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SPECIAL ARTICLE
Dyslipidaemias

Familial hypercholesterolaemia in children and adolescents: a European Atherosclerosis Society consensus statement

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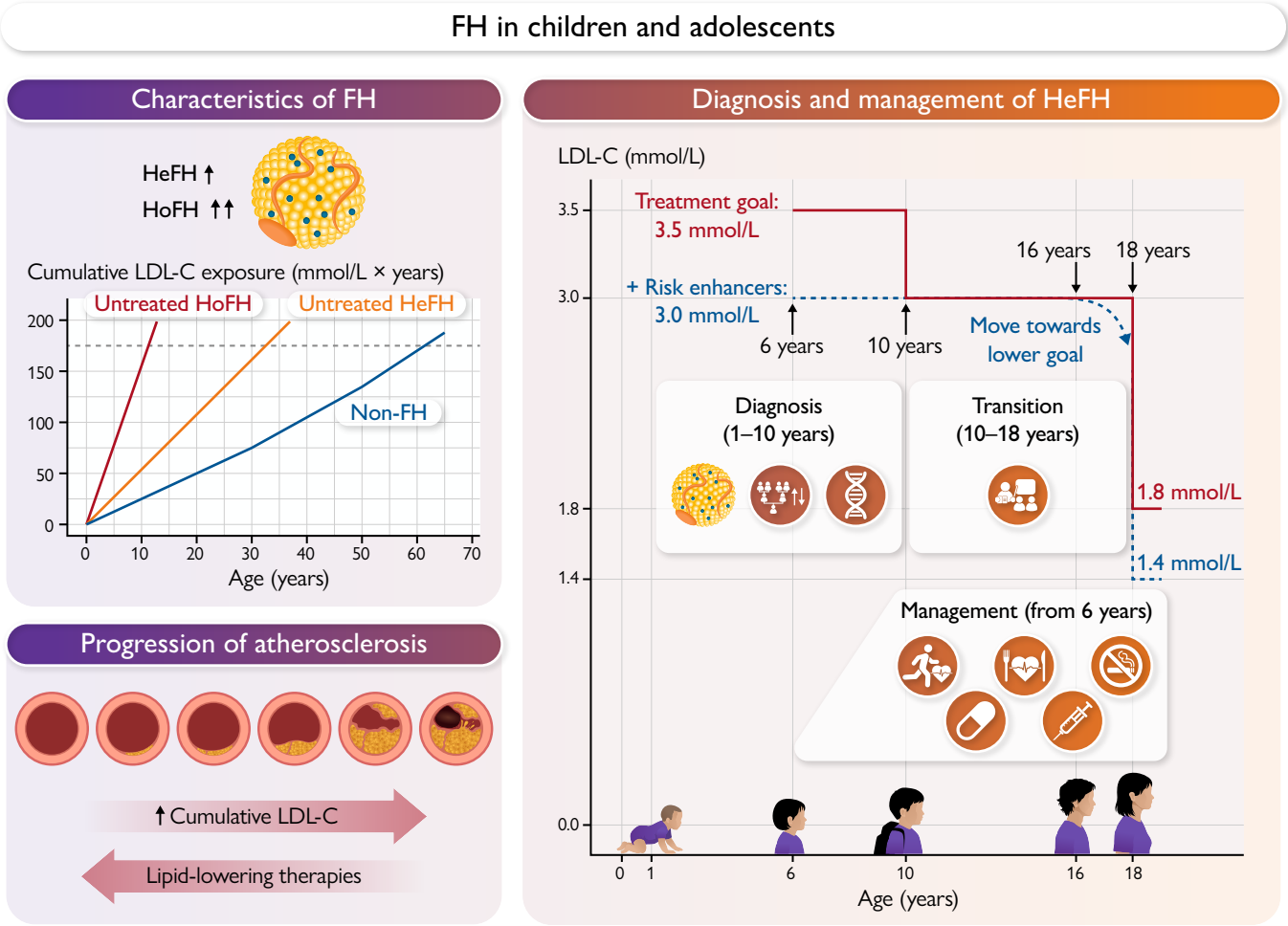
Abstract

Familial hypercholesterolaemia (FH) is a common genetic disorder characterized by lifelong elevated LDL cholesterol (LDL-C) concentrations. FH exists in two forms: heterozygous FH (HeFH), which affects around 1 in 300 people worldwide, and homozygous FH (HoFH), which affects around 1 in 300 000. Individuals with FH are at increased risk of premature atherosclerotic cardiovascular disease (ASCVD) and death, and those with HoFH are, if untreated, at extreme risk of ASCVD manifestations even before adulthood. Early diagnosis and treatment in childhood can extend or normalize life expectancy, but limited awareness, underdiagnosis, and undertreatment remain major challenges. This consensus statement aims to address these challenges, supported by increased knowledge of the pathogenesis of FH and the availability of an increasing range of lipid-lowering therapies (LLTs) that can be used from early ages. To increase the detection rate of FH, all countries are encouraged to establish a paediatric screening programme and, given that current diagnostic criteria often fail to identify children with an FH-causing genetic variant, revised diagnostic criteria are presented. Updated LDL-C treatment goals are proposed, and the importance of starting LLTs before puberty in children with HeFH, and, if needed, from 6 years, is highlighted. Guidance on how to manage FH is provided, including treatment algorithms for use in children with either HeFH or HoFH and a discussion on how to promote a smooth transition to adult care. Early detection and optimal treatment as advocated in this consensus statement are crucial to improving life expectancy for children and adolescents with FH.

Graphical Abstract



FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol

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Individuals with untreated heterozygous familial hypercholesterolaemia (HeFH) or homozygous familial hypercholesterolaemia (HoFH) have high or extremely high LDL cholesterol (LDL-C) concentrations and are at increased risk of premature atherosclerotic cardiovascular disease. Lipid-lowering therapies reduce the cumulative LDL-C exposure and slow the progression of atherosclerosis.

For HeFH, diagnosis (by lipid and/or genetic testing) should occur between 1 and 10 years, and management (lifestyle advice and pharmaceutical treatment) should start from 6 years and by no later than 10 years. The LDL-C treatment goal is 3.5 mmol/L from 6 to <10 years and 3.0 mmol/L from 10 to <18 years or from 6 years if major risk enhancers are present. Children with familial hypercholesterolaemia (FH) should be given knowledge about their condition and management from 10 years at the latest to improve long-term adherence to clinical management. From the age of 16 years, adolescents with FH and major risk enhancers present should start moving towards lower LDL-C treatment goals to bridge the gap to recommended levels for adults with FH and another major risk factor.

Keywords Familial hypercholesterolaemia • Children • Adolescents • Lipid-lowering therapy • Cumulative low-density lipoprotein cholesterol exposure • Cardiovascular risk

Introduction

Heterozygous familial hypercholesterolaemia (HeFH) is one of the most frequent monogenic disorders, affecting ~1 in 300 people worldwide.[1,2] Heterozygous familial hypercholesterolaemia is characterized by elevated concentrations of LDL cholesterol (LDL-C) that if untreated, or undertreated, result in an increased risk of premature atherosclerotic cardiovascular disease (ASCVD).[3,4] Homozygous familial hypercholesterolaemia (HoFH) is rare with an estimated global prevalence ranging between 1 in 250 000 and 1 in 360 000.[1,2] Individuals with HoFH may have extremely high LDL-C concentrations and are at very high risk of coronary and aortic stenosis and even death in childhood or adolescence if untreated.[5]

Underdiagnosis remains a major issue. Familial hypercholesterolaemia (FH) affects around 500 000 children in Europe,[1,2] but <10% of these children are identified.[6] The European Atherosclerosis Society (EAS) Familial Hypercholesterolaemia Studies Collaboration, which included over 42 000 adults from 56 countries, showed that the median age for diagnosis of FH is 44 years; of note, only 2% of the adults included were diagnosed before the age of 18 years.[7] Family cascade or universal screening programmes (using genetic and/or lipid tests) have been shown to increase the detection rate, but these are not widespread globally. Even if diagnosed, many children with FH are not adequately treated throughout childhood and adolescence.[8,9] Functional and morphological changes in the arterial wall, indicative of the early stages of atherosclerosis, have been observed in children with FH, even before adolescence.[10–13] Therefore, diagnosis in the first decade of life and appropriate treatment of FH in children is essential. Strategies are thus required to increase awareness of FH and to emphasize the importance of treating a disorder in childhood that is unlikely to present cardiovascular symptoms until later in life.

In the decade since the 2015 EAS consensus statement on FH in children,[4] our knowledge of the pathogenesis of FH has increased markedly, and clinicians now have access to a wider range of lipid-lowering therapies (LLTs). In this current EAS consensus statement, we present revised diagnostic criteria, the current screening options, proposals for lower LDL-C treatment goals, and revised treatment algorithms, with a focus on HeFH. In addition, we provide updates on the information presented in the 2023 EAS consensus statement on HoFH,[5] in particular on the LLTs that are approved for children with HoFH. We also outline how to manage FH in children and adolescents in the context of the newly available treatments. Finally, we discuss how to manage the transition to adult care and implementation strategies. Box 1 summarizes the updated information included in this current EAS consensus statement.

Diagnosis of familial hypercholesterolaemia

Diagnostic criteria and tools

The 2015 EAS consensus statement on FH in children proposed that any child with an LDL-C ≥5.0 mmol/L (190 mg/dL) measured twice after dietary intervention has a high probability of genetically based FH; this threshold was lowered to ≥4.0 mmol/L (155 mg/dL) if there was a family history of premature ASCVD and/or high baseline cholesterol in one parent, and further lowered to LDL-C ≥3.5 mmol/L (135 mg/dL) if one parent had a genetic diagnosis of FH.[4] However, a recent study showed that although high specificity is achieved when using these criteria, early diagnosis in almost half of children with an FH-causing variant would have been missed.[14]

To improve diagnostic sensitivity, here we propose a modification of these criteria, as shown in *Figure 1* for the different entry points for a child suspected to have FH. A child should be referred to a healthcare professional with experience in managing children with FH for further testing according to the following scenarios: When the child has (1) a parent with a known pathogenic FH variant regardless of the LDL-C value of the child (cascade screening); (2a) LDL-C >4.5 mmol/L (175 mg/dL) identified either from inclusion in a universal FH

Box 1 What is new in this European Atherosclerosis Society consensus statement on children with familial hypercholesterolaemia?

- Updated diagnostic criteria to improve diagnostic sensitivity.
- Proposed lower age to start treatment.
- Proposed lower LDL-C treatment goals, made possible by the availability of new LLTs.
- Emphasis on the importance of reducing cumulative LDL-C exposure.
- Updated treatment algorithms and the latest evidence supporting the use of novel LLTs.
- Proposals to facilitate improved transition to adult care and implementation strategies.

