

**Title: Importance of early recognition of heterozygous familial hypercholesterolaemia.**

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# **Importance of early recognition of heterozygous familial hypercholesterolaemia.**

## **Purpose of review**

To outline recent updates in the diagnosis and management of heterozygous familial hypercholesterolaemia (HeFH).

## **Recent findings**

Recent guidelines have suggested that FH is vastly under-diagnosed in most countries worldwide. Improvements in next generation sequencing (NGS) have led to the detection of novel mutations and the cheaper cost of this technology makes the early identification of asymptomatic individuals a feasible option. With more widespread use of high doses of more potent statins in affected adults, cardiovascular mortality has decreased in adults with HeFH.

## **Summary**

Barriers to cascade testing of relatives of index cases remain worldwide despite improvements in gene technology and the marked recent decrease in costs of genetic testing. Recent guidelines recommending screening of young children e.g. 8-10 years with measurement of LDL-C concentrations will increase the diagnosis of FH amongst children but long term safety data of the use of statins in this young age group is not available. To date the benefit of statin-induced decreases in LDL-C concentration in children is based on effects of treatment on proxy measures of cardiovascular disease and not a reduction in cardiovascular events.

## **Keywords**

Screening, genetic variants, age of treatment commencement

## **Introduction**

Familial hypercholesterolaemia (FH) comprises a group of inherited genetic defects, characterised by a highly penetrant autosomal dominant pattern of inheritance which produces a marked increase in low-density lipoprotein cholesterol (LDL-C) concentrations (1). The vast majority of affected families show only dominant inheritance with heterozygous transmission of the causal gene. Recent developments in genetic technology have made establishing the diagnosis relatively simple, although a clearly defined case finding and cascade testing protocol has not been implemented in many countries worldwide. The purpose of this brief review is to discuss the importance of early recognition of heterozygous familial hypercholesterolaemia (HeFH). Specifically, we will discuss the pros and cons of early identification of HeFH.

## **Prevalence and natural history of FH**

The prevalence of HeFH in most populations is believed to be between 1/200 to 1/500 and therefore worldwide there are estimated to be 14 and 34 million FH patients (2). However the estimated prevalence of HeFH exceeds currently diagnosed cases worldwide and that is reflected in the screening methodology and the populations tested. The estimated percentage of diagnosed FH patients ranges from less than 1% in Russia, to 44% in Iceland and 71% in Holland where a targeted screening programme operates (2).

Long term follow up cohort studies exploring the natural history of HeFH have been somewhat limited (2). A recent report from an FH registry in Norway (3), examined 4688 genetically confirmed FH patients between 1992-2010. There were 113 deaths and the mean age of death was 61.1 years. Cardiovascular disease was the most common cause of death (46.0%), followed by cancer (30.1%). Compared with the Norwegian population, cardiovascular disease mortality was significantly higher in the Registry in all age groups younger than 70 years (standardized mortality ratio 2.29, 95% CI 1.65 to 3.19 in men and women combined; standardized mortality ratio 2.00, 95% CI 1.32 to 3.04 in men; standardized mortality ratio 3.03, 95% CI 1.76 to 5.21 in women)) The mean age at inclusion in the registry of those who had died was 54.8 years compared with 33.6 years for surviving patients emphasising the adverse consequences of late diagnosis and treatment for FH. The mean age for starting lipid lowering therapy was 33.4 years, with 89% of adults > 18 years on lipid lowering medication, with a mean low-density lipoprotein cholesterol (LDL-C) on treatment of 4.7 mmol/L. This evidence emphasises the potential cardiovascular consequences of late FH diagnosis, and suboptimal treatment of LDL-C concentration.

