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Familial hypercholesterolaemia

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This publication is intended as an educational resource for general practitioners and cardiologists in NZ to assist with the identification of unrecognised familial hypercholesterolaemia (FH) and its care. It emphasises the importance of screening for this prevalent but underdiagnosed disease and gives guidance on early and aggressive treatment. Most patients with FH remain undiagnosed even after presentation with major adverse cardiovascular events (MACE).This review is supported by an educational grant from Sanofi.

Introduction

Familial hypercholesterolaemia (FH) is a prevalent inherited autosomal dominant genetic disorder resulting from alterations such as variations or deletions in any of three major genes (*LDLR, apoB and PCSK9*) involved in LDL metabolism.[1] The 4th other (recessive) gene of LDLRAP1 is very uncommon and will not be discussed. In adult patients with FH, LDL-C levels usually (but not always) exceed 6 mmol/L and are associated with premature coronary heart disease (CHD).[2]

There are two main forms of FH, heterozygous FH (HeFH), affecting possibly 1 in 250 to 1 in 500 individuals (NZ prevalence unknown), and the less common, but aggressive homozygous FH (HoFH), estimated to affect 1 in 800,000 individuals, but once again, true prevalence for NZ is not known.[3-6] Anyone under the age of 35 years presenting with CHD needs to be assessed for HoFH. Both disorders need to be considered for South African and certain other ethnic migrant groups who have elevated LDL-C levels (see page 2).[3-5]

HoFH is characterised by very high LDL-C levels in adults and children, often >13 mmol/L with total cholesterol levels ranging from 12 to 20+ mmol/L.[4,7] Those with this condition generally develop CHD early in life, and if untreated, many will not survive beyond their early 20s.[4]

HeFH usually results when an individual inherits a single *LDLR* gene variant, while in HoFH, two identical variants or deletions are inherited, one from each parent.[1,3] Compound heterozygous FH implies two different variants or deletions (one from each parent) and is typically included under the diagnostic label of HoFH. In approximately 2-3 % of FH cases in NZ, the *apoB* gene is involved (called familial defective apoB or FDB) and screening for this is routine in the molecular biology reference centre in Christchurch. LDL-C levels are generally lower in FDB than when the LDL receptor is the cause of FH. Approximately 1% of FH cases relate to the *PCSK9* gene.[5,6] The genetic cause of many clinically obvious FH cases currently cannot be determined.[5]

CHD risk is estimated to be approximately 20-fold higher in untreated patients with FH than in individuals without FH.[3,8] In the heterozygous condition the cumulative risk of CHD by the age of 60 years without effective treatment is at least 50% in men and 30% in women.[9,10] The recently published UK CVD outcome study in those with FH reports a CHD hazard ratio of 15.3 for those with undiagnosed FH; only 12% were on lipid-modifying treatment at baseline (13.8 median years of follow-up).[11] Any person presenting with ischaemic heart disease under the age of 60 years needs to be investigated for FH. Besides elevated LDL-C levels, other 'traditional' risk factors such as smoking, diabetes, hypertension, high triglycerides/low HDL-C and raised lipoprotein(a) further elevate risk.[4] The presence of these conditions provides a clinical opportunity to question the presence of undetected FH.

Despite lipid-modifying therapy, FH patients still develop premature cardiovascular events, emphasising the need to diagnose and treat FH early (from childhood) and to aggressively manage other risk factors.[12] Worldwide, FH remains largely undiagnosed and undertreated.[4,13-15] NZ has no active program to correct this. The diagnostic challenge in FH is complicated by the fact that clinical signs of FH occur in less than 50% of patients and even when clinically obvious, are often overlooked.[16] However, GPs and cardiologists can use the Dutch scoring system (**Table 1**) to formally diagnose the condition. With delayed FH diagnosis, statin and other supportive therapy may be started too late in life, when severe atheroma is already established. In such cases, the ability to reduce LDL cholesterol sufficiently will be inadequate given the absence of funding for the new era treatments such as PCSK9 inhibitors.[4] There is an urgent need to improve diagnostic screening for FH, and to implement early treatment.[4]

