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Primary prevention of coronary heart disease

In Australia, coronary heart disease is a major cause of morbidity and mortality; however, there has been a drop in mortality rates due to improvements in treatments and better risk factor control.

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Coronary heart disease (CHD) remains a major cause of death and disability in the Australian community, although there has been a significant decrease in mortality since the late 1960s.[1] About 45% of this decrease has been attributed to an improvement in medical treatment and the remainder to risk factor control, particularly smoking and hypertension.[2] This review is largely confined to examining CHD, rather than other cardiovascular diseases (CVD) such as stroke and peripheral vascular disease (PVD).

Primary and primordial prevention

Primary prevention of CHD refers to the prevention of sudden death and new-onset myocardial infarction, arrhythmia, angina or congestive cardiac failure.[3-5] The term 'primordial prevention' is sometimes used to describe primary prevention of CHD in childhood and adolescence, the aim of which is to prevent the formation of significant atherosclerotic plaques.[6]

Question: *'What's the difference between primary and secondary prevention?'*

Answer: *'Potentially one minute – the time between plaque rupture, occlusive thrombosis and presentation with an acute coronary syndrome'.*

This statement highlights that significant coronary atherosclerosis may be present in many adults without symptoms of CHD.

Risk factors

Risk factors are variables that have a statistical association with an increased incidence of disease. More than 100 risk factors for CHD have been defined. These can be classified as nonmodifiable and modifiable (Table 1). Risk factors do not necessarily imply causation, but may be markers for underlying disease.

Many epidemiological studies have shown interactions between CHD risk factors, whereby the presence of additional risk factors has a greater than additive effect on overall or absolute risk.[2-10] Absolute or global risk assessment aims to identify those at greatest risk of CHD who could benefit the most from preventive interventions and who may need more aggressive targets.

The New Zealand Guidelines Group (NZGG) risk factor charts for men and women are commonly

IN SUMMARY

- **Coronary heart disease (CHD) remains a major cause of death and disability in Australia.**
- **There have been more than 100 risk factors for CHD defined.**
- **More than 90% of CHD risk can be attributed to nine modifiable risk factors.**
- **Absolute risk assessment can be determined using New Zealand Guidelines Group or Framingham risk charts.**
- **More than 90% of CHD events occur in patients with one or more risk factors, although CHD is uncommon in those with no risk factors.**
- **Lifestyle interventions are an important aspect of primary prevention of CHD.**

continued

Table 1. Major risk factors for coronary heart disease (CHD)

Major nonmodifiable CHD risk factors	Major modifiable CHD risk factors	Other modifiable CHD risk factors
Age	LDL-C and HDL-C levels	C-reactive protein level
Sex	Cigarette smoking	Homocysteine level
Family history	Hypertension	Lipoprotein (a) level
Left ventricular hypertrophy on electrocardiogram	Diabetes	Triglyceride level
	Chronic renal failure	Uric acid level
	Microalbuminuria	Fibrinogen level
	Central abdominal obesity	
	Lack of physical exercise	
	Alcohol consumption	
	Psychological factors	

used in Australia to estimate absolute risk of CVD (see the box on page 25).[7]

The NZGG charts use age, gender, blood pressure (BP), smoking habit, presence or absence of diabetes, and the ratio of total cholesterol to high-density lipoprotein cholesterol (HDL-C) to estimate five-year risk of CVD, including stroke and CHD. Interpretation of the NZGG charts is unreliable in people who are or have the following:

- aged under 35 years or over 70 years
- a BP of more than 180/105 mmHg (if younger than 65 years) or BP of more than 160/100 mmHg (if older than 65 years), confirmed by multiple readings on separate occasions
- a total cholesterol above 8.0 mmol/L
- the metabolic syndrome
- familial hypercholesterolaemia
- known renal disease
- of Aboriginal or Torres Strait Islander origin
- a history of CVD.

Many Framingham-derived risk factor charts are also available, and they usually estimate 10-year risk of CHD rather than five-year risk of CVD. Framingham risk charts classify individuals as having high (more than 15%), intermediate (10 to 15%) or low (less than 10%) 10-year CHD risk, which approximate five-year CVD risks using the NZGG charts.

Single compared with multiple risk factors

More than 90% of CHD events occur in patients with one or more risk factors, but CHD is uncommon in those with no risk factors.

A US study of more than 380,000 men and women showed a sevenfold greater CHD risk for those with both a total cholesterol of 6.25 mmol/L or more and a systolic BP of 160 mmHg or higher compared with those with both a total cholesterol of less than 4.75 mmol/L and a systolic BP of less than 130 mmHg.[11] The increases in risk had a more than additive but less than multiplicative effect.

