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REVIEW

Prevention

Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment

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Familial hypercholesterolaemia (FH) is a common genetic cause of premature coronary heart disease (CHD). Globally, one baby is born with FH every minute. If diagnosed and treated early in childhood, individuals with FH can have normal life expectancy. This consensus paper aims to improve awareness of the need for early detection and management of FH children. Familial hypercholesterolaemia is diagnosed either on phenotypic criteria, i.e. an elevated low-density lipoprotein cholesterol (LDL-C) level plus a family history of elevated LDL-C, premature coronary artery

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disease and/or genetic diagnosis, or positive genetic testing. Childhood is the optimal period for discrimination between FH and non-FH using LDL-C screening. An LDL-C ≥5 mmol/L (190 mg/dL), or an LDL-C ≥4 mmol/L (160 mg/dL) with family history of premature CHD and/or high baseline cholesterol in one parent, make the phenotypic diagnosis. If a parent has a genetic defect, the LDL-C cut-off for the child is ≥3.5 mmol/L (130 mg/dL). We recommend cascade screening of families using a combined phenotypic and genotypic strategy. In children, testing is recommended from age 5 years, or earlier if homozygous FH is suspected. A healthy lifestyle and statin treatment (from age 8 to 10 years) are the cornerstones of management of heterozygous FH. Target LDL-C is <3.5 mmol/L (130 mg/dL) if >10 years, or ideally 50% reduction from baseline if 8–10 years, especially with very high LDL-C, elevated lipoprotein(a), a family history of premature CHD or other cardiovascular risk factors, balanced against the long-term risk of treatment side effects. Identifying FH early and optimally lowering LDL-C over the lifespan reduces cumulative LDL-C burden and offers health and socioeconomic benefits. To drive policy change for timely detection and management, we call for further studies in the young. Increased awareness, early identification, and optimal treatment from childhood are critical to adding decades of healthy life for children and adolescents with FH.

Keywords Familial hypercholesterolaemia • Children • Adolescents • LDL cholesterol • Diagnosis • Treatment • Statin • Ezetimibe • PCSK9 inhibitor • Consensus statement

Introduction

On his 10th birthday, a boy whose father died exactly 1 year ago aged 30 years, comes to consult you with his mother. The mother is worried that her son will have the same fate, because he also has bad cholesterol. What is your approach in this case?

Familial hypercholesterolaemia (FH) is a common genetic cause of premature coronary heart disease (CHD). With one very rare recessive exception, FH is an autosomal dominant disorder. Both homozygous and heterozygous FH result in markedly reduced hepatic capacity to clear atherogenic cholesterol-rich low-density lipoproteins (LDLs) from the circulation, with consequent accumulation of LDL cholesterol (LDL-C).[1] In severe cases, LDL-C levels exceed 13 mmol/L (500 mg/dL).[2] Beginning in the foetus, sustained exposure of the arterial wall to elevated LDL-C levels accelerates cholesterol deposition and vascular inflammation, developing atherosclerosis, especially in the coronary arteries and aorta, and premature CHD.[3,4]

Heterozygous FH (HeFH) is common (*Figure 1A*), present in ~1 per 200–250 of the general population, about two-fold higher than previously thought.[2,5,6] Among a CHD-free control population, 1 in 217 carried a mutation in the gene encoding the LDL receptor (*LDLR*) and had LDL-C >190 mg/dL.[7] Consequently, there are potentially as many as 4.5 million individuals in Europe with HeFH and probably 35 million worldwide (*Figure 1B*), of whom 20–25% are children and adolescents. Given that there are 255 worldwide births per minute,[8] one baby is born with FH every minute. Children with untreated HeFH have a dramatic increase in risk of premature CHD after age 20 years.[9,10] Familial hypercholesterolaemia in its homozygous form (HoFH) is a rare disease with an estimated prevalence of 1 per 160 000–300 000 in European populations.[2,11] Individuals with HoFH are at extremely high risk and, if untreated, many will manifest coronary or other cardiovascular disease in childhood or adolescence.

Familial hypercholesterolaemia is diagnosed either on phenotypic criteria, involving an elevated LDL-C level plus a family history of elevated LDL-C, premature CHD, and/or genetic diagnosis, or with genetic testing. With few exceptions, however, FH is underdiagnosed and undertreated globally,[5] and systematic screening strategies are inconsistently implemented.[12] Given the proven atherogenicity of LDL-C in experimental models and in humans with FH, with evidence that exposure to even moderate hypercholesterolaemia increases the long-term risk of a new CHD event,[13] and given the lifelong benefit of genetically determined low LDL-C concentrations,[14] there is an urgent need to identify and treat FH early to maximize therapeutic benefit (*Table 1*). Importantly, statins are safe and effective in lowering LDL-C in children,[15] restore endothelial function, and regress thickening of the intima of the vessel wall at a young age.[16–18]

The aim of this consensus paper is to encourage improvement in early detection, diagnosis and treatment of FH by creating a paradigm shift in its clinical perception in children and adolescents. We discuss the current status of pathophysiology, diagnosis, genetic testing, screening and management of FH. *Figure 2* demonstrates the potential of early recognition of FH, combined with treatment from a young age, to substantially delay atherosclerosis progression. New findings support our recommendations to improve recognition and initiation of early treatment with lifestyle, diet, and pharmacotherapy.[19]

Pathophysiology

Genetic causes

Familial hypercholesterolaemia is most often caused by mutations in the *LDLR* gene, resulting in absent or dysfunctional receptors on the surface of hepatocytes, identifying the liver as the principal site of LDL catabolism. More than 1700 mutations in the *LDLR* gene on chromosome 19 have been identified, of which 79% are probably expressed as a hypercholesterolaemic phenotype.[20] Defects in the genes encoding apolipoprotein B (*APOB*) and proprotein convertase subtilisin/kexin type 9 (*PCSK9*) account for ~5% and <1% of FH cases, respectively. The LDL receptor adaptor protein (*LDLRAP1*) gene is a very rare recessive form of FH.[5,21] However, 5–30% of cases of phenotypic FH may arise from mutations in unidentified genes, or have a polygenic cause as distinct from a dominantly inherited disorder.[22–24] All of the monogenic defects result in reduced efficiency of LDL uptake and clearance in hepatocytes and increased circulating total cholesterol and LDL-C concentration. Inheritance of a mutation in the gene from one parent causes HeFH; inheritance of a mutation from each parent causes HoFH. Many individuals considered homozygous have two different genetic defects related to

