Levels of evidence for clinical interventions and grades of recommendation

Level of evidence	Study design	*Grades of recommendation*	
I	Evidence obtained from a systematic review of all relevant randomised controlled trials.	A	Rich body of high-quality RCT data
II	Evidence obtained from at least one properly designed randomised controlled trial.	B	
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).	B	Limited body of RCT data or high-quality non-RCT data
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group.	B	
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series with a parallel control group.	C	Limited Evidence
IV	Evidence obtained from case series, either post-test or pre-test and post-test.	C	
		D	No evidence available –panel consensus judgment[a]

Note: The levels of evidence and grades of recommendations are adapted from the National Health and Medical Research Council levels of evidence for clinical interventions and the US National Institutes of Health clinical guidelines.
[a]Expert opinion.

KEY MESSAGES AND SUMMARY OF RECOMMENDATIONS

This 2005 position statement aims to serve as an interim update to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Lipid Management Guidelines—2001, pending a fuller review when other clinical trial data are available.

Risk assessment

In order to initiate the most cost-effective cardiovascular disease (CVD) risk factor management strategies, it is necessary to identify those individuals at higher absolute risk of a CVD event, and who therefore have the most to benefit.

The groups at higher risk are:

- Those with clinical evidence of:
  - vascular disease including coronary heart disease, stroke, peripheral arterial disease
  - diabetes mellitus (including diagnostic biochemical criteria)
  - chronic kidney disease
  - familial hypercholesterolaemia
- Aboriginal and Torres Strait Islander peoples
- Those with absolute risk of ≥15% risk of a CVD event in the next 5 years using 1991 Framingham equation (e.g. New Zealand CVD absolute risk calculator)

- Those with absolute risk of 10–15% of a CVD event in the next 5 years when any of the following is present:
  - family history of premature CHD (first degree relative who developed CHD before age 60)
  - the metabolic syndrome (in which central adiposity is now considered to be of paramount importance)

Management

Lifestyle measures

- Lifestyle interventions, including attention to dietary modification, must underpin lipid management in all people. — I A

Initiation of lipid-modifying therapy

Vascular disease

- Statin therapy is recommended for all people with clinical evidence of vascular disease (coronary heart disease, stroke, peripheral arterial disease) and should be commenced in hospital for those admitted with coronary heart disease events. — I A
- Fibrates could be considered in combination with statins, particularly in those with manifestations of the metabolic syndrome (high triglyceride levels, low HDL-C levels and/or those who are overweight). — I A

Diabetes

- Those with type 2 diabetes who have an LDL-C >2.5 mmol/L after interventions to modify lifestyle and improve blood glucose control should be considered for statin therapy. — II B
- Those with type 2 diabetes who have triglycerides >2.0 mmol/L after interventions to modify lifestyle and improve blood glucose control should be considered for fibrate therapy. — II B

Chronic kidney disease

Pending the results of trials it is recommended that the decision to start treatment with a statin for people with kidney impairment be made on an individual basis. — C

Familial hypercholesterolaemia

Statin therapy recommended. — B

Aboriginal and Torres Strait Islander people

Commence screening for lipid levels at 18 years of age, and consider statin therapy if LDL-C >2.5 mmol/L after lifestyle modification. — C

Others with elevated absolute risk of CVD

Lipid-modifying therapy is indicated for those with: — C

- absolute risk ≥15% of a CVD event in the next 5 years *or*
- absolute risk 10–15% of a CVD event in the next 5 years when either of the following is present:
  - family history of premature CHD (first degree relative who developed CHD before age 60)
  - the metabolic syndrome

PBS criteria for eligibility for subsidy should be taken into account, particularly for those assessed to be in the lower risk group described above.

