

## Management of familial hypercholesterolemia in children and young adults: Consensus paper developed by a panel of lipidologists, cardiologists, paediatricians, nutritionists, gastroenterologists, general practitioners and a patient organization

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### ABSTRACT

Since heterozygous familial hypercholesterolemia (HeFH) is a disease that exposes the individual from birth onwards to severe hypercholesterolemia with the development of early cardiovascular disease, a clear consensus on the management of this disease in young patients is necessary. In Belgium, a panel of paediatricians, specialists in (adult) lipid management, general practitioners and representatives of the FH patient organization agreed on the following common recommendations.

1. Screening for HeFH should be performed only in children older than 2 years when HeFH has been identified or is suspected (based on a genetic test or clinical criteria) in one parent.
2. The diagnostic procedure includes, as a first step, the establishment of a clear diagnosis of HeFH in one of the parents. If this precondition is satisfied, a low-density-lipoprotein cholesterol (LDL-C) level above 3.5 mmol/L (135 mg/dL) in the suspected child is predictive for differentiating affected from non-affected children.
3. A low saturated fat and low cholesterol diet should be started after 2 years, under the supervision of a dietician or nutritionist.
4. The pharmacological treatment, using statins as first line drugs, should usually be started after 10 years if LDL-C levels remain above 5 mmol/L (190 mg/dL), or above 4 mmol/L (160 mg/dL) in the presence of a causative mutation, a family history of early cardiovascular disease or severe risk factors. The objective is to reduce LDL-C by at least 30% between 10 and 14 years and, thereafter, to reach LDL-C levels of less than 3.4 mmol/L (130 mg/dL).

**Conclusion:** The aim of this consensus statement is to achieve more consistent management in the identification and treatment of children with HeFH in Belgium.

**Keywords :** Familial hypercholesterolemia ; Children ; Cardiovascular disease ; Cholesterol ; Treatment consensus paper ; LDL-receptorgene ; Apolipoprotein B ; Statins ; Ezetimibe ; Fibrates ; Plant sterols ; Stands ; Diagnostic criteria

## 1. Introduction

In patients with heterozygous familial hypercholesterolemia (HeFH), hypercholesterolemia is already present at birth [1] and results in early atherosclerotic lesions, which can be detected by carotid intima media thickness (IMT) measurement as early as 10 years of age [1]. It is reasonable to question when to identify individuals at risk and when to start treatment of HeFH. These questions are not easily answered because there is little evidence to support any particular course of action (or even lack of action). Recently, however, intervention studies in children have provided scientific arguments in favour of treating FH children [2,3]. Firstly, high cholesterol in children has a substantial subclinical impact, which is already measurable from the age of 5 years. In children with a mutation, endothelial dysfunction can be observed (measured by the dilatation of the brachial artery associated with an intense post-ischaeamic flow of arterial blood) [4], as well as a greater IMT thickening detected by carotid echography [5-7]. Secondly, high cholesterol levels in childhood increasingly appear to be a good predictor of cardiovascular risk later in life [8,9]. Thirdly, some interventional studies with statins in children were well tolerated at least in the short-term [10,11]. The statins were highly efficacious at reducing low-density-lipoprotein cholesterol (LDL-C) by -30 to -40% in studies up to 2 years, and, above all, the development/progression of atherosclerosis measured by endothelial function [12] or IMT [13,14]. It should be noted that the Food and Drugs Administration (FDA) approved treatment with simvastatin in 1995, atorvastatin 10-20 mg in 2000 and pravastatin in 2002 for children aged 10 years or more.

While the benefits, objectives and treatment of HeFH are well defined in adults [15], a clear consensus does not exist for the management of children with HeFH. There is, nevertheless, an urgent need for a consensus between paediatricians, general practitioners and specialists in internal medicine, as the HeFH patient will be successively confronted with these specialities in the course of his/her life. Consistent recommendations are pivotal to ensure compliance with the long-term treatment of these patients. The rationale to develop HeFH guidelines is obvious. Firstly, HeFH is a clearly defined condition where elevated levels of cholesterol in young people persist into adulthood. This is not always the case with other causes of hypercholesterolemia, especially those associated with polygenic disorders, where the elevated levels of cholesterol depend to a greater extent on gene-environmental interaction, and thus, where cholesterol levels vary with the exposure of the patients to a variable environment (food intake, physical activity, etc.). Secondly, HeFH is a dominantly inherited disease, resulting in the transmission of the disease to 50% of the offspring of the parent with HeFH. Thirdly, HeFH may be clearly defined by genetic testing in both the parent and the child. Finally the hypercholesterolemia associated with HeFH is clearly considered as a high risk condition for cardiovascular disease (CVD), even higher than the risk of non-FH-hypercholesterolemia at similar LDL-C levels [16]. The objective of this consensus is to propose recommendations for the diagnosis and treatment, and to define the objectives to be attained in the management, of children and adolescents presenting with FH, taking into account recently available data.

