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Why patients with familial hypercholesterolemia are at high cardiovascular risk? Beyond LDL-C levels ☆

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ABSTRACT

Familial hypercholesterolemia (FH) is a common genetic cause of elevated low-density lipoprotein cholesterol (LDL-C) due to defective clearance of circulating LDL particles. All FH patients are at high risk for premature cardiovascular disease (CVD) events due to their genetically determined lifelong exposure to high LDL-C levels. However, different rates of CVD events have been reported in FH patients, even among those with the same genetic mutations and comparable LDL-C levels. Hence, additional CVD risk modifiers, beyond LDL-C, may contribute to increase CVD risk in the FH population. In this review, we discuss the overall CVD risk burden of the FH population. Additionally, we revise the prognostic impact of several traditional and emerging predictors of CVD risk and we provide an overview of the role of specific tools to stratify CVD risk in FH patients in order to ensure them a more personalized treatment approach.

Introduction

Familial hypercholesterolemia (FH) is a frequent genetic disease characterized by a lifelong elevation of low-density lipoprotein (LDL) cholesterol (LDL-C) levels that has been unequivocally associated with a premature atherosclerosis onset and an increased risk of cardiovascular disease (CVD) [1–3]. Despite LDL-C elevation being unequivocally the main determinant of CVD risk in FH, a significant variability in the incidence of CVD events has been reported in FH patients, even among those carrying the same genetic mutations and comparable LDL-C levels [4,5]. In addition, some FH patients may experience premature CVD events despite receiving maximal lipid-lowering therapy, while others do not develop symptomatic CVD despite having marked LDL-C elevation [6]. Indeed, without questioning the central causal role of the genetically determined high LDL-C levels in the accelerated atherosclerosis progression in the FH population, it is plausible that a complex interplay of multiple CVD risk modifiers beyond LDL-C, including environmental and genetic factors, may represent potential variables explaining the variability of CVD manifestations in FH patients.

Some traditional CVD risk factors, either modifiable or not, are highly prevalent in FH patients and have been independently associated with CVD risk in the FH population [6]. Moreover, some genetic factors beyond FH-causing mutations, such as single nucleotide polymorphisms (SNPs) or genetic variants in different genes either controlling lipoprotein metabolism or not and telomere length in somatic cells, have been shown to predict the FH phenotype and CVD prognosis. Finally, some circulating molecules, which variably contribute to modulate atherosclerosis progression, have been described as surrogate markers of CVD risk in the FH population [7] (Fig. 1).

Given the high heterogeneity of phenotypic expression of FH, it would be desirable for the intensity of cholesterol-lowering therapeutic strategies to be calibrated according to the individual atherosclerotic burden and CVD risk, by reserving the most effective and expensive drugs for patients with higher CVD risk. The assessment of atherosclerotic burden through several instrumental

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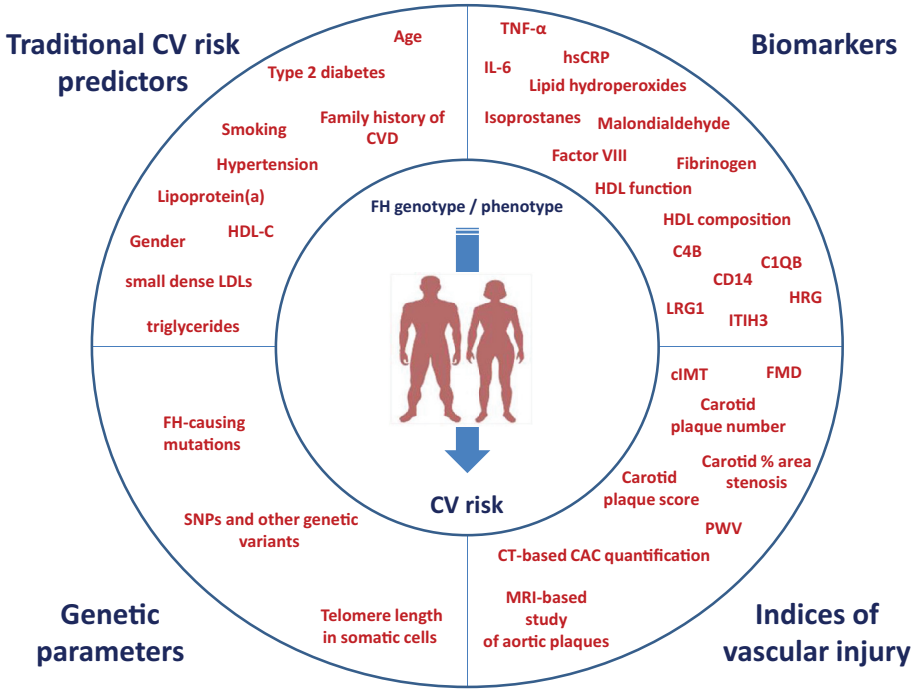

Fig. 1. Traditional and emerging predictors of CVD risk beyond LDL-C in FH. In the FH population, the risk of future CVD events has been reported to be predicted by multiple variables beyond LDL-C, including traditional CVD predictors, genetic parameters other than FH-causing mutations, some biomarkers of different biological functions and indices of subclinical and clinical vascular injury. CAC, coronary artery calcium; CD14, monocyte differentiation antigen; C1QB, complement C1q subcomponent subunit B; C4B, complement protein 4B; cIMT, carotid intima-media thickness; CT, computer tomography; CVD, cardiovascular disease; FH, familail hypercholesterolemia; FMD, flow mediated dilation; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HRG, histidine-rich Q11 glycoprotein; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; ITIH3, inter-alpha-trypsin inhibitor heavy chain H3; LRG1, leucine-rich alpha-2-glycoprotein; MRI, magnetic resonance; PWV, pulse wave velocity; SNPs, single nucleotide polymorphisms; TNF-α, tumor necrosis factor-α.

indices of vascular injury, which may provide comprehensive information on the cumulative individual exposure to different CVD risk factors, has been suggested as a helpful tool to refine CVD risk stratification in FH patients. However, the development and validation of proper FH-specific algorithms for CVD risk stratification integrating the prognostic information from plasma LDL-C levels with that provided by the assessment of additional CVD risk modifiers and indices of vascular injury may be crucial to ensure a more accurate CVD risk estimation [7]. Recently, some clinical and genetic CVD risk scores specific to FH population have been proposed. However, they should be rigorously validated before their clinical application is recommended.

