

## **Familial Hypercholesterolaemia: What's new?**

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### **Abstract:**

Autosomal Dominant Familial Hypercholesterolaemia (FH) is the commonest inherited disorder of lipoprotein metabolism. Untreated monogenic FH caused by mutations in the *LDLR*, *APOB* or *PCSK9* genes result in early onset cardiovascular death (below the age of 60 years). In the UK the prevalence of heterozygous FH is 1 in 270 and homozygous FH is 160,000 approximately.

The introduction of statins nearly three decades ago has altered the natural history of FH, with a significant reduction of cardiovascular related morbidity and mortality. There is increasing evidence that early childhood interventions such as lifestyle choices, healthy eating and commencing statins by the age of 10 years would potentially prevent early onset cardiovascular disease and mortality in monogenic FH. The medium term safety of statins in children has been demonstrated. The UK paediatric FH register data has shown that children with FH are less obese than the normal population and the register aims to monitor the longer-term safety of statins in children with FH. Child-parent screening would potentially benefit the child and enables identifying a parent with FH, before the onset of a life threatening cardiovascular event. In addition, genetic cascade testing of relatives of an affected individual has been shown to be highly cost effective.

We review the current literature with brief updates on genetics, the UK paediatric FH register data, published recommendations for the management of homozygous and heterozygous FH, lipid lowering therapies in children and screening for FH in childhood.

**Key words: Familial Hypercholesterolaemia, children, statins, cascade screening, child-parent screening, safety of statins, management of FH.**

### **Key learning points:**

- People with familial hypercholesterolemia (FH) are at greater risk of heart disease
- 1 in 250 people in the UK are believed to have FH
- Over 260,000 people in the UK may have FH, with fewer than 10% diagnosed
- 56,000 children in the UK may have FH but only 600 of these are known

- Statins have altered the natural history of FH and has prevented premature heart disease in adults with FH
- NICE FH guidelines (CG71, 2017) recommend children with a confirmed diagnosis of FH are managed in a child-friendly health care setting.
- NICE FH guidelines (CG71, 2017) recommends considering statins by the age of 10 years.
- Medium term data have demonstrated statins in children to be safe.
- Children with FH have normal growth and sexual maturation when compared to the general population.
- Cascade testing of relatives of index cases with FH has been shown to be highly cost effective.

### **Introduction:**

Familial hypercholesterolemia (FH) FH, OMIM #143890 is an autosomal dominant inherited metabolic disorder of lipoprotein metabolism characterized by elevated levels of LDL-cholesterol (LDL-C) and increased risk of premature cardiovascular disease. Monogenic heterozygous FH (HeFH) affects between 1:250 to 1:500 subjects in the general population, with a penetrance of >90%. Based on the above, the expected prevalence is approximately 34 million worldwide but the vast majority remains undiagnosed and untreated. Estimates are that less than 1% of FH have been identified to date, and this poses a significant public health concern worldwide. HeFH is approximately five times commoner than disorders such as cystic fibrosis, duchenne muscular dystrophy, sickle cell disease etc (Figure 1).

Clinical diagnosis of FH is made using validated scoring tools including the Simon Broome Criteria, Dutch lipid network criteria, Medped Criteria (Table 1), although only the Simon Broome has child-specific criteria. Where there are founder effects, the prevalence of FH mutations amongst Finns, Icelanders, Christian Lebanese, Tunisians, Gujarati South African Indians, South African Afrikaners and French Canadians can be up to 1 in 200 and as high as high as 1 in 67 for Ashkenazi Jews. Undiagnosed, the average age at first premature cardiovascular event occurs by the age of 55 years in males and 60 years in females. Half of all untreated HeFH men and 15 % of women will die of CHD-induced myocardial infarction (MI) before these ages.

Homozygous FH (HoFH) is rare, with an estimated global prevalence of 1/160,000–300,000 (Figure 2). Undiagnosed and untreated patients with HoFH can die as teenagers secondary to a MI (myocardial infarction), with the earliest report of death in HoFH in a 4 year old child dying from a coronary heart disease (CHD) related myocardial infarction.

The introduction of statins, hydroxymethylglutaryl coenzyme A (HMG CoA) inhibitors, in the management of HeFH has altered the natural history of this condition. Prior to the discovery of these agents the mortality rates resulting from CHD in FH patients

was nearly 100-fold greater in young adults aged 20– 39, and approximately 4-fold greater in patients aged 40– 59 years compared to the normal population. Coronary artery intima media thickness (CIMT) studies in children have shown that atherosclerosis commences in childhood with reduction in intima media thickness when statins is commenced in childhood.

### **FH genetics:**

The commonest genetic cause of FH is mutations in the *LDLR* gene, which cause in absent or dysfunctional receptors on the surface of hepatocytes, resulting in defective clearance of apo-B containing lipoproteins such as LDL (Figure 3). More than 1700 mutations in the *LDLR* gene on chromosome 19 have been identified world-wide, of which 79% are probably expressed as a hypercholesterolaemic phenotype.

All of the monogenic defects result in reduced efficiency of LDL uptake and clearance in hepatocytes and increased circulating total cholesterol and LDL-C concentration.

Defects in the genes encoding apolipoprotein B (*APOB*) and proprotein convertase subtilisin/ kexin type 9 (*PCSK9*) account for approximately 5% and 1% of FH cases, respectively. Several reports indicate that a specific mutation in the *APOE* gene may also cause the FH phenotype (refs). The LDL receptor adaptor protein (*LDLRAP1*) gene is a very rare autosomal recessive form of FH. While possibly up to 5% of cases of phenotypic FH may arise from mutations in unidentified genes, the majority of cases where no FH-causing mutation can be found are now known to have a polygenic cause as distinct from a dominantly inherited disorder.

