Predicting Cardiovascular Events in Familial Hypercholesterolemia

The SAFEHEART Registry (Spanish Familial Hypercholesterolemia Cohort Study)

BACKGROUND: Although risk factors for atherosclerotic cardiovascular disease (ASCVD) in familial hypercholesterolemia (FH) have been described, models for predicting incident ASCVD have not been reported. Our aim was to use the SAFEHEART registry (Spanish Familial Hypercholesterolemia Cohort Study) to define key risk factors for predicting incident ASCVD in patients with FH.

METHODS: SAFEHEART is a multicenter, nationwide, long-term prospective cohort study of a molecularly defined population with FH with or without previous ASCVD. Analyses to define risk factors and to build a risk prediction equation were developed, and the risk prediction equation was tested for its ability to discriminate patients who experience incident ASCVD from those who did not over time.

RESULTS: We recruited 2404 adult patients with FH who were followed up for a mean of 5.5 years (SD, 3.2 years), during which 12 (0.5%) and 122 (5.1%) suffered fatal and nonfatal incident ASCVD, respectively. Age, male sex, history of previous ASCVD, high blood pressure, increased body mass index, active smoking, and low-density lipoprotein cholesterol and lipoprotein(a) levels were independent predictors of incident ASCVD from which a risk equation with a Harrell C index of 0.85 was derived. The bootstrap resampling (100 randomized samples) of the original set for internal validation showed a degree of overoptimism of 0.003. Individual risk was estimated for each person without an established diagnosis of ASCVD before enrollment in the registry by use of the SAFEHEART risk equation, the modified Framingham risk equation, and the American College of Cardiology/American Heart Association ASCVD Pooled Cohort Risk Equations. The Harrell C index for these models was 0.81, 0.78, and 0.8, respectively, and differences between the SAFEHEART risk equation and the other 2 were significant (P=0.023 and P=0.045).

CONCLUSIONS: The risk of incident ASCVD may be estimated in patients with FH with simple clinical predictors. This finding may improve risk stratification and could be used to guide therapy in patients with FH.

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Clinical Perspective

What Is New?

- Risk of atherosclerotic cardiovascular disease is variable among patients with familial hypercholesterolemia (FH).
- Models for predicting incident atherosclerotic cardiovascular disease in FH have not been reported, and prospective cohort data in patients with well-defined FH are rare.
- The SAFEHEART registry (Spanish Familial Hypercholesterolemia Cohort Study) is a nationwide, long-term, prospective contemporary cohort of a molecularly defined FH population.
- A robust risk prediction equation has been developed in this unique cohort that shows that the risk of incident atherosclerotic cardiovascular disease may be estimated in patients with FH using clinical and laboratory parameters, including age, sex, history of atherosclerotic cardiovascular disease, blood pressure, body mass index, smoking, and plasma low-density lipoprotein cholesterol and lipoprotein(a) levels.

What Are the Clinical Implications?

- This information will allow more accurate atherosclerotic cardiovascular disease risk prediction in FH and will potentially increase the efficiency of care and use of newer lipid-lowering therapies.
- The SAFEHEART risk equation is a simple, accurate, and widely applicable tool for use in primary and specialist care settings.

Heterozygous familial hypercholesterolemia (FH) is the most common genetic disorder associated with premature atherosclerotic cardiovascular disease (ASCVD).[1] Recent data suggest that the prevalence of FH may be as high as 0.4%.[2,3] Patients with FH have a 3- to 13-fold greater risk of premature ASCVD compared with individuals without FH.[2,4–6] Sudden death and acute ischemic heart disease are the main causes of death among these subjects.[7,8] Early diagnosis and lowering of low-density lipoprotein cholesterol (LDL-C) significantly reduce ASCVD and improve quality of life in people with FH.[9]

Risk of cardiovascular disease in FH can be highly variable, however. It is therefore incumbent on physicians caring for patients with FH to develop tools for predicting those at greatest risk of developing incident ASCVD to apportion the best use of resources, including new therapies that potently lower LDL-C.[10,11] Although the risk factors for incident ASCVD in FH have been well described, the findings have been based on small cohorts of patients attending specialist clinics, and recommendations on risk assessment have been qualitative and derived from expert opinion.[12,13] No accurate risk prediction models for predicting incident ASCVD in patients with FH have been described, chiefly because of lack of reliable, longitudinal data from registry cohorts. The SAFEHEART registry (Spanish Familial Hypercholesterolemia Cohort Study) provides a unique opportunity to address this need.

