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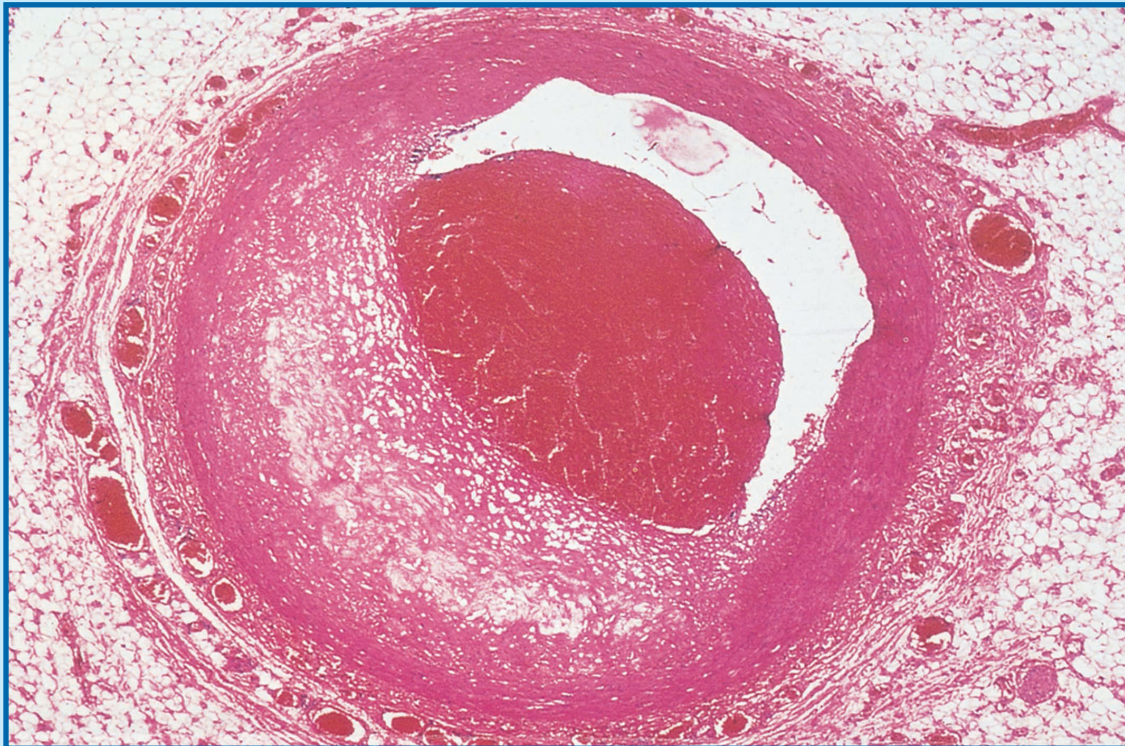


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Lipid Management Guidelines – 2001



National Heart Foundation of Australia

The Cardiac Society of Australia and New Zealand



The Lipid Management Guidelines — 2001 have been endorsed by the following organisations



Lipid Management Guidelines – 2001



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Lipid Management Guidelines – 2001

WHILE LIPID LEVELS ALONE make only a relatively small difference to the risk of early coronary heart disease (CHD), when combined with other risk factors they make an important difference. There is strong evidence that lipid-modifying treatment reduces CHD progression, morbidity and mortality for people who are at high risk of CHD events. Also, treating those at highest risk to lower plasma lipid levels has been shown to be cost-effective.^{1,2} Such findings have stimulated many countries, including Australia, to develop lipid management guidelines. However, despite the potential for significant health gain, information from overseas and Australia shows that effective lipid-modifying therapies are significantly underused.³⁻⁵

The need to focus and draw the attention of medical practitioners, other health professionals, patients and policy makers to this “treatment gap”, particularly in high risk patients, and the need to revise recommendations based on the latest evidence, is the underlying rationale for these guidelines.

These clinical practice guidelines aim to summarise current evidence to serve as a prompt for practitioners for best clinical practice, encouraging consistency of care in managing plasma lipid levels to prevent CHD. It should be understood that both the nature of clinical trials and the specific practice environment must always be considered when implementing the guidelines.

Development of these guidelines involved a small core writing group (see Key contributors, *page S58*) who presented an early draft for discussion, and further development by consensus at a full-day forum in October 2000, followed by further consultation. A wide range of representative cardiologists, other cardiovascular health experts, general practice representatives and others contributed to the formulation of the final document (see Other contributors, *page S59*).

These guidelines are based on a comprehensive review of the key evidence-based literature. The process has necessarily entailed a degree of expert-based consensus and cross-reference to other evidence-based guidelines, especially in the lifestyle areas. However, it should be noted that the highest level of evidence comes from randomised controlled trials of lipid modifying which have been reviewed here according to strict inclusion criteria.

The new guidelines differ from the previous National Heart Foundation of Australia (NHFA) guidelines in that there is increased emphasis on low-density lipoprotein cholesterol (LDL-C) as the major atherogenic component of plasma and high density lipoprotein cholesterol (HDL-C) as the anti-atherogenic component.

Another important difference from the previous guidelines is that risk categorisation has been simplified by defining only one high-risk group. This has been done to draw attention to the need to focus on those high-risk individuals who have the most to gain in terms of risk reduction from lifestyle modification and the appropriate use of lipid-modifying medication. Focusing on this high risk group is likely to be more cost-effective than extending intervention to lower-risk individuals. However, formal health-economic and cost-effectiveness analyses were beyond the scope of these guidelines. We recognise that, in Australia, there is an existing system through the Pharmaceutical Benefits Advisory Committee and Pharmaceutical Benefits Scheme (PBS) to consider cost-effectiveness of medications and to regulate prescribing on the basis of these considerations.

The previous NHFA guidelines contained recommendations on both initiation points for lipid-modifying therapy and target lipid levels. These new guidelines consider the indication for which treatment is appropriate within the context of overall risk assessment in primary prevention (rather than cholesterol levels alone), as well as suggesting target lipid levels once a decision to treat has been made, while emphasising that any movement towards the targets will be beneficial even if they are not reached. Doctors need to determine whether their high risk patients (as defined in these guidelines) have lipid levels which satisfy Australian PBS regulations for starting lipid-modifying medication before beginning treatment.

Rating of the evidence for recommendations

Evidence is graded according to the level-of-evidence classifications endorsed by the National Health and Medical Research Council (NHMRC) in 1995.

E1 Level I: Evidence obtained from a systematic review of all relevant randomised controlled trials.

E2 Level II: Evidence obtained from at least one properly designed randomised controlled trial.

E3 Level III: Evidence obtained from all well-designed controlled trials without randomisation, well-designed cohort or case-control analytic studies, preferably from more than one centre or research group, or from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

E4 Level IV: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Glossary

CHD: coronary heart disease

HMG-CoA reductase: 3-Hydroxy-3-methylglutaryl coenzyme A reductase

LDL-C: Low-density lipoprotein cholesterol

HDL-C: High-density lipoprotein cholesterol

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Summary of key recommendations

Initial assessment

- All adults should receive ongoing risk assessment and preventive and lifestyle advice within a general practice or equivalent setting. (E4)
- Regular blood lipid testing is recommended for all adults 45 years and older and for those less than 45 years old, who may be at higher risk because of other (non-lipid) risk factors. (E4)
- All adults at high risk should have lipid levels measured at least annually as part of ongoing assessment and management of overall cardiovascular disease (CVD) risk. (E4)
- Before treatment, an initial (preferably fasting) blood sample should be taken to allow measurement of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride and glucose levels. (E4)
- Mass screening for lipid levels in the general population, regardless of age, is not currently recommended. (E4)

Treatment initiation

- The criteria for higher absolute risk of coronary heart disease (CHD) to guide treatment decisions are shown in Box 1.
- For those considered to be at higher absolute risk and above target levels:
 - a) Monitor diet fortnightly for six weeks, then retest lipid levels. If these are still above target levels consider commencing lipid-modifying therapy (taking into account Pharmaceutical Benefits Scheme [PBS] criteria).
 - b) Retest fasting lipids every two months until a satisfactory and stable response has been achieved.
- In those who are known to have CHD, and particularly in those who have been hospitalised with CHD events and who have a total cholesterol level of 4.0 mmol/L or above, it is appropriate to consider starting drug treatment without awaiting assessment of the effects of dietary intervention. (E2)

Lipid target levels

Less evidence exists for target levels than for populations in whom treatment should be initiated. Suggested targets are:

LDL-cholesterol	< 2.5 mmol/L
Total cholesterol	< 4.0 mmol/L
HDL-cholesterol	> 1.0 mmol/L
Triglycerides	< 2.0 mmol/L

The target levels may be higher (eg, LDL-C < 3.0 mmol/L) in lower-risk patients. It should be emphasised that any lowering of plasma total cholesterol and LDL-C levels and any raising of the HDL-C level is likely to be beneficial even if the recommended target is not achieved.

Children

- Cardiovascular disease risk factors affect arteries from an early age. (E3)

1: Criteria for higher absolute risk of coronary heart disease to guide treatment decisions (E4)

1. Known coronary heart disease (CHD)
2. Other known manifestations of atherothrombotic disease — peripheral arterial disease (lower limb atherosclerosis), ischaemic cerebrovascular disease, abdominal aortic aneurysm
3. Diabetes mellitus
4. Chronic renal failure or renal transplantation
5. Aboriginal peoples and Torres Strait Islanders
6. Familial hypercholesterolaemia
7. Familial combined hyperlipidaemia
8. Absolute risk of 10%–15% or greater in the next five years according to the New Zealand cardiovascular risk calculator
9. Increased absolute risk judged by levels of low-density lipoprotein cholesterol (LDL-C) > 4.0 mmol/L or total cholesterol > 6.0 mmol/L **plus** any two (or more) other risk factors (high-density lipoprotein cholesterol [HDL-C] level < 1.0 mmol/L, significant family history, hypertension, overweight or obesity, smoking, impaired fasting glucose or glucose intolerance, microalbuminuria and/or renal impairment, age ≥ 45).

• Most people satisfying the above criteria should be treated. The threshold for initiating treatment is based on assessing absolute risk in the individual and Pharmaceutical Benefits Scheme (PBS) guidelines. However, clinical judgement may be necessary in patients who are classified inappropriately by this definition of risk. A high cholesterol level alone may not warrant aggressive drug treatment. However, apparently healthy subjects with an LDL-C level > 6.0 mmol/L as the only known coronary risk factor should be considered for more active intervention, which may include drug therapy, because of the possibility of underlying familial hypercholesterolaemia. Drug treatment should be associated with, and, in those without known CHD, preceded by, dietary measures. Attention to other risk factors is essential.

• PBS criteria allow eligibility for subsidy for treatment in men aged 35–75 years and postmenopausal women up to 75 years with levels of total cholesterol > 7.5 mmol/L or triglyceride > 4.0 mmol/L and in other age groups with levels of total cholesterol > 9.0 mmol/L or triglyceride > 8.0 mmol/L, regardless of other risk factors.

- Most attention should be directed towards ensuring a healthy pattern of eating and physical activity, together with avoidance of smoking. (E4)
- Clinical and laboratory assessment of cardiovascular risk factors, including LDL-C and HDL-C levels, should be considered for the children in families in which there is a clear history of premature onset of CHD (< 60 years in a first-degree relative). (E4)
- Lipid levels should be measured in children with diabetes. (E4)
- There is a lack of information in relation to using lipid-modifying therapy in high-risk children. The treatment of children at high risk of CHD remains an area where clinical judgement is vital. (E4)

Lifestyle interventions

Healthy eating recommendations (E3-4)

Encourage patients to base their eating patterns on the following guidelines:

- Use spreads instead of butter or dairy blends.

- Use a variety of oils for cooking, such as canola, sunflower, soybean and olive oils.
 - Use salad dressings and mayonnaise made from oils such as canola, sunflower, soybean and olive oils.
 - Choose low or reduced fat milk and yoghurt or calcium-fortified soy beverages. Restrict cheese and ice cream intake to twice a week.
 - Have fish (fresh or canned) at least twice a week.
 - Select lean meat (trimmed of fat, chicken without skin) and limit fatty meats, including sausages and delicatessen meats such as salami.
 - Snack on plain, unsalted nuts and fruit.
 - Incorporate legumes into two meals a week.
 - Base meals around vegetables, and grain-based foods such as bread, pasta, noodles and rice.
 - Limit take-away foods such as pastries, pies, pizza, hamburgers and creamy pasta dishes to once a week.
 - Limit snack foods such as potato and corn crisps to once a week.
 - Limit cakes, pastries and chocolate or creamy biscuits to once a week.
 - Limit cholesterol-rich foods such as egg yolks and offal.
- Consider referral to an Accredited Practising Dietitian.

Fish oil and fish: Fish oils may have an important place when used in combination with statins to lower the triglyceride level in combined hyperlipidaemia. However, at this time, it is uncertain whether the use of fish oil capsules adds anything over and above the inclusion of a moderate consumption of fish. Therefore, patients should be encouraged to consume fish at least twice per week. (E4)

Plant sterol esters: Plant sterols may provide a useful and acceptable way of enhancing cholesterol lowering in people taking statins. (E2)

Smoking cessation

Counselling to strongly encourage patients and their families to stop smoking is vital. Passive smokers should be provided with appropriate facts on smoking.

Consider referral to the Quitline (phone 131 848) or a smoking cessation program. If the patient is smoking more than 20 cigarettes/day and the first cigarette is within 30 minutes of waking, consider nicotine replacement therapy to assist with smoking cessation.

Physical activity (E3-4)

- At least 30 minutes of moderate-intensity physical activity should be undertaken on most, preferably all, days of the week.

