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Review

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Risk factors for coronary artery disease in familial hypercholesterolemia

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Abstract

Individuals with familial hypercholesterolemia are at markedly increased risk of coronary artery disease (CAD). Accurate risk assessment and appropriate management in this population are therefore crucial. In this review, we summarize findings from several studies that have investigated predictors of CAD in familial hypercholesterolemia (FH). The main categories of predictors include demographic variables and comorbidities, lipid-related parameters, physical findings such as xanthomas, genetic characteristics, and imaging markers of atherosclerosis. We also highlight risk prediction models developed from these previously published findings.

Keywords: Genetic diseases, inborn, hyperlipoproteinemias, atherosclerosis

INTRODUCTION

The most recent European guidelines on lipid-lowering therapy classify patients with familial hypercholesterolemia (FH) as either very high or high risk[1]. Risk stratification is particularly important when patients do not yet have established atherosclerotic cardiovascular disease (ASCVD). In the United States and Europe, the Pooled Cohort Equation and SCORE system, respectively, are widely used to estimate cardiovascular risk. However, these tools often underestimate risk in FH patients, who are exposed to lifelong elevations in blood cholesterol. Therefore, improving the accuracy of cardiovascular risk

estimation in this population is critical and may support more personalized therapeutic approaches.

Several common factors have been identified as predictors of coronary artery disease (CAD) in FH. For example, male sex, hypertension, smoking, and low high-density lipoprotein cholesterol (HDL-C) levels are consistently associated with elevated risk[2]. Nevertheless, the predictive value of these factors often depends on the characteristics of the study cohort, and individual studies have inherent limitations[3]. As a result, research into optimal approaches for risk prediction remains ongoing.

In this review, we provide a comprehensive overview of CAD predictors in FH, with particular emphasis on recent advances in genetic analyses and imaging studies, in addition to traditional risk factors.

PREDICTORS OF CORONARY ARTERY DISEASE

Demographic factors and comorbidities

Age, sex, hypertension, smoking, body mass index, and levels of low-density lipoprotein-cholesterol (LDL-C), lipoprotein(a) [Lp(a)], and HDL-C have been shown to predict cardiovascular risk in individuals with FH[4-6]. Patients who experience vascular events are more likely to have a family history of cardiovascular disease[4,5]. In contrast, the predictive value of diabetes mellitus in FH remains inconsistent across studies[5,7]. Some studies report increased cardiovascular risk in FH patients with diabetes mellitus[5]; however, the prevalence of diabetes varies by cohort and participant age, which may influence the magnitude and significance of its impact on cardiovascular risk[6].

A recent study of a large Spanish FH cohort demonstrated sex-based differences in cardiovascular risk. The adjusted hazard ratio for ASCVD was 1.90 in men compared with women, and cardiovascular event-free survival was lower in men (hazard ratio 3.52)[8]. Hypertension has consistently been identified as a predictor of CAD in patients with FH[9-11]. In a global study of FH patients from 50 countries, obesity was associated with an increased risk of CAD in both children and adults, independent of LDL-C levels and lipid-lowering therapy[12].

Table 1 presents the categories and detailed descriptions of cardiovascular risk predictors in patients with FH.

Xanthoma

Among patients with severe hypercholesterolemia, those exhibiting clinical signs of FH, such as xanthoma and/or a family history of the disease, demonstrate a 3.4- to 4.6-fold higher risk of CAD[7]. Skin and tendon xanthomas are key manifestations of FH. Skin xanthomas typically appear on extensor surfaces, including the elbows, knees, wrists, and gluteal regions. Tendon xanthomas often present as thickening of the Achilles tendon[13,14]. Progressive Achilles tendon thickening is associated with poorer cardiovascular outcomes in FH patients. In Japan, an Achilles tendon thickness > 8.0 mm in men or > 7.5 mm in women, measured via X-ray, is considered abnormal. Patients with progressive thickening had a > 2-fold higher risk of cardiovascular events compared with those without thickening at baseline and follow-up, whereas patients with thickening at both time points had a > 6-fold higher risk[15]. Achilles tendon thickness can also be assessed by ultrasonography, typically with the patient in a kneeling or supine position. A short-axis image is first acquired to identify the thickest area, which is then measured on a long-axis image delineating this area[13].

