

# CSP

## Common Sense Pathology

A REGULAR CASE-BASED SERIES ON PRACTICAL PATHOLOGY FOR GPs

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# LIPIDS & CARDIOVASCULAR *disease*

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# Lipids and cardiovascular disease

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## Introduction

In the past decade, lipid metabolism has become more clearly established as a major treatable risk factor for the prevention of cardiovascular disease (CVD).<sup>1</sup> Current guidelines recommend that clinical assessment should include all major risk factors so that management decisions may be based on the absolute risk of future CVD events.<sup>2</sup>

The term “absolute risk” refers to the chance that a particular patient will suffer an event in a given time. It is preferable to “relative risk”, which reflects the proportional increase in risk compared with risk-free people. Absolute risk tends to reflect the overall clinical picture, whereas relative risk tends to deal with individual risk factors in isolation. Several charts and algorithms have been developed to help calculate the approximate level of absolute risk, but there is room for the development of more precise risk-prediction techniques.

The National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand guidelines identify clinical situations and risk factor thresholds that help to identify those patients at

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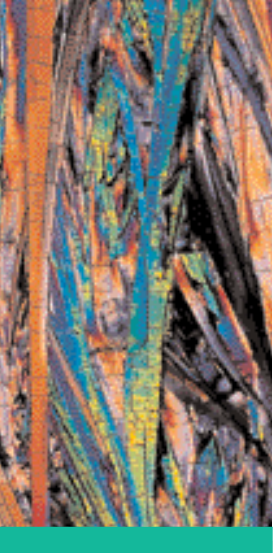
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greatest risk (table 1) in whom aggressive lipid target levels are recommended (table 2).

This approach is consistent with progress in the understanding of the atherosclerotic process that underlies CVD. It is now clear that chronic inflammation plays a pivotal role in plaque composition and progression of atherosclerotic lesions.<sup>3</sup>

Lipid-rich plaques tend to be more prone to macrophage infiltration and erosion of the protective fibrous cap, thereby raising the risk of acute plaque fissuring or rupture. These so-called “vulnerable” plaques are not necessarily the most severe in terms of luminal narrowing because the disease process is often associated with compensatory dilation of the vessel. It seems likely that new laboratory and imaging techniques may therefore replace some of the traditional reliance on angiographic appearance.

### Case 1

Mr AR is a 43-year-old panel beater who returns after diet and lifestyle intervention for hypertension and mild cholesterol elevation. Waist circumference has declined 2cm to 97cm, blood pressure has fallen by 10% to 145/90 and total cholesterol has fallen by 5% to 6.3mmol/L.

### Question 1: What additional information do you require to assess his absolute risk of CVD?

It is important to assess all major CVD risk factors. Age, gender, blood pressure and total cholesterol are known in this case, but it would be preferable to assess cholesterol in terms of the LDL fraction. Smoking status and HDL cholesterol should also be determined. The presence or absence of diabetes should be established.

Variation between risk calculators leads to differences in emphasis. For example, calculations based on the Prospective Cardiovascular Munster (PROCAM) study data allow inclusion of components of the metabolic syndrome.<sup>4</sup> On the other hand, other risk calculators include information that may no longer be routinely evaluated. For example, calculations based on Framingham data allow for assessment of the left ventricular hypertrophy. Family history of premature CVD (before age 60) is an important risk factor that should always be assessed, but it is omitted from most risk calculations.

This highlights some of the shortcomings of risk calculators. Practical constraints, such as the need to condense information, result in omission of some risk factors and compression of other continuous variables into broad categories. Nevertheless, these risk calculators represent a useful starting point that should improve with the advent of computer-based alternatives.

Additional results for Mr AR include a positive family history of premature CVD, HDL = 0.9mmol/L, and normal fasting glucose in an ex-smoker. Measurement of fasting triglyceride at 2.7mmol/L allows calculation of LDL, which is 4.2mmol/L.