In this state of the art review, we discuss the overall burden of CVD risk in FH patients and we revise the most current knowledge about the prognostic impact of different traditional and emerging predictors of CVD in the FH population. In addition, we provide an overview of the currently available tools for CVD risk stratification in this population.

FH: Genetic, epidemiological and clinical aspects

To date, four main FH-causing genetic mutations, with either autosomal dominant or autosomal recessive patterns of inheritance have been described. Autosomal dominant FH has been associated with high-penetrance genetic mutations in three different genes (i.e., loss-of-function mutations in low-density lipoprotein receptor [*LDLR*] and apolipoprotein B [*APOB*] genes and gain-of-function mutations in the proprotein convertase subtilisin/kexin type 9 [*PCSK9*] gene) [8,9]. Different mutations in one allele of these genes lead to the heterozygous FH (HeFH) phenotype, whereas two mutated alleles in the same gene cause the more severe homozygous FH (HoFH) phenotype. In addition, when one allele in two different genes is mutated the condition of double heterozygosis occurs, which leads to an intermediate phenotype between HeFH and HoFH. In contrast, compound heterozygosis is defined by the presence of two different mutations in two alleles of the same gene; this latter condition is similar to the HoFH phenotype. An additional rare FH genetic variant, autosomal recessive FH, has been described; this condition is due to mutations in the LDLR adaptor protein 1 (*LDLRAP1*) gene that encodes for a protein that promotes the internalization of the LDLR/LDL complex [10].

HeFH is estimated to affect approximately 1 in 225–500 persons worldwide. In contrast, the estimated worldwide prevalence of HoFH is between 1:300,000 and 1:1000,000 [1,11]. However, in some populations, including French Canadians, Lebanese and South Afrikaners, higher prevalence rates have been reported due to genetic founder effect [1].

In HeFH patients, plasma LDL-C levels range from 5 to 13 mmol/L (from 190 to 500 mg/dL), and coronary heart disease typically occurs before 55 years in men and before 60 years in women [12]. In the HoFH population, plasma LDL-C levels are commonly above 13 mmol/L (500 mg/dL), and CVD clinical manifestations appear very early, even in the childhood [13].

The diagnosis of FH may be either clinical or genetic. The clinical diagnosis is based on specific diagnostic criteria. The Dutch Lipid Clinic Network Score (DLCNS) and the United Kingdom Simon Broome Register criteria, which combine clinical, biochemical and molecular genetic parameters, are the most commonly used criteria for the diagnosis of HeFH [14]. An alternative, less specific, diagnostic tool for the diagnosis of HeFH is the United States-Make Early Diagnosis to Prevent Early Deaths (US-MEDPED), based only on age-specific cut-off points for total cholesterol (TC) [15]. Clinical diagnosis of FH is often made after a premature CVD event or after an incidental discovery of very elevated plasma LDL-C levels in

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patients with a family history of hypercholesterolemia and/or premature CVD events along with suggestive physical findings (e.g., tendon xanthomas and arcus cornealis). Current guidelines recommend molecular genetic testing only to confirm a clinical diagnosis of FH or as a part of a genetic screening program of first-degree relatives of FH patients. Of note, up to 60% of the patients with a clinical diagnosis of FH have no detectable genetic mutations [16,17], which has led to hypothesize that their phenotype may be due either to unknown FH-causing mutations or to a polygenic predisposition to severe hypercholesterolemia [18].

FH: Therapeutic aspects

Current guidelines, with minor differences, recommend treating FH patients to reach LDL-C targets <1.8–2.5 mmol/L (70–100 mg/dL) for adults without CVD, <1.4–1.8 mmol/L (55–70 mg/dL) for adults with CVD or diabetes and <3.5 mmol/L (135 mg/dL) for children [19–22]. Cholesterol-lowering pharmacotherapy is required in FH patients to reach these LDL-C targets and should start as early as possible after the diagnosis (in children, drug initiation is recommended after 8–10 years of age). Lifestyle interventions, including a low-fat diet, physical activity and smoking cessation, along with the treatment of additional CVD risk factors, are strongly recommended in association with cholesterol-lowering therapy. Several pharmacological options are currently available for the treatment of HeFH, including statins, ezetimibe, and anti-PCSK9 monoclonal antibodies. High-potency statins are the first-choice drugs for HeFH patients [19]. However, a combination of additional drugs is often required to reach recommended LDL-C targets specific to the FH population [19]. To treat HoFH, additional pharmacological strategies have been approved, including lomitapide (i.e., a microsomal triglyceride transfer protein [MTP] inhibitor) and mipomersen (i.e., an antisense oligonucleotide that triggers the degradation of *APOB* mRNA by binding to its coding region) [19]. Novel cholesterol-lowering therapies, including inclisiran (i.e., a short interfering RNA molecule that inhibits the intracellular synthesis of PCSK9), evinacumab (i.e., a monoclonal antibody against angiopoietin-like 3 [ANGPTL3]), and bempedoic acid (i.e., a citrate lyase inhibitor) may represent future therapeutic strategies for the treatment of FH [19]. In addition, cell- and gene-based therapies are currently under investigations as possible therapeutic options for FH [23]. Clear evidence of their efficacy and safety is expected from the results of phase 3 studies.

Magnitude of CVD risk in FH populations

In the last decades, a number of observational studies with different designs, data sources, and sample sizes have estimated the CVD risk in the FH population [24,25]. Overall, these studies have provided variable results regarding the magnitude of the prognostic impact of FH on CVD risk; in addition, the reliability of these results is sometimes limited by methodological issues.