Lipid-related parameters and biomarkers

High LDL-C levels are a key predictor of CAD risk. For example, the International Atherosclerosis Society

Table 1. Predictors of coronary artery disease in FH

Category	Predictors	Effect	References
Demographic Factors/comorbidities	Age	Associated with higher cardiovascular risk (OR 1.07)	[5]
	Male sex	Associated with higher cardiovascular risk (HR 3.52)	[8]
	Hypertension	Consistently associated with CAD risk	[9-11]
	Diabetes mellitus	Predictive value for CAD risk is inconsistent	[5,7]
	Smoking	Associated with higher cardiovascular risk (OR 1.71)	[5]
	Family history of cardiovascular disease	FH patients more frequently have a family history of premature CVD	[4]
	Obesity	Associated with higher CAD risk	[12]
Xanthoma	Tendon xanthoma	Associated with 3.4-4.6-fold higher CAD risk	[7]
	Progression of Achilles tendon thickness	Associated with 2-6-fold higher cardiovascular risk	[15]
Lipid parameters	LDL-C and cumulative LDL-C exposure	Associated with higher CAD risk	[16-18]
	Low HDL-C	Associated with higher CAD risk in multiple studies	[9,21,22,23]
	Lipoprotein(a)	> 50 mg/dL is significant in prediction models	[20]
Genetic variants	*LDLR* variants	LDL receptor-deficient variants are associated with 7-fold higher CAD risk	[7]
	Other variants (*PCSK9, ABCG8*)	Variants of *PCSK9* and *ABCG8* are associated with higher CAD risk	[11]
Imaging data	Coronary artery calcium score	> 100 associated with HR 32.05; annual event rate is 0 when score is 0	[30,31]
	Carotid plaque	Presence of plaque associated with a 2.4-fold higher event risk; higher plaque scores associated with HR 2.24 for cardiovascular events	[32,33]

FH: Familial hypercholesterolemia; OR: odds ratio; HR: hazard ratio; CAD: coronary artery disease; CVD: cardiovascular disease; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; Lp(a): lipoprotein(a); CAC score: coronary artery calcium score.

classifies severe forms of FH as LDL-C > 400 mg/dL, LDL-C > 310 mg/dL with one additional risk factor, or LDL-C > 190 mg/dL with two additional risk factors[16]. Both cumulative LDL-C exposure[17,18] and Lp(a) levels[17] independently predict CAD. In one study, smoking and LDL-C exposure particularly amplified cardiovascular risk. Additionally, a Dutch study found that Lp(a) levels reclassified up to 18% of individuals to a higher ASCVD risk category[19]. Spanish Familial Hypercholesterolemia Cohort Study (SAFEHEART), incorporating Lp(a) levels > 50 mg/dL into a cardiovascular outcome prediction model provided significant predictive value[20].

Across studies in various countries, low HDL-C levels have also been independently associated with cardiovascular risk in FH patients[9,21,22]. Several studies have highlighted the functional properties of HDL, emphasizing its role in reverse cholesterol transport and atherosclerosis in FH[23]. Notably, serum cholesterol uptake capacity remained significantly associated with CAD in FH patients after adjusting for other clinical variables, whereas HDL-C levels did not[24]. Cholesterol efflux capacity was inversely associated with ASCVD presence in FH patients[25], with patients without CAD showing higher efflux capacity than those who had experienced cardiac events[26].

The relationship between triglyceride levels and CAD risk in FH has been inconsistent[4,9,20]. While some studies reported a positive association, it was not statistically significant in multivariate analyses[4,20]. Collinearity between variables, such as HDL-C and triglycerides, may attenuate the apparent independent effect of triglyceride levels when adjusted for stronger CAD predictors.

Genetic variants

In FH patients, the predictive value of adult cholesterol measurements may be limited. In contrast, genetic variants can provide additional predictive value for cardiovascular outcomes[27].

Pathogenic variants are associated with a three- to five-fold increased risk of CAD[7,28]. Different *LDLR* variants confer varying levels of risk: carriers of *LDLR* deficiency-associated variants have approximately a seven-fold increased risk, while carriers of other *LDLR* variants have about a four-fold higher risk compared with non-carriers[28]. Variants in other genes, including *PCSK9*, *CETP*, *ABCG8*, and *LPL,* are also linked to cardiovascular risk[11]. A Canadian study demonstrated that a polygenic risk score based on 192 single nucleotide polymorphisms predicted cardiovascular events in FH patients, suggesting that common variants may contribute to risk even in monogenic diseases[29].

