

*Society: NHFA/CSANZ*

**National Heart Foundation of Australia  
and the  
Cardiac Society of Australia and New Zealand**



**Position Statement on Lipid Management—2005**

**L**evels 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	No evidence available –panel consensus judgment <sup>a</sup>
		D	

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.

<sup>a</sup>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  $\geq 15\%$  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  $\geq 15\%$  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.

## Introduction

The current Lipid Management Guidelines of the National Heart Foundation of Australia (NHFA) and the Cardiac Society of Australia and New Zealand (CSANZ) were published in late 2001.<sup>1</sup>

This 2005 position statement aims to serve as an interim update, pending a fuller review when other clinical trial data are available. In the meantime, this position statement is considered appropriate for the following reasons:

- the publication of further major clinical trials since 2001<sup>2–9</sup>
- important new epidemiologic data (such as those from the INTERHEART study<sup>10</sup>)
- increasing recognition of the importance of the assessment of absolute risk of future events in treatment decisions
- greater emphasis on lipid subfractions (particularly low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C)) rather than total cholesterol alone; and
- improved understanding of the pathophysiology of atherosclerosis associated with these and other data.

The key recommendations of this update are outlined at the beginning of this document, while the most important changes from the 2001 Lipid Management Guidelines are summarised in Table 1. This position statement references primarily evidence which has become available since the publication of the 2001 guidelines. Older references and a summary of previous landmark trials are available in these guidelines, available at [www.heartfoundation.com.au](http://www.heartfoundation.com.au).

## Indications for Lipid-Modifying Therapy: The Importance of Absolute Risk

In order to initiate the most cost-effective cardiovascular disease (CVD) risk factor management strategies there is a need to identify those individuals who have the most to benefit. There is an international trend realising that the best way to achieve this is to implement an absolute risk approach. Absolute risk can be expressed as the chance of experiencing the predefined outcome(s), usually expressed as a percentage over a particular period of time (typically 5 or 10 years). This contrasts with relative risk which is the ratio of risk for future events in individuals with a particular risk exposure (e.g. current smoking), compared to those without.

Table 2 indicates the manner in which the benefits of an intervention which achieves a nominal 25% relative risk reduction depend on the baseline risk of the future events. The approach can be applied to different categories of patients who might be treated.

### *Patients with Clinical Evidence of Vascular Disease*

People who have already presented with clinical manifestations of atherosclerosis (coronary heart disease, stroke,

peripheral arterial disease) are at high risk of future events; at least 15–20% risk of major CVD events such as cardiovascular death, non-fatal myocardial infarction or non-fatal stroke over the next 5 years.

The Heart Protection Study (HPS)<sup>2</sup> extended observations in previous landmark trials (summarised in the 2001 lipid management guidelines<sup>1</sup>) to reinforce the importance of added drug therapy in patients with known disease. Although subjects with total cholesterol levels less than 3.5 mmol/L were not included in HPS, epidemiologic studies suggest there should be no threshold below which treatment should not be initiated in such patients.

In the HPS, among 20,536 patients aged 40–80 years with coronary heart disease, other occlusive arterial disease or diabetes, treatment with simvastatin 40 mg daily over 5 years reduced all-cause mortality from 14.7% to 12.9% ( $p=0.0003$ ).<sup>2</sup> The reduction in vascular events was similar and significant in important pre-specified subgroups. These included those with different manifestations of vascular disease, men and women, those aged less than or over 70 years at entry, and those with LDL or total cholesterol levels less than 3.0 or 5.0 mmol/L, respectively, as well as those with higher total and LDL cholesterol levels.

There is evidence that treatment with a fibrate particularly reduces risk in those with high triglyceride levels, low HDL-C levels or who are overweight,<sup>11–14</sup> and fibrates may be considered in combination with statins in such patients with vascular disease.

**PATIENTS WITH CORONARY HEART DISEASE.** Over a 3 year period, a Western Australian study has shown that about half of coronary heart disease (CHD) deaths or non-fatal myocardial infarcts occurred in those still alive after previous hospitalisation with CHD events (Michael Hobbs, personal communication). This emphasises the importance of treatment in such patients.

Clinical trial data support commencement of statin treatment at the time of hospitalisation of patients with previous acute coronary syndromes or other CHD events.<sup>7</sup> This approach will also enhance the likelihood of adherence to prescribed therapy.<sup>15</sup>

**PATIENTS WITH PREVIOUS STROKE.** The HPS also confirmed a reduction in subsequent vascular events (but not recurrent stroke) in patients who had previous stroke but no previous manifestations of CHD—from 23.6% to 18.7% ( $p=0.001$ ).<sup>2</sup> It is noted that stroke patients included in HPS were younger, less likely to be hypertensive and differed in some other features from usual patients with stroke. At this time, statin therapy is supported for patients with previous stroke.