### **Homozygous familial hypercholesterolaemia (HoFH)**

HoFH is very rare and a life-threatening disease. Total cholesterol levels are typically 13 mmol/L (500 mg/dL). Tendon xanthomas and corneal arcus in childhood is characteristic of HoFH and should alert the clinician to consider this diagnosis without delay (Table 2). Marked premature and progressive atherosclerotic heart disease is typical in HoFH with significant morbidity and mortality (Table 3). Treatment for HoFH include statins ± ezetimibe. Mutations in both alleles of the gene encoding the LDL receptor (*LDLR*) or mutations in *APOB*, *PCSK9*, and *LDLRAP1* have been described in HoFH. The currently available licensed cholesterol lowering agents act primarily by up-regulating LDLR activity. Their effectiveness in HoFH is determined mostly by the residual LDLR activity depending on the specific effect of the mutation present.

Lipoprotein (Lp) apheresis physically removes LDL particles and is an established, safe and effective treatment for HoFH in the UK but access is limited. There is good evidence of the safety of Lp apheresis in children.

Newer therapies include Lomitapide and two PCSK9 inhibiting drugs, evolucumab and

alirocumab, have recently been approved by the European Medicines Agency (EMA). Lomitapide is a small molecule inhibitor of microsomal triglyceride transfer protein. It reduces the hepatic assembly of very low density lipoprotein (VLDL) and intestinal chylomicrons and consequently reduces LDL-C production, an action independent of LDLR activity. The high cost, gastrointestinal side effects and dietary restrictions required whilst on this therapy, has limited its use in the UK. Trial data on lomitapide are only available on adults over 18 years old.

Evolocumab and alirocumab are monoclonal antibody inhibitors of PCSK9 protein, which reduce LDLR catabolism and their effectiveness is determined by LDLR activity. Thus when the FH-causing mutation means there is no residual LDL-R activity to “rescue” by PCSK9 inhibition (ie receptor-null alleles), these agent have been shown to be ineffective. Currently only evolocumab is licensed for children over 12 years old. Mipomersen , a second generation antisense oligonucleotide, which inhibits hepatic APOB synthesis has been shown to be an effective agent for lowering plasma LDL-c levels in HoFH, but is not licensed by the EMA due to significant side effects. Finally, liver transplantation is also a therapeutic option for HoFH, but is viewed as a treatment of last resort because of the life-long immunosuppression needed.

### **Heterozygous FH:**

Unlike HoFH, children with heterozygous FH seldom present with identifiable clinical features. However, there is progressive atherosclerosis through childhood, demonstrated by CiMT studies (Wiegman et al 2014). Children with HeFH have roughly twice the normal LDL-C levels from birth and thus their LDL-C burden (average level x years of age) increases at twice the rate of their non-FH sibling.

As a consequence of this they develop atherosclerosis that is detectable as significant carotid intima media thickness (CiMT) as compared with their siblings by the age of 10 years. In a randomised controlled trial of the use of pravastatin, further change in CiMT was prevented. Based on this data the NICE guidance is that the use of statins should be considered in children with HeFH by the age of 10 years using clinical judgement, based on the child’s LDL-C level, the age of onset of CHD in the parent or relatives, and the presence of other CHD risk factors.

### **The UK FH paediatric register data:**

The UK National Paediatric FH Register was established in 2012. The register collects baseline and long-term follow-up data on all children with FH in UK, to document how well current NICE guidance on the diagnosis and management of children with HeFH is being adhered to, and to determine the safety and efficacy of statins commenced below the age of 16 years. The data confirms that use of statins in early childhood and

adolescence is primarily influenced by the age of the patient, the diagnostic level of TC and LDL-C, which are the major determinants of future risk of atherosclerosis, and of having a history of CHD in a parent or relative. In the published manuscript in 2017, 64% of the 147 patients had a confirmed diagnosis based on genetic testing. However, knowing the family mutation did not appear to influence commencing lipid-lowering drugs.

### **Why treat early?:**

Vascular risk is very high and associated with cholesterol burden, with lowering of LDL-C the mainstay of cardiovascular prevention in FH (Figure 4). There is increasing evidence of low dose statin use from the age of 10 years to reduce the life-long cholesterol burden and hence delaying/preventing early onset coronary artery disease. The burden of life-long high cholesterol and early treatment applies equally to males and females with confirmed FH. Most recent guidelines indicate that it is desirable to reduce LDL-C to 50% of baseline levels or <2.5mmol/l (<100 mg/dL) in adults with FH.

214 Dutch children with FH, aged 8-18 years were followed up for over ten years. Comparisons were made on Carotid IMT (CIMT) in patients with FH and unaffected siblings (adjusted for sex, age, blood pressure, and body mass index [BMI]); and the association between carotid IMT and age at statin initiation (adjusted for sex, BMI, baseline carotid IMT, and duration of follow-up) was also evaluated. This cohort had previously participated in a randomised double blind placebo controlled study of pravastatin. At completion of the two-year study in 1999, all participants were commenced on pravastatin and followed up for ten years. Ten-year follow-up was achieved in 91% of FH patients with FH and 87% of siblings, all aged 18 to 30 years. After 10 years of statin therapy, whilst children who started on statins in early childhood had a significant reduction in CIMT from baseline, these children continued to have significantly high CIMT compared to their unaffected siblings. The authors conclude that more robust lipid-lowering therapy or earlier initiation of statins maybe required to completely restore arterial wall morphology and prevent early onset coronary heart disease. (Figure 5).

Despite these strong lines of evidence, currently there is no clear target level for LDL-C reduction children. Based on expert opinion, the European consensus recommendation in 2015 proposes a 50% reduction in LDL-C from baseline should be achieved if possible. Statins licensed for the use in children are detailed in Table 4.

### **Safety of Statins:**

A recent Cochrane review on the safety of statins included 26 potentially eligible studies, which included nine randomized placebo-controlled studies (1177 participants). The review concluded that statin use in childhood was safe in the medium term. However, longitudinal studies are necessary to ascertain the long term safety of statins started in children (Vuorio et al 2017). The magnitude of LDL cholesterol lowering varied from study to study, most likely due to different statins and doses and possibly due to different definitions about true monogenic heterozygous FH.