Weight reduction (E3-4)

- Aim for a body mass index (BMI) of < 25 (set intermediate achievable goals).
- Waist circumference for men should be < 90cm and, for women, < 80cm (these are based mainly on evidence of increased risk of death in European populations and may not be appropriate for all age and ethnic groups).

- Encourage patients to enjoy regular moderate-intensity physical activity and change their eating habits to modify energy intake. Consider referral to an Accredited Practising Dietitian for individual counselling and advice.

Alcohol

- Advise patients with elevated plasma triglyceride levels to limit their alcohol intake. (E4)

Salt

- Reduction of salt intake is important for people with hypertension, as it has been shown to reduce blood pressure in this group and lower cardiovascular disease risk. (E1)

Further information

For further information about lifestyle interventions contact the Heart Foundation's Heartline on 1300 36 27 87 for the cost of a local call.

Lipid-modifying therapy (E4)

- HMG-CoA reductase inhibitors are the agents of choice for LDL-C lowering.
- Liver function should be tested at least once about six weeks after starting therapy with an HMG-CoA reductase inhibitor and care is needed in patients with pre-existing liver disease. The dose of HMG-CoA reductase inhibitor must be reduced in patients taking cyclosporin.
- Fibrates are effective triglyceride-lowering/HDL-C-raising agents.
- The combination of an HMG-CoA reductase inhibitor and fibrate may be considered in high-risk people whose lipid profile remains unacceptable after a trial on monotherapy. In general, combination therapy should be initiated by a specialist. Levels of creatine kinase (CK) and liver enzymes should be monitored within the first six weeks and then at six-monthly intervals in patients taking such combination therapy.
- Resins can be used to increase the lowering of LDL-C substantially when given in combination with HMG-CoA reductase inhibitors. This additional benefit can be achieved with relatively low (and usually well tolerated) doses of the resins.
- The addition of low dose nicotinic acid to an HMG-CoA reductase inhibitor is well tolerated by most people, and substantially enhances triglyceride lowering and HDL-C raising and, to some extent, also LDL-C lowering.

Adherence

- When relevant, commence lipid-modifying therapy in patients with CHD while patients are still in hospital. (E2)
- When possible, consider ancillary measures (eg, special clinics, telephone support, coaching) to help patients achieve and maintain target lipid levels. (E2)
- Assess patients' adherence to medications at each visit. (E4)

1. Plasma total cholesterol and low-density lipoprotein cholesterol

Biological mechanism linking low-density lipoprotein cholesterol to coronary heart disease

Most of the cholesterol in plasma is transported as a component of low-density lipoproteins (LDLs). Thus, the evidence linking CHD to plasma total cholesterol and LDL-C is essentially the same.

The mechanisms by which LDLs cause atherosclerosis and by which existing atherosclerotic plaques become unstable are now reasonably well understood, although many of the finer details remain to be elucidated. Box 2 summarises current knowledge regarding how LDLs and other plasma lipoproteins are associated with atherosclerosis.

Prospective human population studies

Cholesterol and CHD

Epidemiological associations do not necessarily mean there is a causal relation between a risk factor and disease. However, prospective population studies tend to underestimate the strength of associations such as that between cholesterol and CHD because of measurement error and biological variability associated with data based on a single cholesterol measurement ("regression dilution bias").

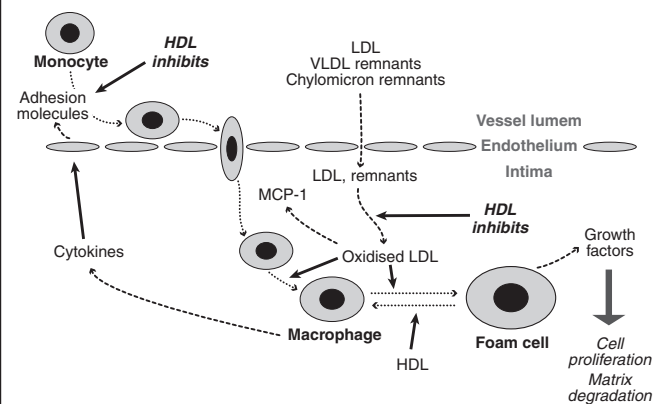
It is noteworthy that most patients who develop CHD have cholesterol levels which are not markedly elevated and which overlap substantially with those of the general population.

There are many large-scale, prospective population studies of the association between plasma total (and LDL) cholesterol levels and the future risk of developing CHD. These include the Multiple Risk Factor Intervention Trial (MRFIT),⁶⁻⁸ the Framingham Heart Study⁹ and the Prospective Cardiovascular Munster (PROCAM) Study.¹⁰ The **Multiple Risk Factor Intervention Trial (MRFIT)**,⁶⁻⁸ a prospective study of more than 360 000 men, with follow-up now more than 10 years, shows a continuous positive curvilinear relationship between plasma cholesterol concentration and rates of death from CHD (see Box 3). There is no evidence of a threshold (at least down to levels of about 4.5 mmol/L) below which plasma cholesterol levels are no longer predictive. The curve appears to flatten at lower levels, although the small number of people with cholesterol levels below 4.5 mmol/L makes it difficult to draw firm conclusions.

The **Framingham Heart Study** commenced in 1948 and has followed 5209 men and women over five decades. Subjects were aged 28 to 62 at entry into the study. CHD events and CHD mortality have been closely monitored over the past 50 years and the incidence has been related to a variety of measurements. As with the MRFIT study, the CHD risk correlates positively and curvilinearly with levels of plasma total cholesterol and LDL-C. The offspring of the original participants also show similar relationships between risk factors and future CHD.

The prospective **PROCAM Study** of more than 30 000 individuals in Germany was commenced in 1978. There are

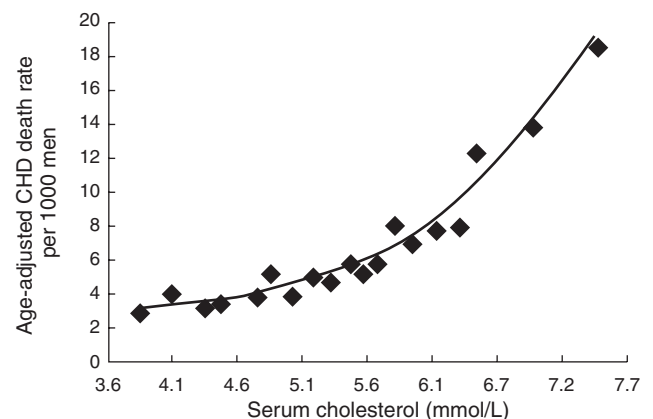
2: Lipoproteins and atherosclerosis



Plasma low-density lipoproteins (LDLs) cross the endothelial layer and enter the subendothelial space. Unless the concentration in plasma is low, the rate of entry of LDLs into the artery wall is greater than the rate of exit and the lipoproteins slowly accumulate. The LDLs in the subendothelial space become modified in several ways, including by chemical changes that lead to aggregation of the lipoproteins and oxidation of the various lipid and protein constituents. The modified LDLs promote the differentiation of monocytes into macrophages. The macrophages subsequently express scavenger receptors that recognise and take up the modified LDLs. This uptake results in an accumulation of cholesterol in the macrophages, which are converted into foam cells, the presence of which is a hallmark of atherosclerosis. Macrophages and foam cells express a range of growth factors and proteinases that lead to cell proliferation, matrix degradation and ultimately to the progression and rupture of the atherosclerotic plaque. Macrophages also release cytokines, some of which activate endothelial cells to express adhesion molecules that recruit more monocytes from blood, continuing the formation of macrophages. Thus, the lesion progresses unless the plasma LDL level falls, removing the stimulus to lesion growth.

LDL = low-density lipoprotein; VLDL = very-low-density lipoprotein; HDL = high-density lipoprotein; MCP-1 = monocyte chemoattractant protein-1.

3: Serum cholesterol concentration and coronary heart disease (CHD) in 361 662 men: the Multiple Risk Factor Intervention Trial



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follow-up data on 5200 men aged 40–65 years at entry. The relationship between LDL-C and CHD event rate in PROCAM is consistent with the results in MRFIT and the Framingham study, although the PROCAM investigators placed a greater emphasis on interactions of LDL-C with the levels of triglyceride and HDL-C and the combination of abnormalities.

Conclusions from population studies

The results of prospective population studies regarding the relationship between plasma total cholesterol and LDL-C and the risk of CHD are consistent and support several general conclusions:

- Most patients with known CHD do not have markedly elevated levels of plasma total cholesterol or LDL-C.
- Prospective studies show an association between total cholesterol and LDL-C and the risk of developing CHD, but do not establish that the relationship is one of cause and effect.
- There is a continuous positive but curvilinear relationship between the concentration of plasma total (and LDL) cholesterol and the risk of a future coronary event and of dying of CHD.
- There is less evidence on the relationship between cholesterol levels less than 4.5 mmol/L and CHD risk, as prospective population studies have entailed many fewer events in individuals with cholesterol levels in this range.
- The evidence is strong that the risk of CHD decreases progressively, at least down to plasma total cholesterol levels of 4.5 mmol/L (equating with LDL-C levels of 2.5–3.0 mmol/L), although the curve is clearly flattening at lower levels of plasma total cholesterol and LDL-C.
- There is no evidence that a low level of plasma total (or LDL) cholesterol predisposes to an increase in non-coronary mortality (the excess non-coronary mortality at low cholesterol levels in the Honolulu Heart Study^{11,12} was apparent only in people who smoked and is consistent with a view that smokers may have occult smoking-related disease that is responsible for both an increased mortality and a low total cholesterol level).

Intervention studies

Clinical trial data are most generalisable when the participants are very similar to the general population who are to be treated. Net benefit of an intervention depends not only on the demonstrated relative risk reduction but baseline risk (eg, risk is usually greater in those with known disease compared to the general population, and in the elderly or people with diabetes), and also on its tolerability and safety. Data in subgroups of the cohort are often over-interpreted because studies are usually not powered to address effects reliably in such subgroups. It should also be remembered that clinical trials generally test the intervention (eg, HMG-CoA reductase inhibitors [statins]) in a particular dose, rather than the mechanisms by which the intervention exerts its effects.

Criteria for inclusion of studies

Over the past 10 years there have been several well designed studies of interventions which principally lower LDL-C. The evidence base for recommendations in these guidelines includes intervention studies that were large-scale (more than 2000 patients), long-term (more than four years), double-blind, placebo-controlled in which the primary outcome measures were “hard” clinical end-points, and had adequate power to address their aims reliably.

Intervention studies assessing the effects of lowering LDL-C

To August 2001, six studies with drugs that act primarily to reduce LDL-C met the above criteria.

Primary prevention trials: The three primary prevention studies are the Lipid Research Clinics–Coronary Primary Prevention Trial (LRC–CPPT),^{13,14} West of Scotland Coronary Prevention Study (WOSCOPS),¹⁵ and Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS).¹⁶ Details of these studies are provided in Box 4, and the relationship between the “on-treatment” LDL-C level and rates of myocardial infarction in the placebo and active groups in these trials is shown in Box 5.

- **LRC-CPPT:** This trial included 3806 hypercholesterolaemic men without known CHD at entry into the trial. The active treatment was cholestyramine (24 g per day) and the mean follow-up was 7.4 years. The primary endpoint was definite CHD death or definite non-fatal myocardial infarction (MI). The primary endpoint was reduced from 8.6% in the placebo group to 7.0% in the cholestyramine group ($P < 0.05$). There were relatively few deaths in the study, and mortality differences between the active and placebo-assigned groups were not significant.
- **WOSCOPS:** This trial included 6595 men with hypercholesterolaemia, but without clinical CHD, at entry into the trial. The active treatment was pravastatin (40 mg per day) and the mean follow-up was 4.9 years. The primary endpoint was a composite of non-fatal MI or death from CHD. The primary endpoint was reduced from 7.9% in the placebo group to 5.5% in the pravastatin group ($P < 0.001$). The CHD death rate was also reduced from 1.9% to 1.3% ($P = 0.042$). The reduction in all-cause mortality from 4.1% to 3.2% almost reached the conventional boundary for significance ($P = 0.051$).
- **AFCAPS/TexCAPS:** This trial included 5608 men aged 45–73 years and 997 postmenopausal women aged 55–73 years who had “average” plasma cholesterol levels and no clinical CHD at entry into the study. The active treatment was lovastatin (20–40 mg per day) and the mean follow-up was 5.2 years. The primary endpoint was a composite of sudden death, fatal or non-fatal MI and unstable angina. The primary endpoint was reduced from 9.3% in the placebo group to 6.2% in the lovastatin group ($P < 0.001$). There were relatively few deaths in the study, with no difference between the two groups.

4: Major cholesterol-lowering trials: the Lipid Research Clinics–Coronary Primary Prevention Trial (LRC-CPPT),^{13,14} West of Scotland Coronary Prevention Study (WOSCOPS),¹⁵ Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS),¹⁶ Scandinavian Simvastatin Survival Study (4S),¹⁷ Cholesterol and Recurrent Events (CARE) study,¹⁸ and the Australian and New Zealand Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study¹⁹

(a) Design features

Trial	Prevention strategy	Drug	No. of patients and sex	Age (years)	Baseline cholesterol level (mmol/L)	Follow-up period (years)	Primary end-point
LRC-CPPT	Primary	Cholestyramine	3806, M	35–59	≥ 6.8	7.4	CHD events
WOSCOPS	Primary	Pravastatin	6595, M	45–64	≥ 6.5	4.9	CHD events
AFCAPS/TexCAPS	Primary	Lovastatin	5608, M 997, F	45–73 55–73	4.6–6.8	5.2	CHD events
4S	Secondary	Simvastatin	3617, M 827, F	35–70	5.5–8.0	5.4	Total mortality
CARE	Secondary	Pravastatin	3583, M 576, F	21–75	< 6.2	5.0	CHD events
LIPID	Secondary	Pravastatin	7498, M 1516, F	31–75	4.0–7.0	6.0	CHD mortality

M = male; F = female; CHD = coronary heart disease.

