The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/155263

Please be advised that this information was generated on 2019-03-14 and may be subject to change.
Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment


1Department of Paediatrics, Academic Medical Center, University of Amsterdam, The Netherlands; 2Nemours Cardiac Center, A.I. DuPont Hospital for Children, Wilmington, DE, USA; 3School of Medicine and Pharmacology, Royal Perth Hospital Unit, The University of Western Australia, Western Australia, Australia; 4Pierre and Marie Curie University, Paris, France; 5National Institute for Health and Medical Research (INSERM), Pitie-Salpetriere University Hospital, Paris, France; 6Columbia University College of Physicians and Surgeons, New York, NY, USA; 7Irving Institute for Clinical and Translational Research, Columbia University Medical Center, New York, USA; 8Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; 9Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway; 10Lipid Clinic, Oslo University Hospital, Oslo, Norway; 11Department of Internal Medicine, University of Palermo, Italy; 12Diderot Medical School, University Paris 7, Paris, France; 13Genetics Department, Bichat University Hospital, Paris, France; 14INSERM U698, Paris, France; 15Department of Medicine, Sahlgrenska Academy, Goteborg University, Gothenburg, Sweden; 16Wallenberg Laboratory for Cardiovascular Research, Gothenburg, Sweden; 17Department of Endocrinology and Prevention of Cardiovascular Disease, University Hospital Pitie-Salpetriere, Paris, France; 18Department of Pharmacology, Faculty of Pharmacy, University of Milano, Milan, Italy; 19Multimedica IRCSS, Milan, Italy; 20Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, The Netherlands; 21Centre Hospitalier Jolimont-Lobbes, Nivelles-Tubize, Belgium; 22Robarts Research Institute, University of Western Ontario, London, ON, Canada; 23Centre for Cardiovascular Genetics, University College London, Institute of Cardiovascular Sciences, London, UK; 24Wihuri Research Institute, Helsinki, Finland; 25Department of Pediatrics, Section Molecular Genetics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; 26Vascular Medicine and Metabolic Unit, Department of Medicine and Surgery, University Rovera and Virgili, Reus-Tarragona, Spain; 27Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, Herlev, Denmark; 28Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; 29Department of Human Genetics, Center for Metabolic Disease Prevention, University of California, Los Angeles, USA; 30Department of Endocrinology and Metabolism, University of Munich, Munich, Germany; 31Carbohydrate & Lipid Metabolism Research Unit; and Division of Endocrinology & Metabolism, University of the Witswatersrand, Johannesburg, South Africa; 32Department of Primary Care and Public Health, School of Public Health, Imperial College, London, UK; 33Lipid Clinic of the Heart Institute (InCor), University of Sao Paulo, Sao Paulo, Brazil; 34Department of Cardiology, University of Sao Paulo Medical School, Sao Paulo, Brazil; 35Department of Medicine, Radboud University Medical Center, Nijmegen, The Netherlands; 36Evangelisches Geriatriezentrum Berlin gGmbH (EGZB), Berlin, Germany; 37Charité – Universitätsmedizin, Berlin, Germany; 38Research Programs Unit, Diabetes & Obesity, University of Helsinki and Heart & Lung Centre, Helsinki University Hospital, Helsinki, Finland; 39Department of Clinical Biochemistry, Section for Molecular Genetics, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; 40Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; 41Department of Experimental and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; and 42Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden

Received 16 February 2015; revised 8 April 2015; accepted 19 April 2015; online publish-ahead-of-print 25 May 2015

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...
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). In severe cases, LDL-C levels exceed 13 mmol/L (500 mg/dL). 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.

Heterozygous FH (HeFH) is common (Figure 1A), present in ~1 per 200–250 of the general population, about two-fold higher than previously thought. 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. 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, 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. 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. 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, and systematic screening strategies are inconsistently implemented. 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, and given the lifelong benefit of genetically determined low LDL-C concentrations, 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, restore endothelial function, and regress thickening of the intima of the vessel wall at a young age.

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.

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. 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. 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. 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...
LDLR (i.e. compound HeFH), with mutations in APOB or PCSK9 genes, as well as an LDLR mutation.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{31}

Increased carotid intima-media thickness (cIMT) and detection of coronary artery calcification by computed tomography (CT) scanning are confirmed markers of early atherogenesis.\textsuperscript{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.\textsuperscript{32} The difference in mean cIMT between children with FH and unaffected siblings may be significant as early as age 7 years (Figure 3A).\textsuperscript{33} Similar findings were observed for mean femoral artery IMT.\textsuperscript{34} Coronary calcification is present in \( \approx 25\% \) of 11–23 year olds with phenotypic HeFH.

### 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.

![Figure 2](https://example.com/figure2.png)

**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.
and especially in the aorta in most adolescents with HoFH, although coronary and aortic calcium score is rarely, if ever, positive in preadolescent 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. \(^{34,39}\)

### Diagnosis

Pediatric 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 \(\geq 5\) 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 baseline high cholesterol in one parent, an LDL-C \(\geq 4\) 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 hypercholesterolemia. \(^{24}\) If the parent has a genetic diagnosis and the child has an LDL-C \(\geq 3.5\) mmol/L (130 mg/dL) suggests FH in the child.