In some studies, the inclusion of FH patients with a history of previous CVD events may have contributed to an overestimation of the CVD risk. Moreover, higher CVD risk estimates were reported in studies that included both HoFH and HeFH patients, possibly because of a greater affect of FH homozygosity than heterozygosity on CVD risk. In some studies, the exclusive assessment of either fatal CVD outcomes or cardiac outcomes, may have concurred to an underestimation of the CVD risk. Moreover, in some studies lower CVD risk estimates were reported due to the pooling of treated and untreated FH patients. Finally, underestimation of the relative CVD risk in the FH population might be expected in case-control studies, due to the possible inclusion of undiagnosed HeFH patients in the control groups. The latter issue is relevant in the light of the extremely high rate of undiagnosed HeFH patients in the general population [26] (Fig. 2).

Notably, registries have provided the most abundant evidence for CVD risk estimation in FH patients [25–30]. Most registries have enrolled FH patients without a history of previous CVD events, either treated with lipid-lowering therapies or not, whereas few of them have evaluated treated FH patients with a history of previous CVD events. Among untreated FH patients, Mabuchi et al. described a 10.9-fold increased proportional mortality ratio for coronary heart disease [25,27]. Among treated FH patients, lower risk estimates emerged in primary prevention groups than in secondary prevention groups. Thus, for instance, the standardized mortality ratio for coronary heart disease ranged from 1.03, among FH subjects without previous CVD events (primary prevention) [25,29], to 5.15 in FH patients with previous CVD events (secondary prevention) [25,30]. Overall, the strength of these studies results from their large sample size, due to their convenient and easy methods of recruiting. However, registry-derived data are known to be susceptible to selection, detection and performance biases, which may reduce the reliability of their CVD risk estimation [25].

A few hospital- and family-based studies of European FH patients on lipid-lowering therapy and without a history of previous CVD events have been performed [24,25]. In these studies, the standardized mortality ratio for fatal events ranged from 1.32 to 2.88 [4,25,31]. Compared with registries, hospital- and family-based studies are characterized by a lower performance bias. However, their high selectivity inclusion criteria and small sample size expose them to a high degree of selection bias, limiting the generalizability of their results.

Population-based studies may be considered to provide the most reliable data, due to their large sample size and a very low selection bias. To our knowledge, only one population-based study, which enrolled 69,016 individuals from the Danish general population, that is the Copenhagen General Population Study, examined the CVD risk and its determinants in FH patients [32]. This study, by comparing FH patients with non-FH patients, reported significant odds ratios for coronary artery disease of 10.3 and 13.2 in subjects treated and not treated with lipid-lowering therapy, respectively. The systematic review of Wong et al. used a predefined quality check list and described this study as that currently providing the most credible estimate of the increased CVD risk in FH patients [25]. From its reported odds ratios (ORs) a CVD event rate ratio (FH patients versus non-FH patients) of 7.1 (95% CI: 5.7–8.7) was calculated by Villa et al. [33]. The main limitation to the reliability of this high-quality population-based study concerns the fact that its results are not generalizable to other European non-Danish and non-European populations. Thus, further population-based studies are warranted to confirm the magnitude of its CVD risk estimation (Fig. 2).

Traditional predictors of CVD in FH

Different traditional predictors of CVD risk, including a family history of CVD, a personal history of previous CVD events, age, gender, smoking, hypertension, type 2 diabetes, high-density lipoprotein (HDL) cholesterol (HDL-C), triglycerides, small dense LDLs, and lipoprotein(a) [Lp(a)], have been investigated as potential predictors of atherosclerotic burden and/or CVD prognosis in the FH population [6,34] (Fig. 1).

Available evidence indicates that a family history of CVD event in first-degree or second-degree relatives of FH patients and a personal history of previous CVD events in FH patients may confer a higher CVD risk. In a family-based study of CVD risk and its predictors in HeFH, the standardized mortality ratio in patients with a family history of premature coronary artery disease was

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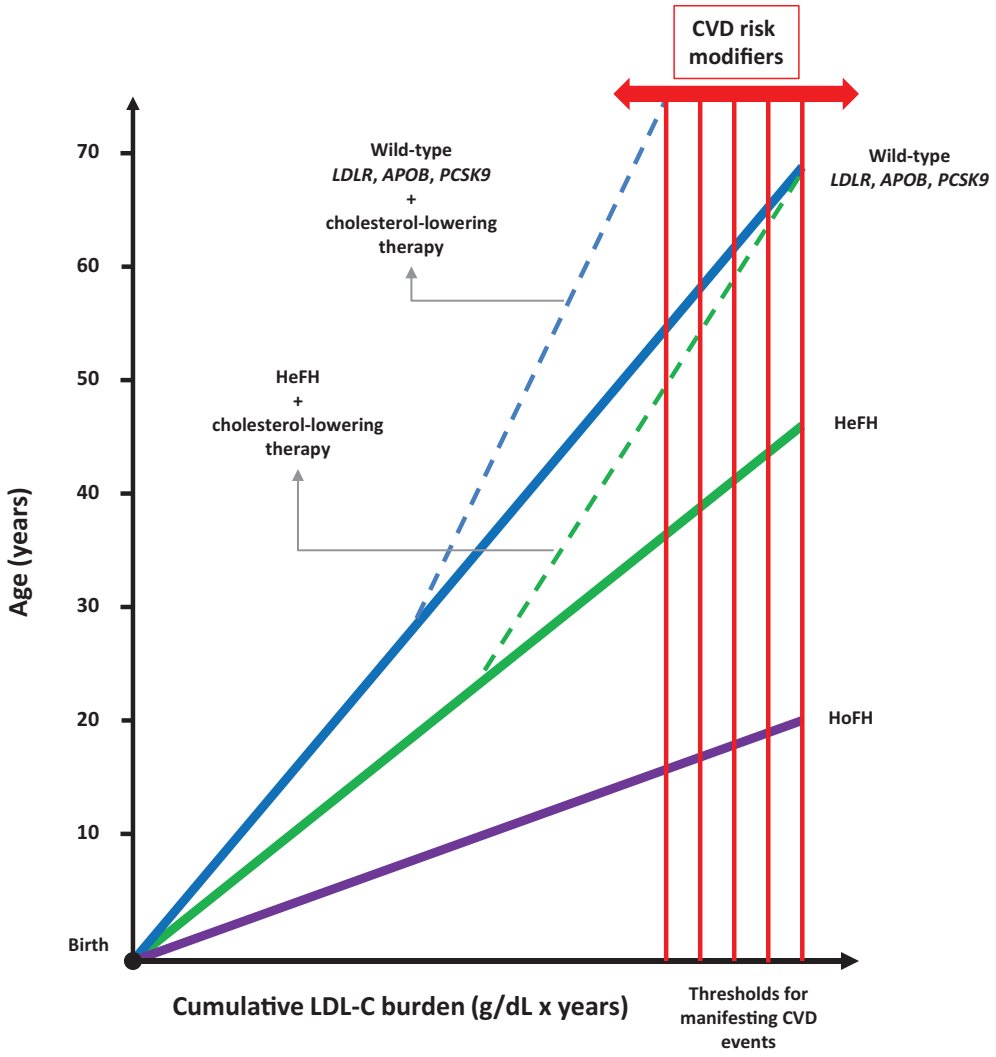