## 2. Methods for the establishment of the present guidelines

A first panel (DOS, TS, SX, GI, BV, LMC, DBC, DWK) collected all the papers related to this subject using a MEDLINE search focusing first on reviews and current national and international guidelines, after having agreed the methodology and clearly defining the questions to be answered. This first panel wrote the first draft of the consensus, which was then distributed amongst a comprehensive panel of national experts (the other co-authors).

### 2.1. *Current literature on national and international guidelines*

There are many reviews and opinions on clinical management of FH (see most recently: [3,17]), but very few national guidelines developed by consensus. National guidelines exist in the United States [18] and more recently in the UK [19]. There are also some position papers from experts in Spain [15] and in The Netherlands [20]. There are currently no international guidelines.

### 2.2. *Questions addressed by these guidelines*

In children, the questions to be resolved are : (a) When should we search for HeFH in children and how? (b) When should we suspect HeFH and how can we confirm the diagnosis? (c) When should we start treatment,

what type of treatment should be used and which target level of LDL-C should be recommended? Furthermore, we discuss other important practical issues, such as oral contraception in FH girls, physical activity and use of certain medications that potentially affect cholesterol levels.

### 2.3. *Methods of decision making amongst the panellists*

All panellists read the various published guidelines and opinion papers. We also performed a careful analysis of some specific questions by delegating 2 or 3 panellists to study these questions. For each question, alternatives and arguments FOR and AGAINST each alternative were established. The best alternative for each question was decided by voting according to the AGREE (Appraisal of Guidelines Research & Evaluation) protocol [21], which is commonly used to develop clinical practice guidelines.

**Table 1** *Recommendations on screening and diagnosis.*

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1. When to measure cholesterol in children?
    - No universal screening-After 2 years
    - In a family where HeFH has been identified or suspected (clinical/genetic criteria)
    - In a family with a history of premature cardiovascular disease (<55 (M), <65 (W))
    - If one parent has primary hypercholesterolemia
    - If at least 1 risk factor is present: obesity, high blood pressure, diabetes, smoking, HIV
  2. What to measure?
    - 1st measurement at the time when suspicion is raised: total cholesterol, LDL-C, HDL-C, TG (fasted state is not mandatory)
    - 2nd measurement in fasting state (with biochemical analyses to exclude secondary dyslipidemia)
    - 3rd measurement after 2-3 months of normocholesterolemic diet
  3. Diagnostic criteria for HeFH
    - Confirm vertical transmission (collect cholesterol data of the relatives)
    - Confirm HeFH in one of the parents (includes genetic testing, if needed)
    - LDL-C > 3.5 mmol/L (>135 mg/dL) in the suspected child. NB: if LDL-C < 3.5 mmol/L (<135 mg/dL), repeat the LDL-C measurement one year later (<5% HeFH).
    - Confirm by genetic test (LDL-receptor; APOB) in the suspected child
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## 3. First question: screening for HeFH in children

### 3.1. *Who to screen?*

There are three situations (Table 1) where children can be suspected of FH (with probability decreasing from a to c): (a) a child from a family where HeFH has been identified or suspected (clinical/genetic criteria), (b) a child from a family with a history of premature (before age 55 years in men and 65 years in women) CVD or (c) a child from parents of whom one or both displayed primary hypercholesterolemia. This emphasises the importance of assessing, in all children visiting a doctor (whatever the reason), the family history regarding cholesterol levels, CVD and confirmed or suspected genetic conditions.

The last situation in Table 1 (presence of at least 1 risk factor: obesity, high blood pressure, diabetes, smoking, HIV, etc.) is not strictly related to the search for HeFH, but is given as a matter of completeness for cholesterol screening in general. We must keep in mind that screening for FH is part of the effort to identify children at high cardiovascular risk, whatever the cause of this high risk. These causes include not only genetic dyslipidemia, but also the presence of risk factors, such as hypertension, obesity, metabolic syndrome and active or passive smoking, as well as diseases associated with cardiovascular complications such as diabetes, HIV infection, systemic lupus erythematosus, kawasaki's disease, organ transplantation or being a survivor of childhood cancer. We refer to some of the specific guidelines regarding these situations [22-24].