**PATIENTS WITH PERIPHERAL ARTERIAL DISEASE.** In the HPS, simvastatin reduced vascular events over 5 years from 30.5% to 24.7% ( $p<0.0001$ ) in patients with manifest peripheral arterial disease but no CHD.<sup>2</sup> Such patients are at very high risk of future coronary events and stroke even if they have had no such events previously and an aggressive approach to

**Table 1. Important Changes to 2001 Guidelines**

	2001: NHFA/CSANZ Lipid Management Guidelines	2005: NHFA/CSANZ Position Update
<b>CVD risk</b>	<p><b>High risk groups</b></p> <p><i>Those with known disease</i> Those with known CHD and other manifestations of atherothrombotic disease, diabetes, kidney failure/kidney transplantation, familial hypercholesterolaemia, familial combined hyperlipidaemia.</p> <p><i>Others at high risk</i> Categorical risk assessment using individual risk factors as well as CVD absolute risk assessment methods described. Higher absolute risk defined as <math>\geq 10\text{--}15\%</math> risk of a CVD event in the next 5 years.</p>	<p><b>High risk groups</b></p> <p><i>Those with known disease</i> Similar emphasis on high risk status of people with vascular disease and other conditions listed opposite. Chronic kidney disease: Broader categorisation of risk beyond those with kidney failure/kidney transplantation to include those with chronic kidney disease/impairment.</p> <p><i>Others at high risk</i> Increased emphasis on CVD absolute risk assessment. Higher absolute risk defined as &gt;15% risk of a CVD event in the next 5 years or 10–15% risk of a CVD event in the next 5 years when any of following is present: - family history of premature CHD (first degree relative who developed CHD before age 60) - metabolic syndrome.</p>
<b>Aboriginal and Torres Strait Islander People</b>	Attention drawn to high CVD risk status of Aboriginal and Torres Strait Islander people.	Continued emphasis. Explanation given that 1991 Framingham equation for CVD absolute risk is not validated for use with Aboriginal and Torres Strait Islander people  Inclusion of specific recommendation that statin therapy be considered if LDL-C >2.5 mmol/L after lifestyle modification.
<b>People with diabetes</b>	Identification of high CVD risk status of people with diabetes.	Continued emphasis on high CVD risk status of people with diabetes.  Inclusion of specific recommendations (after lifestyle and blood glucose interventions) for considering: <ul style="list-style-type: none"> <li>• statin therapy for LDL-C &gt;2.5 mmol/L</li> <li>• fibrate therapy for TG &gt;2.0 mmol/L.</li> </ul>
<b>Targets</b>	<p>TC: &lt;4.0 mmol/L</p> <p>LDL-C: &lt;2.5 mmol/L</p> <p>HDL-C: &gt;1.0 mmol/L</p> <p>TG: &lt;2.0 mmol/L</p>	<p>Increased emphasis on LDL-C rather than TC</p> <p>LDL-C Recent trials have demonstrated the benefit of lowering LDL-C to levels substantially below the current recommended target of &lt;2.5 mmol/L in high risk patients with existing CHD. The results of these trials support a target LDL-C of &lt;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.</p> <p>HDL-C: &gt;1.0 mmol/L</p> <p>TG: &lt;1.5 mmol/L</p>

Table 1 (Continued).

	2001: NHFA/CSANZ Lipid Management Guidelines	2005: NHFA/CSANZ Position Update
<b>Management</b>	<p><i>Lifestyle</i> Importance of lifestyle modification for all emphasised.</p> <p><i>Statins</i> Statins indicated as agents of choice for lowering LDL-C.</p> <p><i>Fibrates</i> Fibrates noted as effective triglyceride-lowering/HDL-C-raising agents.</p> <p><i>Other, new and combined therapies</i> Caution advised regarding statin/fibrate combination.</p> <p>Reference to use of fish oils, low-dose nicotinic acid and bile acid binding resins.</p>	<p><i>Lifestyle</i> Similar emphasis on lifestyle modification.</p> <p><i>Statins</i> Increased emphasis on benefits of statins for all with vascular disease regardless of LDL-C level.</p> <p><i>Fibrates</i> Acknowledgement that fibrates effectively reduce cardiovascular risk in those with type 2 diabetes, high TG, low HDL, or who are overweight.</p> <p><i>Other, new and combined therapies</i> Reference to statin/fibrate combination, noting lower risk of myopathy with fenofibrate/statin combination compared to gemfibrozil/statin.</p> <p>Reference to new agent ezetimibe, as well as use of fish oils, slow-release nicotinic acid, and bile acid binding resins.</p>
<b>Safety</b>		Increased reassurance regarding safety of statins. Reference to the lower risk of myopathy with fenofibrate/statin combination, compared to gemfibrozil/statin combination.
<b>Implementation</b>	Strategies to address the evidence–treatment gap recommended include in-hospital commencement of lipid-modifying therapy, recall systems and ancillary measures (e.g. ‘coaching’).	Similar emphasis on need for systematic approaches to address patient-related, doctor-related and other factors to reduce the evidence–treatment gap.  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.
<b>Disadvantaged groups</b>	–	New emphasis on relationship between lower socioeconomic position and increased CVD risk and the need for particular measures to support appropriate treatment and treatment adherence in these groups.

Table 2. Absolute Risk Determines the Significance of Relative Risk Reduction (RRR)

Estimated 5 Years Absolute Risk of CVD Events (%)	CVD Events Prevented (per 100 People) with 25% RRR	NNT for 5 years
>30	≥7.5	≤13
25–30	6–7	14–16
20–25	5–6	16–20
15–20	4–5	20–27
10–15	3	27–40
5–10	1–2	40–80
2.5–5	1	80–160
<2.5	≤0.6	≥160

CVD: cardiovascular disease; NNT: number of patients needed to be treated to prevent one event.

drug therapy is indicated irrespective of cholesterol level.

