



## Featured Commentary May 2015

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### Hot off the Press: Landmark Position Paper on Paediatric Familial Hypercholesterolaemia from the EAS Consensus Panel

Familial hypercholesterolaemia (FH) is the most common inherited cause of premature coronary heart disease (CHD), affecting about 1 in 200-250 people.<sup>1-3</sup> Based on current estimates, this means that worldwide, one baby is born with FH every minute. Yet most FH patients are not diagnosed, and even if recognised and treated, few attain low-density lipoprotein (LDL) cholesterol goal.

The European Atherosclerosis Society (EAS) has risen to the challenge of improving the care of FH patients. One of the critical catalysts for change was publication of the EAS Position Statement on FH, which highlighted the extent of underdiagnosis and undertreatment of FH.<sup>4</sup> Considering the burden of death and disability associated with untreated – or undertreated – FH, there is a clear rationale to identify and treat children with FH early to prevent atherosclerosis progression and coronary complications.

***The message is clear: early identification and optimal treatment of children with FH saves lives. According to Paediatric Cardiologist, Dr Albert Wiegman (Academic Medical Center, Amsterdam, the Netherlands), one of the lead authors***

***of the EAS Consensus Paper: 'We owe it to our patients to identify and treat children with familial hypercholesterolaemia early, so that they can lead a long and healthy life'.***

This third FH paper from the EAS Consensus Panel focusing on paediatric FH is a landmark for the FH community. The paper is free to download from:

Wiegman A, Gidding SS, Watts GF, Chapman MJ, Ginsberg HN, Cuchel M, Ose L, Averna M, Boileau C, Borén J, Bruckert E, Catapano AL, Defesche JC, Descamps OS, Hegele RA, Hovingh GK, Humphries SE, Kovanen PT, Kuivenhoven JA, Masana L, Nordestgaard BG, Pajukanta P, Parhofer KG, Raal FJ, Ray KK, Santos RD, Stalenhoef AFH, Steinhagen-Thiessen E, Stroes ES, Taskinen M-R, Tybjærg-Hansen A and Wiklund O for the European Atherosclerosis Society Consensus Panel. Familial Hypercholesterolaemia in Children and Adolescents: Gaining Decades of Life by Optimising Detection and Treatment. *European Heart Journal* 2015

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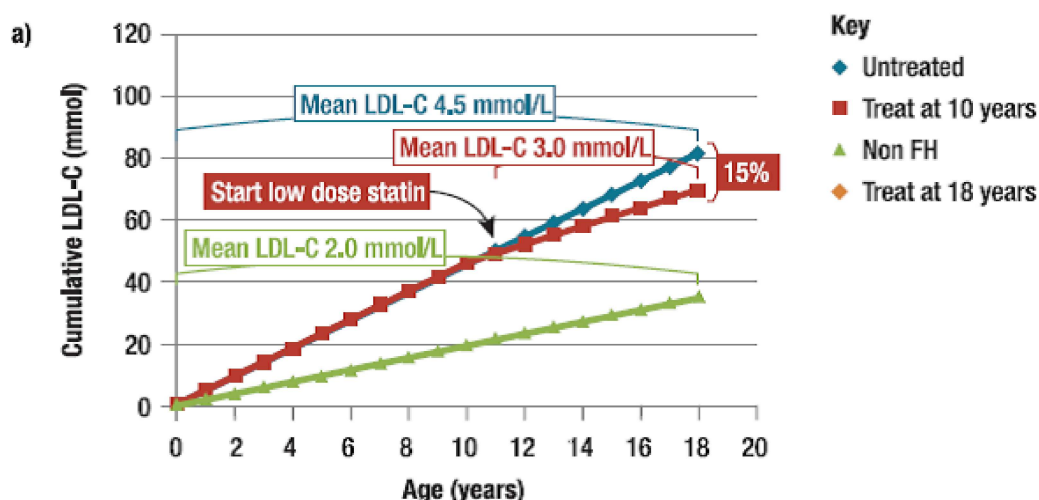
Link: <http://eurheartj.oxfordjournals.org/content/early/recent/>

