

Clinical management of familial hypercholesterolemia: new insights from international guidelines and recent studies

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Abstract

This review article assesses the clinical features, diagnosis and management of familial hypercholesterolemia (FH). FH is mostly an autosomally dominantly inherited with an incidence of 1 in 250. Tendon xanthomata are pathognomonic. Untreated FH is associated with 100-200 fold increase in risk of cardiovascular disease (CVD). FH is diagnosed by screening for elevated low density lipoprotein cholesterol (LDL-C) and confirmed by DNA techniques. Once index cases have been identified cascade family screening should occur. FH is primarily treated with high dose statin therapy. This reduces progression of surrogate markers of coronary arterial disease and registry studies show a 70% long-term decrease in CVD mortality. The justification for other lipid-lowering therapies *e.g.* ezetimibe relies on the high population attributable risk of LDL-C in FH. Novel therapies with greater LDL-C reducing actions such as proprotein convertase subtilisin kexin-9 inhibitors show promise in FH Children with FH should be identified through cascade screening but drug treatment is dependent on LDL-C and family history. They should be managed in specialist paediatric units or in family clinics. Cases of homozygous FH are rare. This orphan condition should be managed in specialist centers with a combination of drug therapy, apheresis and liver transplantation. Novel therapies for the treatment of homozygous FH such as mipomersen and lomitapide are gradually coming into use FH is a common underdiagnosed condition. Current, let alone future, therapies are extremely effective in reducing both LDL-C and CVD events in patients with FH. Identification and treatment of FH should be a feature of preventative CVD medicine programmes.

Introduction

Familial hypercholesterolemia is the commonest autosomal dominant disorder in

man.^{1,2} It has a prevalence of 1 in 250 in most countries and is caused by a multiplicity defects in the low-density lipoprotein receptor (LDL-R) pathway.³ In some countries and ethnic groups (*e.g.* South Africa Afrikaaners, French Canadians, Lebanese) the prevalence increases to 1% with a far more restricted mutation spectrum.⁴ Recently a number of guidelines for the identification and management of patients with familial hypercholesterolemia (FH) have been promulgated in the UK,^{5,6} Europe^{7,8} and the USA⁹ and integrated into a consensus guideline.¹⁰ This paper reviews the recommendations made for the clinical diagnosis and management of FH in those statements. Heterozygote FH cases are diagnosed by a combination of lipid-related criteria and a family history of premature cardiovascular disease (CVD) - usually coronary arterial disease (CAD). Preliminary screening criteria include the use of LDL-cholesterol cut-offs (*e.g.* Simon Broome criteria)¹¹ or point scores (Dutch FH score)¹² allied with the presence of physical signs such as tendon xanthomata or arcus and a family history of hypercholesterolemia and/or coronary heart disease. The diagnosis is ideally confirmed by genetic techniques. A small number of patients have homozygous familial hypercholesterolemia and require paediatric diagnosis and specialist management. This review is based on a systematic search for articles on *familial hypercholesterolemia* with additional search terms including *guideline, meta-analysis, systematic review or review*.

Diagnosis of familial hypercholesterolemia

The original diagnostic algorithms for FH rely on identifying cases of FH by clinical criteria such as the presence of tendon xanthomata or less specifically corneal arcus allied with the presence of severe hypercholesterolemia showing usually an autosomal dominant pattern of inheritance. This can be associated with the presence of CAD in family members and usually premature CAD is used. The exact age definition of premature CAD varies between diagnostic systems. The degree of hypercholesterolemia required for index cases is usually derived from the 95th centile of the population LDL-C distribution. The systems used include the Dutch lipid criteria based on a points score comprising clinical signs, LDL-C and family CAD or lipid profiles. A score >6 is usually suggested to be likely FH.¹² The Simon Broome criteria are similar but simpler and use a cut-off value for adults (>4.7 mmol/L) or children (>4.0 mmol/L) for LDL-C.¹¹ Clinically there seems to be little difference between the Dutch and Simon Broome criteria in diagnos-

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Conflict of interests: ASW is a clinical investigator in trials run by Merck (anacetrapib), Amgen (evolocumab), and Pfizer (bococizumab) in the field of cardiovascular medicine including familial hypercholesterolemia. ASW was an expert assessor for the National Institute of Health and Clinical Excellence (NICE) technology appraisal panel for ezetimibe (TA132), a guideline group member for the familial hypercholesterolemia guideline (CG71) and chaired the Lipids and cardiovascular risk assessment guideline group (CG181). The views in this article are his own and do not represent those of the guideline groups.

