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Secondary prevention of coronary heart disease

Risk factors must be assessed and treatment targets met to prevent patients with coronary heart disease having a further cardiovascular event.

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Patients with established coronary heart disease (CHD) are at high risk of developing further coronary, as well as noncoronary, events.[1] These include:

- acute coronary syndrome (ACS)
- sudden death
- congestive cardiac failure
- arrhythmia
- need for revascularisation (coronary artery bypass grafting [CABG] or angioplasty and stenting)
- stroke (cerebral infarction or haemorrhage)
- transient ischaemic attack (TIA)
- abdominal aortic aneurysm
- peripheral vascular disease (PVD).

One or more of these events are likely to occur in more than 20% of individuals with CHD over a period of five years.[1] For example, after an MI, patients have a 44-fold increased risk of a first stroke within 30 days. The risk of stroke then remains two to three times higher than in the general population over the next three years.[2,3]

The aim of secondary prevention is to optimally reduce the rate of recurrent events. This requires the use of strategies that are:[1]

- evidence based
- cost-effective
- easy to monitor and maintain
- acceptable to the patient in terms of cost, lack of side effects and burden of medications.

Several authoritative guidelines have been published in the USA, Europe and Australia for the secondary prevention of CHD.[1,4-6] This review summarises these recommendations for Australian GPs, and follows a review of primary prevention of CHD published in the December 2008 issue of *Medicine Today*.[7] The recommendations given do not necessarily meet the criteria for Pharmaceutical Benefits Scheme subsidies, and may be further modified at the GP's discretion according to best practice guidelines.

The team approach

Perhaps the most important issue in the management of patients with CHD is communication.

IN SUMMARY

- **Patients with coronary heart disease (CHD) have a more than 20% risk of having a further cardiovascular disease event within five years.**
- **Patients with CHD should be screened for dyslipidaemia at six to eight weeks after an MI and for diabetes at least eight weeks after an MI.**
- **Duplex ultrasound can be used to check for carotid, abdominal aortic and femoropopliteal atherosclerosis in patients with CHD.**
- **It is standard to give the SAAB regimen (a statin, aspirin, an angiotensin-converting enzyme inhibitor and a beta blocker) to patients who have had an acute coronary syndrome.**
- **Blood pressure targets in patients with CHD are determined by the presence of diabetes, renal dysfunction and proteinuria.**
- **Assessment and treatment of depression and social isolation are important in the overall management of patients with CHD.**

Clear, timely and consistent communication is needed between the teams of professionals who are caring for the patient. These may include hospital staff, private specialists, physiotherapists, dietitians, exercise physiologists, rehabilitation staff and, most importantly, the GP.

A care plan is essential for the management of patients with CHD, not least to facilitate communication between professionals and the patient.

Risk factors to be assessed

The presence and severity of traditional risk factors for CHD, including age, gender, smoking habit, systolic blood pressure (BP), ratio of total cholesterol to high-density lipoprotein cholesterol (HDL-C) and diabetes, must be assessed. Targets for therapy can then be set (Table). It is not necessary to determine overall (global) risk of cardiovascular disease (CVD) using Framingham or other risk charts because patients with established CHD are already at high risk. They have a more than 20% risk of having recurrent events over five years.

Many patients presenting with ACS will have revascularisation, either angioplasty and stenting or CABG, performed in hospital. Other patients will have specific tests performed for residual ischaemia such as exercise testing, tests for arrhythmias such as electrophysiology studies or tests such as echocardiography for impaired left ventricular function. These investigations provide additional risk stratification and may need to be performed after hospital discharge. As the province mainly of the treating cardiologist, they will not be discussed further in this article.

Blood glucose levels may be transiently raised after ACS, indicating an increased risk of subsequent hyperglycaemia and CVD. Levels suggesting diabetes should be confirmed two months later. Patients who then have impaired fasting glucose levels of 5.5 to 6.9 mmol/L (random glucose level of 5.5 to 11.0 mmol/L) require oral glucose tolerance tests.