(b) Baseline plasma lipid levels (mmol/L) and per cent change on treatment*

Trial		Total cholesterol	LDL-C	HDL-C	Triglycerides
LRC-CPPT	Baseline lipid level (mmol/L)	7.2	5.3	1.15	1.8
	% change	–8.5%	–12.6%	+3.6%	+14%
WOSCOPS	Baseline lipid level (mmol/L)	7.0	5.0	1.14	1.9
	% change	–20%	–26%	+5.0%	–12%
AFCAPS/TexCAPS	Baseline lipid level (mmol/L)	5.7	3.9	0.94	1.8
	% change	–18%	–25%	+6%	–15%
4S	Baseline lipid level (mmol/L)	6.8	4.9	1.19	1.5
	% change	–25%	–35%	+8%	–10%
CARE	Baseline lipid level (mmol/L)	5.4	3.6	1.01	1.8
	% change	–20%	–28%	+5%	–14%
LIPID	Baseline lipid level (mmol/L)	5.6	3.9	0.93	1.6
	% change	–18%	–25%	+5%	–11%

* Per cent change on treatment relative to placebo; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.

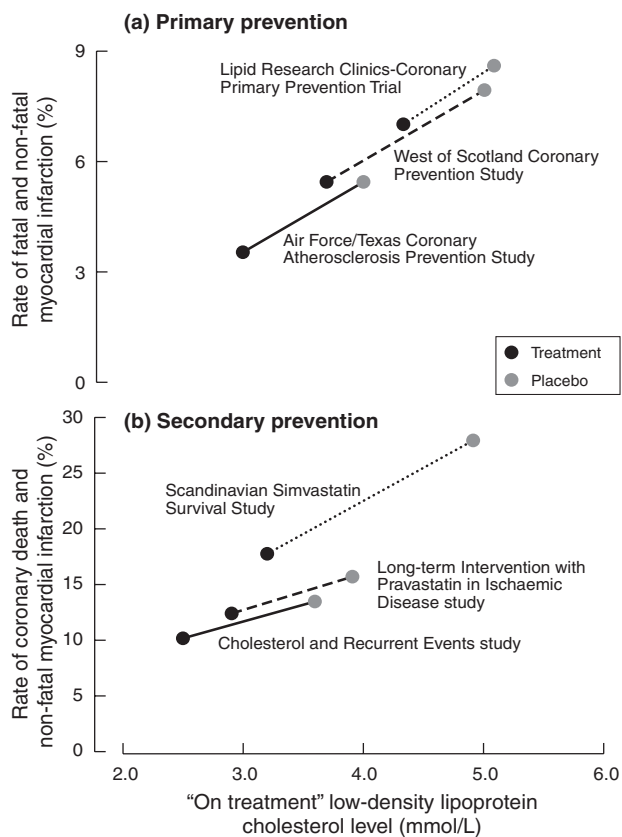
(c) Major cardiovascular end points*

Trial and treatment	CHD mortality	Total mortality	Myocardial infarction (fatal and non-fatal)	Unstable angina pectoris	Coronary artery bypass grafting	Percutaneous coronary intervention	Stroke
LRC-CPPT							
Placebo	2.0%	3.7%	9.8%	—	5.9%	—	—
Cholestyramine	1.6%	3.6%	8.1%	—	4.9%	—	—
WOSCOPS							
Placebo	1.9%	4.1%	6.5%	—	2.5%	—	1.4%
Pravastatin	1.3% [†]	3.2%	4.6% [§]	—	1.7% [‡]	—	1.4%
AFCAPS/TexCAPS							
Placebo	0.9%	2.3%	5.6%	5.1%	9.3%	—	—
Pravastatin	0.6%	2.4%	3.3% [‡]	3.5% [†]	6.2% [§]	—	—
4S							
Placebo	8.5%	11.5%	15.2%	14.9%	17.2%	—	4.3%
Simvastatin	5.0% [§]	8.2% [§]	9.0% [‡]	13.3%	11.3% [§]	—	2.7%
CARE							
Placebo	5.7%	9.4%	10.0%	17.3%	10.0%	10.5%	3.8%
Pravastatin	4.6%	8.7%	7.5% [‡]	15.2%	7.5%	8.3%	2.6%
LIPID							
Placebo	8.3%	14.1%	10.3%	24.6%	11.6%	15.7%	4.5%
Pravastatin	6.4% [‡]	11.0%	7.4% [§]	22.3% [‡]	9.2% [§]	13.0%	3.7%

* The primary end-point differed between studies. Also, because of different definitions of CHD events, it is inappropriate to present the numbers needed to treat to prevent an event to allow comparisons between the trials.

† $P < 0.05$; ‡ $P < 0.01$; § $P < 0.001$.

5: Relationship between the “on-treatment” LDL-C level and rates of myocardial infarction (grouped mean data) in the three primary prevention trials, and rates of CHD events (grouped mean data) in the three major secondary prevention trials



Secondary prevention trials: The three major secondary prevention trials are the Scandinavian Simvastatin Survival Study (4S),¹⁷ the Cholesterol and Recurrent Events (CARE) study¹⁸ and the Australian and New Zealand Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study.¹⁹ Details of these studies are provided in Box 4.

- **4S:** This trial included 3617 men and 827 women aged 35–70 years with hypercholesterolaemia and pre-existing CHD. The active treatment was simvastatin (20 mg, up-titrated to 40 mg per day in 37% of patients) and the median follow-up was 5.4 years. The primary endpoint was all-cause mortality, which decreased from 11.5% in the placebo group to 8.2% in the simvastatin group ($P < 0.001$). There was also a significant reduction in major coronary event rate from 22.6% in the placebo group to 15.9% ($P < 0.001$), and in the coronary death rate from 8.5% to 5.0% in the simvastatin group ($P < 0.001$).
- **CARE:** This trial included 3583 men and 576 women aged 21–75 years (mean, 59 years) who were normocholesterolaemic and had had previous MI. The active treatment was pravastatin (40 mg per day) and the median follow-up was 5.0 years. The primary endpoint was coro-

nary death or non-fatal MI, which was significantly reduced from 13.2% in the placebo group to 10.2% in the pravastatin group ($P = 0.003$). Mortality differences were not significant.

- **LIPID:** This trial included 7498 men and 1516 women aged 31–75 years with previous acute coronary syndromes and total cholesterol levels of 4.0–7.0 mmol/L. The active treatment was pravastatin (40 mg per day) and the mean follow-up was 6.1 years. The primary endpoint was CHD mortality, which was reduced from 8.3% in the placebo group to 6.4% in the pravastatin group ($P < 0.001$). All-cause mortality was reduced from 14.1% to 11.0% by pravastatin ($P < 0.001$).
- **Other evidence:** The largest of the reported randomised controlled trials of the effects of cholesterol lowering early after acute coronary syndromes is the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study.²⁰ This study included 3086 adults aged 18 years or older with unstable angina or non-Q-wave acute MI, who were randomly assigned to receive atorvastatin (80 mg per day) or matching placebo commencing 24–96 hours after hospital admission; the follow-up was 16 weeks. The primary endpoint was a composite of death, nonfatal acute MI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischaemia with objective evidence and requiring emergency rehospitalisation. One of these events occurred in 14.8% of the atorvastatin group and 17.4% of the placebo group ($P = 0.048$). Of the individual components of the composite endpoint, only the reduction in symptomatic ischaemia was significant (6.2% v 8.4%; $P = 0.02$). These and other data show that it is safe to initiate therapy very early after an acute event, with the possibility that early therapy may further reduce events.

- **Overview of secondary prevention trials:** The relationship between the on-treatment LDL-C level and CHD events in the placebo and active groups in the 4S, CARE and LIPID trials is shown in Box 5.

The main conclusions of a recent meta-analysis of the major statin intervention trials²¹ were:

- a statin-induced reduction in LDL-C decreases the risk of CHD and all-cause mortality in people at high risk of CHD; and
- the relative risk reduction is similar in men and women and for middle-aged and elderly people.

Another meta-analysis²² concluded:

- lowering of plasma cholesterol is clinically beneficial;
- use of statins does not increase non-cardiac mortality; and
- the beneficial effects of statins on CHD and total mortality can be explained by their lipid-lowering ability and appear to be directly proportional to the degree to which lipids are lowered.

Conclusions from low-density cholesterol-lowering trials: Several generalisations can be made from these trials with statins.

- The results of the intervention trials are consistent with the prospective population studies from which (excluding possible regression dilution bias) it is essential that a

1.0 mmol/L reduction in plasma total cholesterol translates into an approximate 20% reduction in the risk of future coronary events. However, it should be emphasised that the epidemiological relation is non-linear and this conclusion does not necessarily apply beyond the range of cholesterol levels which have been tested in these studies.

- The benefits are apparent in people with and without CHD. (E1)
- The benefits are apparent in patients with a wide range of baseline total cholesterol and LDL-C levels. (E1)
- While the trials were not designed (or powered) to show benefits of lipid lowering in specific groups, such as those with diabetes, women and the elderly, there was no evidence that any of these subgroups responded differently from the group as a whole. (E4)
- Adequately powered studies show that the percentage reduction in coronary mortality is no different from the percentage reduction in non-fatal coronary events. (E2)
- Trial drugs are well tolerated and safe. There is no evidence in these trials of an excess of non-coronary mortality in the treated groups. (E2)
- The reduction in coronary risk in these intervention trials can be largely explained in terms of the cholesterol levels achieved. The magnitude of any other potential effects and the extent to which they are independent of LDL-C lowering is unclear (eg, effects on coronary plaque stability). Trials investigating the importance of the non-lipid effects of statins are currently under way.
- It is safe to initiate therapy very early after an acute coronary syndrome, and possible that such therapy may further reduce subsequent events. (E2)

2. Plasma triglyceride and high density lipoprotein cholesterol

There is an inverse relationship between the concentrations of plasma triglyceride and HDL-C.²³ This has been responsible for much confusion and for some apparently conflicting views of the roles played by triglyceride and HDL-C in the development of CHD. For example, it has been argued that the apparent ability of HDL-C to protect against CHD may be an epiphenomenon reflecting the association of low HDL-C with an elevated level of plasma triglyceride. The converse has also been argued. However, as outlined below, it is probable that triglyceride and HDL-C are each independently related to CHD. Triglyceride concentration has been found in several studies to be an independent predictor of risk.²³ It is therefore important to include measurements of triglyceride and HDL-C in an overall assessment of CHD risk. Some guidelines use the ratio of total cholesterol to HDL-C, or LDL-C to HDL-C, as a predictor of risk. While these ratios have been shown to improve predictive value in epidemiological studies, the intrinsic error in the calculation of such ratios is considered by some to limit their value in assessing individual patients.

Biological mechanism relating triglyceride and high-density lipoproteins to coronary heart disease

Triglyceride

Triglyceride within uncatabolised lipoproteins (chylomicrons and very low-density lipoproteins (VLDL)) appears to be non-atherogenic, as evidenced by the absence of an increased CHD risk in patients with a deficiency of lipoprotein lipase, in whom plasma triglyceride levels may be very high (often > 20 mmol/L). It is likely that the positive relationship between plasma triglyceride and CHD, as observed in many population studies, is because in many people an elevated level of plasma triglyceride is a reflection of an accumulation of the atherogenic remnants of chylomicrons and VLDL. These particles are rich in both triglyceride and cholesterol and appear to be at least as atherogenic as LDL. This view is supported by the observation that the remnants of triglyceride-rich lipoproteins are the particles that occur in dysbetalipoproteinaemia, a condition associated with a very high risk of premature atherosclerotic vascular disease.

High-density lipoproteins

Possible mechanisms by which HDLs may protect against the development of atherosclerosis are shown in Box 2. There are several well documented functions of HDLs that may explain the ability of these lipoproteins to protect against atherosclerosis.²⁴ The best recognised of these is the promotion by HDLs of cholesterol efflux from cells in a process that may minimise the accumulation of foam cells in the artery wall. The major proteins of HDLs, and also other proteins (eg, paraoxonase) that co-transport with HDLs in plasma, have antioxidant properties. Thus, HDLs have the ability to inhibit the oxidative modification of LDLs and may thereby reduce the atherogenicity of these lipoproteins. HDLs have also been shown to inhibit the expression of adhesion molecules in endothelial cells, and thus block the recruitment of blood monocytes into the artery wall, a key early step in the development of atherosclerosis.

The ability of HDLs to protect against the development of atherosclerosis has been clearly demonstrated in several in-vivo animal models of atherosclerosis. Animals made transgenic with human apoA-I, the main protein component of HDLs, have an increased concentration of HDLs and a marked protection against the development of atherosclerosis.²⁵ Infusion of HDLs into rabbits has the same effect.²⁶

Thus, there is considerable evidence from experimental data that HDLs have a direct protective effect against the development of atherosclerosis.

Prospective human population studies

Predictive power of plasma triglyceride concentration

Three of the larger prospective studies that have had the ability to investigate the relationships between triglyceride and HDL-C and CHD event rates are the Framingham Heart Study,²⁷ the PROCAM study¹⁰ and the group assigned

placebo in the Helsinki Heart Study.²⁸ These studies provide consistent results that may be summarised as follows.

The level of plasma triglyceride was predictive of premature CHD in the PROCAM Study only in those who also had either an LDL-C level that was mildly to moderately elevated, a low level of HDL-C, or both. Thus, if the ratio of LDL-C to HDL-C was less than 5, the plasma triglyceride level did not appear to be predictive. If, however, the LDL-C to HDL-C ratio (which was used by the PROCAM investigators) was greater than 5, the CHD event rate was significantly greater in those with triglyceride levels > 2.3 mmol/L than in those with triglyceride levels < 2.3 mmol/L.