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tic efficiency in European populations though the lipid cut-offs/scores may not be appropriate in other countries/regions of the world. The MedPed criteria rely more on population centile derived lipid levels within families but are rarely used.

Data on lipid distributions within FH show that the overlap with polygenic and/or environmental hypercholesterolemia is far larger than just the 5% cut-off used in index case identification.¹³ Patients with FH can even have LDL-C levels in the lower half of the population distribution though their prognosis seems to relate to their level of LDL-C rather than their genotypic mutation.¹⁴ This large overlap causes significant diagnostic problems as genetic testing is not cheap and the exact functional status of some sequence changes (variants) can be unclear and may not necessarily follow computer-based structure-function predictions. In addition physical signs such as tendon xanthomata seem to be becoming rarer even allowing for the finding that patients are being diagnosed earlier. Similarly rates of premature CAD are falling in the general population as rates of CVD decline with reductions in rates of smoking and improvements in

lifestyle. High levels of LDL-C can occur secondary to hepatic steatosis or post-menopausal elevations in LDL-C which can confound the diagnostic algorithms. Thus increasing use is being made of measures that integrate cholesterol-exposure of which imaging is most well established.¹⁵ Both carotid intima-media thickness (cIMT) and coronary artery calcium (CAC) scores integrate cholesterol exposure but suffer from problems such as insufficient standardization (cIMT), loss of sensitivity with age (cIMT) or poor sensitivity in younger patients (CAC). Thus though these tools are promising as methods to differentiate FH from other causes of dyslipidemia they are not widely used and require further work before being used in routine practice.

Ideally FH would be diagnosed by genetic methods. However, there are no common mutations in FH in contrast to the example of the F508 mutation in cystic fibrosis. The nearest equivalent is the apoB R3500Q mutation responsible for causing the familial defective apolipoprotein (apo) B form of FH which can account for up to 10% of cases in some countries.¹⁶ Mutations in the LDLR are found in 90-95% of patients with FH but these comprise a highly heterogeneous group of >1000 mutations with some founder effect restrictions as occur in South Africa or Quebec in Canada. Mutations in pro-protein convertase subtilisin kexin-9 (PCSK-9) comprise about 1-2% of FH mutations and again multiple different mutations have been described. A few cases of FH are caused by autosomal recessive mutations [autosomal recessive hypercholesterolemia (ARH)]. This type of FH affecting clathrin pit LDL receptor adaptor protein function has been most often described in Sardinia.¹⁷ Patients with tendon xanthomata have higher LDL-C, increased risks of CAD and mutations can be found in 75% of probands in contrast to 10-20% of patients lacking tendon xanthomata.¹⁸ The heterogeneity of FH means that restricted genotyping panels are clinically of little use and that comprehensive sequencing allied with detection of insertion-deletions is required.¹⁹ Costs may fall with the introduction of next generation sequencing techniques.²⁰ However, mutations cannot be found in the *LDLR*, *apoB* or *PCSK-9* genes in all patients with an autosomal dominant pattern of inheritance of severe hypercholesterolemia. Even in patients with homozygous FH (HoFH) 25% can lack a definitive double allele pattern.²¹ The causes of the remaining cases of clinical FH remain obscure though some seem to be caused by mutations in apoB outside exon 26 or in other genes.²² However studies of FH in children suggest that 95% of FH is potentially identifiable with the remainder of cases being caused by phenocopies of FH such as familial combined hyperlipidemia which share many clinical features with FH.²³ Analyses of

the health economics of FH show that cascade screening is the optimal strategy to find cases of FH²⁴ and that comprehensive genetic typing allied with cascade family screening by genetic techniques is best²⁵ but value is also gained from lipid-related screening in those where mutations are not identified.^{19,26,27} A strategy based on family lipid-based testing alone is ineffective as it is likely to give the incorrect diagnosis in 25% of index cases and a similar proportion of family members.^{16,19}