### Diabetes

The diagnosis of diabetes implies a high absolute risk for future CVD events. Although it has been proposed

that this risk for future CVD events is the same as in patients with known coronary heart disease but not diabetes, more recent data challenge this view. People with diabetes represent a heterogeneous group in whom risk, while significantly increased, may vary. Diabetes is associated frequently with other CVD risk factors and it is those people with diabetes and additional risk factors who should be particularly considered for preventive treatment.

There are now substantial data on the benefits of drug treatment in people with diabetes. The Collaborative Atorvastatin Diabetes Study (CARDS) randomised 2838 people with type 2 diabetes plus retinopathy, microalbuminuria, hypertension or smoking and no history of macrovascular disease to atorvastatin or placebo. Allocation to atorvastatin 10 mg daily compared with placebo reduced the combined primary endpoint of major coronary events, revascularisation or stroke from 9.0% to 5.8% over 4.5 years ( $p=0.001$ ).<sup>6</sup> In the HPS, major vascular events over 5 years in the total group of 5963 people with diabetes were reduced by treatment with simvas-

tatin from 25.1% to 20.2% ( $p < 0.0001$ ).<sup>16</sup> For the 2912 people with diabetes without prior vascular disease, simvastatin reduced the rate of major CVD events from 13.5% to 9.3% ( $p = 0.0003$ ).

Consistent with local NHMRC guidelines,<sup>17</sup> it is recommended that an individual risk assessment approach is adopted while awaiting development of appropriate absolute risk tools specifically for Australian people with diabetes. The NHMRC guidelines recommend that those with type 2 diabetes who have an LDL cholesterol  $>2.5$  mmol/L after interventions to modify lifestyle and improve blood glucose control should be considered for statin therapy; and that those who have triglycerides  $>2.0$  mmol/L after interventions to modify lifestyle and improve blood glucose control should be considered for fibrate therapy.

### Chronic Kidney Disease

Patients with even mild chronic kidney impairment are at higher absolute risk of vascular disease.<sup>18</sup> However, there have been few reports of outcome studies using statin therapy in patients with kidney disease. The HPS<sup>2</sup> included 1329 patients with slightly elevated creatinine (0.11 mmol/L or above for women and 0.13 mmol/L or above for men, but less than 0.20 mmol/L for both). In this group the rate of major cardiovascular events (major CHD events, strokes of any type, coronary and non-coronary revascularisations) was reduced from 39.2% to 28.2% over 5 years with simvastatin treatment, compared with a reduction from 24.2% to 19.2% in the 19,207 people with normal creatinine levels.

Pooled data from primary and secondary prevention studies with pravastatin 40 mg daily for about 5 years showed a reduction in major CVD events from 34.1% to 27.7% in 3988 people with moderate chronic kidney disease (calculated glomerular filtration rate 30–59.9 mL/min per 1.73 m<sup>2</sup>, hazard ratio 0.79, 95% CI 0.71–0.88); from 27.9% to 22.7% in 7351 people with mild chronic kidney disease (GFR 60–89.9 mL/min per 1.73 m<sup>2</sup>, HR 0.81, 95% CI 0.75–0.88); and from 25.6% to 21.8% in 1771 people with normal kidney function (GFR  $\geq 90$  mL/min per 1.73 m<sup>2</sup>, HR 0.81, 95% CI 0.74–0.89).<sup>18</sup>

There is limited evidence of benefit from statin therapy after kidney transplantation. In the Assessment of LEscol in Renal Transplantation (ALERT) study of 2102 kidney transplant recipients, treatment with fluvastatin resulted in a non-significant reduction in MI or CHD death from 12.7% to 10.7%, a reduction of cardiac death from 5.1% to 3.4% ( $p = 0.031$ ), but no reduction of total mortality, stroke or vascular intervention rate.<sup>19</sup>

In a study of 1255 patients with type 2 diabetes and kidney failure on haemodialysis, atorvastatin (20 mg daily over 4 years) did not show a significant reduction in the primary endpoint of CVD death, nonfatal myocardial infarction and stroke (37% in the treatment group and 38 in the placebo group).<sup>20</sup>

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

kidney failure on dialysis or pre-dialysis (GFR below 30 mL/min per 1.73 m<sup>2</sup>). Pending the results of these trials it is recommended that the decision to start treatment with a statin is made on an individual basis. The risk of myositis is increased in chronic kidney failure and high doses of statins are not recommended.

### Familial Hypercholesterolaemia

The absolute risk for future events in subjects with familial hypercholesterolaemia (FH) is greater than that associated with cholesterol level alone. This underscores the need for aggressive treatment of such patients. The diagnosis and management of FH have been discussed elsewhere.<sup>21</sup>

All patients with FH need to be encouraged to follow a healthy lifestyle including enjoying healthy eating, being physically active and being smoke free. In addition, lipid abnormalities in FH are extremely responsive to statins, and all adults with FH should be considered for treatment. As approximately 50% of first-degree relatives will have inherited FH, it is inappropriate to wait until the onset of clinical symptoms before treating. Although the serum cholesterol level shows a moderate degree of overlap between patients with and without FH, the presence of an elevated level in a member of an affected family is highly predictive. This is particularly the case in younger relatives.<sup>21</sup>

### Aboriginal and Torres Strait Islander Peoples

Aboriginal and Torres Strait Islander peoples have a much higher age-standardised mortality from cardiovascular disease than other Australians which has not shown the downward trend seen in the rest of the community in recent decades.<sup>22</sup> There is similar evidence from New Zealand regarding the high cardiovascular mortality in Maori and Pacific people.<sup>23</sup>

