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Familial hypercholesterolaemia: Walking time bombs and digging for gold

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Familial hypercholesterolaemia
walking time bombs and digging for gold

Treatment of familial hypercholesterolaemia, one of medicine's most cost-effective measures, can delay the onset of coronary heart disease and prolong life expectancy.

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Patients with familial hypercholesterolaemia (FH) are the classic 'walking time bombs', at high risk for premature heart attack and stroke. Half of all men with FH have coronary heart disease (CHD) by the time they reach 50 years. As the US cardiovascular geneticist Professor Roger Williams used to say, 'People who inherit the gene for FH have bought a ticket on a jumbo jet that's destined to crash, unless they get early and effective treatment'. This was Professor Williams' rationale for setting up the Make Early Diagnosis to Prevent Early Death (MEDPED) project at Salt Lake City in 1989, which involved screening families of patients with FH in the process now called cascade family screening.[1]

Professor Williams likened the MEDPED project to digging for gold: 'For every FH you find, you diagnose another eight among the relatives, so MEDPED is like digging for gold'. It was a very effective strategy for FH case-detection, and offered the real potential for disease prevention.

Treatment of FH with statins is regarded as one of the most cost-effective interventions in preventive medicine. Before the statin era in the UK, young patients with FH had more than 80 times the standardised mortality rate of the population without FH. With the advent of statins, survival has improved significantly. Statin therapy has been shown to prevent thickening of the carotid arteries in children treated at 10 years of age, and

IN SUMMARY

- **Most GPs will have in their practice patients with heterozygous FH, whether recognised or not.**
- **Most adults with FH are diagnosed sporadically. FH in children remains largely undiagnosed and untreated.**
- **Coronary atherosclerosis in adult patients with FH can be controlled with effective LDL-C lowering, but this requires maximum doses of potent statins in combination with ezetimibe, and often resins and nicotinic acid as well.**
- **Referral of patients with FH to a lipid clinic with experience in this area is the preferred option for family screening, a key component of FH management.**
- **Ongoing management of patients with FH should be undertaken jointly by GPs and the lipid clinic.**
- **There is a need for improved health professional and community awareness of FH as a serious and relatively common genetic disorder for which effective treatments are available.**

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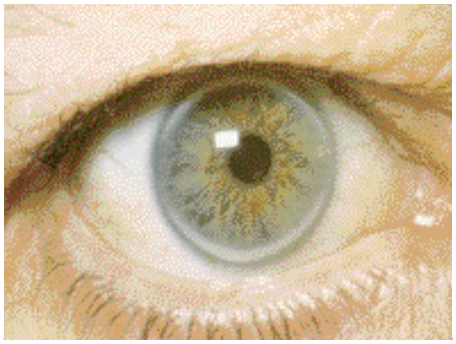

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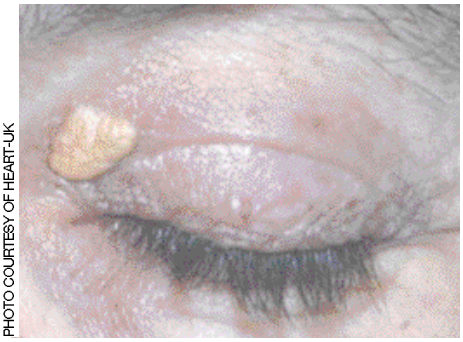

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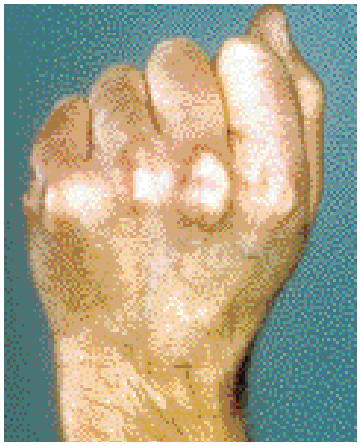

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Figures 1a to c. Clinical features of familial hypercholesterolaemia. These are due to deposition of LDL-cholesterol and include corneal arcus senilis (a, left), xanthelasmas (b, middle) and tendon xanthomas (c, right).

regression of coronary plaque has been shown in adults treated with these agents.

What causes FH?