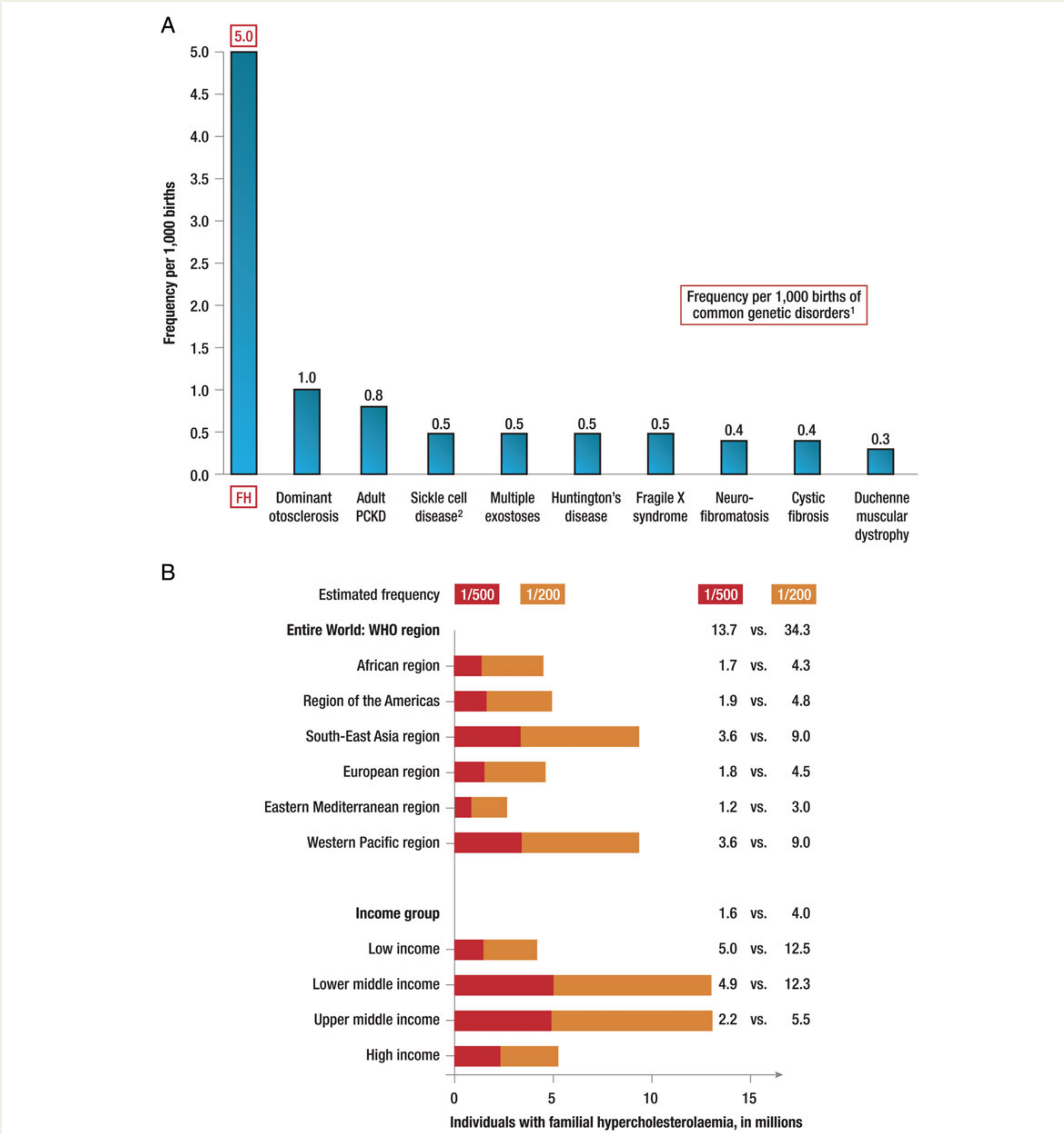

Figure 1 Prevalence of familial hypercholesterolaemia. (*A*) Familial hypercholesterolaemia is more common than other genetic diseases. 1 Genetic Alliance UK. Incidence of genetic disorders. http://www.geneticalliance.org.uk/education3.htm (13 February 2015); 2 Streetly *et al.*[140] FH, familial hypercholesterolaemia; PCKD, polycystic kidney disease. (*B*) The estimated prevalence of FH globally, based on estimated frequencies of 1 : 500 and 1 : 200 (as suggested by recent research), reproduced with permission from Nordestgaard *et al.*[5]

LDLR (i.e. compound HeFH), with mutations in *APOB* or *PCSK9* genes, as well as an *LDLR* mutation.[11]

Early atherosclerotic disease

In FH, attenuated clearance of plasma LDL-C by the LDL receptor leads to increased numbers of circulating LDL which penetrate and then accumulate in the artery wall, become oxidatively modified, and subsequently initiate an inflammatory response, which results in vascular injury and formation of atherosclerotic plaque.[25,26] Additional alterations in the lipoprotein profile in FH may involve elevated levels of lipoprotein(a) [Lp(a)] and triglyceride-rich lipoprotein remnants, together with low levels of dysfunctional high-density lipoproteins (HDLs), which collectively may contribute to accelerated atherosclerosis and CHD.[27,28]

Both pre-mortem (the Bogalusa Heart Study) and post-mortem studies (the Pathobiological Determinants of Atherosclerosis in Youth [PDAY] study) have revealed a strong, continuous and graded relationship between non-HDL cholesterol levels (i.e. total cholesterol − HDL-C, comprising the atherogenic apoB-containing lipoproteins) and atherosclerotic disease.[29,30] Indeed, every 0.25 mmol/L (10 mg/dL) increment in non-HDL-C is associated with an increase in atherosclerotic burden equivalent to 1 year of aging. Although pathology studies have not been systematically performed in children and adolescents with FH, observations in non-FH individuals strongly suggest that very high LDL-C levels sustained from childhood and adolescence in FH subjects would be associated with future vascular disease. Collective evidence demonstrates that elevated circulating markers of vascular inflammation and endothelial dysfunction are present in children with FH, reflecting early atherogenesis.[31]

Table 1 Key points about familial hypercholesterolaemia

- FH is one of the most common genetic disorders, affecting 1 : 200 to 1 : 250 people in the European population, inherited in an autosomal dominant fashion.
- HeFH, and to an even greater degree HoFH, can be disabling at a young age and shorten life expectancy.
- If LDL-C levels are >13 mmol/L (500 mg/dL) and paediatric manifestations include premature CHD, aortic valve disease, and tendon xanthomas in the hands and Achilles tendons, homozygosity is assumed. However, HoFH may be considered at lower LDL-C levels following recent recognition of the clinical and genetic heterogeneity of FH.
- The presence of FH presents a psychological challenge for families because of the inherited nature of the condition, the lack of early symptoms in HeFH, and the need for long-term lifestyle changes and pharmacotherapy.
- Early detection of FH and early initiation of lifestyle and pharmacological treatment is imperative to reduce the lifelong burden of elevated LDL-C levels.

Increased carotid intima-media thickness (cIMT) and detection of coronary artery calcification by computed tomography (CT) scanning are confirmed markers of early atherogenesis.[31] A systematic review of published data shows that cIMT is higher in phenotypic FH patients (from age 10 years) than normolipidaemic controls, and that this difference directly relates to LDL-C levels.[32] The difference in mean cIMT between children with FH and unaffected siblings may be significant as early as age 7 years (*Figure 3A*).[33] Similar findings were observed for mean femoral artery IMT.[34] Coronary calcification is present in ∼25% of 11–23 year olds with phenotypic HeFH,