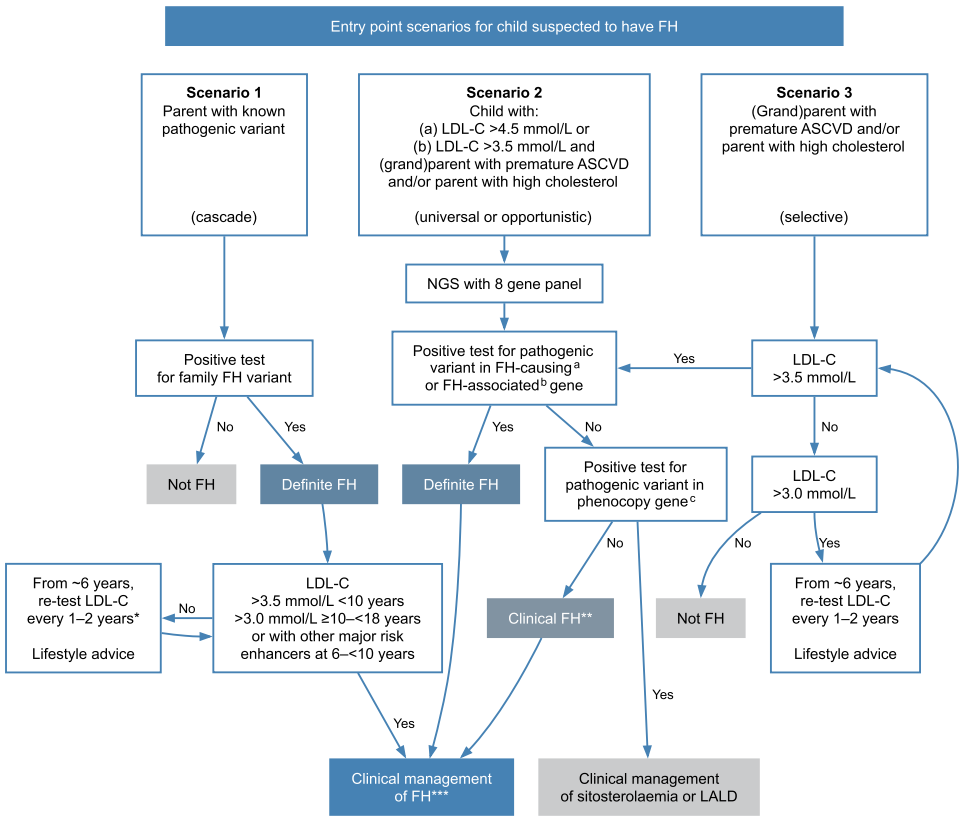

Figure 1 Entry points for diagnosis and clinical management of children suspected to have familial hypercholesterolaemia. Premature atherosclerotic cardiovascular disease is defined as a coronary event before 55 years in men and 60 years in women. [a]Monogenic or biallelic/digenic *LDLR*, *APOB*, and *PCSK9* variants. [b]Variant p.(Leu167del) in *APOE* and biallelic *LDLRAP1* variants. [c]Biallelic/digenic *ABCG5 and ABCG8* and biallelic *LIPA* variants. Definite familial hypercholesterolaemia is defined as genetic confirmation of at least one familial hypercholesterolaemia–causing variant. *Rule out primary hypocholesterolaemia. **Consider elevated lipoprotein(a) and (other) secondary causes. ***Comprises lifestyle advice from diagnosis and starting lipid-lowering therapy between 6 and <10 years for heterozygous familial hypercholesterolaemia and from 6 months for homozygous familial hypercholesterolaemia. To convert LDL cholesterol from mmol/L to mg/dL, multiply the mmol/L value by 38.67. ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolaemia; LALD, lysosomal acid lipase deficiency; LDL-C, LDL cholesterol; NGS, next-generation sequencing

screening programme or an unrelated (opportunistic) blood test; (2b) LDL-C >3.5 mmol/L (135 mg/dL) identified by universal or opportunistic screening and a (grand)parent known to have premature ASCVD (defined as a coronary event before 55 years in men and 60 years in women) and/or a parent with elevated total cholesterol or LDL-C; or (3) a (grand)parent with premature ASCVD and/or a parent with high cholesterol (selective screening). Second-degree relatives (e.g. grandparents) are included because first-degree relatives (i.e. parents and siblings) of children with suspected FH are usually too young to have developed premature ASCVD.

In Scenario 1 in *Figure 1*, a child with a positive test for an FH-causing variant (and therefore 'definite FH') should be referred to clinical management of FH if LDL-C is >3.5 mmol/L (135 mg/dL) when aged below 10 years or >3.0 mmol/L (115 mg/dL) when aged 10 years and above or if other major risk enhancers are present (see footnote in *Table 1*). If a parent has a genetic diagnosis but the child does not undergo genetic testing (because it is not available or the parents do not consent), then the child should be considered to have 'clinical FH' if LDL-C is >3.0 mmol/L (115 mg/dL) and referred to clinical management of FH according to the criteria for definite FH above. This LDL-C threshold is based on data from mutation-positive and mutation-negative children <15 years identified from cascade testing from a mutation-positive parent from the Netherlands, Denmark, and Norway.[17] In the other scenarios, all children with LDL-C >4.5 mmol/L (Scenario 2a) or LDL-C >3.5 mmol/L (Scenarios 2b and 3) should be referred to clinical management of FH regardless of the result from genetic testing; however, genetic testing for FH should be considered in all cases (see Box 2). *Table 1* presents a comparison of the modified criteria with those presented in the 2015 EAS consensus statement.[4]

In children with a clinical diagnosis of FH but no known FH-causing variant, one in three have high concentrations of lipoprotein(a) [Lp(a)].[18,19] We therefore propose that a test for Lp(a) is performed in all children with suspected FH at the same time as paediatric screening (but not before 5 years of age). Genetic association and Mendelian randomization studies support a causal relationship between elevated Lp(a) and risk of ASCVD.[20] We therefore also encourage cascade testing of

Table 1 Comparison of the diagnostic criteria and LDL cholesterol treatment goals proposed in the current consensus and in the 2015 European Atherosclerosis Society consensus statement[4] for children with familial hypercholesterolaemia

2015	2026
Diagnostic criteria	
Highly probable FH	Clinical FH
• LDL-C ≥5.0 mmol/L (190 mg/dL) measured twice after dietary intervention	• LDL-C >4.5 mmol/L (175 mg/dL)
• LDL-C ≥4.0 mmol/L (155 mg/dL) if family history of premature ASCVD and/or high baseline cholesterol in one parent	• LDL-C >3.5 mmol/L (135 mg/dL) if family history of premature ASCVD and/or high baseline cholesterol in one parent
• LDL-C ≥3.5 mmol/L (135 mg/dL) if one parent has a genetic diagnosis of FH	• LDL-C >3.0 mmol/L (115 mg/dL) if one parent has a genetic diagnosis of FH
Definite FH	Definite FH
• If a child has a genetic diagnosis of FH	• If a child has a genetic diagnosis of FH
LDL-C treatment goals	
Start pharmacological treatment at 8 years	Start pharmacological treatment ideally at 6 years
Reduce LDL-C concentration	Reduce LDL-C concentration
• by 50% from baseline at 8–10 years	• to ≤3.5 mmol/L (135 mg/dL) at 6–<10 years
• to 3.5 mmol/L (135 mg/dL) at >10–<18 years	• to ≤3.0 mmol/L (115 mg/dL) at 10–<18 years or with other major risk enhancers[a] at 6–<10 years

ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolaemia; LDL-C, LDL cholesterol.
[a]Major risk enhancers: lipoprotein(a) ≥250 nmol/L (120 mg/dL)—a high concentration associated with a doubled risk of ASCVD in the adult population[15,16]; diabetes; hypertension; chronic inflammatory diseases; chronic kidney disease; Kawasaki disease; human immunodeficiency virus; cancer survivor (discussed in Clinical Management of Heterozygous Familial Hypercholesterolaemia).

Box 2 Advantages and disadvantages of genetic testing for familial hypercholesterolaemia

Advantages of a confirmed genetic diagnosis of FH

Confirms definitive FH and establishes the FH diagnosis unequivocally.
Supports the clinician when deciding which LLT to use.
Helps the parents decide whether and when their child should start LLT.[36]
Enables access to special therapies.
Prompts testing of parents and siblings who are at 50% risk of carrying the FH-causing variant.
Encourages cascade testing in the extended family.
Creates awareness that FH is passed on to the next generation.
Encourages adherence to LLT.[37]
Encourages adherence to a healthy lifestyle[38] and not smoking/vaping.
Creates awareness that atherosclerosis starts at birth.[39]

Disadvantages

Potential confusion of diagnosis if a variant of uncertain significance is found.
Life and health insurance issues in some countries.
Potential stigmatization.
Psychological distress for individuals and their family.

the parents and grandparents of a child found to have elevated Lp(a) [>105 nmol/L (50 mg/dL)][15] to identify those at increased cardiovascular risk and who would benefit from immediate treatment.

Tools to improve the accuracy of diagnosing FH have been developed in adults and include the Simon Broome,[21] Dutch Lipid Clinic Network (DLCN),[22] and Make Early Diagnoses to Prevent Early Deaths[23] criteria. However, these scoring systems fail to sufficiently identify children with FH.[14] A new scoring system, termed the Familial Hypercholesterolaemia Paediatric Diagnostic Score (FH-PeDS), has recently been designed specifically in children using data from a universal screening cohort from Slovenia and validated using data from the Portuguese FH study.[24] This score has been shown to diagnose children with genetically confirmed FH more accurately compared with the DLCN or Simon Broome criteria (for details, see Supplementary data online, *Table S1*)[24] and could be a useful tool in the future to stratify children with suspected FH for genetic testing. A machine-learning version of FH-PeDS is also available as an online tool.[24] However, validation of FH-PeDS and the machine-learning version is required in multiple other cohorts that include genetic testing[25] and individuals of different genetic ancestry.

