

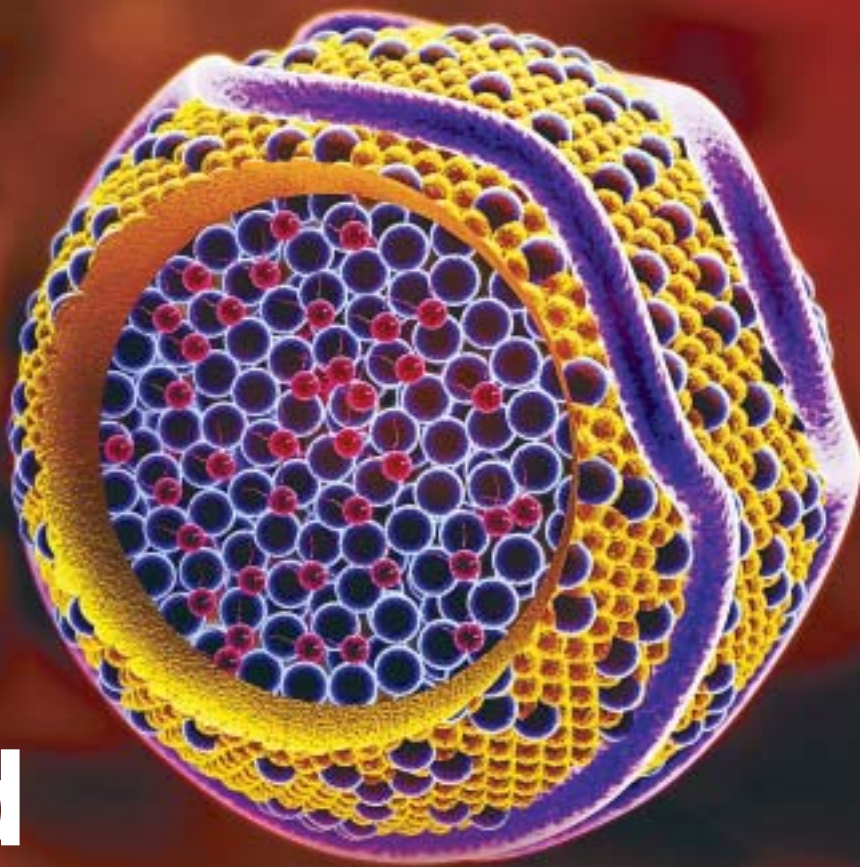
# CSP

## Common Sense Pathology

A REGULAR CASE-BASED SERIES ON PRACTICAL PATHOLOGY FOR GPs

### CONTENTS

- Summary of updated lipid guidelines
- Test interpretation
- Case studies



# LIPIDS and CARDIOVASCULAR DISEASE — the goalposts have moved

A JOINT INITIATIVE OF

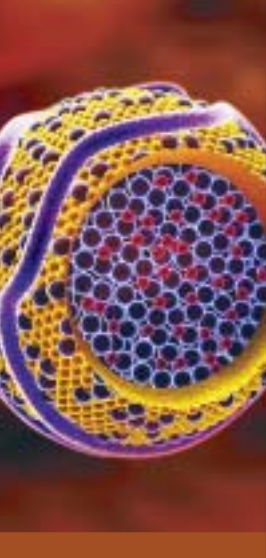


The Royal College of Pathologists of Australasia

Australian  
**Doctor.**



Australian Government  
Department of Health and Ageing



# Lipids and cardiovascular disease — the goalposts have moved



**Dr David Sullivan**, Department of Clinical Biochemistry,  
Royal Prince Alfred Hospital, Missenden Road,  
Camperdown NSW 2050

**Dr David Tognarini (PhD)**, Independent researcher

## Introduction

The management of lipid disease is evolving and the National Heart Foundation of Australia lipid management guidelines were updated in December 2005 (Tables 1, 2 and 3).

Conclusions from the update include:

- When assessing vascular prognosis, there should be a greater emphasis on absolute risk (the likelihood of experiencing an event within a specified period) than relative risk (the percentage increase in risk in comparison to a healthy individual of the same age).
- There should be a greater emphasis on low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) than total cholesterol.