Prevalence and disease burden

Among the Caucasoid population, the prevalence of HeFH is estimated to be around 1 in 250 to 1 in 500.[3-6,9] Prevalence in Maori and Pacific Islanders is not known and NZ has no program for resolving this, creating obvious inequality for care should rates be unfavourable. To illustrate, the prevalence is much greater in certain world regions because of a 'founder effect' in these populations; for example, HeFH is present in 1 in 170 Christian Lebanese, 1 in 67 Ashkenazi Jews, 1 in 100 Afrikaners and 1 in 100 South African Indians.[17] Medical assessment by Immigration NZ is more stringent now and FH needs to be considered in such ethnic groups. As a key example, the estimated world-wide prevalence of HoFH is thought to be around 1 per 800,000 individuals, but in Christchurch NZ it is closer to 1 in 100,000 because a few affected South African families have arrived over recent years and have increased the prevalence of this previously extremely rare disorder (previously 1 or nil families in NZ).[3-6] Other regions in NZ need to assume they are in a similar situation and start actively screening and treating FH. Effective management requires input from multiple healthcare professions including paediatricians, lipid experts, cardiologists, radiology services, molecular genetics, dietetics, and blood transfusion services in respect of LDL apheresis etc.[7,14] This has implications for NZ, since nursing and medical training in this field will need to occur.

One estimate for NZ suggests that approximately 10,500 individuals are affected by FH, but as stated the actual numbers may be higher, reflecting immigration change and no certainty of true prevalence.[14] In Australasia, it has been estimated that approximately 77,000 individuals have FH, but fewer than 10-20% of cases are accurately diagnosed, with only 5-10% adequately treated.[14,18,19] National FH data is not collected in NZ, but it is estimated that less than 2% of those affected are diagnosed.[14]

FH is associated with substantial costs to healthcare systems.[4] Failure to diagnose FH leads to disease-management costs of early untreated CHD presentations and results in a detrimental effect on quality of life for affected individuals and families, and fiscal burden to the patient and government. In patients with treated FH, costs comprise cholesterol-lowering therapies and visits to healthcare professionals.[4]

The NZ CVD 2018 consensus statement recommends screening from age 45 years for Caucasoid NZ males, 55 years for females and 10-15 years earlier for so-called high-risk groups.[20] This strategy will completely fail to identify FH cases early enough to prevent premature cardiac disease/early atheroma, thus there is a need to consider other approaches that are relevant to this genetic condition.

Diagnosis and testing

Identifying 'index cases' (the first individual diagnosed with FH in a family) is extremely important because it represents the starting point for family tracing, referred to as 'cascade screening' (see below).[18] GPs are critically placed for detecting such cases as the condition needs to be identified decades before screening age as per guidelines.[18] FH should be considered when LDL-C levels are >4.9 mmol/L in adults or >4.0 mmol/L in children; at least two measures of plasma LDL-C should be obtained, which need not be fasting unless triglycerides are elevated beyond 2.3 mmol/L.[13,16] Secondary causes (or artefactual) of raised cholesterol need to be excluded first.

Secondary causes of very high total cholesterol levels include*:

- Hypothyroidism
- Nephrotic syndrome
- Primary biliary cirrhosis
- Myeloma
- Anorexia nervosa
- Obesity and high fat diet

* many drugs and other health conditions may elevate total cholesterol and triglyceride levels and alter HDL, but the above are often associated with total cholesterol levels that are typically found in FH

Cholesterol elevations will often coexist with high triglycerides and are associated with excess VLDL, IDL, or chylomicrons (Types 1, 3, 4, and 5 – WHO Fredrickson classification). However, the LDL will usually be low in these situations and cannot be reliably calculated and thus should not be reported by the laboratory unless directly measured.

The Cardiac Society of Australia and New Zealand (CSANZ) and the International FH Foundation recommend that any person presenting to cardiology and stroke units, or to primary care with ischaemic heart disease under the age of 60 years should be investigated for FH and index FH patients be sought amongst those presenting with evidence of CVD with a family history of hypercholesterolaemia.[16] The CSANZ also recommend that all potential cases of FH be referred to a genetic service and/or lipid clinic for confirmation of diagnosis and risk assessment, and that initial management and predictive testing or cascade screening be performed on all first-degree relatives.[16] In practice, however, in 2019 this is not possible since only Christchurch has a dedicated Lipid Disorders Service. For other regions of NZ, the appropriate referral services may be within adult or adolescent endocrine services (private or public), or cardiological units/private cardiologists with interest in managing patients with FH. Genetic testing can be done in Christchurch at Canterbury Health Laboratories.

