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Review article

Current management of children and young people with heterozygous familial hypercholesterolaemia - HEART UK statement of care

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HIGHLIGHTS

- Children with heterozygous familial hypercholesterolaemia (FH) should be managed by paediatric health professionals with expertise in FH.
- Statin to be considered by the age of 10 years and use age appropriate target LDL-C level in children with FH.
- Dietary and life style advice should begin in early childhood.
- From the age of 14 years, consider joint review with adult lipidologist in transition clinic with transfer to adult lipid clinic at 16 to 18 years.

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ABSTRACT

This consensus statement on the management of children and young people with heterozygous familial hypercholesterolaemia (FH) addresses management of paediatric FH in the UK, identified by cascade testing when a parent is diagnosed with FH and for those diagnosed following incidental lipid tests. Lifestyle and dietary advice appropriate for children with FH; suggested low density lipoprotein cholesterol (LDL-C) targets and the most appropriate lipid-lowering therapies to achieve these are discussed in this statement of care. Based on the population prevalence of FH as ~1/250 and the UK paediatric population, there are approximately 50,000 FH children under 18 years. Currently only about 550 of these children and young people have been identified and are under paediatric care.

1. Aim

This is a consensus statement by HEART UK on a strategy with age-appropriate guidance for managing children and young people with heterozygous FH in the UK. Martin and colleagues have recently reviewed knowledge about FH in children [1]. The existing NICE CG71 guideline does not address in detail the management of children with FH. We aim to do this here and suggest practical LDL-Cholesterol target concentrations. We have not included formal evidence grading of the recommendations since this is a position statement of UK paediatric FH expert opinion.

2. Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant inherited metabolic disorder characterised by elevated low-density lipoprotein cholesterol (LDL-C) concentrations from birth with premature coronary heart disease (CHD) occurring in approximately half of men by age 50 and one third of women by age 60 [2]. Lifetime exposure to LDL-C correlates with increased risk of cardiovascular disease [3]. Prospective studies and randomized trials are consistent in showing that the relationship between LDL-C cholesterol and CHD is causal [4,5], with a direct proportional relationship between LDL-C and risk.

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In addition, using a 9-SNP LDL-C "genetic score" Ference et al. [6] have demonstrated that prolonged exposure to lower LDL-C beginning early in life is associated with a substantially greater reduction in the risk of CHD than the current practice of lowering LDL-C beginning later in adulthood.

In more than 90% of the UK FH patients where a mutation is found the underlying genetic cause is within the *LDLR* gene, which encodes the low-density lipoprotein receptor (LDL-R). In around 5% of UK patients the genetic cause is a single mutation in apolipoprotein B (*APOB*), and in about 2% a single mutation in proprotein convertase subtilisin/kexin type 9 (*PCSK9*) [7]; a single deletion variant in *APOE* (p.Leu167del) is also reported to cause the FH phenotype in a few families [8]. In patients where no causative mutation can be found a polygenic cause of their hyperlipidaemia is most likely [9]. Finding the underlying monogenic cause of FH in an index case allows cost effective DNA-based "cascade testing" in their relatives, an approach recommended in most FH guidelines, that will increase the number of FH children identified. A HEART UK consensus statement on Homozygous FH (including children) was published in 2016 [10] and Homozygous FH will not be further discussed here.

No randomised, placebo-controlled trials of cholesterol reduction to reduce CHD events have been carried out in children with FH because, as for adults, their high risk makes a placebo arm unethical. Since a child is likely to develop CHD in their 5th-6th decade, it is also impractical to fund an RCT of the benefit of statin therapy because of the time needed to observe such a benefit. Mendelian randomization studies (natural randomized trials) indicate that individuals with genetic polymorphisms that lower LDL cholesterol from birth have an approximate 90% lower risk of CHD in adult life compared with individuals without such polymorphisms and higher LDL cholesterol from birth. It follows that children with FH have a markedly elevated risk of future CHD because of their life-long elevated LDL-C and that reducing their LDL-C will reduce their future risk of CHD.

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. Many studies have reported that the prevalence of T2D is low in adults with FH, and in a study of over 63,000 subjects from Holland [11], even in treated adults with FH the prevalence of T2D was significantly lower than in their unaffected relatives (1.75% vs 2.93%). Also, the benefits of statin treatment in FH for preventing CHD outweighs any modest potential excess risk of Type 2 diabetes [12]. 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 [13].

The psychological effects of any screening or testing process include how a person thinks (risk perception and understanding of diagnosis), feels (levels of anxiety, depression, reassurance) and behaves (coming for repeat screening, taking medication, changing lifestyle). It is possible that relatives may become anxious, or angry, when they receive news that they are at risk of having an inherited disorder like FH. However, studies suggest that relatives usually believe that genetic information is beneficial [14]. There are fewer data on the additional psychological impact of DNA testing (over and above cholesterol testing) in FH patients, and also few data examining this specific issue in children. An early study of 152 boys and girls aged 7–16 years from Norway [15] concluded that the prevalence of psychosocial dysfunction was no greater in children treated for FH than in the normal population. In summary, we are not aware of any short or medium term studies that have reported any evidence of harm in children identified as having FH through cascade testing programmes.