## Why we need to do better at identifying FH early

There is a clear rationale to identify children and adolescents with FH early to impact the atherosclerotic process and prevent coronary complications. Mutations in the low-density lipoprotein (LDL) receptor gene (*LDLR*), resulting in absent (null) or dysfunctional (defective) LDL receptors on hepatocyte cells, underlie most cases of FH.<sup>4</sup> As these receptors are less able to clear LDL cholesterol from the circulation, plasma levels of LDL cholesterol increase. Correspondingly, there is an increase in the numbers of LDL that penetrate and accumulate in the artery wall, which in turn initiates an inflammatory response, the precursor to vascular injury and formation of atherosclerotic plaque.

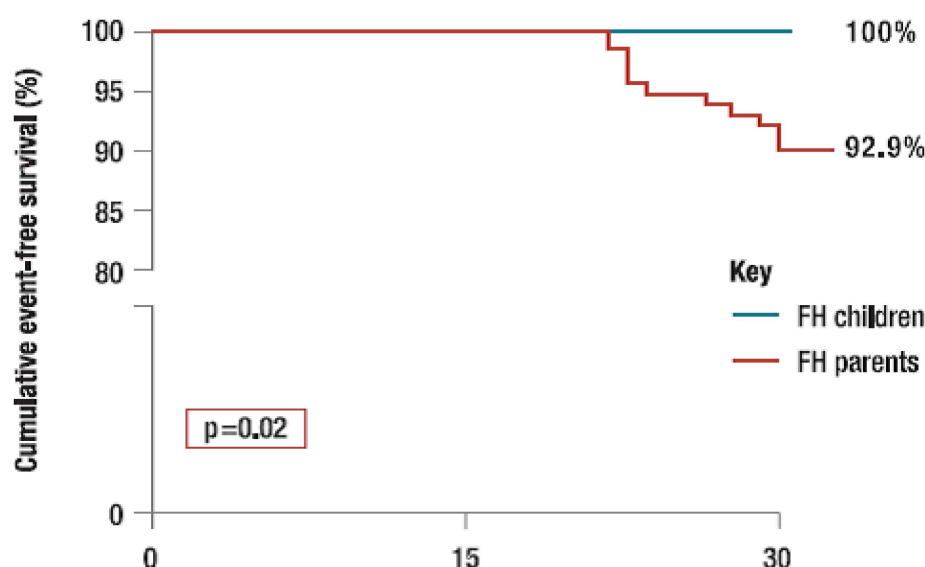
There is already evidence of early atherogenesis in children with FH. Increased carotid intima-media thickness, a marker of early atherosclerotic changes, can be seen as early as 7 years in children with (heterozygous) FH, compared with their unaffected siblings.<sup>5</sup> If untreated, children with FH will be at higher risk of coronary events due to the cumulative burden of elevated LDL cholesterol levels, with many experiencing their first heart attack in early middle age. However, early treatment with statins, together with lifestyle intervention, can reduce the burden of high LDL cholesterol levels (**Figure 1**), which in turn restores endothelial function, attenuates progression of atherosclerosis and improves outcome.<sup>6, 7</sup>

**Figure 1. FH patients who start a statin at age 10 years have a 15% decrease in their cumulative LDL cholesterol burden by age 18 years, compared with no treatment (70 vs. 80 mmol). Adapted from Vuorio et al (2013).<sup>7</sup>**



Given the legacy effect observed from statin trials (although not specifically in FH patients),<sup>8,9</sup> there is likely to be greater benefit in those starting treatment earlier rather than later. Indeed, there is evidence of improved event-free survival in children with FH who start a statin earlier than their affected parents (Figure 2).<sup>10</sup>