Several sets of diagnostic criteria for FH, based on a combination of elevated cholesterol levels, clinical signs (**Figure 1**), family history of early CHD, and identified genetic alterations, have been developed, including the Dutch Lipid Clinic Network Score (DLCNS) for adults (**Table 1**), which is the recommended tool for NZ. An online DLCNS calculator is available at https://www.athero.org.au/fh/calculator/

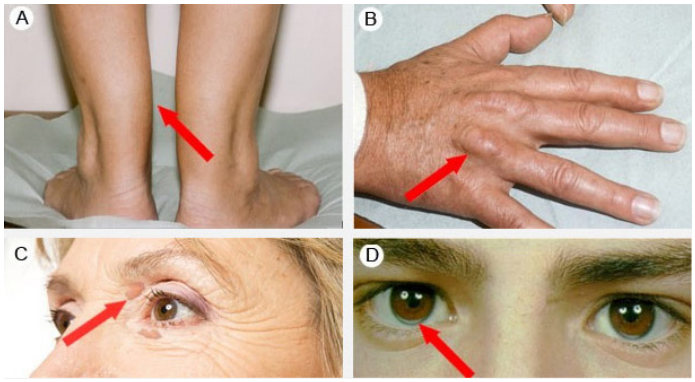

Figure 1. Clinical signs associated with FH. Untreated patients can present with cutaneous deposits of cholesterol, called xanthoma, in the Achilles tendon (A), the extensor tendons of the hands (B) and/or the eyelids (C). Arcus cornealis (D) before the age of 45 is also a significant indicator for suspicion of FH.[20]

Although the FH Australasia Network Consensus Group suggest a Dutch Lipid score of ≥3 for consideration of FH (**Table 1**), in practice in NZ, a score of ≥6 may be more appropriate in order to reduce the numbers being screened with low probability of identification of a monogenetic variation.[18] Those with a 'possible' FH score of 3-5 need individual clinical assessment to determine whether they should proceed to further assessment to define FH. Those with this score will be more likely to have another lipid classification such as familial combined dyslipidaemia. This scoring would need to be undertaken in the primary care sector to be effective.

ABOUT RESEARCH REVIEW

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Educational Series are a summary of the most important international and local literature which impacts on treatment of a specific medical condition. These Reviews provide information on a disease, current treatment and local /international guidelines. They are intended as an educational tool.

Table 1. Dutch Lipid Clinic Network Criteria for the diagnosis of FH in adults[4]

Group 1 Family history	Points
First degree relative with	
• Known premature CHD (<55 years ♂, <60 years ♀)	1
OR	
• Known LDL cholesterol >95th percentile by age and gender for country	1
• Tendon xanthoma and/or corneal arcus	2
OR	
• Children <18 years with LDL cholesterol >95th percentile by age and gender for country	2
Group 2 Clinical history	
Subject with	
• Premature CHD (as defined above)	2
• Premature cerebral or peripheral vascular disease	1
Group 3 Clinical examination	
• Tendon xanthoma	6
• Corneal arcus in a person <45 years	4
Group 4 Biochemistry (LDL cholesterol)*	
• >8.5 mmol/L	8
• 6.5-8.5 mmol/L	5
• 5.0-6.4 mmol/L	3
• 4.0-4.9 mmol/L	1
Group 5 Molecular genetic testing	
Causative mutation in the *LDLR, apoB*, or *PCSK9* genes	8
Diagnosis (based on the total number of points obtained)	
The highest single score in each group is considered. >8 definite Familial Hypercholesterolaemia (FH) 6-8 probable FH 3-5 possible FH 0-2 unlikely FH	

* Patients on statins, or other cholesterol-lowering medications may have a falsely low DLCNS and pre-treatment values must be obtained to accurately assess the score

