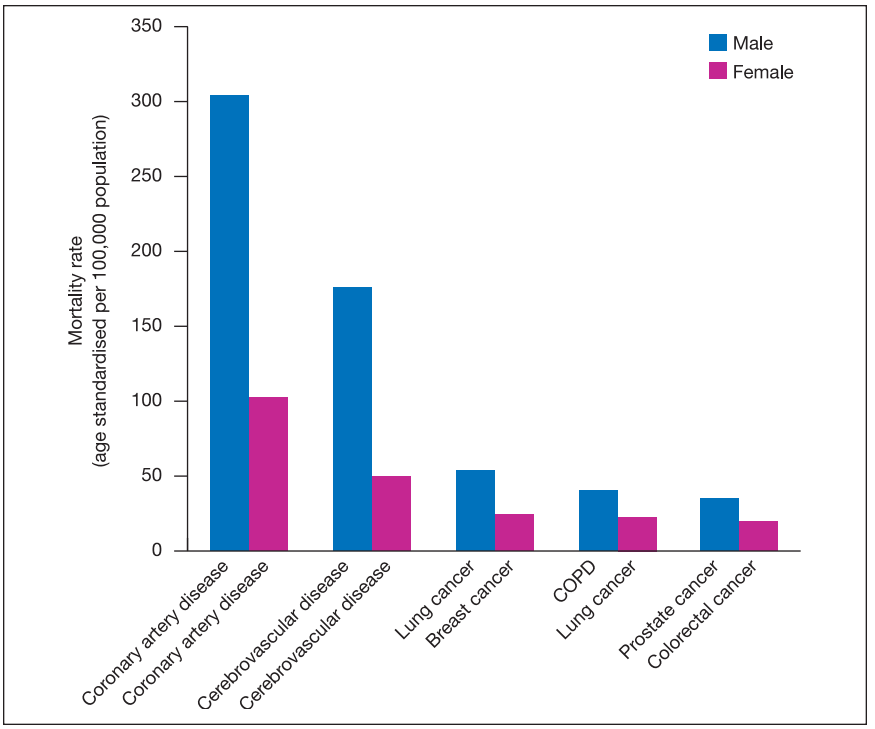


Figure 1. Leading causes of death in Australia, 2001.[2]

patients with chronic obstructive airways disease without bronchodilator response, peripheral vascular disease and diabetes.

Calcium channel blockers

If beta blockade is contraindicated or its side effects are unacceptable, long acting calcium channel blockers can be used as an alternative – examples include diltiazem (Cardizem, Coras, Diltahexal, Dil - zem, Vasocardol) or verapamil (Anpec, Cordilox, Isoptin, Veracaps, Verahexal).

If angina persists despite optimal beta blockade, agents such as amlodipine (Norvasc) and felodipine (Agon, Felodur, Plendil) can be given to provide additional antianginal action.

Short acting calcium channel blockers (e.g. nifedipine) should be avoided because of an increased risk of mortality.[42]

Statins

Statins are recommended for all cases of coronary artery disease, irrespective of cholesterol levels. An example of an atherosclerotic plaque is shown in Figure 2. There is emerging evidence that statins have atherosclerotic effects additional to lipid lowering – they have been shown to decrease systemic markers of inflammation such as C-reactive protein[43] and to improve endothelial function.[44] The Heart Protection Study showed that simvastatin 40 mg daily is safe and effective in high risk patients. In this study, patients with known atherosclerotic vascular disease, diabetes or hypertension had a 24% reduction in major cardiac events and 12% reduction in total mortality, regardless of baseline LDL cholesterol level, age, gender or presence of diabetes.[12]

ACE inhibitors and angiotensin receptor antagonists

Individuals who are at high risk of cardiovascular events benefit from ACE inhibition. After myocardial infarction, use of an ACE inhibitor reduces mortality,[45] especially in patients with a low ejection

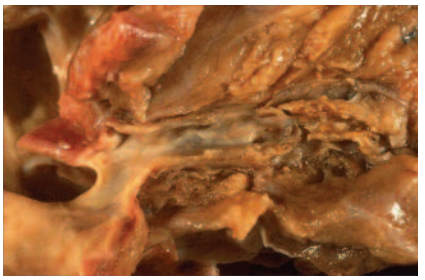


Figure 2. Atherosclerotic plaque in the left main coronary artery and proximal left anterior descending artery.

