Predictors of cardiovascular risk in familial hypercholesterolemia

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Purpose of review
Familial Hypercholesterolemia is associated with an increased risk of cardiovascular disease. The current international guidelines of the main scientific societies consider that all people with familial hypercholesterolemia have a high or very high cardiovascular risk. However, the occurrence of atherosclerotic cardiovascular disease is very heterogeneous in this population. Stratifying risk within people with familial hypercholesterolemia is essential to identify individuals who require intensive cholesterol-lowering therapies.

Recent findings
In the last year, several studies have been published focusing on the contribution of diabetes to familial hypercholesterolemia, the role of stroke, as a manifestation of atherosclerotic disease, and the external validation of the SAFEHEART risk equation in the English population diagnosed with Familial Hypercholesterolemia.

Summary
It is necessary the development of a tool that allows us to identify, in a simple, reproducible, and universal way, patients who may have a high risk of suffering a cardiovascular event and who are susceptible to more intensive treatments to reduce cholesterol levels.

Keywords
cardiovascular disease, familial hypercholesterolemia, risk prediction

INTRODUCTION

Familial hypercholesterolemia is a codominant and highly penetrating monogenic disorder that markedly elevates the concentration of low-density lipoprotein-cholesterol (LDL-C) from birth and, if left untreated, leads to a premature atherosclerotic cardiovascular disease (ASCVD) [1]. Familial hypercholesterolemia is a level 1 genomic condition, which means that it is a preventable cause of premature disease and death from ischemic heart disease, with substantial public health effects [2▪▪]. Its prevalence is high and, according to the latest estimates, it can affect up to 35 million people worldwide, but currently, only 10% are diagnosed, and more than 80% of those treated do not reach the recommended LDL-C targets [3].

The current international guidelines for the management of dyslipidemia of the main scientific societies consider the diagnosis of familial hypercholesterolemia as high risk, and very high risk if it is associated with another risk factor. The European Society of Cardiology (ESC) guidelines [4] automatically classify people with familial hypercholesterolemia as high risk and recommend a 50% reduction from baseline, with a target LDL-C of less than 1.8 mmol/l (70 mg/dl). If people have familial hypercholesterolemia and one or more additional risk factors, such as diabetes mellitus, coronary artery disease (CAD), or chronic kidney disease, they are classified as very high risk and the goal is a 50% reduction from baseline and a target LDL-C less than 1.4 mmol/l (55 mg/dl). The American College of Cardiology (ACC), American Heart Association (AHA) and multisociety cholesterol guidelines [5] define patients with primary severe hypercholesterolemia (LDL-C levels ≥ 4.9 mmol/l [≥

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KEY POINTS

- Physicians need to establish cholesterol control goals based on simple risk equations that allow for treatment strategies of different intensities in familial hypercholesterolemia.
- Familial hypercholesterolemia is a protective factor for type 2 diabetes mellitus, but its presence increases the risk of atherosclerotic cardiovascular disease.
- Familial hypercholesterolemia increases the risk of atherosclerotic cardiovascular disease while sparing the brain. We need more research to confirm the paradox of cerebral atherosclerosis in familial hypercholesterolemia.

190 mg/dl]) as a high-risk statin benefit group from ASCVD. The Canadian Cardiovascular Society (CCS) guidelines [6] classify patients with familial hypercholesterolemia as high risk and with a condition that requires statins. If the LDL-C level is above 2.5 mmol/l (100 mg/dl), despite statins, ezetimibe or PCSK9 inhibitors can be added to statin therapy [7].

NEED TO ESTIMATE THE RISK IN INDIVIDUALS WITH FAMILIAL HYPERCHOLESTEROLEMIA

The genetic diagnosis of familial hypercholesterolemia is widely accepted as evidence of substantially increased cardiovascular risk. However, recent large-scale population studies challenge this concept, since a portion of patients with a genetic diagnosis of familial hypercholesterolemia do not have marked hypercholesterolemia, and not all individuals with severe hypercholesterolemia have a causal familial hypercholesterolemia mutation identified. Khera *et al.* [8] included a series of case-control studies to assess the prevalence of 14 117 individuals within the Myocardial Infarction Genetics Cohort and only 164 (1.2%) were positive for a causative variant of familial hypercholesterolemia. In the Mayo Clinic study by Saadatagah *et al.* [9], 1682 individuals (50.2 ± 8.6 years, 41.3% male) from southeastern Minnesota with primary hypercholesterolemia (LDL-C ≥ 155 mg/dl in the absence of identifiable secondary causes), the familial hypercholesterolemia phenotype was defined as a Dutch Lipid Clinic Network (DLCN) score at least 6 points and 17.1% had an identifiable genetic cause and the overlap between genotypic and phenotypic familial hypercholesterolemia was modest. Therefore, we can affirm that the expression of monogenic familial hypercholesterolemia is highly variable. These results agree with those previously reported by Abul-Husn *et al.* [10]. On the other hand, the LDL-C in cases of heterozygous familial hypercholesterolemia (HeFH) due to a pathogenic variant may overlap with the values observed in homozygous familial hypercholesterolemia (HoFH), while, on the contrary, in cases of molecularly proven HoFH, they have been documented LDL-C levels in the typical range for HeFH, not HoFH [11].