Carotid Intima Media Thickness (CIMT) represents the combined intima and media thickness of the arterial wall and could potentially be a useful predictor of CHD in later life. Whilst there were many studies that assessed CIMT, the numbers were small. Only the study in the Netherlands discussed above used CIMT as a primary outcome measure to assess efficacy of Pravastatin in children. The authors found that two years of pravastatin therapy induced a small but significant regression in mean change in IMT between statin-treated and placebo groups in children with FH. Further studies are required to confirm this finding. In addition, CIMT is not routinely available in all centres treating children with FH.

The Cochrane review did not identify any clinically significant side effects with statins. Abnormal liver transaminase was defined as a 3-fold increase and Creatine Kinase values over a 10 fold increase from normal ranges, and neither were found as reported side effects. Sexual maturation was not dissimilar to normal population groups. In addition, data from the UK paediatric FH register has recently confirmed that while the prevalence of being overweight was similar to the normal population, the prevalence of obesity was ~50% lower in children FH, which was a clinically relevant finding, supporting the added benefit of early diagnosis and life-style advice to maintain a healthy diet and exercise programme.

Although statin use in the general population has been associated with an increased risk of developing type 2 diabetes (T2D), this risk seems not to be high in patients with FH (ref). Also, the benefits of statin treatment in FH for preventing CHD outweighs the modest potential risk of Type 2 diabetes. However it is important to mitigate this risk with the dietary and lifestyle advice for the prevention of T2D/metabolic syndrome, as is used in the general population. A study in 2014, reported on a 10-year follow-up of 194 statin-treated children (mean age at baseline 13 years) and identified one new case of Type 2 Diabetes with a similar incidence in their 83 non-FH siblings. Based on published evidence, pravastatin is associated with the lowest risk of T2D, although long-term follow-up studies of treated FH children are needed to confirm if this is true.

A cross-sectional and prospective cohort study from the Spanish FH registry data in 2015, reported on 2558 adults with FH and 1265 unaffected relatives with a mean follow-up of 5.9 years. Demographic and additional risk factors, including age, gender,

metabolic syndrome, lipid profile, body mass index (BMI), waist circumference, HOMA-IR, dose, duration and type of statins, were analysed as predictors for the onset of type 2 diabetes. The new onset diabetes was 1.7% in FH and 0.2% in non-FH relatives ( $p=0.001$ ), with evidence of metabolic syndrome as an additional risk factor in patients with FH. The authors concluded that statins did not increase the risk of Type 2 diabetes in this study.

#### **Other Therapies licensed in children with FH: are shown in Table 4**

Ezetimibe selectively blocks the absorption of dietary cholesterol by the intestinal cells and increases cholesterol secretion into the bile at the same time, through interfering with the Niemann-Pick C1-like 1 protein (NPC1L1). This leads to reduced intrahepatic cholesterol concentrations and consequent LDLR up-regulation, hence the circulating LDL levels are effectively decreased. More recently, Lomitapide, a microsomal transfer protein inhibitor has been licensed as an adjunctive therapy for HoFH.

#### **Management of FH in children:**

The current European consensus guidelines for the management of homozygous and heterozygous FH (Tables 6 and 7). Lifestyle choices, with healthy eating and exercise underpin the management of FH. Total Fats should be less than 30% of total daily calorie intake, of which, saturated fat intake should ideally be less than 10%. Children with Heterozygous FH should be monitored at least annually: monitoring growth, diet, side effects of statins, measuring lipid profile, liver function tests, creatine kinase and lifestyle including exercise and smoking as appropriate. Other cardiovascular risk factors should be monitored and treated if indicated. The therapeutic target for LDL-C reduction in children is  $< 3.5\text{mmol/l}$  ( $<135\text{m/dl}$ ). However, there is very little data confirming that children are achieving this target with FH on statins.

Homozygous FH patients should be managed in an experienced metabolic centre and have regular cardiology review as recommended by a cardiologist with experience in managing rare heart diseases.

#### **NICE update:**

In 2017, NICE updated the 2008 CG71 guidelines on case finding, diagnosis, and pharmacological monotherapy to reflect improvements in the cost-effectiveness of cascade testing and the efficiency of DNA diagnosis technology, as well as including more evidence surrounding the use of statins. The 2017 amendments include the following: offering statins to children with FH by the age of 10 years or at the earliest opportunity thereafter; for children and young people with FH, consider a statin that is licensed for use in the appropriate age group; statin therapy for children and young

people should be initiated by a healthcare professional with expertise in treating children and young people with FH, and in a child-focused setting.

### **Reverse cascade screening:**

With increasing prevalence of FH and the resulting morbidity and mortality due to coronary heart disease in young adults with FH, often the first cardiovascular event occurring before an established diagnosis of FH, Wald et al published an interesting study. The authors conducted a pilot study of reverse cascade screening, i.e. child–parent screening for FH to identify persons at high risk for inherited premature cardiovascular disease.

Capillary blood samples for cholesterol were taken at GP surgeries from 10,095 children during routine immunisation visits between 1-2 years. Screen positive was defined as children with elevated cholesterol and these had either an FH-causing mutation or no mutation but a repeat elevated cholesterol level 3 months later (and probably had a polygenic cause of their elevated cholesterol although this was not tested directly). The parent of the identified child was considered screen positive for FH, if they had the same mutation, or if no mutation was identified in the child, the parent with the higher cholesterol of the two parents was considered screen positive. The use of a pre-specified cholesterol cutoff value of 1.53 multiples of the median (MoM, corresponding to a percentile of 99.2) identified 28 children (0.3% of 10,095 children screened) with positive screening results for familial hypercholesterolemia. A total of 17 children who had a cholesterol level of less than 1.53 MoM also had a familial hypercholesterolemia mutation. The overall mutation prevalence was 1 in 273 children (37 in 10,095; 95% CI, 1 in 198 to 1 in 388).