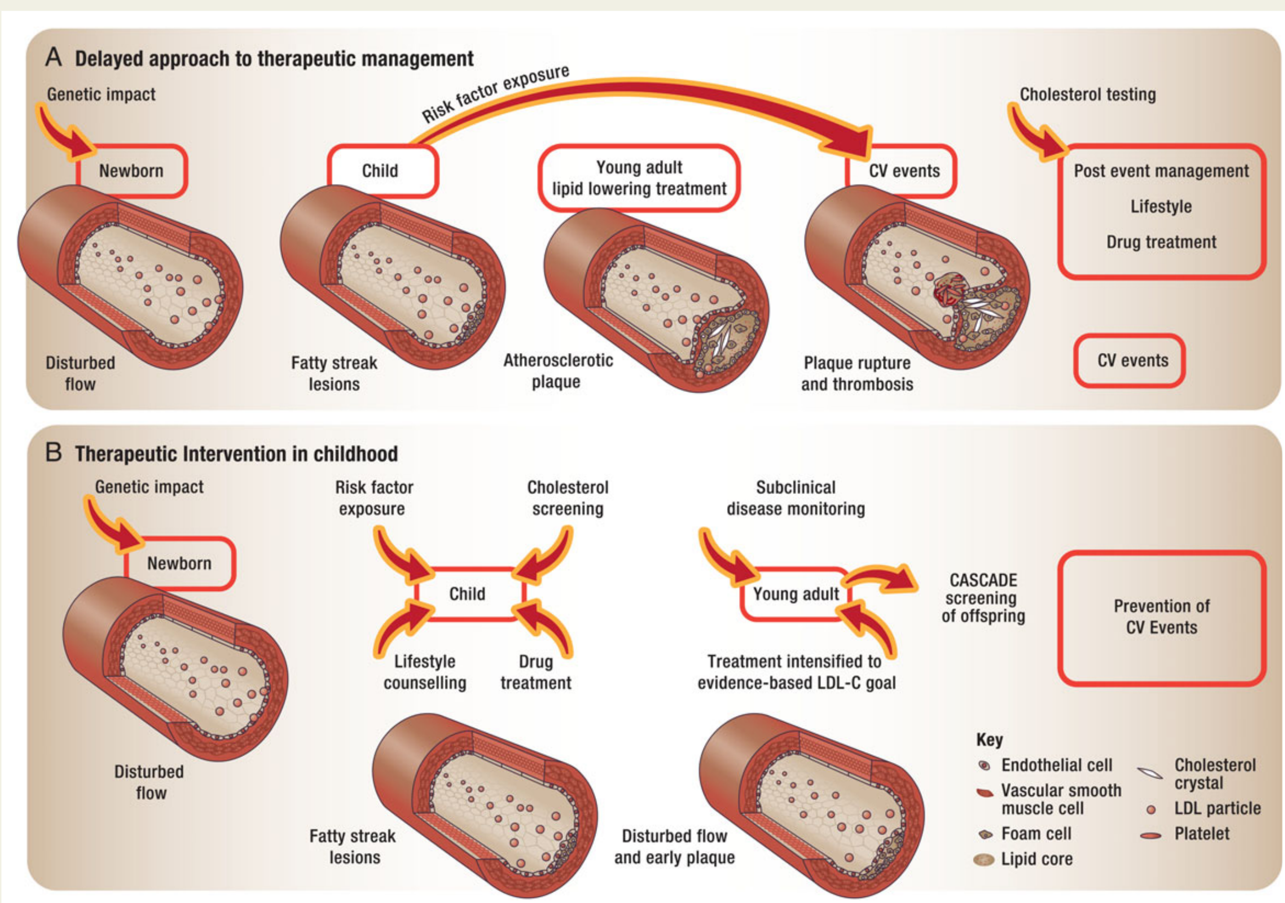

Figure 2 Development of early atherosclerotic vascular disease in familial hypercholesterolaemia showing the potential impact of early recognition and treatment on evolution of the condition. CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol.

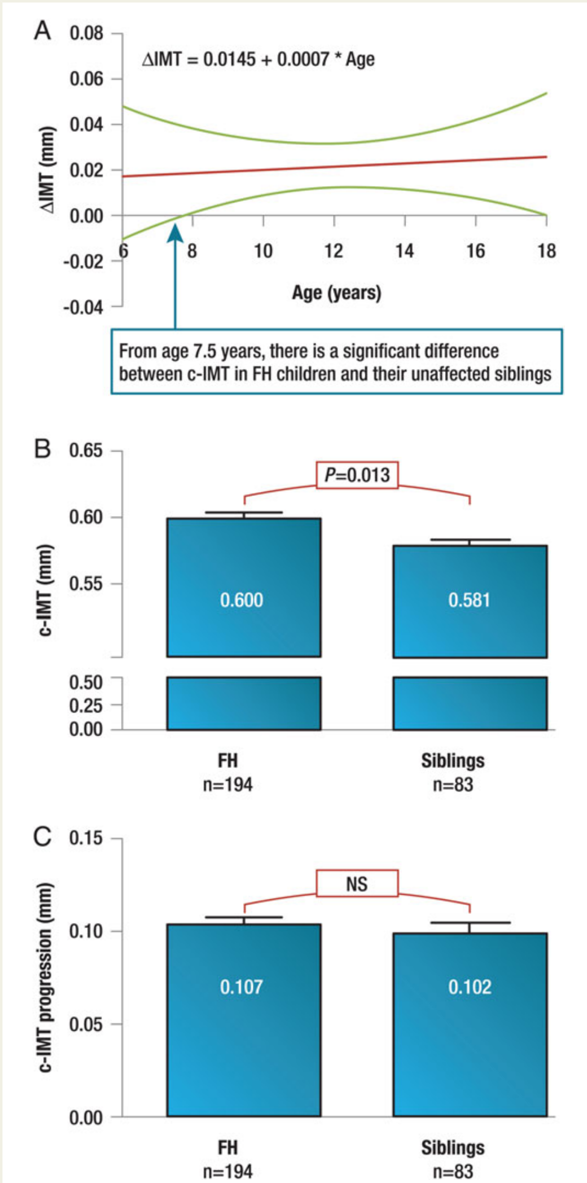

Figure 3 Carotid intima-media thickness is a marker of early atherogenesis in children with familial hypercholesterolaemia. (*A*) Increased carotid intima-media thickness is already evident at age 7 years in familial hypercholesterolaemia children. Data from Kusters *et al.*[33] After 10 years treatment with a statin, while mean carotid intima-media thickness is higher in familial hypercholesterolaemia children than their unaffected siblings (*B*), there is no significant difference between the two groups in carotid intima-media thickness progression over this period (*C*). Data from Kusters *et al.*[98] Data in (*B*) and (*C*) are given as mean ± SEM and are adjusted for age, gender, blood pressure, body mass index, smoking, and family relations. cIMT, carotid intima-media thickness; FH, familial hypercholesterolaemia; NS, not significant.

and especially in the aorta in most adolescents with HoFH, although coronary and aortic calcium score is rarely, if ever, positive in pre-adolescent HoFH children.[11,35–37] In contrast, coronary calcium is barely detectable in atherosclerotic lesions in adolescents in the general population.[38] When compared with children with *LDLR*-defective alleles, those with *LDLR*-null (complete loss of function) alleles have higher LDL-C levels, more advanced atherosclerosis and, correspondingly, increased cIMT.[34,39]

Table 2 Diagnosis of familial hypercholesterolaemia in children and adolescents

- Family history of premature CHD plus high LDL-C) levels are the two key selective screening criteria: (F + H = FH).[a]
- Cholesterol testing should be used to make a phenotypic diagnosis.
- An LDL-C level ≥5 mmol/L (190 mg/dL) on two successive occasions after 3 months diet indicates a high probability of FH. A family history of premature CHD in close relative(s) and/or baseline high cholesterol in one parent, together with an LDL-C ≥4 mmol/L (160 mg/dL) indicates a high probability of FH. If the parent has a genetic diagnosis, an LDL-C ≥3.5 mmol/L (130 mg/dL) suggests FH in the child.
- Secondary causes of hypercholesterolaemia should be ruled out.
- DNA testing establishes the diagnosis. If a pathogenic *LDLR* mutation is identified in a first-degree relative, children may also be genetically tested.
- If a parent died from CHD, a child even with moderate hypercholesterolaemia should be tested genetically for FH and inherited elevation in Lp(a).

[a]Acknowledgement to the FH Foundation (http://thefhfoundation.org/).

Diagnosis

Paediatric FH is diagnosed phenotypically by the presence of an LDL-C level consistent with FH plus a family history of premature CHD and/or baseline high cholesterol in one parent and/or an FH-causing mutation (*Table 2*).[11,21] Childhood is the optimal period to discriminate between FH and non-FH on the basis of LDL-C concentration, due to minimal dietary/hormonal influences. After dietary intervention, any child with an LDL-C level ≥5 mmol/L (190 mg/dL) has a high probability of genetically based FH. If there is a family history of premature CHD in close relatives and/or a baseline high cholesterol in one parent, an LDL-C ≥4 mmol/L (160 mg/dL) is indicative of a high probability of genetically based FH.

Detection of a pathogenic mutation, usually in the *LDLR* gene, is the gold standard for diagnosis of FH.[6,21,40–43] A child of a parent with FH has a 50% probability of inheriting FH, thereby emphasizing the importance of a family pedigree to identify relatives for screening. Typically, there will be a marked difference in LDL-C levels between children with and without genetically defined FH. In one study, a functional mutation was identified in 95% of children meeting phenotypic criteria for FH and with an autosomal dominant pattern of inheritance of hypercholesterolaemia.[24] If the parent has a genetic diagnosis and the child has an LDL-C ≥3.5 mmol/L (130 mg/dL), an *LDLR* mutation is to be anticipated.[40]

The applicability of current diagnostic tools varies. While the Dutch Lipid Clinic Network criteria are not valid in children,[41] the Simon Broome criteria have specific cut-offs for LDL-C in this group. The LDL-C threshold is 4 mmol/L (160 mg/dL) in children with FH aged <10 years.[24,44] A lower LDL-C threshold (3.5 mmol/L or 130 mg/dL) may be used when children are tested as part of cascade screening.[40,45] LDL-C levels should be measured at least twice over 3 months to confirm the diagnosis of FH.[5,6] An LDL-C level >13 mmol/L (500 mg/dL) is consistent with phenotypic HoFH, but may be lower given recent recognition of the clinical and genetic heterogeneity of FH.[2,11]