There have been two comprehensive reviews of the relationship between plasma triglyceride and CHD event rates.^{23,29} One concluded that triglyceride is not an independent predictor of CHD and is probably not causally related to its development,²⁹ while the other advanced a compelling case for a causal role for some triglyceride-rich lipoproteins.²³

Conclusions from population studies of plasma triglyceride and the risk of CHD:

- An elevated concentration of plasma triglyceride (> 2.0 mmol/L) is predictive of CHD when associated with either an increased concentration of LDL-C or a decreased concentration of HDL-C.
- The relationship between CHD risk and plasma triglyceride is less clear than for cholesterol, but there is evidence that CHD risk is greatest in those with triglyceride levels between 2 mmol/L and 6 mmol/L.

Predictive power of HDL-C

An inverse relationship between the level of HDL-C and the risk of developing premature CHD has been consistently found in a large number of prospective population studies, and in many the level of HDL-C has been the single most powerful lipid predictor of future CHD events.

Key studies of the relationship between HDLs and CHD include the Framingham Heart Study,²⁷ the PROCAM study,¹⁰ the Helsinki Heart Study²⁸ and the MRFIT study.^{6,7} The HDL-C data from Framingham, the Lipid Research Clinics Prevalence Mortality Follow-up Study and MRFIT have been analysed.³⁰ Overall, it has been concluded from these prospective population studies that, for every 0.025 mmol/L increase in HDL-C, the CHD risk is reduced by 2%–5%. A review of the relationship between HDL-C and CHD is presented elsewhere.²⁴

Conclusions from population studies of HDL-C and the risk of CHD:

- HDL-C concentration is a strong negative predictor of CHD risk.
- If the LDL-C level is very low (< 2.5 mmol/L, as is commonly observed in populations in whom the fat intake is low), a low HDL-C level may be of little importance.
- For every 0.025 mmol/L increase in HDL-C level there is a 2%–5% decrease in coronary risk (excluding possible regression dilution bias).

- Population study findings are consistent with a recommendation that HDL-C levels should ideally be 1.0 mmol/L or above.

Human intervention studies with fibrates

Over the past few years there have been four fibrate intervention studies in humans that meet the inclusion criteria as applied to the studies of interventions which, with statins, might particularly lower LDL-C, as described above. The studies of fibrates that meet these criteria include the World Health Organization (WHO) clofibrate study,³¹ the Helsinki Heart Study,³² the Veterans Administration-HDL Intervention Trial (VA-HIT)³³ and the Bezafibrate Infarction Prevention (BIP) Study.³⁴ Details of these studies are summarised in Box 6.

- **WHO study:** This clofibrate study included individuals whose predominant lipid abnormality was hypercholesterolaemia. Triglyceride and HDL-C levels were not measured during the study. CHD events in the WHO trial were reduced from 7.4% in the placebo group to 5.9% in the clofibrate group ($P < 0.05$). However, there was also a small but significant excess of non-coronary deaths in the group receiving clofibrate, an observation that led many to be cautious about the continued use of this drug class. Subsequent re-analysis on an intention-to-treat basis showed that the increase in non-CHD deaths was not significant. It is relevant that subsequent trials with other fibrates, with gemfibrozil (Helsinki Heart Study and VA-HIT study) and bezafibrate (BIP study) have not observed a significant excess of non-coronary deaths.
- **Helsinki Heart Study:** This double-blind, placebo-controlled trial included 4081 men aged 40–55 years who were free of manifest CHD at entry to the study. The active treatment was gemfibrozil (1200 mg daily) and the mean follow-up was five years. The primary endpoint (CHD events) was reduced from 4.1% in the placebo group to 2.7% in the gemfibrozil group ($P = 0.02$). In a post-hoc analysis, it was found that most of the benefit in this trial was confined to patients in whom the main abnormality was an elevation of plasma triglyceride concentration (> 2.3 mmol/L) in combination with a reduced level of HDL-C (< 1.0 mmol/L). In this subgroup, CHD events were reduced by about 70%, from 6.3% to 2.0% ($P < 0.005$).
- **VA-HIT:** This double-blind, placebo-controlled trial included 2531 men aged less than 74 years and with known CHD. The active treatment was gemfibrozil (1200 mg daily) and the mean follow-up was 5.1 years. The primary endpoint (non-fatal MI or coronary death) was reduced from 21.7% in the placebo group to 17.3% in the gemfibrozil group ($P = 0.006$). The on-treatment HDL-C level was predictive of CHD events in both the active and placebo groups.
- **BIP:** This double-blind, placebo-controlled trial included 2825 men and 265 women aged 45–74 years and with existing CHD. The active treatment was bezafibrate

6: Major trials with fibrates: World Health Organization (WHO) clofibrate study,³¹ the Helsinki Heart Study (HHS),³² the Veterans Administration-HDL Intervention Trial (VA-HIT),³³ and the Bezafibrate Infarction Prevention (BIP) Study³⁴

(a) Design features

Trial	Primary or secondary	Drug	No. of patients and sex	Age (years)	Baseline lipid level (mmol/L)	Follow-up period (years)	Primary end-point
WHO	Primary	Clofibrate	10 627, M	30–59	Upper tertile of TC	5.3	CHD events
HHS	Primary	Gemfibrozil	4081, M	40–55	Non-HDL-C 5.2	5.0	CHD events
VA-HIT	Secondary	Gemfibrozil	2531, M	< 74	LDL-C < 3.6 HDL-C < 1.0 TG < 3.4	5.1	CHD events
BIP	Secondary	Bezafibrate	2825, M 165, F	45–74	TC 4.7–6.5 HDL-C < 1.16 TG < 3.4	6.2	CHD events

M = male; F = female; CHD = coronary heart disease; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.

(b) Baseline lipid levels (mmol/L) and per cent change on treatment*

Trial		Total cholesterol	LDL-C	HDL-C	Triglycerides
WHO	Baseline lipid level (mmol/L)	6.4	—	—	—
	% change	–9%			
HHS	Baseline lipid level (mmol/L)	7.0	4.9	1.22	2.0
	% change	–10%	–11%	+11%	–35%
VA-HIT	Baseline lipid level (mmol/L)	4.5	2.9	0.83	1.8
	% change	–4%	0	+6%	–31%
BIP	Baseline lipid level (mmol/L)	5.5	3.8	0.89	1.7
	% change	–5%	–5%	+14%	–25%

*Per cent change on treatment relative to placebo; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.

(c) Major cardiovascular end points*

Trial and treatment	CHD mortality	Total mortality	Myocardial infarction (fatal and non-fatal)	Unstable angina pectoris	Coronary artery bypass grafting	Percutaneous coronary intervention	Stroke
WHO							
Placebo	1.2%	3.8%	7.4%				
Clofibrate	1.3%	4.9%	5.9%†				
HHS							
Placebo	0.9%	2.1%	4.1%				
Gemfibrozil	0.7%	2.2%‡	2.7%†				
VA-HIT							
Placebo	9.3%	17.4%	21.7%	35.8%	13.7%	11.6%	6.9%
Gemfibrozil	7.4%	15.7%	17.3%†	26.2%	13.0%	9.5%	5.1%†
BIP							
Placebo	5.7%	9.9%	15.0%	5.3%	10.2%	5.7%	5.0%
Bezafibrate	6.1%	10.4%	13.6%	4.9%	9.3%	5.9%	4.6%

*The primary end-point differed between studies. Also, because of different definitions of CHD events, it is inappropriate to present the numbers needed to treat to prevent an event to allow comparisons between the trials.

† $P < 0.05$; ‡ $P < 0.001$.

(400 mg daily) and the mean follow-up was 6.2 years. There was no significant difference in the primary outcome, the combined incidence of non-fatal MI or death from CHD at 5 years, nor at 6.2 years. There was a decrease in the difference between groups during the last 1.2 years of the trial, perhaps because of a decrease in the incidence of events in the placebo group. This may have been caused by a substantial uptake of statins by the placebo group. Post-hoc analysis suggested that there was benefit for the subset of patients in whom the entry triglyceride level was > 2.25 mmol/L, in whom the event rate was 19.7% in the

placebo group and 12.0% in the bezafibrate group ($P = 0.02$).

Studies with statins

It is difficult to interpret the results of statin intervention trials, because they were associated with substantial LDL-C reductions. However, analysis of some studies suggested that HDL-C increase might predict benefit.

To date there are no reported studies that have directly compared the benefits of statins and fibrates in preventing CHD events.

Conclusions from the trials of triglyceride lowering and high-density lipoprotein cholesterol raising

- Treatment that reduces plasma triglyceride and raises HDL-C levels is accompanied by a significant reduction in CHD risk. (E2)
- With fibrates, this benefit may be limited to people whose baseline triglyceride level is elevated ($> 1.5\text{--}2$ mmol/L). (E2)
- The benefits of lowering triglyceride and raising HDL-C are apparent in both primary and secondary prevention. (E2)

3. Plasma lipids and stroke

Population studies relating cholesterol and stroke

Studies investigating the relationship between plasma cholesterol and stroke include the Prospective studies collaboration,³⁵ MRFIT³⁶ and the Eastern Heart and Stroke Study.³⁷ An overview of several trials has also been published.³⁸

- **Prospective studies collaboration:** An overview of 45 prospective studies in around 45 000 individuals included more than 13 000 strokes of all types. This showed no relationship between cholesterol levels and stroke rate when adjusted for age, sex, ethnicity, blood pressure and history of cardiac disease.
- **MRFIT:** Another analysis of the 360 000 people screened in the MRFIT study related total cholesterol levels to stroke categorised by subtype. This showed a positive relationship between increasing total cholesterol level and non-haemorrhagic stroke, but an increase in haemorrhagic stroke at low total cholesterol levels, in those with hypertension.
- **Eastern Heart and Stroke Study:** Similar findings to MRFIT have been found in predominantly Asian populations — a positive continuous relationship between cholesterol and non-haemorrhagic stroke, but a shallow, continuous, negative relationship between cholesterol and haemorrhagic stroke. It is noted that Asian populations typically have a high prevalence of hypertension.

Stroke in primary prevention trials

There have been very few studies assessing the effects of lipid lowering on stroke in primary prevention. One that provided data was WOSCOPS.¹⁵

- **WOSCOPS:** There was a non-significant reduction in stroke with pravastatin (40 mg per day) in patients who had hypercholesterolaemia but no known CHD or cerebrovascular disease at entry into the trial. This finding is consistent with the non-significant reduction in stroke in a meta-analysis of all trials of statins in primary prevention.³⁹

Thus, it is not yet known whether stroke can be prevented by lipid-modifying therapy in patients without manifest atherosclerosis.

Stroke in secondary prevention trials in coronary heart disease patients

The effect of lipid lowering on stroke in the secondary prevention trials has been reported for LIPID,⁴⁰ CARE,¹⁸ 4S¹⁷ and VA-HIT.³³ However, these secondary prevention studies were undertaken in patients with CHD, and thus it is not known if the decrease in the stroke risk observed in these trials would be observed in patients with previous stroke or transient ischaemic attacks (TIAs). This aspect is being addressed in several ongoing large prospective randomised controlled clinical trials.

- **LIPID:** All-cause and ischaemic strokes were specified secondary endpoints in this study. Stroke of all causes was reduced from 4.5% to 3.7% with pravastatin ($P < 0.05$). There was no increase in haemorrhagic stroke in those assigned pravastatin, despite an 18% reduction in total cholesterol in the pravastatin group.
- **CARE:** Stroke was a specified secondary endpoint in the CARE study, and was reduced from 3.8% to 2.6% ($P = 0.03$) with pravastatin, with no increase in haemorrhagic stroke rate.
- **4S:** The 4S group also reported a reduction in stroke with simvastatin from 4.3% to 2.7% ($P = 0.02$).
- **VA-HIT:** This trial studied gemfibrozil in CHD patients with low HDL-C levels (< 1 mmol/L) and relatively normal LDL-C levels (< 3.6 mmol/L). Stroke was a secondary endpoint in the study (ischaemic or haemorrhagic not specified), and was reduced from 6.9% to 5.1% ($P = 0.04$). This effect was considered to be related to an elevation of HDL-C levels in the gemfibrozil group, as there was no difference in LDL-C levels after treatment. Thus, there is high level evidence that, in patients with existing CHD, lipid intervention therapy with either a statin to lower LDL-C or with gemfibrozil in people with low HDL-C reduces the risk of subsequent stroke. Whether these results will apply in patients with existing cerebrovascular disease is currently not resolved.

Conclusions on the relationship between plasma lipids and stroke

- Although variable, population-study findings show a positive relationship between total cholesterol levels and the risk of non-haemorrhagic stroke, which is partially offset by a shallow negative association between total cholesterol levels and the risk of haemorrhagic stroke.
- There has been no increase in haemorrhagic stroke associated with cholesterol reduction in lipid-intervention trials to date.
- In patients with existing CHD, lipid-modifying therapy with either a statin or gemfibrozil can reduce the risk of subsequent stroke. (E2)

- Whether lipid intervention in those with existing cerebrovascular disease is beneficial is being tested in ongoing trials.
- Lipid-modifying therapy in those with existing ischaemic cerebrovascular disease may also be beneficial in terms of reducing CHD risk. (E4)

4. Plasma lipids and vascular disease in other conditions

Diabetes

Statins: Each of the three major secondary prevention statin trials included a significant number of patients with type 2 diabetes, in whom cholesterol levels and changes with treatment were similar to those without diabetes.