FH is an autosomal dominant disease and thus family screening is highly effective with a theoretical detection rate of 50%.²⁷ In practice this tends to be less as some family members decline screening or especially at greater family distances knowledge of contact details declines. Usually about 30% of family members cannot be located or do not wish to participate.²⁸ A combination of family screening allied with systematic population-based screening may be most effective way to optimize detection rates for FH.²⁹ The optimal age for lipid-based screening of the population for FH is about 10-12 years based on the greatest divergence between inherited and environmental lipid levels.³⁰ but most CVD screening programmes target the general population at age 40-75. At these ages there is substantial confounding of lipid profiles by factors such as diet, lifestyle, alcohol intake and in women post-menopausal lipid rises.

Management of lipids in heterozygous familial hypercholesterolemia

The main axiom behind management of CVD risk in FH is to reduce LDL-C as up to 90% of the attributable risk in this population is caused by hyperlipidemia as over a 5year period about 50% of the population attributable risk in FH is due to LDL-C in contrast to 5% in the general population.³¹ In general the prevalence of smoking and diabetes in FH population is lower than in the general population though the prevalence of hypertension seem similar.³² CVD risk in patients with FH is increased by about 40% overall but original data on untreated prognosis suggest CVD risk is increased by 50-100 fold leading to a 15-20 year shortening of life span.¹¹ For this reason, and given their lifetime exposure of elevated LDL-C the standard algorithms for management of CVD risk do not apply in FH. This CVD risk calculation is not advised in any patient with FH. Originally patients with FH were treated with bile acid sequestrants and fibrates, but with the launch of statins in the 1990s these drugs have become the first line drug therapy for management of LDL-C in FH.

Cardiovascular disease outcome trial data in FH is limited as it has been viewed as unethical to randomize patients with FH to placebo treatment. Data on the efficacy of statins in FH is limited to small series and to surrogate outcome trials. The Familial Atherosclerosis Treatment study (FATS) of 132 patients included many with FH and using a coronary angiographic endpoint suggested that LDL-C needed to be reduced to <2.5 mmol/L to reduce progression.³³ The only data that really followed from FATS was the publication of registry data (e.g. Simon Broome) showing the effects of better LDL-C reduction with statins in reducing morbidity and mortality in FH from CAD, stroke and eventually cancer.³⁴ Retrospective analysis of cohort data sets on countries with large registries and screening programmes such as the Netherlands showed that statin therapy reduced mortality by 70% and normalized life expectancy but have provided no data on optimal target levels.³⁵

Better evidence for the treatment of FH came from the Atorvastatin Simvastatin Atherosclerosis Study (ASAP) in 1250 patients which used a cIMT endpoint and showed that simvastatin 40 mg therapy was associated with progression while atorvastatin 80 mg treatment resulted in stabilization of cIMT.³⁶ This study has been used as the basis to recommend a 50% reduction in LDL-C from pre-treatment levels as a goal for therapy in FH though it could equally be argued that simple prescription of atorvastatin 80 mg to all patients with FH aged >40 years would be a truer reflection of the evidence base.

The treatment of FH beyond statins is controversial. Almost all lipid-lowering compounds have been shown to reduce LDL-C and these are typically added to regimes on the basis that reduction of plasma LDL-C is the paramount clinical issue in FH. The actual cellular basis of atherosclerosis is the lipid-laden macrophage (foam cell) and its likely role in controlling other cell types in the vasculature involved in atherosclerosis. In most cases plasma LDL-C seems to correlate with foam cell activity. Actual clinical data is far rarer with no CVD outcomes studies including patients with FH and there only being a few surrogate outcomes trials using coronary artery mean lumen diameter or cIMT as endpoints. The issue of LDL-C treatment targets in FH is controversial and relies on extrapolation from general CVD and levels attained in surrogate outcome studies. Targets for LDL-C have been removed in the latest US³⁷ and UK NICE guidelines³⁸ for general CVD but previous suggested LDL-C targets in FH were difficult to meet in many patients.⁷ The FATS study was underpowered and poorly clinically defined but suggested that a combination of statin, niacin and bile acid sequestrants might be beneficial in FH.³³ The Ezetimibe and Simvastatin in Hypercho-