Factors that complicate diagnostic accuracy include the presence of multiple genes that have a small positive effect on LDL-C concentration, raising levels to those consistent with FH, or the presence of 'compensatory' genes that lower LDL-C below thresholds defined above.[46–48] There is also overlap between those with HeFH and HoFH at LDL-C levels of ∼8–13 mmol/L (∼300–500 mg/dL).[2,11] Secondary causes of elevated LDL-C, including hypothyroidism, nephrotic syndrome, obstructive liver disease, obesity, anorexia nervosa, and drug treatment (e.g. isoretinoids) should be considered in patient evaluation.[42–44,49] Sitosterolaemia, particularly if xanthoma are present, or cholesteryl ester storage disease when liver transaminases are elevated, although extremely rare, should also be considered.[41] Recent evidence suggests that the marked hypercholesterolaemia in sitosterolaemia may be transient and also diet dependent.[50]

Genetic testing of families

It is best practice to first genetically test a phenotypically affected parent or a second-degree relative in the absence of a parent.[39,42,51,52] If a mutation is identified, genetic testing and counselling should be offered to all family members, ideally co-ordinated centrally in association with a clinical genetics service.[39,53] To increase acceptability, genetic testing for FH in children should be available using DNA extracted from buccal samples.[39] The psychological sequelae of genetic tests must be considered, with pre-test counselling essential to the consent/assent procedure, taking account of the child's level of comprehension and parental literacy.[51,52] In circumstances in which FH is suspected but no parents or second-degree relatives are available or the parents refuse testing, after obtaining appropriate assent/consent genetic testing and measurement of Lp(a) should be carried out in minors, especially if a parent died from CHD and the child has only moderate hypercholesterolaemia.

Laboratory aspects

Laboratories for genetic analyses should be fully accredited by local, national, or international authorities. Established procedures should be followed for classifying variants as clearly pathogenic (a mutation), clearly non-pathogenic (a benign variant) or of uncertain significance (5–8% of molecular diagnostic reports), based mainly on *in silico* assessment coupled with a search of the literature and established databases.[6,39] Failure to detect a mutation does not exclude a diagnosis of FH. One reason may be insufficient sensitivity or specificity of the technology; additionally, some paediatric phenotypic index cases do not have known FH-causing mutations.

Most laboratories involved in FH genetic testing will utilise a number of mutation detection methods, including Sanger-based exon-by-exon sequence analysis and Multiplex Ligation Probe Amplification for large deletions and duplications; whole- and targeted exome sequencing are newer options.[21,22] All results from commercial chip or kit technology that identify a gene variant as being present should be confirmed using a second validated testing method. 'Next Generation' exome sequencing is a newer option, which also identifies insertions and deletions.[21,22,48]

Table 3 Screening for familial hypercholesterolaemia in children and adolescents

- If DNA testing is available, cascade screening of families is recommended using both a phenotypic and genotypic strategy. If DNA testing is not available, a phenotypic strategy based on country, age- and gender-specific LDL-C levels should be used.
- Children with suspected HeFH should be screened from the age of 5 years; screening for HoFH should be undertaken when clinically suspected (both parents affected or xanthoma present) and as early as possible.
- Age at screening should be similar for boys and girls.
- Universal screening in childhood may also be considered.

Screening

Screening for FH meets World Health Organization guidelines:[54] childhood represents a latent stage of the disease, a simple test to diagnose FH acceptable to the general population exists, there is effective treatment, and case-finding can be made part of routine medical practice. *Table 3* summarizes key features of potential screening strategies. Research is needed to ascertain the exact age to begin treatment and the long-term safety of cholesterol-lowering treatment.[55]

In families with a known *LDLR* mutation, molecular testing is the most reliable and effective method to identify affected family members including children and adolescents. Theoretically, genetic testing of first-degree relatives has a sensitivity and specificity of 100%, whereas for clinical diagnosis, sensitivity and specificity is in the range of 70–85%.[44] In the Netherlands, >28 000 individuals with FH have been identified, almost 23 000 via cascade screening, carrying >500 different mutations.[56,57] But even with this strategy, ∼30% of the 33 300 estimated cases are not identified,[5] due to lack of an index case. In the Norwegian genetic screening programme, >5600 individuals of the estimated 15 000–20 000 FH patients have been identified, carrying >140 different mutations. Legal restrictions require relatives to contact family members directly, which restricts the efficiency of detecting new FH cases. Clinical diagnosis of FH in general practice has a sensitivity of 46% and a specificity of 88%.[58] In the UK, a family cascade testing approach for FH is recommended, starting with adults and proceeding to testing children from the age of 10 years in families known to have a clear diagnosis of FH. The programme has been fully implemented in Wales, Scotland, and Northern Ireland.[59]

Universal screening of children for hypercholesterolaemia in Europe has only been implemented in Slovenia from the age of 5 years.[60] In the USA, universal screening at age 9–11 years has been recommended, in part because selective screening based on family history is not efficient in identifying children with LDL-C in the FH range.[61,62] Screening can be performed in conjunction with routine health visits such as at the time of immunization,[44] and cascade screening of first-degree family members can follow

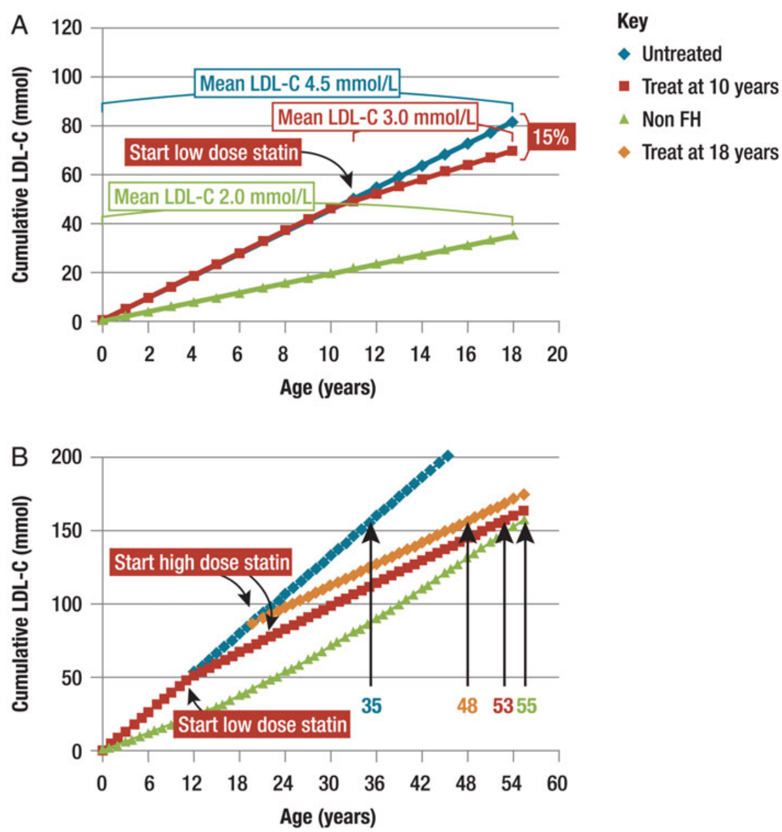

Figure 4 Impact of statin treatment on cholesterol burden in familial hypercholesterolaemia. Early initiation of statin treatment reduces the low-density lipoprotein cholesterol burden* in subjects with familial hypercholesterolaemia. Reproduced with permission from Vuorio *et al.*[70] (*A*): Cumulative low-density lipoprotein cholesterol burden by age of 18 years is 15% lower in familial hypercholesterolaemia subjects treated with low dose statin from age 10 years (70 mmol) than in untreated familial hypercholesterolaemia subjects (80 mmol). (*B*) Cumulative low-density lipoprotein cholesterol burden of a 55-year-old non-familial hypercholesterolaemia subject is 160 mmol. In an untreated familial hypercholesterolaemia subject, this is attained by age 35 years, but is delayed in familial hypercholesterolaemia patients treated from age 18 years (48 years), and further delayed in those treated from age 10 years (53 years). *For calculation of the low-density lipoprotein cholesterol burden, the following assumed mean low-density lipoprotein cholesterol values were used. Non-familial hypercholesterolaemia subjects: 2.0 mmol/L for the age range of 0–15 years; 2.5 mmol/L for 15–24 years; 3.0 mmol/L for 25–34 years; 3.5 mmol/L for 35–44 years; and 3.5 mmol/L for 45–54 years. Familial hypercholesterolaemia subjects: 4.5 mmol/L in untreated familial hypercholesterolaemia patients; 3 mmol/L in familial hypercholesterolaemia patients treated during the age range of 10–18 years, and 2.5 mmol/L in familial hypercholesterolaemia patients with treatment started at the age of 18 years. FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol.