Children with heterozygous FH seldom present with identifiable clinical features. However, using ultrasound to measure carotid intima media thickness (CIMT), it has been shown that there is progressive development of atherosclerosis through childhood [16]. CIMT is widely accepted as marker of the presence of atherosclerosis in the arterial tree in adults. Individuals in the top quintile of CIMT have a higher future risk of CHD [17] and CIMT in childhood is therefore a useful predictor of CHD in later life. As a consequence of having roughly twice the normal LDL-C concentrations from birth children with FH develop atherosclerosis that is detectable as significantly increased CIMT compared with their non-FH siblings by the age of 8–10 years [18]. The finding that children with FH have increased carotid intima media thickening (an early marker of atherosclerosis) compared with their non-FH siblings supports the view that atherosclerosis starts early in life and justifies treatment also beginning early in life.

The European guidelines for children with FH recommend that statin treatment in children with FH should be considered by the age of 8 years and that LDL-C be lowered by 50% in children less than 10 years and lowered to below 3.5 mmol/l in those over 10 years [19]. NICE CG71 recommends consideration of statins by the age of 10 years but with no specific LDL-C targets [20].

3. Diagnosis

Children and young people with FH are, based on current service provision, most likely to be identified through cascade testing in a family where a mutation has been identified in an index case, as shown in Fig. 1 [adapted from reference [19]].

NICE CG71 recommends that children who are at 50% risk of having FH, because they have an affected parent, should be offered a DNA test before their 10th birthday, or as soon as possible after that age. Children can be tested soon after birth if the parents want this. Cascade testing is currently being carried out in many centres throughout the UK [21], and since 2015 approximately 250 children aged less than 10 years and 250 young people aged 10–20 years have been identified. These individuals are being referred to and managed in 60–70 centres across the UK, at paediatric or specialist lipid clinics across the UK with paediatric health care professionals.

DNA analysis for the mutation identified in the index patient is unambiguous and therefore recommended for family cascade testing for FH. Lipid measurements can be used for relatives of patients with a clinical diagnosis of FH in whom the mutation is unknown. Though fasting lipid measurements are ideal, results from a non-fasting sample have acceptable accuracy to indicate whether a child is affected and may be more feasible for young children where fasting is difficult. The total-cholesterol and LDL-C thresholds for a diagnosis of an FH proband from the general population are too high for use in relatives, given the greater prior probability of a first-degree relative having FH (50% vs 1/250). To overcome this, sex-specific total- and LDL-C diagnostic cut-offs were established by Starr et al. [22] and recommended by NICE CG71 [2008]. These charts (Supplement S1) were derived from measurements made in mutation positive and negative relatives and assign a post-test probability of FH (illustrated by red/grey/green banding) in relatives with a pre-test probability of 50%. The presence of a grey zone further emphasises the value of an unambiguous diagnosis with a DNA test, which eliminates the diagnostic uncertainty of the lipid "grey zone".

4. Statement 1: identification

a. It is recommended that cascade testing of children be undertaken by age 10 years in families where an FH mutation has been identified, by testing for the mutation identified in the index case.
b. Children and young people are referred to a professional with expertise in managing paediatric FH for screening and confirmatory tests for FH.
c. Full informed parental consent for DNA testing should be obtained with child assent if appropriate.
d. Mutation analysis, if not already done in the affected parent, should include the child and parent and be done by comprehensive DNA sequencing of introns and exons of all known FH-causing gene loci in an accredited laboratory.