## **Genetic variants causing FH**

HeFH is mainly caused by either loss of function mutations in low density lipoprotein receptor (LDL-R) affecting LDL uptake (4). Less commonly HeFH is due to heterozygous mutations in APO-B that affect the LDL-R-binding domain of apolipoprotein B or heterozygous gain-of-function mutations in PCSK9 which increase LDL-R degradation (4). Currently approximately 1700 mutations have been described worldwide in LDL-R (5) causing FH. A single mutation Arg3500Gln is the most common mutation in APO-B amongst northern Europeans (6) and > 160 different mutations have been detected in PCSK9 (7). Given the advances in NGS, (as reviewed elsewhere (8)), there will be an increase in the detection of genetic variants of unknown clinical relevance. It may be possible to clarify whether these variants are pathological using affected family co-segregation studies, but such studies require large numbers of relatives of the affected individual. Other methods include using functional ex vivo studies to determine the effects of detected gene variants on LDL protein expression levels (9).

The detection of a causative genetic mutation in FH will depend on whether the patient is deemed to have definite or possible FH (10), and will be increased in those with higher LDL-C and lower triglycerides pre-treatment (11). In definite FH the yield for genetic testing for identification of a pathogenic variant approaches 70% and in possible FH this decreases to

20% (12,13,14). Importantly, how the type of gene mutation affects the response to statin is often uncertain, with considerable overlap between LDL-R and APO-B mutations. In contrast, null LDL-R mutations produce higher LDL-C concentrations and reduced responsiveness to statin treatment (15). Different LDL-R mutations tend to be associated with higher pre-treatment LDL-C levels and differing response to statin treatment (16). In patients with PCSK9 mutations these tend to have a poor response to statins (17). Using NGS technology, a recent study has shown that a proportion of mutations in known familial hypercholesterolaemia genes were missed by older mutation detection assays, emphasising that improvements in technology should help increase mutation detection rates in FH (8).

A recent study involving patient samples from six different countries has suggested that polymorphisms in particular genes may explain why mutation negative patients have LDL-C levels similar to mutation positive patients (18). The variation in those polymorphisms sequenced consistently distinguished FH mutation negative from healthy individuals. The authors concluded that hypercholesterolaemia in 88% of mutation-negative patients was likely to have a polygenic basis (18). Interestingly in this study mutation positive HeFH patients with LDLR and PCSK9 mutations were also noted to have a high 6SNP LDL-C gene score which may help explain the variability in penetrance of certain FH mutations in the relatives of FH probands. Although these findings need to be replicated on a larger scale and cost benefit analysis will need to be undertaken, use of this score may be valuable in confirming cases of polygenic hypercholesterolaemia in patients with very high LDL-C who will not benefit from cascade screening.

### **Diagnostic criteria for FH in patients and populations**

There are a number of validated criteria for diagnosing FH which are briefly summarised in table 1 (for more specific information see relevant references in Table 1) and the exact total cholesterol or LDL-C levels vary between each criteria. The best characterised are the Simon Broome Register Diagnostic Criteria (19) for FH, the Dutch Lipid Clinic Network Diagnostic Criteria (DLCNC) for FH (20), the US Make Early Diagnosis Prevent Early Death (MEDPED) Program Diagnostic Criteria for FH (21) and the Japanese criteria (22).

Studies have explored alteration in population based total cholesterol cut offs to increase FH detection rates. One such study suggested that 88% of the general population in the US, over the age of 40 years with total cholesterol > 9.3mmol/L and LDL > 6.8mmol/L and triglycerides <2.3mmol/L were expected to have an FH-causing mutations (21). This hypothesis has recently been tested in a UK-based population of 4896 public service workers, mean age 44 (+/- 6) years, of whom 25 (0.5%) were found to have a baseline total cholesterol >9.3mmol/L (23). This group were then subjected to next generation sequencing and the detection rate increased to 39% by excluding 8 participants with triglycerides over 2.3mmol/L and reached 75% in those with total cholesterol >10.4mmol/L. The authors conclude by extrapolation that the detection rate of 25% would be achieved with a diagnostic cut off of 8.6mmol/L, which would be more clinically useful for FH in the general population.

## **Screening for FH**

FH fulfils the WHO criteria for screening programmes. Cascade testing from index patients with both clinically defined definite and possible FH is highly cost effective when using a combination of DNA testing for the family mutation and LDL cholesterol when it cannot (24). Over time with the improvements in NGS have reduced the cost of genetic screening which combined with off patent medication has resulted in significant cost reductions of up to 50% for potential screening programmes (25). Universal population screening rather than targeted screening has been shown in the UK population to be the least cost effective, however population screening of a sub-group of 16 year olds was potentially as cost effective, but only if at least 55% of those attended (24). A recent systematic review concluded that whether FH screening is cost effective will depend on the modelling methods used, validity of the screening tests for the relevant population, the price and the efficacy of lipid lowering therapy (26).