identification of a child with severely elevated LDL-C. However, the acceptability, practicability, specificity, and cost-effectiveness of this approach have yet to be evaluated.[63]

Other risk factors

Given independent associations of type 2 diabetes, hypertension, tobacco use (including passive smoking), and obesity with atherosclerosis development,[38] a patient with FH and an additional risk factor is at even greater risk than a patient with FH alone, as supported by natural history data in FH cohorts.[64,65] There is also prognostic value in screening for plasma lipoprotein(a) [Lp(a)] concentration given that high Lp(a) (>50 mg/dL or 80th percentile) increases risk for premature CHD (by 1.5-fold).[6,40,66] In childhood, FH may co-exist with other diseases known to accelerate atherosclerosis, including type 1 diabetes mellitus, chronic kidney disease, connective tissue disorders, and HIV infection.[67]

Management

Early treatment of FH can reduce LDL-C burden (*Figure 4*), improve endothelial function, substantially attenuate the progression of atherosclerosis (*Figure 3B* and *C*), and improve coronary outcomes (*Figure 5*),[17,18,68–71] all of which emphasizes the rationale for greater long-term benefit with initiation of treatment earlier rather than later in life.[70,71] Furthermore, long-term follow-up from statin trials, albeit not specifically in FH patients, suggests a legacy effect, i.e. better CHD outcomes in those initially randomized to statin treatment.[72,73] *Table 4* summarizes key points related to FH management.

Diet and risk factor control

Diet and lifestyle underpin the management of FH in children. In considering dietary fat content, the major dietary drivers of serum

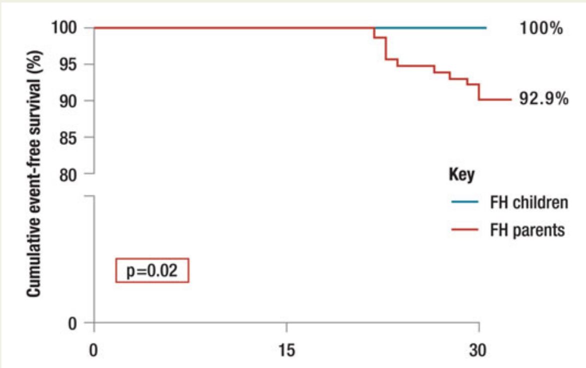

Figure 5 Reduction in low-density lipoprotein cholesterol burden associated with early initiation of statin treatment in children with familial hypercholesterolaemia translates to improvement in coronary outcomes. Kaplan–Meier curves of event-free survival in a cohort of 214 familial hypercholesterolaemia subjects treated from childhood ($n = 214$) compared with their parents with familial hypercholesterolaemia, treated from adulthood ($n = 156$). Data from Braamskamp *et al.*[99] FH, familial hypercholesterolaemia.

Table 4 Clinical management of FH in children and adolescents

- Early identification of children with FH ensures that adherence with lifestyle intervention is already established before puberty.
- Children with HeFH should be treated with a fat-modified, heart-healthy diet at diagnosis, and begin statins at age 8–10 years.
- In HoFH, pharmacologic treatment should start at diagnosis.
- Early initiation of lifestyle is essential for ensuring long-term adherence.
- Children diagnosed with FH should have lipoprotein(a) [Lp(a)] measured for risk stratification.
- Boys and girls should start treatment at similar ages.
- For children aged 8–10 years, the Panel recommends that LDL-C is ideally reduced by 50% from pre-treatment levels.
- For children aged ≥10 years, especially if there are additional cardiovascular risk factors, including elevated Lp(a), the target LDL-C should be <3.5 mmol/L (130 mg/dL).
- The benefits of LDL-C reduction should be balanced against the long-term risk of treatment side effects.
- Adherence should be checked if HeFH children fail to achieve LDL-C targets with combination lipid-lowering treatment. If patients are non-adherent, consider referral to a dedicated, multidisciplinary clinic.
- Children with HoFH should be referred to and cared for at a specialised centre.

cholesterol levels are saturated fats and trans fats with a small contribution from dietary cholesterol.[74,75] Limitation of foods high in saturated fat will secondarily limit dietary cholesterol intake; cholesterol-containing foods without saturated or trans fats may be allowed.[76] Reduction of saturated fat intake has not been associated with altered physical growth during long follow-up.[77] Consequently, the Panel recommends a heart-healthy, fat-modified diet (<30% of calories from total fat, <7% of calories from saturated fat, and <200 mg of cholesterol/day),[68,78] ideally incorporating nutrient-dense foods with appropriate energy to maintain optimal body weight. Intake of fruit and vegetables, whole grains, low-fat dairy products, beans, fish, and lean meats should be encouraged. Diet choices are by nature diverse; emphasis should be on a culturally acceptable heart-healthy diet, such as Mediterranean-style diets.

There should be annual or bi-annual monitoring of weight, growth and developmental milestones. Physical activity should be promoted and smoking strongly discouraged. Identifying children with FH early ensures that adherence with lifestyle interventions is established before puberty. Other cardiovascular risk factors should be monitored and treated if indicated.

Pharmacotherapy for heterozygous familial hypercholesterolaemia

Statins are the cornerstone of FH management. Simvastatin, lovastatin, atorvastatin, pravastatin, fluvastatin and rosuvastatin are approved in the USA and Europe for use in children with FH. In the USA, these are approved from age 10 years, except for pravastatin which is approved from age 8 years.[6] Prescribing information is broadly similar in Europe, although rosuvastatin is approved from the age of 6 years. Atorvastatin is approved from age 6 years in Australia. Treatment may be started earlier in severe cases.[79] The short-term efficacy and safety of these statins, including during puberty, have been confirmed.[15,68,80]

Treatment should be initiated at the lowest recommended dose and up-titrated according to the LDL-C lowering response and tolerability. Evidence for an absolute target for LDL-C in children with FH does not exist. Expert consensus recommends a target LDL-C level <3.5 mmol/L (130 mg/dL) from age 10 years, or ideally 50% reduction from pre-treatment levels for children 8–10 years, particularly in those with high-risk conditions or other major risk factors.[6,11,42,43,67] In patients with chronic kidney disease, a statin that is not excreted by the kidney, such as atorvastatin or simvastatin, should be used. Clinicians should be aware of the potential for drug-drug interactions with statins, notably, for drugs metabolised by cytochrome P450 (CYP) 3A4 with simvastatin and atorvastatin, and for drugs metabolised by CYP 2C9 with rosuvastatin and fluvastatin. Pravastatin, although a weak statin, does not interfere with CYP enzymes and is therefore a safe drug for initiating treatment in children.

Addition of ezetimibe or a bile-acid sequestrant may be required to attain LDL-C goal in some patients.[42,43,81,82] Ezetimibe is approved for use from age 10 years in the USA and Europe, and is very well tolerated with minimal side effects. The bile-acid sequestrants cause gastrointestinal side effects; colesevelam is the best tolerated of these agents and is approved in the USA from age 10 years although not in Europe.[83] As these agents can affect the absorption of folate and fat-soluble vitamins, appropriate supplementation and monitoring will be required with longer-term use. Niacin should rarely be used to treat paediatric FH due to poor tolerability and concerns regarding the risk of glucose intolerance, myopathy, hyperuricaemia and hepatitis. For all treatments, drug dosing regimens should follow those evaluated in clinical trials and approved by local regulatory agencies, except in severe FH or when FH is complicated by additional cardiovascular risk factors, in which expert clinical judgment is needed to weigh the risks vs. benefits of more aggressive treatment (*Table 4*).