FH is caused by a mutation in the gene coding for the LDL receptor. Defective LDL-receptor function leads to elevated plasma LDL-cholesterol (LDL-C) levels and accelerated atherosclerosis. FH is a monogenic autosomal dominant disorder – i.e. it occurs through the inheritance of a single copy of a defective gene. Males and females are affected in equal proportions. FH inherited from one parent (heterozygous FH) is quite common – one in 500 in most populations and up to one in 80 in Lebanese and some other groups.[2] FH inherited from both parents (homozygous FH) is rare.

How is FH diagnosed?

The first clue to the diagnosis of FH is the family history. Many patients will tell of forebears who died prematurely on one side of the family and had normal life expectancy on the other. Early deaths have occurred in people who are heterozygous for the FH gene (hetFH), following the inheritance of the FH gene from one parent. Sudden death is not uncommon, and is often wrongly attributed to noncardiovascular causes ('Grandpa fell off a horse and died when he was 45').

The second clue is the presence of tendon xanthomas, usually in the Achilles tendons and the extensor tendons of the fingers at the knuckles. These are firm nontender thickenings, although sometimes in the Achilles tendons they can be painful. Corneal arcus and eyelid xanthelasma are also signs of FH, but only in the young as they may occur in older people with normal cholesterol levels. Figures 1a to c illustrate some of the signs of FH.

The third clue is the fasting lipid profile. Patients with heterozygous FH have levels of LDL-C about twice that of normal (greater than 6 mmol/L). The high LDL-C level then causes accelerated atherosclerosis with a propensity to affect the coronary arteries. The level of total cholesterol (TC) is high (reflecting the high LDL-C levels), while the HDL-cholesterol (HDL-C) level is normal or slightly low and the triglyceride level is usually normal.

FH diagnostic criteria

Various diagnostic criteria have been established to distinguish FH from other causes of high cholesterol such as polygenic hypercholesterolaemia. The UK and Dutch criteria use family history, the presence of xanthomas and LDL-C levels to classify patients as having definite, probable or possible FH (Tables 1 and 2). The US MEDPED criteria use age-specific and relative-specific criteria for total cholesterol only (Table 3).[3] It is very important to be aware of the lower total cholesterol diagnostic cut-off levels in patients with first-, second- and third-degree relatives with FH compared with the cut-off levels

Table 1. UK (Simon Broome Foundation) diagnostic criteria for FH[2]

Criterion	
a:	DNA mutation (either LDL-receptor or *apoB* gene)
b:	Tendon xanthomas in patient or first- or second-degree relative
c:	Family history of myocardial infarction in second-degree relative aged <50 years or in first-degree relative aged <60 years
d:	Family history of cholesterol >7.5 mmol/L in first- or second-degree relative
e:	Total cholesterol >7.5 mmol/L (adult) or >6.7 mmol/L (age <16 years)
f:	LDL-C >4.9 mmol/L (adult) or >4.0 mmol/L (age <16 years)

Diagnosis

Definite FH: criterion a, or criteria b + e or f

Probable FH: criteria c + e or f, or criteria d + e or f

for the general population, which are much higher (see Table 3).

The jury is still out on which are the optimal criteria, but for ease of use the MEDPED criteria may be most suitable for general practice.

Cascade family screening

Once a patient has been diagnosed with FH it is important to perform cascade family screening of all living relatives as advocated by MEDPED. Interviewing, examining and measuring LDL-C levels in near relatives of a known (index) case of FH is, however, time consuming and probably best performed by experienced lipid clinics, in conjunction with genetic counselling and expert lipid management.

The Australian Privacy Act was amended on 14 September 2006[4] to allow disclosure of genetic information to relatives by doctors, but only in the private sector and only under guidelines yet to be developed by the NHMRC and approved by the Privacy Commissioner. This is clearly unsatisfactory, as further delays in instituting these key reforms seem inevitable and the public sector has not been included. Thus currently doctors are prevented from informing near relatives of patients that they have a potentially serious or fatal illness because of a genetic disorder. Index FH patients are left to contact relatives themselves, which can lead to poor results for several reasons. Many relatives are not contactable, while others refuse screening because they are unaware of the nature of FH and the benefits of early treatment.