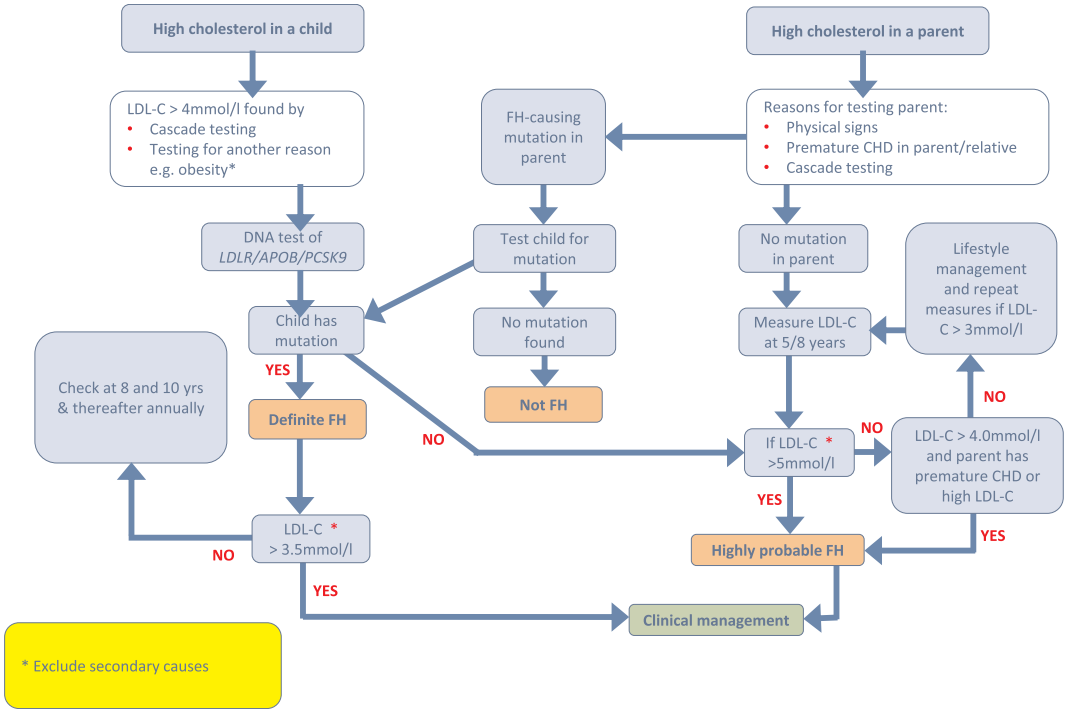

Fig. 1. Identification of childhood heterozygous FH.
Exclude secondary causes of high cholesterol. For children and young people with definite FH, clinical follow up and management is detailed in Figs. 2 and 3.

e. In FH families where the genetic basis is unknown, LDL-C concentrations can be used for cascade screening with the cut-offs established by Starr et al. [22; Supplement 1].

5. Clinical management of children and young people with FH

The proposed care pathway for FH children identified either by cascade testing (CT) or following the detection of elevated cholesterol concentration is presented in Fig. 2.

The first clinic visit after identification should be by a health care professional with expertise in managing children and young people with FH. This may be a paediatrician or a paediatric clinical nurse specialist; we will refer to them as paediatric FH professionals. The paediatric FH professional should ensure a child friendly setting & refer to the 'National service framework for children, young people and maternity services' (www.dh.gov.uk) [23]. We anticipate that General Practitioners (GPs) will play a larger role in the management of paediatric FH in the future, and that paediatric FH professionals will develop shared care arrangements, with clear guidelines on management, follow up and indications for referral back to secondary care. Cascade screening and the management of FH in childhood are relatively new, however, so we believe that it would be premature for GPs to undertake this at present.

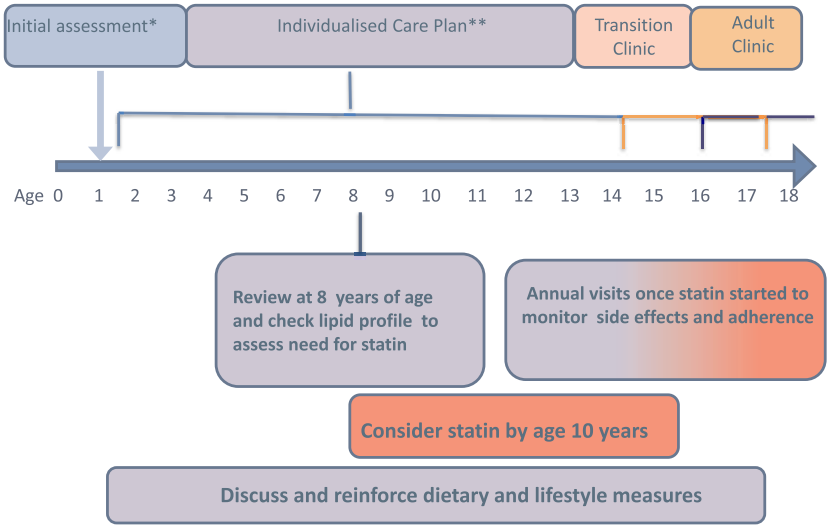

Fig. 2. Clinic visit pathway for children and young people with FH.
The first clinic visit after identification should be a review by a healthcare professional with expertise in paediatric FH.
Following that, an Individualised Care Plan should be drawn, detailing timing and setting for further clincial reviews. Follow up should be by a paediatric FH healthcare professional. A lipid profile should be taken at age 8 years to assess whether lipid lowering therapy should be considerd or defered until age 10 years. Following initiation of statin treatment, patients should be reviewed by a paediatric FH professional every 6–12 months to monitor side effects and to assess tolerabilty and efficacy or more frequently as required. Follow up could be a combination of face to face and telephone consultations as appropriate.

• Initial assessment includes cascade testing or incidental finding of raised LDL-C at any age (less than 18 years)

** The Individualised Care Plan should be shared with parents and GP and sets out frequency of follow-up. Follow up should be by a paediatric FH Healthcare professional.
The above pathway is also recommended for future universal screening programmes when approved (child-parent screening).

Box 1
Confirmed diagnosis of FH: Guidance on LDL-C target concentrations on statin treatment.

- < 10 years of age: if drug treatment is considered appropriate, aim for a 30–50% reduction in LDL-C from baseline or a level < 3.5 mmol/L.
- ≥10 years: aim for a 50% reduction in LDL-C from baseline or a level < 3.5 mmol/L.
- ≥14 years: if there are additional co-morbidities (e.g, type 1 diabetes) or a very strong family history of early coronary events in adults in their 2nd and 3rd decade, assuming compliance to statin therapy, we suggest slowly increasing the statin dose and/or addition of Ezetimibe 10 mg daily, aiming towards a target LDL-C concentration of < 2.5 mmol/l over the next 3–5 years.