Similarly, levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C) fall significantly in the few weeks after an MI, with concomitant elevation of triglyceride levels. Fasting lipid profiles should be performed six to eight weeks after an MI, when creatine kinase (CK) and transaminase levels can also be checked to exclude

Table. Targets for therapy after an acute coronary syndrome

Lipids
- Low-density lipoprotein cholesterol <2.0 mmol/L
- High-density lipoprotein cholesterol >1.0 mmol/L
- Triglycerides <1.5 mmol/L

Blood pressure
- <140/90 mmHg for adults ⩾65 years, unless they have diabetes and/or renal insufficiency and/or proteinuria ⩾0.25 g per day (see below)
- <130/85 mmHg for adults <65 years, and adults with renal insufficiency and/or diabetes and/or proteinuria 0.25 to 1.0 g per day (see below)
- <125/75 mmHg for adults with proteinuria >1 g per day with and without diabetes (see below)

Diabetes
- HbA_{1c} < 7%

Weight and waist
- Waist measurement
  - Men ⩽94 cm
  - Women ⩽80 cm
- BMI 18.5 to 24.9 kg/m²

Exercise
- 30 minutes of moderate exercise on most days; a minimum of 150 minutes per week. This level of exercise equates to a moderate, noticeable increase in depth and rate of breathing while still being able to talk comfortably
- All patients should enrol in a rehabilitation exercise program

Smoking
- No active or passive smoking

Alcohol
- Patients with hypertension: no more than two standard drinks per day in men or one standard drink per day in women
- If an abstainer or previous drinker, do not encourage drinking

Diet
- Follow a healthy diet as described in the healthy foods section of the text
- Include 1 g of the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and > 2 g alpha linolenic acid (ALA) per day

Psychosocial factors
- All patients must be assessed for depression
- Those with depression should receive appropriate psychological and medical management

Assessing proteinuria[9]

When proteinuria (⩾ 1+ protein) is detected on dipstick testing:

- in a patient with hypertension but no diabetes: 24-hour urinary protein excretion or spot urine albumin/creatinine ratio should be determined
- in a patient with hypertension and diabetes: spot urine albumin/creatinine ratio best determines the intensity of antihypertensive therapy
- in a patient with microalbuminuria: 24-hour urine collection should be obtained for accurate quantification.

Reasons why treatment targets are not achieved

- Initial level of risk factor is high (e.g. high levels of low-density lipoprotein cholesterol in a patient with familial hypercholesterolaemia)
- Doses of medications not uptitrated
- Inappropriate medication (e.g. fibrate for lowering low-density lipoprotein cholesterol)
- Inadequate lifestyle modification (especially with regards to HbA_{1c}, weight and waist)
- Poor patient compliance
  - patient is not convinced of the need for treatment
  - patient experiences side effects
  - cost of medication
  - misleading advice (e.g. media reports and internet information)
  - patient unaware of need for continuing treatment

hepatic and muscle side effects of statin therapy, which is usually initiated in hospital in those not previously treated.

Treatment targets

Current recommendations for treatment targets of risk factors after ACS are shown in the Table.[1,4-6,8-14]

In general, 'lower is better' with regards to LDL-C, systolic BP (as long as postural hypotension is avoided and renal perfusion maintained) and glycated haemoglobin (HbA_{1c}; as long as hypoglycaemia is avoided).

For HDL-C, 'higher is better'. A case can be made to achieve HDL-C levels above 1.2 mmol/L in women and above 1.0 mmol/L in men, because of the gender difference in HDL-C levels within populations.

Are treatment targets being achieved?

The '50% rule' has been shown to apply to several cardiometabolic risk factors such as hypertension and elevated total cholesterol and LDL-C levels. The rule refers to 50% of patients being aware of their condition, of whom 50% are being treated, and of whom 50% of those treated achieve treatment targets. Case management, recall plans and careful attention to detail in general practice can achieve significantly better outcomes.

Patients with CHD are usually aware of their risk factors, but achievement of treatment targets is far from optimal, being as low as 27% in some surveys, for a variety of reasons (see the box on this page).[5] Long-term patient compliance remains a major factor in achieving treatment targets. The treating doctor should ensure the patient understands the rationale for treatment, emphasising the likely improvements in CVD event rates as shown in clinical trials.

If targets are not achieved, it is important to reassure the patient that any movement of risk factor levels towards targets is likely to be of benefit, especially when several risk factors improve simultaneously.

Screening for atherosclerosis in other vascular beds

Atherosclerosis is a systemic disease, so it is important to assess other vascular beds in patients with CHD.

Femoropopliteal stenosis is indicated by a low ankle/brachial index of less than 0.8, using Doppler ultrasound. Alternatively, femoropopliteal and aortic duplex ultrasound studies can assess flow and detect the presence of plaques and aneurysm formation.