Cascade screening

Cascade screening is an outward moving process to identify affected biological relatives, through LDL-C measurement and genetic testing. *LDLR*, *apoB* and *PCSK9* gene testing is recommended as standard of care by the JACC Scientific Expert Consensus Panel.[3,4,22] *PSCK9* testing is able to be done in Christchurch at request using next generation screening. A family pedigree should be drawn up. Initially, biological first-degree relatives (i.e. parents, siblings and children aged above 8 years of age or earlier at parental decision) are screened. Subsequently, consideration should be given to screening second-degree relatives (i.e. grandparents, grandchildren, aunties, uncles, nieces, nephews and half-siblings).[4] A recent systematic review has confirmed the cost-effectiveness of cascade screening in FH.[23]

Cardiovascular risk assessment

Adult patients diagnosed with probable or definite FH according to the DLCNS criteria (score ≥6) are automatically assigned high risk and cannot be assigned a risk level using any CVD risk algorithm; they must however be assessed for non-lipid cardiovascular risk factors such as hypertension and diabetes. The usual information needed in those with possible FH is age, gender, history of prior CVD, family history, risk factors of smoking, BP, diabetes, weight, waist circumference and BMI, clinical markers for FH (**Figure 1**), medications, and menopausal status in women. Biochemistry of lipids (non-fasting) including HDL, apoB, lipoprotein(a), HbA1c, SPEP, thyroid function, liver tests, renal function, albumin excretion, and fasting glucose should be obtained. In certain situations, other tests of CCS, ABI, and Achilles tendon ultrasound can be considered.

Treatment

Model of care for FH in adults

All patients should be informed about the need for lifestyle modification and smoking cessation or avoidance, and all major non-lipid cardiovascular risk factors should be treated in line with local guidelines.[18] As per **Table 2**, the recommended LDL cholesterol target for treatment in adult patients is <2.5 mmol/L, and <1.8 mmol/L for adults with CHD or diabetes, based on the EAS consensus panel which harmonises with the 2018 NZ recommendations for high CVD risk subjects; targets are the same in HeFH and HoFH.[24]

Model of care for children and adolescents

In children and adolescents, CVD risk determination is not applicable. Treatment is similar to that in adults; a healthy lifestyle and statin treatment (from age 8 to 10 years) are the cornerstones of management of HeFH. Target LDL-C is <3.5 mmol/L if >10 years of age, or if not easily achieved, ideally 50% reduction from baseline in those with very high LDL-C, elevated lipoprotein(a), a family history of premature CHD or other cardiovascular risk factors.[24] Statin treatment should start at diagnosis in those with HoFH.[25]

Table 2: Recommended LDL cholesterol targets for FH patients: EAS Consensus Panel and Joint ESC/EAS guidelines[24]

- Children: <3.5 mmol/L
- Adults: <2.5 mmol/L
- Adults with CHD or diabetes <1.8 mmol/L

Targets are the same in heterozygous and homozygous FH

Treatment options for FH

High-potency statins, which inhibit HMG-CoA reductase, reduce endogenous cholesterol synthesis, and increase LDL receptor expression, are first-line treatment in FH.[4,26,27] Statins should be administered at maximal tolerated doses, in order to achieve lipid targets**.** Patients need to be evaluated 6-8 weeks following the initiation of statin therapy to assess LDL-C levels, treatment adherence, safety and tolerability.[4,18] Subsequently, if LDL-C goals are attained and no clinical problems manifest, patients can be re-evaluated at 6-12-month intervals.

Statin monotherapy is often insufficient in reducing LDL-C to desired levels and the addition of ezetimibe (Special Authority in NZ), may be necessary.[4,18] Niacin and resins may be considered for special cases.[13] Niacin may reduce elevated lipoprotein(a) levels particularly in those in the highest tertile.[13] The atherogenic profile of residual hypertriglyceridaemia and low HDL-C while on statin therapy warrants consideration of additional treatment in those with FH with a refocus on weight, diet, alcohol and lifestyle, and if diabetes is present, review of the treatment package. Niacin, acipimox, a fibrate or high-dose omega-3 fatty acid ethyl ester can be considered. In NZ, no purified omega 3 agents are easily accessible. If used in those with high triglycerides, the dose may need to be at least 4 g per day, unless on antiplatelet therapy when a lower dose of 1-2 g/day should be used.