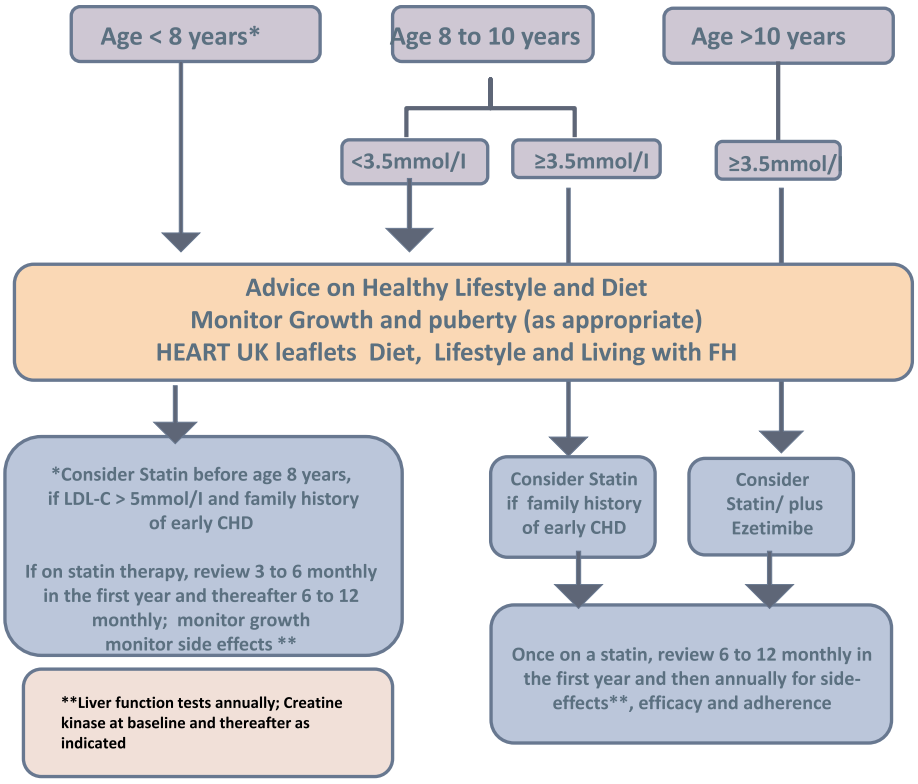

Fig. 3. Clinical management of children and young people with FH.
In children < 10 years of age aim for 3.5 mmol/L or a 30–50% reduction in LDL-C from baseline. In children and young people > 10 years of age aim for 3.5 mmol/L or a 50% reduction in LDL-C from baseline in the first year. From the age of 14 years, if there are additional co-morbidities (e.g, type 1 diabetes) or a very strong family history of early coronary events in adults in their 2nd and 3rd decade, slowly increase statin dose and/or addition of Ezetimibe 10 mg daily, aiming towards a target LDL-C concentration of < 2.5 mmol/l over the next 3–5 years. Liver function tests (LFTs) and serum creatine kinase (CK) should be measured before a statin is commenced. Thereafter, measure CK if indicated and LFTs annually. Also refer to Box 1 and 2 for management guidance.

An individualised care plan should be formulated at the initial meeting and shared with the GP and parents. Until 8 years of age, review by a paediatric FH professional every 2 years is usually sufficient and these may be telephone consultations, though face-to-face follow-up is suggested if there is a strong family history of early onset CHD and a LDL-C level ≥5 mmol/l. Face-to-face review is recommended for all children with FH at 8 years of age, with a lipid profile to help decide whether lipid lowering therapy should be started or defered.

Life-style changes are the first management strategy for all children and young people with FH. Molvin et al., in 2013 [24] and the NICE guideline CG71 [20] recommended that children identified with FH and their families should receive advice on a healthy lifestyle (diet, exercise and smoking) as shown in Box 1. The emerging epidemic of childhood obesity seen in the UK, with over 21% of 11–15 year olds having a BMI in the "obese" range (> 95th percentile for age and gender) [25], makes this lifestyle information particularly important. Data from the UK Paediatric FH register has shown that the prevalence of obesity is around 50% lower in patients with recognized FH than in the UK general population [26], highlighting the direct benefit to the child of early identification.

The decision to start treatment with a statin should be made jointly with the child and their family; it is based primarily on their age, level of LDL-C and the family history of early CHD. Other risk factors for CHD, such as diabetes or renal disease and south Asian ethnicity, should also be considered. In the presence of a family history of elevated Lp(a), it would be of potential clinical utility to measure this in the child [1]. However, there is currently no published evidence to support the routine measurement of Lp(a), nor has it been identified as an added risk factor in children with HeFH. In the absence of a suitable intervention for elevated Lp(a), in our experience, it adds to parental anxiety. Generally, biochemical and inflammatory markers, genetic risk scores, CIMT measurement and other forms of imaging have not predicted risk accurately enough to be of clinical utility [1].