Fig. 2. Familial hypercholesterolaemia and cardiovascular risk. The threshold for manifesting CVD events (red line) varies in FH patients according to the cumulative LDL-C burden (X-axis) as a function of circulating LDL-C levels (slope) and time (y-axis), but also according to a complex interplay of different CVD risk modifiers. HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia.

significantly higher than that of patients with a negative family history [35]. In a recent time-dependent analysis assessing CVD risk in a cohort of 821 HeFH patients on lipid-lowering therapy, patients who developed a CVD event more often had a family history or a personal history of premature CVD [6]. A registry-based study of 781 patients with a clinical or genetic diagnosis of HeFH observed that a personal history of previous CVD events was associated with a higher risk of subsequent CVD events [36].

Age is one of the strongest independent predictors of CVD risk in the HeFH population. Although FH patients of all ages are at higher CVD risk than the general population, a recent systematic review of 17 observational studies estimating CVD risk in patients with FH reported the highest standardized mortality ratio among HeFH patients aged 20–39 years old [24]. Consistent with this result, in a Norwegian cohort of FH patients, the highest excess incidence of CVD events, compared with that of the total Norwegian population, was in the group aged 25–39 years [37]. The finding of a higher CVD risk in this age group may be attributable both to the increase of CVD risk with increasing age in individuals without FH and to the high early mortality of patients with FH.

Whether gender is an independent predictor of CVD in the HeFH population is debated [38]. Overall, data on FH women at any age are less abundant than data on FH men [39,40]. Nonetheless, some studies examined the CVD risk separately in FH men and women, while other studies compared the CVD risk between FH men and women. Some studies showed a higher CVD risk in FH men, whereas others found either no significant difference in the CVD risk between FH men and women [32] or a higher CVD risk in FH women as compared to FH men [41].

In longitudinal studies, smoking was reported as an independent predictor of CVD risk in HeFH patients [42,43]. Moreover, in a cohort of 2400 individuals with FH, smoking cessation was associated with a linear pattern of risk reduction with time [44].

Consistent evidence shows that hypertension is associated with an increased CVD risk in the FH population. Accordingly, a higher prevalence of hypertension was reported in FH patients with diagnosed CVD than in those without CVD [34,45–47]. Furthermore, hypertension was described as an independent predictor of CVD events in patients with HeFH [30,34,45,46].

The contribution of type 2 diabetes to CVD risk in the FH population is not clear. Accordingly, some studies reported a lower prevalence of type 2 diabetes in FH patients than in controls and a lower prevalence of type 2 diabetes in patients with severe FH (defined by a diagnosed LDLR-negative mutation) than in those with non-severe FH (defined by either a diagnosed *APOB* mutation or an LDLR-defective mutation) [47,48]. However, in a retrospective study

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type 2 diabetes was reported as an independent CVD risk predictor in both FH men and women [42].

Low plasma HDL-C levels and a high TC/HDL-C ratio are associated with an increased risk of CVD events in the FH population [49]. However, robust evidence showing that low HDL-C levels predict the CVD risk in FH patients irrespective of other CVD risk factors is lacking.

There is no evidence of an independent direct association between plasma levels of triglycerides/triglyceride-rich lipoproteins and either atherosclerotic burden or CVD risk in the FH population. Indeed, a non-significant trend toward an increase of plasma triglycerides levels was observed in FH children with first-degree relatives reporting a history of premature CVD events as compared to those having premature CVD event-free kindreds [50]. In addition, in a cohort of 282 subjects with clinically diagnosed FH, plasma triglyceride levels did not predict coronary artery disease independently of other CVD risk factors [51]. Moreover, in a retrospective study enrolling 725 individuals with an FH-causing mutation a genetic risk score for plasma triglycerides was not significantly associated with coronary artery disease nor with CVD events [52].

Based on available evidence, small dense LDLs do not independently predict atherosclerotic burden in FH patients [53,54]. Instead, there are no data on the association between LDL particle size/density and CVD risk in the FH population.

Increased plasma concentrations of Lp(a) are detectable in about 30–50% of patients with FH [55] and consistent evidence supports the notion that they may significantly affect CVD risk in the FH population [56–60]. In fact, elevated levels of Lp(a) have been reported to independently predict coronary artery disease in genetically confirmed FH patients [46,56–59]. In addition, serum levels of Lp(a) have been reported to be significantly higher in FH patients with early CVD events than in those with late or no CVD events [57] (Fig. 2).

Other CVD risk modifiers in FH

Recently, several potential CVD risk modifiers in FH patients have been described, including multiple genetic parameters beyond FH-causing mutations, as well as different parameters of HDL composition and function, inflammation, oxidative stress and hemostasis (Fig. 1).