**Figure 2. Children with FH who start statins earlier than their affected parents have improved event-free survival. Data from Braamskamp et al (2013).<sup>10</sup>**



## Diagnosis of FH in the young

After excluding secondary causes of elevated LDL cholesterol (for example hypothyroidism, nephrotic syndrome, obstructive liver disease, obesity, anorexia nervosa and treatments such as isotretinoids), FH is diagnosed either on phenotypic criteria, i.e. elevated LDL cholesterol concentration plus a family history of elevated LDL cholesterol, premature coronary artery disease and/or genetic diagnosis, or by positive genetic testing (see **Table 1**). LDL cholesterol levels should be measured at least twice over 3 months. Given that LDL cholesterol levels are not subject to

hormonal influences during childhood, this is the optimum time to differentiate between FH and non-FH based on phenotypic criteria.

Screening for plasma lipoprotein(a) [Lp(a)] levels may provide added prognostic value given that a high Lp(a) value (>50 mg/dL or 80th percentile) increases the risk for premature CHD (by 1.5-fold).<sup>12</sup>

### Table 1. Diagnosis of FH in children

High probability of FH if LDL cholesterol is:

- <sup>≥</sup>5 mmol/L (190 mg/dL) after 3 months dietary intervention
- <sup>≥</sup>4 mmol/L (160 mg/dL) plus family history of premature CHD and/or high cholesterol in one parent (untreated)
- <sup>≥</sup>3.5 mmol/L (130 mg/dL) and parent has a genetic diagnosis of FH

Detection of an FH-causing mutation (usually in the *LDLR* gene), is the gold standard for diagnosis.

Historically, homozygous FH has been characterised phenotypically by LDL cholesterol levels >13 mmol/L (500 mg/dL), although lower levels have been reported, indicative of the clinical and genetic heterogeneity of FH.<sup>11</sup> As part of the EAS-led FH Studies Collaboration (FHSC), the HoADH International Clinical Collaboration is focusing on homozygous autosomal dominant hypercholesterolemia (hoADH), so as to promote early diagnosis and more effective treatment.

## Screening is critical

***If the parent has FH, there is a 1 in 2 chance that the child also inherits FH. This underlies the importance of screening for FH from index cases.***

Universal, opportunistic or cascade screening have all been suggested as possible approaches to identifying FH. These may be based on phenotypic criteria, genetic testing or both. The EAS Consensus Panel recommends cascade screening of families using a combination of phenotypic criteria and genetic testing. If genetic testing is not available, a phenotypic strategy based on country, age and gender-specific LDL cholesterol levels should be used. However, if the parent has a known FH-causing mutation in the LDL receptor gene, genetic testing is the most reliable approach to identify affected family members. Boys and girls with suspected heterozygous FH should be screened from the age of 5 years (**Table 2**).