Femoral calcification often occurs in the media rather than the intima, and is a less reliable indicator of atherosclerosis than calcification at other sites. Carotid duplex ultrasound may be used to assess carotid flow and plaque severity.

Patients who have had previous PVD, TIA, abdominal aortic aneurysm or stroke need to have their coronary disease status assessed. This should preferably be performed with stress echocardiography, because it avoids exposure to radiation and has a high sensitivity and specificity when performed by an experienced operator.

Medications used after acute coronary syndrome

SAAB regimen

Most patients who present at hospital with an ACS are usually discharged on the SAAB regimen (a statin plus aspirin plus an angiotensin converting enzyme [ACE] inhibitor plus a beta blocker). Each of these drugs should be uptitrated to the recommended maximum doses, unless risk factor targets are achieved at lower doses (Table).

Antithrombotics

All patients should receive 75 to 150 mg aspirin per day. If aspirin is contraindicated or not tolerated (in about 5% of the total population), patients should be treated with 75 mg clopidogrel (Iscover, Plavix) per day.[15] Those patients with recurrent CHD or who have stents should be treated with aspirin plus clopidogrel combination therapy. The duration of therapy is assessed by the patient's cardiologist and depends on the nature of the stent. It may range from three months for those with a bare metal stent to 12 months for those with a drug-eluting stent and to indefinitely for those with complex disease. Patients on clopidogrel should be warned about an increased risk of bleeding during surgery, but should be advised not to cease clopidogrel without the consent of their GP and cardiologist.

Warfarin (Coumadin, Marevan) alone is used for those patients who have had previous embolic events, left ventricular thrombus or atrial fibrillation.[10]

Statins

Statins are recommended for all patients with CHD, irrespective of lipid levels.[11,16] After patients have had an ACS, statins are usually commenced in hospital: 80 mg atorvastatin (Lipitor) per day is recommended in view of the Pravastatin or

Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI-22) study showing benefit of this statin after 30 days of therapy.[12] This dose, however, may need to be reduced in patients who are at risk of muscular side effects from statin therapy (see the box 'Patients at risk of statin myopathy' on this page).

CK and transaminase levels should be checked after eight to 12 weeks of statin therapy. The dose should be reduced in the presence of levels more than three times the upper limit of normal (ULN) or if there are symptoms of myalgia (independent of CK levels).[17] Occasional cases of statin myopathy have been reported in patients with normal CK levels. It is important to check levels of thyroid-stimulating hormone in all patients with statin myalgia, because hypothyroidism may be an underlying factor.[17]

Other lipid therapies for controlling LDL-C

- **Ezetimibe.** Ezetimibe (Ezetrol) is indicated for patients whose LDL-C is not at target despite at least three months' therapy with 40 mg of a statin per day. It is also indicated for patients intolerant to statins and those with LDL-C levels above target whose statin dose has been reduced to 20 mg per day or less because of myalgia, raised CK levels (two times ULN) or raised transaminase levels (three times ULN) on higher statin doses. Ezetimibe lowers LDL-C by an average of about 20%.
- **Resins.** If LDL-C remains above target in spite of statin plus ezetimibe therapy, resins may be added to the regimen (8 g cholestyramine [Questran Lite] or 5 g colestipol [Colestia Granules for Oral Suspension] per day).
- **Plant sterols/stanols.** A daily dose of 2 to 3 g of plant sterols/stanols – that is, two heaped tablespoons of enriched margarine per day – may lower LDL-C levels further.
- **Fenofibrate.** LDL-C levels may be reduced by 145 mg fenofibrate (Lipidil) per day but the response is not as predictable as for other therapy, and LDL-C levels may show little change. Gemfibrozil is not recommended with statins because it may increase statin blood levels and the risk of rhabdomyolysis.

Therapy for triglycerides and HDL-C

Many patients do not achieve triglyceride and HDL-C target levels in spite of maximum statin therapy, and these abnormal lipids contribute significantly to residual risk (CVD events occurring despite statin use).