FH therefore remains largely undiagnosed in this country. Of an estimated 40,000 patients with FH in Australia, about 20% have been diagnosed, fewer than 10% are being adequately treated and fewer than 5% have been formally identified.[5] FH indeed represents a gold mine for the prevention of cardiovascular disease.

Table 2. Dutch Lipid Clinic Network diagnostic criteria for FH[2]

Family history	Points
First-degree relative with premature CVD (men <55 years, women <60 years)	1
First-degree relative with LDL-C >95th percentile	1
First-degree relative with tendon xanthomas and/or arcus senilis	2
Children <18 years with LDL-C >95th percentile	2
Personal history of CVD	
Premature CHD (men <55 years, women <60 years)	2
Premature cerebral or peripheral vascular disease (men <55 years, women <60 years)	1
Physical examination	
Tendon xanthomas	6
Arcus senilis in patients <45 years	4
LDL-C level	
>8.5 mmol/L	8
6.5-8.4 mmol/L	5
5.0-6.4 mmol/L	3
4.0-4.9 mmol/L	1
DNA analysis	
Functional mutation of LDL-receptor gene	8

FH diagnostic category

Definite FH: greater than 8 points; probable FH: 6 to 8 points; possible FH: 3 to 5 points.

Table 3. US (MEDPED) diagnostic criteria for FH[2]

Age (years)	Total cholesterol cut-points (mmol/L)			
	First-degree relative with FH	Second-degree relative with FH	Third-degree relative with FH	General population
<20	5.7	5.9	6.2	7.0
20-29	6.2	6.5	6.7	7.5
30-39	7.0	7.2	7.5	8.8
40+	7.5	7.8	8.0	9.3

A diagnosis of FH is made if total cholesterol levels exceed the cut-point.

In Australia, a cascade family screening program has been established in Western Sydney, focusing on the Lebanese community. Videos and CDs for patients and health professionals have been developed, as have DNA diagnostic methods. In Perth, a government-funded FH program including DNA diagnosis is being established. Other States and Territories have no formal programs at this time. While a positive mutation in the LDL-receptor gene is the most reliable diagnostic test for FH, it is not routinely available. A reliable diagnosis can also be made in patients with definite FH according to the Dutch and UK criteria shown in Tables 1 and 2.

Diagnosis of FH in children

FH in children remains largely undiagnosed and untreated. Most children are diagnosed with FH following the finding of elevated LDL-C levels through cascade family screening. Occasionally a child of a parent with known FH is diagnosed in infancy following the five-day heel-prick blood sample that is used for routine diagnosis of rare inborn metabolic errors. Criteria for the diagnosis of heterozygous FH in children are less precise than those in adults because of the absence of xanthomas and lower LDL-C levels in children.

In the UK, community-wide (universal) screening of 1- to 9-year-olds by measurement of cholesterol levels at the time of immunisation has recently been proposed. Earlier UK studies had suggested universal screening of 16-year-olds was slightly more cost-effective than cascade family screening.[6] Such an approach, however, has yet to be put into practice.

Differential diagnosis

Only one other medical condition causes tendon xanthomas: beta-sitosterolaemia, a genetic condition in which the protein for transporting plant sterols out of cells is defective. Unbalanced plant sterol absorption therefore occurs, with deposition in tendons and arteries in a similar fashion to that of LDL-C. Because beta-sitosterolaemia is rare, the finding of tendon xanthomas is virtually pathognomonic of FH.

About one in 20 patients with clinical FH have a mutation in the gene coding for apoliprotein B (*apoB*), the major protein of LDL. These patients have a condition called familial defective apoB (FDB) and are at slightly lower risk of CHD than those with FH because LDL-C levels are generally lower. Treatment is identical, however, so DNA diagnosis is not essential to determine this mutation.

The one other cause of autosomal dominant hypercholesterolaemia (ADH) is the PCSK9 mutation. The *PCSK9* gene codes for a member of the NARC-1 family of proteins, one of which is involved in controlling LDL-receptor metabolism. Mutations can result in either loss of or gain in function of the receptor with subsequent hyper- or hypocholesterolaemia. Patients with hypercholesterolaemia due to this mutation have clinical features of FH and treatment is the same.