National screening for cholesterol values at birth or later is currently not recommended [26]. Although such universal screening is technically feasible in the context of neonatal screening on filtered paper or later during the school years, it may be expensive (especially if the option of genetic analyses is chosen), requires solving a number of ethical issues and needs governmental decision and support.

### 3.2. When to screen?

The panellists agree that selective screening should be recommended after the age of 2 years. There are three reasons. Firstly, plasma cholesterol levels are lowest at birth [25] and increase rapidly in the first weeks of life, and then gradually until 2 years of age, when lipid levels become quite constant up to the adolescent growth spurt and are almost similar to those seen in young adults [26]. Secondly, dietary treatment is not recommended in the literature before the age of 2 years [26] (although one recent paper reported the safety of early dietary changes, as early as from 12 months onwards [27]). And finally, the younger the children are, the less chance of overlap between LDL-C levels in subjects with HeFH and without HeFH. As with the UK NICE guidelines [19], we recommend screening before the age of 10 years. Indeed, after this age, dietary habits will be more difficult to correct and there is a large variation in LDL-C (with an average 10-20% fall) during adolescence [28] with increasing risk of false negative results.

### 3.3. What to measure?

We agree that the first diagnostic procedure for FH screening is the measurement of LDL-C levels. Still, we recommend that a classic lipid profile including total cholesterol (TC), triglycerides (TG), LDL-C and high-density-lipoprotein cholesterol (HDL-C) should be drawn as soon as there is any suspicion of HeFH. Also, to avoid any delay with the risk of loss to follow up, we propose to perform the venepuncture or capillary blood sampling if near-patient testing is being recommended at the moment of the visit, even if the subject is in a non-fasting state (TG is the only parameter really affected by a meal and this is not critical for the diagnosis of HeFH). LDL-C should be determined as per current practice by calculation according to the Friedewald equation " $LDL-C = TC - (HDL-C + TG/2.2)$ " (all concentrations in mmol/L). If  $TG > 4.5$  mmol/L (or 400 mg/dL; an exceptional scenario in HeFH, unless there is an additional medical condition such as diabetes) this formula cannot be used and direct LDL-C should be measured.

If cholesterol is high (see cut-off values below), we propose a second lipid profile be performed, in a fasting state, along with biochemical analyses to rule out secondary dyslipidemia (including: hepatic enzymes, renal function, thyroid hormones, glycaemia, and albuminuria/proteinuria) and for other risk factors (e.g. lipoprotein(a) which is often elevated in HeFH [1]). In the absence of secondary causes, a third measurement will be important after 2 or 3 months of diet, especially for patients with poor nutritional habits. At this stage, it is reasonable to refer the patients to a specialised centre.

## 4. Second question: criteria for diagnosing HeFH in children

### 4.1. Exclusion of secondary causes of dyslipidemia

When primary hyperlipidemia has been confirmed, the first steps are correction of dietary habits and exclusion of secondary causes of hyperlipidemia. It is important to keep in mind other possible causes mimicking HeFH (pure elevated cholesterol, possibly associated with hypertriglyceridemia), although most are very rare (Table 2).

**Table 2** Secondary causes of hypercholesterolemia mimicking FH in children.

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|                                                                                   |
|-----------------------------------------------------------------------------------|
| 1. Pure elevated cholesterol                                                      |
| - Nephrotic syndrome                                                              |
| - Hypothyroidism, hypopituitarism, idiopathic hypercalcemia                       |
| - Drugs: isotretinoin                                                             |
| - Anorexia nervosa                                                                |
| 2. Mixed dyslipidemia (hypercholesterolemia and hypertriglyceridemia)             |
| - Diabetes type 1 and 2, metabolic syndrome, obesity, lipodystrophy               |
| - Drugs: antiretroviral therapy, anabolic steroid, oral contraception             |
| - Ketogenic diet, alcohol                                                         |
| - Chronic liver and renal disease                                                 |
| - Pregnancy                                                                       |
| - Turner syndrome, Klinefelter's syndrome                                         |
| - Cancer survivor, burns, HIV, systemic lupus erythematosus, rheumatoid arthritis |
| - Glycogenosis (type I), sphingolipidosis (Niemann-Pick)                          |

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#### *4.2. Clinical and biological criteria for FH*

Once primary hyperlipidemia has been confirmed, the likelihood of the genetic nature of hypercholesterolemia should be checked on the basis of the existence of vertical transmission of hypercholesterolemia and of LDL-C levels.