Further analysis with an initial cholesterol cutoff value of 1.35 MoM (95th percentile) plus a mutation, or two cholesterol values of at least 1.50 MoM (99th percentile), identified 40 children with FH (0.4% of the 10,095 children, including 32 children who had a familial hypercholesterolemia mutation and 8 who did not have the mutation). This screening method identified FH in 40 parents, previously undiagnosed.

### **Cost effectiveness:**

In 2017, Russo et al published a systematic review of the cost effectiveness of genetic screening in FH, based on seven economic evaluations that assessed the cost-effectiveness of genetic screening for FH in Europe between 2002 and 2015. The published models had a no-screening strategy as a comparator, focused on relatives of index cases with genetic or clinical diagnosis of FH (cascade screening), and which considered a lifetime overview and also adopted a health care payer viewpoint. The authors concluded that cascade testing, based on genetic testing of relatives of an



index case with confirmed clinical or genetic diagnosis of FH, was the most cost-effective in most healthcare settings.

Cascade testing for FH is only currently available in around 50% of England, with successful models adopted in Wales and Scotland. Kerr et al used a Markov model to estimate the cost effectiveness of cascade testing, using data from UK cascade services. The estimated incremental cost effectiveness ratio (ICER) was £5806 and the net marginal lifetime cost per relative tested was £2781. More than 80% of lifetime costs were diagnosis-related and were noted to be incurred in the 1st year after diagnosis. In UK services studied, 23% of 6396 index cases were mutation-positive. For each mutation-positive index case, 1.33 relatives were tested, resulting overall in a rate of 0.31 tested relatives per tested index case. If the number of relatives tested per tested index case rose to 3.2 (projected by National Institute for Health and Care Excellence in 2008) the ICER would reduce to £2280 and lifetime costs to £1092. This study clearly demonstrated the value of cascade testing of relatives for FH.

Cascade testing of relatives of those with suspected FH identified by GP electronic note searching is also highly cost effective (ref) and is a new recommendation in the 2017 NICE FH guideline. . The current Europe-wide high levels of undiagnosed FH, and associated morbidity and mortality, mean adoption of cascade services should yield substantial quality of life and survival gains.

### **Conclusion:**

Familial Hypercholesterolaemia is the commonest inherited metabolic disorder. Heterozygous FH has a prevalence of ~1 in 250 and if undiagnosed, results in significant morbidity in young adults. More than half of men with FH and about one-third of women will have a cardiovascular event before 60 years of age without lipid-lowering therapy. Statins have changed the natural history of FH and the latest studies indicate that death from coronary heart disease has highly significantly decreased in recent years, at least by 50%, however, the rate is still higher than that of the general population. Childhood cholesterol levels are good predictors of future cardiovascular risk. The use of statins in childhood has demonstrated reduction in coronary intima media thickness, a validated surrogate biomarker of atherosclerosis.

The updated NICE guidelines recommend management of all children with a confirmed diagnosis of FH in a child friendly health care setting; and to consider statins by the age of 10 years in children, in addition to lifestyle and appropriate dietary advice. Child-parent screening is a novel model for screening for FH, and a recent study confirmed the prevalence of heterozygous FH to be approximately 1 in 270. Homozygous FH has serious consequences in early childhood and if untreated results in death in the first to second decades of life.

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Figure 1: Prevalance of FH

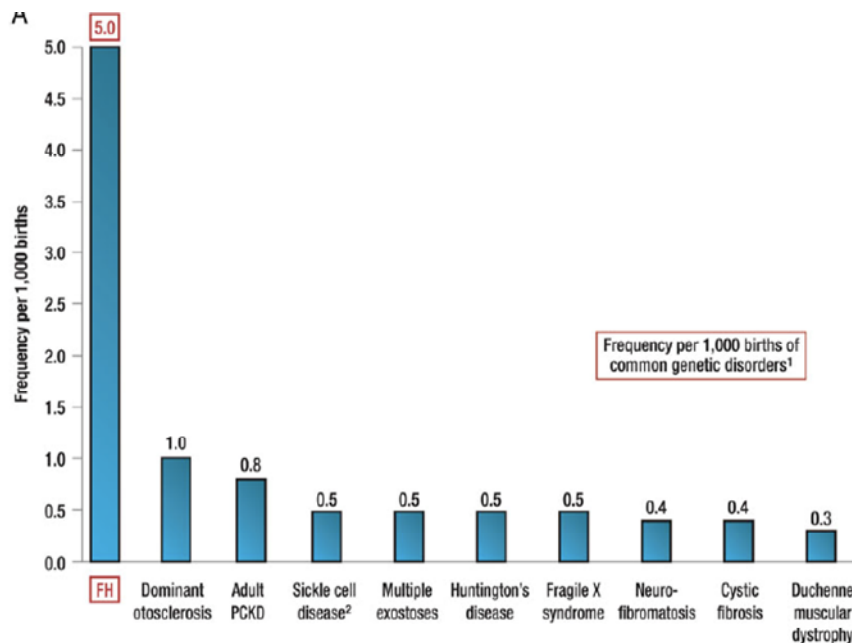


Figure 1: Familial hypercholesterolaemia is more common than other genetic diseases. From Wiegman et al 2015.