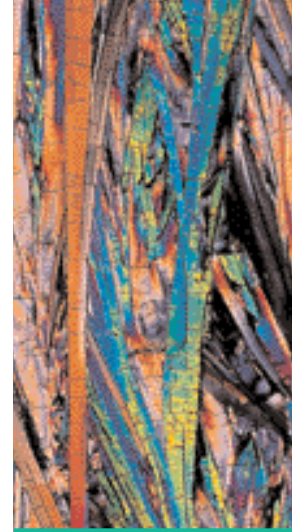
**Table 1: National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand criteria for higher absolute risk of CHD to guide treatment decisions**

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

**Table 2: National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand recommended target lipid levels\***

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

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



### **Question 2: How would you assess his CVD risk according to Heart Foundation/Cardiac Society guidelines?**

Assuming left ventricular hypertrophy is not present, the calculated risk according to Framingham data is 11% over the next 10 years (2.6-fold relative risk). Likewise, use of the New Zealand risk calculation tables,<sup>5</sup> as recommended by the guidelines, estimates the absolute risk at about 5% over the next five years.

Although the LDL is more than 4mmol/L, the absolute risk of a coronary event is not sufficient to classify the patient as very high risk according to point eight of the lipid guidelines, which is categorised as >10-15% (see table 1). On the other hand, the patient does have total cholesterol >6mmol/L, LDL cholesterol >4mmol/L and HDL cholesterol <1mmol/L in addition to positive family history and hypertension (not to mention previous smoking). This is clearly enough to satisfy high-risk status according to point nine of the lipid guidelines.

Furthermore, hypertension guidelines suggest a medium risk level that would warrant specific treatment if blood pressure elevation persists.

Lipid guidelines call for additional measures, including pharmacological treatment, if necessary, to attain target levels (table 2). They also point out that interventions that alter lipids and lipoprotein towards target levels are likely to be of benefit, even if targets are not achieved.

#### **Case 2**

Mrs EC, 78, began statin therapy two years ago for hypercholesterolaemia. Her LDL cholesterol only fell 20% to 6.6mmol/L on 40mg simvastatin, and a mild increase in CK was noted, although she remained asymptomatic.

### **Question 1: What is the aetiology of her hypercholesterolaemia?**

Most cases of hypercholesterolaemia are polygenic, reflecting the interaction between environmental factors such as diet, and multiple gene loci. The Western lifestyle also results in a tendency for LDL cholesterol levels to increase with age due to declining LDL receptor activity. However, it is not appropriate to start from an assumption that the hyperlipidaemia is a primary disorder in all cases. The diagnostic process requires the exclusion of secondary causes of hyperlipidaemia.

Several reports have drawn attention to the high prevalence of subclinical hypothyroidism among elderly patients (particularly women) presenting with hypercholesterolaemia.<sup>6</sup> This has resulted in the recommendation that the TSH level should be measured routinely in this situation. Mrs EC's TSH was found to be 6.2mU/L. CK elevation is consistent with mild (subclinical) hypothyroidism as well as statin therapy.

### **Question 2: What is the likelihood that addition of thyroxine replacement will allow her to achieve target lipid levels without an increase in statin dose?**

Although severe hypothyroidism can cause moderate to severe hypercholesterolaemia, the effect of subclinical hypothyroidism is less dramatic. A recent study suggested that effective thyroxine replacement reduced LDL cholesterol levels by only 0.1-0.4mmol/L.<sup>7</sup> Nevertheless, diagnosis of subclinical hypothyroidism and consideration of treatment is necessary in terms of optimum patient management and minimisation of the use of other lipid-lowering agents.



### Case 3

Mrs GC, 42, has inherited familial hypercholesterolaemia (FH). Her LDL cholesterol level is well controlled on statin therapy, but her older sister, who is 54, recently required an angioplasty.