Treatment with a PCSK9 inhibitor, such as alirocumab or evolocumab, is a well-tolerated, efficacious option for FH patients who have failed to reach LDL-C treatment goals on statins and other lipid lowering therapies, or who are statin-intolerant, or for whom a statin is contraindicated.[28-30] In NZ these agents need to be self-funded and costs differ depending on pharmacy markups. Approximate costs for PCSK9 inhibitors range from $850 - $960 per month. This involves subcutaneous administration every 2 weeks and

will be given in combination with statin-lowering therapy.[29,30] Such therapy is now recommended in a number of international guidelines, including the recently updated ESC/EAS 2019 guidelines and the ACC 2018 guidelines.[31-34] The 2011 FH Australasia Network Model of Care guidelines have not yet been updated to reflect new data on the use of PCSK9-inhibitor therapy in FH. However, the newly updated ESC/EAS 2019 guidelines recommend treatment with a PCSK9 inhibitor in very-high risk FH patients (that is, with ASCVD or with another major risk factor) if the treatment goal is not achieved on a maximal tolerated statin plus ezetimibe.[18,31,35]

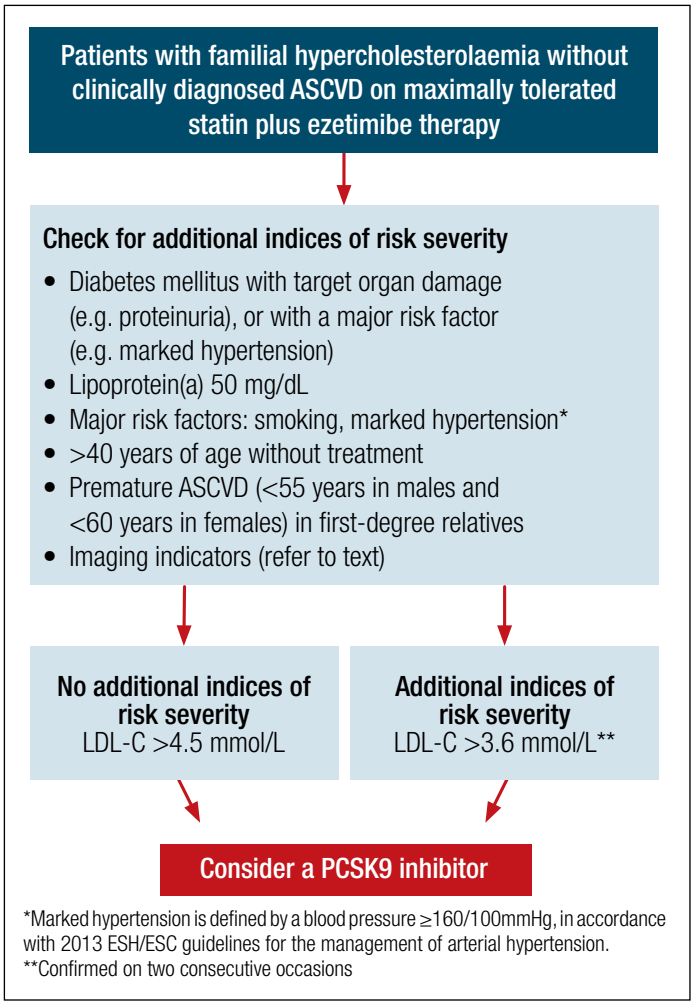

Figure 2. ESC/EAS clinical decision algorithm for the use of PCSK9 inhibitors in FH patients without clinically diagnosed artherosclerotic cardiovascular disease (ASCVD) and with substantially elevated LDL-C levels despite maximally tolerated statin plus ezetimibe therapy.[31]

LDL-apheresis should be considered for patients with HoFH or compound HeFH (including children ≥5 years of age, particularly if the LDL-cholesterol concentration remains ≥7 mmol/L despite maximum tolerated lipid lowering medication) and for HeFH patients with documented CHD who are refractory or intolerant to cholesterol-lowering medication.[18] LDL apheresis is routinely done in Christchurch and most other larger centres have the capability to do this, in cooperation with Blood Transfusion Services. Although this procedure is expensive and time-consuming, if conducted bi-weekly it can reduce LDL-C and lipoprotein(a) levels by 50-75%.[4]