- In 4S there were 483 patients with diabetes diagnosed on history or by a fasting glucose level of 7.0 mmol/L or higher. Treating this group with simvastatin reduced major CHD events from 37.5% to 23.5% over 5.4 years ($P=0.001$), compared with a reduction from 26.2% to 18.6% ($P<0.001$) in 3237 participants with normal glucose status.⁴¹

- In the CARE trial, 586 patients with self-reported diabetes had a non-significant reduction of MI or CHD death from 20.4% to 17.7% over five years versus a reduction from 12.0% to 9.1% in 3553 participants without clinical diabetes ($P=0.004$).⁴²

- The LIPID trial included 782 subjects with self-reported diabetes. In this group, pravastatin resulted in a non-significant reduction in MI or CHD death from 22.8% to 19.2% over six years, compared with a reduction from 15.2% to 11.7% in the 8232 participants without diabetes ($P<0.001$).¹⁹ However, in the LIPID trial, there was no statistical evidence of heterogeneity of effect (ie, there was no significant difference between relative risk reductions in the groups with and without diabetes). Comparisons of treatment effects between these trials are difficult because of their different inclusion criteria relating to both baseline lipid levels and different criteria for the diagnosis of diabetes.

Fibrates: The lipid abnormalities particularly associated with type 2 diabetes include elevated triglyceride and low HDL-C. Therefore, treatment with fibrates could theoretically offer special benefit for this group if lipid changes are the primary means of benefit.

- Gemfibrozil reduced CHD events from 10.5% to 3.4% over five years' follow-up among patients with diabetes in the primary prevention Helsinki Heart Study. However, there were only 135 patients with diabetes in this study and the reduction was not statistically significant.⁴³

- In the secondary prevention VA-HIT study, analysis of the prespecified subgroup with diabetes (627 individuals; 25% of the cohort) showed that, over 5.1 years, gemfibrozil reduced the combined endpoint (nonfatal MI, CHD death and confirmed stroke) from 36.5% to 28.5% in people with diabetes ($P=0.05$) and from 22.6% to 17.8% ($P=0.009$) in others.³³

In the placebo groups of both the trials of statins and

fibrates, the risk for CHD events in the groups with diabetes was substantially greater than in the groups without diabetes. Therefore, even if the relative risk reduction in patients with diabetes is no different from that in patients without diabetes, the higher risk of future events indicates a greater absolute benefit in those with diabetes. Some analyses have also shown that the risk for subjects with impaired fasting glucose (6.1–6.9 mmol/L)⁴⁴ and diabetes diagnosed by fasting glucose testing was intermediate between those with normal blood glucose and self-reported diabetes, but again relative risk reductions with treatment were similar.⁴⁵

Conclusions on relationship between plasma lipid levels and vascular disease in diabetes

- In people with type 2 diabetes with pre-existing CHD, lipid-modifying therapy results in a markedly reduced risk of subsequent CHD events. (E2)
- To date, individual published CHD primary prevention studies have not been powered to determine reliably the effect of lipid lowering in people with type 2 diabetes. However, interpretation of available studies suggests that lipid lowering as a primary prevention measure in people with type 2 diabetes will produce substantial benefits in terms of reduced CHD risk. (E4)

Chronic renal failure

People with chronic renal failure requiring dialysis have a marked increase in cardiovascular mortality, although it is difficult to ascertain how many of these deaths are related to coronary artery disease.⁴⁶ Renal impairment that does not require dialysis has also been associated with increased cardiovascular risk, and in one study of men with a creatinine level ≥ 0.13 mmol/L the age-adjusted risk for CHD was 1.5 and for stroke 3.0.⁴⁷ Microalbuminuria has been well documented as a risk factor for CHD in people with type 2 diabetes, and has also been associated with increased cardiovascular risk in people without diabetes or hypertension, increasing risk by 1.5-fold to twofold.^{48,49} CHD risk is also increased in the nephrotic syndrome⁵⁰ and after renal transplantation.⁵¹

Lipid and lipoprotein abnormalities are likely to contribute to the increased CHD risk in all of these manifestations of renal disease. Low HDL-C levels and mild to moderate elevation of triglyceride levels are the predominant abnormalities in chronic renal failure.⁵² Microalbuminuria has been linked with minor elevation of LDL-C levels,⁵³ and marked elevation of LDL-C and triglyceride levels can occur with the nephrotic syndrome.⁵⁴ After renal transplantation, LDL-C levels are frequently elevated, possibly because of treatment with immunosuppressive agents.⁵⁵ However, there are no prospective studies that have quantified the precise cardiovascular risk conferred by these lipid abnormalities in people with renal disease.

Although there is currently no direct evidence of benefit, ongoing clinical studies are assessing the role of statin therapy for CHD prevention in patients with chronic renal failure on haemodialysis and after renal transplantation. If treatment achieves the same relative reduction of CHD risk

that occurs for the general population, then a higher absolute reduction of risk would be anticipated owing to the higher baseline risk, as is the case in people with diabetes.

Conclusions on the relationship between plasma lipid levels and vascular disease in renal disease

- People with renal impairment, including microalbuminuria, are at increased risk of CHD and have abnormalities of lipid metabolism. Treatment with lipid-modifying therapy is likely to reduce this risk. (E4)

5. Lifestyle factors

Appropriate lifestyle changes are an integral part of dyslipidaemia management. When indicated, improvements in diet, physical activity and in other measures, by themselves or in addition to pharmacological measures, can reduce absolute cardiovascular risk over and above lowering plasma lipid levels.

Unless otherwise indicated, the evidence for benefit from lifestyle changes cited below is based on cohort and cross-sectional data. The epidemiological evidence is often very strong, but demonstrates an association and cannot be as robust as that obtained from randomised clinical trials of a single pharmacological intervention. Further, nutritional evidence often derives from a multiplicity of candidate nutrients that may require interaction within foods for optimal efficacy.

Prospective studies of lifestyle patterns

Very large prospective studies have identified aggregations of lifestyle patterns that are associated with the lowest risk for future cardiovascular events. The 14-year follow up of 84 129 nurses in the Nurses' Health Study identified such lifestyle patterns, each of which had independent predictive value.⁵⁶ These protective factors were not smoking; regular physical activity; body mass index (BMI) <25; and intake of cereal fibre, marine n-3 (omega-3) lipid, a high polyunsaturated fatty acid to saturated fatty acid ratio, folate; a low glycaemic load; and moderate alcohol intake. The women with this profile (the minority overall) had only 17% of the overall group's risk of a CHD event.

Nutrients and eating patterns

In the Health Professionals Follow-up Study,⁵⁷ of 44 875 men, the two extreme quintiles for risk of future CHD events were characterised by the following contrasting eating patterns: subjects in the lowest quintile consumed significantly more whole-grain foods, vegetables, fruits, legumes, fish and poultry. The quintile with the most CHD events consumed significantly more red meat, processed meats, refined grains, high-fat dairy products, sweets, and fried potato chips or

crisps. Similar patterns have been observed in many other studies.

Claims for individual nutrients in the cereal, vegetable and fruit categories are less persuasive. These include antioxidant vitamins and flavonoids, folate and soluble fibre. The mechanisms through which nutrients in plant foods protect are likely to be multiple and probably interact, including effects in lowering LDL-C levels (soluble fibre and plant sterols), lowering blood pressure (higher K⁺/Na⁺ ratio), lowering homocysteine (by folate intake), powerful antioxidant properties (polyphenolics, isoflavones, catechins, etc), improving insulin sensitivity (resistant starch and fibre) and reducing energy density.

Two secondary prevention trials focusing on marine n-3 fatty acids have had sufficient power to test effects reliably. The GISSI-Prevenzione Trial⁵⁸ deserves close scrutiny, as it was the first trial of nutrients to establish a clear protective effect against further cardiovascular events. Approximately 5500 patients received 1 g marine n-3 fatty acids as fish oil; a similar number of patients served as controls. All patients received appropriate secondary prevention therapies, including aspirin, β -blockers, statins and, where indicated, angiotensin-converting enzyme inhibitors. Therefore, the benefit of the n-3 fatty acids was in addition to the expected protection from pharmacological management. After 3.5 years, the primary endpoint (a composite of death, non-fatal myocardial infarction and stroke) was reduced from 14.6% to 12.3% ($P < 0.05$). Treated patients also had a significant reduction in cardiovascular mortality, from 6.2% to 5.1% ($P < 0.05$), and total mortality, from 9.6% to 8.3% ($P < 0.05$). No benefits accrued from treatment with vitamin E in this trial.

Like the GISSI study,⁵⁸ the DART reinfarction trial⁵⁹ also showed significant reduction in ischaemic heart disease death, from 11.4% to 7.7% ($P < 0.01$). Therefore, the evidence seems to support daily intake of at least 1 g n-3 fatty acid from fish and fish oil by CHD patients. Pending further adequate randomised controlled trials, at this time it is reasonable to recommend moderate consumption of fish.

The Lyon Diet Heart Study⁶⁰ is another important secondary prevention trial of dietary intervention in 605 CHD patients. The intervention was a Mediterranean diet rich in the polyunsaturated fat α -linolenic acid. When the study was terminated after 27 months of the intervention, the primary endpoint of cardiac death and non-fatal MI had been reduced from 4.1% in the control group to 1.2% in the intervention group ($P = 0.0001$). This study also supports additional and independent beneficial effects of pharmacological treatment and dietary intervention.

A comprehensive analysis of all relevant trials of the relationship between fats and cardiovascular disease can be found in the Heart Foundation's 1999 position statement on dietary fats.⁶¹ A key finding of the review was that there was good evidence that an increase in the consumption of saturated fatty acids is associated with an increase in risk of CHD. Replacing a proportion of saturated fatty acids with n-6 polyunsaturated fatty acids to achieve a polyunsaturated

to saturated ratio of greater than one will reduce the risk of CHD.

Studies investigating the effect of plant sterols and stanols on blood lipid levels show that their effect is additive to that of fatty acid manipulation and that they are an effective adjunct to statins in lowering blood cholesterol. The esterification of sterols and stanols has allowed for their incorporation into unsaturated margarines. Studies with these foods enriched with sterols and stanols have shown that a daily intake of 2–3 g of plant sterols and stanols reduces LDL-C levels by 10%–15%.⁶²

Dietary modelling (in preparation) shows the emphasis of food-based recommendations to achieve the Heart Foundation's dietary fat guidelines⁶¹ should be on fat modification. The dietary models show that a minimum daily intake of 20 g of fat and oil is required to achieve the Heart Foundation's polyunsaturated fatty acids, saturated fatty acid and α -linolenic acid recommendations. The recommended diet model reflects an eating pattern based on cereals, vegetables and fruit, with regular intake of fish, legumes and nuts, margarine spreads, a combination of oils, lean meat and skinless chicken and low-fat milk and yoghurt. Intakes of full-fat dairy products such as cheese and ice cream should be limited to twice a week, and takeaways, snacks and cakes each limited to once a week.

Conclusions

- There is good evidence that replacing a proportion of saturated fatty acids with n-6 polyunsaturated fatty acids to achieve a polyunsaturated to saturated fatty acid ratio of greater than one will reduce the risk of CHD (E3).
- There is evidence that treating CHD patients with a daily intake of at least 1 g n-3 fatty acids from fish and fish oil is beneficial in reducing CHD endpoints (E2). Therefore, consumption of fish is recommended.
- A Mediterranean-style diet rich in α -linolenic acid is protective after MI. (E2)
- An intake of 2–3 g of plant sterols or stanols reduces LDL-C levels by 10%–15% (E2); however, there are no published studies addressing their effects on CHD endpoints.
- Studies support the view that pharmacological and dietary preventions have additional and independent beneficial effects.

Physical activity and exercise

Many studies have examined the relationship between physical activity and CHD as a specific cardiovascular disease outcome. Most of these studies have been longitudinal, population-based (cohort) studies, similar to those used to link tobacco smoking and health status. The more recent studies have been better designed and have included improved measures of physical activity and CHD outcomes. These studies have shown stronger associations, with the least active subjects typically having almost twice the risk of CHD when compared to those with sufficient activity levels.

The US Surgeon General's Report on Physical Activity and Health, published in 1996,⁶³ was a landmark review. It summarises the evidence supporting a new physical activity health message, concluding that regular moderate physical

activity of as little as 30 minutes on most or all days of the week will confer a health benefit. It also concluded that additional health benefits can be gained through greater amounts of physical activity.

This new recommendation on the intensity and duration of physical activity also pertains to cardiovascular disease. Reviews of the epidemiological literature have concluded that the level of physical activity is inversely related to CHD risk, with the dose–response relationship indicating that greater activity confers additional benefit.^{64–66} Research also shows that increased physical activity can have a positive impact on other CVD risk factors, such as overweight and obesity, high blood pressure and blood lipid profiles.

A number of studies have extensively reviewed the relationship between physical activity and blood lipid and lipoprotein levels.^{67–71} Most of these reviews conclude that exercise training is associated with an increase in HDL-C. From cross-sectional studies, there is a dose–response relationship, so that endurance-trained athletes have HDL-C levels 20% to 30% higher than in healthy, age-matched sedentary controls.

Further information can be found in the National Heart Foundation of Australia's Physical Activity Policy 2001.⁷²

Conclusions

- Regular moderate-intensity physical activity confers cardiovascular health benefits. (E3)

Tobacco smoking

Cigarette smoking is a major cause of heart attack, stroke and peripheral arterial disease.⁷³ Smokers have a 70% greater risk of CHD death than non-smokers. It is generally accepted that cigarette smoking:

- doubles the risk of MI;
- doubles the risk again in those with hypertension or high blood cholesterol levels;
- increases the risk of MI 10 times in women taking the contraceptive pill; and
- doubles the risk of stroke.

Evidence indicates that a smoker's excess risk of CHD is reduced by 50% after only one year of smoking abstinence, and that, 15 years after stopping smoking, the risk of CHD is about the same as in those who have never smoked.

Conclusions

- Smoking cessation is a vital component of CHD prevention strategies, independent of approaches to cholesterol lowering. (E3)

Other lifestyle factors

Other lifestyle cardiovascular risk factors include overweight and obesity, excessive alcohol consumption and salt consumption associated with raised blood pressure. Information on the management of these risk factors can be found at the National Heart Foundation's website <<http://www.heartfoundation.com.au>>.