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 with moderate hypercholesterolemia should be tested genetically for FH and inherited elevation in Lp(a). \(^{a}\) Acknowledgement to the FH Foundation (http://thefhfoundation.org/).

---

**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 \(\geq 5\) 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 \(\geq 4\) mmol/L (160 mg/dL) indicates a high probability of FH. If the parent has a genetic diagnosis, an LDL-C \(\geq 3.5\) mmol/L (130 mg/dL) suggests FH in the child.
- Secondary causes of hypercholesterolemia 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 with moderate hypercholesterolemia should be tested genetically for FH and inherited elevation in Lp(a). \(^{a}\) Acknowledgement to the FH Foundation (http://thefhfoundation.org/).
cascade screening. LDL-C levels should be measured at least twice over 3 months to confirm the diagnosis of FH. 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.

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. There is also overlap between those with HeFH and HoFH at LDL-C levels of ~8–13 mmol/L (~300–500 mg/dL). 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. Sitosterolaemia, particularly if xanthoma are present, or cholesteryl ester storage disease when liver transaminases are elevated, although extremely rare, should also be considered. Recent evidence suggests that the marked hypercholesterolaemia in sitosterolaemia may be transient and also diet dependent.

### 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. 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. To increase acceptability, genetic testing for FH in children should be available using DNA extracted from buccal samples. 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. 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. 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. 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.

### Screening

Screening for FH meets World Health Organization guidelines: 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.

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%. In the Netherlands, >28 000 individuals with FH have been identified, almost 23 000 via cascade screening, carrying >500 different mutations. But even with this strategy, ~30% of the 33 300 estimated cases are not identified, 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%. 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.

Universal screening of children for hypercholesterolaemia in Europe has only been implemented in Slovenia from the age of 5 years. 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. Screening can be performed in conjunction with routine health visits such as at the time of immunization, and cascade screening of first-degree family members can follow...
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.

Other risk factors
Given independent associations of type 2 diabetes, hypertension, tobacco use (including passive smoking), and obesity with atherosclerosis development, 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. 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). 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.

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), all of which emphasizes the rationale for greater long-term benefit with initiation of treatment earlier rather than later in life. 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. 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 cholesterol burden are:

**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. (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.
be allowed. Reduction of saturated fat intake has not been thoroughly evaluated, but it is recommended to reduce the intake of cholesterol-containing foods without saturated or trans fats. Consequently, the Panel recommends a heart-healthy, fat-modified diet, which is approved from age 8 years or ideally from childhood. Treatment may be started earlier in severe cases.

**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. Prescribing information is broadly similar in Europe, although rosuvastatin is approved from the age of 6 years. Treatment may be started earlier in severe cases.

### 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. Limitation of foods high in saturated fat will secondarily limit dietary cholesterol intake; cholesterol-containing foods without saturated or trans fats may be allowed. Reduction of saturated fat intake has not been associated with altered physical growth during long follow-up. 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), 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.

**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. FH, familial hypercholesterolaemia.
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).\(^8\)\(^4\)\(^,\)\(^8\)\(^5\) There was, however, no improvement in endothelial function despite significant LDL-C lowering.\(^8\)\(^6\)\(^,\)\(^8\)\(^7\) Reduction in levels of some fat-soluble vitamins and carotenoids can be compensated by ensuring adequate intake of fruit and vegetables.\(^8\)\(^4\) Currently, the use of foods enriched with plant sterols/stanols is not recommended for children under 6 years.\(^8\)\(^4\)

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.\(^8\)\(^8\)–\(^9\)\(^6\) 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).\(^5\)\(^,\)\(^6\)\(^,\)\(^6\)\(^1\) 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.\(^9\)\(^7\) 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).\(^9\)\(^8\) 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).\(^9\)\(^9\)