Genetic parameters

Several lines of evidence indicate that different genetic parameters, including FH-causing mutations, such as SNPs or genetic variants in different genes either controlling LDL metabolism or not and telomere length in somatic cells, may influence the disease phenotype and CVD risk in FH patients. In a study by Khera et al. [61] patients with severe hypercholesterolemia carrying an identified FH-causing mutation had an increased CVD risk as compared to mutation negative patients with severe hypercholesterolemia (likely including also FH patients carrying unknown monogenic or polygenic mutations), suggesting that mutation status beyond LDL-C may influence CVD prognosis in the FH population. Among FH patients with positive genetic testing, the impact of different FH-causing genetic mutations (*LDLR* mutations versus either *APOB* or *PCSK9* mutations) on the severity of the disease phenotype and CVD risk is not clear [62,63]. Regarding *LDLR* mutations, a higher risk of premature atherosclerotic disease was observed in FH patients carrying LDLR-negative mutations than in those carrying LDLR-defective mutations [64]. Overall, whether genetic testing for FH-causing mutations may provide prognostic information potentially contributing to a more accurate CVD risk stratification in the FH population needs to be further investigated.

Various SNPs and other genetic variants of genes affecting lipoprotein metabolism, oxidative stress, inflammatory response, renin angiotensin aldosterone system (RAAS), coagulation, expression of red blood cell antigens and other biological functions, have been associated with an increased CVD risk in the FH population.

In a recent study of Japanese HeFH patients carrying an *LDLR* mutation, a gain-of-function genetic variant (rs186669805) of *PCSK9* was associated with an increased prevalence of coronary artery disease [65]. The Taq1B polymorphism of the cholesteryl ester transfer protein *(CETP)* gene was reported as a significant predictor of CVD events in statin-treated HeFH patients [66]. In a population of 221 HeFH patients and 349 FH relatives with diagnosed *LDLR* mutations, a higher prevalence of the 54TT genotype of the fatty acid-binding protein 2 (*FABP-2*) gene was reported among patients with coronary artery disease [67]. Two genetic variants of the ATP-binding cassette sub-family G member 8 (*ABCG8)* gene were associated with a higher CVD risk in FH patients [68]. The E4 genotype of the apolipoprotein E (*APOE)* gene was associated with an increased CVD risk in FH patients [69]. In addition, the N291S genetic variant of the lipoprotein lipase (*LPL*) gene was associated with a higher risk of CVD in FH patients [70] (Fig. 2).

Carrying the rs11053646 (or K167N) genetic variant of the ox-LDL receptor 1 (*OLR1)* gene was associated with a three-fold increased risk of coronary events in HeFH patients, irrespective of other CVD risk factors [71]. In a population of 197 Caucasian FH patients, the frequency of the Ser311 polymorphism in the paraoxonase 2 (*PON2)* gene was significantly higher in the subgroup of patients with clinical manifestations of CVD [72]. Genetic variants of 5-lipoxygenase-activating protein *(ALOX5AP)* gene, encoding for a protein involved in the biosynthesis of proinflammatory leukotrienes, were associated with an increased CVD risk in a cohort of 1817 FH patients [73]. FH patients carrying five or six SNPs of several genes affecting RAAS were demonstrated to have a 2.3-fold higher risk of coronary heart disease than FH patients with none or only one genetic variant [74]. The DD genotype of the angiotensin converting enzyme (*ACE)* gene was associated with an increased CVD risk in HeFH patients [75]. Recently, in a population of 668 FH adults with diagnosed *LDLR* mutations, the rs579459 SNP associated with the presence of the A1 antigen on red blood cells was linked with a 2-fold higher CVD risk than that of individuals with the functional rs514659 SNP associated with the expression of the O blood group [76]. The G20210A polymorphism of the gene encoding for prothrombin was strongly associated with an increased CVD risk in a large FH cohort [77]. In addition, carrying the rs1333047 SNP of the 9p21.3 locus was described as a significant genetic risk factor for atherosclerotic CVD in FH patients, independent of traditional CVD risk factors [78,79].

In contrast, other SNPs and genetic variants of various genes affecting the lipoprotein metabolism, innate immunity and cell motility have been associated with a lower CVD risk in FH patients. For instance, FH patients carrying the CC genotype of the rs1061170 variant of the complement factor H (*CFH)* gene were reported to be protected against CVD [80]. The rs12526453 SNP of the phosphatase and actin regulator 1 (*PHACTR1*) gene, encoding for a protein that binds actin and regulates the reorganization of the cytoskeleton, was associated with a 50% reduction in the risk of CVD events in FH patients [81]. The K allele of the R219K polymorphism of the ATP-binding cassette transporter A1 (*ABCA1*) gene was associated with a lower risk of premature coronary artery disease in HeFH patients [82] (Fig. 2).

Overall, these findings support the suggestion that screening for these genetic variants may help to obtain a more precise CVD risk estimate [18]. However, future studies should evaluate the utility of this approach for CVD risk stratification in FH patients.

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Finally, telomere length in somatic cells is an emerging genetic parameter that might be useful for the identification of FH patients with a more severe disease phenotype and a higher CVD risk. Telomeres are nucleotide sequences located at the end of chromosomes [83]. In physiological conditions, shortening of telomeres occurs during cellular mitosis and cellular telomerases counteract this process by adding telomeric DNA to shortened chromosomes, thus preserving chromosome structure, genomic consistency and normal cellular function. However, telomerase activity is not 100% effective and somatic cells variably undergo a progressive shortening of their telomeres in parallel with the number of their replication cycles [83]. Thus, from a biological perspective, shorter telomere length may be considered a genetic measure of cellular senescence. In pathological conditions, the shortening of telomeres may be accelerated due to molecular pathways that impair telomerase function [84]. For example, several cardiometabolic risk factors, including type 2 diabetes, obesity, hypertension and inflammatory conditions, have been associated with shorter telomeres [84]. Recently, in a population of adult Americans, shorter telomere lengths of replicating somatic cells were reported in HeFH patients than in non-FH hypercholesterolemic patients [85]. This suggests that telomere length might be a potential feature of HeFH as well. However, whether telomere length, as a biological index of accelerated cellular aging, may also correlate with disease severity phenotype, risk of premature onset of CVD, life expectancy or mortality in HeFH patient has not been investigated. Future studies should address this issue, to clarify whether this genetic parameter may be useful for CVD risk stratification in the HeFH population (Fig. 2).