6. Risk issues: who should receive lipid-modifying therapy?

Having established that lipid modification reduces CHD risk in both secondary and primary prevention settings, and that the benefits are apparent even in people with relatively low baseline cholesterol levels, and recognising the importance of lifestyle measures, three fundamental questions arise:

- Who should receive lipid-modifying therapy?
- What should be the targets of such therapy?
- What should be the drug therapy of first choice?

The published studies indicate that a 10% reduction in LDL-C level (at least in the range of levels which have been tested conclusively) translates into a 10%–20% relative reduction in CHD risk. However, the implications of a 10%–20% reduction in CHD risk are very different in people whose absolute (or “global”) risk for future events varies widely. For example, a 20% reduction in risk in an individual with a 50% risk of having a CHD event in the next 10 years (10% absolute risk reduction) has a potential impact that is much greater than even a 50% relative risk reduction in an individual whose absolute risk of an event is only 2% over the next 10 years.

Thus, a case can be made for confining lipid-modifying medication to people whose absolute risk is high and in whom target lipid levels (as defined below) are not achieved by reasonable lifestyle modification.

In other people the absolute CHD risk is not high enough to justify the use of lipid-modifying drugs. These people, especially if they have one or two of the modifiable risk factors, should be given advice about risk reduction by adopting a healthy lifestyle.

Definition of higher coronary heart disease risk for the purposes of guiding lipid-modifying medication

Clinical features other than just the cholesterol level are used to define risk of future CHD events. These clinical features include:

■ Known cardiovascular disease

- **CHD:** People with existing clinical CHD have very much higher risk of a further event when compared with those who do not have manifest CHD.⁷⁴
- **Ischaemic cerebrovascular disease:** People with known ischaemic cerebrovascular disease also have markedly increased risk of a CHD event when compared with those who have not had an ischaemic cerebrovascular event.⁷⁵
- **Other major arterial disease:** People with peripheral arterial disease (lower limb atherosclerosis) and abdominal aortic aneurysm also have much higher risk of a CHD event.^{75,76}

■ Diabetes

People with diabetes are at higher risk of developing premature CHD. Diabetes *per se* is not only an independent risk factor for CHD, it is also associated with an increased prevalence of a range of other risk factors, including high triglyceride and low HDL-C levels, hypertension and overweight or obesity. Compared with matched non-diabetic subjects, people with diabetes have 2–5 times the risk of developing

CHD.⁷⁷ In one study, those with diabetes without previous MI were found to have a risk of future CHD events comparable to that of people without diabetes who had already experienced an MI.⁷⁸ The relative risk of CHD associated with diabetes is particularly high in women, so that the usual protective effect of female sex is lost.

■ Chronic renal failure/renal transplantation

Chronic renal failure requiring dialysis and renal transplantation have both been associated with a CHD risk increased twofold or more. Renal disease is also frequently associated with hypertension and diabetes, further increasing risk of CHD.⁴⁶

■ Aboriginal peoples and Torres Strait Islanders

Aboriginal peoples and Torres Strait Islanders have an exceedingly high age-standardised mortality from cardiovascular disease which has not shown the downward trend seen in the rest of the Australian community in the past 20 years. Surveys have also shown a high prevalence of CHD risk factors.⁷⁹

Hypercholesterolemia is relatively frequent but mixed dyslipidaemia is a major concern. The clustering of hypertriglyceridaemia and low HDL-C levels with diabetes and abdominal obesity is considerably more prevalent in Aboriginal peoples and Torres Strait Islanders than in the general Australian population. Further, the high prevalence of both diabetes and renal disease among these groups also contributes to their high risk.

Screening for lipid disorders in the Aboriginal and Torres Strait Islander populations should focus on these associated abnormalities, and active treatment of the lipid disorder should be undertaken in conjunction with management of the other risk factors, particularly diabetes.

■ Familial hypercholesterolaemia

This is a dominantly inherited condition that results in elevated LDL-C levels beginning at birth. In the rare homozygous state, LDL-C levels are typically in the range of 10–20 mmol/L and patients suffer MI in early life, often before age 10. In the much more common heterozygous state (about 1 in 300 of the Australian population), the LDL-C level tends to be in the range of 6–12 mmol/L and, if untreated, MI is common before age 50, with more than 50% of such people developing clinical CHD before age 60.⁸⁰

■ Familial combined hyperlipidaemia

This is an inherited disorder in which affected individuals have elevated LDL-C levels (usually in the range 4–7 mmol/L) and elevated plasma triglyceride levels (typically 3–8 mmol/L). The level of HDL-C is usually below 1.0 mmol/L. However, the expression of this disorder is quite variable, with those affected sometimes having isolated elevated LDL-C or isolated elevated triglyceride levels. Untreated, people with familial combined hyperlipidaemia have a risk of developing clinical CHD before age 60 that is comparable to that in people with familial hypercholesterolaemia.⁸¹

■ Absolute risk of 10%–15% or higher in next five years according to the New Zealand cardiovascular risk calculator

The New Zealand cardiovascular disease absolute risk charts⁸² are discussed with GPs during academic detailing

conducted by the National Prescribing Service. These charts have already been used by many GPs, although, as yet, there has still not been any formal evaluation of levels of use in Australia. The following criteria are suggested for use if the New Zealand cardiovascular disease absolute risk charts are not being used.

■ **LDL-C >4.0 mmol/L or plasma total cholesterol level >6.0 mmol/L, plus any two of the following other risk factors**

On the basis of available evidence, it is reasonable to conclude that an LDL-C level >4.0 mmol/L or plasma total cholesterol level >6.0 mmol/L, plus a combination of any two (or more) of the additional risk factors listed below, increases CHD risk substantially. In each case, presence of these risk factors in general increases risk by up to around twofold. However, because of the coexistence of risk factors, in some cases the absolute risk may approach that in someone who is already known to have CHD.

Additional risk factors

- **Smoking:** Doubles the risk of developing clinical CHD.⁸³
- **HDL-C level <1.0 mmol/L:** A level below 1.0 mmol/L increases risk approximately twofold.^{10,30}
- **Family history of CHD in first-degree relative:** A family history of premature CHD (defined, for simplicity, as age less than 60 years in both men and women) in a first-degree relative increases CHD risk 2–5-fold.⁸⁴
- **Hypertension:** Approximately doubles the risk of CHD.⁸⁵
- **Overweight or obesity:** Association of overweight (particularly abdominal adiposity) with insulin resistance, dyslipidaemia and hypertension places overweight people at increased risk.⁸⁶ The separate increase in risk associated with overweight is difficult to quantify.
- **Impaired fasting glucose or impaired glucose tolerance:** Fasting plasma glucose between 6.1 and 6.9 mmol/L, or glucose intolerance following an oral glucose load,⁴⁴ are associated with an increase in CHD risk 1.5–2 times greater than in the general population.^{87,88}
- **Microalbuminuria and/or renal impairment (defined by serum creatinine level ≥ 0.13 mmol/L):** Are associated with 1.5 times or more average risk.⁴⁶
- **Age 45 years or older:** Absolute risk of CHD increases progressively in middle and older age in both men and women.⁷⁹

A number of these risk factors are linked, so that risk factors tend to cluster in individuals.⁸⁹ Thus, impaired fasting glucose or impaired glucose tolerance, overweight or obesity with a central distribution of body fat, reduced HDL-C level and hypertension tend to cluster in association with the metabolic syndrome and are then associated with much higher risk of CHD.⁹⁰ In Australia, risk factors also tend to cluster in the lower socioeconomic groups.

Physical inactivity is a very important risk factor for CHD. It influences a number of other risk factors, including lipid levels, hypertension and diabetes. However, physical inactivity *per se* is not used to guide decision making with regard to lipid-modifying therapy.

Key points concerning risk assessment

- People with manifest atherosclerotic disease should be considered to be at high absolute risk of further events.
- Both diabetes and chronic renal failure also imply high risk.
- Biomedical risk factors frequently coexist and, in this context, even “average” cholesterol levels may warrant aggressive treatment.

Influence and implications of sex differences

Women are as likely as men to have a CHD event and to die of CHD, except that events in women are delayed about 10 years.⁷⁹ The precise reason for the delayed onset is not known, but may relate to hormonal effects that protect premenopausal women.

7. Safety of lipid-modifying drugs

With the exception of skeletal muscle side-effects with cerivastatin, and possibly the initial evidence of gastrointestinal conditions with clofibrate in the WHO study, the available drugs in the statin and fibrate classes have been found to be very safe. The frequency of serious hepatic and skeletal muscle side effects is acceptably low for agents that must be taken long-term. The evidence supporting this conclusion has been provided by comparisons of the active and placebo groups in large-scale clinical trials of almost 50 000 patients who were followed for five years or more. The incidence of significant drug-related liver disease in these trials (compared with the incidence in the placebo groups) has ranged from 0–0.8%, while the incidence of clinically significant myositis has been 0–0.25%. With skeletal muscle effects, the incidence of myositis is increased with combination statin and fibrate therapy. Expert opinion is divided on the need for serial measurement of liver function and creatine kinase levels, although many recommend measurement in patients receiving statin or fibrate therapy. It is important that very long term safety data, for example relating to cancer incidence, are also obtained, as, once initiated, drug therapy is usually life-long.

8. Adherence to the pharmacological management of dyslipidaemia

The Australian studies

There is evidence that, even if patients are managed appropriately, many patients will discontinue their own treatment. A study conducted in metropolitan Sydney in 1994 and 1995 investigated discontinuation rates in 610 patients newly prescribed lipid-modifying drug therapy.⁴ Over the 12-month follow-up period, 60% of patients stopped taking their medication. Half discontinued their medication within three

months and a quarter within one month of starting treatment. The reasons for discontinuation were patient unconvinced about the need for treatment (32%), poor efficacy (32%) and adverse events (7%).

In 1999, a larger, Australia-wide assessment of discontinuation rates in patients newly prescribed lipid-modifying drugs was reported.⁵ Of 32 384 patients who commenced a lipid-modifying drug (statins in 92%), 30% had stopped taking the drug by 6–7 months. The significant predictors of discontinuation were age (patients below the median age of 68 years had higher discontinuation rates) and not living in a capital city.⁵

Maximising adherence

Several studies have investigated the effect of strategies to maximise adherence with lipid-modifying therapy on subsequent lipid levels, but to date there are no hard end-point data available.

Studies of early initiation of lipid-modifying therapy

■ **The CHAMP study**⁹¹

Commencing lipid-modifying therapy in-hospital improves adherence to therapy and achieves a lower LDL-C level at 12 months. (E2)

■ **Early lipid-modifying therapy versus dietary intervention in secondary prevention**⁹²

This study compared the effectiveness of immediate versus deferred simvastatin treatment in conjunction with dietary advice in reducing lipid levels in patients with hypercholesterolaemia who had experienced acute coronary syndromes. At three months, only 7% of patients given dietary advice alone achieved the target LDL-C level, compared with 90% of patients receiving dietary advice plus immediate simvastatin treatment. However, at 12 months, when both groups were receiving simvastatin therapy, the reductions in LDL-C were similar.

These studies support initiation of statin therapy while a patient is in hospital to increase the likelihood of better lipid management. (E2)

Follow-up after hospital discharge

■ **“Coaching” to reduce the treatment gap in CHD**

It has been shown that empowerment of patients by a dietitian or nurse “coach” can lower serum cholesterol level⁹³ (E2). Retrospective evaluation of an Australian study⁹³ indicated that the reason was likely to be patient adherence to dietary advice and the medical treatment prescribed. Important in the coaching process is setting goals and encouraging patients to pursue these while working in partnership with the treating doctor.

■ **American Heart Association (AHA) consensus statement on compliance**⁹⁴

The AHA Special Report from the Expert Panel suggested that compliance can be improved by a combination of educational and behavioural strategies. The AHA statement presents evidence to support a multilevel approach in which

patients, providers and healthcare organisations must integrate their efforts to manage the problem of non-compliance. Actions that enhance compliance with prevention and treatment recommendations to reduce risk include (i) providing clear, direct messages about importance of a behaviour or therapy; (ii) including patients in decisions about prevention and treatment goals and related strategies; (iii) incorporating behavioural strategies into counselling; (iv) an evidence-based practice; (v) assessing patient compliance at each visit; and (vi) developing reminder systems to ensure identification and follow-up of patient status (eg, telephone follow-up).

9. Areas of uncertainty

Special groups

There are still no reported studies designed solely to define the benefits of lipid intervention in women, in the elderly and in a variety of specific disease groups, such as those with diabetes. It should be stressed, however, that many trials have included substantial numbers of women, people aged over 70 years and people with diabetes. In these studies there has been no evidence that these specific groups respond differently from the group as a whole. Therefore, until there is evidence to the contrary, it is reasonable to assume the benefits observed in the trials will broadly apply to each of these groups. Indeed, meta-analyses have shown significant benefits in a number of them.

Children

- Cardiovascular disease risk factors affect arteries from an early age.⁹⁵ (E3)
- Most attention should be directed towards ensuring a healthy pattern of eating and physical activity, together with avoidance of smoking. (E4)
- Clinical and laboratory assessment of cardiovascular risk factors, including LDL-C and HDL-C levels, should be considered for the children of families with a clear history of premature onset of CHD (<60 years in a first-degree relative). (E4)
- Lipid levels should be measured in children with diabetes. (E4)

The age at which testing should be performed in children is a matter of judgement. Affected children may warrant more intensive intervention from early adolescence onwards. There is no evidence of adverse effects of a prudent diet in children, but saturated fat restriction is usually not justified until about five years of age.