Some risk factors, such as low-density lipoprotein cholesterol (LDL-C) and BP, have a continuous relation with risk, even when they are within normal ranges, and no lower threshold has been demonstrated. Therefore 'the lower the better' applies to LDL-C and BP, as long as BP lowering does not cause postural hypotension or renal dysfunction. Lowering LDL-C to an average level between 1.4 and 1.6 mmol/L has been shown to be safe in recent statin trials.[12-14]

Risk factors in the INTERHEART Study

In the INTERHEART study of 15,152 cases of myocardial infarction and 14,820 controls from 52 countries, nine potentially modifiable factors accounted for more than 90% of risk for a first myocardial infarction.[8] They included (in order of predictive power):

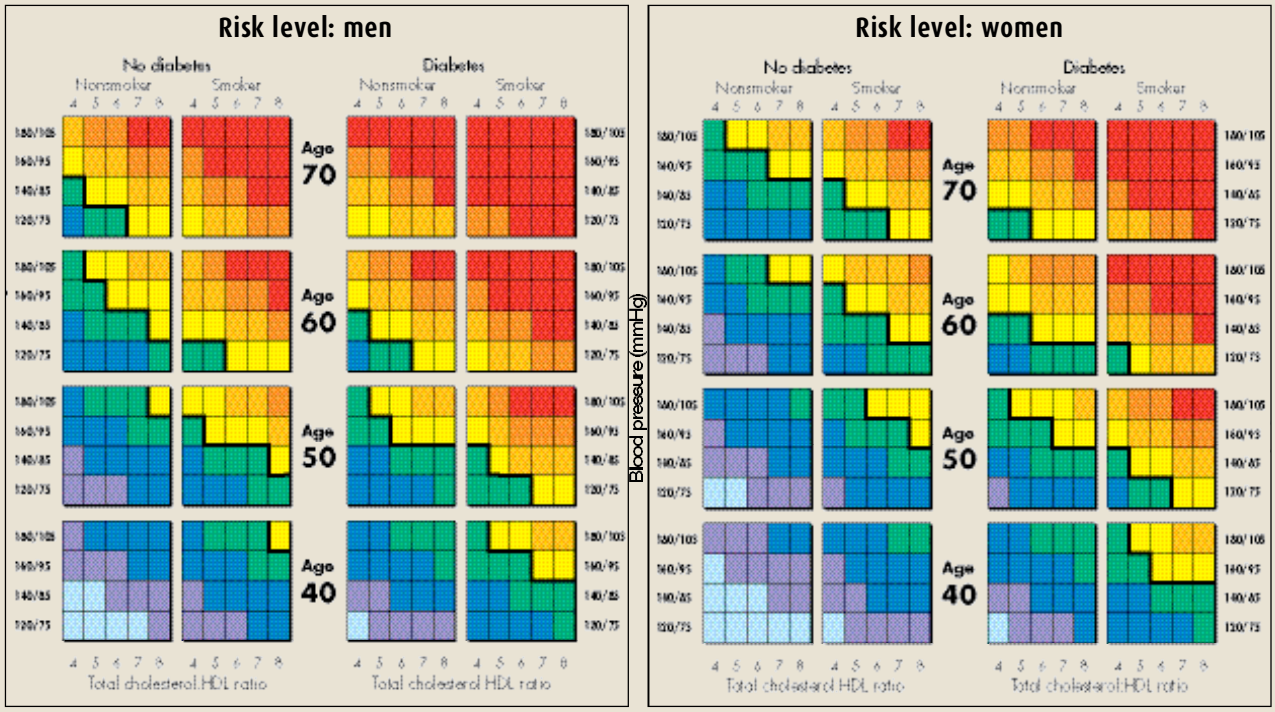
- high apolipoprotein (apo) B to apoA-1 ratio
- cigarette smoking
- psychosocial factors (depression, social isolation, stress and significant life events)
- abdominal obesity
- hypertension
- regular fruit and vegetable intake (protective)
- moderate physical exercise (protective)
- diabetes
- moderate alcohol intake (less than two standard drinks [20 g alcohol] per day; protective).

Priorities for primary prevention

Four groups of patients are priority targets for primary prevention because they are at highest risk of CHD and the benefits of intervention are likely to be greatest:[2,3,9]

- asymptomatic individuals at highest CHD/CVD risk based on multiple risk factors
- individuals with type 1 or type 2 diabetes and microalbuminuria
- individuals with one extremely abnormal (above the 95th percentile) risk factor, especially associated with

The New Zealand cardiovascular risk calculator: estimating absolute CVD risk



Risk level (for women and men)

five-year CVD risk (fatal and nonfatal)

Very high	>30%	
	25-30%	
	20-25%	
High	15-20%	
Moderate	10-15%	
Mild	5-10%	
	2.5-5%	
	<2.5%	

ABBREVIATIONS: CVD = cardiovascular disease, HDL = high-density lipoprotein.