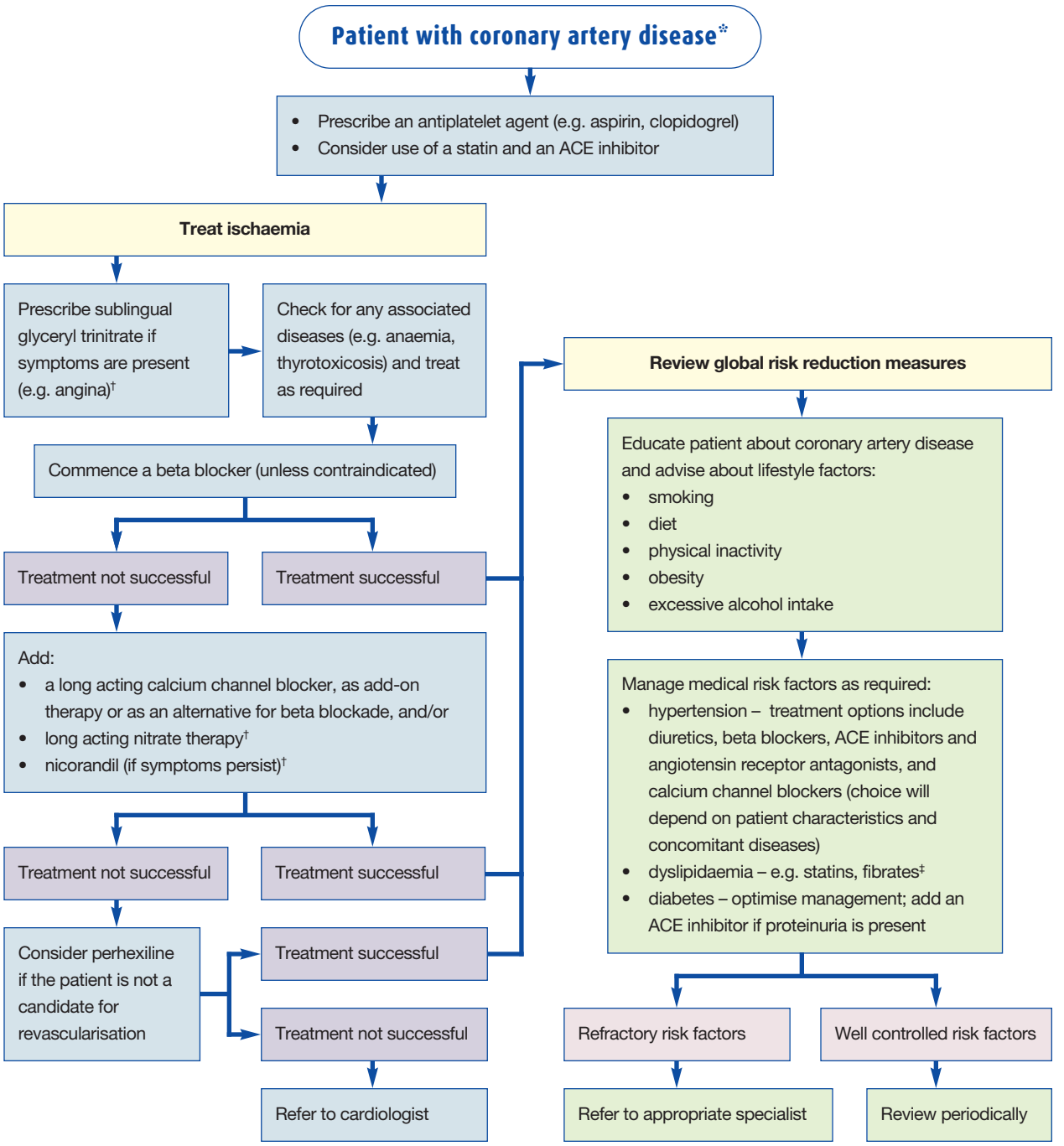
fraction (<40%).[46] Findings from the HOPE study of ramipril (10 mg daily) suggest that benefits of ACE inhibitors extend to patients with clinical cardiovascular disease and diabetes, even in the absence of left ventricular dysfunction; ramipril is marketed as Ramace and Tritace.[47] Therefore, ACE inhibition is recommended for all post-infarct patients and for those with or at high risk of cardiovascular events. Angiotensin receptor antagonists can be used if patients develop unacceptable side effects from ACE inhibitors.