When reporting lipid and lipoprotein results, pathology services now highlight Heart Foundation recommendations to help clinicians estimate their patients' individual risk of a cardiovascular event.

This article will provide investigation and management recommendations based on recently published data and the updated guidelines, as well as real-life cases.

This issue of *Common Sense Pathology* is a joint initiative of *Australian Doctor* and the Royal College of Pathologists of Australasia.

It is published by Reed Business Information  
Tower 2, 475 Victoria Ave, Locked Bag 2999  
Chatswood DC NSW 2067.  
Ph: (02) 9422 2999 Fax: (02) 9422 2800  
E-mail: mail@australiandoctor.com.au  
Web site: www.australiandoctor.com.au  
(Inc. in NSW) ACN 000 146 921  
ABN 47 000 146 921 ISSN 1039-7116

© 2006 by the Royal College of Pathologists of Australasia  
www.rcpa.edu.au

CEO Dr Debra Graves  
E-mail: debrag@rcpa.edu.au

While the views expressed are those of the authors, modified by expert reviewers, they are not necessarily held by the college.

**Common Sense Pathology editor:** Dr Matthew Meerkin  
E-mail: mmeerkin@ozemail.com.au

**Chief sub-editor:** Jacqueline George  
E-mail: jacqueline.george@reedbusiness.com.au

**Australian Doctor**  
**Editor:** Nadine Meehan  
E-mail: nadine.meehan@reedbusiness.com.au

**Medical editor:** Dr Kerri Parnell  
E-mail: kerri.parnell@reedbusiness.com.au

**Commercial director:** Suzanne Coutinho  
E-mail: suzanne.coutinho@reedbusiness.com.au

**Graphic designer:** Edison Bartolome  
E-mail: edison.bartolome@reedbusiness.com.au

**Production manager:** Marlene Dickinson  
E-mail: marlene.dickinson@reedbusiness.com.au

Cover: Computer artwork of LDL-C and HDL-C. Hybrid Medical Animation/Science Photo Library.

For an electronic version of this and previous articles, you can visit [www.australiandoctor.com.au](http://www.australiandoctor.com.au) Click on Clinical and Library, then *Common Sense Pathology*. You can also visit the Royal College of Pathologists of Australasia's web site at [www.rcpa.edu.au](http://www.rcpa.edu.au) Click on Publications and Forms, then *Common Sense Pathology*.



**Table 1: Summary of changes<sup>6</sup>**

	2001 Lipid guidelines	2005 Lipid update
Total cholesterol	<4.0mmol/L	Increased emphasis on LDL-C rather than total cholesterol
LDL-C	<2.5mmol/L	<2.0mmol/L
HDL-C	>1.0mmol/L	>1.0mmol/L
Triglycerides	<2.0mmol/L	<1.5mmol/L

*Target levels for patients at high risk of cardiovascular disease. NHFA/CSANZ Position statement on lipid management 2005<sup>6</sup>.*



### Case study 1

B.H. has recently recovered from an episode of acute coronary syndrome, after which he was started on simvastatin 40mg at night. Two months later, his total cholesterol was 4.0mmol/L, fasting triglyceride was 1.1mmol/L and HDL-C was 1.08mmol/L. His calculated LDL-C was 2.4mmol/L.

### Is intensification of lipid-lowering therapy justified?

Using simvastatin as secondary prevention of cardiovascular disease is in accordance with much data from clinical trials, particularly the Heart Protection study.<sup>1</sup> Initial trials suggested that a 1% reduction in LDL-C yielded about a 1% reduction in the rate of cardiovascular events. These trials involved the use of early statins such as simvastatin or pravastatin at doses of about 40mg/day, which resulted in LDL-C reductions of about 1mmol/L. When used in patients with average baseline levels, this treatment reduced LDL-C levels to about 2.5mmol/L. This became the target LDL-C level for high-risk patients in public health guidelines in most countries, including Australia.<sup>2</sup>

The availability of more intensive treatments posed the question of whether more vigorous cholesterol-lowering therapy would result in further reductions in the rate of cardiovascular events. A series of clinical trials has recently answered this question. In comparison to standard treatment, a higher dose of the stronger agent, atorvastatin 80mg, achieved further modest improvements in angiographic outcome and reductions in cardiovascular disease events that

were significant in most studies.<sup>3-5</sup> These improvements were associated with on-treatment LDL-C levels between 1.6 and 2.0mmol/L, suggesting that “lower is better” with regard to LDL-C in very-high-risk patients.