Monitor for adverse events

The potential for statin-drug interactions, particularly for drugs metabolised by the cytochrome P450 3A4 (relevant to simvastatin and atorvastatin) and 2C9 systems, must be considered.[18] Gastrointestinal adverse events (e.g. abdominal discomfort and constipation) are common with bile acid-binding resins and may lead to reduced absorption of fat-soluble vitamins and other drugs. Resins should therefore be administered with food, patients should increase fluid and fibre intake, and the use of stool softeners may be needed. Flushing may be problematic with niacin, but this event can be reduced by concurrent aspirin administration.[18]

Musculoskeletal adverse events with statins in FH subjects necessitate specialist care.[18] Special vigilance for such events is warranted in the elderly and in patients treated with a statin plus fibrate. Drugs that interfere with statin clearance should not be used or if clinically necessary, should be a signal to withhold the statin until the course is concluded. Interactions of statins with other drugs can easily be researched through NZ Formulary. In clinical risk situations such as renal or liver impairment, creatine kinase should be measured. If the creatine kinase level is >3 times the upper limit of normal, statin withdrawal, dosage reduction or use of an alternative treatment may be needed.[18]

The importance of early and prompt treatment

Early (from childhood) and effective long-term treatment with LDL-C-lowering therapy can markedly reduce or eliminate the excess lifetime risk of CHD in patients with FH; CHD risk may even be reduced to levels equivalent to those in the general population.[4,8] Cholesterol-lowering drug therapy should be started as soon as FH is diagnosed in adults. It should also be used in children with HeFH aged 8-10 years unless clinical reasons suggest otherwise.[4]

Evidence for the use of statins

The most effective statins (atorvastatin and rosuvastatin) at maximum tolerated doses can reduce LDL-C levels by 50-60%.[37] Furthermore, a large body of clinical evidence confirms that statins reduce the occurrence of major cardiovascular events.[36] Observational studies have shown that statin administration (before the onset of CHD) to patients with FH significantly increases CHD-free survival to rates similar to those in the general population.[4] A Dutch study involving 413 patients with FH starting statin therapy at diagnosis and 1294 patients who started statin therapy after a mean delay of 4.3 years, found that over a mean follow-up of 8.5 years, early statin versus delayed-statin therapy resulted in an overall CHD risk reduction of 76% (OR 0.24; 95% CI 0.18-0.30; $p < 0.001$; **Figure 3**).[38]

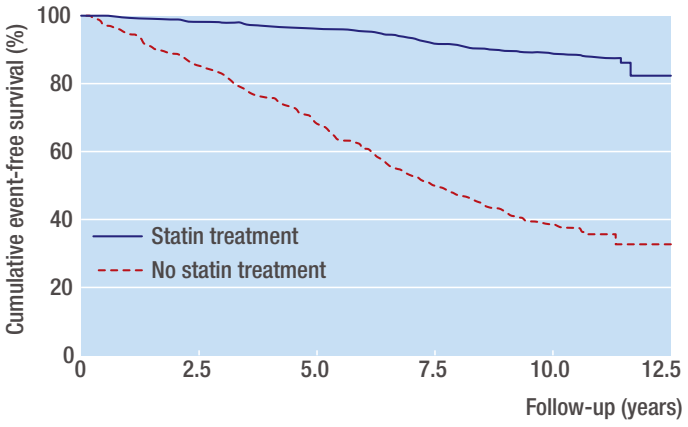

Figure 3. Kaplan-Meier estimates of cumulative CHD-free survival in patients with FH who received statin or no (i.e. delayed) statin therapy.[38]

A systematic review and meta-analysis comparing the risk of stroke in HeFH patients in the pre- and post-statin era revealed a significant reduction in the incidence of stroke after the introduction of statin therapy.[39] There is also evidence for the efficacy and safety of statins in children and adolescents with FH. A meta-analysis of six studies showed that statins significantly reduce LDL-C (weighted mean difference -30%), total cholesterol (-23%) and apoB (-25%), with no significant differences between statin and placebo with regard to adverse events, sexual development, liver toxicity or muscle toxicity.[40] Data from the UK Paediatric FH Register revealed a 35% reduction in LDL-C levels in statin-treated children compared with a reduction of 5.5% in those not treated, and none of those on statins had measured plasma levels of creatine kinase, AMT or AST indicative of statin toxicity.[41]

Evidence for the use of ezetimibe

A number of studies investigating the addition of ezetimibe to statin therapy in FH have found an additional 10-15% reduction in LDL-C levels without safety concerns.[42] In addition, combination ezetimibe + simvastatin therapy in adolescents with HeFH achieved a greater reduction in LDL-C levels than with simvastatin alone at week 33; -54.0% vs -38.1% ($p < 0.01$). The recommended combination in NZ is atorvastatin or rosuvastatin with ezetimibe.