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end-stage organ damage
- first- and second-degree relatives of patients with either premature CVD or high CVD risk.

Lower risk factor targets, as is the case for patients with established CHD, may be appropriate in these groups.

Smoking

Stopping smoking reduces CHD risk by about one-half within one year. After several years, a patient's risk of CHD is similar to that of a nonsmoker. Every opportunity should be taken to counsel smokers about the health benefits of quitting and all potential avenues also used to help with smoking cessation including drug therapy when indicated.

Blood pressure

Almost one-quarter of deaths from CVD can be attributed to hypertension. For every 3 mmHg rise in systolic BP and every 1 mmHg rise in diastolic BP there is about a 1% change in CVD events over a five-year period.

With antihypertensive therapy, recent large trials have shown no evidence of a 'J-curve', in which increased mortality occurs with lower BP.[10] The greatest benefit of BP lowering occurs in patients with the highest BP levels, multiple risk factors and target organ damage – that is, those at highest risk.

There are as yet no outcome data for people with prehypertension (systolic BP of 120 to 139 mmHg and/or diastolic BP of 80 to 89 mmHg) who are nevertheless at increased CVD risk. Weight loss, exercise

Table 2. Targets for blood pressure[10]

- Below 125/75 mmHg for patients with proteinuria (with or without diabetes) more than 1 g/day
- Below 130/80 mmHg for patients with end-stage organ damage or associated conditions. Those patients with the conditions given below warrant immediate treatment with antihypertensive drugs regardless of blood pressure or overall cardiovascular risk profile:
  - cholesterol of more than 7.5 mmol/L
  - family history of premature cardiovascular disease or familial hypercholesterolaemia
  - diabetes
  - chronic renal impairment: estimated glomerular filtration rate less than 60 mL/minute/1.73 m^2; protein/creatinine ratio 30 mg/mmol/L or more on spot urine testing; urine protein more than 300 mg/day on timed urine sample
  - microalbuminuria to albumin to creatinine ratio 2.0 mg/mmol/L or more in males and 2.5 mg/mmol/L or more in females; 24-hour urinary albumin excretion rate 20 µg/minute or more
  - hypertensive retinopathy (grade II or above)
  - ultrasound or radiology evidence of atherosclerotic plaque (aortic, carotid, coronary, femoral, iliac)
- For individuals with none of the above 140/90 mmHg or lower if tolerated

and salt restriction significantly reduce the rate of developing hypertension, as does antihypertensive drug therapy.

Lifestyle intervention for hypertension

Weight management, increasing physical activity, reducing dietary salt and reducing alcohol intake can all contribute to BP control and a reduction in risk of CHD.

Drug therapy for hypertension

Recently, the guidelines for management of hypertension were modified by the National Heart Foundation of Australia (NHFA).[10] The modifications include the following:

- BP should be measured on both arms and the arm with the highest reading should then be used for future measurements
- beta blockers and thiazides are no longer recommended as first-line therapy because of an increased risk of developing diabetes; however, thiazides are still used as first-line therapy in patients aged 65 years and older
- earlier risk assessment is recommended for people of Aboriginal or Torres Strait Islander origin
- antihypertensive drugs should be initiated when there is evidence of associated clinical conditions or end-stage organ disease, regardless of BP. Angiotensin-converting enzyme (ACE) inhibitors are generally recommended as first-line antihypertensive treatment, although angiotensin-receptor blockers (ARBs) may be considered in patients who do not tolerate ACE inhibitors or in patients with diabetes and proteinuria
- many patients require multiple anti-hypertensive therapies. The most effective dual-combination therapy appears to be an ACE inhibitor or ARB plus a calcium-channel blocker.

Targets for BP are shown in Table 2.[10]

Diet

Consumption of wholegrains, fruit, vegetables and fish and reduction in the intake of saturated fats reduces the risk of CHD. The exact relation between diet and CHD is, however, confounded by other lifestyle factors such as body weight, smoking, alcohol consumption and exercise.

Dietary modification is the foundation of all measures to improve risk. It improves lipids, BP and glucose control, especially when combined with increased physical exercise.[15-19]

Fish oil consumption

Epidemiological studies have shown that increased intake of fish oils (omega-3 fatty acids) and increased fish consumption lowers CHD risk. Two or three 150 g serves of oily fish per week or supplementation with omega-3 fatty acids (to supply 500 mg per day) are currently recommended;[10,19] however, no primary prevention studies of omega-3 supplements have been performed.

Alcohol

Low to moderate alcohol intake is associated with a lower risk of CHD. Current guidelines recommend no more than one standard drink (10 g alcohol) per day for women and up to two standard drinks per day for men.