Imaging data and other variables

Several studies have evaluated imaging data for cardiovascular risk prediction in FH patients. In two Spanish national registries, a coronary artery calcium (CAC) score > 100 was associated with a substantially higher risk of ASCVD (hazard ratio 32.05) compared with a score of 0, improving net reclassification by 45.4%[30]. Another study reported that CAC levels predicted cardiovascular events in FH patients on standard lipid-lowering therapy, with an annual event rate of 0% in patients with a CAC score of 0[31].

A Japanese study demonstrated that the severity of coronary and carotid plaques correlated with cardiovascular events[32]. Carotid plaque scores were significantly associated with cardiac events (hazard ratio 2.24), consistent with a Spanish study showing a 2.4-fold higher adjusted event risk in patients with carotid plaque[33]. Although imaging provides valuable risk prediction, cost considerations may limit its widespread implementation.

Low diagnostic rates and delayed diagnosis

FH is frequently underdiagnosed or diagnosed late[34], leading to prolonged arterial exposure to elevated cholesterol and increased cardiovascular risk. Raising awareness among healthcare professionals and the general population is critical. Cascade screening following the diagnosis of a proband is essential, as are aggressive lipid-lowering strategies (pharmacological and non-pharmacological) and ensuring patient adherence.

Prediction models

The SAFEHEART study analyzed 2,404 patients with a molecular diagnosis of FH. Its prediction model included age, sex, ASCVD history, blood pressure, body mass index, smoking, and LDL-C and Lp(a) levels. The model achieved a C-index of 0.8, demonstrating superior discriminatory power compared with the Framingham Risk Score[20]. However, a subsequent UK FH cohort study highlighted limitations in the model's generalizability[3].

The Montreal-FH-SCORE incorporates age, HDL-C, sex, hypertension, and smoking status[21]. The FH-Risk Score, developed by Paquette *et al.*[22], includes sex, age, LDL-C, HDL-C, and Lp(a) levels, hypertension, and smoking status, achieving a Harrell C-index of 0.75 for 10-year event prediction, outperforming the SAFEHEART equation[22].

A comparison of these prediction models is presented in Table 2.

Table 2. Comparison of CAD prediction models in FH

Name	Included variables	Performance	Characteristics	References
SAFEHEART risk equation	Age, sex, ASCVD history, blood pressure, BMI, smoking, LDL-C, Lp(a)	C-index 0.80; Harrell C-index for 10-year events 0.69	Better discrimination than the Framingham risk score; first equation to predict CVD events specifically in FH	[20]
Montreal-FH-SCORE	Age, sex, hypertension, smoking, HDL-C	Score > 20 associated with 10.3-fold higher odds of a CVD event	Combines cardiovascular risk factors independently of LDL-C; greatly improves CVD risk prediction in FH	[21]
FH-risk score	Sex, age, LDL-C, HDL-C, hypertension, smoking, Lp(a)	Harrell C-index for 10-year event 0.75	Outperforms SAFEHEART risk equation in predicting CVD events	[22]

CAD: Coronary artery disease; SAFEHEART: Spanish familial hypercholesterolemia cohort study; ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; LDL-C: low-density lipoprotein cholesterol; Lp(a): lipoprotein(a); C-index: Concordance index; CVD: cardiovascular disease; FH: familial hypercholesterolemia; HDL-C: high-density lipoprotein cholesterol.

CONCLUSIONS

In patients with FH, clinical risk factors, including hypertension, xanthomas, cholesterol levels, and the presence and type of pathogenic genetic variants, are predictive of CAD. Atherosclerosis detected through imaging modalities also serves as an independent predictor of cardiovascular risk. Based on these factors, several risk prediction models have been developed, which may support personalized management of FH patients.

DECLARATIONS

Authors' contributions

Performed data analysis and interpretation, and wrote the manuscript: Choi J

Contributed to the conception, design, and supervision of the study, and wrote the Manuscript and made revisions: Lee SH

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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