Other parameters

Several parameters of HDL composition and function, inflammation, oxidative stress and haemostasis may be useful for CVD risk stratification in the FH population. The presence of HDL particles with abnormal lipid composition (e.g., triglyceride and sphingomyelin enrichment) was reported to differ between FH patients and normolipidemic subjects [86]. Specifically, a lower transfer of unesterified cholesterol and a higher transfer of triglycerides and phospholipids to HDL particles from LDLs have been described in FH patients as compared to normolipidemic patients, due to continuous interactions between HDLs and high concentrations of LDLs [86]. Because entry of unesterified cholesterol into HDLs has a crucial role for reverse cholesterol transport (RCT), such qualitative changes in HDL composition may contribute to impair RCT and increase atherogenesis in FH patients. In addition, different parameters of HDL function, including cholesterol efflux capacity, antioxidant and anti-inflammatory activities have been reported to be defective in FH patients, reflecting a lower HDL-mediated atheroprotective activity [87]. To our knowledge, no studies have investigated the relationship between HDL qualitative and functional abnormalities and CVD risk in FH patients. Thus, future studies are warranted to assess whether HDL abnormalities in FH might provide additional prognostic information for CVD risk stratification [87,88].

Inflammation has been suggested as a crucial pathogenic pathway for atherosclerosis progression in the FH population [89]. Accordingly, higher levels of different inflammatory mediators, including high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6) and tumor necrosis factor (TNF)-α, have been reported in untreated FH patients than in controls [90–93]. However, it is not clear as to whether a pro-inflammatory status may persist in FH patients even after initiation of cholesterol-lowering therapies [92,93]. Only small observational studies have examined a possible correlation between systemic inflammation and CVD risk in FH patients, with inconsistent results [94,95]. Thus, further studies are needed to elucidate if the use of hsCRP and other biomarkers of systemic inflammation may be a valuable option for CVD risk stratification in FH patients.

Another pathogenic mechanism involved in atherosclerosis development and progression in FH patients is oxidative stress. FH is characterized by an increased generation of pro-atherogenic oxidized LDLs (oxLDLs), reactive oxygen species (ROS), malondialdehyde and isoprostanes [96]. OxLDLs promote atherosclerosis by exerting immunogenic and pro-inflammatory effects [97]. However, the predictive value of circulating oxLDLs in the identification of FH patients with increased atherosclerotic burden and at higher CVD risk is uncertain [98]. ROS may induce oxidative injury of the arterial wall and promote atherosclerosis by reducing antioxidants, upregulating pro-inflammatory molecules, promoting the expression of adhesion molecules on endothelial cell surface and inducing foam cell generation from macrophages [99,100]. In previous studies, some oxidative stress biomarkers (e.g., lipid hydroperoxides, plasma malondialdehyde and urine F2-isoprostanes) were shown to predict CVD risk in hypercholesterolemic patients [101]. Thus, the measurement of these biomarkers might also contribute to CVD risk stratification in FH patients. However, further studies specifically addressing this issue are warranted (Fig. 2).

Hemostasis disturbances may potentially contribute to increase the risk of future CVD events in FH patients. Thus, higher platelet volume, activation and aggregability were found in FH patients. In addition, increased levels of factor VIII and fibrinogen were observed in FH as compared to non-FH individuals [102].

Finally, novel biomarkers have emerged with potential utility for the identification of FH patients at higher CVD risk. To this regard, six proteins identified through highly sensitive proteomic techniques (i.e., leucine-rich alpha-2-glycoprotein [LRG1], inter-alpha-trypsin inhibitor heavy chain H3 [ITIH3], complement protein 4B [C4B], complement C1q subcomponent subunit B [C1QB], monocyte differentiation antigen [CD14] and histidine-rich Q11 glycoprotein [HRG]) have been reported to be inversely associated with atherosclerotic burden in statin-treated FH patients [103]. It is likely that these six molecules may exert an atheroprotective effect in the pathogenesis of vascular damage in FH patients. Therefore, the measurement of these circulating biomarkers might provide some clinical utility for a more accurate CVD risk stratification among FH patients. However, further studies should evaluate this issue (Fig. 2).

Tools for CVD risk stratification in FH

Assessment of vascular injury has been proposed as a helpful tool to refine CVD risk stratification in FH as it may provide an opportunity to quantify the individual cumulative lifetime exposure to multiple factors either promoting or reducing the vulnerability to atherosclerosis. However, a more refined and complete tool for CVD risk stratification in FH patients may be that of building specific algorithms providing an integrate measure of CVD risk by incorporating information on the strongest predictors of future CVD events in this population.

Indices of vascular injury

Non-invasive indices of vascular injury, including both morphological and functional measures, might provide important clinical tools for the identification of asymptomatic FH individuals with a higher CVD risk who may be eligible for a more intense treatment approach.

Regarding morphological measures of vascular injury, some research indicates the utility of the ultrasound cIMT and other carotid plaque measurements, computer tomography (CT)-based

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coronary artery calcium (CAC) quantification, and magnetic resonance (MRI)-based study of aortic atherosclerotic plaques for CVD risk stratification among FH patients without a history of symptomatic CVD.

The ultrasound measurement of the cIMT, an index of subclinical atherosclerosis, was reported to identify patients with severe FH (patients carrying a receptor negative FH-causing mutation) with a potentially higher risk for CVD events [104]. Moreover, other morphological parameters of subclinical atherosclerosis derived from carotid ultrasonography, including the three-dimensional cIMT, which describes the vessel wall intima morphology, and the cIMT variability, which describes the surface pattern of carotid arteries, might provide valuable information for CVD risk stratification among FH patients [105,106]. However, carotid ultrasound markers describing atherosclerotic plaques (i.e., plaque number, plaque score and percent area stenosis) have been reported to be more sensitive than the c-IMT for CVD risk prediction in FH patients [107]. Among these markers, the carotid plaque score (the sum of the maximal thickness of atherosclerotic plaques on both near wall and far wall in the bilateral common and internal carotid arteries) was shown to predict coronary artery disease in FH patients [108,109].