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

---

**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.

<table>
<thead>
<tr>
<th>Effect on liver function; no. (%) of patients</th>
<th>FH (n = 194)</th>
<th>Siblings (n = 83)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>† in AST &gt; 3 × ULN</td>
<td>1 (0.5)</td>
<td>1 (1.1)</td>
<td>0.26</td>
</tr>
<tr>
<td>† in ALT &gt; 3 × ULN</td>
<td>1 (0.5)</td>
<td>0</td>
<td>0.51</td>
</tr>
<tr>
<td>† in CK &gt; 10 × ULN</td>
<td>0</td>
<td>2 (2.1)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effect on renal function</th>
<th>FH (n = 194)</th>
<th>Siblings (n = 83)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (mL/min/1.73 m(^2)), median (IQR)</td>
<td>127 (121–131)</td>
<td>125 (119–130)</td>
<td>0.05</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>1 (0.5)</td>
<td>1 (1.2)</td>
<td>0.55</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL), median (IQR)</td>
<td>0.9 (0.3–2.3)</td>
<td>1.2 (0.3–3.0)</td>
<td>0.27</td>
</tr>
<tr>
<td>Age at menarche (year), mean (95% CI)</td>
<td>13.1 (12.2–13.4)</td>
<td>13.4 (12.8–14.1)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level of education, n (%)</th>
<th>FH (n = 194)</th>
<th>Siblings (n = 83)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower</td>
<td>31 (17.1)</td>
<td>13 (16.0)</td>
<td>0.96</td>
</tr>
<tr>
<td>Middle</td>
<td>71 (39.2)</td>
<td>33 (40.7)</td>
<td></td>
</tr>
<tr>
<td>Higher</td>
<td>79 (43.6)</td>
<td>35 (43.2)</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Kusters et al.\(^7\)\(^8\)

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.
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. Long-term statin treatment initiated during childhood in patients with FH was associated with normalization of cIMT progression during aging (Figure 3B and C). 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. There are, however, limitations to the use of these surrogate markers in risk stratification of FH patients, and in monitoring treatment in an individual, 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. 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. Family and transitional care clinics are recommended. All patients should be offered an annual structured clinical review.

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. Oral contraceptives, especially those with high oestrogen content, may increase tri-glyceride 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, 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; however, women who become pregnant accidentally while taking a statin should be reassured that the likelihood of foetal complications is small. 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; colesuvelam is the most tolerable. In women with HoFH, LDL apheresis can be safely and successfully continued during pregnancy.

Given increases in maternal cholesterol levels during pregnancy, 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. While neonates born to mothers with FH have altered haemostatic profiles regardless of FH status, and infants born to hypercholesterolaemic mothers have increased numbers of fatty streaks in their aortas, 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.

**Homozygous familial hypercholesterolaemia**

Homozygous familial hypercholesterolaemia has been the subject of a recent European Atherosclerosis Society Consensus Paper. 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. 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 sitosterolemia excluded.

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.

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, as well as to coronary ostial stenosis, which contrasts with the distal coronary artery involvement seen in HeFH. Angina pectoris, myocardial infarction and death in early childhood have been reported, although the first major cardiovascular events usually occur during adolescence, depending on the severity of the mutation(s). 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...
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. Furthermore, intensive lipid-lowering therapy to reduce the LDL-C burden in FH patients is cost-effective.

Studies from the Netherlands, Spain, and the UK 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. Some experts recommend universal screening, particularly in the young, although cost-effectiveness has not been analysed. 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.

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. Extrapolating to the 500 million population of the EU (with an estimated 1 000 000 [to 2 000 000] FH patients), roughly €470 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.

Gaps in evidence

This document is entirely consistent with current international guidelines for the care of patients with FH. 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, 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...
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.

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 ≥ 5 mmol/L in a child after dietary intervention or an low-density lipoprotein cholesterol level ≥ 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 ≥ 3.5 mmol/L.

natural history studies confirm the benefit of lifelong low LDL-C levels. 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. 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.

Acknowledgements
We are indebted to Dr Jane Stock for critical editorial support. The Co-Chairs and Panel members also thank Sherborne Gibbs Limited for logistical support.
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 expertise 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

Writing committee

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.

Funding
This review was supported by unrestricted educational grants to the EAS from Amgen, Aegerion, AstraZeneca, Genzyme, Hoffman-La Roche, Kowa Europe, Novartis, and Sanofi-Aventis/Regeneron. These companies were not present at the Consensus Panel meetings, had no role in the design or content of the Consensus Statement, and had no right to approve or disapprove the final document. Funding to pay the Open Access publication charges for this article was provided by the European Atherosclerosis Society.


References


85. Vickers AW, Bell D, Garton-Smith J, Kirkie AB, Pang, J, Watts GF. Optimising the de-

86. ThoroHaag M, Seed M, De Mott K, Guideline Development Group. Management of pregnancy in women with familial hypercholesterolemia: summary of NICE guid-

87. Ito MK, McGowan MP, Moriarty PM. Management of familial hypercholesterole-

88. Amundsen AL, Ose, L, Nenester MS, Ntnanos FY. Plant sterol ester-enriched spread lowers plasma total and LDL cholesterol in children with familial hypercholesterole-


92. Napoli C, D’Armiento FP, Mancini FP, Postiglione A, Witztum JL, Palumbo G, Palinski W. Fatty streak formation occurs in human fetal aortas and is greatly enhanced by maternal hypercholesterolemia. Intimal accumulation of low density lipoprotein and its oxidation precede monocyte recruitment into early ath-


97. Angloh M, Engler MB, Arterburn LM, Bailey E, Chiu EY, Malloy MJ, Mietus-Snyder ML. Docosahexaenoic acid supplementation alters plasma phospholipid fatty acid composition in hyperlipidemic children: results from the Endothelial As-