##### *4.2.1. To establish vertical transmission of hypercholesterolemia*

We strongly advocate that it is important to have, or to establish, first a clear diagnosis of HeFH in one of the parents before trying to confirm the diagnosis in the child. The confirmation of HeFH in one parent is needed, since (a) vertical transmission is an important criterion for diagnosing FH in the child, (b) the parent is at greater risk than the child, and (c) the parents' understanding of the genetic nature of the hypercholesterolemia of their child may improve the compliance to treatment of both the parent and the child.

When such certainty is not possible (only a clinical suspicion in the parent or absent parent), the establishment of the vertical transmission of hypercholesterolemia requires the collection of cholesterol levels (or in its absence, cardiovascular data) from as many family members as possible. When available, it is helpful to plot the cholesterol levels to demonstrate the bimodal distribution of these levels in the family, which is typical of a dominantly inherited genetic disease. This procedure is often restricted by the fact that most families are too small.

##### *4.2.2. Criteria for TC and/or LDL-C levels*

The majority of children with HeFH have TC levels above 6.5 mmol/L (250 mg/dL) with levels of LDL-C in excess of 5.5 mmol/L (200 mg/dL). Sometimes LDL-C levels below 4 mmol/L (160 mg/dL) are encountered in children who carry mutations on the LDL receptor or apolipoprotein B (ApoB) genes. In The Netherlands, Wiegman and colleagues [29], after studying 1034 children from families with FH (confirmed by genetic testing), noted that a fasting LDL-C level of 3.5 mmol/L (135 mg/dL) predicted the presence of FH with a post-test probability of 0.98 for differentiating affected children from non-affected children. As in most epidemiological studies of Belgian children, the levels of TC (LDL-C was not measured in these studies) were quite similar to those of Wiegman et al. in the Dutch non-FH children. We therefore decided to use the same cut-off criteria for LDL-C.

##### *4.2.3. Other criteria*

We should not expect to find tendon xanthomas and corneal arcus in young subjects with HeFH, as this pathognomonic clinical sign generally appears later in life [1]. However, if present, these signs do suggest the possibility of homozygous FH (see [8]).

#### *4.3. Genetic testing*

If a mutation has been identified in the parent, the demonstration of the same mutation in the child is unambiguous proof of the diagnosis of HeFH. Only the genetic demonstration of a functional mutation in the genes for the LDL receptor, PCSK9 or ApoB provides an unequivocal diagnosis, which is advisable when lifelong drug treatment is being considered. This testing needs to be carried out only once in a lifetime. As different mutations produce only small differences in LDL-C levels compared to the large variability in LDL-C levels observed in different families, there is no clear evidence of any correlation between specific mutations and the severity of the disease or to suggest any utility in taking into account the type of mutation to make decisions regarding therapeutic strategy.

Listed below are some other recommendations regarding this testing:

- Refer the child to a specialist for carrying out the testing. There is however no need to visit a genetic centre to have the genetic test. FH treatment consists of drugs that, except for their unusually high dosage and frequent use in combination, are commonly used in the general population. HeFH may occasionally require psychological support and family counselling. HeFH patients require follow up by a specialist well aware of the management of this disease, at least partially with the collaboration of their general practitioner.
- Clarify the diagnosis of HeFH in one of the parents first. Therefore, if possible and not yet done, it is necessary to perform the genetic test first in the hypercholesterolemic parent (or the closest relative).

- In children of parents with a FH mutation, genetic testing should only be performed in children with LDL-C levels suggesting possible HeFH (see clinical diagnosis). In other children of the same family with lower cholesterol levels, follow up is required and a genetic test should be performed as soon as their LDL-C levels reach the possible HeFH threshold.
- In children of parents without a positive genetic test: as the genetic test is not 100% sensitive [2], not finding a mutation in the parent does not mean that the child does not have HeFH. Even in the absence of a positive genetic test, a clinical diagnosis of HeFH can be considered with some certainty if the level of LDL-C is above the 95th percentile (3.5 mmol/L or 135 mg/dL) [30] and if the family has a history of early CVD and/or tendon xanthoma.