Figure 2: Prevalence of Homozygous FH

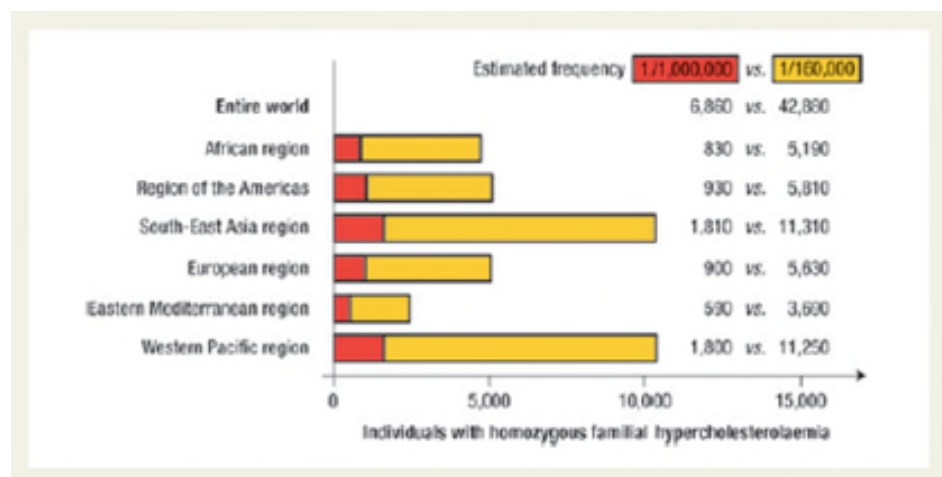


Figure 2: Estimated number of individuals worldwide with homozygous familial hypercholesterolaemia by the World Health Organization region. Estimates are based on historical prevalence data (1 in a million with homozygous familial hypercholesterolaemia), as well as directly detected estimates of familial

hypercholesterolaemia in the Danish general population (1/160 000). From Nordestgaard et al 2013.

**Figure 3: The LDLR Pathway**

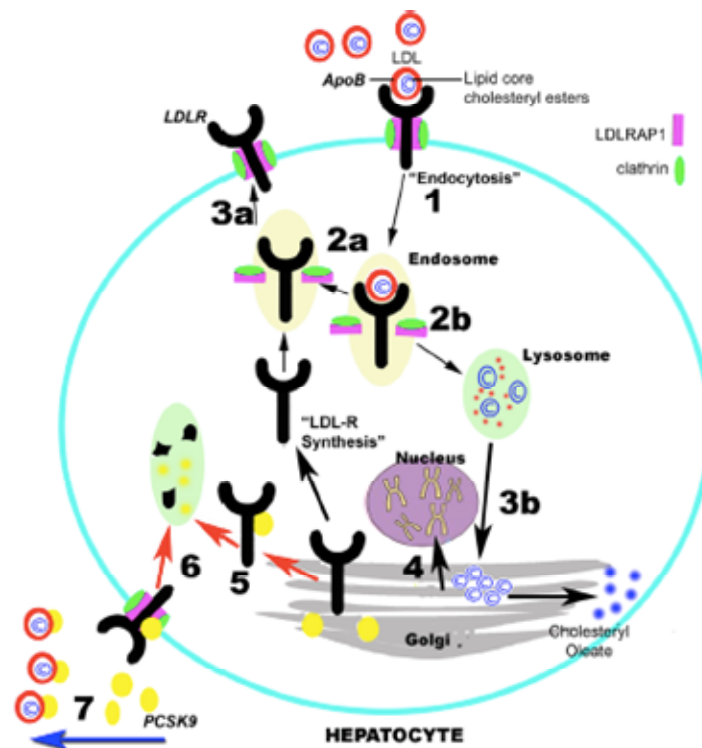


Figure 3: The LDLR pathway. The LDL receptor (LDLR), part of a LDLR/clathrin/LDLRAP1 (ARH) vesicle, binds to the ApoB in LDL particles, internalising them (1). The receptor-ligand complex dissociate and LDLR is either recycled (2a and 3a) or degraded (2b and 3b). Residual cholesterol levels regulate the transcription of LDLR (4). PCSK9 is endogenously secreted from the Golgi apparatus where it binds to LDLR (5). Alternatively, PCSK9 can exogenously bind to LDLR (6). Once internalised to the hepatocyte, PCSK9 directs bound LDLR to the lysosome for degradation. PCSK9 can also bind to LDL via ApoB in free circulation (7).

**Figure 4: LDL-C burden in patients with FH**

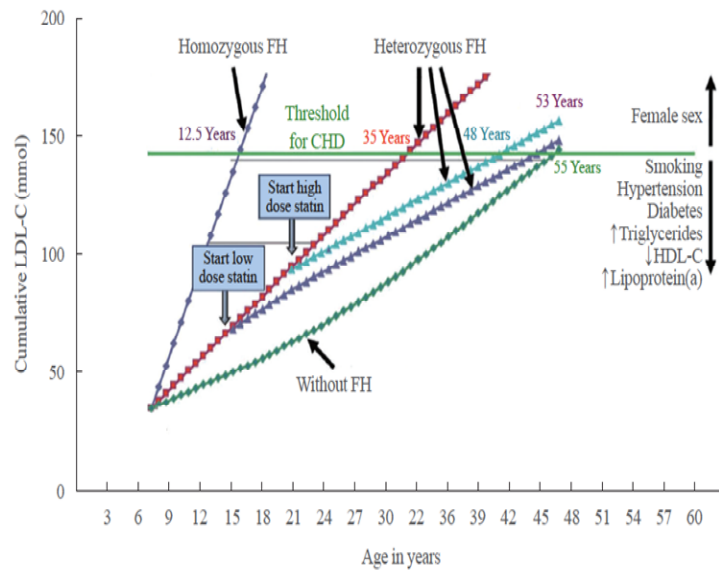


Figure 4: Low density lipoprotein cholesterol (LDL-C) burden in individuals with or without familial hypercholesterolemia (FH) as function of the onset of statin therapy. From Lee S-H 2017. CHD, coronary heart disease; HDL-C, high density lipoprotein cholesterol.