Treatment with a statin should be considered from 8 years if there is a strong family history of early CHD and LDL-C is > 4 mmol/l; it is occasionally appropriate to start a statin before 8 years of age. In patients aged less than 10 years, we suggest aiming for a 30–50% reduction of LDL-C from baseline values. Clinical review is recommended 3–6 monthly in the first year after starting a statin and then every 6–12 months to monitor for possible side effects and to assess the efficacy of treatment.

In children with FH over 10 years of age, a statin should generally be started if LDL-C is > 3.5 mmol/l. This must, however, be agreed with the child and their parents, who are sometimes reluctant to start a statin even after 12 years of age. It may be appropriate to defer treatment for longer, particularly if there is no family history of early CHD; this situation will become commoner if universal screening is introduced (see section 15 below).

The European guidelines for children with FH recommend a 50% reduction of LDL-C from baseline in the first 12 months of commencing statins, with a longer-term goal of maintaining LDL-C below 3.5 mmol/l (19). This is still higher than the target concentrations of < 2.5 mmol/l recommended in adults with FH without CHD, and 1.8 mmol/l in those with CHD [27,28].

Our recommended treatment pathways for children and young people with paediatric FH are shown in Fig. 3. In Box 1, we give LDL-C targets that we consider reasonable and achievable, based on previously published guidelines. These generic guidelines should, however, be discussed with the family and adjusted according to the individual risk factors, particularly the family history.

In addition to their established role in diagnosis, the age and sex specific distributions of LDL-C and TC derived from mutation negative relatives by Starr et al. [22] provides a graphic illustration of expected values in the presence or absence of FH-causing mutations, which may be useful in explaining the range of cholesterol values in affected compared to unaffected relatives and the goals of lipid lowering treatment. In children, using these charts, the overall aim of treatment would be to return LDL-C and TC to the "green zone", as seen in unaffected age-appropriate individuals. This concept is likely to be readily understood by parents and young people, as is the argument that adults who have been in the "red zone" for several years should ideally achieve the greater LDL-C reductions required to get them into the lowest part of the "green zone" as shown in Supplement S1.

6. Statement 2: clinical review

a. All children with a confirmed diagnosis of FH should be reviewed at their initial clinic visit by a paediatric healthcare professional with expertise in FH in a child friendly environment with advice on healthy lifestyle.
b. An individualised care plan for follow-up until 8 years of age should be formulated at the initial meeting. Options include periodic face-to-face or telephone consultations with the paediatric FH professional.
c. Occasionally it may be appropriate to start a statin before 8 years of age.
d. All children with FH should be reviewed at 8 years of age for a repeat lipid profile and reinforcement of dietary and healthy lifestyle advice.
e. Use of a statin should be considered in children aged 8–10 years with LDL-C > 4 mmol/l and a strong family history of early CHD.
f. In children with FH aged more than 10 years, following discussion with the parents, consider statin if LDL-C > 3.5 mmol/l.
g. All children on a statin should be reviewed regularly by a paediatric FH professional, 3–6 monthly in the first year and thereafter 6 to 12 monthly as appropriate. Reviews could be a combination of face to face and telephone consultations as appropriate.
h. All significant side effects to statin should be reported using the yellow card scheme (British National Formulary)
i. It is recommended that children with FH have their diagnosis coded in primary and secondary health care records.

7. Treatment options

Statin: Regulation of cholesterol via the LDL-receptor pathway featuring receptor-mediated endocytosis is critical to the onset of atherosclerosis. Statins lower serum cholesterol by inhibiting hepatic cholesterol biosynthesis and up-regulation of hepatic LDL receptors, with increased clearance of LDL-C. The lipophilic statins cross cell membranes largely by passive diffusion. Hydrophilic statins (Pravastatin and Rosuvastatin) require activated carrier-mediated transport with organic anion transporting polypeptide (OATP) 1B1; they are more selective for hepatic tissues and are the preferred statins for young children less than 10 years of age, whose brain and gonadal tissues are still maturing [29]. Rosuvastatin is licensed for children aged over 6 years; Pravastatin from 8 years, Simvastatin from 5 years and Atorvastatin from 10 years of age (British National Formulary for Children).

Side effects of statins: The most frequently discussed side effects of statin therapy in adults are muscle-related complaints. These are rare in children, possibly because lower doses are used. In 2017, the Cochrane report on statin safety in paediatric FH reviewed 26 potentially eligible studies, of which nine were randomized placebo-controlled studies (1177 participants) [30]. The median time of intervention and follow-up was 24 weeks (range six weeks to two years). Statins reduce the mean LDL-C concentration at all time points. Liver function tests (LFTs) and creatine kinase (CK) levels were similar in the statin treated and placebo groups at any time point. Although elevations of these values occurred in some children, the risks of myopathy and clinical adverse events were very low and similar in both groups. There were no reports of rhabdomyolysis and in seven studies that reported ALT level, there were no abnormal results after up to two years of statin treatment.