lesterolemia Enhances Atherosclerosis Regression (ENHANCE) study was a randomized control trial of ezetimibe in FH using a cIMT endpoint but its results were disappointing.³⁹ Patients with FH and some of those from ASAP were stabilized on simvastatin 80mg and then randomized to ezetimibe or placebo. The therapies were efficacious in reducing LDL-C from a baseline of 8.22 mmol/L to 4.98 mmol/L (-40%; statin arm) and 3.65 mmol/L (-56%; statin-ezetimibe). However, after 2 years no difference was seen in cIMT. This meant either that ezetimibe was not effective despite lowering LDL-C, or that patients had insufficient other CVD risk factors to drive progression of cIMT so that even after partially controlling LDL-C for many years cIMT did not change.⁴⁰ Most clinicians decided on the latter explanation and continued to prescribe ezetimibe in FH. The results of the controversial and delayed IMPROVED Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) were presented in late 2014.^{40,41} Ezetimibe therapy added to basal simvastatin 40 mg in patients with acute coronary syndromes reduced LDL-C by an extra 0.40 mmol/L and CVD events by an extra 7% (P=0.02) with a number needed to treat of 50.

The latest innovation in treatment in FH is the future introduction of PCSK-9 inhibitors. These injectable agents are superior to ezetimibe in reducing LDL-C by 50-65% in FH⁴² compared to the 20%. However no outcome of surrogate outcome studies are planned with PCSK-9 inhibitors in FH so the utility of these drugs in this common genetic condition will not be established and will have to be extrapolated from general CVD. Additional complications will arise from likely expense of PCSK-9 therapies limiting their cost effectiveness to a subgroup in FH and the patent expiry of ezetimibe making it very cheap. Other lipid-lowering drugs in development also can reduce LDL-C⁴³ and the cholesterol ester transfer protein inhibitors such as anacetrapib while raising HDL-C also reduce LDL-C by up to 40% using oral formulations.⁴⁴

Data on the role of additional risk factors in FH is limited. In general rates of hypertension are similar in FH and general populations though rates of smoking and diabetes are lower.³² Biomarkers show similar associations in FH to the general population. Thus increased levels of C-reactive protein or other markers of inflammation are associated with increased CAD risk⁴⁵ but there is no separate intervention data or any subgroup analyses from clinical trials which, if available, case would be underpowered. Elevated levels of lipoprotein (a) (Lp(a)) are recognized to occur in FH^{7,46} and are associated with a worse prognosis. Data from the FATS study combining statins, bile acid sequestrants and niacin in a population including patients with FH sug-

gests in a post hoc analysis that reducing LDL-C to about 2.5 mmol/L negates any excess CAD risk due to Lp(a).³³ This levels of LDL-C is however currently difficult to achieve in many cases of FH.⁴⁷

Patients with severe heterozygous FH (HeFH)⁴⁸ including those with CAD progressing despite maximal lipid-lowering therapy or patients at high risk of developing CAD given high residual levels of LDL-C and extreme family histories of early CAD are considered for apheresis.⁴⁹ The availability of this procedure varies widely between countries as do the indications for it. There seems to be little difference in efficacy of time-averaged LDL-C reduction between the different forms of apheresis or plasmapheresis. There is evidence that apheresis combined with lipid-lowering drug therapy is effective in reducing the progression of angiographic CAD over a 2 year period in patients with HeFH⁵⁰ and HoFH.⁵¹ The need for apheresis may decline in HeFH once more effective add-on therapies to statins are available such as PCSK-9 inhibitors.