Genetic testing

We propose that any child with suspected FH as shown in *Figure 1* should be offered genetic testing to confirm his/her

diagnosis.[4,26] The FH-causing genes are *LDLR*, *APOB*, and *PCSK9*. Some laboratories still use Sanger sequencing and Multiplex Ligation-dependent Probe Amplification approaches to identify FH gene variants, mainly in *LDLR*, or Sanger sequencing alone to study *PCSK9* and exon 26 and 29 of *APOB*. Today, however, with the use of next-generation sequencing (NGS), it is possible to sequence completely *LDLR*, *APOB*, and *PCSK9* and to detect large rearrangements in one run. As proposed by an expert panel on genetic testing for FH,[27] the genetic test for FH should ideally be performed by a NGS panel of eight genes: the three FH-causing genes noted above, the less common FH-associated genes *APOE* and *LDLRAP1*, and the three phenocopy genes (*ABCG5*, *ABCG8*, and *LIPA*). Rigorous criteria have been developed to guide laboratories in *LDLR* variant classification,[28] which are universally accepted and should be used by all labs performing genetic testing for FH. The only known FH-causing variant in *APOE* is p.Leu167del,[29] and biallelic pathogenic variants in *LDLRAP1* alleles cause autosomal recessive hypercholesterolaemia. Biallelic pathogenic variants in *ABCG5* and *ABCG8* cause sitosterolaemia, a recessive disease, which results in accumulation of plant sterols and their corresponding saturated stanols in the body. Clinical features include xanthomas, premature atherosclerosis, and thrombocytopenia.[30] Biallelic pathogenic variants in *LIPA* cause lysosomal acid lipase deficiency (LALD), which is also recessive. Clinical features include liver disease (ranging from steatosis to cirrhosis) and severe dyslipidaemia.[31]

If a child has low LDL-C despite a pathogenic FH variant, consider testing for primary hypocholesterolaemia, which is caused by pathogenic variants in genes for lipoprotein assembly or secretion [*MTTP* and *SAR1B* (both recessive), and *APOB* (dominant)] or for enhanced lipoprotein catabolism [*ANGPTL3* and *PCSK9* loss of function (both dominant)].[32–34] These variants can mask FH by 'normalizing' LDL-C concentrations in an individual with an FH-causing variant, and the variants that modify lipoprotein assembly and secretion can cause malabsorption and steatosis despite reducing cardiovascular risk.[31] Such masking of FH can preclude the detection of FH in family members who lack the cholesterol-lowering variant and therefore have elevated cardiovascular risk.

When the family FH variant is known (from an index family member who previously underwent a genetic test), a full genetic study is not required, and a much cheaper and quicker confirmatory test for the family variant can be carried out. This can also be performed using cord blood at birth or a saliva or buccal swab sample, which is easier to obtain than a blood sample from a young child.

Clear advantages and potential disadvantages of genetic testing are listed in Box 2.[40] A genetic diagnosis gives a clear rationale to parents when considering whether and when their child should start LLT. Where the child is the index case for the family, first-degree relatives, who are at 50% risk of also carrying the FH-causing variant, are then encouraged to be tested. The identification of their FH parent and their subsequent treatment with LLT is of considerable benefit to the child who then has a much greater chance of growing up with two healthy ASCVD-free parents. Several studies have shown that the death of a parent during childhood is associated with lower achievement in school, and poorer mental health.[41,42] One possible disadvantage of genetic testing is that the parents might feel guilt for passing on the genetic variant to their child. However, genetic counsellors are skilled in explaining that inheritance of the FH-causing variant is random and that their identified child can now be considered for early preventative treatment to lower their future cardiovascular risk.

In the setting of a negative genetic test for FH and high LDL-C, polygenic risk scores (PRS) based on 12 common LDL-C-raising alleles have been developed[43] and validated[44] to identify individuals with a polygenic cause for their high LDL-C. The finding of a high score (e.g. above the 80th percentile) provides an explanation for severe hypercholesterolaemia in the absence of an FH-causing variant, which has been found to be useful for clinicians and patients.[45] In adults, these PRS have been shown to considerably increase the diagnostic rate (i.e. the proportion of individuals for whom a genetic cause of their high cholesterol can be given).[45] However, evidence to demonstrate the benefit of PRS in children is not yet available.

Genetic counselling

Genetic testing should be preceded by genetic counselling. Diagnostic genetic testing of a child or adolescent with suspected FH should ideally be requested by a clinician with skills in counselling, genetics, and care of families with FH. Cascade genetic testing of children and adolescents should be based on shared decision-making and fully informed agreement given by the custodial parent or guardian, with results communicated in a timely manner.[46] Informed consent by the parent or guardian (or the child themselves depending on their age and the legal age of consent in each particular country) and notification of genetic results should account for literacy and level of comprehension, sociocultural and psychological background, with full discussion of the possible impact of either a positive or negative result.

Counselling should explicitly communicate the well-established benefits of early diagnosis and timely LLT in FH so that families can make fully informed decisions about cascade testing and appreciate its role in preventing avoidable ASCVD in relatives.

While all children and their families with high LDL-C concentrations and a known pathogenic variant for FH would benefit from genetic counselling, it is especially useful for the children who instead have (i) hypercholesterolaemia with a variant of uncertain significance or a benign variant, (ii) no detectable pathogenic variant but likely to have a polygenic cause of their hypercholesterolaemia, or (iii) cholesterol concentrations within the normal range but in whom a pathogenic variant has been detected.[27] Pre-conception genetic counselling is of major importance if both parents have a known pathogenic FH variant.

How to increase the detection rate of familial hypercholesterolaemia in children

It is imperative to increase the detection rate of FH and to diagnose at younger ages to minimize the lifelong exposure to high LDL-C concentrations and reduce the risk of premature ASCVD in the affected individuals (both children and their family members). We therefore encourage every country to establish a (population-based) paediatric FH screening programme, which is in full accordance with the European Commission's recently announced cardiovascular health plan, the Safe Hearts Plan.[47] The optimal programme for each country (including the specific

age for screening) depends on the healthcare resources, the insurance system, and other country-specific conditions such as geography, infrastructure, population density, social background, and cultural issues.

The ideal age for diagnosis of HoFH is at birth because management should start as early as possible to reduce the particularly high cumulative LDL-C burden. It is less necessary to diagnose HeFH at birth because management does not need to start as early as for HoFH. However, we propose that a diagnosis is made in the first decade of life because (i) children are more likely to adopt and maintain a healthy lifestyle (including eating a healthy diet, exercising, and not starting to smoke or vape) and adhere to drug treatment if encouraged to do so from an early age[48–50]; (ii) it will lead, through cascade testing of first-degree relatives, to earlier identification of FH in relatives who are unaware of their cardiovascular risk; (iii) screening can be combined with other routine health visits; and (iv) when using cholesterol as the initial measure to diagnose FH, screening performance is optimal between the ages 1 and 9 years, and considerably lower in adolescents and young adults.[51]

Paediatric familial hypercholesterolaemia screening programmes

Paediatric FH screening programmes use one or more of the following strategies: cascade screening, where relatives of an individual diagnosed with a genetically confirmed FH variant (index case) undergo genetic testing for this specific variant; universal screening, where all children at a pre-defined age undergo blood lipid screening (and preferably subsequent genetic testing in those with high LDL-C), regardless of other risk factors; opportunistic testing, where tests are offered to children and adolescents who present to healthcare for other reasons (e.g. they have diabetes); and selective screening, where high-risk groups (e.g. with parents or grandparents with premature ASCVD) are targeted for testing.[8,52–55]

The Netherlands, which was the first country to launch a national screening programme for FH, uses cascade screening.[52] This approach proved to be both cost-effective from a healthcare perspective and cost-saving from a societal perspective, with a more than 8 euro return on every euro invested.[56] Similar programmes have been established in other countries, including Norway and the Czech Republic,[55,57] and its success is recognized worldwide. In Slovenia, the first country to establish a universal screening programme for FH, total cholesterol is measured in all children at the age of 5–6 years followed by genetic testing in those considered at risk and cascade testing of parents and siblings of a child diagnosed with FH.[58,59] Universal screening has been introduced elsewhere in Europe (e.g. in Bavaria, Germany, reported in the VRONI study[60]). Although universal screening has been shown to be cost-effective in some countries (e.g. in the UK[61] and Argentina[62]), a recent study found that universal screening was not cost-effective in the USA,[63] suggesting that cost-effectiveness is influenced by country-specific healthcare systems. Opportunistic testing combined with cascade screening has been introduced in Lithuania.[55] Selective screening combined with cascade screening has been used in Italy[64,65] and Portugal.[55,66] In the UK, approaches for universal screening at the age of 12 months have been trialled,[67] but are not yet approved for national roll-out; cascade testing of children from adult probands is, however, in use.[68]

Barriers and facilitators of screening for FH have been described in detail recently.[40,69] In 2022, the FH European Community published a call for action in the Prague Declaration to encourage all European countries to adopt FH paediatric screening as part of European and national strategies to prevent premature ASCVD and to promote cardiovascular health.[70] International networks to promote models for FH diagnosis, screening, and treatment across different countries have been compared.[71]

Newborn screening

Newborn screening programmes to detect rare but treatable diseases are established in most countries and achieve near-universal coverage at birth (≥99.9%).[72] Inclusion of FH in a newborn screening programme could offer a unique opportunity for early detection of FH, and would be particularly useful for children with HoFH, allowing them to be diagnosed and treated as early as possible. Identifying a neonate with FH could also lead to the detection, through cascade testing, of FH in a parent and other family members in whom treatment can be started immediately. However, there are several challenges that need to be overcome before this approach can be recommended.

Ongoing studies are investigating which clinical variable would most accurately predict FH in newborns using venous cord blood and dried blood spots.[73–76] In the first year of life, total cholesterol and LDL-C concentrations increase and show high variability[77–79] (see Supplementary data online, *Figure S1*). Although LDL-C concentrations above the 80th percentile at birth are associated with significantly higher LDL-C concentrations at 14–16 months,[79] they have not yet proven reliable enough to be used for the diagnosis of FH in newborns.[80]

Pilot studies have shown that genetic testing can detect FH in newborns.[81] However, genetic testing will also identify babies who have variants of uncertain significance or variants with mild phenotypes, leading to complexities in treatment recommendations and unnecessary worry in some cases. Both underdiagnosis and overdiagnosis are potential issues, and robust systems would need to be established for timely recall and confirmatory diagnostics. More reliable tools are needed to promote newborn screening in the future.