Other factors that may help patients achieve target triglyceride and HDL-C levels include:

- **Lifestyle modification.** Weight loss and increased exercise may improve levels. Alcohol restriction may be required for lowering triglyceride levels, and smoking cessation may further increase HDL-C levels.
- **Fibrates.** The addition of a fibrate to statin therapy may further improve triglyceride and HDL-C levels. Fenofibrate is used in preference to gemfibrozil because it has a lower risk of rhabdomyolysis.
- **Fish oils.** Both triglyceride and HDL-C levels may be improved by taking fish oils. Liquid fish oil supplements contain about 160 mg/mL eicosapentaenoic acid (EPA) and about 100 mg/mL docosahexaenoic acid (DHA). To meet EPA and DHA requirements, 5 to 15 mL per day may be required.[18] This regimen is inexpensive, well tolerated, lowers 'pill burden' by avoiding the use of capsules and is an alternative to eating fish three times per week.

ACE inhibitors and ARBs

For BP control, ACE inhibitors are first-line therapy. Angiotensin-receptor blockers (ARBs) can be substituted if ACE inhibitors are not tolerated. Most patients need more than one agent to achieve target levels, and calcium-channel blockers (CCBs) or diuretics (for those over the age of 65 years) are recommended as next-line add-on therapy. Diuretics may be used in patients who have heart block or impaired left ventricular function, which may be aggravated by CCBs.[5]

Recent clinical trials have shown a benefit with either ACE inhibitors or ARBs for high-risk patients, even in the absence of hypertension or left ventricular dysfunction. Combination ACE inhibitor plus ARB therapy confers no additional benefit but has a higher incidence of side effects and is not recommended.[5]

Patients with 'white coat' hypertension may be best monitored either by home or ambulatory BP measurements.

Beta blockers

Beta blockers are indicated in most patients with ACS, especially those with significant

Patients at risk of statin myopathy[17]

- Elderly, thin patients, especially women, with multiple comorbidities
- Patients with hypothyroidism
- Patients who had uptitration or initiation of a statin
- Patients taking fibrate cotherapy, especially gemfibrozil
- Patients taking atorvastatin or simvastatin and cytochrome P3A4 inhibitors, particularly:
  - macrolide antibiotics (e.g. erythromycin)
  - antifungals (e.g. ketoconazole)
  - protease inhibitors (e.g. ritonavir)
- Patients taking cyclosporin cotherapy
- Patients with renal and hepatic impairment
- Patients with acute illness, infection or surgery
- Patients with previous statin myalgia
- Patients with an underlying muscle disorder (e.g. glycogen storage disease)

myocardial necrosis, left ventricular systolic dysfunction, persistent evidence of ischaemia and ventricular arrhythmia.[13,19]

Antiarrhythmics

Long-term antiarrhythmic drugs have the potential to cause fatal arrhythmias, and their routine use is not recommended, especially in patients with depressed left ventricular function.[20-23] Patients with ventricular ectopics *per se* do not require antiarrhythmics. Patients with documented symptomatic or sustained ventricular tachycardia should be referred for specialist opinion.

Calcium-channel blockers

Nondihydropyridine CCBs (diltiazem or verapamil [Anpec, Isoptin, Tarka]) may be used to treat angina when beta blockers are contraindicated,[17] provided there is no evidence of congestive cardiac failure or heart block.[24] Controlled-release verapamil (Anpec SR, Cordilox SR, Isoptin SR, Veracaps SR) reduces the incidence of CVD in patients with stable angina and may decrease the risk of re-infarction and death after an MI.[17]

Influenza and pneumococcal vaccinations

Unless contraindicated, all patients with CHD should receive pneumococcal and annual influenza vaccinations.[23]

Hormone replacement therapy

Hormone replacement therapy is no longer prescribed for primary or secondary prevention of CHD. If used for other reasons (e.g. osteoporosis), all risk factors must be controlled carefully and consideration given to lower targets in order to counteract potential adverse effects of HRT on CVD risk.[25]

Antioxidants

Vitamins A, C and E and beta-carotene are not recommended for secondary prevention of CHD because clinical trial data have shown no benefit.[26,27]

Homocysteine

Homocysteine is a risk factor for CVD and supplementation with folic acid, vitamin B_{12} and B_6 lowers homocysteine levels. However, randomised controlled trials of these vitamins have shown no benefit in patients with CHD and their use is not recommended.[14,28-30]

Aldosterone antagonists

Eplerenone (Inspra) may be prescribed within three to 14 days after an MI if the left ventricular ejection fraction is less than 40% with symptoms of heart failure.[13,19] Spironolactone (Aldactone, Spiractin) can be used if eplerenone is not available, but has a higher risk of side effects.

Diet and lifestyle factors

Diet and lifestyle are important factors in patients with CHD. All means of support must be used to promote a healthy lifestyle, including partners and groups such as rehabilitation clinics. Self-monitoring can be assisted with regular feedback to nurses or other 'prevention coaches'.