Other lipid lowering drugs: In some patients, it may not be possible to achieve the LDL-C targets we recommend with the statin doses licensed in children. In these patients, we recommend adding Ezetimibe [31]. This inhibits intestinal cholesterol absorption and has a synergistic effect with statins. The licensed dose is 10 mg daily from 10 years of age. Diarrhoea is the commonest side effect but it is usually transient. Bile acid sequestrants (such as Colestipol and Colestyramine) can also lower the LDL-C but they are unpalatable and therefore unpopular for use in children. Monoclonal antibodies to PCSK9 (Evolocumab and Alirocumab) are now used in adults with FH and paediatric trials are in progress but they need to be given by injection and will seldom be warranted in children.

8. Adherence to treatment

Adherence should be checked if there is a poor response to statins, particularly during adolescence, before increasing the dose or potency of the drug. Long term compliance with treatment is unlikely unless patients understand and believe the benefits; frequent contact can also help and may be most conveniently done by telephone. Studies in adults with FH have shown reasonable treatment adherence but, for many chronic disorders, adherence is poor during adolescence. Good adherence was, however, reported in the only study specifically considering statins in adolescents and young adults with FH [32]. A questionnaire was sent to 214 young adult FH patients who had initiated statin therapy at least 10 years previously and replies were received from 205 subjects (95.8%). Of these, 169 (82.4%) remained on statin treatment and 78.7% (148 out of 188) had taken at least 80% of their lipid-lowering drugs over the previous month. Side effects were reported by 40 patients (19.5%), mainly muscle complaints and gastrointestinal symptoms, but only 3 patients (1.5%) discontinued statin therapy because of side effects. No rhabdomyolysis or other serious adverse events were reported.

9. Statement 3: treatment

a. Children and young people aged ≥10 years with LDL-C > 3.5 mmol/l should be considered for lipid lowering therapy and commenced initially on a once daily dose of Atorvastatin 10 mg, Pravastatin 20 mg or Rosuvastatin 5 mg, the doses being titrated up as required within the licensed range.
b. In children < 10 years of age with FH, LDL-C > 4 mmol/l and a family history of early CHD, initially consider once daily Pravastatin 10 mg or Rosuvastatin 5 mg once daily.
c. All children and young people with FH on a statin must be monitored regularly by a paediatric FH professional.
d. All children and young people should have baseline CK and LFTs measured before commencing a statin and repeated when the dose is altered. LFTs should be monitored annually. Measure CK if muscle symptoms are reported.
e. All children with FH on a statin should have regular monitoring of weight and growth (and puberty if appropriate).
f. The suggested target for children aged less than 10 years is 3.5 mmol/l or a 30–50% reduction in LDL-C concentration from baseline.
g. The recommended target for children and young people aged > 10 years is 3.5 mmol/l or a 50% reduction in LDL-C concentration from baseline in the first 12 months. The addition of Ezetimibe 10 mg daily as an adjunctive therapy to statin should be considered to achieve target levels of LDL-C concentration as above.

h. In adolescents from 14 years of age, if there are additional co-morbidities (eg type 1 diabetes) or a very strong family history of early coronary events in adults in their 2nd and 3rd decade, assuming compliance to statin therapy, we recommend slowly increasing the statin dose and/or addition of Ezetimibe 10 mg daily, aiming towards a target LDL-C concentration of < 2.5 mmol/l over the next 3–5 years (Box 1).

10. Diet and life-style

Tobacco smoking greatly increases the risk of heart disease in people with FH and the importance of avoiding this should be emphasized from the time of diagnosis. Parents should be encouraged to stop smoking, partly to reduce the risk of their children adopting the habit. Although e-cigarettes are associated with a much lower risk of cancer and probably of heart disease, uncertainties remain and they can lead to nicotine addiction. Life-long avoidance of both smoking and/or vaping, is strongly recommended.

It is important to ensure that children and young people with FH have adequate calories, including calories from fats, to support and maintain growth. The emphasis should always be on healthy eating and not dietary or calorie restrictions. The dietary guidance for children with paediatric FH is described in Box 2.

Molven et al. [24] demonstrated that counseling children with FH in Norway on healthy eating resulted in a long lasting effect, with children and adolescents choosing foods with an appropriate fatty acid composition, with less saturated fat.

The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) suggest that based on the level of LDL-C lowering, functional foods with plant sterols/stanols (at least 2 g/day with the main meal) may be considered in children (> 6 years) with FH [24]. The possible decrease in carotenoid and fat-soluble vitamin levels by sterols/stanols can be prevented with a balanced diet rich in these nutrients. The nutritional adequacy of the overall diet should be assessed to ensure all nutrient requirements for healthy growth are being met.

The cumulative exposure of coronary arteries to the lifelong LDL-C elevation can be estimated by calculating the LDL-C burden (LDL-C concentration x age in years), which can also be used to demonstrate the potential usefulness of dietary stanol/sterol treatment. Compared to untreated FH patients, the LDL-C burden from the age of 10 years was reduced by 15% on a statin and by 21% on a statin and dietary plant stanol [33]. Longer-term studies are required to confirm these positive findings.