Dietary supplementation with functional foods

Several controlled clinical trials have shown that foods containing added plant sterols/stanols (1.5–3 g/day) reduce LDL-C levels by 9–19% in children and adolescents with FH (aged 4–15 years).[84,85] There was, however, no improvement in endothelial function despite significant LDL-C lowering.[86,87] Reduction in levels of some fat-soluble vitamins and carotenoids can be compensated by ensuring adequate intake of fruit and vegetables.[84] Currently, the use of foods enriched with plant sterols/stanols is not recommended for children under 6 years.[84]

Table 5 Monitoring treatment in FH children and adolescents

- Hepatic aminotransferases, creatine kinase (CK) and creatinine levels should be measured before starting treatment.
- After starting treatment, lipid levels, weight, growth, physical and sexual development, and hepatic aminotransferases should be monitored.
- Hepatic aminotransferases should be monitored at least every 3 months if there is a history of liver disease, or more frequently if levels rise to 3-fold greater than the upper limit of normal; bilirubin may be used to gauge liver toxicity.
- Plasma CK levels should be measured if musculoskeletal symptoms are reported.
- Fasting plasma glucose and/or random glycated haemoglobin should be measured every 6 months in children on higher doses of statins who are obese or have impaired glucose tolerance.

A wide range of other nutrients and supplements, including psyllium-enriched cereal, garlic extract, omega-3 fatty acids, rapeseed oil and soy protein, have been assessed in small studies in FH patients and in children with hypercholesterolaemia.[88–96] No firm recommendation regarding the use of any of these agents in children and adolescents can be made at this time.

Monitoring therapy and adherence

Life-long treatment critically involves collaboration between families and physicians. Recommendations for monitoring the safety and tolerability of lipid-modulating agents in paediatric FH are similar to those in adults (*Table 5*).[5,6,61] Particular vigilance is required in patients receiving higher statin doses, or in those predisposed to statin side effects due to participation in vigorous contact sports or the use of other medication, such as fibrates (notably gemfibrozil). Adolescent girls should be counselled to suspend statin therapy when contemplating pregnancy (see below).

At recommended statin doses, the dose–response curve is not linear. Most of the reduction in LDL-C occurs at lower doses, with each subsequent doubling in dose yielding incremental reductions of 6–7% in LDL-C.[97] Therefore, the need to intensify treatment with higher doses should be balanced against any long-term side effects due to greater exposure to medication. While more data concerning myopathy and the risk of diabetes in children treated with statins over many years is needed, recent long-term follow-up showed an excellent safety profile (*Table 6*).[98] Even more importantly, at the age of 30 years, CHD-free survival was 100% in FH children initiated early on statin vs.. 93% in their affected parents ($P = 0.02$) (*Figure 5*).[99]

Adherence and response to statin therapy should be checked in FH patients who fail to achieve target LDL-C levels despite polypharmacotherapy. Non-adherent patients can be optimally managed in a

Table 6 Safety indices of familial hypercholesterolaemia subjects, initiated on pravastatin in childhood (aged 8–18 years) and treated for 10 years, compared with their unaffected siblings

	FH (n = 194)	Siblings (n = 83)	P-value
Effect on liver function; no. (%) of patients			
↑ in AST >3 × ULN	1 (0.5)	1 (1.1)	0.26
↑ in ALT >3 × ULN	1 (0.5)	0	0.51
↑ in CK >10 × ULN	0	2 (2.1)	0.03
Effect on renal function			
eGFR (mL/min/1.73 m^2), median (IQR)	127 (121–131)	125 (119–130)	0.05
Diabetes, n (%)	1 (0.5)	1 (1.2)	0.55
C-reactive protein (mg/dL), median (IQR)	0.9 (0.3–2.3)	1.2 (0.3–3.0)	0.27
Age at menarche (year), mean (95% CI)	13.1 (12.2–13.4)	13.4 (12.8–14.1)	0.27
Level of education, n (%)			
Lower	31 (17.1)	13 (16.0)	0.96
Middle	71 (39.2)	33 (40.7)	
Higher	79 (43.6)	35 (43.2)	

Adapted from Kusters *et al.*[98]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CK, creatine kinase; eGFR, estimated glomerular filtration rate; IQR, interquartile range; ULN, upper limit of normal range.

dedicated, multidisciplinary clinic with possible support from psychologists.[100] Action plan interventions may be more effective in FH than interventions aimed at altering perceptions about statin therapy. Health literacy must be also considered. Although rare in childhood, patients who are intolerant of pharmacotherapy, notably statins, require special support and follow-up.[41,100]

Carotid IMT imaging and coronary artery calcium assessment have been used in research settings to evaluate early subclinical atherosclerosis and response to statins in FH.[33,34,98,101,102] Long-term statin treatment initiated during childhood in patients with FH was associated with normalization of cIMT progression during aging (*Figure 3B* and *C*).[98] In a recent trial, children with HeFH aged from 6 years treated with rosuvastatin showed slowing of cIMT progression after 2 years, whereas in previous reports, untreated FH children had shown marked progression over this time.[18,103] There are, however, limitations to the use of these surrogate markers in risk stratification of FH patients,[5,40] and in monitoring treatment in an individual,[104] as well as uncertainties relating to the potential benefit of repeat measurement, independent of LDL-C lowering, on clinical outcomes. Consequently, the use of IMT for monitoring patients is not recommended until evidence of its clinical utility is established. Nonetheless, the use of vascular imaging, including IMT, can be highly informative for research purposes. Coronary artery calcium measurement is not recommended because it may be absent when significant atherosclerosis is present, does not usually develop until adulthood, and importantly, repeated CT scans carry an increased lifetime risk of exposure to radiation.

Paediatric patients with uncomplicated and well-controlled phenotypic FH may be managed by experienced primary care practitioners.[5,6,105] However, patients with severely elevated LDL-C levels, multiple cardiovascular risk factors or complications of pharmacologic therapy, or those with HoFH, should be managed with specialist care involving both a (paediatric) cardiologist and lipidologist.[6] Family and transitional care clinics are recommended.[41] All patients should be offered an annual structured clinical review.[6,53]

Contraception and pregnancy-related issues

The risks for the patient and foetus should be discussed at least annually with all women and girls of childbearing age. Low oestrogen oral agents, intra-uterine devices and barrier methods are the preferred contraceptive measures in adult women with FH.[106] Oral contraceptives, especially those with high oestrogen content, may increase triglyceride and LDL-C concentrations in FH, so monitoring of the lipid profile after initiation of these agents is required. More research is needed on the long-term implications of oral contraceptive use in FH.

Counselling is recommended for all women considering pregnancy,[6,106–108] especially when both prospective parents have FH, because of the 25% risk of having a child with HoFH. Statins should be discontinued 3 months before planned conception and during pregnancy and lactation;[106] however, women who become pregnant accidentally while taking a statin should be reassured that the likelihood of foetal complications is small.[109,110] In most patients, statin therapy can be interrupted safely during pregnancy and lactation, especially when treatment is started early in life. Bile-acid resins are the only safe agents for management of hypercholesterolaemia during pregnancy and breast-feeding, although efficacy is modest and poor gastrointestinal tolerability is a major problem;[107] colesevelam is the most tolerable. In women with HoFH, LDL apheresis can be safely and successfully continued during pregnancy.[106,107]

Given increases in maternal cholesterol levels during pregnancy,[111] maternal FH has been associated with atherosclerosis in the uteroplacental spiral arteries, as well as hypercoagulation, local thrombosis, placental infarctions, and placental insufficiency. Available evidence, however, indicates that women with FH are not at increased risk for pre-term delivery, and infants are not at increased risk of congenital malformations or intra-uterine growth retardation.[112] While neonates born to mothers with FH have altered haemostatic profiles regardless of FH status,[113] and infants born to hypercholesterolaemic mothers have increased numbers of fatty streaks in their aortas,[114] the long-term consequences of these manifestations are uncertain. More data on the outcomes of pregnancy in women with FH and the effect of statins on fertility and the foetus in the first trimester are required.[115,116]