#### **Question 1: How does the passage of time affect Mrs GC's risk of CVD? Is treatment important?**

The relative risk of CVD in familial hypercholesterolaemia is greatest in young adults, but in absolute terms the risk becomes even greater with increasing age. Mrs GC's risk of symptomatic coronary heart disease (CHD) has increased from 3% before age 40 to 20% in the decade between 40 and 50 years. It would be prudent to monitor more closely for the emergence of CHD symptoms and to consider additional preventive measures such as aspirin.

The continued use of statin therapy is supported by the findings of the Atherosclerosis Progression in Familial Hypercholesterolaemia (ASAP) trial in which progression of carotid intimal-medial thickness was reversed by aggressive statin treatment.<sup>8</sup>

#### **Question 2: Mrs GC has become anxious about the possibility that other family members may have inherited familial hypercholesterolaemia. What advice would you give about her relatives? She also asks about genetic testing for her son, who is now 10.**

There is a strong argument in favour of testing the relatives of patients with the condition, but several practical issues need to be considered. It is important to recognise that, unlike some other inherited conditions, familial hypercholesterolaemia is responsive to treatment. In theory, about 50% of first-degree relatives will have inherited the condition, and the high rate of morbidity and mortality associated with the onset of CHD makes it inappropriate to wait until the onset of clinical symptoms. Although the serum cholesterol level shows a moderate degree of overlap between patients with and without familial hypercholesterolaemia, the presence of an elevated level in a member of an affected family is highly predictive. This is particularly the case in younger relatives.

The management of young patients with familial hypercholesterolaemia is still evolving. Conservative measures that concentrate on diet and avoidance of smoking are safe and effective,<sup>9</sup> but statin therapy may eventually become appropriate for children in more severely affected families.<sup>10</sup>

Family follow-up has been demonstrated to be a cost-effective form of case detection,<sup>11</sup> but it is often overlooked for a variety of reasons.

There has been uncertainty about privacy issues. The Australian Law Reform Commission's issues paper on protection of human genetic information (para 18.67, p485) notes that "disclosure to genetic relatives by, or with the consent of, the patient is obviously preferable", and proposal 18-1 suggests that "NPP2.1(e)(I) of the Privacy Act should be amended so that disclosure of genetic information by a health professional to the genetic relatives of a patient is permitted where failure to disclose would place the health or life of a genetic relative at serious risk". In this case, the patient seems likely to give consent.

Even in the absence of any legal impediment, the resources required to identify and inform family members are often beyond the scope of the primary care physician. A collaborative organisation known as MEDPED (Make Early Diagnosis, Prevent Early Death), which has been established to assist with this task, may be accessed at [www.medped-aust.com/](http://www.medped-aust.com/)

Although the clinical picture of familial hypercholesterolaemia will be clear-cut in many instances, genetic testing can provide certainty of diagnosis in some cases where confounding factors such as borderline cholesterol levels, or tendon injuries that mimic tendon xanthomas, have resulted in a diagnostic dilemma.

Trying to detect a genetic abnormality de novo is expensive and time-consuming, and failure to find a

mutation is inconclusive. Nevertheless, new techniques are improving the yield, and familial hypercholesterolaemia seems likely to be one of the first conditions for which a diagnostic gene chip is made available. Once a mutation has been identified in a family, the process of confirming the presence or absence of that specific mutation in individual family members is much more straightforward.

A simple cholesterol level is probably sufficient for Mrs GC's son at this stage. However, in situations of uncertainty, DNA testing may be required. In this case, the attendant ethical issues should be dealt with.

Furthermore, if testing was considered, genetic counselling would be prudent to cover proper understanding of the significance of the process and the result, as well as issues such as disclosure of results to insurance organisations. Patient information can be accessed via the NSW genetics education program at [www.genetics.com.au](http://www.genetics.com.au)

#### Case 4

Mr LK presents for cardiovascular risk factor assessment because he is anxious following his older brother's recent presentation with acute coronary syndrome requiring angioplasty. Mr LK is 39, whereas his brother, who was a heavy smoker, is 53. Mr LK's blood pressure is 125/80, total cholesterol is 5.9mmol/L, HDL cholesterol is 1.4mmol/L and fasting triglyceride is 1.3mmol/L. His fasting blood sugar is 4.9mmol/L.