11. Statement 4: diet and lifestyle

a. Life-long avoidance of smoking/vaping should be strongly recommended.
b. Children with FH should be educated on food groups and healthy food choices
c. Dietary guidance on age appropriate fat intake should be provided by a paediatric dietitian and ensure adequate growth. The dietitian should also monitor intake of plant stanol/sterol as appropriate.
d. Age appropriate activity and energy intake should be encouraged in all children with FH.
e. The importance of avoiding excessive alcohol should be discussed when appropriate with adolescents.

12. Adolescence and transition to adult services

Transition describes the process of transferring a child to an adult model of health care. Adolescents and young adults often consider healthcare of low importance compared with the other aspects of their transition to adulthood (e.g. education, employment, relationships) and they often demonstrate poor engagement with healthcare. It is, therefore, important to start teaching children with FH about their condition and its management from 10 to 12 years of age. Better education of young FH patients should improve long-term adherence [34–38], and HEART UK have produced information sheets for different aged children [39].

Patients should be offered the opportunity to attend part of the consultation alone from about 14 years of age, depending on their wishes and capacity. This provides an opportunity to discuss treatment plans, lifestyle, pregnancy/contraception issues and medication compliance, before the parents/guardians are invited to join the consultation for further discussion. When lipid-modifying drug therapy is first considered, girls should be advised of the potential for adverse effects on the foetus during pregnancy, and this should be revisited annually. Girls with FH should be offered a choice of effective contraceptive methods if appropriate [20] and advised to take folic acid and discontinue statins 3 months before a planned conception and throughout pregnancy and breastfeeding.

Smooth transition to adult services is facilitated if the patient is seen jointly by the paediatric FH professional and adult lipidologist on a few occasions prior to transfer. Joint clinics are particularly useful from 14 years of age onwards but throughout childhood family follow-up clinics for children and adults can enhance the family's quality of life, reducing travel costs and time off work. They also reinforce the healthy life-style interventions and dietary habits that apply to all affected individuals within the family. Family clinics must, however, include a paediatric FH professional and take place in a child friendly setting.

Individuals or families may be concerned about the implications of a FH diagnosis for insurance and employment. There is a moratorium from the Association of the British Pharmaceutical Industry (ABPI) on asking about predictive genetic tests, but they can ask about confirmed diagnoses. Although the outcome for a diagnosed child/young person is excellent, the concept of lifetime exposure (or lack of exposure) to elevated LDL-C is generally not well understood by employers or insurance companies. Patients may find that their condition is not completely understood outside the clinical arena, and may need further advice from their own clinician or an appropriate representative body, such as HEART UK.

In the Netherlands, an agreement between insurers and other parties in society to avoid genetic discrimination has been established to improve access to insurances for pre-symptomatic subjects with genetic FH. In 2003 insurers agreed to underwrite FH according to a set of specific guidelines. These guidelines stipulate that subjects with genetic FH and free of cardiovascular disease should be offered an unconditional life insurance policy under most conditions. The main requirements were that individuals had LDL-cholesterol levels, either treated or untreated, at or below 4.0 mmol/l although other cardiovascular risk factors, such as smoking, hypertension, diabetes or obesity, had to be absent at the time of life insurance application [40].

In 2012, Huijgen et al. [41] tested the effectiveness of the 2003 implementation of life insurance guidelines for FH in The Netherlands. A total of 2825 subjects that had participated in the genetic testing for FH between 1998 and 2003 were included in a survey. Comparisons of

Box 2
Lifestyle advice: Adapted from [18], [21].

Diet: Total fat intake is 30% or less of total energy intake; saturated fats are 10% or less of total energy intake; intake of dietary cholesterol less than 300 mg/day; saturated fats to be replaced by increasing the intake of monounsaturated and polyunsaturated fats.
Physical exercise: Age appropriate activity and energy intake to achieve and maintain a healthy body weight.
Smoking: Total avoidance of smoking/vaping should be strongly recommended.

unconditional acceptance rates before and after FH diagnosis and before and after the guidelines were analysed. The percentage of applicants without FH obtaining insurance on normal terms was 98.6%, which was significantly greater than for applicants with genetic FH. However, the vast majority (86.3%) of FH patients had been accepted for life insurance and this percentage was significantly higher when compared to data before implementation of these guidelines. The authors conclude that their results cautiously suggest that access to life insurance for individuals with genetic FH improved in The Netherlands following the introduction of guidelines for insurers. Unconditional acceptance for life insurance for FH in the Netherlands has significantly improved when compared to a decade ago. The authors conclude that an agreement between insurers and other parties in society to avoid genetic discrimination has proven a viable strategy to improve access to insurance for pre-symptomatic subjects with genetic FH in The Netherlands. They suggest that this approach could encourage health care workers in other countries to reach similar settlements with insurance companies.

13. Statement 5: adolescence and transition to adult services

a. Children with FH should be taught about their condition and its management from 10 to 12 years of age.
b. Family clinics for FH are encouraged but should always include a paediatric FH professional and take place in a child friendly setting.
c. From about 14 years of age onwards, adolescents should be seen partly on their own if they wish and joint clinics with an adult lipidologist should be considered.
d. Adherence to statins should be monitored (using medication adherence reporting scales)
e. The importance of diet, healthy lifestyle measures and avoidance of smoking/vaping should be stressed and girls on statin therapy should be given advice on contraception if appropriate.
f. Children with FH should be transferred to an adult lipid clinic at 16–18 years of age.