The justification for using drugs to treat lipid abnormalities in children is uncertain, and major outcome trials seem unlikely in the foreseeable future. The safety of bile acid sequestrants (resins) and of nicotinic acid has been established in children, but the high incidence of side-effects militates against life-long compliance. Statins have been shown to be safe and effective in children in the short term,

but the likelihood of life-long therapy has constrained their use until very long-term data on their safety are available. In situations in which the risk of premature CHD is extreme, such as familial hypercholesterolaemia, thresholds for the commencement of various forms of drug therapy have been published.⁹⁶ The treatment of children remains an area where clinical judgement is vital.

Choice of lipid-modifying agents

Some uncertainty exists about the choice of lipid-modifying agent that should be used. There is general agreement, justified by the evidence presented in these guidelines, that statins are the agents of choice when the baseline LDL-C level is > 3 mmol/L. There is less published evidence of benefit from use of statins if the initial LDL-C level is lower than this. However, there is evidence of benefit of fibrates in patients with low LDL-C levels in whom the HDL-C level is also low (< 1.0 mmol/L), as long as the triglyceride level is elevated (> 1.5 mmol/L). Until evidence becomes available that demonstrates equivalence or superiority of statins over fibrates in high risk individuals with low LDL-C, low HDL-C and elevated triglyceride levels, it is reasonable to use fibrates. (E4)

Other agents

Recent large-scale trials of vitamin E have not shown it to be beneficial in reducing CHD events or all-cause mortality.⁹⁷ Positive trial data are necessary before vitamin E therapies are recommended for effects on CHD outcomes alone.

On the basis of limited trial data, at present there is no definite evidence to suggest a benefit of unopposed oestrogen or combined hormone replacement therapy (HRT) in primary and secondary prevention of cardiovascular disease (CVD) in women. There have been no cardiovascular risks demonstrated in women who are currently taking HRT for other reasons, and therefore there is no reason to cease treatment in this context. However, the commencement of postmenopausal HRT requires careful assessment and consideration of the possibility of the slight early hazard demonstrated in women with manifest CHD in the single large trial which has been reported to date.⁹⁸ For further details and review of the literature, see the National Heart Foundation of Australia position paper *Hormone replacement therapy and CVD*.⁹⁹

What should the target low-density lipoprotein cholesterol concentration be?

There is still uncertainty about the target LDL-C level. Results of both the prospective population studies and the end-point intervention studies could be interpreted (with some assumptions) as supporting the view that, in high risk people, the LDL-C concentration should be reduced to 3.0 mmol/L in primary prevention and to 2.5 mmol/L in secondary prevention (see Box 7). It should be stressed, however, that none of the reported intervention studies to date have been designed specifically to determine what the LDL-C target should be. Until such studies have been conducted,

7: Recommended target lipid levels*

LDL-cholesterol	< 2.5 mmol/L
Total cholesterol	< 4.0 mmol/L
HDL-cholesterol	> 1.0 mmol/L
Triglycerides	< 2.0 mmol/L

* These targets are based on the best available evidence. Intervention studies have not been designed to determine lipid targets. Any movement towards targets should be beneficial, even if they are not reached.

any recommendations about LDL-C targets will have to be those that are most consistent with what has been reported in the population and intervention studies.

What should be the target levels for triglyceride and high-density lipoprotein cholesterol?

There is no information from intervention studies regarding desirable target levels for these lipids. At this time, recommendations can be based only on evidence provided by population studies. The recent NCEP ATP-III recommendations¹⁰⁰ include the statement that risk is increased if the HDL-C level is < 1.0 mmol/L. While it is reasonable to recommend an HDL-C target of > 1.0 mmol/L (see Box 7), it is acknowledged that the evidence supporting this is circumstantial.

Other predictors of risk and possible targets for therapy

Other areas of uncertainty include the roles played by other lipid measurements, both as predictors and as potential targets for therapy. These include small, dense LDL particles, HDL subfractions, and a range of apolipoproteins and other factors that regulate plasma lipoprotein levels. Elevated levels of Lp(a) are another important factor which may amplify the effects of dyslipidaemia.¹⁰¹

There is increasing evidence that atherothrombotic disease should be regarded as an inflammatory process. Compelling observational data consistently show that the level of high-sensitivity C-reactive protein, a non-specific inflammatory marker, is a strong predictor of future CHD risk independent of cholesterol levels. These data have been demonstrated in those with and without manifest CHD. Similar evidence is accruing for other markers of the inflammatory process. However, pending the results of ongoing trials which incorporate levels of high-sensitivity C-reactive protein among inclusion criteria, its measurement is not incorporated in routine algorithms used to define future CHD risk.

Homocysteine is another non-lipid factor which is the subject of intense interest.^{102,103} Intervention trials designed to test the effects of reducing homocysteine levels with folic acid and, possibly, B vitamins are currently in progress.

Screening for plasma lipid levels

There is no hard evidence to support any particular strategy for screening the whole population for plasma lipid disorders. There is no evidence that screening reduces cardiovascular morbidity or mortality. A systematic review of randomised

controlled trials neither established nor refuted the proposition that cholesterol reduction lowers overall mortality in people who have no evidence to suggest existing cardiovascular disease.¹⁰⁴ Two randomised controlled trials of cardiovascular risk assessment, including cholesterol screening of middle-aged people encountered in general practice, suggest that mass screening may not be a cost-effective strategy for reducing cardiovascular risk.^{105,106}

In the case of people at high risk, measurement of plasma lipid levels should be regarded as an essential component of the risk management strategy. In the case of those who are not in the high-risk category, any decision is based on expert opinion rather than hard evidence. (E4) Recommendations for screening in the general population are given later.

Surrogates for atherosclerosis

Apart from patients who have clinically manifest CHD, assessment of risk status is based on the measurement of risk factors that have been shown in epidemiological studies to predict future disease. There has been considerable effort over the years to develop simple, non-invasive techniques for providing an objective measure of the presence of atherosclerosis and its susceptibility to the instability that precedes most cases of acute vascular events. To date, there are no proven techniques that satisfy all of these aspects, although there are some promising approaches.

One involves the measurement of carotid artery intima media thickness by B-mode ultrasonography. The use of fast-gated computed tomography or other measures to determine a coronary calcium score that may correlate with the presence, and possibly the extent, of atherosclerosis has attracted considerable recent attention. However, neither technique provides an indication of the instability of atherosclerotic plaques. Other imaging techniques, such as high resolution magnetic resonance imaging, have great potential in that they may be able to identify not only the presence but also the constituents, and the possible stability, of the plaque. Again, evaluation of this technique is essential before it can be recommended for routine use as a predictor of cardiovascular disease risk.

10. Overall recommendations

Lifestyle interventions for the management of abnormal plasma lipid levels and cardiovascular disease risk

The following lifestyle interventions are recommended as first-line management for improving the lipid profile and preventing CHD. Lifestyle interventions remain important even when drug intervention is indicated. In addition, these lifestyle changes also have a positive impact on other risk factors for cardiovascular disease, such as hypertension.

8: Physical activity intensity defined⁷²

Physical activity: Any movement involving large skeletal muscles such as walking, walking up stairs, gardening, playing sport, work-related activity.

Exercise: Planned physical activity for recreation, leisure or fitness, with a specific objective, such as improving fitness, performance, health or social interaction.

Moderate activity: Activity that is energetic, but at a level at which a conversation can be maintained.

Vigorous activity: Activity at a higher intensity, which may, depending on fitness level, cause sweating and puffing.

Healthy eating (E3-4)

Encourage patients to base their eating patterns on the following guidelines:

- Use spreads instead of butter or dairy blends.
- Use a variety of oils for cooking, such as canola, sunflower, soybean and olive oils.
- Use salad dressings and mayonnaise made from oils such as canola, sunflower, soybean and olive oils.
- Choose low-fat or reduced-fat milk and yoghurt or calcium-fortified soy beverages. Restrict cheese and ice cream to twice a week.
- Eat fish (fresh or canned) at least twice a week.
- Select lean meat (trimmed of fat and chicken without skin), and limit fatty meats including sausages and delicatessen meats such as salami.
- Snack on plain, unsalted nuts and fruit.
- Incorporate legumes into two meals a week.
- Base meals around vegetables, and grain-based foods such as bread, pasta, noodles and rice.
- Limit take-away foods such as pastries, pies, pizza, hamburgers and creamy pasta dishes to once a week.
- Limit snack foods such as potato and corn crisps to once a week.
- Limit cakes, pastries and chocolate or creamy biscuits to once a week.
- Limit cholesterol-rich foods such as egg yolks and offal.

Consider referral to an Accredited Practising Dietitian.

Physical activity (E3-4)

Patients should be given the following information about physical activity (defined in Box 8).

- At least 30 minutes of moderate-intensity physical activity should be undertaken on most, preferably all, days of the week.
- Increasing duration of physical activity beyond 30 minutes of moderate-intensity physical activity on most days of the week will produce additional benefits.

Weight reduction (E3-4)

- Aim for a body mass index (BMI) < 25 (set intermediate achievable goals)
- Waist circumference: men, ≤ 90 cm; women, ≤ 80 cm. (These are based mainly on evidence of increased risk of

death in European populations and may not be appropriate for all age and ethnic groups.)

- Encourage patients to enjoy regular moderate-intensity physical activity and change eating habits to modify energy intake. Consider referral to an Accredited Practising Dietitian for individual counselling and advice.
- Energy intake, rather than macronutrient composition, is the most important determinant of weight loss in overweight and obese individuals.¹⁰⁷ That is, a focus on dietary fat reduction alone will not necessarily achieve weight reduction.

Alcohol

Given the reported benefits of moderate alcohol consumption, there is no reason why most people who consume alcohol in moderate amounts should not continue this practice. (E4)

However, alcohol intake can raise plasma triglyceride levels, although it is uncertain how this impacts on CHD risk. Nevertheless, it is reasonable to advise patients with elevated plasma triglyceride levels to limit their alcohol intake. (E4)

Restriction of alcohol is especially important in people with hypertension, because alcohol is known to raise blood pressure. (E3) Patients with hypertension and those taking anti-hypertensive medication should be advised to limit their intake of alcohol to two standard drinks per day or less. (E4)

It is not recommended that abstainers should take up drinking or that drinkers should increase their alcohol intake. (E4)

Smoking cessation

Counselling to strongly encourage patients and their families to stop smoking is vital. Passive smokers should be provided with appropriate facts on smoking (refer to National Heart Foundation of Australia position statements on *Passive smoking*¹⁰⁸ and *Cigarette smoking*⁷³).

Consider:

- referral to the Quitline (Phone, 131 848) or a smoking cessation program;
- using nicotine replacement therapy if the patient is smoking more than 20 cigarettes per day and the first cigarette is within 30 minutes of waking.

Salt

Reduction of salt intake is important for people with hypertension, as it can reduce blood pressure in this group. (E1)

People vary in their blood pressure response to dietary salt reduction, with a greater response being more likely in older patients. (E2)

People with hypertension should be encouraged to eat plenty of fresh fruit and vegetables, low salt bread and cereals and to choose other low salt foods (foods with sodium content of 120 mg/100g or less). They should also be advised to avoid seasonings, processed foods, snack and takeaway foods that are high in salt and not to add salt during cooking or at the dinner table. (E4)

Fish oil, fish and plant sterol esters

Fish oils may have an important place when used in combination with statins to lower the triglyceride level in combined hyperlipidaemia. However, at this time, it is uncertain whether the use of fish oil capsules adds anything over and above the inclusion of a moderate consumption of fish. Therefore, patients should be encouraged to consume fish at least twice per week. (E4)

For people at increased risk of CHD, plant sterols provide an additional option for risk reduction through lowering the level of plasma cholesterol. A daily intake of 2–3 g of plant sterols is recommended (1–1.5 tablespoons of plant sterol-enriched spreads daily). Amounts greater than this have no added benefit and are not recommended. Patients using sterol spreads should also be encouraged to consume yellow and orange vegetables and fruits daily to minimise any decrease in plasma carotenoids which may occur, although the effect of this in maintaining plasma carotenoid levels has not been subjected to scientific study. Plant sterols may provide a useful and acceptable way of enhancing cholesterol lowering in people taking statins. (E2) The issue of safety related to long-term consumption of plant sterols is currently under review.

Further information

For further information about lifestyle interventions contact the Heart Foundation's Heartline on 1300 36 27 87 for the cost of a local call.

What should be measured?

At the very least, plasma total cholesterol, triglyceride and HDL-C levels should be measured and LDL-C levels calculated in all people at high risk by virtue of non-lipid coronary risk factors. These tests require a fasting blood sample, with individuals having taken only water for the previous 12 hours.

As outlined above:

- plasma total cholesterol level is a predictor of future CHD events;
- plasma triglyceride level is also predictive of future CHD events if accompanied by an elevated LDL-C or a low HDL-C level, or both;
- elevated HDL-C level is a negative predictor of future CHD events;
- elevated LDL-C level is a positive predictor of future coronary events. The level is usually calculated from the Friedewald equation,¹⁰⁹ which depends on knowing the levels of plasma total cholesterol and HDL-C and the fasting level of plasma triglyceride. The formula is:

$$\text{LDL-C} = \text{Plasma total cholesterol} - \text{HDL-C} - \frac{\text{fasting plasma triglyceride}}{2.2}$$

(Note that this equation becomes unreliable when the plasma triglyceride concentration exceeds 4.5 mmol/L.)

Note also that while lipid levels are reliable for the first 24 hours after the onset of acute coronary syndromes, cholesterol levels subsequently fall by up to 10% and may be unreliable for six weeks after the event.

Lipid levels should be measured by laboratories or prac-

tices accredited by the National Association of Testing Authorities, as this indicates satisfactory compliance with the many facets of good practice that are required to ensure confidence in the reliability of these measurements. It is unusual for the operators of near-to-patient devices, such as those that provide on-the-spot cholesterol results, to have undertaken these.