Exercise

The amount of regular physical activity undertaken is inversely proportional to CHD risk. Current recommendations are to do 30 minutes or more of brisk walking per day.[9,18] An adequate degree of activity is indicated by breathlessness, fatigue or sweating.

Achieving such exercise levels is difficult for many patients, especially the elderly, those at any age with joint and muscle problems and the severely obese. Individually-prescribed exercise given by exercise physiologists, in which patient preference, available time and ability to exercise are all taken into account, is the ideal approach.

Diabetes

The presence of diabetes doubles the risk of CHD in men and increases risk up to fourfold in women.[20] About 7% of the Australian adult population has diabetes and the prevalence is increasing in parallel with that of obesity and the metabolic syndrome.

Patients with diabetes should maintain an optimal glycated haemoglobin (HbA_{1c}) level below 7%, using lifestyle interventions and drug therapy when indicated. It is particularly important to treat associated risk factors including dyslipidaemia, hypertension and overweight.[9]

Lipids

Criteria for lipid-modifying therapy

Current Pharmaceutical Benefits Scheme (PBS) guidelines for subsidising lipid-lowering therapy are shown in the box on this page.

According to the NHFA and Cardiac Society of Australia and New Zealand (CSANZ) position statement on lipid management, a threshold of a 15% five-year CVD risk is suggested for lipid-modifying therapy in those with no CVD or diabetes.[21] A recent analysis of the Australian Diabetes, Obesity and Lifestyle (AusDiab) study estimated that 717,000 Australians aged 30 to 74 years reached this threshold, but more than 80% were not being treated, indicating 'current primary prevention of CVD is suboptimal'.[22] In addition, 13% of women and 44% of men without CVD or diabetes were at high risk of CVD in spite of lipid-lowering therapy.

Low-density lipoprotein cholesterol

A meta-analysis of several trials with statins has shown that for every 1% reduction in LDL-C there is about a 1% reduction in cardiovascular events over a period of five years.[23] The linear relation between the percentage of cardiovascular events and achieved level of LDL-C occurs for both primary and secondary prevention; however, the association with primary prevention is not as strong as that with secondary prevention and there are fewer cardiovascular events for a given LDL-C level (Figure 1). As for BP, no lower threshold for benefit has been shown, therefore, the lower the LDL-C the better.[23]

The 2007 NHFA/CSANZ position statement on lipid management recommend an LDL-C goal of less than 2.5 mmol/L for high-risk patients who do not have CHD.[21] For people with diabetes, an LDL-C target of 2.0 mmol/L is recommended.[21]

Statins are used as first-line agents to reduce LDL-C levels. Before statin therapy, musculoskeletal symptoms should be assessed and blood tests performed to measure baseline creatine kinase (CK) levels and hepatic transaminases.[24,25] Renal and thyroid function should also be assessed. Transaminase and CK levels should be checked after six to 12 weeks and CK tests repeated if musculoskeletal symptoms occur.

Prescribing doctors need to be aware of conditions and possible drug interactions predisposing to muscle side effects of statins (Table 3).[24,25]

Patients who are unable to tolerate statins or who require back-titration of statins because of myalgia (with or without clinically important CK elevation) or raised transaminases, are eligible for PBS subsidised ezetimibe. Ezetimibe partially inhibits intestinal cholesterol absorption, resulting in increased hepatic LDL – receptor activity and an average 20% further reduction in LDL-C levels. Myalgia and raised transaminases generally resolve while patients take ezetimibe therapy, which is well-tolerated. The results of large-scale controlled clinical trials of ezetimibe in combination with statins are awaited; the first (IMPROVE-IT) is expected to be reported in 2012.[26]

Lipoprotein (a)

Lipoprotein (a) [Lp(a)] is a lipid fraction that resembles LDL and carries one apoB molecule attached to a plasminogen-like

Australian PBS criteria for eligibility of subsidy of lipid-lowering therapy

- Individuals other than those with very high risk of coronary heart disease (CHD) require a minimum of 16 weeks of lifestyle intervention before lipid-lowering treatment.
- Individuals in any of the following groups at very high risk of CHD can be treated simultaneously with lipid-lowering therapy and lifestyle modification at any cholesterol level:
  - symptomatic coronary, peripheral or cerebrovascular disease
  - diabetes and one of the following: microalbuminuria, age over 60 years, total cholesterol above 5.5 mmol/L or of Indigenous origin
  - family history of symptomatic CHD before age 55 years in two first-degree relatives or before age 45 years in one first-degree relative.
- Cholesterol and triglyceride criteria for eligibility in various groups are as follows:
  - total cholesterol above 6.5 mmol/L or a total cholesterol above 5.5 mmol/L and high-density lipoprotein cholesterol (HDL-C) below 1 mmol/L
  - hypertension and either total cholesterol above 6.5 mmol/L or total cholesterol above 5.5 mmol/L and HDL-C below 1 mmol/L
  - HDL-C below 1 mmol/L and total cholesterol above 6.5 mmol/L
  - men aged 35 to 75 years or postmenopausal women aged up to 75 years with total cholesterol above 7.5 mmol/L or triglycerides above 4 mmol/L
  - those not otherwise included with total cholesterol above 9 mmol/L or triglycerides above 8 mmol/L.