## 5. Third question: the treatment of HeFH in children

### 5.1. Dietary recommendations

#### 5.1.1. Basic dietary recommendations

A restricted fat and cholesterol diet is mandatory. This diet should restricted fat intake to 28% and includes <8% saturated fat and <75 mg/1000 kcal cholesterol [31]. Furthermore, a hypocaloric diet is recommended in case of excess weight. These recommendations can be implemented after 2 years of age, under the supervision of a dietician or nutritionist. The composition of fatty acids and cholesterol is an important aspect of the dietary recommendations made to the parents and the young HeFH patient [32]. Saturated fatty acids (SFAs), and above all palmitic acid, the most common SFA, present in dairy products, reduce the expression of the LDL receptor and increase the synthesis of VLDL (very-low-density lipoprotein). In contrast, unsaturated fatty acids, such as linoleic and oleic acid, reduce LDL-C when they replace SFAs (oleic acid being a better choice as linoleic acid reduces HDL-C). Reducing saturated fats and cholesterol in the diet of children does not alter their nutritional status, growth, or pubertal development [33].

#### 5.1.2. Supplements

To date, all studies of supplements are small in size and have short follow up periods. The most studied supplements are phy-tosterol esters and stanol esters. These supplements inhibit the intestinal absorption of cholesterol, even in the presence of a diet poor in cholesterol, and reduce LDL-C by 10-15% in children with FH. However, sterols do not improve flow mediated dilatation [34], they accumulate in atheroma [35] and reduce the level of some fat-soluble vitamins [36]. Therefore, we currently do not recommend the use of sterol- and stanol-enriched foods or supplements in young children.

Supplements containing fatty acid *n*-3 poly-unsaturates (alpha-linolenic acid [ALA] of plant origin, eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA] found in oily fish) are known to have a positive effect on cardiovascular health in adults post myocardial infarction, but there is a lack of clear evidence in primary prevention [37]. Two studies with fatty acid *n*-3 polyunsaturates in children demonstrated slight increases in cholesterol levels (mainly the HDL fractions) and beneficial effects on flow mediated dilation [38]. We do not recommend supplementation with omega-3 capsules in children. However, the basic diet must include poly-unsaturated fatty acids, preferably by increasing consumption of fish.

Another potentially interesting supplement is soy protein. One meta-analysis showed that consumption of soy protein, containing isoflavones, was associated with a 3% reduction of LDL-C, a 1.5% increase of HDL-C and a 5% reduction of triglycerides [39]. It is still unclear whether the cholesterol lowering effect is due to the soy protein or the isoflavones. A recent study in children using a dose of 0.25-0.5 g/kg/day of soy protein showed promising results with an LDL-C/TC decrease of 6.4%/7.7% [40], but more data are needed before we can systematically recommend the medicinal use of soy protein in children. In rare cases, soy protein intake can also cause gynecomastia [41].

Other supplements mentioned in the literature are cereals, grape pips, tea, linseed, psyllium, guar gum, garlic, dried fruits, etc., but these have not been the subject of randomised studies in children and are therefore not recommended.

## 5.2. Pharmacological treatments

### 5.2.1. State of the art

Intervention studies with statins in children were shown to be well tolerated (no side effects, no growth problems, no muscle or liver toxicity) [11] and efficacious at reducing LDL-C (-30 to -40% for study lengths of 2 years). Statins have demonstrated efficacy at improving the clinical outcome in adults [42] but there have been no long-term outcome studies in children. However, short-term studies have demonstrated improvement in coronary heart disease surrogate endpoints for atherosclerosis in children, such as improvement in endothelial function after 28 weeks' treatment [12] and a change in IMT after 2 years' treatment [13,14].

### 5.2.2. When to start pharmacological treatment in children?

The panellists suggest considering pharmacological treatment routinely in children over the age of 10 years and after 6-12 months of dietary treatment (restricted fat and cholesterol), in the conditions summarised in Table 3. Early treatment is mainly motivated by the fact that starting a treatment before puberty will ensure better control by the parents and better acceptance by the child. It was decided that drug therapy needed to be restricted to those for whom we have the strongest confirmation of HeFH (e.g. those carrying a clear causative mutation). Since the presence of LDL-C > 5 mmol/L (190 mg/dL) and of familial premature CVD (in the presence of LDL-C above 4mmol/L [160 mg/dL]) are both not only indicative of HeFH but also of greater CVD risk. It is therefore reasonable to start drug therapy early in this condition.