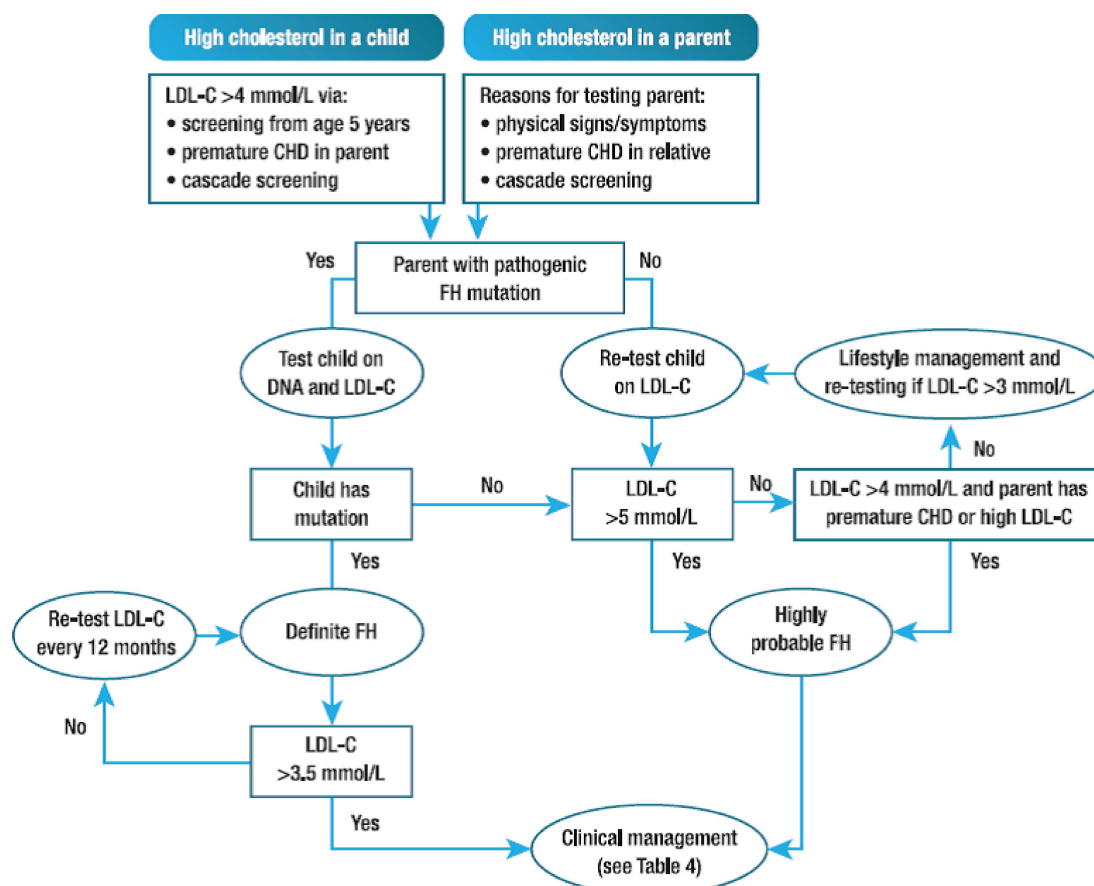
The EAS Consensus Panel emphasises the importance of taking into account the psychological sequelae of genetic testing. Pre-test counselling, in line with the child's level of comprehension and parental literacy, is essential to the consent/assent procedure.

**Table 2. Key points about screening for FH in children**

- The EAS Consensus Panel recommends cascade screening of families using a combined phenotypic and genotypic strategy. However, if genetic testing is not available, phenotypic screening based on country, age and gender-specific LDL cholesterol levels should be used.
- Children (both boys and girls) with suggested FH should be screened from the age of 5 years.
- If homozygous FH is suspected (both parents with FH or xanthoma are evident), children should be screened as early as possible.
- Universal screening of children may be another option, depending on practical and cost considerations.

A diagnostic algorithm is shown in **Figure 3**.

**Figure 3. EAS Consensus Panel recommendation for a potential strategy for diagnosis of FH in children and adolescents.**



## Managing young patients with FH

Lifestyle and statin treatment underpin the management of children and adolescents with FH. Lifestyle recommendations are summarised in **Table 3**. By identifying children

with FH early, lifestyle changes become ingrained before the onset of puberty, and the child is also less likely to start smoking during adolescence.

**Table 3. Lifestyle recommendations in FH**

- Limit foods with saturated fat (<7% of calories from saturated fat).
- Recommend a heart-healthy diet, such as Mediterranean style diets (<30% of calories from total fat, <200 mg cholesterol/day), which has sufficient energy for normal growth. Encourage the intake of fruit and vegetables, whole grains, low-fat dairy products, beans, fish and lean meats.
- Encourage exercise
- Discourage smoking.

Statins are the cornerstone of pharmacotherapy; the age of starting treatment depends on the individual statin (**Table 4**). Patients should start at the lowest dose, with the dose titrated according to the LDL cholesterol lowering response. Boys and girls should start treatment at the same age.