Surveys have also shown a high prevalence of risk factors in these populations. Although there are no national data, lipid abnormalities are highly prevalent in some northern Australian communities and can be apparent in those aged from 15 to 25 years old.<sup>24</sup> Cholesterol levels are variable between different Indigenous populations,<sup>25,26</sup> and are important predictors of CVD risk even at levels below 5.0 mmol/L (Hoy W., unpublished data). Mixed dyslipidaemia is a major concern, as the clustering of hypertriglyceridaemia and low HDL-C levels with diabetes and abdominal obesity is considerably more prevalent in Aboriginal and Torres Strait Islander peoples than in the general Australian population,<sup>25,26</sup> as is kidney impairment (including proteinuria and other manifestations of chronic disease).<sup>27</sup>

There are no trial outcome data for Aboriginal and Torres Strait Islander peoples which can specifically guide recommendations for the initiation of lipid-modifying therapy in individuals within these groups. In the absence of such data it is the view of the NHFA and the CSANZ that lipid-modifying therapy for Aboriginal and Torres Strait Islander people who have an LDL-cholesterol  $>2.5$  mmol/L after interventions to modify lifestyle should

**Table 3.** Estimation of Absolute Risk with the 1991 Framingham 5 Year Risk Assessment Equation

The recommended equation for assessment of absolute risk includes the following variables<sup>29</sup>:

- Age
- Sex
- Systolic blood pressure (the average of at least two measurements)
- Ratio of total:HDL-cholesterol
- Smoking (smoked *any* cigarette within the past 12 months)
- Diabetes (current treatment with insulin or oral agents, or fasting glucose >7.8 mmol/L)
- Left ventricular hypertrophy (based on electrocardiogram evidence)

The equation is not recommended for use in, or will underestimate risk, in individuals with:

- Age >70 years
  - Blood pressure >180/105 mmHg if under 65 years, >160/100 mmHg if over 65 years (confirmed from multiple readings on several separate occasions)
  - Total cholesterol >8.0 mmol/L
  - Atrial fibrillation
  - History of CVD event, such as stroke, transient ischaemic attack, or acute myocardial infarction
  - Familial hypercholesterolaemia
  - Known kidney disease or kidney impairment
- and in Aboriginal and Torres Strait Islander people

be considered for statin therapy, even without pre-existing vascular disease or diabetes. It is recommended that screening for lipid levels in Aboriginal and Torres Strait Islander people commence at 18 years old and continue annually thereafter<sup>28</sup> (see section 'disadvantaged groups').

#### *Those Not Falling into the Above Categories*

**ABSOLUTE RISK ASSESSMENT.** The absolute risk approach should be applied to individuals in the general population not falling into the above categories to determine which individuals are at highest risk of future vascular events.

The outcomes of interest and time frame over which risk for these events is estimated varies between guidelines. However, this group recommends that 5-year risk of CVD events (defined as myocardial infarction + CHD + stroke + congestive heart failure + peripheral arterial disease) is used. This is done by applying equations derived from analyses of the Framingham study in the United States<sup>29</sup> which requires assessment of systolic blood pressure, total and HDL-cholesterol, smoking status, presence or absence of diabetes and ECG evidence of left ventricular hypertrophy, in addition to age and sex.

Tools for assessment of absolute risk will be further developed and particularly their presentation designed in a manner which can best convey individual risk and the multifactorial nature of atherosclerosis to support adherence with lifestyle and drug therapy. Until this time, the New Zealand CVD risk assessment charts<sup>#1</sup> are suitable for use in Australian practice.

**CAVEATS.** Caveats related to use of the Framingham risk equation and patient populations in which the equation is likely to underestimate risk are shown in Table 3. If these pertain, the particular circumstance should be managed in its own right, without necessarily the need to conduct a formal CVD absolute risk assessment. It should also be

noted that Framingham-based CVD risk assessment is not valid for use in younger adults (subjects younger than 35 years were not included in the Framingham study). Nevertheless, in younger adults who proceed to having a lipid test because of the presence of non-lipid risk factors, an estimation of absolute CVD risk projected to 35 years old can be considered. This may also assist with patient education.

In addition to the caveats in Table 3, significant family history of vascular disease (first degree relative who developed CHD before age 60) and presence of the metabolic syndrome can increase risk. The metabolic syndrome includes a range of CVD risk factors but the associated risk is higher than that associated with these risk factors alone. Various definitions have been proposed, but the metabolic syndrome has been most recently defined in a statement of the International Diabetes Federation so as to ascribe a central role to abdominal adiposity. This definition is shown in Table 4.

As noted previously, Aboriginal and Torres Strait Islander peoples are at very high risk of CVD. Recent work has demonstrated that in an Aboriginal community in the Northern Territory, the Framingham risk equation substantially underestimated actual risk of CHD, particularly in young adults and women.<sup>30</sup>

There are insufficient data available with which to adjust the Framingham equations for appropriate use in Australian Aboriginal and Torres Strait Islander peoples, and their use is not generally recommended in these groups. Instead, lipid management for these people should be based around the recommendations provided earlier. If clinicians choose to proceed with a Framingham-based risk assessment for Indigenous individuals, the 'National guide to a preventive health assessment in Aboriginal and Torres Strait Islander peoples' (NACCHO and RACGP) suggests the following corrections should be considered<sup>28</sup>:

<sup>#1</sup> Available at [http://www.nzgg.org.nz/guidelines/0035/CVD\\_Risk\\_Chart.pdf](http://www.nzgg.org.nz/guidelines/0035/CVD_Risk_Chart.pdf)  
or [http://www.nps.org.au/resources/Patient\\_Materials/nz\\_cardiovascular\\_risk\\_calculator.pdf](http://www.nps.org.au/resources/Patient_Materials/nz_cardiovascular_risk_calculator.pdf).