Age

Although the 1991 Framingham equation is not reliable for use in people over 70 years, older individuals are at higher absolute risk of future CVD events compared to younger individuals and it is important that drug therapy is not withheld on the basis of age alone. — B

Other, new and & combined therapies

- Fibrates are known to reduce coronary risk, especially in people with type 2 diabetes or with features of the metabolic syndrome, and can be considered in combination with a statin to achieve both HDL-C raising and LDL-C lowering. However, the risk of myopathy must be considered, particularly with the combination of gemfibrozil and a statin. The risk of myopathy is lower with the combination of fenofibrate and a statin. — II B
- Ezetimibe is a member of a new class of drugs that inhibit the absorption of cholesterol by the intestine. It is well tolerated, and reduces the concentration of LDL-C by 15–20% when given either as monotherapy or when added to a statin. Further long-term safety data are awaited, particularly relating to the combination of ezetimibe and a statin. — II B

Targets

- LDL-C

  Recent trials have demonstrated the benefit of lowering LDL-C to levels substantially below the current recommended target of <2.5 mmol/L in high-risk patients with existing CHD. The results of these trials support a target LDL-C of <2.0 mmol/L for this patient population. The validity of this suggestion will be reviewed in the light of results of trials currently in progress. — II B
- HDL-C > 1.0 mmol/L — B
- Triglycerides < 1.5 mmol/L — B
- Other potential targets:
  - Levels of C-Reactive protein (CRP) are independently related to risk of future CHD events. However, due to insufficient data to indicate the benefit of targeting CRP with treatment, it is premature to use CRP routinely in the assessment of CVD risk, or to propose a particular goal for treatment. — D
  - It is anticipated that future guidelines will ascribe greater importance to apolipoprotein B (or non-HDL cholesterol as a lesser alternative), particularly in those individuals who have elevated triglyceride levels. — D

Safety

- In general, current cholesterol-modifying treatments are well tolerated and very safe.
- The risk of rhabdomyolysis should be borne in mind with statins, especially with higher-dose, long term therapy.
  - It is recommended that creatine kinase (CK) is measured at commencement of therapy and, if suggestive muscle symptoms are reported, it is measured again with blood levels compared to the earlier measurement.
  - Routine monitoring of CK is not recommended, although particular caution and monitoring is appropriate for patients taking particular concomitant medications and those of advanced age or with kidney dysfunction.
  - Statin therapy should be suspended for the duration of treatment with macrolide antibiotics.
- The risk of rhabdomyolysis is increased with statin/fibrate combination therapy, particularly with gemfibrozil.
- The incidence of statin-related elevation of hepatic enzymes in clinical trials has ranged from 0 to 0.8% and is dose-dependent. Modest elevations of alanine transferase (ALT) are common and usually settle on cessation or lowering of dose.
- There is no evidence that statins increase the risk of cancer.
- Despite case reports of memory impairment with statins, available trial data have shown no evidence of statin-induced changes in formal tests of neuropsychological function.
- Ezetimibe appears to be well tolerated; however, further long-term safety data are awaited, particularly relating to ezetimibe/statin combination therapy.

Implementation and the gap between evidence and treatment

- Only a minority of patients with CHD achieve the target levels for their modifiable risk factors due to patient-related, doctor-related and other factors.
- Measures to overcome the gap between the evidence base and practice include in-hospital initiation of treatment, recall systems and alternative systems of care (e.g. coaching).
- Once at target, all patients at high risk should have their lipid levels measured every 6–12 months as part of the ongoing assessment of adherence and management of overall cardiovascular risk.

Disadvantaged groups

- There is an independent association between cardiovascular death and disease incidence and markers of socioeconomic position.
- The gap between evidence and practice may be greater for some disadvantaged communities both with respect to prescribing (doctor) and adherence (patient) factors.
- Although aspects of socioeconomic position are not considered in absolute risk equations, these factors are important in suggesting the need for particular measures to support appropriate treatment and treatment adherence.
- The use of multidisciplinary teams in general practice has been identified as an important way to overcome the barriers faced by doctors and patients in providing high quality preventive care in disadvantaged areas.