#### Question 1: How high is Mr LK's LDL cholesterol and what is his absolute risk of a cardiac event?

The Friedewald equation\* can be used to calculate Mr LK's LDL cholesterol as 3.9mmol/L.<sup>12</sup> His absolute risk of a cardiac event in the next 10 years is only 3%, according to Framingham data, and in relative terms his risk is not increased. It is possible that the positive family history could be attributable to the non-heritable environmental risk factor of smoking. Mr LK should be encouraged to remain a non-smoker to avoid the gene-environment interactions that may have affected his brother. [\*The Friedewald equation is:  $\text{LDL cholesterol} = (\text{total cholesterol} - \text{HDL cholesterol}) - (\text{fasting TG}/2.2)$  in mmol/L, assuming fasting TG <4.4mmol/L.]

Clinical judgment should guide the decision about the need to test for less common heritable risk factors such as total homocysteine or apolipoprotein (a). Homocysteine is currently looking more promising.

Hyperhomocysteinaemia<sup>13</sup> is associated with all forms of atherothrombotic vascular disease, but it is uncertain whether reduction in homocysteine will reduce the risk of CVD events. A recent study reported that the combination of folic acid, vitamin B<sub>12</sub> and pyridoxine reduced the risk of restenosis and recurrent events post-angioplasty. This may be of relevance to Mr LK's brother, but the effect did not depend on the demonstration of pre-existing plasma homocysteine elevation.

Continuation of healthy lifestyle measures is advised for the time being, but Mr LK remains concerned that he requires more aggressive intervention.

#### Question 2: What is the role of further investigation?

Several non-invasive tests have come into use in an attempt to detect subclinical CVD. Exercise stress testing is classically interpreted with the assumption that angina-like symptoms are present, but this is not the case in this instance. On the other hand, the association between reduced ankle:brachial blood pressure ratio and CVD does not depend on symptoms. Imaging techniques such as ultrasound, ultrafast CT and MRI are reasonably specific methods for detecting intimal changes or atheroma, but the relationship between these findings and absolute risk of CVD events is yet to be determined.

One of the most promising approaches has been the use of a recalibrated (high sensitivity) assay for the acute-phase reactant, C-reactive protein (CRP). Reports in the literature concentrate on the association between high levels of CRP and future risk of CVD.<sup>14,15</sup> However, intra-individual variability can be quite marked and inter-laboratory standardisation has not progressed far. Overall, CRP is sensitive rather than specific,<sup>16</sup> and as such it is more appropriate to regard a low level of CRP as indicative of a low risk of CVD in cases of borderline risk. In this context, it may be a reasonable test to consider in Mr LK.





### Conclusions

The National Heart Foundation of Australia recommends ongoing risk assessment and preventive lifestyle advice for all adults, with regular lipid testing for all those aged 45 or older, as well as those younger than 45 with other risk factors.

Laboratory investigation of major cardiovascular risk factors is an important step in the assessment of the absolute risk of CVD. This usually requires the measurement of fasting glucose, triglyceride, cholesterol and HDL cholesterol, but glucose tolerance testing and evaluation of urinary microalbumin excretion may be indicated when carbohydrate metabolism is impaired. Although the classical major risk factors account for most of the attributable risk of CVD, new tests may eventually enhance risk assessment.

Plasma homocysteine is strongly associated with future risk of CVD, but it remains to be shown that intervention can reduce CVD event rates. High-sensitivity C-reactive protein is a non-specific indicator of inflammatory processes that may or may not involve the cardiovascular system. At this stage it is not possible to include these new risk factors in the overall estimation of absolute risk, so widespread use would be premature.

Genetic testing raises many challenging issues, but the disorder familial hypercholesterolaemia represents one situation in which this technology could be appropriate because it could confirm the diagnosis of a common treatable condition.

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