How should we assess cardiovascular risk in people affected by familial hypercholesterolemia? Should risk equations be trusted to stratify atherosclerotic cardiovascular disease risk?

The use of risk stratification tools can help increase the cost-effectiveness of new lipid-lowering therapies (LLT) and thus increase access to those who need them most in cost-contained healthcare settings [12]. Risk stratification can identify patients who require treatment intensification and guide the best use of healthcare resources [13]. Male sex, late initiation of LLT, smoking, low high-density lipoprotein cholesterol (HDL-C), obesity, diabetes mellitus, hypertension, chronic kidney disease, and elevated lipoprotein (a) [Lp(a)] levels are independent predictors of the risk of ASCVD in patients with familial hypercholesterolemia [14▪▪,15]. There is a clear need for improved assessment of sex-specific risk factors for ASCVD in women with familial hypercholesterolemia, such as reproductive history. Improved tools are also required to predict the lifetime risk of ASCVD in children and younger patients with HeFH [16,17].

Risk scores such as SCORE or the US pooled risk equations widely used in the general population underestimate risk in people with FH. This occurs because people with familial hypercholesterolemia are exposed to elevated levels of LDL-C throughout their lives. In addition, risk estimation may become even more difficult since statins, which are frequently used in people with familial hypercholesterolemia, not only lower LDL-C, but may mitigate the risk of ASCVD [18].

In recent years, equations have been developed to estimate the risk of suffering a cardiovascular event in individuals with familial hypercholesterolemia. The SAFEHEART risk-equation (SAFEHEART-RE) was developed in a Spanish cohort where all individuals with familial hypercholesterolemiaFH were molecularly confirmed, with more than 80% undergoing LLT (with a mean treatment period of 12.9 years). In this study, Pérez de Isla *et al.* [19] evaluated 2404 individuals with familial hypercholesterolemia (45.2% men, mean

age 45.5 years, mean baseline LDL-C 178 mg/dl) and were followed up for a mean of 5.5 ± 3.2 years and 0.5% ($n = 12$) and 5.1% ($n = 122$) suffered fatal and nonfatal events, respectively. Equations for the prediction of events in people with or without previous manifestations of ASCVD were derived, covering parameters such as age, sex, previous ASCVD, blood pressure, BMI, smoking status, and LDL-C and Lp(a) concentrations. The equations for predicting risk at 5 and 10 years had a Harrel C index of 0.8 and better discriminated ASCVD than Framingham risk scores. In 2022, this same group published the determinants and characteristics of patients with familial hypercholesterolemia who were protected against ASCVD and had a normal life expectancy, the so-called 'resilient' familial hypercholesterolemia. Being female, having a defective LDL receptor mutation, higher plasma HDL-C levels, lower Lp(a) levels, and absence of hypertension were associated with this condition [14▪▪].

The SAFEHEART-RE has been tested in the French registry of Familial Hypercholesterolemia (REFERCHOL) [20]. This group also analyzed the influence of the cholesterol index per year, which assesses the duration and intensity of vascular exposure to elevated cholesterol levels. This simple estimation requires knowing the individual's annual LDL-C. Thus, having access to the history of LDL-C analysis, throughout life, and having an adequate number of determinations, allows a correct calculation, however, the performance was adequate considering that a lower LDL score years of 6000 mg/dl is associated with low risk and levels above 16 000 mg/dl with high risk.

McKay *et al.* [21▪] evaluated the performance of SAFEHEART-RE in a historical cohort of patients followed in UK primary care clinics ($n = 3643$, 57% male, mean age 51 years). In most cases, familial hypercholesterolemia was diagnosed based on clinical criteria, the mean available LDL-C was 141 mg/dl, and 68.8% used LLT and 147 outcome events were observed during a median of 3.73 (IQR 1.59–6.48) years of follow-up.

The original SAFEHEART-RE model had limited generalizability to the routinely identifiable English primary care familial hypercholesterolemia population. However, this group differs considerably from individuals with genetically confirmed familial hypercholesterolemia.

Paquette *et al.* [22▪] developed the FH-Risk-Score in a multinational population from North America and Europe ($n = 3881$, 45% men, mean age 43 years, 74% with molecular diagnosis), using the variables age, sex, HDL-C, Lp(a), smoking, hypertension, and LDL-C with a Harrel C index of 0.75.