**Table 4. Statins in children with FH (US and Europe)**

- Simvastatin, lovastatin, atorvastatin, pravastatin, fluvastatin and rosuvastatin are approved for use in FH.
- Pravastatin can be used from 8 years, rosuvastatin from 6 years (Europe).
- The remaining statins can be used from 10 years.

#### *LDL cholesterol targets*

There is a lack of definitive evidence for an absolute target for LDL cholesterol in children with FH. Consistent with the previous EAS Position Paper on FH,<sup>4</sup> this EAS Consensus Panel recommends a target LDL cholesterol <3.5 mmol/L (130 mg/dL) in FH children aged 10 years or more. In children aged 8-10 years, clinicians should ideally aim for 50% reduction from pre-treatment LDL cholesterol levels. Addition of ezetimibe (from the age of 10 years in the US and Europe) or a bile-acid sequestrant such as colesevelam (from the age of 10 years in the US) may be considered to attain LDL cholesterol goal.

#### *Monitoring patients*

Children with FH should have weight, growth and developmental milestones monitored. In general, recommendations for monitoring the safety of lipid-modulating agents in paediatric FH are similar to those in adults. However, recognising that individuals will be on treatment for life, clinicians need to be aware of balancing the need to treat with higher doses of a statin against the potential for long-term side effects.

Long-term adherence can be helped by better education of young FH patients, together



with frequent follow-up. However, if patients with heterozygous FH fail to achieve target LDL cholesterol levels despite multiple LDL-lowering treatments and after checking adherence, they should be referred to a specialised lipid clinic for management.

In the context of the routine practice setting, the Panel does not recommend the use of vascular imaging, such as measurement of carotid intima-media thickness, for monitoring FH patients until evidence of its clinical utility is established. Coronary artery calcium measurement is also not recommended as it may be absent when significant atherosclerosis is present and does not usually develop until adulthood. Moreover, repeated computed tomography scans carry an increased lifetime risk of exposure to radiation.

### *Organisation of care*

While recognising that children with well-controlled FH may be managed by experienced primary care practitioners, the Panel recommends that those with very high or poorly controlled LDL cholesterol levels, multiple cardiovascular risk factors or complications of pharmacologic therapy should be referred to a specialist lipid clinic. As recommended by a previous EAS Consensus Panel position paper, it is essential that children with homozygous FH are managed with specialist care involving both a (paediatric) cardiologist and lipidologist.<sup>11</sup>

For management of children with homozygous FH, the reader is referred to the previous EAS Consensus Panel paper.

Click here to read this paper <http://www.eas-society.org/consensus-position-paper-on-hofh.aspx>

## **Societal impact**

Evidence supports the cost-effectiveness of a cascade screening approach for FH in adults together with early initiation of high-intensity of statin.<sup>13-15</sup> It is expected that early identification and optimal treatment of children with FH would also be at least cost-effective, if not cost-saving, from a societal perspective. Indeed, extrapolation based on the 500 million population of the EU (with an estimated 1,000,000 [to 2,000,000] FH patients), suggests that about €86 million per year could be saved from cardiovascular events avoided if all relatives of index cases were identified and treated optimally over a 55 year period. However, so far we lack economic analyses specifically in the younger population with FH, clearly essential to driving policy change for FH.

Other gaps in evidence also remain, including the role of vascular imaging, the long-term efficacy and safety of current and novel treatments, including potential effects on fertility, as well as the organisation of FH care.

## Take home messages

- FH is the most common inherited cause of premature atherosclerosis and CHD, with 1 in 200-250 people affected.
- Acting early to identify and treat children with FH is the key to reducing the burden of early death and disability. This approach will allow children with FH to gain decades of healthy, normal life.
- The Panel stresses that education and improved FH care from childhood will not only save lives, but also have major socioeconomic benefits.
- Action is needed to implement these recommendations and drive policy change on FH.

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