**Table 1: Characteristics of four clinical diagnostic criteria for FH**

|                      | Simon Broome   | Dutch   | MEDPED   | Japanese  |
|----------------------|--|---|--|---|
| Process of diagnosis | Mutation or cholesterol plus xanthoma or family history  | Sum of score for each item  | Cholesterol level alone                            | Any two of cholesterol, xanthoma, or family history                       |
| Items                | Total cholesterol >290 or LDL-C >190 mg/dL; xanthoma; mutation; family history of MI or hypercholesterolemia | Family history of CAD or hypercholesterolemia; history of CAD, cerebral or peripheral vascular disease; xanthoma or corneal arcus; LDL-C ≥150–330 mg/dL | Total cholesterol ≥290–360 or LDL-C ≥220–260 mg/dL | LDL-C ≥180 mg/dL; xanthoma; family history of hypercholesterolemia or CAD |

MEDPED, Make Early Diagnosis to Prevent Early Deaths; LDL-C, low density lipoprotein cholesterol; MI, myocardial infarction; CAD, coronary artery disease.

Table 1: from Lee et al 2017. Cholesterol mmol/l = mg/dl ÷ 38.6

**Table 2: Criteria for the diagnosis of homozygous familial hypercholesterolaemia**

Presence of 2 disease causing alleles affecting introns and exons of the LDLR, APOB, PCSK9 and LDLRAP1 gene loci

Or

LDL-C >11.0 mmol/L in children with tendon or cutaneous xanthomata before age 10 or 13.0 mmol/L in adults with clinically obvious tendon or cutaneous xanthomata.

But because of the now recognized genetic and clinical heterogeneity of HoFH, lower LDL-C does not exclude HoFH. Genetic diagnosis, supplementary to clinical assessment including cholesterol, is preferred.

Or

Qualifying cholesterol level and both parents with genetically confirmed HeFH  
LDLR, low density lipoprotein receptor; APOB, apolipoprotein B; PCSK9, proprotein convertase subtilisin/kexin type 9; LDLRAP1, low density lipoprotein receptor adaptor protein 1 gene loci.

Table 2: From France et al 2016

**Table 3: Cardiovascular complications of HoFH**

- HoFH is characterized by accelerated atherosclerosis, typically affecting the aortic root, although other vascular territories may also be affected.
- The first major cardiovascular events often occur during adolescence, possibly younger when patients are LDLR-negative and/or untreated.
- In young children, early symptoms and signs are often linked to aortic stenosis and regurgitation, due to massive accumulation of cholesterol at the valvular levels.
- As aortic and supra-valvular aortic valve diseases may progress even when cholesterol levels are reduced, regular screening for subclinical aortic, carotid, and coronary heart disease is indicated.

Table 3: From Cuchel et al 2014

**Table 4: Licensed Lipid lowering therapies for children with FH**

| Drug class  | Drug Function  | Drug names Licensed in Childhood*  | Benefits  | Possible side effects*  |
|---|--|--|---|---|
| Statins   | Inhibits the enzyme the body needs to make cholesterol   | Lovastatin*<br>Rosuvastatin*<br>Fluvastatin*<br>Atorvastatin*<br>Pravastatin* (preferred choice under 10 years of age)<br>Simvastatin* | Decrease LDL and triglycerides; slightly increase HDL   | Constipation, nausea, diarrhea, stomach pain, cramps, muscle soreness and possible damage, memory loss, forgetfulness, confusion, pain and weakness, increased risk of diabetes; possible interaction with grapefruit juice |
| Bile acid binding resins                                | Prevents bile from being reabsorbed into the circulatory system                                | Colestipol*<br>Cholestyramine*<br>Colesevelam*   | Decrease LDL  | Constipation, bloating, nausea, gas; may increase triglycerides   |
| Cholesterol absorption inhibitors                       | Blocks the amount of cholesterol that is absorbed by the small intestine                       | Ezetimibe*   | Decrease LDL; slightly decrease triglycerides; slightly increase HDL<br>Often used as an adjunctive therapy with Statins      | Stomach pain, fatigue, muscle soreness  |
| Combination cholesterol absorption inhibitor and statin | Inhibits production of cholesterol and blocks absorption of cholesterol by the small intestine | Ezetimibe and simvastatin*   | Decreases LDL and triglycerides, increases HDL  | Stomach pain, fatigue, gas, constipation, abdominal pain, cramps, muscle soreness, pain and weakness; possible interaction with grapefruit juice  |
| Fibrates  | Reduces production of triglycerides  | Bezafibrate<br>Fenofibrate*<br>Gemfibrozil   | Decrease triglycerides; increase HDL  | Nausea, stomach pain, gallstones  |
| Niacin  | Lowers the liver's ability to produce LDL  | Niaspan  | Decreases LDL and triglycerides; increases HDL  | Seldom used due to significant side effects. Facial and neck flushing, nausea, vomiting, diarrhea, gout, high blood sugar, peptic ulcers  |
| Combination statin and niacin                           | Inhibits production of cholesterol   | Niacin and lovastatin  | Decreases LDL and triglycerides; increases HDL  | Seldom used due to significant side effects. Facial and neck flushing, dizziness, heart palpitations, shortness of breath, sweating, chills; possible interaction with grapefruit juice                                     |
| Omega-3 fatty acids                                     | Inhibits production of triglycerides in the liver  | Lovaza (prescription omega-3 fatty acid supplement)  | Decreases triglycerides   | Belching, fishy taste, increased infection risk   |
| Lomitapide  | Microsomal Transfer Protein Inhibition   | Lomitapide*  | Decreases cholesterol<br><br>Used as an adjunctive therapy and for patients who are unable to tolerate lipoprotein apheresis. | Abnormal liver function tests, gastrointestinal.  |

Table 4: From Ramaswami U Chapter 31 Saudubray. Lipid lowering drugs Reference to SPC recommended prior to licensed indication of lipid lowering therapies in children and for complete list of side effects.