Current paediatric dyslipidaemia guidelines have recommended checking LDL-C concentration at aged 8 to 10 years and even testing children as young as aged 2 years, in those with a relevant family history of FH (27,28,29). Observational studies in children as young as 8 years, have shown increased carotid intima-media thickness in HeFH compared with normal controls (30).

Barriers to effective cascade testing for identification of FH have been noted in a recent study on follow up post-cascade screening in the Netherlands (31). This has shown that less than 30% of patients were seen by a paediatric lipid specialist within 18 months of diagnosis. This clearly has implications not only for advocating early adherence to optimal lifestyle measures for cardiovascular risk reduction but also for starting treatment to decrease LDL-C concentrations. The authors emphasised the need for a coordinated approach such that positive screening results in lipid clinic referral within 6 months to ensure such measures are put in place (31).

## **Early recognition of heterozygous familial hypercholesterolaemia management and risk stratification**

Current European society guidelines recommends that all patients with FH and their families undergo intensive education targeting lifestyle management (2). A consensus has yet to be reached on optimum diet for FH and a recent meta-analysis has shown that the number of studies were limited and of short duration (32). The use of plant sterols in FH reduced mean LDL cholesterol was by 0.6mmol/L and the authors concluded that there is insufficient evidence to support effectiveness of cholesterol lowering diet (32).

For adults, cholesterol lowering medications should be initiated immediately at diagnosis. For children, treatment should be strongly considered starting at age 8-10 years in childhood, along with lifestyle management (2). Current non-FH lipid lowering therapy guidelines have moved away from LDL targets and moved toward assessing risk and fixed dose statin treatment based on statin potency (33,34). In a review of RCTs in asymptomatic CVD

evidence of titration to a specific LDL target has not been found as these trials mainly used statins at a fixed dose strategy (34). Guidance recommends the following LDL targets: <3.5mmol/L in children, < 2.5mmol/L in adults and <1.8mmol/L in adults with CVD or diabetes (2). Statins are first line for both adults and children and at present there are no safety data on the use of statins before age 8-10 years. Currently there are no randomised controlled trials in HeFH to support these targets however they are based on the evidence obtained about the efficacy of statin treatment to lower LDL-C concentration and decrease cardiovascular events in large randomised placebo-controlled trials, in non-FH patients.

A recent meta-analysis of statin treatment in paediatric HeFH has shown that statins effectively lower LDL-C concentrations to levels comparable with adult preventive trials, however this study has emphasised that the majority of these trials were of short duration, involved surrogate end points, and did not have long term safety data (35). RCT evidence that early treatment in childhood with statins is beneficial is currently not available in terms of reductions in primary cardiovascular outcomes such as death or myocardial infarction and is based on short term RCTs and extrapolation from non FH RCT evidence where primary cardiovascular outcomes are available.

LDL-C burden has also been proposed as concept for supporting early statin introduction in children (2). This concept has been extrapolated from an observational study studying age related LDL-C concentrations in a Nordic based population with HeFH (36). However the cumulative LDL-C threshold of 150mmol/L for development of CVD that was suggested in recent guidelines has not been validated (2). Furthermore the threshold used was not explored in the main observational study referenced, so ultimately applying this to individual patient management must be queried. The challenge for clinicians will be balancing clinical benefits of treating children from the age of 10 years with lifelong statin therapy, risk of non-compliance, low event rates and the risk of potential adverse effects such as incident diabetes, myalgia or interference with central nervous system lipid metabolism.

