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Review article

Familial hypercholesterolemia treatments: Guidelines and new therapies

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ABSTRACT

Familial hypercholesterolemia (FH) is a genetic disorder resulting from mutations in genes encoding proteins involved in the metabolism of low density lipoproteins (LDL) and characterized by premature cardiovascular disease due to the exposure to high levels of LDL-cholesterol (LDL-C) from birth. Thus, the early identification of FH subjects, followed by appropriate treatment is essential to prevent or at least delay the onset of cardiovascular events. However, FH is largely underdiagnosed; in addition, FH patients are frequently not adequately treated, despite the availability of several pharmacological therapies to significantly reduce LDL-C levels. Current guidelines recommend LDL-C targets for FH (either heterozygotes [HeFH] or homozygotes [HoFH]) <100 mg/dL (<2.6 mmol/L) for adults or <70 mg/dL (<1.8 mmol/L) for adults with CHD or diabetes, and <135 mg/dL (<3.5 mmol/L) for children. With the pharmacological options now available, which include statins as a first approach, ezetimibe, and the recently approved monoclonal antibodies targeting PCSK9, the guideline recommended LDL-C target levels can be achieved in the majority of heterozygous FH subjects, while for the most severe forms of homozygous FH, the addition of therapies such as lomitapide either with or without apheresis may be required.

1. Introduction

Familial hypercholesterolemia (FH) is a genetic disorder characterized by very high levels of circulating low density lipoprotein cholesterol (LDL-C) from birth. This does result in the fast development of atherosclerosis with detrimental outcomes such as myocardial infarction and death occurring early in life in patients with FH, especially in those who are not or inadequately treated [1–4]. Despite several effective cholesterol-lowering drugs now being available, a main gap in the management of this disease is the lack of early detection and appropriate pharmacological intervention of FH subjects. In fact, the most severe forms, such as homozygous FH, generally exhibit unambiguous physical signs from the childhood; in contrast, less severe forms of FH may remain hidden until the occurrence of the first cardiovascular event. Thus, the early identification of these subjects is crucial to reduce the burden of cholesterol exposure and the incidence of cardiovascular events.

Genetic defects in several genes involved in LDL metabolism may cause FH; mutations in the *LDLR* gene, encoding for the LDL receptor (LDLR) are the most common cause of FH, but mutations in the *APOB* gene and gain-of-function (GOF) mutations in the *PCSK9* gene can also result in the FH phenotype [5–7]. A rare recessive form of hypercholesterolemia (autosomal recessive hypercholesterolemia, ARH) is caused by the loss-of-function mutations in the *LDLRAP1* gene (encoding for a protein that promotes the internalization of LDLR/LDL complex) [8,9]. However, among subjects with a clinical diagnosis of FH, only 40–80%, depending on the criteria used, exhibit a mutation in one of the classical genes causative of FH, which suggests that a relatively high proportion of "mutation-negative" FH patients are likely to have a polygenic cause underlying their marked hypercholesterolemia [10,11].

The heterozygous form of FH (HeFH) has a prevalence of ~1/500

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Table 1
Summary of the guidelines in adults and children with HeFH [15].

Recommendations	Class of recommendation and level of evidence
FH is recommended to be suspected in:	I; C
patients with early CHD (<55 y men; <60 women)	
subjects with relatives with premature CVD	
subjects with relatives with xanthomas	
subjects with very high LDL-C (adults: >190 mg/dL; children >150 mg/dL)	
Diagnosis of FH is recommended to be confirmed with clinical criteria and genetic testing	I; C
Family cascade screening of an FH index case is recommended	I; C
FH patients are recommended to be treated with high-dose statin, with or without ezetimibe	I; C
LDL-C targets should be < 100 mg/dL or 70 mg/dL in presence of CVD; or alternatively, the maximal reduction with combination therapies	IIa; C
PCSK9 inhibitors should be used in FH patients at very high risk, such as those with CVD or having additional cardiovascular risk factors	IIa; C
Testing in children is recommended from age 5 y (or earlier if suspected of HoFH)	I; C
Children should be educated to a healthy lifestyle and treated with statin from 8 to 10 y; LDL-C target should be < 135 mg/dL	IIa; C

CHD: coronary heart disease; CVD: cardiovascular disease.
Class of recommendations: I: is recommended/indicated; IIa: should be considered.
Level of evidence C: consensus of opinion of the experts and/or small studies, retrospective studies, registries.

to 1/200 in the general population and is characterized by a 2–3 fold increase of LDL-C levels and the occurrence of coronary heart disease (CHD) before age 55 (60 for women) [1,2,12]; the homozygous form (HoFH) is rarer, with a prevalence of ~1/160,000–1/300,000, and HoFH patients are generally characterized by an even more severe LDL-C level phenotype. This greater cholesterol burden does result in the onset of extremely premature cardiovascular disease, with HoFH patients who suffer from a myocardial infarction well before their 10th year of age [2], particularly in HoFH patients who carry two receptor-negative mutations [2,5]. Subjects carrying mutations in *APOB* or *PCSK9* genes generally exhibit a milder phenotype [6,13].

The diagnosis of FH can be based either on clinical criteria or genetic testing; the last provides a definitive diagnosis of FH, but there are some patients with clinical diagnosis of FH in whom no mutation can be identified in the genes classically associated to this condition, suggesting the involvement of unknown genes or a polygenic cause. However, a positive genetic test allows one to discriminate a FH subject from a “normal” hypercholesterolemic individual on the one hand [14], and on the other aids in the identification of FH among relatives. Due to the high number of possible mutations causing FH and due to the possible involvement of additional genes, the phenotype of FH is highly variable, and subjects carrying the same mutation may exhibit profoundly different lipid and clinical profiles as well as different responses to the same pharmacological treatment; in addition, subjects with HoFH may present LDL-C levels well below those expected for this condition and thus may not be recognized.

2. Guidelines for the management of familial hypercholesterolemia

Based on a prevalence of 1/200-1/500, it can be estimated that there are between 14 and 34 million individuals having FH worldwide, but in most countries less than 1% are diagnosed (with some exceptions) [1]. Another major key point is that subjects with FH have an at least 10-fold increase risk of CHD, which may manifest early in life, and the risk remains high even among patients treated with statins, which suggests that they are treated with therapies that are inadequate (low dose, late in life) to achieve the LDL-C levels recommended for their category of cardiovascular risk [1].

To reduce the cumulative burden of elevated LDL-C levels and prevent or delay the onset of cardiovascular events, most guidelines recommend LDL-C targets for FH (either HeFH or HoFH) of <100 mg/dL (<2.6 mmol/L) for adults, or <70 mg/dL (<1.8 mmol/L) for adults with CHD or diabetes, and <135 mg/dL (<3.5 mmol/L) for children [1,15]. A summary of the recommendations in adults and children with FH is presented in Table 1. The most effective approach to identify new cases of FH is cascade screening of family members of a known FH subject, with a simple evaluation of LDL-C levels. Of particular importance is the early diagnosis and management of FH in children, especially in those with the homozygous form of the disease, who may present signs of cardiovascular disease very early in the life if untreated [16–19] (Table 1). A selective screening of children with family history of premature cardiovascular disease and/or high LDL-C levels is recommended; a universal screening of children for hypercholesterolemia might be also considered, for example taking advantage of visits for immunization, followed by the screening of the parents of children with total cholesterol >230 mg/dL (>6 mmol/L) [1].

In clinical practice, FH is commonly diagnosed using criteria based on familial or personal history of premature cardiovascular disease, clinical signs (tendon xanthoma, corneal arcus) and high LDL-C levels, with or without genetic testing; the pharmacological