



Management of hyperlipidaemia

BACKGROUND Hyperlipidaemia is a general term for elevated concentrations of any or all lipids in the plasma. An elevated cholesterol is one of several risk factors for coronary heart disease (CHD). In Australia, the use of cholesterol lowering drugs, mainly statins, consumes over \$880 million or 16% of the Pharmaceutical Benefits Scheme drug budget and is growing.

OBJECTIVE This article focusses on primary hypercholesterolaemia, its relationship with CHD, and its management in the community setting.

DISCUSSION There is strong evidence that treating middle aged men with statins who have established CHD will reduce overall mortality, CHD morbidity, or mortality and stroke. There is weaker but reasonable evidence for treating men aged over 65 years and women of any age who have CHD, or people without CHD but at high risk. There may be some benefits for patients with stroke and peripheral vascular disease who are at risk of CHD. While discontinuation rates are high, the occurrence of serious adverse reactions are infrequent.

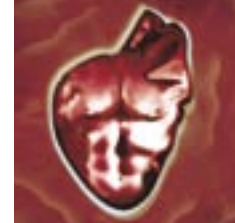
Hyperlipidaemia is a general term for elevated concentrations of any or all lipids in the plasma. Primary hyperlipidaemia is rarely caused by genetic abnormalities and commonly caused by an unhealthy diet and inactivity. Primary hyperlipidaemia can be divided into hypercholesterolaemia, hypertriglyceridaemia and combined hyperlipidaemia. Secondary hyperlipidaemia can be due to diabetes, excess alcohol intake and adverse drug effects.

Coronary heart disease (CHD) is a major cause of morbidity and mortality in Australia.¹ The use of cholesterol lowering drugs, mainly statins, consumes over \$880 million or 16% of the Pharmaceutical Benefit Scheme (PBS) budget, and this figure is growing.² Statins are subsidised when used within PBS restrictions (*Table 1*). Alternate guidelines for lipid management, not based on cost benefit data, have been published in the *Medical Journal of Australia*.³

Lipids and CHD – the evidence

There is a curvilinear relationship between total serum cholesterol and deaths from CHD.⁴ Consequently a drop in cholesterol level has a greater impact on reducing CHD death at the high end of the cholesterol range than at the lower end. However, while there is strong evidence that reducing cholesterol levels in individuals with existing CHD also reduces morbidity and mortality (*Table 2*), many individuals with high levels of cholesterol do not develop CHD, and 35% of those with CHD have cholesterol levels less than 5.2 mmol/L (*Figure 1*).

Increasing levels of HDL are associated with a reduced relative risk of CHD.³ Because of this relationship, the LDL/HDL ratio is useful in assessing the absolute risk of CHD in an individual and is used in risk factor calculators.⁵



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Screening

The Royal Australian College of General Practitioners' *Guidelines for preventive activities in general practice* recommends screening (every 5 years) for cholesterol from the age of 45 years for the general population, and from 20 years for those with a first degree relative with premature CHD (men <55, women <65). For those with established CHD, or those at high risk, screening should be yearly.⁶ Mass screening is not recommended.⁷

Primary prevention

Serum cholesterol alone is a relatively poor predictor of individual CHD risk, so clinicians should be guided by absolute risk when making decisions about management and consider the relative benefits of treating other risk factors such as hypertension and smoking. Absolute risk should be calculated using risk factor tables that are usually based on the Framingham data, eg. the New Zealand Risk Calculator.⁵

Lifestyle improvements – smoking cessation, weight reduction, healthy eating (reduced intake of saturated fats and cholesterol) and regular physical exercise – remain the foundation for the primary prevention of CHD, especially as they have additional benefits for the health and welfare of an individual. A systematic review of individual lifestyle interventions, although showing modest improvements in cholesterol levels, did not demonstrate changes in all cause mortality. Similarly trials of multiple risk factor interventions, including drug therapy, for the primary prevention of CHD are not cost effective in those at low risk.⁸

Meta-analyses of primary prevention trials (mainly middle aged men without a history of myocardial infarction) using lipid lowering medication demonstrate a relative risk reduction of 30% (summary OR: 0.70, 95% CI: 0.62–0.79) for CHD events (nonfatal myocardial infarction and deaths from CHD) but not all cause mortality compared with placebo.⁹