Clinical management of heterozygous familial hypercholesterolaemia

Rationale for lowering LDL cholesterol treatment goals in children with heterozygous familial hypercholesterolaemia

Key recommendations from the 2015 EAS consensus statement on the management of HeFH in children were to start pharmacological treatment at 8 years of age and to reduce LDL-C by 50% from baseline at 8–10 years and to 3.5 mmol/L (135 mg/dL) at >10 years.[4] However, it is increasingly recognized that treatment of FH should focus on reducing the cumulative burden of LDL-C, a strong predictor of ASCVD,[82,83] supporting earlier and more intense treatment to prevent the development of atherosclerosis in childhood. Carotid intima–media thickness

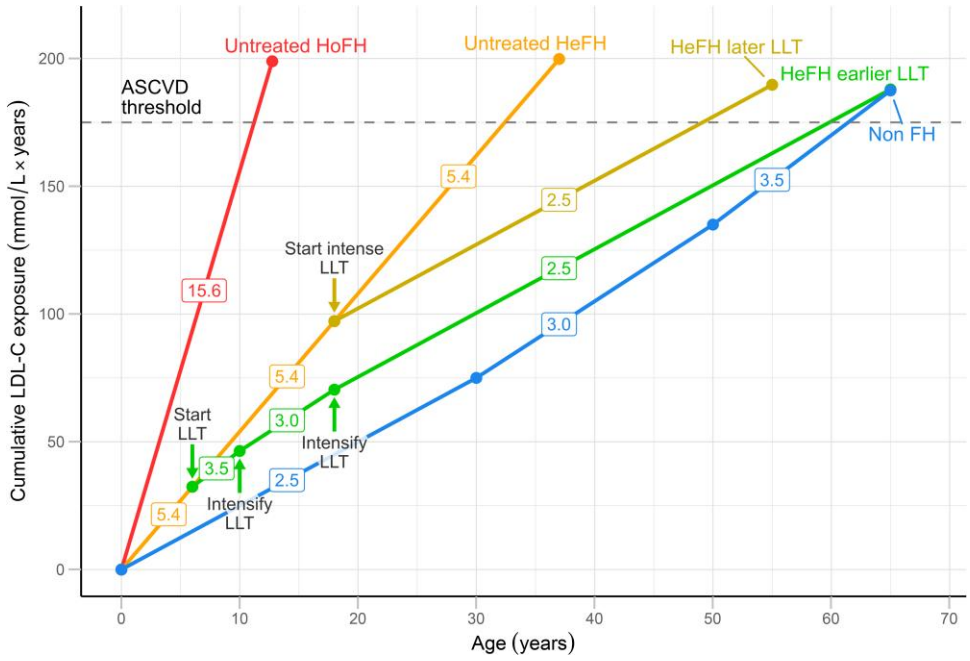

Figure 2 Cumulative LDL cholesterol exposure in individuals with or without familial hypercholesterolaemia and the impact of starting lipid-lowering therapy at 6 years or 18 years in heterozygous familial hypercholesterolaemia. Values in boxes are the mean LDL cholesterol concentration (in mmol/L) in the time period between the dots. To convert LDL cholesterol from mmol/L to mg/dL, multiply the mmol/L value by 38.67. The threshold for doubling the risk of atherosclerotic cardiovascular disease is 175 mmol/L × years (6800 mg/dL × years). Data are from Starr *et al.*,[17] Vuorio *et al.*,[93] Reijman *et al.*,[35,94] Tromp *et al.*,[95] Zhang *et al.*,[83] and Ibrahim *et al.*[82] ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; LDL-C, LDL cholesterol; LLT, lipid-lowering therapy

(cIMT), an indicator of early arterial injury,[84] has been shown to be greater in children with FH than their unaffected siblings,[11] with evidence of significant differences before the age of 10 years.[12] Numerous studies have shown that LLTs are safe and effective at reducing LDL-C concentrations in children with FH and that appropriate treatment at a young age can markedly reduce cIMT.[85–88] Thus, regression of atherosclerotic lesions is possible if treatment starts early.

New classes of LLTs are now available and several LLTs have been approved from the age of 6 years, allowing lower LDL-C treatment goals to be achieved and treatment to start earlier if considered appropriate. In this current EAS consensus statement, we propose starting pharmacological treatment of HeFH in the first decade of life, ideally from 6 years (but with the precise age decided by the treating physician in discussion with the family). We also propose an LDL-C treatment goal of ≤3.5 mmol/L (135 mg/dL) in children aged 6 to <10 years and a lower treatment goal of ≤3.0 mmol/L (115 mg/dL) in children from 10 years or from 6 years if other major risk enhancers are present (see *Table 1* and below). This lower treatment goal was selected based on a recent study showing that an increase in plaque volume over a 6-month period in children with HoFH can be prevented if the time-weighted cumulative LDL-C exposure is reduced to ≤3.0 mmol/L (115 mg/dL) per year.[89] However, shared decision-making is required to ensure that the optimal treatment strategy is chosen for the individual child,[90,91] with an emphasis on starting treatment of any intensity before puberty and ensuring adherence to treatment. A comparison of these modified LDL-C treatment goals with those presented in the 2015 EAS consensus statement is presented in *Table 1*.

Why is it important to focus on cumulative LDL cholesterol exposure?

Although cumulative LDL-C exposure drives cardiovascular risk in individuals with FH, current treatment guidelines are based on LDL-C concentrations at the time of diagnosis.[82,92] The limitation of these guidelines is exemplified in *Figure 2*. The risk of symptomatic ASCVD doubles when the cumulative LDL-C burden crosses a threshold of 175 mmol/L (6800 mg/dL) × years.[83] In individuals without FH, this threshold is crossed on average after the age of 60 years. This threshold, however, is reached before the age of 33 years in an individual with untreated HeFH and by 12 years in a child with untreated HoFH [assuming mean LDL-C concentrations of 5.4 mmol/L (210 mg/dL) and 15.6 mmol/L (600 mg/dL), respectively].[35,94,95] Treatment with statins (or other LLTs) will change this trajectory, and the earlier treatment is started the better. Thus, for an individual with HeFH, starting moderate- to high-intensity statin at 18 years will increase the age at which the threshold is reached to almost 50 years, but starting low- to moderate-intensity statin at 6 years will increase the age at which the threshold is reached to almost 60 years (i.e. another decade of symptom-free survival and close to those without FH).

It is important to note that the focus should not only be on starting treatment early but also on intensifying sufficiently and adhering to treatment to reduce the cumulative LDL-C exposure. A recent study in individuals with HeFH highlighted this point by showing that the prevalence or volume of coronary plaque did not differ between groups divided by age of treatment start (mean age at start of LLT: early, 15 ± 4 years; late, 37 ± 4 years).[82] However, the risk of ASCVD was markedly lower in those with below-median cumulative LDL-C exposure [175 mmol/L (6800 mg/dL) × years] than in those with above-median cumulative LDL-C exposure.[82]

Other major risk enhancers that may trigger lower LDL cholesterol treatment goals

The 2015 EAS consensus statement on the management of HeFH in children emphasized treatment and control of additional risk factors but did not propose altering LDL-C targets.[4,92] However, epidemiologic studies indicate that the presence of conventional risk factors increases risk equivalent to an increase of LDL-C of ∼0.75 mmol/L (30 mg/dL).[96] Here, we propose lowering the LDL-C treatment goal by 0.5 mmol/L in children with FH between 6 and <10 years if they have other major risk enhancers (see *Table 1* and discussed below). Only risk factors that would dramatically increase risk and cannot be corrected by lifestyle have been selected as major risk enhancers.

Lipoprotein(a) concentrations are primarily genetically determined, and thus elevated concentrations are potentially harmful from childhood onwards.[97] Although pharmacological agents designed to lower Lp(a) are being evaluated in clinical trials in adults,[98] paediatric studies are not anticipated in the near future. Atherosclerotic cardiovascular disease risk rises continuously with increasing Lp(a)[99] and a clinically relevant Lp(a) concentration is hard to define. We propose using a high cut-off, ≥250 nmol/L (120 mg/dL),[15,16] as a trigger to lower the LDL-C treatment goal in children with HeFH from 6 to <10 years of age to the treatment goal of those ≥10 years of age, as there are currently no other ways to correct for this increased risk related to elevated Lp(a).

If a child with HeFH has diabetes or hypertension, known cardiovascular risk factors in FH,[100] we propose lowering the LDL-C treatment goal from 6 years. This is also the case in the rare instances of children with HeFH and diseases such as chronic inflammatory diseases (e.g. rheumatoid arthritis, lupus, and inflammatory bowel disease), chronic kidney disease, Kawasaki disease, HIV, and cancer survivorship, all of which are associated with an increased risk of ASCVD.[101]

Smoking and obesity are also known to increase the risk of ASCVD in FH.[100] A more recently recognized lifestyle risk factor is the use of e-cigarettes (vaping),[102,103] which is increasing in (young) children. Children with HeFH should be discouraged from starting to smoke or vape by discussing the risk at first visit. If a child with HeFH already smokes or vapes or has developed obesity, extra lifestyle advice is required rather than striving for lower treatment goals.

Can cardiovascular imaging support risk stratification in children with heterozygous familial hypercholesterolaemia?

Imaging to detect subclinical atherosclerosis is known to add information about future cardiovascular risk in adults with FH,[104,105] but it is not routinely used in the clinic in children with HeFH. Carotid intima–media thickness is used in research settings to monitor response in a treatment group.[87,106] However, we do not propose using cIMT to monitor atherosclerosis in clinical practice in individual children with HeFH because of the following limitations: (i) many centres have little experience of cIMT, (ii) normal values of cIMT are not known in children, and (iii) across and within centres, there are variations in measurement protocols, the location of the measurement (common carotid artery, internal carotid artery, bulb, or a combination of these), the type of equipment used, the individuals performing the ultrasound, and variability in interpretation by different readers.

Subclinical atherosclerosis in adults can be assessed using coronary artery calcium (CAC) scoring, determined by computed tomography (CT), and coronary CT angiography (CCTA), which can assess both calcified and non-calcified plaques. However, calcium may not be present despite significant atherosclerosis,[4] and a recent study showed that CCTA-detected atherosclerosis was not present in children with severe HeFH.[107] Therefore, given the increased lifetime risk of exposure to radiation, we do not advise using CAC scoring or CCTA in children with HeFH.

Lifestyle measures

Lifestyle measures should be the first step in the management of a child diagnosed with HeFH,[108] although a healthy lifestyle alone is generally not sufficient to achieve LDL-C treatment goals. In cases of early diagnosis, some children are too young to start pharmacological treatment but not too young to be introduced to a healthy lifestyle. Lifestyle measures, implemented in parallel with or followed by timely pharmacological treatment, give the child and their parents a feeling of being in control. In the current era with genetic confirmation of a diagnosis, we can identify children carrying a mild FH-causing variant, with LDL-C levels close to treatment goal, who might benefit from lifestyle measures alone.