In several studies, the CT-based evaluation of coronary artery calcium (CAC) with the Agatston score, identifying the presence or absence of coronary calcific atherosclerotic lesions, was reported as a reliable modality to predict the risk of future CVD events in the general population. Particularly, a CAC of 0 was associated with a very low risk of future CVD events even in individuals exposed to multiple CVD risk factors [110]. Recently, some prospective studies have confirmed the utility of CAC score for the prediction of CVD risk in the FH population, as well [111–113]. However, it should be considered that the screening of young FH patients with the CAC score may be challenging, as the prevalence of positive CAC (CAC score >0) is likely to decrease with decreasing age of the screened population and a higher number needed to screen may be expected to detect a positive CAC among young FH patients as compared to adult FH patients [114]. Therefore, the identification of specific criteria to selectively recommend CAC scoring in the FH population, possibly take into account age along with other CVD risk modifiers, is warranted.

The MRI-based study of aortic atherosclerotic plaques was proposed as a potential tool for CVD risk stratification in FH patients. Among 36 genetically diagnosed FH patients on lipid-lowering therapy without diagnosed CVD, a higher frequency of lipid-rich plaques, detected through descending thoracic aorta MRI, was observed than in unaffected controls [115]. In addition, their presence was associated with a family history of premature CVD events [115].

Regarding functional measures of vascular injury, few clinical studies with small sample sizes have investigated the association between either endothelial dysfunction or arterial stiffness and CVD risk in the FH population. Available data from cross-sectional studies suggest that endothelial dysfunction, assessed as flow mediated dilation (FMD), may be a very early marker of vascular injury in FH patients. Indeed, a greater impairment of FMD was reported in FH children compared to matched controls [116,117]. In addition, a more pronounced impairment of FMD was described in FH children with a positive family history of premature CVD compared to children with a negative family history [117]. Data about the utility of arterial stiffness for the CVD risk stratification in the FH population are inconsistent. Accordingly, in two cross-sectional studies arterial stiffness did not differ significantly between FH patients and unaffected controls [116,118]. Conversely, a recent study of 245 FH patients reported a significant independent association between arterial stiffness, assessed by the brachial-ankle pulse wave velocity (PWV), and CVD risk [119]. Further prospective studies are warranted to investigate the prognostic value of endothelial dysfunction and arterial stiffness as markers of increased CVD risk in the FH population.

Algorithms for the assessment of the cumulative prognostic impact of CVD risk predictors

An accurate tool for the CVD risk stratification specific to a population should combine multiple independent predictors of CVD in that population. In addition, it should be validated in that population. Therefore, existing algorithms for CVD risk prediction that were validated in general populations (e.g., the Framingham Risk Score, the European SCORE risk charts and the Reynolds risk score) are not adequate to assess the CVD risk in the FH population. Certainly, because of the lifelong elevation in LDL-C levels among FH patients, they would vastly underestimate the real CVD risk in this high-risk population.

The International Atherosclerosis Society (IAS) has proposed a definition of severe FH (including both HeFH and HoFH), potentially associated with a higher CVD risk, based on three criteria (Table 1): 1) LDL-C levels at presentation (untreated LDL-C) alone or in combination with other high-risk conditions (i.e., age >40 years without treatment, smoking, male gender, Lp(a) >50 mg/dL [75 nmol/L], HDL-C levels <40 mg/dL [1 mmol/L], hypertension, diabetes mellitus, family of history of early CVD in first degree relatives [<55 years old in males and <60 years old in females], chronic kidney disease and body mass index >30 kg/m^2); 2) the presence of advanced subclinical atherosclerosis (i.e., CAC score >100 Agatston units or >75th percentile for age and gender, plaques assessed with computed tomography angiography [CTA] having >50% obstruction or non-obstructive plaques in more than one vessel); and 3) the presence of clinically manifest atherosclerotic CVD (Table 1) [120]. According to this definition, severe FH is diagnosed when at least one of these three criteria is fulfilled [120]. However, the utility and reliability of this definition for the identification of those FH patients with a more severe phenotype and a potentially higher CVD risk has been questioned. In fact, by evaluating clinical characteristics of 1732 subjects of the Dyslipidemia Registry of Spanish Arteriosclerosis Society, Pérez-Calahorra et al. showed that LDL-C >400 mg/dL but not the IAS definition of severe FH was significantly associated with the prevalence of CVD when adjusted for traditional CVD risk factors [121].

Recently, two CVD risk prediction algorithms specific to HeFH were proposed. The first, the Montreal-FH-SCORE (MFHS), emerged in 2017 from a Canadian cross-sectional study of 670 adults carrying an FH-causing *LDLR* mutation (Table 1) [122]. The MFHS combined numerical values attributed to the five strongest independent predictors of CVD in that population (i.e., age, gender, smoking, hypertension, and untreated HDL-C levels) and was shown to be an accurate tool for CVD risk prediction. Patients with a high MFHS (>20) had a 10.3-fold higher risk of experiencing CVD events than did patients with a lower MFHS. However, the MFHS was developed to predict retrospectively prevalent, but not incident, CVD events. In addition, it was validated in a small HeFH population including only patients with FH-causing *LDLR* mutations. Thus, its predictive accuracy needs to be evaluated in larger prospective studies of HeFH patients also carrying non-*LDLR* mutations, before it can be broadly applied to CVD risk prediction in HeFH patients. The second risk prediction algorithm specific to HeFH patients, the SAFEHEART Risk Equation, was developed from a large, long-term, prospective study conducted in Spain (Table 1) [123]. In this study, 2404 adults with molecularly defined HeFH were observed for a mean follow-up of 5.5 years. The SAFEHEART Risk Equation was built by combining eight items (i.e., age, male gender, history of previous CVD events, high blood pressure, increased body mass in-

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Table 1
CVD risk stratification tools specific to FH patients.