**Table 4. Metabolic Syndrome: New International Diabetes Federation Definition<sup>70</sup>**

Central obesity (waist circumference  $\geq 94$  cm for Europid men and  $\geq 80$  cm for Europid women [ethnicity specific values for others])

Plus any two of:

- Raised TG level:  $>150$  mg/dL (1.7 mmol/L), or specific treatment for this
- Reduced HDL-C:  $<40$  mg/dL (1.03 mmol/L) in males and  $<50$  mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality
- Raised blood pressure: SBP  $\geq 130$  mmHg or DBP  $\geq 85$  mmHg, or treatment of previously diagnosed hypertension
- Raised fasting plasma glucose  $\geq 100$  mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes<sup>a</sup>

DBP: diastolic blood pressure; TG: triglycerides; HDL-C: high density lipoprotein cholesterol; SBP: systolic blood pressure; FPG: fasting plasma glucose; OGTT: oral glucose tolerance test.

<sup>a</sup> If FPG is above 5.6 mmol/L, OGTT is strongly recommended, but not necessary to define presence of the syndrome.

- tables for females may not apply to Aboriginal women
- adjust the cardiovascular risk upwards. Clinical judgement is required to estimate the incremental cardiovascular risk incurred.

INDICATIONS FOR LIPID-MODIFYING THERAPY—THOSE AT HIGHER ABSOLUTE RISK OF CVD. The NHFA/CSANZ consensus view is that lipid-modifying drug therapy is indicated for those individuals estimated from the 1991 Framingham equation<sup>29,31</sup> to be at  $\geq 15\%$  risk of a CVD event in the next 5 years.

Drug therapy should also be considered in those estimated to be at 10–15% risk of a CVD event in the next 5 years if any of the following are present:

- family history of premature CHD (first degree relative who developed coronary heart disease 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.

It must be appreciated that 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.

## Goals and Targets

Recent data provide further information regarding potential targets with treatment, although this is less robust than the evidence base concerning indications.

### Low Density Lipoprotein-Cholesterol (LDL-C)

Epidemiologic data have shown a continuous log-linear relationship between cholesterol levels and CHD events.<sup>32,33</sup> A similar relationship probably exists relating cholesterol levels to risk of ischaemic stroke.<sup>32</sup> A series of trials has been performed to examine whether or not achieving lower levels of LDL-cholesterol translates to increased therapeutic benefit.

The PROVE-IT TIMI 22 trial<sup>7</sup> compared 40 mg pravastatin daily and 80 mg atorvastatin daily in 4162 patients randomised within 10 days of an acute coronary syndrome. Median LDL-cholesterol achieved during treatment was 2.46 mmol/L and 1.60 mmol/L for those on 40 mg of pravastatin and 80 mg of atorvastatin, respectively ( $p < 0.001$ ). Over a mean 24 months follow-up, the primary endpoint

(a composite of all-cause death, myocardial infarction, unstable angina requiring rehospitalisation, revascularisation (at least 30 days after randomisation) and stroke), was reduced from 26.3% in the pravastatin group to 22.4% in the atorvastatin group ( $p = 0.005$ ). There was a difference in treatment effect according to baseline LDL-C levels with no benefit with more aggressive treatment in those with baseline LDL-C less than 3.2 mmol/L. However, this may have been because this was a non-randomised comparison with potential imbalance in baseline risk factors between the treatment subgroups.

A more recent analysis of this study has shown particular benefit in those who achieved LDL-cholesterol less than 1.8 mmol/L (and CRP levels  $< 2$  mg/L).<sup>34</sup>

The A-Z trial<sup>8</sup> was a similar study which compared early initiation of an intensive statin regimen (40 mg daily of simvastatin for 1 month then 80 mg simvastatin daily) with delayed initiation of a less intensive regimen (placebo for 4 months then 20 mg simvastatin daily) in 4497 patients following acute coronary syndromes (ACS). Mean LDL-C at 8 months was 1.63 and 1.99 mmol/L in those assigned to the more and less intensive regimen, respectively. The primary endpoint—a composite of cardiovascular death, non-fatal myocardial infarction, readmission for ACS, and stroke over follow-up to 24 months, occurred in 16.7% of the less intensive group and 14.4% in the more intensive group ( $p = 0.14$ ). Cardiovascular death was reduced with more intensive therapy (4.1% versus 5.4%,  $p = 0.05$ ), but there were no other differences in other individual components of the primary end-point.