These new findings have been reflected in updated clinical guidelines, including those of the Heart Foundation.<sup>6</sup> These guidelines continue to emphasise the identification of patients at a higher absolute risk of cardiovascular disease according to revised criteria (Table 2, page 4). They also set lower LDL-C and triglyceride target levels for very-high-risk patients (Table 3, page 4). Similar modifications to the Pharmaceutical Benefits Schedule have been recommended.

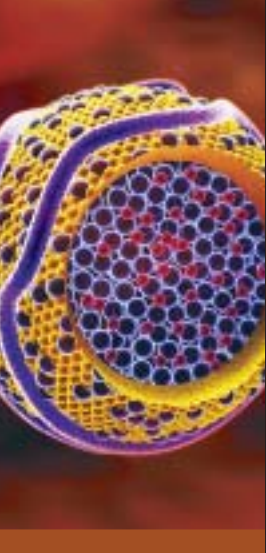
B.H.’s lipid-lowering treatment should be increased or altered to reduce LDL-C to the new target of less than 2.0mmol/L.

### If lipid-lowering treatment is intensified, what subsequent laboratory testing should be undertaken?

After a change in treatment, it is appropriate to repeat blood tests to assess response. Statins achieve most of their effect on plasma lipid levels within the first few weeks, so repeat measurement within two months will determine whether target levels have been achieved. Follow-up lipid measurements are then recommended every 6-12 months to assist compliance.

Major statin side effects involving muscle or liver abnormalities usually emerge within the first few months of therapy. The prevalence and severity of these side effects are dose dependent. The revised Heart Foundation guidelines recommend that





**Table 2: Risk assessment<sup>6</sup>**

Individuals at higher absolute risk of a cardiovascular disease event have the most to benefit from treatment.

The groups at higher risk are:

- Those with clinical evidence of:
  - vascular disease including coronary heart disease, stroke or peripheral arterial disease.
  - diabetes mellitus.
  - chronic kidney disease.
  - familial hypercholesterolaemia.
- Aboriginals and Torres Strait Islanders.
- Those with absolute risk of 15% or more of a cardiovascular disease event in the next five years using a 1991 Framingham equation (for example, New Zealand cardiovascular disease absolute risk calculator).
- Those with absolute risk of 10–15% of a cardiovascular event in the next five years with any of the following present:
  - family history of premature coronary heart disease (first-degree relative who developed coronary heart disease before the age of 60).
  - the metabolic syndrome (in which central adiposity is now considered to be of paramount importance).

creatinine kinase (CK) and alanine aminotransferase (ALT) levels be measured before treatment is started. Monitoring of CK and ALT levels is no longer thought to be necessary unless there is a high risk of side effects, such as in patients with impaired renal function or of advanced age. Repeat CK measurement for comparison to starting levels is recommended if muscle symptoms arise.

A subsequent review of statin safety<sup>7</sup> has reinforced this approach. The review found that the absolute

risk of developing liver failure due to statin therapy, and the chances of preventing such an episode by regular testing, were exceedingly small. Furthermore, it concluded that muscle symptoms were a better predictor of muscle side effects than asymptomatic CK elevation, suggesting that CK measurements only be undertaken when muscle symptoms develop. The safety review also found adverse effects such as peripheral neuropathy were extremely rare. This should be kept in mind when interpreting common

**Table 3: Target lipid levels for high-risk patients<sup>6</sup>**

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

biochemical tests during lipid-lowering therapy (see Case study 3). Some biostatisticians have recently questioned the frequency of regular lipid testing for patients on treatment and less frequent testing may be recommended in the future, but the effect on compliance will need to be considered.

### Case study 2

A.M., 58, is a smoker whose two brothers experienced fatal atherothrombotic strokes in their 50s. A.M.'s total cholesterol was 6.7mmol/L, triglycerides were 1.6mmol/L, HDL-C was 1.1mmol/L and LDL-C was 4.8mmol/L. The only other member of her large family with diagnosed hypercholesterolaemia is her 79-year-old mother (total cholesterol of 7.9mmol/L and LDL-C of 5.35mmol/L), who is otherwise well. On examination, blood pressure is 165/95mmHg despite antihypertensive treatment, but there are no other abnormal physical findings.