Other risk factors may also lead to early prescribing of drug treatment, but this is left at the discretion of the prescriber, depending on the number and severity of risk factors. Such conditions are: diabetes, metabolic syndrome, hypertension, HIV infection, systemic lupus erythematosus, organ transplantation or survivor of childhood cancer. In the case of diabetes, and when a genetic test cannot confirm the genetic origin of the dyslipidemia, to decide whether a child has obesity-related hypercholesterolaemia or HeFH may be difficult. However, in both cases, if LDL-C is above 4 mmol/L (>160mg/dL), we recommend starting treatment. This view is in line with the current recommendation of statin treatment in diabetic children [43]. Other less severe conditions which may be indicators for treatment, especially if they are present in combination, are: obesity, male sex, active or passive smoking, oral contraception in girls and emerging risk factors or markers such as lipoprotein(a), homocysteine and hsCRP.

Some children with a mutation in the LDL receptor, who therefore have HeFH, have LDL-C levels below 4 mmol/L (160 mg/dL). In these children, in the absence of other risk factors, it is not necessary to prescribe a pharmacological treatment before the age of 18 years.

### 5.2.3. What treatment to start?

**5.2.3.1. Statins.** For children who meet the criteria for starting pharmacological treatment, a statin is recommended as the first line treatment. In children, the efficacy and safety profile appears to be the same as in adults. The choice of statin may depend on local (regulatory) availability for use in children. For example, in Belgium, reimbursement modalities and indications for children (age >10 years) exist only for atorvastatin 10-80 mg/day and rosuvastatin 10-20 mg/day. However, this may change in the future.

**5.2.3.1.1. Efficacy and safety.** A recent systematic review and meta-analysis [44] has been conducted on clinical trials and observational studies (10 trials;  $N = 947$  individuals) to assess the evidence for efficacy and safety of statin therapy in children and adolescents (age range 8-18 years) with HeFH, treated for a duration ranging from 6 to 96 weeks. The pooled reduction in LDL-C was 2 mmol/L (73 mg/dL) compared to placebo ( $p < 0.0001$ ), but efficacy varied according to the statin and dose used. In these trials, and other prospective case series, there were no significant adverse events. Amongst all statins, pravastatin has so far been the only drug studied for its effect on the surrogate endpoints of atherosclerosis [12-14]. It must be noted that while most clinical trials are of short duration, practical experience with statins now exceeds 20 years, without any report of long-term undesirable effects, and in particular, no reports of side effects on pubertal, intellectual or physical development.

**5.2.3.1.2. Cautions.** Monitoring creatine kinase levels is mandatory, but it is necessary to be aware that increases in enzymes in teenagers will most often be due to other causes, such as vigorous physical activity, especially contact sports, body building, athletics, football, etc. Serum creatine phosphokinase (CK) activity (muscle), alanine aminotransferase (ALAT) and aspartate aminotransaminase (ASAT) levels need to be measured before starting therapy and during follow up (1-3 months after starting, then yearly). The cut-off value

that should lead to an interruption in treatment with the current lipid-lowering drug is five times the upper limit of normal for CK and three times the upper limit of normal for ALAT and ASAT, measured on two separate occasions. Thereafter, we propose to carefully reintroduce the current drug at a lower dosage or another drug (probably another statin) after 3 months of withdrawal. When none of the statins are well tolerated, prescription of ezetimibe can be proposed. Eventually, if LDL-C remains too high, bile acid sequestrants, colestyramine, colestipol or better tolerated, colessevelam may be prescribed in combination with the statin.

**Table 3** Recommendations on drug therapy: age of start, indications, types of treatment and targets. These recommendations are only aimed for children with confirmed HeFH (proven mutation) or highly suspected of HeFH (LDL-C > 3.5 mmol/L or 135 mg/dL plus one parent with clinically diagnosed HeFH). In Tables 3 and 4, these two conditions are aggregated under the term "HeFH children".

| Ages        | Indications                                                                                                                                                                                                                                                                                                                   | Treatments                                                                                                                                                             |
|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <2 years    | All HeFH children                                                                                                                                                                                                                                                                                                             | R/no active screening, no diet.                                                                                                                                        |
| >2 years    | All HeFH children                                                                                                                                                                                                                                                                                                             | R/lifestyle, diet, no smoking, physical activity                                                                                                                       |
| 10-14 years | Only HeFH children with LDL-C > 4 mmol/L (>160 mg/dL) despite effort of diet and one of the following conditions:<br>- a proven mutation<br>- or a familial premature CVD<br>- or LDL-C > 5 mmol/L (>190 mg/dL)<br>- or presence of disease at risk of CVD <sup>a</sup><br>- or presence of several risk factors <sup>b</sup> | R/prescribe statin to achieve a LDL-C reduction of at least 30%. If intolerance to statin, ezetimibe 10 mg/D                                                           |
| 14-18 years | Same indications as above                                                                                                                                                                                                                                                                                                     | R/titrate dosage of statin, change to more potent statin or add ezetimibe 10 mg/D (if intolerance to higher statin dosage), to target LDL-C < 3.4 mmol/L (<130 mg/dL). |
| >18 years   | All HeFH patients                                                                                                                                                                                                                                                                                                             | R/titrate dosage of statin, change to more potent statin or add ezetimibe (or nicotinic acid if high TG or low HDL-C) to target LDL-C <2.5 mmol/L (<100 mg/dL).        |