Patients with severe polygenic hypercholesterolaemia may have LDL-C levels that overlap with those of FH but tendon xanthomas are absent, a bimodal family history of premature CVD is absent, and response to dietary and drug therapy is more pronounced than in those who have FH. Patients with FH usually respond poorly to dietary intervention and require maximum doses of combination drugs to effectively lower LDL-C levels.

How is FH treated?

Treatment in adults

The aim of treatment of FH in adults is to lower LDL-C levels as far as possible. This can result in regression of tendon and eyelid xanthomas, regression of atherosclerosis and improved life expectancy. Arcus senilis, however, does not regress.

Ideally, patients with FH should be referred to a clinic specialising in FH, where investigations can be carried out and treatment initiated and monitored in co-ordination with the GP. Cascade family screening can also be performed by the lipid clinic.

The flowchart on page 44 summarises the management of FH in adults.

First-line treatment

The most potent LDL-lowering statins should be used in maximum tolerated dosages in combination with ezetimibe (Ezetrol). This regimen is capable of lowering LDL-C levels by 60 to 70%, depending on the individual's response to either agent. Levels of LDL-C may normalise in some patients, but LDL-C targets for high risk patients (currently less than 2.0 mmol/L) are often very difficult to achieve because baseline LDL-C levels are usually greater than 6.0 mmol/L. Any movement of LDL-C levels towards target is likely to be beneficial.

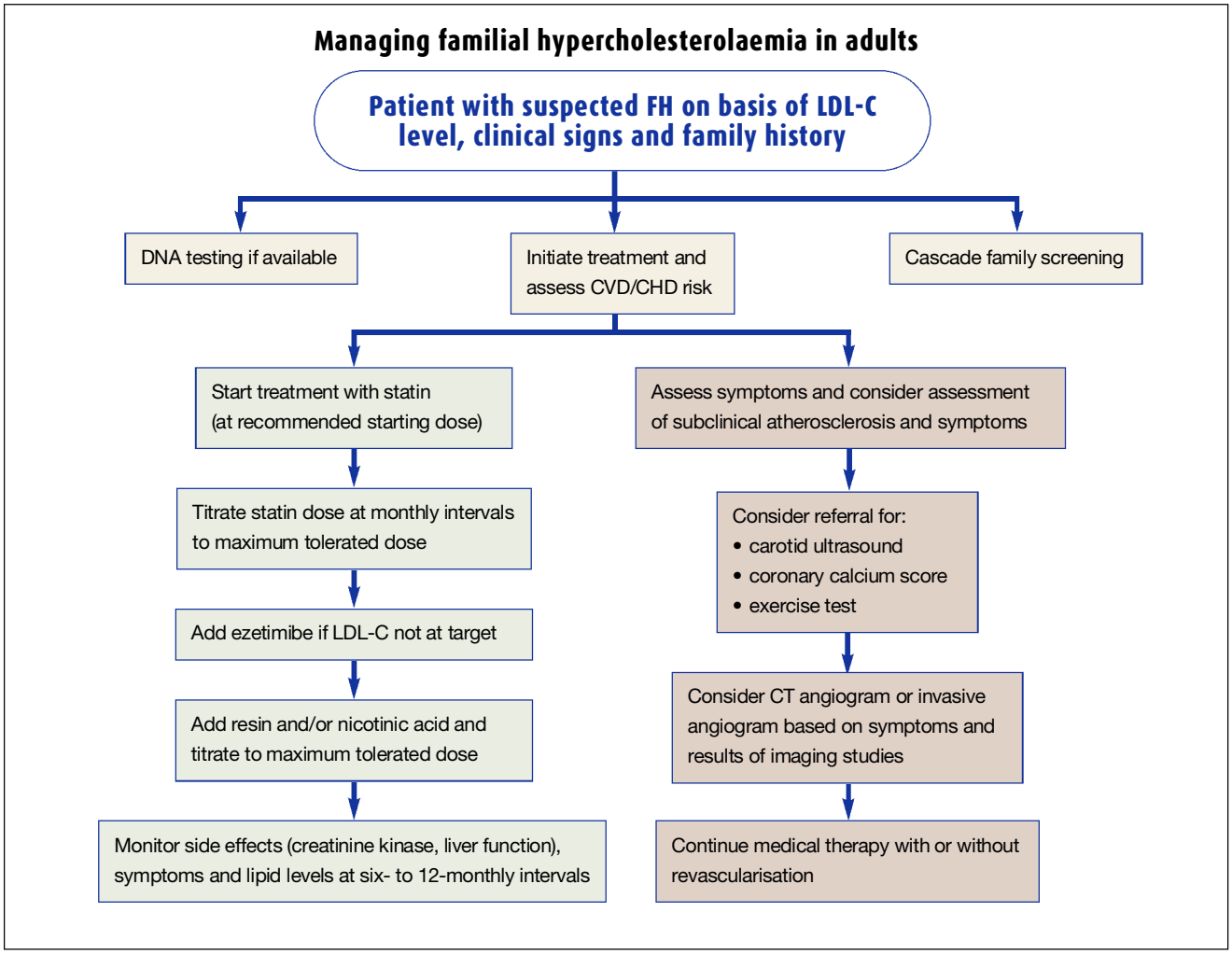
A cholesterol-lowering diet is also recommended as drug therapy is more effective with such a diet; however, most patients with FH show little change in LDL-C levels with diet alone.