Proposed FH-specific CVD risk stratification tool	Items	Validation setting	CVD risk measure	Ref.
IAS (severe FH versus non-severe FH)	Severe FH items: • LDL-C >400 mg/dL (10 mmol/L) at presentation *or* LDL-C >310 mg/dL (7.5 mmol/L) at presentation *plus* one high-risk condition* *or* LDL-C >190 mg/dL (5 mmol/L) *plus* two high-risk conditions* • Advanced subclinical atherosclerosis - CAC score >100 Agatston units or >75th percentile for age and sex - CTA with obstructions >50% or presence of non-obstructive plaques in more than one vessel • Clinical atherosclerotic CVD (myocardial infarction, angina, coronary revascularization, non-embolic ischemic stroke, transitory ischemic attack, intermittent claudication)	None	None	[120]
MFHS (higher risk - MFHS >20 versus lower risk - MFHS <20)	Score items: • Age (scores of 0, 4, 8, 12, 16, 20, 24, and 28 are attributed to ages of ≤21, 22–28, 29–35, 36–42, 43–49, 50–56, 57–63, and >63 years, respectively) • Gender (a score of 3 is attributed to the male gender, whereas a score of 0 is attributed to the female gender) • Smoking (a score of 1 is attributed to smoking, whereas a score of 0 is attributed to never smoking) • Hypertension (a score of 2 is attributed to the presence of hypertension, whereas a score of 0 is attributed to the absence of hypertension) • Untreated HDL-C (scores of 12, 9, 6, 3, and 0 are attributed to HDL-C levels of ≤0.60, 0.61–0.90, 0.91–1.2, 1.21–1.5, and >1.5 mmol/L, respectively)	670 adults carrying an FH-causing *LDLR* mutation	Prevalence of CVD (coronary, peripheral cerebrovascular events)	[122]
SAFEHEART Risk Equation	Equation for the 5-year risk of incident CVD events: $1 - 0.9532^{\exp(\sum\beta^{X-5.4078})}$ Equation for the 10-year risk of incident CVD events: $1 - 0.9025^{\exp(\sum\beta^{X-5.4078})}$ In both equations β is the regression coefficient and X is the level for each of the following items: • Age • male gender • history of previous CVD events • high blood pressure • increased body mass index • active smoking • untreated LDL-C • untreated Lp(a)	2404 adults with molecularly defined heterozygous FH	5-year% risk of incident CVD events	[123]
GRS_{CAD} (low risk versus high risk)	Score items: • among 192 SNPs with a genome-wide significant association with coronary artery disease, the number of risk alleles (0, 1 or 2) carried by each individual weighted by the effect size (β) for each SNP	725 individuals carrying an FH causing mutation	Prevalence of CVD	[124]

Abbreviations: CAC, coronary artery calcium; CTA, computed tomography angiography; CVD, cardiovascular disease; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; IAS, international atherosclerosis society; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; Lp(a), lipoprotein(a); MFHS, Montreal-FH-SCORE; SNP, single nucleotide polymorphism.

* High risk conditions: older age (Men: ≥30 years Women: ≥45) or > 40 years without treatment, smoking, male gender, lipoprotein(a) >50 mg/dL (75 nmol/L), HDL-C <40 mg/dL (1 mmol/L), hypertension, diabetes mellitus, family of history of early CVD in first degree relatives (<55 years old in males and <60 years old in females), chronic kidney disease, body mass index >30 kg/m^2.

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dex, active smoking, untreated LDL-C and Lp(a) levels) identified among the independent predictors of incident CVD events in that population. This algorithm was reported to estimate incident CVD events with high accuracy and better than other predictive algorithms validated in the general population [123]. Accordingly, the SAFEHEART Risk Equation showed a good calibration and a better performance in terms of discrimination as compared to the Framingham's risk equation and the American College of Cardiology/American Heart Association CVD Pooled Cohort Risk Equations. However, two main limitations to its generalizability need to be taken into account. First, the short follow-up period of the study in which this equation was validated makes its use not reliable for risk prediction over 10 years. Second, because this equation was developed in a selected European HeFH population, an external validation in other HeFH populations should be performed.

Recently, a genetic risk score to predict the CVD risk (GRS_{CAD}) specific to the HeFH population [124] was validated in 725 HeFH patients with a diagnosed FH-causing mutation from the Institut de recherches cliniques de Montréal (Table 1). This score, based on 192 SNPs with a genome-wide significant association with coronary artery disease, significantly predicted prevalent CVD events (odds ratio 1.80; 95%, CI 1.14–2.85; $P = 0.01$) even after adjustment for CVD risk factors. However, it should be emphasized that its predictive value was evaluated retrospectively in a small Canadian HeFH population. Therefore, its reliability also needs to be assessed in larger prospective studies of multiethnic HeFH populations. Moreover, whether the addition of this genetic risk score to other clinical scores, such as the MFHS, can further refine and improve the CVD risk stratification in HeFH patients needs to be investigated.

In summary, irrespective from their individual characteristics, all the available algorithms for CVD risk stratification specific to the HeFH population (i.e., the MFHS, the SAFEHEART Risk Equation and the GRS_{CAD}) have some common limitations with respect to their clinical applicability. First, since each of them was built considering a single ethnic group, they all need external validation in other populations. Second, since their performance was evaluated in populations of adult HeFH only (mean age ranging from 35 to 50 years old) [122–124], their potential utility and accuracy in estimating the CVD risk either in younger or older HeFH patients needs to be investigated.

Conclusions

The CVD risk varies substantially among FH patients. Beyond LDL-C, whose negative prognostic value is unquestionable, various traditional CVD risk factors have been reported to additionally affect atherosclerotic burden in the FH population. However, even classical CVD risk factors cannot explain all of the variability in the severity of clinical manifestations in this population and additional parameters have emerged as potential modifiers of disease phenotype and predictors of CVD risk in FH. Different indices of atherosclerotic vascular damage, providing an integrated measure of the cumulative lifetime exposure to multiple proatherogenic factors, have been proposed as a helpful tool for an accurate quantification of CVD risk in the FH population. However, there is still no consensus on their clinical use. Recently, several CVD risk stratification algorithms combining multiple predictors of CVD specific to this high-risk population have been proposed to refine CVD risk stratification. However, they require further validation before their wide clinical application might be recommended. Thus, it still remains difficult to tailor the intensity of cholesterol-lowering drug strategies on individual CVD risk of FH patients beyond the systematic correction of traditional modifiable CVD risk factors.

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