To improve the accuracy of these equations, the detection of subclinical atherosclerosis has been investigated. In fact, Gallo *et al.* [13] demonstrated that the coronary artery calcium (CAC) score helps improve risk discrimination and reclassification in addition to SAFEHEART-RE in the same populations as SAFEHEART and REFERCHOL.

Previously, Miname *et al.* [23] had suggested that a CAC score was better than the Framingham score to estimate the cardiovascular risk in primary prevention for ASCVD in 206 molecularly tested Brazilian individuals with familial hypercholesterolemia. Vascular age rather than biological age increased the ROC curve of the Framingham risk score (an equation not intended for people with familial hypercholesterolemia) from 0.70 to 0.88 in predicting ASCVD events.

To assess the efficacy of clinical scores in predicting CAD in heart failure, a coronary computed tomography angiography (CCTA) study of the LIPIGEN-HF registry was performed in Italy [24▪▪], comprising 139 patients with a clinical diagnosis of familial hypercholesterolemia. The asymptomatic patients with familial hypercholesterolemia included in the cohort showed a high prevalence and wide extension of CAD, which reaffirms the idea that familial hypercholesterolemia should be considered a group at high risk of premature atherosclerotic vascular damage. The main drawback of this study was that Lp(a) values were not available, so SAFEHEART-RE and FH-Risk-Score were recalculated considering their null value in all patients.

In line with previous investigations, the asymptomatic patients with familial hypercholesterolemia included in the present cohort showed a high prevalence and wide extension of CAD, which reaffirms the idea that familial hypercholesterolemia should be considered a group at a high risk of premature atherosclerotic vascular damage. In addition, this study investigated the performance of the most widely accepted ASCVD risk stratification scores to predict the extent and severity of CAD, the Montreal-FH-Score, FH-Risk-Score, and SAFEHEART-RE (Table 1). It was revealed that while the traditional clinical staging of the disease with the DLCN score does not correlate with the severity of CAD detected by CCTA, higher values of Montreal-FH-Score, FH-Risk-Score and SAFEHEART-RE were shown to be associated with a higher prevalence of CAD [24▪▪].

These results only partially agree with the previous findings of the SAFEHEART investigators [25]. However, not taking into account the values of Lp(a) is a limitation, since it has a great influence in the SAFEHEART-RE.

A systematic review related to predictors of vascular risk in people with molecular diagnosis is

being carried out [26▪▪] and it will broaden the knowledge of this population. We currently have equations with a high prediction rate of cardiovascular events in the familial hypercholesterolemia population. Although they use similar variables, in our opinion the SAFEHEART-RE has the advantage of representing a homogeneous population with a molecular diagnosis of familial hypercholesterolemia, and therefore should be incorporated into our routine practice. It would be desirable to obtain 10-year follow-up data from this cohort.

Imaging tests allow risk stratification for ASCVD in this population. However, they have a high cost and their use is not implemented in the clinical practice. However, performing equations with clinical and analytical parameters allows us to identify the risk of these patients in a simple and effective way.

WHAT ROLE DOES DIABETES PLAY IN FAMILY HYPERCHOLESTEROLEMIA?

The prevalence of type 2 diabetes mellitus (DM2) has recently been published in the Hellenic Registry of Familial Hypercholesterolemia (HELLAS-FH). A total of 1173 individuals (873 men) with HeFH were included, 123 of whom (7.2%) had DM2. The risk of established ASCVD was four times higher among diabetic patients compared with nondiabetic individuals [unadjusted odds ratio (OR) 4.0 (95% confidence interval, 95% CI: 2.8–5.9)] [27▪▪].

Indeed, it has been speculated that significantly elevated LDL-C levels in patients with pathogenic HeFH mutations confer some protection against the development of DM2 because impaired LDL receptor function might protect pancreatic beta cells against the possible entry of LDL-C harmful particles [28], as well as the diabetogenic effect of statins, an important point considering that the relationship between high potency statins and the development of diabetes has been demonstrated [29]. However, the SAFEHEART study showed that prolonged treatment with high doses of statins was not associated with an increased risk of DM2 in patients with familial hypercholesterolemia [30].

This decrease in the prevalence of DM2 observed in familial hypercholesterolemia patients can be seen in different cohorts, including the Canadian cohorts (5 vs. 8.3%) [31]; Spanish (5.94% vs 9.44%) [32]; Greek (7.2 vs. 11.6%) [33]; and Dutch (1.75 vs. 2.93%) [34]. Nevertheless, it must be taken into account that familial hypercholesterolemia registries are heterogeneous; some are based mainly on phenotypic diagnosis using clinical criteria and not mostly on molecular diagnosis. Those familial hypercholesterolemia registries with higher phenotypic diagnosis of familial hypercholesterolemia and including older patients have a greater prevalence of DM2 [35–37].