The recent EUROPA study showed that perindopril (8 mg daily) significantly improves cardiac outcomes in low risk patients with stable coronary artery disease,[48] which suggests that ACE inhibition should be considered in all coronary artery disease patients. (Perindopril is marketed in Australia as Coversyl.)

Nitrates

Nitrates rapidly relieve symptoms of angina. All patients with coronary artery disease should receive sublingual nitroglycerine (Anginine, Lycinate, Nitrolingual Pumpspray) and be educated about its proper use – it is important that patients be aware that it is a short acting medication with no known long term side effects. The most common side effects are dose-dependent headache and hypotension. An action plan should be in place and patients instructed to seek immediate medical attention if chest pain

Coronary artery disease: a strategy to medically manage symptoms and prevent coronary events



* Patient suitability for revascularisation should be reassessed regularly. † Nitrates should be avoided if a patient has used sildenafil, tadalafil or vardenafil in the previous 24 hours.
‡ The combination of a statin and fibrate should be used with caution because of increased risk of myositis and rhabdomyolysis.

Medical and lifestyle risk factors for coronary artery disease

Hypertension

Although hypertension has a linear relationship with risk of coronary artery disease, it is often clinically silent.[5] Up to one-third of hypertensive individuals evade diagnosis, and only one-quarter receive effective treatment.[6]

The benefits and safety of hypertension treatment are well established: reducing diastolic blood pressure by 5 to 6 mmHg reduces the risk of coronary artery events by 15%.[7] The National Heart Foundation of Australia has set the following targets:[8,9]

- <140/90 mmHg for lower risk patients
- <130/85 mmHg for patients with cardiovascular disease, diabetes, renal insufficiency and/or proteinuria 0.25 to 1 g/day
- <125/75 mmHg for patients with proteinuria >1.0 g/day.

Lifestyle modifications are recommended for all hypertensive patients, whereas initiation of drug therapy should depend on blood pressure and an individual's absolute risk. The choice of drug treatment should be based on the characteristics of the patient and concomitant diseases – options include diuretics, beta blockers, ACE inhibitors and angiotensin receptor antagonists, and calcium channel blockers. Combination therapies are often required for optimal control.

Dyslipidaemia

Lipid lowering has unequivocal benefit in coronary artery disease: a 10% reduction in serum cholesterol reduces cardiovascular death by 15%.[10] The National Heart Foundation of Australia suggests the following targets for lipid lowering:[11]

- total cholesterol <4.0 mmol/L
- LDL cholesterol <2.5 mmol/L
- HDL cholesterol >1.0 mmol/L
- triglycerides <2.0 mmol/L.

Reducing dietary intake of saturated fat and cholesterol decreases serum lipid levels and lowers an individual's risk of coronary artery disease. Statins are potent lipid lowering medications and are the agents of choice for lowering LDL cholesterol. The following are well tolerated and safe in all age groups:

- simvastatin (Lipex, Zocor)[12]
- pravastatin (Pravachol)
- fluvastatin (Lescol, Vastin)
- atorvastatin (Lipitor).

Fibrates are effective in lowering triglycerides and raising HDL cholesterol levels. The combination of a statin and a fibrate should be used with caution because of the increased risk of myositis and rhabdomyolysis.

Diabetes

All individuals with diabetes are at high risk of coronary artery disease:[13] age adjusted rates are two to three times higher in people with diabetes.[14] All patients with coronary artery disease should be screened for diabetes, which is often unmasked during an acute coronary presentation.