Secondary prevention

Meta-analysis of studies examining the effectiveness of statin therapy in adults with CHD indicate that use of statins at doses equivalent to 40 mg simvastatin lowers overall mortality by 16% (RR: 0.84, 95% CI: 0.79–0.89), cardiovascular mortality by 23% (RR: 0.77, 95% CI: 0.71–0.83), and CHD mortality or nonfatal MI by 25% (RR: 0.75, 95% CI: 0.71–0.79).¹⁰ Benefits were seen within 2 years of starting therapy. The reduction in CHD risk in those taking statins increases with duration of treatment.¹¹ A recent observational cohort study has indicated that groups (women and elderly men aged >65 years) that were not well represented in the original clinical trials derive similar but lesser benefits.¹²

Statin use in women and the elderly

Overseas research suggests that women do not get the same standard of care for CHD as men.¹³ However in Australia, there is some evidence that women – using age standardised rates – receive more statins at lower levels of risk than men.¹⁴ Although there is less trial data for women than men, it does appear

Table 1. PBS criteria for statins

- The patient must have received dietary therapy (typically for 6 weeks)
- Fasting lipid levels must be checked after completion of dietary therapy

Patient characteristics

Qualifying total cholesterol level

Patients with existing CHD

Total cholesterol >4 mmol/L

Patients with:

- Diabetes mellitus
- Familial hypercholesterolaemia
- Family history of CHD (first degree relative <60 years of age)
- Hypertension

Total cholesterol level >6.5 mmol/L
or
Total cholesterol level >5.5 mmol/L with HDL <1 mmol/L

Peripheral vascular disease

Patients with HDL <1 mmol/L

Total cholesterol level >6.5 mmol/L

Men aged 35–75 years

Total cholesterol level >7.5 mmol/L

Postmenopausal women aged up to 75 years

or a triglyceride level >4 mmol/L

Other patients not included above

Total cholesterol level >9 mmol/L or a triglyceride level >8 mmol/L

that women derive similar but smaller total mortality benefit for secondary prevention of ischemic heart disease. The benefits for primary prevention are less clear but it would appear reasonable that women be assessed for their absolute risk of developing CHD on the same basis as men and treated accordingly.

A review of several studies that included patients over 65 years of age indicate that statins are effective in reducing cardiovascular events with the combined relative risk reduction being 21% (95% CI: 17–25) and numbers needed to treat 23 (95% CI: 17–29).¹⁵

Prevention and treatment of stroke

Observational studies indicate that high levels of cholesterol are associated with increased risk of ischemic stroke, but low levels with increased risk of haemorrhagic stroke. Intervention studies show that statins reduce the risk of nonfatal stroke in patients with CHD or elevated serum cholesterol,¹⁶ however they do not have any benefit (or harm) in patients with a history of transient ischemic attack or stroke (and no history of CHD).¹⁷ Any possible increased risk of haemorrhagic stroke appears to be offset by reduction in CHD and ischemic stroke risk.¹⁸

Treatment of peripheral vascular disease

Lipid lowering drugs may slow peripheral vascular disease progression,¹⁹ and trials of statins for the treatment of intermittent claudication show some benefits (eg. self reported waking distance).^{20,21}

Pharmacological treatment of hyperlipidaemia

An outline of the pharmacological treatment of hyperlipidaemia is shown in *Figure 2*.

How low should you go?

In individuals with established heart disease or high absolute risk, the current targets recommended are:

- LDL cholesterol <2.5 mmol/L
- total cholesterol <4.0 mmol/L
- HDL >1.0 mmol/L, and
- triglycerides <2.0 mmol/L.³

Lower levels have been achieved in trials^{11,22} and the results of the recently reported TNT study confirm that lowering LDL cholesterol levels below current recommendations can have clinical benefit (an absolute risk reduction in major cardiovascular events of 2.2% but no reduction in overall mortality).²³ Statin therapy appears to be subject to a law of diminishing

Table 2. Type of statin, dosage and evaluation in clinical trials

Statin	Dosage (max)	Trials
Pravastatin (Pravachol)	40 mg (80 mg)	CARE ³⁸ WOSCOPS ³⁹ LIPID ⁴⁰
Simvastatin (Lipex, Zocor)	20–40 mg (80 mg)	HPS ^{11,16} 4S ⁴¹
Lovastatin* (Mevacor)	10–40 mg (80 mg)	TexCAPS ⁴²
Atorvastatin (Lipitor)	10–20 mg (80 mg)	ASCOT ⁴³
Rosuvastatin* (Crestor)	10–20 mg (40 mg)	No clinical outcome trial evidence