<sup>a</sup> Disease at risk of CVD: diabetes, metabolic syndrome, hypertension, HIV infection, systemic lupus erythematosus, Kawasaki's disease, organ transplantation or survivor of childhood cancer.

<sup>b</sup> Risk factors: obesity, male sex, active or passive smoking, oral contraception in girls and emerging risk factors or markers such lipoprotein(a), homocysteine, hsCRP.

5.2.3.2. *Others.* Fibrates and derivatives of nicotinic acid are generally not used in children with HeFH. There is only one (pre-statin era) study published in 1985 [45] on the use of fibrates (bezafibrate) in HeFH children, which showed a 15% reduction of TC (LDL-C was not reported). Although ezetimibe is already registered for children aged over 10 years with HeFH, it has not yet been studied in a suitable way in children with HeFH. There is at present no evidence on the benefit of ezetimibe on cardiovascular outcomes and there are some controversial results on the benefit on surrogate endpoints of atherosclerosis in adults [46]. There is however a retrospective review in HeFH children [47], which showed that addition of ezetimibe (10 mg/day) to treatment with atorvastatin or simvastatin achieved an additional LDL-C reduction. The incidence of side effects and the safety profile in co-administration were similar to those of patients receiving statins alone. We recommend that unless a statin is not tolerated, ezetimibe should not be considered before age 18 at the present time. Bile acid chelators like colestyramine and colestipol which were studied [48] and considered in the past as first choice, are currently rarely used, because of a bad tolerance profile leading to very poor compliance, especially amongst adolescents. The recently marketed, colessevelam hydrochloride, is better tolerated in children [49].

#### 5.2.4. Cholesterol targets in children and adolescents

In children, it is not appropriate to recommend a "therapeutic target" since no clinical studies have yet demonstrated the regression or the absence of progression of clinical parameters according to the level of LDL-C. In adults, there is clear evidence that larger LDL-C reductions produce larger reductions in vascular disease risk [42]. For children above 10 years and below 14 years, we only recommend that a reduction in LDL-C of 30% be achieved. After 14 years of age, reaching a specific target: below 3.4 mmol/L (130 mg/dL) becomes more important. After 18 years of age, the target could even be lowered to 2.5 mmol/L (100 mg/dL), depending

on the presence of other risk factors, as discussed by Civeira [15]. For each patient, before taking a decision about the target LDL-C and starting lifelong treatment, it is highly desirable to refer the patient to a centre specialised in the management of HeFH.

**Table 4** *Classes of recommendation and levels of evidence for the screening, diagnosis and treatment of HeFH children and young adults (see what encompasses the term "HeFH children" in the legend of Table 3).*

| Recommendations                                                                                                                                        | Class of recommendation | Level of evidence |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------|
| Children of parents with HeFH should be screened after age 2                                                                                           | I                       | C                 |
| Diagnosis of HeFH in children of HeFH parents is highly suspected by a LDL-C levels above 3.5 mmol/L (>135 mg/dL)                                      | I                       | C                 |
| Diagnosis of FH in children of HeFH parents should be confirmed by DNA testing                                                                         | I                       | C                 |
| HeFH young adults (after age 18) should receive statin therapy and their LDL-C levels reduced below the common adult target (<2.5 mmol/L or 100 mg/dL) | I                       | C                 |
| HeFH children younger than 18 years should receive statin from the age 10 years, in certain conditions (see Table 3)                                   | II a                    | C                 |
| In HeFH children, LDL-C should be reduced by 30% between age 10 and 14 years and below 3.4 mmol/L (<130 mg/dL) after 14 years                          | II a                    | C                 |
| Children with HeFH need to be treated as early as possible                                                                                             | I                       | C                 |

## 6. Other matters

### 6.1. Complementary examinations

It is not recommended to perform carotid echography, cardiac exploration or ankle brachial index in routine practice. Outside of clinical trials, these examinations have not shown to have clear additional value for HeFH diagnosis, treatment decisions and prognostic information or for evaluating the effect of drugs on an individual subject. For example, in one study in HeFH children, the carotid IMT progressed on average at the rate of 0.005 mm per year [13], an increase that cannot be detected on an individual basis.