Regular physical activity should be highly encouraged. Smoking and vaping should be strongly discouraged. Obesity should be avoided and other cardiovascular risk factors (e.g. chronic inflammatory diseases and chronic kidney disease) should be treated. Nutritional management goals for children with HeFH are to reduce LDL-C concentrations and global cardiovascular risk while maintaining optimal growth and neurocognitive development.[101] We propose implementing nutritional advice for the entire family and promoting a healthy diet rather than focusing solely on food categories.[109,110]

Dietary components that should be limited or promoted in children with FH are listed in *Table 2*. A cautious low-fat diet has shown to be safe in children aged 8–10 years with elevated LDL-C.[121] In the randomized Special Turku Coronary Risk Factor Intervention Project, a low-fat diet was shown to be safe in children from 7 months of age.[126] Although plant stanols and sterols lower LDL-C,[127–129] no intervention studies showing an effect of these dietary supplements on ASCVD have been performed and therefore no clear recommendation can be made.[15,130]

Outpatient dietary counselling in children with FH has been shown to increase the consumption of products with a more favourable fatty acid and cholesterol composition[131] and improve

Table 2 Dietary components that should be limited or promoted in children with familial hypercholesterolaemia

Limit	Goals
Dietary cholesterol[111–114]	200–300 mg/day
Saturated and trans fatty acids[113,115,116]: processed foods, animal fat, red meat, whole-fat dairy products, pastries, palm oil, and coconut oil	<7% DEI
Added simple sugars, including fructose[117]	<10% DEI
Promote	**Goals**
Balanced diet	Carbohydrate 45%–60%, fat 25%–35%, protein 12%–15% of DEI adapted to age[118]
Structured complete and regular meals; stress importance of breakfast[119,120]	
Low-fat dairy foods[121]	
Long-chain PUFA[122]: oily fish twice a week, pulses, nuts, seeds, tofu, vegetable oils (rapeseed, soybean, corn, sunflower)	Promote n-3 PUFA; total PUFA 5%–10% DEI
Monounsaturated fatty acids[123,124]: vegetable oils (rapeseed, olive, canola, peanut, sesame), avocados, nuts, and seeds	10%–15% DEI
Fibre[125]: fresh fruits and vegetables, wholemeal bread, cereals, legumes	25–40 g/day, 7%–13% soluble fibres
Intake of lean and fatty fish, shellfish, lean chicken and turkey (white meat, skinless), limited lean red meat ('>93% lean', fat trimmed, free range)[123]	

DEI, daily energy intake; PUFAs, polyunsaturated fatty acids.

the lipid profile of children.[132] Saturated fat should be substituted with polyunsaturated fat.[133] Risks of nutritional interventions in children with FH to be aware of and avoid include (i) insufficient intake of energy, essential fatty acids, and vitamin E[134] and (ii) the development of eating disorders.

Pharmacological treatment

Statin treatment initiated in childhood has been shown to reduce the risk of ASCVD in individuals with FH to that of the general healthy population.[87] As noted earlier, treatment should not only focus on 'the lower the better' but also 'the earlier and the longer the better'. With the availability of new therapies, our proposed LDL-C targets can today nearly always be achieved in children with HeFH using a maximum of two drugs. To promote adherence to LLT, three drugs should be avoided as much as possible and only given in the rare cases when the treatment goal is not achieved otherwise.

Table 3 lists the LLTs currently approved in children, the age from which they are approved and the extent of LDL-C reduction to be expected with each therapy. A treatment algorithm for children with HeFH is presented in *Figure 3*.

Statins remain the first line of LLT in children with FH. Statin treatment is well tolerated among children, with few reports of side effects.[4,156–164] High-potency statins such as rosuvastatin and atorvastatin should be preferentially considered for therapy initiation. The cumulative incidence of cardiovascular events and death from cardiovascular causes before the age of 40 has been shown to be lower amongst children with HeFH treated early with statins than amongst their parents with FH for whom statins were available much later in life.[87] The dose and/or intensity of statin given should be increased according to the LDL-C concentration, residual LDL receptor (LDLR) activity and age-dependent treatment goal. Lipid profile, creatine kinase, and aminotransferases (alanine transaminase and aspartate transaminase) should be measured 8–12 weeks after increasing the dose or introducing a (new) statin and annually thereafter.

If LDL-C targets are not achieved with statin monotherapy but are close to goal [i.e. <4.0 mmol/L (155 mg/dL)], ezetimibe can be added.[146] In the rare case of statin intolerance,[166] consider reducing the statin dosage or switching to another statin.[87,167,168] If the child remains intolerant to statins, consider replacing statins with ezetimibe. Ezetimibe monotherapy has been shown to reduce LDL-C concentrations in children between 6 and 10 years (by 27% after 12 weeks of treatment) and is very well tolerated.[145]

If LDL-C concentrations on statin monotherapy are not close to goal [i.e. ≥4.0 mmol/L (155 mg/dL) measured at least twice], consider a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor instead of ezetimibe. The monoclonal antibody PCSK9 inhibitors evolocumab[148,149] and alirocumab[147] are approved for children with HeFH from 10 years and 8 years, respectively, by both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA); evolocumab is also approved for children with HoFH from 10 years.[150] The FDA recently approved inclisiran, a small interfering RNA PCSK9 inhibitor, for adolescents from 12 years with either (i) HeFH[151] or (ii) HoFH and some residual LDLR function (i.e. excluding those with two *LDLR* null variants).[152] It is currently being tested in children with HeFH from 6 years of age (NCT06597019) and in those with HoFH from 2 years of age (NCT06597006). Lerodalcibep, a small binding protein inhibitor of PCSK9, has been tested in children from 10 years and adults

Table 3 Approved lipid-lowering therapies for children with familial hypercholesterolaemia[135]

Lipid-lowering therapy	Age approved/tested	Approved (or tested) dose range and route of administration	LDL-C reduction[a]	Key publications
Statins (β-hydroxy β-methylglutaryl-CoA reductase inhibitors)				
Pitavastatin	≥6 years	1–4 mg (PO)	23%–39% (placebo adjusted)	Braamskamp *et al.*, 2015[136]
Rosuvastatin	≥6 years	5–20 mg (PO)	35%–45%	Braamskamp *et al.*, 2015[137] Stein *et al.*, 2017[138] (HoFH)
Pravastatin	≥8 years	20–40 mg (PO)	24% (placebo adjusted)	Wiegman *et al.*, 2004[85]
Atorvastatin	≥10 years	10–20 mg (PO)	40% (placebo adjusted)	McCrindle *et al.*, 2003[139] Raal *et al.*, 2000[140] (HoFH)
Fluvastatin	≥10 years	20–80 mg (PO)	34%	van der Graaf *et al.*, 2006[141]
Lovastatin	≥10 years	10–40 mg (PO)	17%–27% (placebo adjusted)	Stein *et al.*, 1999 (in boys)[142] Clauss *et al.*, 2005 (in girls)[143]
Simvastatin	≥10 years	10–40 mg (PO)	31%–40% (placebo adjusted)	de Jongh *et al.*, 2002[144]
Inhibitor of intestinal cholesterol absorption				
Ezetimibe	≥6 years EMA; ≥10 years FDA	10 mg (PO)	27% as monotherapy (placebo adjusted) 15% on top of simvastatin (placebo adjusted)	Kusters *et al.*, 2015[145] van der Graaf *et al.*, 2008[146]
PCSK9 inhibitors				
Alirocumab	≥8 years (not approved for HoFH <18 years)	If <50 kg: 150 mg (SC) q4w and 40 mg (SC) q2W If ≥50 kg: 300 mg (SC) q4w and 75 mg (SC) q2W	34%–43% on top of background LLT (placebo adjusted)	Santos *et al.*, 2024[147]
Evolocumab	≥10 years	420 mg (SC) q4w and 140 mg (SC) q2w	38% on top of background LLT (placebo adjusted)	Santos *et al.*, 2020[148] Santos *et al.*, 2022[149] Raal *et al.*, 2024[150] (HoFH)
Inclisiran	≥12 years[b]	300 mg (SC) at 0 and 90 days and then q6m	29%–34% on top of background LLT (placebo adjusted)	Wiegman *et al.*, 2026[151] Wiegman *et al.*, 2025[152] (HoFH)
Bile acid sequestrant				
Colesevelam	10 years (avoid in HeFH[c])	1.875–3.75 g (PO)	6%–12% (placebo adjusted)	Stein *et al.*, 2010[153]
Angiopoietin-like 3 inhibitor				
Evinacumab	≥6 months EMA; ≥1 year FDA (approved for HoFH)	15 mg/kg (IV) q4w	48%	Wiegman *et al.*, 2024[154] (HoFH)
Microsomal triglyceride transfer protein inhibitor				
Lomitapide	≥2 years[b] (approved for HoFH)	2–60 mg based on age, weight, and tolerability (PO)	53%	Masana *et al.*, 2024[155] (HoFH)

EMA, European Medicines Agency; FDA, Food and Drug Administration; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; IV, intravenous; LDL-C, LDL cholesterol; LLT, lipid-lowering therapy; PO, oral; SC, subcutaneous.
[a]LDL-C reductions are mean, median, or ranges, and placebo adjusted where indicated.
[b]Approved by the US FDA but not yet by the EMA.
[c]For HeFH, use only in situations when the newer LLTs are not available or tolerated.
To date, no data are available on the use of the adenosine triphosphate-citrate lyase inhibitor bempedoic acid in children or adolescents; however, a Phase 2 trial has recently been completed in children with HeFH aged 6–17 years (NCT05694260).