In patients with diabetes (i.e. fasting plasma glucose ≥7 mmol/L),[15] the goal is to maintain normoglycaemia (HbA_{1c} ≤7%).[16] Tight glucose control with insulin for three months or more should be considered in patients following myocardial infarction.[17] All patients with diabetes and proteinuria should be treated with an ACE inhibitor.[18,19]

Smoking

Smoking remains one of the strongest risk factors for the development of coronary artery disease in all age groups.[20] Cessation is one of the most effective approaches to preventing disease progression: the risk of a cardiac event is reduced by 50% in the first year or two, with much of this gain in the first few months. The risk for former smokers reaches that of nonsmokers after five to 15 years.[21]

Complete smoking cessation is the goal, but this is often difficult to achieve. Behavioural and psychosocial approaches such as smoking cessation programs can be considered, in combination with nicotine replacement therapy or bupropion (Zyban SR).

Physical inactivity

The risk of coronary artery disease in sedentary individuals is twice that of their active counterparts.[22] Long term prospective studies consistently show that regular physical activity protects against death from coronary artery disease – this is mainly due to its beneficial effects on body weight, blood pressure,[23] cholesterol profile[24] and glucose intolerance.[25] The aim is to maintain at least 30 minutes of moderate intensity physical activity on most, if not all, days of the week (i.e. a minimum of 150 minutes per week).[26]

Obesity

Overweight (25>BMI>30 kg/m^2) and obesity (BMI ≥30 kg/m^2) are common. Weight reduction is important for overweight and obese patients, because excess body weight is associated with increased risk of coronary artery disease and mortality and contributes to other coronary risk factors such as hypertension and glucose intolerance.[27] Abdominal obesity is particularly associated with increased risk – this is consistent with a waist circumference of more than 94 cm in men and 80 cm in women.[28]

Heavy alcohol consumption

Heavy alcohol consumption increases total and cardiovascular mortality.[29] However, moderate alcohol intake (one to two standard drinks per day) appears to be protective against coronary artery disease compared with complete abstinence.[30] Possible mechanisms include raised HDL concentration,[31] improved fibrinolytic capacity,[32] and reduced platelet aggregation.[33]

Diet

A healthy diet is recommended, including:[8]

- mainly plant based foods (vegetables and fruits)
- moderate amounts of poultry, lean meats and fish
- moderate amounts of polyunsaturated or monounsaturated fats
- reduced fat dairy products.

is prolonged (more than 15 minutes in duration) and not relieved by sublingual nitroglycerine (three tablets taken five minutes apart).

Slow release or long acting nitrate therapy is effective in symptom control in addition to beta blockers and is available as glyceryl trinitrate patches (Minitran, Nitro-Dur, Transiderm Nitro) or isosorbide mononitrate tablets. It is important to ensure a nitrate-free interval of 10 to 12 hours each day to avoid tolerance.

Concomitant use of phosphodiesterase type 5 inhibitors and nitrates may cause life threatening hypotension and is an absolute contraindication.[49]

Nicorandil

Nicorandil (Ikorel), a vasodilator that has some nitrate properties, is an antianginal agent that is useful for the patient who is already taking a beta blocker, calcium channel blocker and long acting nitrate. The usual dose is 5 to 20 mg twice a day.

Perhexiline

Perhexiline (Pexsig) is used for refractory angina when all other medical therapies have failed and the patient is not a candidate for revascularisation. It is generally well tolerated and without significant risks of hepatotoxicity or peripheral neuropathy if the dosage is adjusted to give a plasma concentration of 0.15 to 0.60 mg/L.[50] The usual maintenance dose range is 100 to 400 mg daily; it is administered orally.

Therapies not indicated

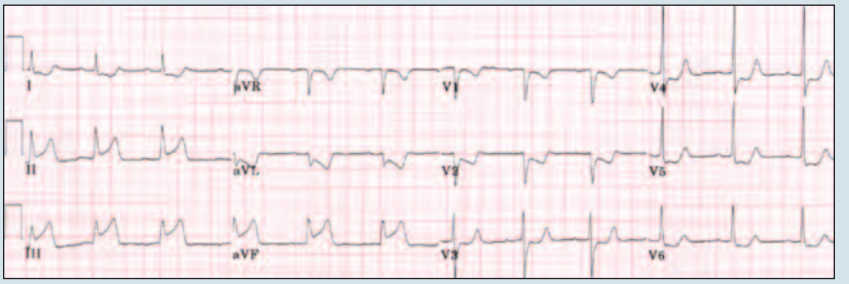
Hormone replacement therapy is not recommended in postmenopausal women for primary prevention of coronary artery disease. Commencing hormone therapy is not advised in women who have coronary artery disease; however, it may be continued in those who are already receiving hormone replacement therapy for menopausal symptoms.[51]

