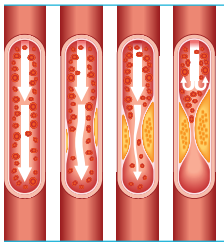

Familial hypercholesterolaemia in Australia: new insights and developments

A model of care is in place but the challenge of early detection remains

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Familial hypercholesterolaemia (FH) is the most common and serious type of inherited hyperlipidaemia. It causes premature atherosclerotic cardiovascular disease (CVD), in particular coronary heart disease (CHD), bringing forward the onset of CVD by one to four decades.[1]

Although early detection and management can slow the progression of atherosclerosis, there are concerns that the majority of people with FH in Australia and New Zealand are undiagnosed and those diagnosed are often undertreated.[1] Similarly, in the United Kingdom, HEART UK, which supports patients with FH, reported recently that only 15% of patients with FH in the UK were aware they had the condition. In addition, a third of 455 respondents to an online survey did not know that abnormal cholesterol levels could be inherited (http://heartuk.org.uk/latest-news/article/heart-uk-extremely-concerned-by-research-highlighting-cholesterol-ignorance).

In 2011, in response to this gap in coronary prevention, the Australian Atherosclerosis Society's FH Australasia Network published a consensus model of care for FH.[1] The model includes guidelines for case detection and cascade screening, assessment and treatment of children and adolescents, and lifestyle and drug-treatment strategies, as well as indications for low-density lipoprotein (LDL) cholesterol apheresis (a process similar to haemodialysis to remove LDL cholesterol from the blood). The model of care has been endorsed by the National Heart Foundation, the Cardiovascular Genetics Council and Cardiovascular Nursing Council of the Cardiac Society of Australia and New Zealand, and the Australasian Association of Clinical Biochemists.[1]

FH is an autosomal dominant disorder caused by gene mutations encoding the LDL cholesterol receptor and, less commonly, mutations encoding apolipoprotein B-100 (apoB-100) and proprotein convertase subtilisin/kexin 9 (PCSK9).[1] It is manifest by levels of LDL cholesterol > 5.0 mmol/L, premature CDH and clinical signs of LDL cholesterol deposition (arcus senilis, tendon and cutaneous xanthomas and xanthelasmas).[1]

About 70 000 Australians have heterozygous FH, and 20–30 have the rare, more severe homozygous FH. Thus, an average general practice may have several patients with heterozygous FH, from whom cascade screening of close relatives can detect up to eight affected individuals per index case.[1] Diagnostic criteria for FH are given in the Box.[1,2]

Diagnosing familial hypercholesterolaemia in an index case*[1]

Criteria	Score
Family history	
First-degree relative with known premature coronary and/or vascular disease (men, < 55 years; women, < 60 years) *or* First-degree relative with a known low-density lipoprotein (LDL) cholesterol level > 95th percentile for age and sex	1
First-degree relative with tendon xanthoma and/or corneal arcus *or* Children < 18 years with LDL cholesterol level > 95th percentile for age and sex	2
Clinical history	
Patient with premature coronary artery disease (ages as above)	2
Patient with premature cerebral or peripheral vascular disease (ages as above)	1
Physical examination	
Tendon xanthoma	6
Corneal arcus at age < 45 years	4
LDL cholesterol level (mmol/L)	
⩾ 8.5	8
6.5–8.4	5
5.0–6.4	3
4.0–4.9	1
Stratification	**Total score**
Definite FH	⩾ 8
Probable FH	6–8
Possible FH	3–5
Unlikely FH	< 3

* Based on the Dutch Lipid Clinic Network Criteria.[2] ◆

In untreated FH, about 5% of those affected manifest symptomatic CHD by the age of 30 years, although non-invasive imaging can detect subclinical atherosclerosis earlier.[1-4] By the age of 60 years, 85% and 58% of untreated men and women, respectively, develop symptomatic CHD.[1-4] Age-standardised mortality rates in people with untreated FH are twice those of people without FH, but are reduced to near-normal with statin therapy.[4]

While FH can be detected at all ages by measuring LDL cholesterol levels,[1] clinical signs are usually absent in young adults and children, and in phenotypically mild FH.[1] As patients with FH have life-long hypercholesterolaemia, Framingham-based and other CHD risk assessment tools underestimate risk and are inappropriate.[1]

Treatment with high doses of statins, in combination with ezetimibe (a lipid-lowering drug which inhibits intestinal absorption of cholesterol and phytosterols), is widely accepted as cost-effective and may lower plasma LDL cholesterol levels by 65%–75% (to normal levels), thus providing normal life expectancy.[1,4,5]

However, many patients with FH receive suboptimal treatment, and premature CHD still occurs in this group, as well as in those with poor adherence to therapy. Heavy cigarette smokers are particularly at risk — smoking is especially dangerous in FH, partly through a prothrombotic effect.[1]

For patients with FH whose LDL cholesterol levels remain above target after lipid-lowering treatment (2–4 mmol/L, depending on baseline risk[1]), two new injectable therapies can safely and effectively lower LDL cholesterol levels: monoclonal antibodies to PCSK9 and antisense oligonucleotides to apoB-100 messenger RNA.[1] These may be particularly useful in patients intolerant to statins, and longer-term clinical outcomes, safety, acceptability and cost-effectiveness are currently under investigation. In addition, LDL cholesterol apheresis is available in Victoria, New South Wales and Western Australia for the small number of patients with homozygous FH, or heterozygous FH with uncontrolled hypercholesterolaemia and progressive CHD.[1]

Publication of the model of care follows on from other initiatives to improve outcomes for people with FH. In 1996, the international FH project *Make early diagnosis to prevent early death* (MEDPED) began in Australia with the aim of promoting research, improving clinical management and increasing professional and public awareness of FH.[6] This led to other initiatives: establishment of the FH Australasia Network to coordinate research, promote best practice for primary and specialist practitioners and provide consumer information (http://www.athero.org.au/FH); a national FH web registry being planned with the WA Department of Health; jurisdictional FH services supported by WA, NSW and Queensland state health departments for clinical services and research (eg, the Barossa Family Heart Study: http://www.barossaheart.com); the LDL cholesterol apheresis services already mentioned;[1] and the Genetic Support Council WA's FH family support group (http://www.fhfamilysupportgroup.websyte.com.au/).

Implementing the model of care for FH and other FH initiatives relies on index case detection. To increase case detection, we support recommendations for the establishment of a national, federally funded FH screening program, with universal cholesterol testing of young adults aged 20–25 years, consistent with United States guidelines.[7] This should be combined with genetic testing of FH within families after detection of a mutation in an index case.[1,3] Such a national program promises to reap the benefits of modern DNA technology, and the efficacy of current lipid-lowering therapy, to achieve a normal life expectancy for those with FH.

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