*not available in Australia

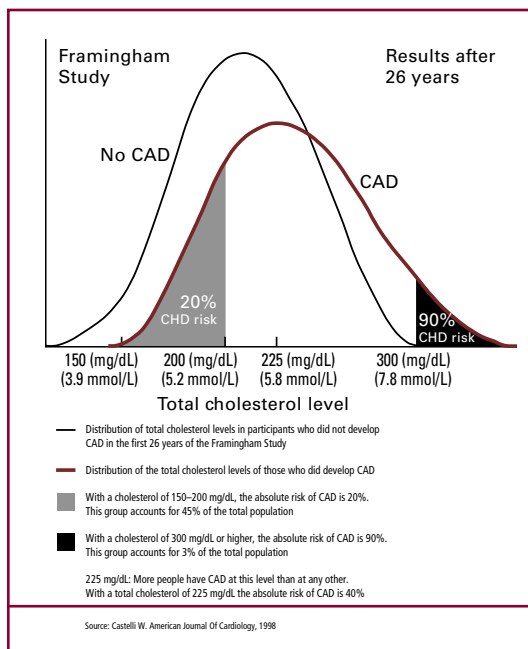


Figure 1. Incidence of CHD vs. total cholesterol

returns as might be expected with the curvilinear relationship between cholesterol and CHD mortality. Given the evidence about compliance (see below) it may be prudent to spend time and money on those not accessing treatment – but at high risk – rather than incrementally reducing risk in those who are already benefiting.

Type of statin

Comparison of the safety and effectiveness of statins is difficult because studies have enrolled subjects with different characteristics. *Table 2* shows the major

trials. Currently atorvastatin 20 mg (2.7 million scripts) and simvastatin 20 mg (2.4 million scripts) are the most frequently prescribed statins in Australia and are effective at lowering total cholesterol.² Rosuvastatin (5 mg and 10 mg [not available in Australia]) appears to be the most effective at reducing LDL cholesterol from baseline for the same dose of drug in milligrams,²⁴ however concerns have been raised about its safety.²⁵ It should be remembered that another potent statin, cerivastatin, was withdrawn because of adverse effects. As there is no convincing evidence that any of the statins available in Australia is better than another, the choice should be based on cost.

Problems with statin use

Side effects

Muscle aches and pains are among the most commonly reported side effects of patients taking statins in general practice. Myopathy (musculoskeletal symptoms and elevated creatine kinase) is the main side effect in patients taking statins and is more common with higher doses.²⁶ Broadly, if the patient

has symptoms and a creatine kinase four times the upper limit of normal, the statin should be ceased.²⁷ Statins can also be hepatotoxic and 3% of users can experience dose dependant elevations of alanine transaminase (ALT) and aspartate transaminase (AST). These rises often resolve without discontinuation of the statin. Nevertheless, patients with severe liver disease, chronic hepatitis or heavy alcohol consumption should not take statins. Rhabdomyolysis occurs in 0.04–0.2% of users, but deaths are rare (0.03 per 100 000 patient years).²⁸ There is conflicting evidence about the effect of statins on memory (adverse effect) and cognitive function (improvement).

Discontinuation and compliance

Treating those at high risk is cost effective, but identifying patients at risk can be problematic. There is evidence that prescribing varies between,²⁹ and within, countries.^{14,30} Discontinuation rates range from 6–30% in clinical trials,¹⁵ but are much higher in the community.³¹ Compliance in the elderly – at least – can also be poor with variable adherence to dosing schedules.³² No specific intervention