#### **Does A.M. have familial hypercholesterolaemia?**

A.M. has a mildly elevated LDL-C and a family history of hypercholesterolaemia in a first-degree relative. Taken on their own, these two factors are not sufficient for the positive diagnosis of the dominantly inherited disorder familial hypercholesterolaemia. Her mother's LDL-C is high, but LDL-C is a poor discriminator of familial hypercholesterolaemia in older age groups.

A.M. also has a positive family history of premature cardiovascular disease in other first-degree relatives (ie, her two brothers). This supports the diagnosis, but familial hypercholesterolaemia is uncommon in patients with LDL-C less than 5mmol/L.

The clearest indication of familial hypercholesterolaemia in the family would be severely elevated LDL-C (>5mmol/L), particularly in a young member of the family, or the presence of tendon xanthomas in a hypercholesterolaemic relative. Likewise, detection of a genetic mutation associated with familial hypercholesterolaemia would confirm the diagnosis in the family.<sup>8</sup>

However, in most cases, the diagnosis of familial hypercholesterolaemia is multifactorial, partly depending on lipid levels and looking at LDL-C levels alone is over-simplistic. UK guidelines for the clinical diagnosis of familial hypercholesterolaemia

refer to combinations of six separate criteria which are outlined in figure 1 (page 6)<sup>9</sup>.

A.M. may or may not have familial hypercholesterolaemia. The important issue with this condition is that diagnosis of familial hypercholesterolaemia should trigger the implementation of a strategy known as family cascade screening. This aims to identify close relatives to assess their cardiovascular disease risk factor status, particularly LDL-C. In the family of an individual with heterozygous familial hypercholesterolaemia, 50% of the first-degree relatives would be expected to be similarly affected. The risk of cardiovascular disease is accelerated by 20-30 years in familial hypercholesterolaemia, so it is vital to detect and treat these individuals.<sup>10</sup>

In A.M.'s case, her nieces and nephews (children of her deceased brothers) would be at risk if familial hypercholesterolaemia was present in the family. This highlights the importance of identification through family cascade screening beyond first-degree relatives. Confirmation may be facilitated by increased availability of genetic tests, which are able to detect a causative genetic abnormality in about 70% of patients with definite familial hypercholesterolaemia. This information can be used to identify affected family members with greater certainty.

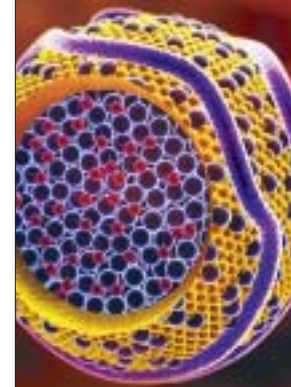
In the absence of additional information, A.M. does not fulfil diagnostic criteria for familial hypercholesterolaemia.

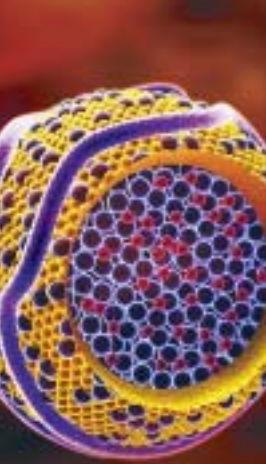
#### **Does A.M warrant initiation of lipid-lowering treatment?**

Given the above, A.M.'s need for lipid-lowering therapy should be assessed in terms of absolute risk of future cardiovascular disease events. This can be estimated as about 18% over the next five years. Unfortunately, risk calculators do not include family history. Recent reviews highlight the importance of cardiovascular disease in siblings as a risk indicator.