### 6.2. Contraception

Recommendations about contraception in most guidelines on HeFH, and even in general guidelines on cardiovascular prevention focusing on women [50], are often absent, except in the latest UK NICE guidelines [19]. Because of the increased risk of myocardial infarction, stroke and peripheral artery disease [51] associated with oral contraception, it is advised to prescribe a statin as soon as girls are prescribed contraception. This applies to any form of contraceptive, including vaginal rings, as these are also known to increase ApoB, triglycerides and LDL-C [52]. Because statin teratogenicity remains controversial [53], it is advisable to prescribe contraception in female teenagers who are receiving statins and conversely to prescribe statins in those who are receiving oral contraception. It is important to prescribe a contraceptive formulation that increases LDL-C levels to the least extent and to carefully monitor LDL-C levels during oral contraceptive use. Young women treated with statins should also be warned to stop statin therapy before (planned) conception or as soon as pregnancy is diagnosed.

### 6.3. Physical activity

There is no contraindication for physical activity in children with HeFH. As in any other high risk condition for CVD, increased physical activity remains of great importance for the many benefits it can induce. It is however important to understand that physical activity does not have a significant effect on lipids and cannot be used as a substitute for drug therapy when LDL-C lowering is required.

### 6.4. Other drugs that influence cholesterol levels

Amongst the drugs increasing LDL-C levels, and regularly prescribed during this period of life, are the isotretinoin used for the treatment of acne. These treatments increase thromboembolic risk as well as cardiovascular risk. Therefore they should be avoided in untreated HeFH children. However, if the LDL-C is

lowered to within the normal range by an optimal treatment, it is likely that such a risk would equal that of children without HeFH. As in any other child, follow up of lipid levels is recommended.

## **7. Homozygous familial hypercholesterolemia**

These cases are extremely rare (1/1,000,000), but it is important to detect them at birth. The diagnosed cases bear characteristic skin abnormalities: planar or tuberous cutaneous xanthomas. These are marks or small yellowish elevations, present since birth, which may be found anywhere on the skin but mostly in the intercommissural spaces of the hands and the extension faces of the joints (elbows and knees). The other extra-vascular deposits of cholesterol (corneal arcus, xanthelasmas and tendon xanthomas) generally appear later, rarely before the age of 8 or 10 years. Biologically, there is an increase in TC to over 16 mmol/L (600 mg/dL) before the age of 10 years, and of LDL-C to more than 13 mmol/L (500 mg/dL) with normal triglycerides (often with reductions in HDL-C). The atherogenic risk in these children is very high, with cardiovascular complications presenting at a very early age (usually aortic valve stenosis), sometimes under the age of 10 years. Life expectancy, in the absence of effective treatment, does not exceed 20 years, so it is important to look out for these cases in all couples in which both parents are carriers of HeFH (the risk for the offspring being 1/4). Besides standard treatments (statins from the youngest age), these patients can benefit from the addition of ezetimibe and/or bile acid chelators, as well as exceptional therapeutic options, such as LDL apheresis [54], liver transplant, liver cell grafts [55,56] or gene or antisense RNA therapy [57].

## **8. Conclusions**

The aim of this consensus statement is to achieve more consistent management in the identification and treatment of children with HeFH in Belgium and Europe. Although we are confident that these recommendations are easily acceptable to most practitioners, we must acknowledge that there is little clear evidence to support some of the recommendations (grading in Table 4). Therefore, we advocate future collaborative studies to clarify the benefits of different treatment strategies with regards to age at initiation of therapy, specific indications and statin dosage.

In many countries, the critical problem of reimbursement of lipid-reducing drugs in children is still a burning issue. For example, in Belgium, it has up to now, been limited to those with TC above 8 mmol/L (300 mg/dL) and a positive genetic test or a positive cardiovascular history in a first degree relative.

Of course, besides recommendations, the overall management process in these children also necessitates specific skills and strategies for facilitating change and adherence to medical treatment by the provision of information, including communication of the diagnosis. Regarding this issue, we refer to the excellent book of Edwards and Davis [58]. It is of course imperative to obtain the acceptance, understanding and advice of the parents in order to facilitate compliance of the child to the prescribed treatment, especially regarding drug treatment. That is why, in our recommendation, one of the first steps in the management of FH children is also to ensure the confirmation of the diagnosis and the treatment of the FH parent (see Section 4.2.1 ).

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