Ezetimibe has been shown to have additional effects in lowering LDL-C concentration when combined with a statin in patients with FH., However a randomised control trial studying the combination of ezetimibe with a statin failed to detect a difference in carotid intima media thickness, compared with statin alone (37). At present there is limited randomised controlled trial (RCT) evidence in HeFH, to guide use of ezetimibe and guidelines have recommended its use as either in combination with a statin or in those patients with statin intolerance. A meta-analysis studying the additional LDL-C reduction attributed to ezetimibe showed a decrease of 18% in LDL-C concentration compared with 16% reduction in non-FH RCTs.(38). Recent clinical trials have shown some promise in terms of providing new treatment for those who fail to reach optimum targets despite statin or ezetimibe therapy. These trials have been recently reviewed elsewhere (39).

Currently diagnosis and management of HeFH is heavily reliant on LDL cholesterol levels, however most clinical laboratories do not measure LDL-C directly, and the variation maybe as much as 25% between direct and indirect measurement of LDL-C (40). Use of apoB and non-HDL cholesterol has been shown in meta-analysis to be superior in terms of predicting CVD risk and also the statin response and CVD risk (41). However use of these markers in

HeFH not yet been fully explored. A recent Spanish based study found that in a study of nearly 2000 HeFH patients Lp(a) levels >50mg/dl was an independent predictor of CVD risk in men and women (42), however again these findings will be evaluated in terms of clinical outcomes in planned subsequent studies. Elevated PCSK9 as a consequence of a gain of function mutation is a known genetic cause of HeFH, however elevated plasma levels regardless of mutation type have been shown to influence LDL cholesterol (43) and therefore if the findings of this study are replicated in a larger RCT then measuring PCSK9 levels may become part of work up as well as a target for treatment in FH. Recent development in small molecule inhibitors of the LDL-R pathway are of interest and may in the future add to therapeutic regimens for HeFH.

Given that most of the cases detected will be possible FH, most genetic tests will produce negative results for FH, with the identification of some genetic variants of uncertain pathological significance. The therapeutic management of these variants and mutation negative patients remains unclear to date. Although current recommendations indicate that these cases should be labelled as polygenic causes of hypercholesterolaemia, this has implications for screening and the FH detection rate. That said a low detection rate does not alter the treatment of affected cases (44). Further studies on the clinical management, and long term studies of the natural history of possible cardiovascular disease with these gene variants, and mutation negative patients, are urgently required.

### **Conclusion**

FH is markedly under diagnosed and under treated worldwide. The increased availability of NGS screening will mean that the clinician will be faced with previously uncharacterised genetic variants and the optimum method of assessing or managing these remains to be clarified.

Current guidance based on limited evidence, suggests commencement with statin medication from the age of 10 years with lifestyle advice advocated beforehand. Optimum methods for risk stratification for patients with HeFH need to be better refined.

For adults, registry data suggests that the mean age of diagnosis is often very late (e.g. in the fifth decade) giving rise to decades of untreated LDL-inducing atheroma burden and even when a diagnosis is established, treatment of LDL-C concentration is often inadequate.

### **Key points:**

- Modern registry data suggests an association between late diagnosis and premature cardiovascular death in HeFH patients.
- The use of next generation sequencing has increased genetic mutation detection however the significance and management of genetic variants of unknown significance remains to be clearly defined.
- Targeted screening programmes for HeFH have yet to be implemented in many countries worldwide.
- Undertreatment based on LDL-C levels in HeFH is common however validated methods of risk stratification beyond LDL-C and family history remain to be fully explored.
- The optimum age for commencement of lipid lowering treatment in children is not known and the proven benefits of treatment-induced decreases in LDL-C concentration in childhood extending into adulthood remain to be confirmed

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## Conflicts of interest

None

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Criteria	Dutch	Simon Broome	MEDPED	Japan
Family History premature CVD	+	+		+
Family History tendon xanthoma	+	+		
Patient premature CVD	+			
Patient premature PVD	+			
Tendon Xanthoma	+	+		+
Arcus cornealis	+			
Cholesterol	+	+	+	+
Family History Cholesterol		+	+	+
DNA mutation	+	+		

**Table 1. Summary diagnostic criteria for FH.** (Dutch)Dutch Lipid Clinic Network (21). (UK) Simon Broome Familial Hypercholesterolaemia Register (20). (MEDPED, USA) Make Early Diagnosis to Prevent Early Deaths (22). (Japan) Japanese diagnostic criteria for HeFH (23).