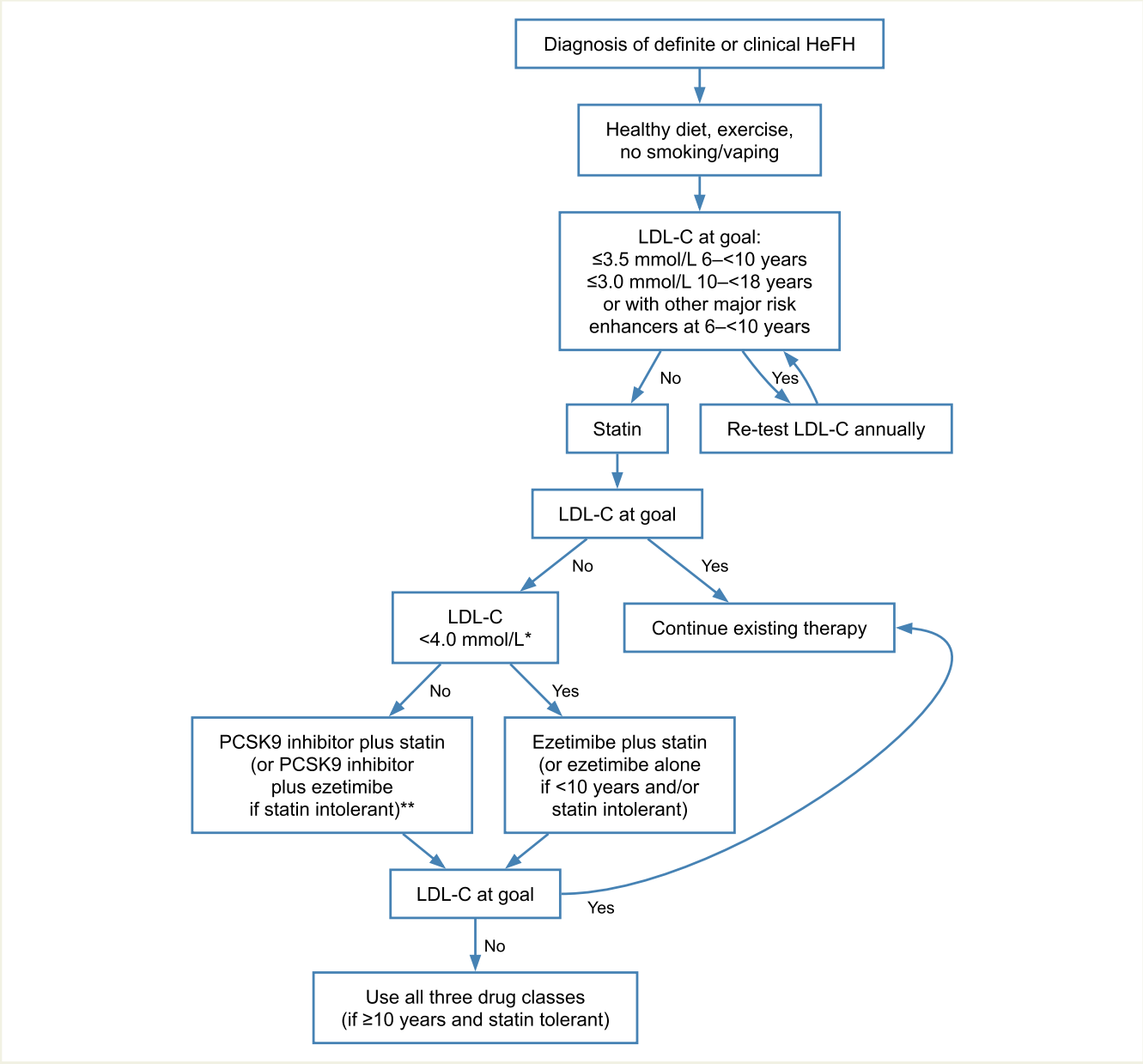

Figure 3 Treatment algorithm for children with heterozygous familial hypercholesterolaemia. *Ezetimibe reduces low LDL cholesterol concentrations in statin-treated children by ~15% (*Table 3*), which may be sufficient when LDL cholesterol <4.0 mmol/L. If greater reductions are needed to achieve the treatment goal, add PCSK9 inhibitors to statin treatment (or to ezetimibe if a child is statin intolerant). Only in rare cases should three drugs be used. **PCSK9 inhibitors are approved for children with familial hypercholesterolaemia from 8 years (alirocumab), 10 years (evolocumab), or 12 years (inclisiran; Food and Drug Administration approved). To convert LDL cholesterol from mmol/L to mg/dL, multiply the mmol/L value by 38.67

with HoFH[169] and is currently being evaluated in a phase 3 trial in children with HeFH from 6 years (NCT07102511). The oral PCSK9 inhibitor enlicitide is currently being tested in a Phase 2 trial in children with HeFH from 6 years of age (NCT07058077).

Of the bile acid sequestrants, colesevelam is the best tolerated.[153] However, given the availability of new LLTs, these agents should be considered only for specific situations where newer medications are unavailable or not tolerated. A Phase 2 trial for bempedoic acid, an oral inhibitor of cholesterol biosynthesis, has recently been completed in children with HeFH aged 6–17 years (NCT05694260).

In situations where LDL-C goals are not met despite the use of age-appropriate, guideline-recommended statin doses and when PCSK9 inhibitors are unavailable, consider using the highest tolerated doses of statins and ezetimibe, along with a cholesterol-lowering diet. Bile acid sequestrants could also be an option (as noted above), and supplementing with plant sterols/stanols may help reduce LDL-C in these situations, if available and affordable.

Does sex matter?

Although men with FH have a higher risk of developing premature ASCVD, women with FH have a higher LDL-C burden compared with men at a young age[170] owing to (i) higher LDL-C in childhood[6,170,171] and (ii) treatment discontinuation in relation to family planning, pregnancy and breastfeeding (on average, women with FH have 2.3 years pregnancy-related off-treatment time).[172] To compensate for the increased LDL-C burden in relation to family planning, pregnancy and breastfeeding, it is particularly important to start treatment as early in girls as in boys.

Safety

As observed in all paediatric FH clinical trials, the frequency of side effects in children is much lower than in adults. The most common reported side effects of statins are muscle symptoms. A meta-analysis of large-scale, randomized, double-blind trials in adults concluded that most of the muscle symptoms reported are probably not caused by statin therapy.[173] Elevations in creatine kinase are rarely observed in children.[157,158] Increases in concentrations of hepatic aminotransferases are rarely observed with statins in children[157,158] and are not associated with an increased risk of liver disease in adults.[174]

Statin use in adults is associated with a small increased risk of new-onset diabetes especially in people who are at risk of developing diabetes.[175] Changes in insulin sensitivity were not observed in children and adolescents after 7 months of statins (in contrast to adults where changes could be observed after 10 weeks on treatment).[176] Although it is not possible to exclude a potential long-term risk of Type 2 diabetes in children with FH who start statin therapy at a young age,[165] any risk will likely be outweighed by the highly proven cardiovascular benefit of statin therapy.[159] Nevertheless, this potential risk reinforces the importance of emphasizing a healthy lifestyle to avoid obesity in children with FH.

Ezetimibe is well tolerated in children and adolescents; reported adverse events do not differ from those reported using placebo or statins alone.[145,146,177] Bile acid sequestrants can cause gastrointestinal side effects.[153]

The safety of evolocumab and alirocumab has been tested in children and adolescents with HeFH in double-blind trials with open-label extension phases lasting 24 and 80 weeks, respectively.[147–149,178] Both medications were well tolerated, with the most frequent adverse events being injection site reactions compared with placebo. There were no issues related to liver and muscle function, growth, pubertal maturation, or neurocognitive parameters.[178] Additionally, no adverse events were reported concerning glucose homeostasis, liposoluble vitamins, or steroid hormones. No anti-drug antibodies were detected. Inclisiran is reported to be well tolerated, with injection site reactions being the most frequent adverse events.[151] However, data on the long-term (5–10 years) use of PCSK9 inhibitors in children are not yet available.

Clinical management of homozygous familial hypercholesterolaemia

Importance of early diagnosis

Homozygous familial hypercholesterolaemia is suspected in individuals with untreated LDL-C concentrations >10 mmol/L (>400 mg/dL) or evidence from medical and family history and/or genetic testing.[5] Classical symptoms are cutaneous or tendon xanthomas before the age of 10 years.[5] Premature onset of atherosclerosis mainly affects the aortic root, coronary ostia and the aortic valves and can be observed in the first two decades of life.[179] Aortic disease may progress even when LDL-C concentrations are reduced, potentially as a result of haemodynamic stress and progressive fibrosis.[4,180] Therefore, it is important that HoFH is diagnosed as early as possible and that treatment starts soon after diagnosis.

Children with clinically suspected HoFH (mainly because of xanthomas) or at risk of HoFH (as both parents are known to have FH) should be tested as early as possible (from newborn up to 2 years of age), with measurement of LDL-C concentrations followed by genetic confirmation.[92] As pointed out in the 2023 EAS consensus statement on HoFH,[5] implementation of current guidelines should be improved to promote early detection of HoFH. This earlier statement proposed that paediatric guidelines should be expanded to include newborn lipid screening in high-risk settings and national screening programmes should be established where these are lacking. Early life lipid screening is supported by the recently announced European Union Safe Hearts Plan.[47]

It is important to note that clinically defined HoFH does not necessarily imply homozygosity for the same allele in a strict genetic sense, but instead it encompasses all biallelic pathogenic variants that impair the LDLR pathway. An individual with genetically confirmed HoFH will have inherited two pathogenic variants in one (biallelic monogenic HoFH) or two (biallelic digenic HoFH) of the FH-causing genes *LDLR*, *APOB*, and *PCSK9* or the FH-associated gene *LDLRAP1* (see Table 1 in Cuchel *et al.*[5]). If the child has consanguineous parents or is from a country with a high rate of genetic founder effects, the two variants may be identical (previously called 'true' HoFH; now called 'biallelic identical variant' HoFH). In other cases, a child will have two different pathogenic variants either in the same causative gene (previously called 'compound heterozygous FH'; now called 'biallelic different variant' HoFH) or in two different causative genes (previously called 'double heterozygous FH'; now called 'digenic' HoFH). Most commonly, a child with HoFH will have inherited one FH-causing variant from each parent, both of whom have HeFH. However, in the rare case of digenic HoFH, it is possible that one parent has digenic HoFH and the other parent has no pathogenic FH variant and the child inherited both variants from the digenic parent. All of these different genetic scenarios mean that the individual has HoFH, and we propose that genetic laboratory reports should include text stating this clearly to avoid confusion of interpretation and eligibility for future treatment options.