The TNT trial<sup>9</sup> was designed to assess the efficacy and safety of treating subjects with stable CHD to low density lipoprotein (LDL) cholesterol levels significantly below 2.6 mmol/L. Subjects with clinically manifest CHD had an 8-week period of open label treatment with atorvastatin 10 mg/day. After this open label run-in, 10,001 subjects who had achieved an LDL-C  $< 3.4$  mmol/L were randomised to double-blind therapy with either atorvastatin 10 or 80 mg/day and followed up for a median of 4.9 years. The primary end-point – a composite of CHD death, non-fatal non-procedure-related myocardial infarction, resuscitation after cardiac arrest or fatal or non-fatal stroke – occurred in 10.9% of subjects given 10 mg atorvastatin daily (who achieved a mean LDL-C of 2.6 mmol/L) and 8.7% of those given 80 mg atorvastatin daily (who achieved a mean LDL-C of 2.0 mmol/L) ( $p < 0.001$ ). There were no differences in overall mortality. It is of interest that the

absolute mortality rates of 5.6% and 5.7% in the TNT trial (in the treated and non-treated groups, respectively) were much lower than those observed in the LIPID, CARE, 4S and HPS trials.<sup>2,35–37</sup>

In each of these three trials, some side-effects were more common in those on the more intensive regimen. Clinicians' use of all treatments should take the balance between benefit and harm into consideration. In the case of statins, the risk of rhabdomyolysis should be borne in mind, especially with higher dose, long-term therapy (although trial evidence to date with the available statins is very reassuring)—see later.

The recent PROVE-IT and TNT trials have both demonstrated a benefit in lowering LDL-C to levels substantially below the currently recommended target of <2.5 mmol/L in high-risk patients with existing CHD.<sup>7,9</sup> The results of these trials support a target LDL-C of <2.0 mmol/L for this patient population. A similar conclusion has been reached by the National Cholesterol Education Program—Adult Treatment Panel,<sup>38</sup> who suggested a target LDL-C of 70 mg/dL (1.8 mmol/L) was a very reasonable therapeutic option in very high-risk patients. The validity of this suggestion of a lower LDL-C target will be reviewed in the light of upcoming results from additional trials that are currently in progress.

#### *High Density Lipoprotein-Cholesterol (HDL-C)*

Despite the very large body of epidemiologic evidence identifying low HDL-C as a powerful risk factor in humans, there are very few intervention studies that have put this proposition directly to the test. While there are several human intervention studies in which drug-induced elevations of HDL-C are associated with a reduction in atherosclerosis, most of these trials were not designed specifically to test the benefits of raising the level of HDL-C. However, the VA-HIT study has shown a benefit of gemfibrozil in patients with CHD, even though LDL-C was not lowered by this treatment.<sup>12</sup>

In addition, a recent study in humans provides support for the proposition that raising the level of HDLs is of substantial therapeutic advantage.<sup>39</sup> This was a small study in which a preparation of reconstituted HDL was infused into human subjects after an ACS. The HDL contained a variant of apolipoprotein A-I (known as apoA-I<sub>Milano</sub>) complexed with a phospholipid. Thirty six subjects in the two treatment groups received intravenous injections of the HDL preparation at weekly intervals for just 5 weeks. This resulted in a significant reduction in the atheroma burden in the coronary arteries as assessed by intravascular ultrasound. While the study included only a small number of subjects, the result was consistent with a profound protective action of HDL.

On the basis of the epidemiologic data<sup>40</sup> it is reasonable to recommend an HDL-cholesterol target >1.0 mmol/L.

#### *Triglycerides (TG)*

Plasma triglyceride levels are predictive of future CVD events, independent of the levels of other lipid subfractions.<sup>41</sup> However, to date, there is no definitive

evidence that reducing the level of plasma triglycerides translates into a reduction in events. Despite this, on the basis of the epidemiologic association, it is reasonable to recommend a triglyceride target of <1.5 mmol/L.

#### *Apolipoproteins*

Apolipoproteins are proteins in the phospholipid external monolayer of lipoproteins. Levels of apolipoprotein B (ApoB) measure the total number of atherogenic lipid particles, including very low density lipoprotein (VLDL) and chylomicrons, as well as LDL. One molecule of apoB<sub>100</sub> is present in each VLDL and LDL particle. ApoB levels are particularly relevant when there is a shift to more atherogenic small dense LDL rather than large buoyant LDL particles, as in the context of diabetes or the metabolic syndrome. This is important because measurement of LDL-cholesterol concentrations alone take no account of the LDL phenotypes present in an individual. ApoA<sub>1</sub> is the major apolipoprotein component of HDL particles.

The level of ApoB has been demonstrated in a number of (but not all) studies<sup>42,43</sup> to be superior to LDL-cholesterol for CVD risk prediction.

Although at this time particular emphasis is attached to LDL-C and HDL-C rather than measurement of total cholesterol alone, it is anticipated that future guidelines will ascribe greater importance to apolipoprotein B (or non-HDL cholesterol as a lesser alternative<sup>44</sup>), particularly in those individuals who have elevated triglyceride levels.

#### *Other Targets*

There is considerable evidence that atherosclerosis and its acute manifestations represent an inflammatory process. Among the various markers of inflammation, most data are available relating to C-reactive protein (CRP). Although an acute phase reactant, CRP is directly involved with other inflammatory mediators in the development and complications of atherosclerosis. Levels of CRP have been reported to be independently related to risk of future CHD events.<sup>45</sup> In PROVE-IT TIMI 22, CRP levels at 30 days after treatment with either atorvastatin or pravastatin were independent of LDL-C levels.<sup>34</sup> In particular, this study also showed that those subjects who achieved CRP levels less than 2 mg/L with treatment had a similar reduction in cardiovascular events to those individuals in whom LDL-C was less than 1.8 mmol/L. Event reduction was greatest when treatment was associated with achievement of both goals.<sup>34</sup>

However, until data indicate the benefit of treatment based upon targeting CRP, it is regarded as premature to include this routinely in the screening of individuals for future CVD risk or to propose a particular goal for treatment.