Homozygous familial hypercholesterolaemia

Homozygous familial hypercholesterolaemia has been the subject of a recent European Atherosclerosis Society Consensus Paper.[11] Low-density lipoprotein cholesterol levels in children with HoFH are typically $>$13 mmol/L (500 mg/dL), although affected individuals with lower levels have been identified with wider and increased use of genetic testing.[2] Homozygous familial hypercholesterolaemia should be strongly suspected if the parents have cholesterol levels compatible with heterozygous status; if parental cholesterol levels are normal, a recessive form of FH due to mutations affecting the *LDLRAP1* should be considered and sitosterolaemia excluded.[117] Xanthomas can appear within the first few months of life and usually before 10 years of age, and are often the reason why these children come to medical attention; however, their absence or late appearance does not exclude the diagnosis of HoFH.[118]

Children with suspected HoFH should be referred promptly to specialized centres due to the aggressive nature of this condition. Earlier cardiovascular symptoms and signs are typically related to aortic stenosis and regurgitation due to massive accumulation of cholesterol in the valvular and supravalvular regions of the aortic valve,[118] as well as to coronary ostial stenosis, which contrasts with the distal coronary artery involvement seen in HeFH.[11] Angina pectoris, myocardial infarction and death in early childhood have been reported,[49,119–121] although the first major cardiovascular events usually occur during adolescence, depending on the severity of the mutation(s).[118] If HoFH is suspected, an extensive cardiovascular evaluation is imperative, with coronary CT angiography recommended to evaluate the aorta and coronary arteries and magnetic resonance imaging to evaluate the aorta. Invasive coronary angiography is indicated on a patient-by-patient basis depending on clinical status and outcome of non-invasive cardiac investigations. Follow-up investigations should be conducted regularly to monitor aortic and coronary artery disease based on the age of the child and disease severity.

A very aggressive cholesterol-lowering approach should be initiated as soon as possible to prevent or delay the development of CHD.[11] Treatment with a statin and ezetimibe must be started at diagnosis. If available, lipoprotein apheresis should be started as soon as technically possible; this may be as early as age 2 years in specialized centres.[11] In retrospective studies, both approaches have delayed cardiovascular events and increased survival.[122,123] Despite the known risks, liver transplantation is increasingly considered as a therapeutic approach in difficult cases.[11] Two new agents, oral lomitapide, a microsomal triglyceride transfer protein inhibitor, and injectable mipomersen, an antisense RNA therapy, both of which target hepatic production of atherogenic apoB-containing lipoproteins, were recently approved in the USA as adjunct therapy for HoFH in patients aged $\geq$18 and $\geq$12 years, respectively; lomitapide is also approved in Europe and Canada. Although there are no data in children, it is pertinent that lomitapide has been shown to be effective in HoFH patients on apheresis.[11,124] With both agents, fat accumulation in the liver has been observed; other adverse effects include gastrointestinal intolerability with lomitapide and injection site reactions with mipomersen. Given these concerns, the long-term use of these new agents may be limited. Of novel therapies in development, monoclonal antibody therapies to PCSK9 (alirocumab, evolocumab and most recently, bococizumab) show the most promise, lowering both LDL-C and Lp(a),[125] although patients homozygous for *LDLR*-null mutations showed a poor therapeutic response, as expected from the mechanism of action.[126] Paediatric trials of these agents are underway or planned.

Health economics of detection and treatment of familial hypercholesterolaemia

In adults, health economic modelling shows that FH treatment leads to considerable savings on healthcare. Compared with universal screening, cholesterol testing in patients in whom the causative mutation is known, together with cascade testing of immediate family and relatives using DNA information is very cost-effective, because ~50% of them inherit the mutation.[127] Furthermore, intensive lipid-lowering therapy to reduce the LDL-C burden in FH patients is cost-effective.[128,129]

Studies from the Netherlands,[130] Spain,[131] and the UK[132] suggest that the cost per Life Year Gained for DNA-based cascade testing and intensive statin therapy in FH is in the region of €3000–€4000, which compares favourably with other screening strategies, e.g. mammography for breast cancer. Existing cost-effectiveness analyses of cascade screening are limited by different methodologies and assumptions, with most studies from European communities and evaluations restricted to adults.[133] Some experts recommend universal screening,[61,134] particularly in the young, although cost-effectiveness has not been analysed.[127] Where DNA testing is not feasible, it remains to be seen whether screening with a lipid profile alone is cost-effective, although preliminary data from the UK and USA suggest this to be true.[135,136]

A recent report on the health, social, and economic benefits of treating FH estimated that high-intensity statin therapy would lead to 101 fewer cardiovascular deaths per 1000 FH patients treated (between the ages of 30 and 85 years), compared with no treatment.[137] Extrapolating to the 500 million population of the EU (with an estimated 1 000 000 [to 2 000 000] FH patients), roughly €4700 million could be saved from cardiovascular events avoided if all relatives of index cases were identified and treated optimally over a 55-year period, equating to €86 million per year. Clearly, more country-specific health economic evaluations, including estimates of societal benefits that focus on the young, are critical to drive policy change and government funding for early detection and management programs for FH.

Table 7 Gaps in evidence

- Evaluation of the potential contributions of invasive and non-invasive cardiac imaging for assessment of clinical and incident atherosclerotic vascular disease.
- Clinical trials showing reduction in coronary events as a consequence of lowering of LDL-C, although such studies are not ethically acceptable.
- Efficacy and acceptability of new biologics in refractory FH.
- Long-term safety of current and future cholesterol-lowering treatments, including effects on future fertility.
- Cost–benefit analyses of FH identification in childhood.
- Value, cost-effectiveness, and acceptability of universal screening and reverse cascade screening strategies.
- Organization of care between community and specialist settings.

Gaps in evidence

This document is entirely consistent with current international guidelines for the care of patients with FH.[6,134,138,139] However, all of these documents recognize that gaps in evidence remain, which require further study (*Table 7*). Recognition of the value of Mendelian randomization studies as evidence for the benefit of lifelong low LDL-C (e.g. due to loss-of-function genetic variants in *PCSK9*) in the context of FH,[14] together with observational studies comparing outcomes of FH children with FH adult relatives, and equally long-term studies of lipid lowering in FH cohorts, would address these gaps.

Conclusions

Returning to our case...

When the boy was 11, he was referred for genetic testing. A pathogenic LDLR mutation within the promoter region was discovered, and he started on lifestyle management. Statin treatment was initiated around his 12th birthday. After nearly 20 years, he is achieving all treatment goals. He is now older than his father was at time of death, and there is no evidence of the chest pain his father first reported when he was 27 (3 years before his death), which was not thought to be angina pectoris. Because of the young age. Recently, his youngest daughter of 5 was found to carry the same gene promoter mutation, and is currently managed with a heart-healthy diet. Within 3 years, she will start statin therapy. Early identification and optimal treatment from childhood should provide decades of healthy life for the man and his daughter. Finally, 33 of the man's relatives took advantage of cascade screening. Fourteen had high LDL-C levels and were positive for the mutation; they are now appropriately treated, with two cousins receiving stents. This family scenario highlights the value of cascade screening for FH.