Use of cardiovascular imaging

Children diagnosed with HoFH should be screened for subclinical ASCVD including aortic valve disease by cardiovascular imaging, as described in the 2023 EAS consensus statement on HoFH.[5] Coronary computed tomography angiography should be performed at least once after age 3 years and thereafter as clinically indicated to guide treatment decision-making and tailor treatment frequency and intensity.[181] The rapid development of CCTA, particularly photon-counting CT with its increasingly

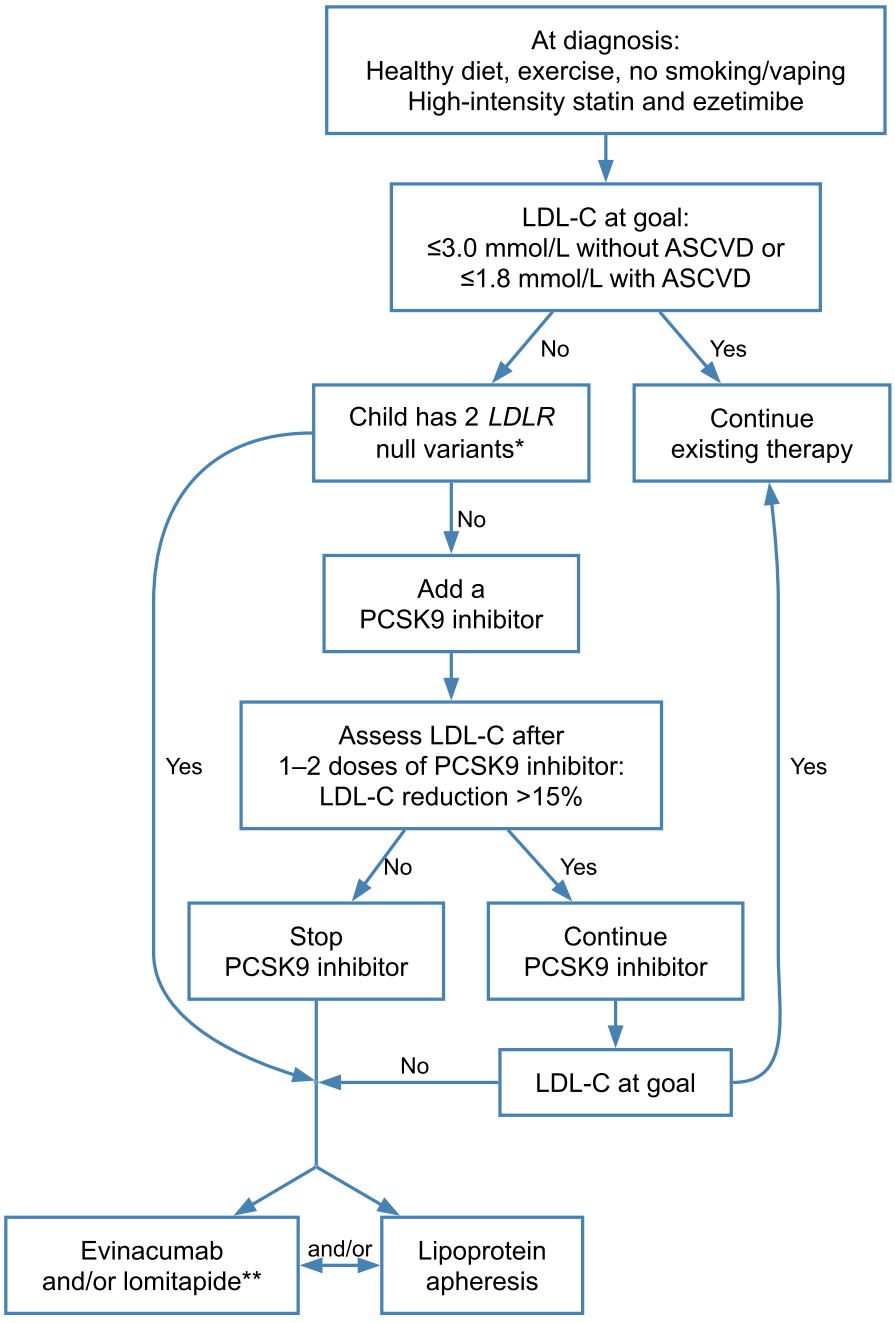

Figure 4 Treatment algorithm for children with homozygous familial hypercholesterolaemia. *<2% LDL receptor activity. **Evinacumab is approved by the European Medicines Agency and the US Food and Drug Administration from the age of 6 months and 1 year, respectively. Lomitapide is approved by the Food and Drug Administration from 2 years

detailed plaque-characterization capabilities, underscores the value of this modality in children with HoFH.[182,183]

LDL cholesterol treatment goals

The LDL-C treatment goal in children/adolescents with HoFH is ≤3.0 mmol/L (115 mg/dL) from diagnosis, in agreement with the 2023 EAS consensus statement on HoFH.[5] A reduction to this concentration is supported by the recent study showing that an increase in plaque volume over a 6-month period was prevented in children with HoFH who achieved a time-weighted cumulative LDL-C exposure of ≤3.0 mmol/L (115 mg/dL) per year.[89] For children with ASCVD, a treatment goal of ≤1.8 mmol/L (70 mg/dL) should be considered.[181]

Lifestyle measures and pharmacological treatment

A treatment algorithm for children with HoFH is presented in *Figure 4*. A step-by-step treatment plan is proposed starting

with a healthy diet and a combination of high-intensity statin and ezetimibe at the time of diagnosis.[5] Regular physical activity should be highly encouraged. Smoking and vaping should be strongly discouraged. As statins and PCSK9 inhibitors are dependent on LDLR function, their effectiveness depends on the level of residual LDLR activity. If LDL-C concentrations are not at goal on statins and ezetimibe within a few weeks and the child does not have two *LDLR* null variants, a PCSK9 inhibitor should be added. PCSK9 inhibitors should be continued if the LDL-C reduction is >15% after one to two dose applications. LDL receptor–independent treatments should be considered instead of adding a PCSK9 inhibitor when a child is known to have no LDLR activity or when treatment goals are not achieved with these initial treatments (see below).

LDL receptor-independent pharmacological treatments are evinacumab (administered by intravenous infusion every 4 weeks) and lomitapide (administered orally). Evinacumab is a human monoclonal antibody that targets angiopoietin-like 3, an inhibitor of lipoprotein lipase and endothelial lipase, and thereby reduces LDL-C concentrations.[184] Evinacumab has been shown to reduce baseline LDL-C by 48% in children with HoFH aged 5–11 years after 24 weeks of treatment (*Table 3*).[185] A study in two adolescents (aged 12 and 16 years) with *LDLR* null/null variants showed that plaque volume was reduced by 76% and 85% after 6 months on evinacumab.[186] Evinacumab has recently been approved by the EMA and FDA for the treatment of children with HoFH from the age of 6 months and 1 year, respectively. It can therefore be used to treat children with no LDLR activity at an earlier age than lipoprotein apheresis (see below).

Lomitapide is a microsomal triglyceride transfer protein inhibitor[187] and has been shown to reduce LDL-C by around 50%[188] (*Table 3*). Because of its mechanism of action, hepatic and gastrointestinal adverse effects are of concern. A low-fat diet may help to avoid these side effects. A recent open-label, single-label Phase 3 trial in children aged 5–17 years showed that lomitapide was effective at reducing LDL-C in this age group and adverse events were mostly mild.[155] Lomitapide has recently been approved by the FDA from the age of 2 years.

Lipoprotein apheresis

Lipoprotein apheresis is an effective LDLR-independent option to rapidly lower LDL-C in children with HoFH. Expert consensus states that lipoprotein apheresis be considered as early as age 2–3 years when the target LDL-C concentration is not achieved with healthy lifestyle and pharmacological therapy (*Figure 4*).[5,181,189–191] Although there are no randomized, placebo-controlled trials, there is increasing evidence that lipoprotein apheresis started in childhood leads to longer cardiovascular event-free survival.[94,190,192]

Several lipoprotein apheresis methods exist to selectively remove LDL and other apolipoprotein B-containing lipoproteins, including Lp(a).[181,191] This treatment also removes inflammatory and thrombogenic substances.[191] At each visit, blood is withdrawn from the body, anticoagulated, the lipoproteins removed and the remainder returned over a 2–3 h period. The preferred access is through peripheral veins or arterio-venous fistula.[181,193] The frequency of visits ranges from twice a week to once every 4 weeks, with once every 1–2 weeks being the most common.[190]

Biweekly lipoprotein apheresis in children and adolescents has been shown to reduce baseline LDL-C concentrations by 75% acutely and by 48% chronically.[193] Because LDL-C concentrations rebound quickly after lipoprotein apheresis, we consider that the Kroon formula should be used to estimate the mean reduction between lipoprotein apheresis sessions[194]:

$$\text{LDL-C}_{\text{mean}} = \text{LDL-C}_{\text{post}} + K(\text{LDL-C}_{\text{pre}} - \text{LDL-C}_{\text{post}})$$

where $\text{LDL-C}_{\text{pre}}$ is the LDL-C concentration directly before the session, $\text{LDL-C}_{\text{post}}$ is the LDL-C concentration directly after the session, and K is the rebound coefficient. K is estimated to be 0.65 for adults with HoFH on statin therapy and undergoing biweekly apheresis.[195] However, the formula has not been validated in children or when the procedure is performed with an interval different than biweekly. A high $\text{LDL-C}_{\text{pre}}$ in children could indicate the need for more frequent apheresis or for the addition of other LDLR-independent therapies even if the Kroon formula estimates a mean LDL-C ≤3.0 mmol/L (115 mg/dL).

Safety, quality of life, and emotional impact of the therapy should be considered. Serious adverse effects such as hypotension and anaphylactoid reactions are rare. Every effort should be made to employ skilled nurses with expertise in catheter placement in children, and interpersonal skills are essential to establish close relationships with both the child and caretaker(s). Prolonged travel time, school and work demands, and high cost may limit adherence to and availability of this procedure.

The combination of lipoprotein apheresis with LDLR-independent drugs such as evinacumab makes it now possible for the most severely affected children with *LDLR* null/null variants to reach LDL-C goals and even rapidly regress plaque.[186] The newest treatments, however, might not always be available. If lipoprotein apheresis is not available or feasible (e.g. in low- or middle-income countries or in children with small blood volume), plasma exchange should be considered.[92]

Liver transplantation

In exceptional cases, liver transplantation can be considered in children with HoFH who have persistently elevated LDL-C concentrations and ASCVD despite optimal available and tolerated treatment.[196]

Clinical management of sitosterolaemia and lysosomal acid lipase deficiency

For sitosterolaemia, individuals should avoid plant sterols. The primary pharmacological treatment is ezetimibe, which acts by reducing intestinal absorption of plant sterols.[197]

For LALD, individuals should consume a low-fat diet. The primary pharmacological treatment is sebelipase alfa (lipid-metabolizing enzyme replacement), which has been shown to reduce disease-related hepatic and lipid abnormalities.[198]

Transition to an adult model of health care for familial hypercholesterolaemia

The transition from paediatric to adult health care involves changes in care teams and system design. As a result,

Box 3 Proposals to facilitate a smooth transition to an adult model of health care for familial hypercholesterolaemia

(1) Children with FH should be taught about their condition and its management as early as possible, and definitely by the age of 10 years.
(2) The importance of diet, healthy lifestyle measures, and avoidance of smoking/vaping should be explained and stressed before puberty.
(3) Adherence to LLT should be monitored, especially during puberty.
(4) Girls should be given advice on contraception.
(5) If adolescents wish, they can be seen (partly) without their parents.
(6) Before transfer to the adult service, adolescents should be made aware that from age 18: (i) LLTs other than those used in childhood are approved and prescribed and (ii) LDL-C treatment goals will be lowered to 1.8 mmol/L (70 mg/dL).
(7) Upon transfer to the adult service, the hospital physician taking over care from the paediatrician should actively review and, if necessary, adjust the lipid-lowering regimen. This should be clearly emphasized during the handover of care.
(8) If other major risk enhancers are present, one could strive from age 16 for a lower LDL-C goal to facilitate transition to adulthood when the treatment goal will be lowered to LDL-C <1.4 mmol/L (55 mg/dL) according to the 2025 focused update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias.[15]
(9) An adolescent with FH, and especially those with HoFH, should preferably attend a transition clinic or a joint clinic with the paediatrician and internist/cardiologist at least once before transfer to the adult service.

adolescents and young adults are often overlooked, leading to a lack of follow-up and loss of compliance. Moreover, adolescents and young adults often consider health care of low importance compared with the other aspects of their transition to adulthood, such as education, employment and relationships. It is, therefore, important to start the process of empowering children with FH with knowledge about their condition and its management as early as possible and by 10 years at the latest. Better education of young FH patients should improve long-term adherence to clinical management.