**Table 5: New Therapies FH**

|                  | Lomitapide   | Mipomersen   | PCSK9 inhibitors (evolocumab,   |
|------------------|--|--|---|
| Action mechanism | Inhibition of microsomal TG transfer protein; reduction of VLDL synthesis      | Antisense oligonucleotide that binds to mRNA and blocks apoB translation   | Binds to plasma PCSK9, reduces degradation of LDLR  |
| Efficacy         | Lowers LDL-C & apoB by 40%–50% on top of ongoing therapy                       | Lowers LDL-C & apoB by 20%–30% and lp(a) by 20%–25% on top of ongoing therapy  | Lowers LDL-C by 50%–60%, apoB by 50%, and lp(a) by 20%–30%; 51% reduction in cardiovascular events in preli |
| Safety           | GI disturbance (>90%), liver enzyme elevation (14%–34%), and hepatic steatosis | Injection-site reaction (>75%), influenza-like symptoms (30%–65%), liver enzyme elevation (12%–15%), and hepatic steatosis | Largely well tolerated; slight injection-site reactions, neurocognitive and memory symptoms                 |

Table 5: Licensed therapies in FH: PCSK9, proprotein convertase subtilisin/kexin type 9; TG, triglyceride; VLDL, very low density lipoprotein; apoB, apolipoprotein B; LDLR, low density lipoprotein receptor; LDL-C, low density lipoprotein cholesterol; lp(a), lipoprotein(a); GI, gastrointestinal; hoFH, homozygous familial hypercholesterolemia; FH, familial hypercholesterolemia. From Lee Sh et al. 2017

**Table 6: Management of HoFH**

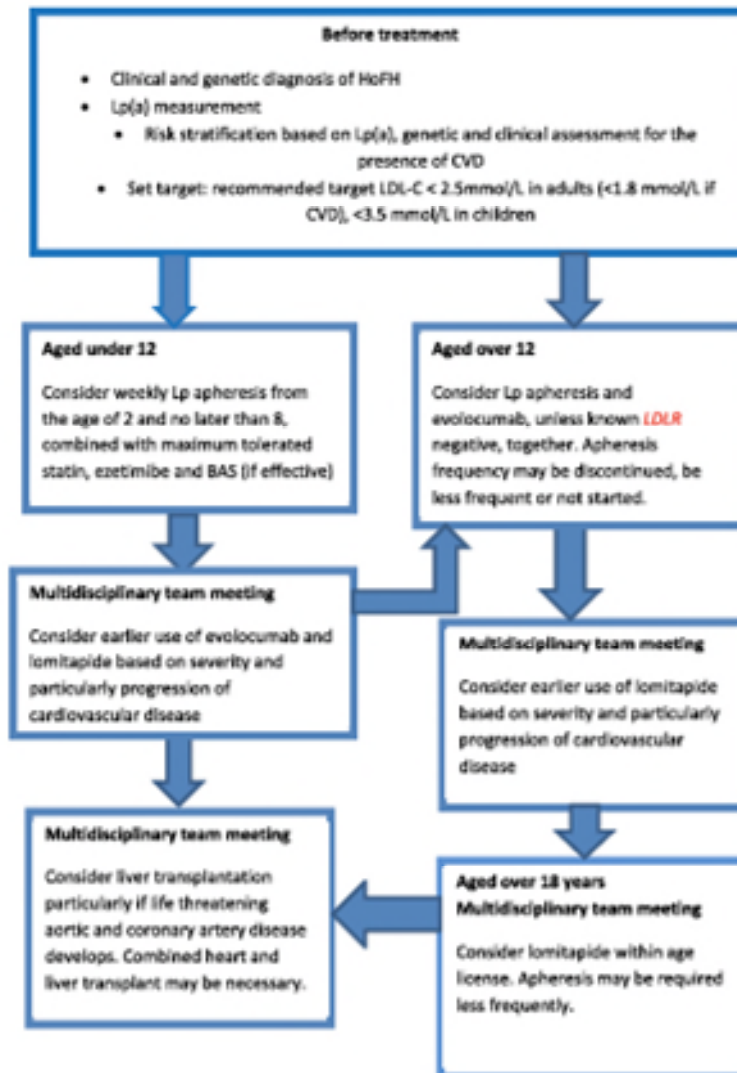


Table 6: From France M et al 2016.