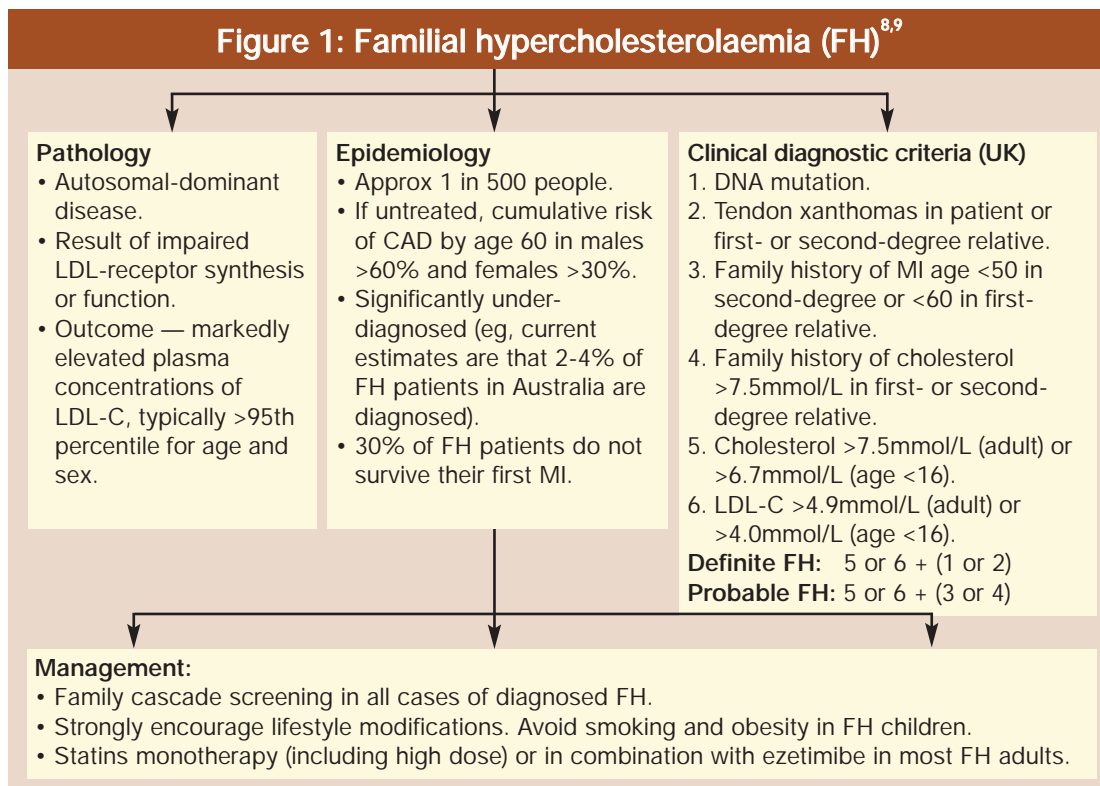
A recent European survey found that only 10% of the siblings and 6% of the children of MI patients had undergone a cardiovascular risk assessment in response to the positive family history.<sup>11</sup> Risk factors were subsequently detected in a high proportion of these relatives.<sup>12</sup>

The revised Heart Foundation guidelines





**Figure 1: Familial hypercholesterolaemia (FH)<sup>8,9</sup>**



recognise the importance of positive family history by recommending that patients like A.M receive treatment if their absolute risk of cardiovascular disease in the next five years is greater than 10% in the presence of a positive family history.

**A.M.'s 79-year-old mother's full lipid levels reveal total cholesterol of 7.9mmol/L, triglycerides of 1.1mmol/L, HDL-C of 2.05mmol/L and a calculated LDL-C of 5.35mmol/L. Would you consider A.M.'s mother for statin therapy?**

Lipid-lowering treatment should not be withheld from elderly patients. Their age is the predominant determinant of their high level of calculated risk of cardiovascular disease in the next five years. On the other hand, the potential benefits in terms of life-years saved is reduced due to shorter life-expectancy. Guidelines have different mechanisms for adjusting for this situation. According to the Heart Foundation guidelines, A.M's mother's LDL-C is elevated and she has a well-sustained HDL-C. The use of so-called "risk ratios" (such as, total cholesterol to HDL-C ratio) might con-

clude that this is a benign situation, but studies have demonstrated that cardiovascular disease events may still occur.<sup>13</sup>