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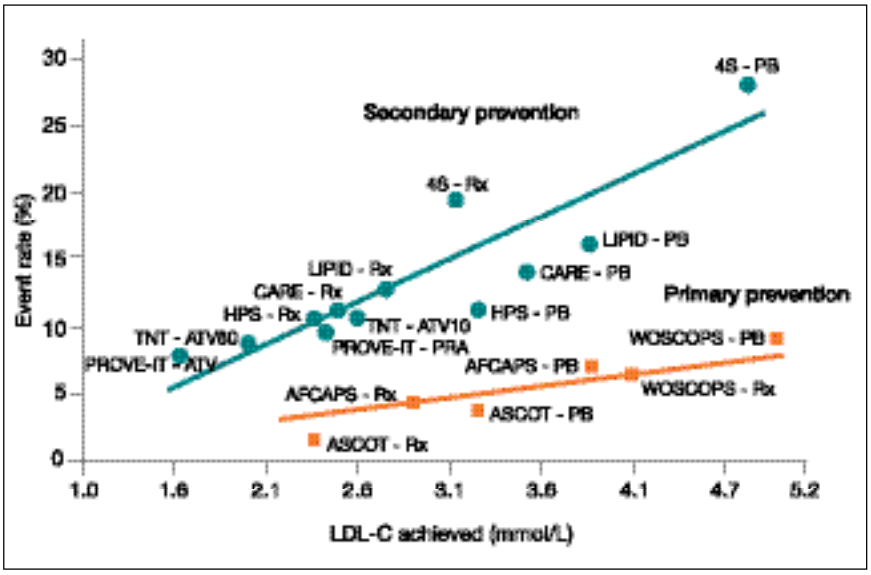

Figure 1. Coronary heart disease (CHD) event rates (%) in relation to low-density lipoprotein cholesterol (LDL-C) levels achieved during statin trials. The green line refers to secondary prevention trials and the orange line to primary prevention trials. The bullet points or squares represent statin (Rx) and placebo (PB) treatment for each trial. There are linear relations between CHD event rates and LDL-C levels achieved (down to about 1.6 mmol/L for secondary prevention and 2.3 mmol/L for primary prevention), with no evidence for a lower threshold.

ABBREVIATIONS: 4S = Scandinavian Simvastatin Survival Study; AFCAPS = Air Force Coronary Atherosclerosis Prevention Study; ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; ATV = atorvastatin; CARE = Cholesterol and Recurrent Events; HPS = Heart Protection Study; LIPID = Long-term Intervention with Pravastatin in Ischaemic Heart Disease; PRA = pravastatin; PROVE-IT = Pravastatin or Atorvastatin Evaluation and Infection Therapy; TNT = Treating to New Targets; WOSCOPS = West of Scotland Coronary Prevention Study.

Table 3. Conditions predisposing to muscular side effects of statins[24,25]

- High dose of a statin
- Statin dose uptitration
- Fibrate cotherapy
- Cotherapy with hepatic cytochrome P450 3A4 inhibitors (for simvastatin and atorvastatin)
  - erythromycin and macrolide antibiotics
  - ketoconazole and antifungals
  - protease inhibitors for human immunodeficiency virus (HIV) infection
  - calcium-channel blockers
  - amiodarone
- Hypothyroidism
- Underlying myopathy
- Thin, elderly female
- Multiple comorbidities
- Acute viral infection
- Major surgery

subunit. Lp(a) is atherogenic because it promotes thrombosis and, like LDL, delivers cholesterol to the arterial wall. Lp(a) levels higher than 300 mg/L are independently associated with an increase in CHD risk.

Lp(a) is not reduced significantly by statin therapy and Lp(a) excess is an important cause of 'statin resistance', in which LDL-C levels appear to be unresponsive to statin therapy. Lp(a) levels should be measured in those with:

- premature CVD and no evident dyslipidaemia or other risk factors
- statin resistance.

There are no clinical outcome trials supporting the lowering of Lp(a). The most effective agent is nicotinic acid, which may lower levels by 10 to 25%. An alternative approach may be to lower LDL-C with a statin and add 75 to 150 mg aspirin per day for its antithrombotic effect.