Motivation for changes in behaviour

The classical methods to induce behavioural change are required. The following questions should be answered.

- Is the patient ready to change?
- Does he or she understand the need for change?
- Have appropriate treatment targets been set?
- Are monitoring programs in place?
- Is referral necessary (e.g. to a dietitian, exercise physiologist, physiotherapist, clinical psychologist, etc)?

Smoking cessation

Smoking cessation programs are now readily available, and patients can call Quitline (tel: 131 848) for advice. Anti-smoking medication is considered for those who smoke more than 10 cigarettes per day. Nicotine replacement therapy (NRT; Nicabate products, Nicorette products, Nicotinell products, QuitX products) is first choice, and is safe for those with stable CVD, but should be used with caution in those with recent MI, unstable angina, severe arrhythmias or recent stroke.[24,31] Bupropion (Clorprax, Prexaton, Zyban SR) is second-line therapy for those with stable CHD and can be combined with NRT, if necessary.[32]

Varenicline (Champix) has recently been introduced and reduces craving and withdrawal symptoms, while simultaneously reducing the rewarding and reinforcing effects of smoking.[33] Patients with pre-existing psychiatric illness may not be suitable for this therapy.[33]

Healthy foods

Emphasis should be placed on whole foods rather than percentage intake or amounts of various nutrients. Most patients are aware of the need to limit or avoid visible animal fats, full-fat dairy products, egg yolks, commercial pastries, cakes, biscuits and added sugars. This will reduce the intake of saturated and trans-saturated fats, cholesterol and refined carbohydrates, and result in lower LDL-C levels with improved insulin sensitivity.[34,35]

Eating a wide variety of healthy foods is recommended, including:

- legumes (dried peas, dried beans and lentils)
- vegetables (including coloured vegetables such as red capsicums and cruciferous vegetables such as cabbage)
- fruits
- whole grain products (such as bread, pasta, noodles and rice)
- nuts
- soy
- lean meats and poultry
- fish (three times per week): fish oil supplements may be necessary if this cannot be achieved
- low-fat dairy products
- moderate amounts of polyunsaturated fats (e.g. safflower and corn oil)
- moderate amounts of monounsaturated fats (e.g. canola and olive oil)
- moderate alcohol consumption (maximum two standard drinks

continued

[20 g alcohol] per day for men and one standard drink [10 g alcohol] per day for women) in previous drinkers
- unsweetened fruit drinks
- water.

Referral to a dietitian should be considered for all patients with CHD.

Exercise

An individualised exercise program needs to be prescribed, with as much attention to detail as prescriptions for medications. Referral to a formal rehabilitation program is preferred, where advice can also be given on return to vocational activity, driving and resumption of sexual activity.

Caution is necessary when prescribing exercise for patients with conditions that may be exacerbated by exercise, including:[36]
- unstable angina
- uncontrolled or severe hypertension
- severe aortic stenosis
- uncontrolled diabetes
- complicated MI
- uncontrolled heart failure
- symptomatic hypotension (BP <90/60 mmHg)
- resting tachycardia
- arrhythmias.

Exercise programs need variety, should be started slowly to avoid musculoskeletal injury and should be adapted to the patient's physical and mental attributes. The 'Lifescripts' tool may be useful.[37]

Weight and waist control

The initial target is to lose 10% of body weight. This will improve insulin sensitivity and mobilise visceral (central abdominal) fat. From there, lower weight and waist targets can be set over an appropriate time period.

Psychosocial aspects

Social support is important through family members, partners, friends, the cardiac rehabilitation service or other groups.

First-line therapy for patients with depression is a selective serotonin reuptake inhibitor (SSRI). This class of agents is safe and effective, although the dose of warfarin may need adjustment.[38,39] High doses of tricyclic antidepressants may be proarrhythmogenic and should be avoided.

Chest discomfort

All patients with CHD require a written action plan to follow in the event of chest pain or discomfort. They should be prescribed a short-acting nitrate with appropriate instruction for its use, including its use-by date.[5]

If chest pain occurs, patients should be advised to:
- take an aspirin
- rest
- use the short-acting nitrate prescribed
- tell someone nearby about the symptoms
- call 000 for severe, rapidly worsening or unrelieved symptoms after 10 minutes. MT

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A list of references is available on request to the editorial office.

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