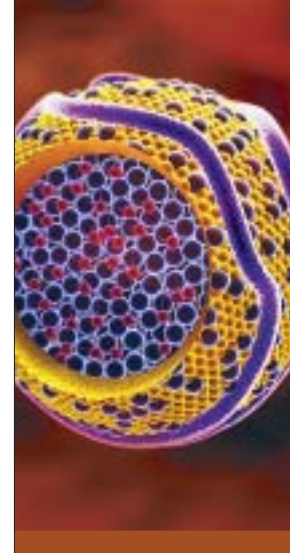
As a result, the absolute risk should be calculated and A.M.'s mother's LDL-C should be treated on its merits. For example, if her systolic blood pressure was 150mmHg, five-year cardiovascular disease risk would be 12% and she would warrant treatment under the same criteria as her daughter.

**Tendon xanthoma**



Photo courtesy of David Sullivan.





### Case study 3

F.B., 63, is normotensive (systolic blood pressure of 125mmHg) but overweight (waist circumference of 107cm). He has impaired glucose tolerance and lipid analysis reveals total cholesterol of 5.2mmol/L, triglycerides of 3.3mmol/L, HDL-C of 1.0mmol/L and calculated LDL-C of 2.7mmol/L.

#### **Does F.B. warrant medical treatment if he fails to respond to dietary measures?**

F.B. manifests the consequences of excess visceral fat to the point where he qualifies for the diagnosis of metabolic syndrome.<sup>14</sup> His five-year risk of cardiovascular disease, assuming he is a non-smoker, is 9.6%. At present, this is below the treatment threshold in the updated guidelines, which requires a five-year risk of between 10% and 15% in the presence of metabolic syndrome to justify treatment. A vigorous program of advice and support to improve diet and exercise offers the best strategy for the avoidance of type 2 diabetes. If he fails to respond to these lifestyle measures, which are likely to reduce his waistline, his cardiovascular disease risk is likely to increase with age such that lipid-lowering treatment may become appropriate.

**He experiences a gradual decline in renal function with age. Would you treat his lipids if, at age 67, his results include creatinine of 188 $\mu$ mol/L (estimated GFR of 33mL/min), total cholesterol of 5.9mmol/L, triglycerides of 3.8mmol/L, HDL-C of 0.9mmol/L and LDL-C of 3.2mmol/L?**

Renal impairment is emerging as one of the most important cardiovascular risk factors. Vigorous management of accompanying cardiovascular disease risk

factors is recommended by the Heart Foundation guidelines. This needs to be tempered by the risk of side effects with his reduced renal clearance. Statins have only minor renal excretion, but renal impairment remains a risk factor for statin-induced myopathy. Fibrates have more pronounced renal excretion, but lower doses are available for use in renal patients. Either class of agent might suit F.B. Evidence of benefits in terms of rates of cardiovascular disease events or renal function awaits more conclusive evidence.

Potent or high-dose statins may explain proteinuria, while fibrates, particularly fenofibrate, may explain the increase in creatinine and homocysteine.

#### **How might lipid-lowering therapy alter factors used to reflect the patient's renal status?**

The imminent introduction of the powerful new statin, rosuvastatin, has highlighted the effect of statins on urinary protein excretion. Rosuvastatin is associated with a dose-dependent increase in renal protein excretion. In vitro tests suggest that this is mainly due to a reduced resorption of low-molecular weight tubular proteins and, as such, may not represent a detrimental effect on renal function. Furthermore, there is evidence to suggest that this is a class effect.<sup>15</sup> The maximum dose of rosuvastatin was reduced to avoid levels where an increase in creatinine had been observed. The effects of statins on renal protein excretion may be transitory. Nevertheless, it is important to be aware of the association because it may influence the assessment of renal function.