## **Treatments**

#### *Lifestyle*

Appropriate lifestyle changes are an integral part of risk management, and must underpin treatment in all peo-

ple. Dietary advice should be based on recommendations to follow a low saturated fat eating plan incorporating moderate amounts of polyunsaturated and monounsaturated fats and oils, marine omega-3s via two to three fish meals per week and at least 2 g of plant omega-3s (Alpha Linolenic Acid) per day, and a wide variety of fruits, vegetables and wholegrain cereal products. This may achieve a cholesterol reduction of up to 15%.<sup>46</sup> Plant sterols and stanols are recommended to contribute to the further lowering of plasma LDL-cholesterol by an additional 10%.<sup>47,48</sup>

Other lifestyle interventions that are recommended for improving lipid profiles include at least 30 min of moderate-intensity physical activity on most, and preferably all, days of the week, reducing weight and avoidance of smoking. Lifestyle management may require ongoing support to be sustainable.

These lifestyle interventions, by themselves or in addition to pharmacological measures, can reduce absolute cardiovascular risk over and above lowering plasma lipid levels. Further information on relevant recommendations and guidelines are available at [www.heartfoundation.com.au](http://www.heartfoundation.com.au) or from the Heart Foundation's Heartline (call 1300 36 27 87 for the cost of a local call). Referral to an Accredited Practising Dietitian should also be considered.

#### *Statins (HMG-CoA Reductase Inhibitors)*

Statins are considered the agents of choice for reducing the level of LDL-C, and have modest triglyceride-lowering and HDL-C-raising effects.<sup>1</sup>

#### *Other, New and Combined Medical Therapies*

Fibrates are known to reduce coronary risk, especially in people with type 2 diabetes or with features of the metabolic syndrome (particularly high triglycerides, low HDL-C or overweight).<sup>11–14,17</sup> This benefit may relate in part to the HDL-C-raising effects of these drugs. However, while fibrates increase the level of HDL-C in most patients, they are much less effective than statins in lowering LDL-C and may need to be given in combination with a statin. This combination is highly effective in terms of LDL-C-lowering and HDL-C-raising but has been reported to be associated with a small but significant increased risk of myopathy. This risk is greater when statins are combined with gemfibrozil, and is much less when the fibrate is fenofibrate.<sup>49</sup>

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.

Fish oils, slow-release nicotinic acid and bile acid binding resins are also used in selected patients.

#### *Safety*

In general, current lipid-modifying treatments are well tolerated and very safe. With the increased time for which

experience with treatment is available and longer follow-up of patients who were recruited to clinical trials, further data are now available concerning safety, particularly for the statins.

**CANCER.** The longest follow-up of trial patients who were treated with a statin related to the 4S study, with follow-up now extending beyond 10 years.<sup>50</sup> The 4S investigators found no difference in incidence of either fatal or all cancers in patients initially randomised to receive simvastatin compared to placebo.

There are some theoretical reasons why statins might even protect against cancer<sup>51</sup> and some epidemiologic data have suggested a possible decrease in cancer with statin use.<sup>52</sup> However, these case-control studies have been of relatively short duration and further data are awaited.

**RHABDOMYOLYSIS.** Skeletal muscle side-effects relate to the statin dose used. Rhabdomyolysis occurs very rarely, probably in less than 1 in 100,000 patients treated with currently marketed statins. The risk (while still low) is increased when patients are treated with a statin in combination with a fibrate, particularly gemfibrozil.<sup>53</sup> Fenofibrate does not have the same pharmacokinetic interaction with statins that has been found with gemfibrozil,<sup>54</sup> and the evidence to this time shows that the combination of a statin with fenofibrate is safer than with gemfibrozil.<sup>55</sup>

It is recommended that creatine kinase (CK) is measured at commencement of statin therapy. Routine monitoring of CK is not recommended, although particular caution and monitoring is appropriate for patients on concomitant medication with fibrates, cyclosporin, certain antifungal agents and cytochrome p450 inhibitors (refer to manufacturers' instructions), advanced age and kidney dysfunction. Statin therapy should be suspended for the duration of treatment with macrolide antibiotics. If any patient reports suggestive muscle symptoms, compare CK blood level to level prior to beginning therapy.

**ELEVATIONS IN HEPATIC ENZYMES.** The incidence of significant drug-related elevations in hepatic enzymes in the clinical trials of statins (compared with the incidence in the placebo groups) has ranged from 0 to 0.8%, and is dose-dependent.<sup>56</sup> Modest elevations of alanine transferase (ALT) are common, and usually settle on cessation or lowering of dose.