Second-line treatment

Second-line drugs include resins and nicotinic acid in maximum tolerated doses. They should be used in combination with baseline therapy.

Low doses of resins (e.g. 8 g cholestyramine [Questran Lite] or 5 to 10 mg colestipol [Colestid] once daily) are often well tolerated and significantly improve LDL-C levels, while maximum doses (8 g cholestyramine or 10 g colestipol twice daily) are often poorly tolerated.

Nicotinic acid usually causes skin flushing that may be so severe that patients refuse to take even small doses. The recommended dosage is 1 to 3 g daily (four to 12 tablets in divided doses). Applications for government approval to market extended-release nicotinic acid, which is far better tolerated than the



immediate-release drug and is used extensively in other countries, have so far been unsuccessful in Australia. If tolerated, high-dose nicotinic acid is the most effective available drug for raising HDL-C levels (by up to 30%), although LDL-C lowering is modest (25 to 30%) compared with that of statins.

Fibrates are generally ineffective in lowering LDL-C levels in patients who have FH.

Other drug therapy

Low dose aspirin is often added to lipid lowering therapy in adults. Control of diabetes and hypertension is also essential and may require additional therapy.

Other treatment options

Plasmapheresis can be used to lower LDL-C levels in hetFH patients not responding to drug therapy or for patients with homozygous FH awaiting liver transplantation. Overseas, LDL-apheresis, in which LDL is selectively removed from the blood *in vitro*, is available in a few centres.

Treatment of FH in children

The American Heart Association has recently updated its 1992 guidelines on the treatment of lipids in children.[7] In the 1992 guidelines, the cut-points for treatment of LDL-C were greater than or equal to 4.9 mmol/L or greater than 4.1 mmol/L with either two or more risk factors or a positive family history of premature CVD. The 2007 guidelines accommodate initiation of therapy at lower LDL-C levels in the presence of high-risk lipid abnormalities, other risk factors or high-risk conditions. Treatment in children under the age of 10 years is also deemed to be appropriate in certain cases – for example, in a child with very high LDL-C levels whose parent died of CVD aged in his or her 20s or 30s.

Prevention of carotid artery wall thickening in children with FH treated with statins has been shown to be more effective with earlier age of treatment initiation, suggesting that statin therapy should begin by the age of 10 years.[8]

The decision to treat children with statins is made in consultation with the family and relies on the LDL-C level of the child, the child's ability to tolerate blood testing and medical supervision, and the age of onset of CHD in near relatives. Finger-prick blood testing is a suitable alternative to venepuncture, especially with the micromethods for LDL-C assay available at laboratories in children's hospitals.

Experience with statins in children with FH has shown no adverse effects on growth and development nor on biochemical profiles.[7,8] Tolerability is similar in adults and children, although less than the maximum adult doses of statins have been used in clinical trials in children with FH (up to 40 mg/day simvastatin and pravastatin and 20 mg/day atorvastatin).[7] Statins are contraindicated in pregnancy so contraception may be necessary in older girls treated with statins.

Nicotinic acid and ezetimibe are not used in children, but low dose resins may augment the effectiveness of statin therapy, as in adults.