High-density lipoprotein cholesterol

Levels of HDL-C have a powerful and inverse relation to CHD risk. So HDL-C is called the 'good cholesterol'.

Lifestyle factors that increase HDL-C levels include weight reduction, increased amounts of physical exercise, drinking alcohol as recommended and smoking cessation. HDL-C levels are increased by oestrogen therapy and drugs that lower triglycerides (including fibrates, fish oils and nicotinic acid). Statins have a small (5 to 10%) effect on increasing HDL-C.

Specific drugs to raise HDL-C, including second-generation cholesterol ester transfer protein inhibitors, are still in development.

Most patients with low levels of HDL-C (less than 1.0 mmol/L) have either insulin resistance (most often associated with central abdominal obesity) and/or hypertriglyceridaemia. The aim of treatment is to control glucose levels, lose abdominal fat through dieting and exercise. In addition therapy with fibrates or fish oils should be considered. Very low HDL-C levels (less than 0.4 mmol/L) in the absence of marked hypertriglyceridaemia are usually genetic in origin and do not respond to lipid-modifying drug therapy.

Triglycerides

Recent meta-analyses have shown that plasma triglycerides are an independent risk factor for CHD, especially in women.[27] Triglycerides are synthesised in the liver and transported in very low-density lipoproteins (VLDL), each molecule of which contains one apoB molecule. VLDL is converted into LDL in the plasma.

Lipoproteins rich in triglycerides may be atherogenic and increased levels of triglycerides (more than 1.7 mmol/L) are associated with increased levels of atherogenic small, dense LDL.[27] For this reason current Australian guidelines are to lower triglycerides below 1.5 mmol/L in patients at high risk of CHD.[22]

Levels of triglycerides and HDL-C are inversely related. So lowering triglyceride levels through fibrates, fish oils, weight loss and/or exercise will often raise HDL-C levels in individual patients.

About 50% of patients on lipid-modifying therapy achieve overall target lipid levels, suggesting the need for more effective management and/or therapeutic agents.[28]

Homocysteine

Homocysteine levels are independently related to CHD risk, possibly through the promotion of thrombosis.[29] Extremely high levels of homocysteine (as in homocystinuria) are associated with arterial and venous thrombosis at multiple sites, but this is a rare condition.[29] Mild elevations of homocysteine can be lowered by administration of folic acid, pyridoxine and vitamin B_{12} supplements, but controlled clinical trials have shown no benefit from this and vitamin supplementation to lower homocysteine is not recommended.[29]

Metabolic syndrome

The metabolic syndrome comprises a cluster of several risk factors that independently increase the risk of CHD.[29] Presence of the metabolic syndrome may increase CHD risk by up to threefold.[30] International Diabetes Federation criteria for the metabolic syndrome are shown in the box on this page.[30]

The first step in the management of the metabolic syndrome is for the patient to undertake lifestyle measures to reduce central obesity ('lose waist, not weight'). Many patients show significant improvement in risk factors with as little as 5% weight loss, because visceral fat (largely responsible for central obesity) is not only more metabolically active, but also is lost in preference to subcutaneous fat. If necessary, specific medication can be added to lifestyle measures to control triglyceride, BP and glucose levels.

The benefit of statin treatment for individuals with the metabolic syndrome was recently shown in the Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER).[14] This was a primary prevention study of men and women with elevated high-sensitivity C-reactive protein (hs-CRP) at or above 2 mg/L, who also had normal or low LDL-C levels. CRP is an acute-phase reactant that has several atherogenic properties and is released by the liver in response to inflammatory cytokines. The metabolic syndrome is one disorder associated with elevated hs-CRP levels.

Slightly more than 41% of people who participated in JUPITER had the metabolic syndrome by US criteria. The trial was stopped prematurely after 1.9 years because of a reduction in CVD events and overall mortality in the group treated with 20 mg rosuvastatin per day compared with placebo.[14] All subgroups, including those with the metabolic syndrome, had similar relative risk reductions of about 50% in CHD and CVD events, including stroke.

JUPITER raises the issue of increased use of hs-CRP as a screening tool to detect at-risk individuals for whom statin therapy may be indicated.[14]

Aspirin

The benefits of aspirin therapy for primary CHD prevention have been shown in several randomised trials.[31] In the large US Physicians' Health Study and the Nurses' Health Study, aspirin users had small but significant increased rates of bleeding, with an absolute increased risk of cerebral haemorrhage of about three per 10,000 and a statistically significant excess of major bleeding of about 60%.[31]

Current American Heart Association guidelines recommend low-dose aspirin for primary prevention of CVD for men and women whose 10-year CHD risk on Framingham risk factor charts is 10% or more.[31] This approximates to a 10% or more five-year CVD risk using NZGG charts.