Despite the fact that the prevalence of DM2 is lower than in the general population, several studies have shown that the severity of ASCVD in individuals with familial hypercholesterolemia and DM2 is greater and that it also acts as an independent risk factor for the development of cardiovascular diseases [32,38–40]. In fact, the coexistence of familial hypercholesterolemia and DM2 doubles the risk of presenting ASCVD [41▪], and those individuals with poorer metabolic control and longer evolution time present greater severity [42]. Thus, a tool to determine the degree of risk that the presence of diabetes confers to these patients that already have a high cardiovascular risk would be very useful.

Moreover, metabolic syndrome and insulin resistance may also play an important role and appear to be related to ASCVD in these individuals, acting as an independent risk factor for LDL-C and other traditional risk factors [43,44▪▪]. The triglyceride-glucose index has also been proposed as a marker of insulin resistance and its association with ASCVD. However, it must be carefully evaluated in specific populations such as familial hypercholesterolemia since this ratio is based on glycolipid metabolism, which is altered in familial hypercholesterolemia, and no specific studies have assessed its applicability in this particular population [43]. The creation of better structured registries where molecular diagnosis predominates are necessary for a deeper understanding of this population and to be able to generate strategies to better stratify the risk of these individuals in a more effective manner.

ATHEROSCLEROTIC CARDIOVASCULAR DISEASE IN FAMILY HYPERCHOLESTEROLEMIA. IS THE BRAIN PROTECTED?

Randomized controlled trials have shown a clear relationship between therapeutic LDL-C reduction and the risk of ischemic stroke [45]. Several studies, including a recent cohort study, found that high LDL-C predicted heart problems, but not stroke [46].

Although the genetic diagnosis of familial hypercholesterolemia does not appear to be associated with an increased risk of total stroke, the data on the risk of ischemic and, in particular, hemorrhagic stroke are less clear.

Svendsen *et al.* [2▪▪] carried out a prospective matched study was carried out in 5691 individuals with genetically verified familial hypercholesterolemia and 112 680 age and sex-matched controls in the Norwegian population, diagnosed between 1992 and 2014, with a 20-year follow-up. During the

study period, 100 strokes occurred in the familial hypercholesterolemia population and 1610 in controls (41 270 person-years of follow-up in familial hypercholesterolemia and 813 134 person-years in controls). No excess risk of global stroke or ischemic stroke was found in the familial hypercholesterolemia population. An increased risk of hemorrhagic stroke was observed, which was strongly attenuated when adjusting for the use of antithrombotic therapies. There was also no association between the levels of cumulative exposure to statins and the risk of total stroke in people with familial hypercholesterolemia. Consistent with these findings, no increased risk of total stroke was found in an observational study of 2752 individuals with genetically determined familial hypercholesterolemia and 993 unaffected relatives [47].

In the same manner, another study based on data from England and Wales found no increase in the standardized death rate from stroke in definite/probable familial hypercholesterolemia compared to the general population [48]. Also, a recent meta-analysis found no association between genetic familial hypercholesterolemia and ischemic stroke. However, for the latter study, having an LDL-C more than 4.9 mmol/l (190 mg/dl) resulted in a significantly increased risk in the same sample (OR: 1.42 (95% CI: 1, 06–1.89) [49].

Nevertheless, the cause of stroke is very varied. The TOAST classification [50], by establishing the type of stroke, allows us to know the contributing mechanism of production and therefore the atherothrombotic etiology. Obtaining stroke data from most registries is based on CIE-10 coding, which provides information on the clinical manifestation of vascular origin but does not specify its driving mechanism. It is difficult to understand that familial hypercholesterolemia is associated with an increase in coronary disease and peripheral arterial disease and, instead, spares the brain. Specific studies would be necessary in the familial hypercholesterolemia population where the prevalence of stroke of atherothrombotic origin is contemplated, before confirming this paradox.

CONCLUSION

Clinical practice guidelines should include the heterogeneity of familial hypercholesterolemia, incorporating new specific risk equations that make it easier for clinicians to establish control objectives and treatment strategies according to risk.

These equations come from solid records, of a prospective nature, with a preferably molecular diagnosis, in which adequate follow-up is demonstrated and with external validation.

Familial Hypercholesterolemia behaves as a protective factor for developing type 2 diabetes mellitus; however, its appearance considerably increases the risk of atherosclerotic cardiovascular disease.

Further research is needed to confirm the paradox of cerebral atherosclerosis in Familial Hypercholesterolemia.

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Conflicts of interest

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