Children with FH should be treated with a cholesterol lowering diet from the age of 2 years onwards.

Counselling

Patients with FH, their partners and their families need to be educated on the:

- nature of the disease
- silent progression of atherosclerosis
- early warning symptoms of CHD
- need for family screening to detect affected individuals as soon as possible.

Cigarette smoking and FH is a particularly high risk combination for early CHD and sudden death; smoking cessation is mandatory for patients with FH. Adolescents and children with FH must be advised never to start smoking. Other family members should be advised to stop smoking, as passive smoking may confer a risk in patients with FH.

Patients need to be aware of the mode of inheritance of FH and that 50% of progeny are affected. Genetic counselling can be useful for patients with FH who plan to become parents. Most patients are well aware of their family history and are motivated to comply with treatment, but counselling on the need for multiple medications for lipid control is often necessary.

As mentioned earlier, the decision to treat a child with statins should be made in consultation with the family.

A handbook for FH patients is currently being prepared by the Australian Atherosclerosis Society FH Subcommittee, and will soon be available to download from the internet (www.athero.org.au). The international MEDPED website provides useful information for both patients and health professionals (www.medped.org).

Which investigations should be carried out?

Subclinical CHD is usually present in adults with FH. There should be a low threshold for investigation with both noninvasive tests (e.g. exercise testing and coronary calcium scoring) and invasive tests (CT angiography and standard angiography) since sudden death is a frequent first presentation of FH. Referral of patients with FH to a cardiologist for these tests should be considered early in management.

Blood tests other than the lipid profile include:

- thyroid, renal and hepatic function tests (to exclude secondary causes of hypercholesterolaemia)
- lipoprotein(a) and homocysteine levels, which if elevated independently increase the risk of CVD
- glucose levels.

The nature of the LDL-receptor mutation also influences risk but is not routinely measured.

Follow up

It is important to maintain regular follow up of patients with FH to:

- monitor lipid levels and side effects of therapy
- detect any symptoms suggesting the need for investigation
- continue to encourage and counsel patients during their life-long need to continue aggressive therapy.

Medicolegal issues

In Australia, family screening is often neglected in both general and specialist practice because of limitations of the Privacy Act, as mentioned earlier, as well as time constraints. A case could be made for medical negligence if family screening were not properly performed, and near relatives not informed of their likelihood of being affected by a potentially lethal disease. The modifications to the Privacy Act regarding contacting relatives about genetic disorders must urgently be finalised.

Attitudes to FH screening can be influenced by awareness of the positive aspects of treatment, as opposed to the potential negative aspects of being labelled with a genetic disorder with implications for life insurance. In this regard, reductions in life insurance loadings for patients with FH have occurred in the UK after demonstration of reduced CHD incidence and mortality rates following treatment.

Diagnosis using DNA technology also raises ethical issues of paternity, storage of DNA and measurement of non-LDL-receptor genes, among others.

Collaboration between members of the medical and legal professions, health authorities, ethicists and the community is necessary to plan effective FH management program, as is currently taking place in Perth and Sydney.

Conclusion

There is a need for improved health professional and community awareness of FH as a serious and relatively common genetic disorder that is associated with a high risk for CHD. Treatment of FH is

one of medicine's most cost-effective measures to delay the onset of CHD and prolong life expectancy. MT

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DECLARATION OF INTEREST. Professor Hamilton-Craig is a member of the FH committee of the Australian Atherosclerosis Society, the Council on Genetic Cardiovascular Diseases of the Cardiac Society of Australia and New Zealand, the US National Lipid Association, the International MEDPED Steering Committee and the Lipid Advisory Boards of Merck, Sharp & Dohme, AstraZeneca and Solvay.

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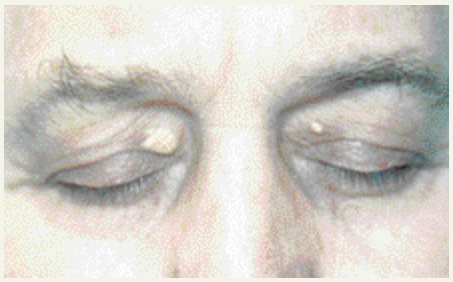

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