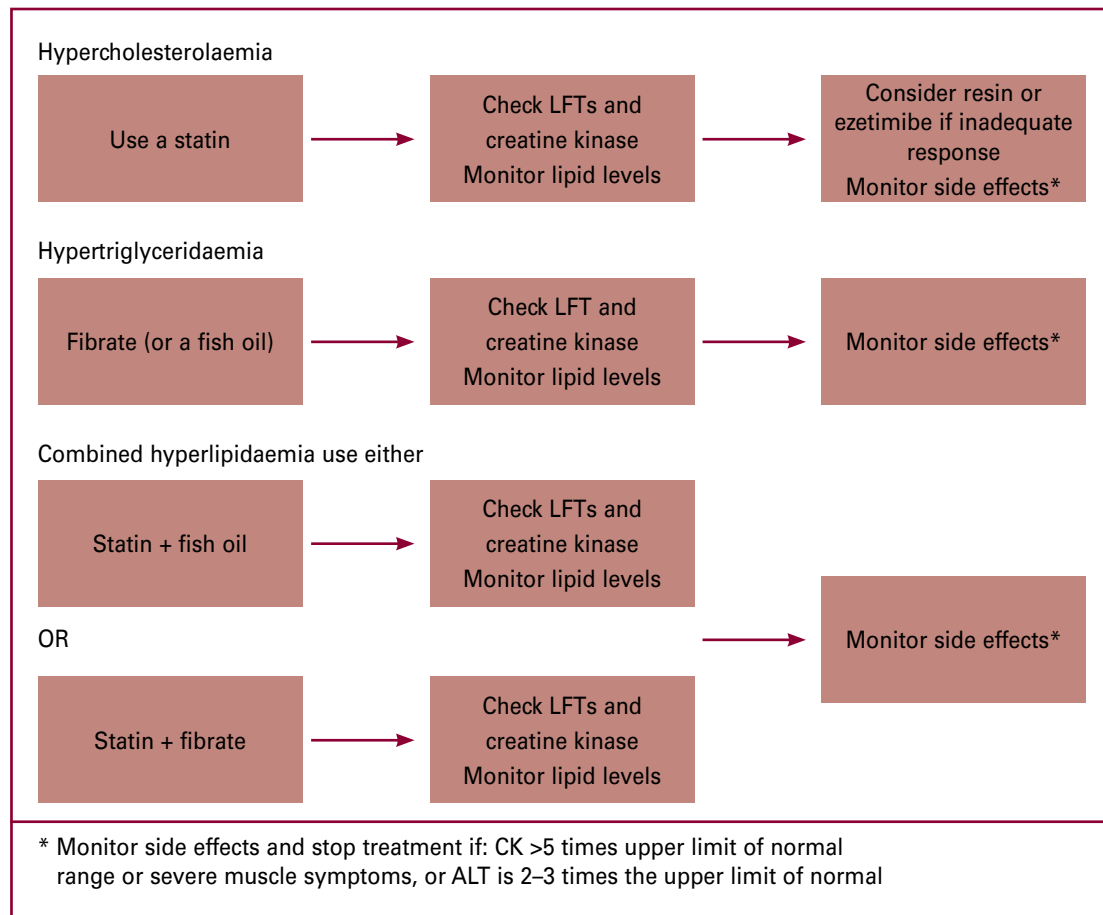


Figure 2. Pharmacological treatment of hyperlipidaemia

can be recommended to improve adherence to statin therapy at this time.³³

Use of ezetimibe

In patients intolerant of statins who do not achieve adequate reductions in serum cholesterol, ezetimibe (Ezetrol) is an alternative to resins, nicotinic acid or fibrates. Ezetimibe works by decreasing the absorption of cholesterol from the small intestine. By itself it can reduce cholesterol levels by 15–20% (10 mg dosage) and the addition of ezetimibe to statins can achieve additional reduction in cholesterol of 24%.³⁴ It appears to be well tolerated, but we lack long term safety data. Likewise, there is no data (unlike statins) on the effect on CHD mortality, morbidity or all cause mortality. Adverse events should be reported and its use should be confined to the PBS Authority guidelines.

Other treatments

Fibrates

Fibrates (gemfibrozil) are effective at lowering triglycerides and increasing HDL cholesterol. They have a role in combined hyperlipidaemia or predominant triglyceridaemia (Figure 2).

Bile acid binding resins

Bile acid binding resins (cholestyramine [Questran Lite] or colestipol [Colestid Granules]) have been shown to decrease LDL cholesterol levels by 15–25% and increase HDL cholesterol by 5%.³⁵ There is a dose response effect, but adverse gastrointestinal effects limit the use of higher doses.

Fish oils

Fish oils – high in omega-3 polyunsaturated fatty acid – have a role in the management of hypertriglyceridaemia in combination with a statin. Whether a diet with moderate amounts (2 serves per week) of fish with high concentrations of omega-3 fatty acids is better than supplements is yet to be determined.

Future developments

C reactive protein

Observational studies have reported an association between levels of C reactive protein (CRP) and morbidity and mortality from CHD.³⁶ Statins reduce CRP levels as well as LDL cholesterol, so it has been speculated that there may be a role for monitoring both during treatment, and adjusting the type or dose of statin to obtain maximum benefit.³⁷

Conclusion

There is strong evidence that treating middle aged men with statins who have established CHD will reduce overall mortality, CHD morbidity or mortality and stroke. There is weaker but reasonable evidence for treating men aged over 65 years and women of any age who have CHD, or people without CHD but at high risk. There may be some benefit for patients with stroke and peripheral vascular disease who are at risk of CHD. While discontinuation rates are high, the occurrence of serious adverse reactions is infrequent. Given the current epidemic of obesity and diabetes, further consideration needs to be given to the cost effectiveness of statins (vs. other strategies) for the prevention of CHD and reduction in mortality.

Conflict of interest: none declared.

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