The poly-pill

Current guidelines stress the importance of treating global CHD risk, so multiple medications are usually required to control

International Diabetes Federation criteria for the metabolic syndrome[30]

The metabolic syndrome is defined as patients with:

Central obesity with waist circumference:

- 94 cm or more in Caucasian men
- 80 cm or more in Caucasian women
- ethnicity-specific values for other groups

Plus any two of the following:

- triglycerides 1.7 mmol/L or above, or specific treatment for this lipid abnormality
- high-density lipoprotein cholesterol below 1.03 mmol/L in males and below 1.29 mmol/L in females, or taking a specific treatment for this lipid abnormality
- systolic blood pressure 130 mmHg or above, or diastolic blood pressure 85 mmHg or above, or taking treatment for previously diagnosed hypertension
- fasting glucose level 5.6 mmol/L or above, or previously diagnosed type 2 diabetes.

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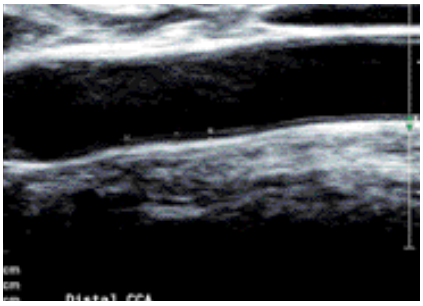

Figure 2. Carotid intima-medial thickness measured at three sites in the distal common carotid artery, with values of 0.071 cm (left and right) and 0.062 cm (centre).

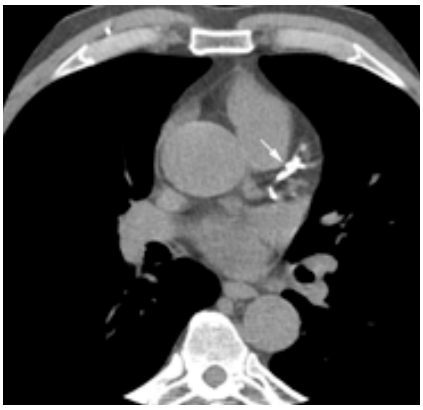

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Figure 3. Coronary calcium scan. The calcified proximal left anterior descending coronary artery is shown by the arrow.

multiple risk factors (e.g. aspirin, an antihypertensive and a statin). Problems of cost, side effects and compliance arise with use of multiple medications and use of fixed-combination tablets has the potential to overcome these problems.

In 2003, Wald and Law proposed that a 'poly-pill' combining half-doses (to minimise toxicity) of a beta blocker, a thiazide diuretic, an ACE inhibitor, a statin, folic acid and aspirin, could reduce the incidence of CVD by more than 80% if taken by everyone aged 55 years and over.[32] They suggested one in three people would gain an average of 11 to 12 years of life free from CVD.

The poly-pill was designed to cost-effectively and simultaneously improve levels of LDL-C, BP and serum homocysteine and improve platelet function with minimal side effects (estimated discontinuation of 1 to 2%, with fatal side effects in less than one per 10,000 patients).[32]

A modified poly-pill containing a statin, an ACE inhibitor and aspirin is about to enter clinical trials in Australia and elsewhere.

Targets for primary prevention

For people who do not have diabetes and are at low or intermediate risk of CHD, current European targets are to achieve the following characteristics of healthy individuals:[9]

- no smoking
- healthy food choices
- 30 minutes of moderate physical activity per day
- body mass index (BMI) below 25 kg/m^2 with avoidance of central obesity (waist circumference less than 102 cm for men and less than 88 cm for women)
- BP lower than 140/90 mmHg
- cholesterol less than 5 mmol/L
- LDL-C less than 3 mmol/L
- fasting glucose less than 6 mmol/L.

For either individuals with diabetes or those at high risk of CVD, the following more rigorous risk factor control is required:[9]

- BP lower than 130/80 mmHg
- cholesterol less than 4 mmol/L, if feasible
- LDL-C less than 2 mmol/L, if feasible
- fasting glucose less than 6 mmol/L and HbA_{1c} less than 6.5%, if feasible in patients with diabetes.

Lower waist circumference may also be appropriate for these people at high risk of CHD, and drug therapy is required in the majority.