It is clear that for FH patients to gain maximum benefit from existing treatments, identification in early childhood is imperative to

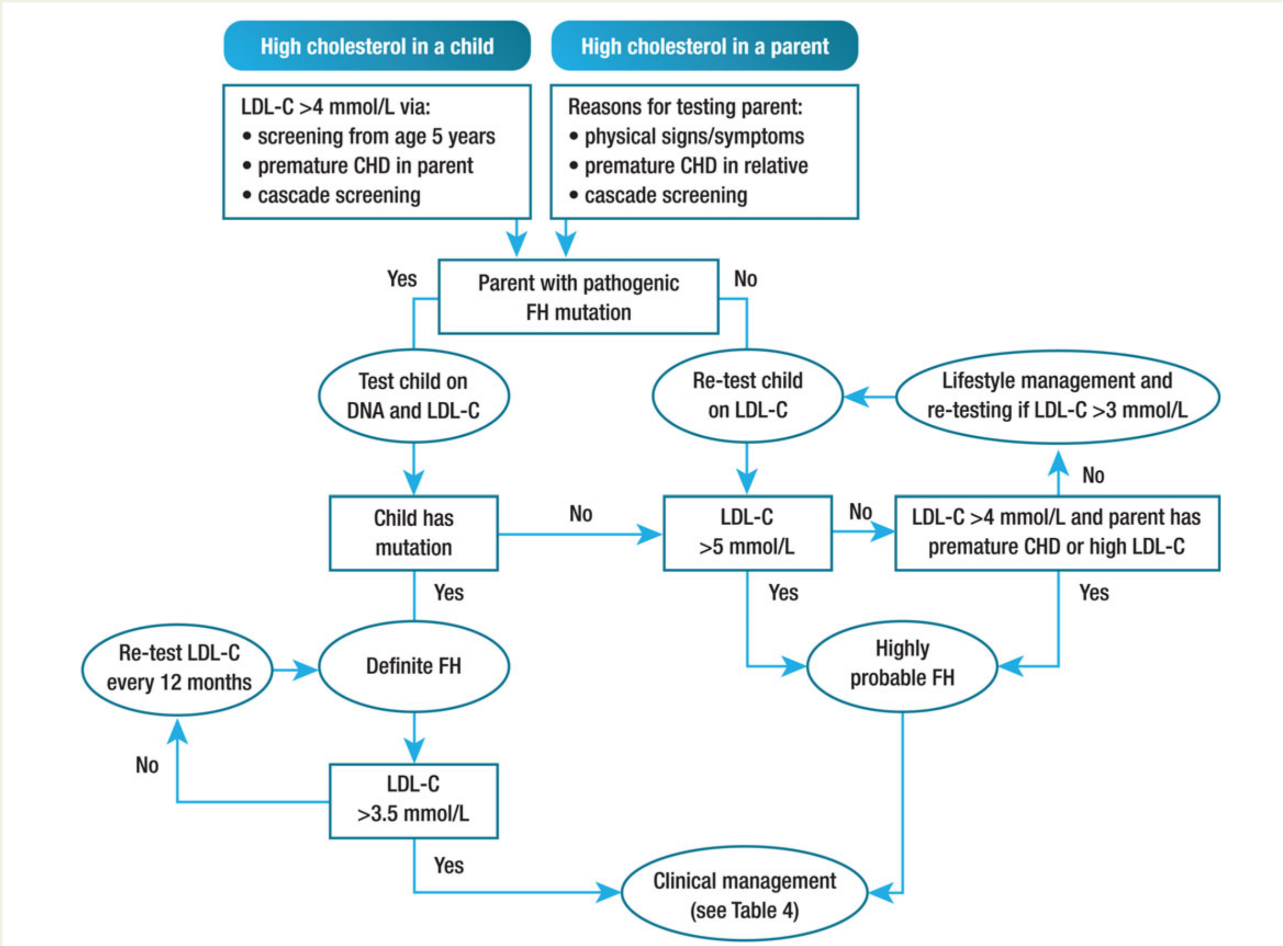

Figure 6 Potential strategy for diagnosis of familial hypercholesterolaemia in children and adolescents.CHD, coronary heart disease; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol. Definitions: Premature coronary heart disease is defined as a coronary event before age 55 years in men and age 60 years in women. Definite familial hypercholesterolaemia is defined as genetic confirmation of at least one familial hypercholesterolaemia-causing genetic mutation. Close relative is defined as 1st or 2nd degree. Highly probable familial hypercholesterolaemia is based on clinical presentation (i.e. phenotypic familial hypercholesterolaemia), either an elevated low-density lipoprotein cholesterol level $\geq$5 mmol/L in a child after dietary intervention or an low-density lipoprotein cholesterol level $\geq$4 mmol/L in a child with a family history of premature coronary heart disease in close relatives and/or baseline high cholesterol in one parent. Cascade screening from an index case with a familial hypercholesterolaemia-causing mutation may identify a child with elevated low-density lipoprotein cholesterol levels $\geq$3.5 mmol/L.

prevent atherosclerosis at the earliest stage of development. Screening for FH in children should be country specific, utilizing all existing screening strategies, including opportunistic screening in the setting of a positive family history, and cascade screening based on genetic testing where available (Algorithm, *Figure 6*). Universal screening might be considered by age 10 years in countries where this is feasible, especially where founder effects with markedly increased frequency of FH are prevalent, such as Quebec in Canada, South Africa and Lebanon. Initiation of statin treatment at a young age is safe in both the short and mid-term, and significantly improves cardiovascular outcomes. Better education of young FH patients, together with frequent follow-up, are critical for ensuring long-term adherence.

Despite evidence gaps regarding the long-term safety and cost-effectiveness of drug treatment from childhood, genetic natural history studies confirm the benefit of lifelong low LDL-C levels.[14] Indeed, recent evidence highlighting the timeliness of statin initiation in FH children on progression of surrogate cardiovascular endpoints implies that statin-mediated LDL-C reduction prevents early cardiovascular events.[18,32,33,70,97,98] Increasing awareness of FH at both clinical and community levels, and recognition and care of FH from childhood, are key to gaining decades of healthy life in children and adolescents with this common inherited disorder.

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Appendix

European Atherosclerosis Society Consensus Panel

This Consensus Panel was comprised of international experts recognized for contributions through basic or clinical research to FH in children, as identified by literature searches. All experts possess expertize in the areas of diagnosis and management of FH, genetic testing and screening for FH, and/or the basic science of the pathophysiology of premature atherosclerosis in FH. The Panel includes a geographic distribution of experts representative of the membership of the European Atherosclerosis Society. Officers and members of the Executive Committee of the Society also participated.

Members

Maurizio Averna, Catherine Boileau, Jan Borén, Eric Bruckert, Alberico L. Catapano, M. John Chapman, Marina Cuchel, Joep C. Defesche, Olivier S. Descamps, Samuel S. Gidding, Henry N. Ginsberg, Robert A. Hegele, G. Kees Hovingh, Steve E. Humphries, Petri T. Kovanen, Jan Albert Kuivenhoven, Luis Masana, Børge G. Nordestgaard, Leiv Ose, Päivi Pajukanta, Klaus G. Parhofer, Frederick J. Raal, Kausik K Ray, Raul D. Santos, Anton F. H. Stalenhoef, Elisabeth Steinhagen-Thiessen, Erik S. Stroes, Marja-Riitta Taskinen, Anne Tybjærg-Hansen, Gerald F. Watts, Albert Wiegman, and Olov Wiklund.

Writing committee

Albert Wiegman, Samuel S. Gidding, Gerald F. Watts, M. John Chapman, Henry N. Ginsberg, Marina Cuchel, and Leiv Ose.

Co-chairs

M. John Chapman, Henry N. Ginsberg and Albert Wiegman.

Search strategy and consensus process

In line with Consensus Panel policy for other papers published by European Atherosclerosis Society Consensus Panels, this manuscript used existing evidence evaluations to make recommendations supported by observational data. We searched Medline, Current Contents, PubMed, the Cochrane Database, and relevant references with the terms FH, inherited hypercholesterolaemia, LDL-C, LDL receptor, apolipoprotein B, children, premature atherosclerosis, event-free survival, diagnosis, treatment, statin, ezetimibe, and PCSK9 inhibitor. Articles published in English between 2000 and 2015 were included.

This review was based on discussions at two meetings of the European Atherosclerosis Society Consensus Panel in London and Lyon organized and chaired by AW, MJC, and HNG, where the search results and drafts of this review were critically appraised; the review results primarily from a consensus of expert opinions.

AW, SSG, GFW, MJC, HNG, MC, and LO each drafted sections and/or outline for the first version, and AW, SSG, and GFW were responsible for revision of the draft. As per the agreed policy, recommendations were not codified for level of evidence nor strength of recommendation, as this Consensus paper was intended principally to raise awareness of FH among clinicians and to provide clinical guidance in diagnosis and management, rather than as a specific guideline. The following terminology was adopted:

Should be: based on systematic review/meta-analysis or trials in young FH patients.

May be: based on clinical or observational data in young FH patients.

Not considered on the basis of available evidence.

All Panel members agreed to conception and design, contributed to interpretation of available data, all suggested revisions for this document and all members approved the final document before submission.

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