**MEMORY IMPAIRMENT.** There has been recent media publicity concerning possible memory loss in patients receiving statins. However, case reports to the Australian Therapeutic Goods Administration have been very rare.<sup>57</sup> A substudy in 1130 coronary patients in the LIPID placebo-controlled study showed no evidence of an effect of pravastatin on psychological well-being (although it is acknowledged that particular at-risk patients may have been excluded).<sup>58</sup>

## Implementation and the Gap between Evidence and Treatment

### *The Evidence-Treatment Gap*

Evidence from Australian as well as international surveys indicates that only a minority of patients with CHD achieve the target levels for their modifiable risk factors or even receive treatment.<sup>59–61</sup> There are three possible reasons for this treatment gap: patients may not attend the doctor; doctors may not prescribe appropriate treatment; and/or there may be poor patient adherence to treatment regimens. Possible solutions to overcome the gap between the evidence base and actual practice are shown in Table 5. Some of these measures are directed towards the treating doctors and some at the patients.<sup>59–61</sup>

### *The Importance of Monitoring*

The Cochrane Collaboration systematic review of interventions for helping patients to follow prescriptions for (all) medications clearly shows that measures to improve adherence are inseparably bound to achievement of the clinical goals for which the drugs are prescribed.<sup>62</sup> This suggests it may be very relevant to measure the short term outcomes of effective treatments such as measures of cardiovascular risk factors. For cardiovascular disease, perhaps the most clinically relevant of these are the regular measurement of serum lipids. 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.

### *Other Methods of Improving Adherence*

Particularly noteworthy are the importance of in-hospital initiation of treatment, recall systems and disease management systems which empower the patient. An example of the latter, which has been successfully initiated in Australia, is The COACH Program<sup>63</sup>—a training program for patients with CHD in which a health professional ‘coach’ trains the patient to vigorously pursue the target levels for their risk factors whilst working in partnership with their own doctors.

## Disadvantaged Groups

The burden associated with atherothrombotic disease occurs particularly in those who are disadvantaged on the basis of socioeconomic and other factors. Implementation should take into account such factors to allow specific targeted approaches. Without doing so, guidelines risk increasing health inequalities, by preferentially improving outcomes in those who are advantaged.<sup>64</sup>

Large studies have confirmed the independent association between cardiovascular death and disease incidence and markers of socioeconomic position (SEP).<sup>65</sup> The disease burden in Aboriginal and Torres Strait Islander peoples has already been referred to.

There is currently no evidence to support any different screening in relation to cardiovascular risk for low SEP groups in the population. Although aspects of SEP are not considered in absolute risk equations, as for Aboriginal and Torres Strait Islander people, these factors are important in suggesting the need for particular measures to support appropriate treatment and treatment adherence.

Maximising the capacity of individuals to actively participate in making lifestyle change and to access and adhere to lipid-modifying therapy means comprehensively taking into account a patient’s literacy, income, cultural values and access to services and media, and avoiding blame of people or groups in the community for “non-compliance”.<sup>66</sup>

Concerning lipid-modifying pharmacotherapy, there is no evidence to suggest that safety or efficacy of lipid-modifying medication differs for disadvantaged patients or communities. However, there is evidence to suggest that the gap between evidence and practice may be greater for some disadvantaged communities. A recent study of statin prescribing in Australia found apparent inequities in prescribing rates, suggesting either over-prescribing in the highest socioeconomic groups or under-prescribing in the lowest.<sup>67</sup>

Poor adherence or compliance may also be associated with SEP.<sup>68</sup> Use of multidisciplinary teams in general practice has been identified as an important way to overcome

**Table 5.** *The Treatment Gap between Evidence and Practice: Causes and Solutions*

Problems	Solutions
Patient non-attendance at doctor	<ul style="list-style-type: none"> <li>• Appropriate discussion at discharge</li> <li>• Recall systems</li> </ul>
Doctors do not undertake appropriate investigations, initiate or titrate therapy	<ul style="list-style-type: none"> <li>• Guideline dissemination and implementation</li> <li>• Local ‘ownership’ of guidelines</li> <li>• Computerised decision support systems</li> <li>• Assessment of compliance at each visit</li> </ul>
Patient non-adherence to prescribed treatment	<ul style="list-style-type: none"> <li>• In-hospital initiation of cardioprotective medications</li> <li>• Doses for medications</li> <li>• Disease management systems:                             <ul style="list-style-type: none"> <li>○ Case management</li> <li>○ Coaching programs</li> <li>○ Nurse-led clinics</li> <li>○ Care plans</li> </ul> </li> </ul>

## Acknowledgements

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the barriers faced by doctors and patients in providing high quality preventive care in disadvantaged areas.<sup>69</sup>

## Appendix

### *Process for Development of the Position Statement*

The position statement has been developed primarily by an Executive Writing Group nominated by the Cardiac Society of Australia and New Zealand (CSANZ) and the Clinical Issues Committee and the Nutrition and Metabolism Advisory Committee of the National Heart Foundation of Australia (NHFA) using a consensus approach.

A range of lipid, cardiovascular and general practice and other experts and organisations were invited to comment on drafts. After considering comments received the draft was modified by the Executive Writing Group and then reviewed and approved by the NHFA and CSANZ.

The closure date for review of the evidence was June 2005. A fuller review is planned during 2006, taking into consideration data emerging since this time.

### *Endorsements*

This position statement has been endorsed by the following organisations in addition to the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand:

- Australian Atherosclerosis Society



- Internal Medicine Society of Australia and New Zealand



- Kidney Health Australia



- National Prescribing Service



National Prescribing Service Limited

- National Stroke Foundation



- Royal Australian College of General Practitioners



- Royal College of Nursing, Australia



### Conflict of Interest Statement

Philip Barter has been involved in research initiated by AstraZeneca, Pfizer, Fournier, GlaxoSmithKline and Merck Sharpe & Dohme. He has been involved in research funded by Pfizer and has acted in an advisory capacity, or received travel assistance or fees for service from AstraZeneca, Pfizer, Merck Sharpe & Dohme, Fournier and Merck Pharma (UK).

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