Protocol for primary prevention of CHD in adults

- Measure absolute risk according to NZGG or Framingham risk charts
- Ascertain the presence of other modifiable risk factors, including renal function and microalbuminuria
- For those at low risk of CHD (less than 10% CVD risk in five years or 10% CHD risk in 10 years):
  - monitor risk factors annually and advise on lifestyle modification
- For those at intermediate risk of CHD (10 to 15% CVD risk in five years or 10 to 15% CHD risk in 10 years):
  - monitor risk factors annually and advise lifestyle modification
  - consider low-dose aspirin, statin and antihypertensive therapy
  - current US guidelines recommend the use of imaging studies for those at intermediate risk of CHD to improve risk assessment and help determine the need for further intervention and more aggressive therapy.[33-36] The cost-benefit of these studies has yet to be determined. The imaging studies recommended include:

    Ankle-brachial index. This is usually performed in those with risk factors for PVD (e.g. smoking, diabetes, vascular bruits and/or older age). A finding of below 0.9 is diagnostic of PVD, and a result above 1.1 is usually due to arterial wall calcification, most often in patients with diabetes or chronic renal failure.

    Carotid intima-medial thickness (Figure 2). If the thickness is above the 95th percentile for age and gender (about 0.8 mm or more) or if atherosclerotic plaques are present, further evaluation for the presence of CHD and myocardial ischaemia may be indicated.[37-39] More aggressive therapy, as for people at high risk of CHD, may be appropriate.

    Coronary calcium score (CCS; Figure 3). CCS is the most sensitive test for the presence of coronary atherosclerosis, but it is less reliable for predicting the

severity of stenosis.[35] CCS has also been shown to be more predictive of CHD than Framingham risk charts.[35] Those with high CCS (more than 400 Hounsfield units or above the 75th percentile for age and gender) should be evaluated for the presence of myocardial ischaemia[37-39] and more aggressive therapy, as for people at high risk of CHD, may be appropriate.

- For those at high risk of CHD (15% CVD risk in five years or more than 15% CHD in 10 years):
  - advise lifestyle modification and monitor every six months
  - prescribe aspirin and a statin and consider ACE inhibitor/ARB therapy
  - consider imaging studies to assess the severity of CHD and PVD (see above)
  - target lipids: LDL-C less than 2.0 mmol/L, triglycerides less than 1.5 mmol/L, HDL-C more than 1.0 mmol/L (consider more than 1.2 mmol/L in women)[9,21]
  - target HbA_{1c} below 7%
  - target BMI less than 25 kg/m^2
  - target BP (Table 2)[10]
  - target waist circumference less than 100 cm in males and less than 90 cm in females
  - measure risk factors in near relatives and correct if abnormal.

Protocol for primary CHD prevention in adolescents younger than 16 years and children

Primary prevention of CHD in adolescents younger than 16 years and children is an area of preventive medicine that is becoming increasingly important. This is because of the current epidemics of obesity, metabolic syndrome and diabetes, which are determined to some degree by lifestyle during childhood and adolescence.[16-18]

- Determine fasting lipid profile: current recommendations of the American Academy of Pediatrics[16] are to measure fasting lipids in children or adolescents with:
  - a positive family history of dyslipidaemia
  - a positive family history of premature CVD or dyslipidaemia (age 55 years or less in men and 65 years or less in women)
  - an unknown family history of CVD or dyslipidaemia
  - the presence of any of the following CVD risk factors: BMI in the 85th percentile or above, cigarette smoking, diabetes or BP in the 95th percentile or above.
  - screening should take place after the age of 2 years but no later than age 10 years[16]
- Assess family history and measure risk factors in first- and second-degree relatives
- Correct risk factors by lifestyle modification (in the index patient and near relatives)
- Monitor every one or two years (index patient) or more frequently (adult relatives)
- Consider medication if risk factors are not adequately controlled (index patient and near relatives).

Drug therapy to lower LDL-C should be considered in children aged 10 years or older and in adolescents with:[16]

- LDL-C persistently above 4.9 mmol/L with no other risk factors
- LDL-C persistently above 4.1 mmol/L with other risk factors
- LDL-C above 3.4 mmol/L in those with diabetes.

Pravastatin has been approved for treatment of children aged 8 years or more with familial hypercholesterolaemia, regardless of pubertal status.[16] It should be considered as first-line therapy for hypercholesterolaemia in children and adolescents.

Summary

Absolute risk assessment can be determined using NZGG or Framingham risk charts with adjustment for family history and other risk factors not included in the charts, such as the metabolic syndrome and exercise levels. This is the key to establishing a primary prevention program. People at intermediate risk (10 to 15% five-year CVD risk or 10 to 15% 10-year CHD risk) may benefit from imaging studies to further define risk and guide target levels for lipids and BP.

Lifestyle measures, especially smoking cessation, can improve risk and increase life expectancy significantly. Clinical trials have established the benefits of lipid-modifying therapy and BP control, and guidelines for these are well-established.

In future, primary prevention needs to be aimed at earlier age groups for even greater benefits to be realised. MT

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

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Primary prevention of coronary heart disease

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