Evidence for the use of PCSK9 inhibitors

The safety and efficacy of the PCSK9-inhibiting monoclonal antibodies alirocumab and evolocumab have been evaluated in a number of FH trials.[42-44] The findings of some of these trials, with regard to the reduction of LDL-C and lipoprotein(a), are outlined in **Table 3**.[42-44] Overall, the data from the PCSK9 inhibitor trials indicate that patients with FH, particularly HeFH, who are treated with maximal tolerated lipid-lowering therapy may achieve an additional LDL-C reduction of approximately 60% with the addition of alirocumab or evolocumab, and 80% of patients achieve recommended LDL-C targets.[42-44] Furthermore, the response to alirocumab in HeFH appears to be independent of mutation status.[45]

Real-world experience of PCSK9-inhibitor therapy from the British Colombia FH Registry between 2015 and 2017 showed that 85.4% of PCSK9 inhibitor recipients experienced a ≥50% reduction in LDL-C or LDL-C <2 mmol/L compared to only 50.2% of patients not receiving a PCSK9 inhibitor ($p < 0.001$).[46]

Future therapies

Novel emerging therapies for the treatment of FH include inclisiran (a long-acting synthetic small interfering RNA that is taken up by specific receptors in the liver, inhibiting the production of PCSK9), angiopoietin-like 3 inhibition (a hepatic protein that plays a key part in lipoprotein metabolism), bempedoic acid which inhibits cholesterol production upstream from HMGCoA and gemcabene, a lipid-regulating molecule that enhances the clearance of VLDL, resulting in decreased LDL-C levels.[42]

Table 3. Effects of the PCSK9 inhibitors alirocumab and evolocumab in FH[42-44]

Clinical trial	Subjects	Dosing and schedule		LDL-C (% treatment difference)	Lipoprotein-(a) (% treatment difference)
ALIROCUMAB					
ODYSSEY FH I and FH II	HeFH (78 weeks)	75 or 150mg	Q2W	FH I: –57.9% ($p < 0.0001$) FH II:–51.4% ($p < 0.0001$)	–17.7% ($p < 0.0001$) –20.3% ($p < 0.0001$)
ODYSSEY HIGH FH	HeFH (78 weeks)	150mg	Q2W	–39.1% at week 24 ($p < 0.0001$)	–14.8% ($p = 0.0164$)
ODYSSEY LONG TERM	HeFH (78 weeks)	150mg	Q2W	–61.9% at week 24 ($p < 0.001$)	–25.6% ($p < 0.001$)
ODYSSEY OLE	HeFH (3 years)	75 or 150mg	Q2W	–48.2%* at 3 years	–27.8%*
EVOLOCUMAB					
RUTHERFORD-2	HeFH (12 weeks)	140mg	Q2W	–59.2% ($p < 0.0001$)	–31.6% ($p < 0.0001$)
		420mg	Q4W	–61.3% ($p < 0.0001$)	–28.2% ($p < 0.0001$)
TESLA part A	HoFH (36 weeks)	420mg	Q4W	–16.5%*	–11.7%*
			Q2W	–13.9%*	–18.6%*
TESLA part B	HoFH (12 weeks)	420mg	Q4W	–30.9% ($p < 0.0001$)	–11.8% ($p = 0.09$)
TAUSSIG	HoFH (5 years) Severe HeFH (5 years)	420mg	Q2W or Q4W	–30.1%* at 44 months –52.2%* at 44 months	

Q2W: every 2 weeks; Q4W: every 4 weeks; *: % change from baseline.