Management of familial hypercholesterolemia in children

The high penetrance of FH and the ability to track mutations means that family screening can be performed in children. Based on data from surrogate outcome measures of atheroma progression it seems that treatment from age 6 would be necessary to fully normalize progression of cIMT.^{52,53} Earlier treatment may be necessary in families with a severe history of early onset CAD and in children with homozygous FH. Children should be screened (if blood tests are required) and managed by services that include pediatricians and specialist support staff. Treatment options are limited by the differences of children to metabolize drugs and the lack of licensed indications for many medications. In the case of statins most drugs have a license from age 10-12 years though at reduced doses compared with adults. Similarly bezafibrate and ezetimibe have licenses from age 11 based on their efficacy in reducing LDL-C without obvious side-effects. Drug treatment can be started earlier in some cases at a specialist physician's discretion. Studies in young adults show no disturbance of endocrine profiles, or maturation history with statins over a 2 year period of treatment. The only evidence not dependent on lipid changes alone is one study using pravastatin 20mg in adolescents which showed that pravastatin treatment reduced the rate of progression of cIMT.⁵⁴ A similar trial using the more effective statin - rosuvastatin 10 mg is underway and this is likely to provide the eventual basic standard of care of pediatric FH.⁵⁵

Homozygous familial hypercholesterolemia

Patients with HoFH are rare.²¹ The prevalence is supposed to be 1 in 1,000,000 if the rate of FH is 1 in 500 but may be up to 4 times greater if the incidence of FH is actually 1 in 250.³ Patients with HoFH have more florid presentations with obvious physical signs such as xanthomata occurring often in childhood. They can present with CAD from the age of 6. Their accelerated rate of atherosclerosis also leads to other signs being present such as supraaortic stenosis due to atheroma in the ascending arch of the aorta.²¹ The lack of significant LDL receptor function in FH leads to problems in its treatment. Lipid levels are highly elevated with LDL-C levels typically >10 mmol/L. Patients with HoFH show a reduced or sometimes absent response (if null function) to statin therapy. The efficacy of fibrates, bile acid sequestrants or ezetimibe is unaffected but the high baseline LDL-C present in HoFH mean they have limited efficacy. HoFH should be managed in specialist units. Treatment is currently through maximal lipid-lowering therapy allied with apheresis performed fortnightly. The combination of these approaches while not optimizing lipid levels because of only a 25% decrease in LDL-C still results in a 70% decrease in CVD mortality and an increase in life expectancy from 33 years.⁵⁶ Children can be considered for liver transplantation to restore hepatic LDL-R function once old enough and if technical expertise and suitable donors are available.

The severity and rarity of HoFH lead to it being considered an orphan disorder. As such novel therapies have been devised that are restricted in their licensing to patients with clinical HoFH. Mipomersen, an injected oligonucleotide inhibitor of apoB mRNA stability, is licensed in the USA and can reduce LDL-C by 25%.⁵⁷ Lomitapide, a microsomal transfer protein inhibitor interfering with production of nascent very low density lipoproteins and hence LDL particle production is licensed in Europe and the USA. It can reduce LDL-C by 50% in HoFH.⁵⁸ Lomitapide and to a lesser extent mipomersen are limited by their hepatic toxicity profiles and liver function and structural change (hepatic ultrasound for fat; hepatic elastography for fibrosis or magnetic resonance imaging for liver fat) need to be monitored on a regular basis with these drugs. Their expense and requirement for special monitoring limits their use to specialist units. Recent data suggest that PCSK-9 inhibitors may be useful in some cases of HoFH with some patients showing normal responses, others an attenuated response (similar to statins) and those with null LDL-R function showing no response.⁵⁹

The treatment of ARH is also problematic as functionally no LDL receptor activity exists but patients generally show a less severe phenotype than HoFH and a greater degree of drug responsiveness.¹⁷

Conclusions

FH is probably the commonest inherited error of metabolism in man. It is easily detected, capable of effective treatment in most cases with a statin and ezetimibe and there is evidence that treatment will substantially improve life expectancy. This treatment equates to a greater than 70% reduction in CVD mortality.³⁵ New therapies such as PCSK-9 inhibitors will likely improve prognosis further. Unfortunately knowledge of FH remains poor in the clinical community and general population, and screening efforts are patchy across the world. Most cases of FH remain undiagnosed.⁷ More needs to be done to highlight FH as an easily detectable and treatable form of CVD.

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