Frequency of lipid testing for adults

In general, patients at greater risk of CHD events are likely to benefit more from lower cholesterol levels than people at lower risk, for whom the benefits of cholesterol lowering are too small to justify treatment. Consequently, lipid testing and intense treatment should be focused on those at greatest risk. (E4)

High risk and potentially at high risk groups (E4)

The purpose of lipid testing is to help identify individuals with increased overall CHD risk who could benefit most by reducing blood cholesterol through intensive dietary therapy and lipid-modifying drugs if necessary. As indicated, lipid levels should be tested in the context of an ongoing assessment of absolute CHD risk.

Initial blood lipid test: Adults with the characteristics summarised in Box 9 (and children with a family history of familial hypercholesterolemia) should have an initial, preferably fasting, blood test for levels of total cholesterol, LDL-C, HDL-C, triglyceride and glucose.

Testing in the general population

Mass screening for lipid levels in the general population, regardless of age, is not currently recommended. (E4)

All adults should receive ongoing risk assessment and preventive and lifestyle advice within a general practice or equivalent setting. (E4)

Management and follow-up after absolute risk is determined

The determination of a lipid profile and glucose level enables an assessment of absolute risk for future CHD events as defined previously and in Box 1.

- All patients in Groups A and B described in Box 9 should receive dietary advice (see above). Referral to an Accredited Practising Dietitian should also be considered.
- Full lipid profiles should be obtained before commencing drug treatment.
- In patients in Group A who are known to have CHD, particularly those who have been hospitalised with CHD events and who have a total cholesterol level of 4.0 mmol/L or higher, it is appropriate to consider commencing drug treatment without awaiting assessment of the effects of dietary intervention.
- For those considered to be at higher absolute risk and above target levels (see Box 7):
 - (i) Monitor diet fortnightly for six weeks, then retest lipid levels. If still above target levels consider commencing

9: Risk groups indicating an initial blood lipid test

Group A — definite high risk

- Known CHD
- Known ischaemic cerebrovascular disease
- Known lower limb atherosclerosis, known abdominal aortic aneurysm.
- Diabetes mellitus.
- Chronic renal failure or renal transplantation.
- Aboriginal peoples and Torres Strait Islanders.
- History of familial hypercholesterolaemia.
- History of familial combined hyperlipidaemia

Group B — potentially at high risk (depending on lipid result)

At least one of the following:

- Smoker
- Significant family history of CHD (a first-degree relative affected at < 60 years)
- Overweight or obesity
- Hypertension
- Impaired fasting glucose or impaired glucose tolerance
- Microalbuminuria and/or renal impairment
- Age \geq 45 years

lipid-modifying therapy (taking into account PBS criteria); and

- (ii) Retest fasting lipid levels every two months until a satisfactory and stable response has been achieved.
- All patients at high risk should have lipid levels measured at least annually as part of ongoing assessment and management of overall cardiovascular disease risk.
 - Individuals assessed initially as being at lower risk (eg, those with an isolated abnormality in single risk factors) should also receive ongoing preventive and lifestyle advice and be reassessed within five years to determine whether they satisfy criteria for lipid testing and lipid-modifying intervention.
 - Individuals identified as being at low absolute risk should have their lipid levels tested regularly (at least five-yearly) from the age of 45 years onwards.

Cholesterol levels in the general population

There is a continuous curvilinear relationship between LDL-C levels and CHD risk. As LDL-C levels in the population tend to be distributed “normally”, population approaches to risk factor management may be beneficial because of the cumulative effect of small individual changes over a large number of people.¹¹⁰

All people in the general population, including those at lower risk of CHD, should be given ongoing lifestyle advice urging them to adopt and maintain healthy eating habits and physical activity patterns in an attempt to minimise cholesterol levels and CHD risk. (E3)

Apparently healthy people with an LDL-C level over 6.0 mmol/L as the only known CHD risk factor should be considered for more active intervention, which may include drug therapy, because of the possibility of underlying familial hypercholesterolaemia.

Recommendations for using lipid-modifying drugs

Risk assessment and initiation of drug therapy

There is a growing consensus internationally that decisions to use lipid-modifying therapy should be based on absolute risk of developing CHD. The working group agrees with this view and recommends that lipid-modifying medication should be used only in people at high absolute risk and then only if the recommended target lipid levels are not achieved by reasonable lifestyle modification.

The issue of how best to estimate absolute risk remains to be resolved. The ideal approach is one that gives a precise estimate of risk and is easy to use, thus lending itself to widespread implementation. The most precise estimate of risk is of little value if it is too complicated for routine use by busy practitioners. Conversely, a user-friendly approach has limited value if its precision is poor. Inevitably, a compromise is necessary.

Most available risk assessment tools which could potentially be used to define "high absolute risk" have been derived from the Framingham population and may not be strictly contemporary. Further, studies have shown that this model is not suitable for determining absolute risk in low risk individuals and for populations which have lower CHD morbidity and mortality rates than the Framingham study population.^{111,112} Work has been undertaken to develop risk assessment equations of particular relevance to contemporary Australian populations.¹¹³ This is important in the Australian population, because age-adjusted incidence of CHD has been decreasing over the past 30 years.

Valid equations on which to base risk assessment need to be translated into tools that can be implemented easily in clinical practice. Various tools have been developed to do this, including dedicated computer programs and charts from which risk is determined according to the value of risk factors including, age, sex, smoking status, blood pressure and lipid levels. Within research settings there is evidence that the New Zealand cardiovascular disease risk assessment charts can be used to improve blood pressure management.¹¹⁴ However, there is little evidence internationally that risk assessment tools have been taken up routinely in clinical practice. Nevertheless, there is potential for information technology systems in general practice to further help doctors identify and manage patients at higher absolute risk of CHD.

As an interim position, pending the development of an approach that is precise, easy to use and validated in the Australian population, it is recommended that high risk should be defined as outlined in Box 1, which includes use of the New Zealand cardiovascular disease risk assessment charts as one option. People who are not included in the high risk group should be urged to adopt a healthy lifestyle, but generally should not be given lipid-modifying medication. (E4)

Despite the uncertainties surrounding the use of more "precise" risk assessment tools, the educational concepts they communicate are congruent with those put forward by the system presented here (Box 1). Therefore, other models, such as the United States National Cholesterol Education Program Adult Treatment Panel III (2001)¹⁰⁰ and the joint European CHD prevention guidelines,¹¹⁶ may have an

educational role for doctors and patients and can support these National Heart Foundation of Australia–Cardiac Society of Australia and New Zealand guidelines to help guide clinical decision making.

Target lipid levels in high risk people (Box 7)

The single most important action in high risk people who have not achieved recommended target lipid levels by lifestyle modification is to commence lipid-modifying drug therapy. (E1)

The targets recommended, shown in Box 7 (E4), are consistent with the results of published population and intervention studies. However, it should be emphasised that none of the reported studies were designed to determine precise lipid targets.

It should also be emphasised that any lowering of plasma total cholesterol and LDL-C levels and any raising of HDL-C level is likely to be beneficial, even if the recommended target is not achieved. (E1)

Given that all of the high risk groups identified in Box 1 have a future risk of CHD events that is comparable to that of people with existing CHD, it is logical to have single targets for total cholesterol, LDL-C, HDL-C and triglycerides for all in whom lipid-modifying medication is recommended. (E4)

Choice of therapy

■ Statins

Although there are no contemporary large scale clinical endpoint studies comparing the different drug classes, statins are considered the agents of choice for reducing the level of LDL-C. They inhibit the activity of HMG-CoA reductase, the rate-limiting step in the pathway of cholesterol synthesis. The consequent reduction in cell cholesterol concentration results in a decreased formation of LDL-C and an increase in the activity of LDL receptors, with a consequent increase in the rate of uptake of LDL-C from the plasma.

Statins also have a modest triglyceride-lowering effect and raise HDL-C levels by 5%–10%. The mechanisms by which statins lower triglyceride and raise HDL-C levels are not known. The HDL-C level raising effect of statins is greater when the baseline HDL-C level is below 1.0 mmol/L.

If the LDL-C lowering with a statin is considered to be insufficient, a substantial additional lowering can often be achieved by adding a low dose of a bile-acid sequestrant (resin) to the statin.

It should be noted that the major large-scale trials with statins have used simvastatin at doses of 20 mg and 40 mg per day and pravastatin at 40 mg per day. The optimum dose is still uncertain, although studies currently under way have been designed to determine whether the highest recommended doses of statins are superior to lower doses in their ability to reduce CHD events.

Statins are generally well tolerated and have been shown in the large-scale intervention trials to have a very low incidence of serious adverse effects. Frequency of elevations of liver and muscle enzymes in patients taking statins is of the same order as in the placebo groups. Nevertheless, it is rec-

ommended that liver function tests are measured at least once about six weeks after commencing therapy, and care is needed if statin therapy is commenced in patients with pre-existing liver disease. The dose of statin must be reduced in patients taking cyclosporin. The incidence of cancers, if anything, has been found to be decreased in the patients in large-scale clinical trials taking statins.

■ Fibrates

Fibrates are effective triglyceride-lowering/HDL-C raising agents. In patients with triglyceride levels higher than 2.0 mmol/L, fibrates lower the triglyceride level by 40%–50% and raise the HDL-C level by 5%–20%. Fibrates act by activating a class of nuclear receptors known as peroxisome-proliferator-activated receptor- α (PPAR- α). This results in increased production of lipoprotein lipase (reduces plasma triglyceride levels and raises the HDL-C level) and of the two main proteins of HDL, apoA-I and apoA-II, with a consequent increase in HDL-C concentration.

Like statins, fibrates are generally well tolerated. The evidence from the intervention trials indicates a low incidence of serious adverse events. The previous concern that non-coronary mortality might be increased has been based solely on the results of the WHO clofibrate trial. Subsequent trials with gemfibrozil and bezafibrate have not confirmed these findings.

Fibrates must be used with great care and at reduced dose in patients with renal impairment because of the risk of myositis.

■ Resins

Cholestyramine and colestipol are bile acid sequestering agents that, by binding bile acids in the intestine, reduce their enterohepatic circulation and increase their elimination from the body. This results in increased conversion of cholesterol to bile acids in the liver, a transient reduction in liver cell cholesterol content that leads to an increase in the hepatic expression of LDL receptors, and a consequent reduction in LDL-C concentration. As monotherapy, these agents are nowhere near as effective as statins. Indeed, to achieve a 20% reduction in LDL-C concentration requires a dose of 16–24 g per day. At these or even lower doses patients frequently complain of feeling bloated and often have constipation.

There is, however, a real place for resins. This relates to their ability to increase substantially the lowering of LDL-C when given in combination with statins (see below). This additional benefit can be achieved with relatively low (and usually well tolerated) doses of the resins. It should be noted that new classes of cholesterol-lowering resins that appear to be free of unpleasant side effects are currently undergoing clinical evaluation.

■ Nicotinic acid

Nicotinic acid is an effective agent for reducing plasma triglyceride levels (40%–50%), raising HDL-C levels (5%–25%) and lowering LDL-C levels (10%–15%) when used in doses of 3–4 g per day. Its low rate of use relates to its poor tolerability, with a very large number of patients experiencing unpleasant hot flushes and itching that results in their discontinuing their use of the medication.

The triglyceride lowering is achieved by an inhibition of the release of fatty acids from adipose tissue and their sub-

sequent conversion into triglyceride in the liver. The mechanism of the HDL-C raising is not known.

As with resins, they may be useful as low (and reasonably tolerated) doses when given in combination with statins.

■ Combinations of drugs

Statins plus resins: In patients in whom LDL-C targets cannot be achieved with a statin alone, the addition of low dose resin is often able to achieve an additional 5%–10% reduction in LDL-C level, which may be sufficient to achieve the target level.

Statins plus fibrates: There has been much publicity about the danger of combining statins and fibrates, with a widely held belief that the combination of these two drugs results in an unacceptably high risk of severe myositis. Each class of drug may predispose to myositis, although the incidence, as shown in the large-scale clinical trials, is very low.^{15-19,28,33} The frequency of myositis may be increased when statins and fibrates are combined, although the precise incidence with this combination is not known. Rhabdomyolysis may rarely occur. For this reason, some authorities argue that the combination of statin and fibrate should be used after referral to a specialised clinic. There is a strong case for monitoring the levels of CK and liver enzymes within the first six weeks, and then at six-monthly intervals, in patients taking this combination.

The risk of myositis is almost certainly outweighed by the benefits in people at high coronary risk, especially in people in whom both LDL-C and triglyceride levels are elevated and HDL-C level is low. The addition of low-dose statin to a fibrate lowers LDL-C concentration substantially, and also enhances the HDL-C-raising effects of the fibrate. The addition of fibrate to a statin may enhance the LDL-C-lowering to some extent and will markedly increase the triglyceride lowering and HDL-C raising.

This combination should be seriously considered in high risk people whose lipid profile remains unacceptable after a trial with monotherapy. However, great caution should be exercised when using the combination of statins and fibrates in patients who are taking cyclosporin, protease inhibitors or erythromycin, as the possibility of additional drug interactions further increases the risk of severe myositis.

Statins plus nicotinic acid: The combination of statins and nicotinic acid is not widely used in Australia, but is used increasingly in the United States. There is no doubt that addition of low dose nicotinic acid to a statin is well tolerated by most people and substantially enhances triglyceride lowering and HDL-C raising and, to some extent, also LDL-C lowering.

Adherence to the pharmacological management of dyslipidaemia

- When relevant, start lipid-modifying therapy in patients with CHD while patients are still in hospital. (E2)
- When possible, consider ancillary measures (eg, special clinics, telephone support, coaching) to assist the patient to achieve and maintain target lipid levels. (E2)
- Assess patients' adherence to medications at each visit. (E4)

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The Lipid Management Guidelines — 2001 have been endorsed by the following organisations



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