Abbreviations used in this review:
ABI = ankle-brachial pressure index
ACC = American College of Cardiology
ALT = alanine aminotransferase
apoB = apolipoprotein B
AST = aspartate aminotransferase
CCS = coronary calcium score
CHD = coronary heart disease
CI = confidence interval
cIMT = carotid arterial intima-media thickness
CK = creatine kinase
CVD = cardiovascular disease
DLCNS = Dutch Lipid Clinic Network Score
ESC/EAS = European Society of Cardiology/European Atherosclerosis Society
FDB = familial defective apolipoprotein B
FH = familial hypercholesterolaemia
HDL-C = high-density lipoprotein cholesterol
HeFH = heterozygous familial hypercholesterolaemia
HMG-CoA = 5-hydroxy-3-methylglutaryl-coenzyme A
HoFH = homozygous familial hypercholesterolaemia
IDL = intermediate-density lipoprotein
JACC = Journal of the American College of Cardiology
LDL-C = low-density lipoprotein cholesterol
LDLR = low-density lipoprotein receptor
LDLRAP1 = low-density lipoprotein receptor adapter protein 1
MACE = major adverse cardiovascular events
OR = odds ratio
PCSK9 = proprotein convertase subtilisin/kexin type 9
SPEP = serum protein electrophoresis
VLDL = very-low-density lipoprotein

Useful resources:
DLCNS calculator: https://www.athero.org.au/fh/calculator/
FH Australasian Model of Care: https://www.sciencedirect.com/science/article/pii/S156756881100002X
RACGP FH guidelines: https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/familial-hypercholesterolaemia
ESC/EAS Task Force guidance on PCSK9 inhibition in FA: https://academic.oup.com/eurheartj/article/39/14/1131/4554775

TAKE-HOME MESSAGES

- FH is an inherited autosomal dominant genetic disorder characterised by life-long increases in plasma levels of LDL-C
- In Australasia, it has been estimated that approximately 77,000 individuals have FH, but fewer than 10-20% of cases are accurately diagnosed, and only 5-10% are adequately treated
- High LDL-C levels lead to premature atherosclerotic CVD, especially CHD which occurs in approximately 30% of untreated women by age 60 years and in approximately 50% of untreated men by age 50 years
- The CHD risk is estimated to be approximately 20-fold higher in untreated patients with FH than in unaffected individuals
- Heterozygous FH is present in 1 in 170 Christian Lebanese, 1 in 67 Ashkenazi Jews, 1 in 100 Afrikaners and 1 in 100 South African Indians. With recent immigration from South Africa, the prevalence in NZ may be higher in some communities
- FH should be considered when LDL-C levels are >4.9 mmol/L in adults or >4.0 mmol/L in children and should be followed by characterisation using the Dutch scoring system (**Table 1**)
- Lifestyle management including dietary modification and increased physical activity is imperative for all patients with FH. Smoking cessation and the management of obesity, high blood pressure and diabetes are integral to treatment
- Statins are the mainstay of treatment, usually at maximum-tolerated doses, often in combination with ezetimibe. The recommended combination in NZ is atorvastatin or rosuvastatin with ezetimibe. Rosuvastatin needs to be self funded in NZ
- Most HeFH patients can achieve population average LDL-C levels with appropriate treatment and will experience lower CHD rates and improved life expectancy
- PCSK9 inhibitors may lower LDL-C by 60% and offer an effective option for FH patients who require additional LDL-C lowering therapy or who are unable to take statins
- HoFH and compound heterozygote children should be managed in cooperation with a specialist lipid/endocrine/cardiac service, which should include a paediatrician
- PCSK9 inhibitor non-funding is a problem for CVD management of the highest risk FH subjects
- Data for niacin addition on top of statins is limited for FH patients
- A huge gap in awareness of FH and practical barriers to screening and diagnosis and cascade testing to identify other affected family members exists
- There is a lack of referral centres in NZ and uncertainty as to where to send people for management.

RUSSELL SCOTT CONCLUDING REMARKS

The most important task for better FH management in NZ is improving the detection of cases of FH. Once identified, treatment is relatively straightforward. Primary care has a pivotal role in screening for FH and an unfavorable family history for CVD should be a catalyst for exclusion of FH, and this testing should occur as early as possible in life. Such screening should include a non-fasting lipid profile, as this is the key biochemical trigger to implicate the presence of FH.

Whereas funding for the newer LDL lowering agents would be desirable for FH, by far the greatest health benefit would accrue through higher FH detection rates within all regions of NZ. A realistic target is for every primary care practice to start identifying those with FH as early as possible and to proceed to family screening and treatment of those affected.

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