Vitamins C and E have little cardiovascular benefits. Studies have shown vitamin supplements to have no benefit in preventing or treating coronary artery disease.[47,52]

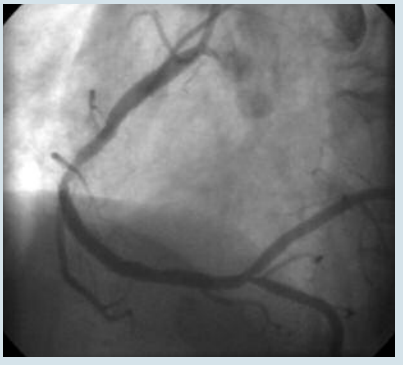
Treatment of associated diseases

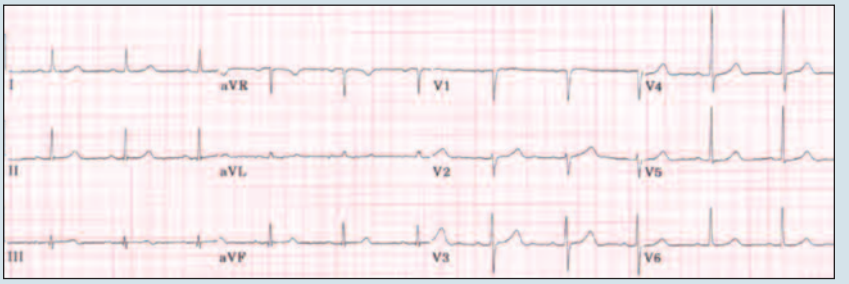
Several common medical conditions can contribute to the onset of new angina pectoris or exacerbate coronary artery disease by increasing oxygen demand or reducing oxygen delivery – examples include anaemia, thyrotoxicosis, infection and tachycardia. Coexisting cardiac diseases such as congestive cardiac failure, aortic stenosis and tachyarrhythmias can increase the frequency and severity of angina. Effective management

Percutaneous coronary intervention



Figures 3a and b. Angiogram (left) and ECG (above) from a patient presenting with acute inferior myocardial infarction.





Figures 4a and b. Angiogram (left) after the patient underwent coronary stenting of the right coronary artery. The final ECG (above) shows no progression to Q-wave myocardial infarction.

of coronary artery disease requires that these associated conditions be identified and treated.

Revascularisation

The indications for revascularisation are symptom control and improvement in prognosis. The two approaches used are percutaneous coronary intervention using catheter-borne balloons and stents (see Figures 3 and 4), and coronary artery bypass graft surgery.

Patients should be referred for an opinion regarding revascularisation if they have:[53]

- new onset angina
- increase in frequency and severity of angina
- angina that is refractory to medical therapy
- objective evidence of ischaemia on functional investigations
- depressed left ventricular function.

Advanced age and comorbidities do not necessarily preclude a patient from revascularisation. In elderly patients, the procedure appears to improve quality of life and morbidity compared with medical therapy.[54] Percutaneous coronary intervention can sometimes be performed in patients who are poor candidates for open heart surgery.

When to refer

Specialist consultation is necessary in a number of situations. The initial diagnosis and risk stratification requires either non-invasive or invasive investigations, and specialists will formulate management plans based on the patient's level of risk and symptoms. Revascularisation may be recommended for high risk patients or refractory angina. Acute coronary syndromes (unstable angina and myocardial infarctions) should be referred to the nearest hospital that has coronary care support.

Conclusion

The optimal medical management of coronary artery disease should include consideration of antiplatelet agents (usually aspirin), beta blockers, statins and ACE inhibitors. Treatment of hypertension and dyslipidaemia and good glycaemic control (HbA_{1c} ≤7.0%) are important, along with strategies to manage lifestyle factors such as smoking cessation, regular exercise, dietary modification, weight loss and excessive alcohol intake. Patient education, which is often overlooked, is an important aspect of management. High risk patients and those with refractory symptoms should be referred to a specialist for consideration of revascularisation. MT

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