Although not frequent in children and adolescents with FH, cardiac events can occur, especially in those with HoFH and in young adults with severe HeFH. Therefore, it is extremely important to ensure that the symptoms of acute cardiac events and the necessity of seeking prompt medical assistance are recognized by young people with FH who often transfer to adult care at the same time as starting to live independently.

Key proposals for transition from childhood to adulthood are summarized in Box 3.[199,200]

Implementation science and practice

Given the overall lack of success in translating evidence into routine practice to date, models of care for children and adolescents with FH should embed processes for implementation, operationalization, and evaluation. Application of implementation science can effectively inform such models.[92,201,202] Strategies that should be considered include personalized and transitional care plans, psychologically and culturally appropriately shared decision-making, tools to improve communication and adherence, use of multi-disciplinary teams, shared care with family medicine,[91] general support for clinicians, application of digital technologies, sharing of resources and expertise among services, and dedicated funding mechanisms. Support from advocacy groups and analyses of quality clinical registry data should be used to influence health policy and improve services. Government funding for comprehensive care of all children and adolescents with HoFH must be secured to establish centres of excellence and schemes for accessing new therapies.[5,92,203,204]

Box 4 Proposals for future studies in paediatric familial hypercholesterolaemia

Establish thresholds in imaging for excessive subclinical atherosclerosis.
Cost-effectiveness studies to compare screening strategies.
Develop more reliable tools to be used for newborn screening.
Include FH in genomic newborn screening studies.
Demonstrate the benefit of polygenic risk scores in children.
Investigate the effectiveness of a cholesterol-lowering diet on ASCVD incidence and mortality.
Examine the combined risk of FH and elevated Lp(a) in childhood.

Future research and conclusions

Further research in paediatric FH is required as indicated in Box 4. A particular focus should be on providing high-level evidence for the effective use of implementation science.[69,201,202] The proposed LDL-C cut-offs for diagnostic criteria are based on observational data.[17] The panel acknowledges that the proposed LDL-C treatment goals have not been tested in clinical trials. Similar to the LDL-C treatment goals recommended in adults,[15] the goals for treatment of children with FH have been derived indirectly from clinical trials comparing LLT with placebo or different dosages of LLT.

Despite advances in understanding the pathogenesis of FH and how to manage the disorder, FH remains underdiagnosed and undertreated. Detection and initiation of treatment of HeFH before puberty is critical to ensure that an individual's lifetime cumulative LDL-C burden is reduced, which would lead to substantially reduced cardiovascular risk and improved life expectancy. Children who start treatment of FH before puberty will not only have additional years of benefit but also adhere better to lifestyle and pharmacological treatment compared with those who start later in adolescence.

To increase detection, we strongly encourage all countries to establish a paediatric screening programme, with the age range for screening tailored to best fit country-specific contexts, but ideally within the first decade of life. To improve

diagnostic sensitivity, we propose lower LDL-C concentrations for suspecting FH in a child than those presented in the 2015 EAS consensus statement on FH in children.[4] We suggest including Lp(a) in the lipid profile to test at least once from the age of 5 and, if elevated, testing Lp(a) in (grand)parents. In addition, we present concrete updated guidance for managing both HeFH and HoFH. For HeFH, we propose lower LDL-C treatment goals than those presented in the 2015 consensus; these revised goals can be achieved in most cases using no more than two drugs because of the availability of new classes of LLTs.

Future research is required as indicated above, with the goal of ensuring that all individuals with FH are identified in childhood, start on best standard of care before puberty, and adhere to such care throughout their lifespan.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

C.J.B. is a consultant for Boehringer Ingelheim, Novartis, SOBI, and Takeda, a board member of Technoclone, and has received honoraria as a speaker and/or grants for travel and research from Amgen, Novartis, and SOBI. M. Bourbon is a consultant for Ultragenyx, Sobi, and Alexion. She has received support from Novartis (for publication) and Ultragenyx (annual meeting travel and accommodation expenses) and research grants from La Caixa Foundation and Horizon Europe. She is part of the scientific advisory committee of the FH Europe Foundation. T.F. is a paid consultant and advisory board member for Medison, Sobi, and Exceed Orphan. He has received speaker honoraria from Novartis and Ultragenyx. He participated in an FH screening project in Slovakia supported by Amgen and is participating in an FH screening project in pre-school children supported by Roche (he did not receive payment from either company). He has received research grants from the Ministry of Health in the Czech Republic and from the EU. He is a member of the scientific advisory committee of the FH Europe Foundation. S.S.G. is a consultant for Esperion Data and a member of the drug and safety monitoring board for Merck. He has received research grants from the National Institutes for Health (related to FH and to implementation science and genomics) and the CDC (related to hypertension). S.G.-P. has received speaker honoraria and travel grants from Ultragenyx, Sobi, Chiesi, Rhythm, and Vertex. She has participated in clinical trials run by Amgen, Sanofi, and Regeneron/Ultragenyx and is participating in clinical trials run by Novartis, Esperion, and Arrowhead. She has received research funding from Ultragenyx, Novartis, Amgen, Chiesi, Sobi, Sanofi, and Rhythm. U.G. has received speaker honoraria from Novartis, PTC Therapeutics, and Ultragenyx and has participated as a PI in clinical trials sponsored by Novartis and PTC Therapeutics. He is a member of the FH Europe Scientific Committee, a World Heart Federation emerging leader and vice-president of the Slovenian Heart Foundation. K.B.H. has received speaker honoraria from Sanofi, Menarini, and Ultragenyx. Through the Research Council of Norway, she has been involved in industrial collaboration projects with e.g. Tine, Mills, and Mowi. Through the Norwegian Seafood Research fund, she has collaborated with EPAX. She has received a travel grant from Ultragenyx and is a member of the scientific advisory committee of the FH Europe Foundation and advisor to the Norwegian FH patient organization. S.E.H is chief scientist of StoreGene (no remuneration) and a consultant for Verve Therapeutics. He has received funding from the UK National Institute for Health and Care Research Health Technology Assessment. B.A.H. is a consultant for Silence Therapeutics. She has received research grants from Silence Therapeutics paid to the institution (Amsterdam University Foundation) for salaries of PhD students. D.I. has received speaker honoraria from Chiesi, Sanofi, Daiichi Sankyo, and Sobi. She has participated in trials run by Novartis, Ionis, Amgen, and Lilly. C.P. has received a speaker honorarium from Ultragenyx. N.P. is a company consultant for Ultragenyx, Sanofi, Chiesi, Alexion and Amgen. He has received speaker honoraria from Chiesi and Ultragenyx. He has participated in trials run by Amgen and research financed by Amgen. He has received support from Alexion. F.J.R. has received research grants, honoraria, or consulting fees for professional input and/or delivered lectures from Amgen, MSD, Novartis, Sanofi, Regeneron, Ultragenyx, Chiesi, and LIB Therapeutics. He has participated in clinical trials with novel lipid-lowering drugs for the treatment of homozygous and heterozygous FH for MSD, Regeneron, Ultragenyx, Arrowhead, and LIB Therapeutics. Fees received from clinical trials are used to support the running of his research unit. He has received travel grants to attend and speak at international lipid meetings from the EAS, Ultragenyx, Chiesi, and LIB Therapeutics. He was the Secretary of the Lipid and Atherosclerosis Society of Southern Africa and was a board member of the International Atherosclerosis Society until 2024. U.R. has received honoraria for advisory board meetings from Esperion. J.R.v.L. received a research grant from Novartis. She has participated in clinical trials for Amgen, MSD, Novartis, Eli Lilly, New Amsterdam, and Ionis. She is on the steering board for MILOS (Daiichi Sankyo). S.R. declares equity from Heptabio; received honoraria as a consultant and/or speaker from Ultragenyx, Amgen, Sanofi, Ribocure, Wave Life Sciences, AstraZeneca, Chiesi, and Novartis; received research grants from AstraZeneca; and has acted as a principal investigator for Balance, Core, Horizon and Orion studies. V.S. has received speaker honoraria from Novartis, Sanofi, Amgen, and Daiichi Sankyo. R.D.S. is a consultant for Daiichi Sankyo, Eli Lilly, Esperion, Novartis, Novo Nordisk, and Ultragenyx. He has received speaker honoraria from Amgen, Novo Nordisk, Novartis, Eli Lilly, Daiichi Sankyo, Torrent, Libbs, and Chiesi. He has participated in trials run by Amgen, Novartis, Ionis, Sanofi/Regeneron, MSD, and Arrowhead and in research funded by Amgen, Novartis, Ionis, Sanofi/Regeneron, Esperion, MSD, and Arrowhead. He has received other support from Sanofi and research grants from Novartis. He is the World Heart Federation Editor in Chief Global Heart. 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trials run by Amgen and Arrowhead and participates in research funded by Novartis. He has received travel grants from Arrowhead, Novo Nordisk, and Amgen. A.W. has received speaker and/or consultant fees from Algorithm, Chiesi, Merck, Novartis, Sanofi, Silence Therapeutics, and Ultragenyx and research grants from Amgen, Sanofi/Regeneron, Novartis, Silence Therapeutics, Esperion, and Ultragenyx. Fees and research grants received are used to support the running of his research institute. He is secretary of the board of FH Europe Foundation. M.Benn, L.C.H., and R.P. do not have any existing or known future financial relationships or commercial affiliations to the health industry to disclose.

Data Availability

No data were generated or analysed for or in support of this paper.

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Appendix

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