14. The UK FH Children's register

Following the 2010 UK National Audit of FH services, the UK paediatric FH register was developed specifically to collate information on children with FH and to monitor the safety of statin use in paediatric FH. The register has ~70 clinicians entering routine clinical care data annually. The register currently has over 600 children registered and 880 annual follow up data. In 300 children (51% boys, 75% Caucasian), the untreated mean (SD) LDL-C was 5.50(1.49) mmol/L. As expected, the proportion of children on statins varied significantly ($p < 0.005$) by age group (< 5 years = 0%, 5–10 years = 16.7%, 10–15years = 57.1%, > 15years = 73.2%). Those subsequently on statin treatment had significantly higher LDL-C concentrations at diagnosis than the overall group (6.01(1.46) mmol/L v 5.31(1.37) mmol/L, $p = 0.00007$), and a higher proportion had a family history of early CHD in a parent or first degree relative (28.4% v 19.0%, $p = 0.09$). Overall, statin treatment reduced LDL-C by 31%, and no child showed elevated levels of markers of liver toxicity or muscle damage [42]. The data indicate that treatment decisions in children with FH are being appropriately based on a stronger family history of CHD and the LDL-C concentration.

The annual follow up data has allowed the register to monitor growth rates in those taking or not taking statins. There were no differences in annual growth rate in statin vs no-statin groups. The long-term continuation of the register activities, including monitoring into adulthood, will help to reassure clinicians and parents about the safety and efficacy of statin therapy. All children and young people with FH should be invited to join the Registry.

15. Potential future universal screening for FH

Unfortunately, except in the Netherlands, current cascade screening programs have failed to identify most FH patients in the community, primarily because relatively few index cases are identified [1]. A pathway for identification of children with FH using universal Child-Parent Screening was proposed and tested by Wald et al. [43]. In this study of 10,095 children at 92 UK general practices, the authors demonstrated that screening children for FH was feasible and acceptable at the time of routine immunization between 1 and 2 years of age (median age 13 months), when a cholesterol measurement is most discriminatory for identifying individuals with FH. The results showed that screening 10,000 children identified 40 children with FH, with a total cholesterol ≥1.35 Multiples of the Median or MoM (95th centile) and an FH mutation and 8 with two total cholesterol measurements > 1.50MoM (99th centile) without an FH mutation. For every child who had mutation positive FH, a parent with the same mutation was also identified. In the study all parents were offered statin treatment immediately and dietary advice was offered to both parent and child with a recommendation to consider a statin in the child from age 8 years. In a subsequent, paper, the Child-parent screening approach was combined with cascade testing (Child-parent Cascade Screening), based on two new per known FH cases identified, with results showing that an integrated strategy would identify 1 new individual with FH for every 70 children screened, at a cost of about £5 per child screened and £960 per new FH case identified [44].

The cost effectiveness of such an approach has been modeled, including the cost for monitoring and treating the children and adults identified and suggests a cost per Quality Adjusted Life Year Gained of £12,480 [45], which is well under the NICE threshold for an intervention to be recommended. The UK National Screening Committee is currently considering the feasibility and acceptability of this approach, and if approved we anticipate that children identified in this way should enter the care pathway as shown in Fig. 3 and be managed as described above.

16. Conclusions

This consensus statement builds on previous guidelines [19,20] and provides a comprehensive care pathway for children and young people with heterozygous FH. Statins have been used in adults with heterozygous FH and in those in the general population since the late 1980s [2–4], and in the ensuing 40 years no major long term safety issues have been identified. Children and young people with heterozygous FH seldom present with overt clinical features of disease. However, early onset atherosclerosis has been documented by CIMT studies in children with FH [16], and prevention of progression of CIMT can be achieved with statin treatment [17]. Studies in children have also found no long-term safety concerns, and the 2017 Cochrane review concluded that statin use in childhood was safe in the medium term [30]. This finding is fully supported by the UK FH Children's Register which found no instances of safety issues and an equal growth rate in statin treated and non-treated children [26]. However, longitudinal studies are lacking and will be helpful to confirm the long-term safety of statins started in children.

We believe that this is the first consensus statement that addresses the follow up of children identified on cascade testing, those identified whilst measuring lipid profiles incidentally, and if universal child-parent screening is made available. This consensus statement also provides defined guidance on the initiation of statin and target goals for LDL-C on a statin for children and young people with heterozygous FH.

Conflicts of interest

1. Uma Ramaswami: no conflict of interest related to this manuscript
2. Steve Humphries: no conflict of interest related to this manuscript.
3. Lorraine Priestley-Barnham: No relevant conflict of interest
4. David Wald: No relevant conflict of interest
5. Mark Anderson: no relevant conflict of interest
6. Peter Dale: No relevant conflict of interest
7. Nigel Capps: No relevant conflict of interest; HEART UK Medical and Scientific Committee member.

8. Andrew Morris: no relevant conflict of interest
9. Peter Green: No relevant conflict of interest; Trustee of HEART UK

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Appendix A. Supplementary data

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