F.B.'s lipid profile may also be amenable to cautious fibrate therapy. A sub-study within the recent FIELD trial revealed that fenofibrate use is associated with sustained elevation of creatinine and

### Conclusions

- The 2005 version of the Heart Foundation guidelines place a greater focus on absolute risk, LDL-C and HDL-C rather than total cholesterol.
- New clinical evidence suggests that in patients at high risk of cardiovascular disease, aggressive lowering of LDL-C results in a reduction of cardiovascular disease events.
- The revised targets for patients at high risk of cardiovascular disease according to the updated guidelines are triglycerides <1.5mmol/L, HDL-C >1mmol/L and LDL-C <2.0mmol/L.
- Emerging safety data does not indicate any major problems with lipid-lowering therapy.
- Lipid-lowering therapy should not be withheld from elderly patients, but high absolute risk needs to be balanced against a reduced opportunity to extend disability-adjusted life expectancy.
- Renal impairment is emerging as one of the most important cardiovascular risk factors.



homocysteine.<sup>16</sup> Both resolve after cessation of therapy. Small studies suggest that the creatinine increase is not associated with a decrease in GFR but it will nevertheless result in a decrease in estimated GFR. The clinical significance of these changes is under investigation. Fenofibrate use is also associated with significant falls in fibrinogen and uric acid.

## References

1. Heart Protection Study Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; 360:7-22.
2. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand. Lipid Management Guidelines 2001. *Medical Journal of Australia* 2001; 175:S57-S58.
3. Nissen SE, et al. REVERSAL Investigators. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *Journal of the American Medical Association* 2004; 291:1071-80.
4. Ray KK, et al. PROVE IT-TIMI 22 Investigators. Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT-TIMI 22 trial. *Journal of the American College of Cardiology* 2005; 46:1405-10.
5. Waters DD, et al. TNT Steering Committee Members and Investigators. Treating to New Targets (TNT) Study: does lowering low-density lipoprotein cholesterol levels below currently recommended guidelines yield incremental clinical benefit? *American Journal of Cardiology* 2004; 93:154-58.
6. Tonkin A, et al. National Heart Foundation of Australia. Cardiac Society of Australia and New Zealand. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: position statement on lipid management 2005. *Heart, Lung & Circulation* 2005; 14:275-91.
7. Guyton JR. Benefit versus risk in statin treatment. *American Journal of Cardiology* 2006; 97:95C-97C.
8. Civeira F. International Panel on Management of Familial Hypercholesterolemia. Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. *Atherosclerosis* 2004; 173:55-68.
9. Familial hypercholesterolaemia. Information for doctors. National Heart Foundation of Australia information sheet 2004. [www.heartfoundation.com.au](http://www.heartfoundation.com.au)
10. Hadfield SG and Humphries SE. Implementation of cascade testing for the detection of familial hypercholesterolaemia. *Current Opinion in Lipidology* 2005; 16:428-33.
11. De Backer G, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of eight societies and by invited experts). *Archives des Maladies du Coeur et des Vaisseaux* 2004; 97:1019-30.
12. Nam BH, et al. Search for an optimal atherogenic lipid risk profile: from the Framingham Study. *American Journal of Cardiology* 2006; 97:372-75.
13. Euroaspire II Study Group. Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries; principal results from EUROASPIRE II Euro Heart Survey Programme. *European Heart Journal* 2001; 22:554-72.
14. Zimmet P, et al. The metabolic syndrome: a global public health problem and a new definition. *Journal of Atherosclerosis and Thrombosis* 2005; 12:295-30.
15. URANUS study investigators. Effect of rosuvastatin or atorvastatin on urinary albumin excretion and renal function in type 2 diabetic patients. *Diabetes Research and Clinical Practice* 2006; 72:81-87.
16. The FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005; 366:1849-61.

## Further reading

- The 2005 updated position statement on lipid management and the 2001 Lipid Management Guidelines can be downloaded from the Heart Foundation web site. [www.heartfoundation.com.au/index.cfm?page=40](http://www.heartfoundation.com.au/index.cfm?page=40)
- Recommendations or guidelines on lifestyle interventions are available at [www.heartfoundation.com.au](http://www.heartfoundation.com.au)
- The NZ Cardiovascular risk calculator tool can be printed from [www.nps.org.au/resources/Health\\_Professional\\_Tools/nz\\_cardiovascular\\_risk\\_calculator.pdf](http://www.nps.org.au/resources/Health_Professional_Tools/nz_cardiovascular_risk_calculator.pdf)
- The Heart Foundation statement on familial hypercholesterolaemia can be found at [www.heartfoundation.com.au/downloads/FamHyperch\\_Mar04\\_FINAL\\_HS.pdf](http://www.heartfoundation.com.au/downloads/FamHyperch_Mar04_FINAL_HS.pdf)