**Table 7: Management of Heterozygous FH**

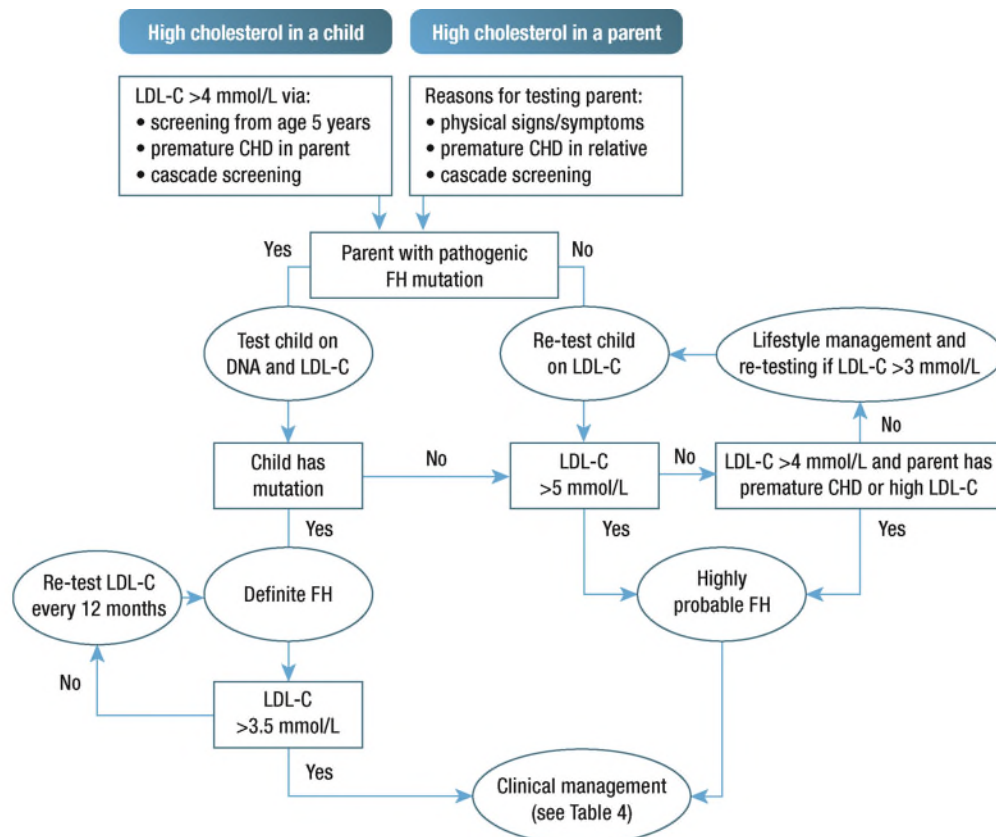
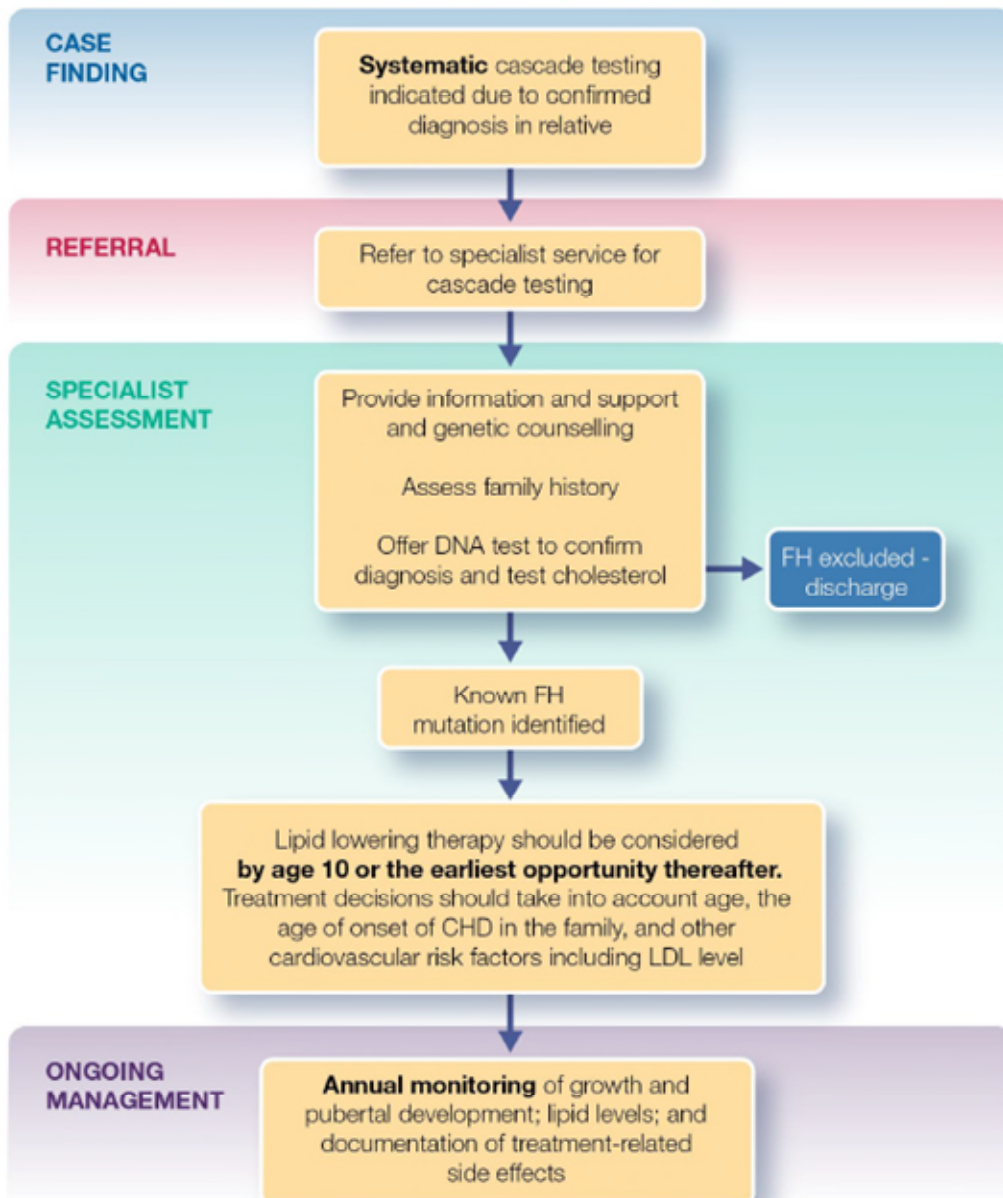


Table 7: From Wiegman et al 2015. Potential strategy for diagnosis of familial hypercholesterolaemia in children and adolescents. CHD, coronary heart disease; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol. Definitions: Premature coronary heart disease is defined as a coronary event before age 55 years in men and age 60 years in women. Definite familial hypercholesterolaemia is defined as genetic confirmation of at least one familial hypercholesterolaemia-causing genetic mutation. Close relative is defined as 1st or 2nd degree. Highly probable familial hypercholesterolaemia is based on clinical presentation (i.e. phenotypic familial hypercholesterolaemia), either an elevated low-density lipoprotein cholesterol level  $\geq 5$  mmol/L in a child after dietary intervention or an low-density lipoprotein cholesterol level  $\geq 4$  mmol/L in a child with a family history of premature coronary heart disease in close relatives and/or baseline high cholesterol in one parent. Cascade screening from an index case with a familial hypercholesterolaemia-causing mutation may identify a child with elevated low-density lipoprotein cholesterol levels  $\geq 3.5$  mmol/L.

**How about this figure from our PHE implementation guide?**

## FH Child Patient Pathway



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