Our aim was to use the prospective SAFEHEART registry to determine the predictors of incident ASCVD in patients with FH with or without previous ASCVD.

METHODS

Study Design and Population

SAFEHEART is a multicenter, nationwide, long-term, prospective cohort study in a molecularly defined heterozygous population of patients with FH in Spain with and without previous ASCVD.[14] Data analyzed for this work were obtained between January 2004 and October 2015, and only subjects ≥18 years old were included. This study was approved by the local ethics committees, and all eligible subjects gave written informed consent. This article has been written following the TRIPOD (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) requirements.[15] Treatment goals for the management of these patients were based on consecutively released international recommendations.[2,16] The Coordinating Center was responsible for managing the follow-up.[14] Patients were contacted annually by telephone by trained staff using a standardized phone call protocol from the Coordinating Center.

Clinical Measurements

Demographic and clinical characteristics were recorded as described elsewhere.[14] Venous blood samples were taken after a 12-hour fast. Plasma lipid profile and lipoprotein(a) [Lp(a)] levels were determined as previously described.[17] Because many patients were on lipid-lowering therapy (LLT) at inclusion, pretreatment LDL-C levels were estimated according to previous recommendations.[18] Hypertension was defined as systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg on 2 measurements on 2 different days or need of antihypertensive drugs. DNA was isolated from whole blood, and the genetic diagnosis of FH was made.[19] Mutations were classified as receptor negative or receptor defective, depending on their functional class. Mutations without a functional class in the literature were classified as unclassified mutations.[20] The potency of LLT was calculated as reported elsewhere with a modification to include the effect of ezetimibe.[21,22] Ezetimibe was considered to decrease LDL-C by 15%, and this effect was added to the statin effect when appropriate.[22] LDL-C life-years were calculated as previously described.[2]

Definition of Previous ASCVD

Previous ASCVD was defined as the presence before enrollment of any of the following: (1) myocardial infarction, proved by at least 2 of the following: classic symptoms, specific ECG changes, and increased levels of cardiac biomarkers; (2) angina pectoris, diagnosed as classic symptoms in combination with at least 1 unequivocal result of one of the following:

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exercise test, nuclear scintigram, dobutamine stress ultrasound scan, or >70% stenosis on a coronary angiogram; (3) percutaneous coronary intervention or other invasive coronary procedures as indicated by the treating physician; (4) coronary artery bypass grafting; (5) ischemic stroke demonstrated by computed tomography or magnetic resonance imaging scan or documented transient ischemic attack; (6) peripheral artery disease: intermittent claudication, defined as classic symptoms and at least 1 positive result of an ankle/arm index<0.9, stenosis>50% on angiography or ultrasonography, or abdominal aortic aneurysm; or (7) peripheral arterial revascularization, that is, peripheral artery bypass grafting or percutaneous transluminal angioplasty. Premature familial ASCVD was defined as the occurrence of the first event before 55 years of age in men and before 65 years of age in women in the patient's relatives. Cardiovascular risk factors were defined according the European Society of Cardiology recommendations.[23] Maximum statin dose, maximum combined therapy, and maximum LLT were defined as previously reported.[24]

Definition of Incident ASCVD

Incident ASCVD during follow-up was defined as the occurrence after enrollment of the first one of the following: fatal or nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, coronary revascularization, peripheral artery revascularization, or cardiovascular death (any death related to cardiovascular disease or derived of cardiovascular therapeutic procedures not described in the previous definitions).

Statistical Analysis

Statistical analyses were carried out with Stata version 13.0 (StataCorp LP, College Station, TX). Variables were analyzed for normal distribution with the Kolmogorov-Smirnov test. Quantitative data were expressed as mean and standard deviation or median and interquartile range (IQR) and qualitative data as absolute number and percentage. Two populations were defined: population at entry (n=2746) and population at follow-up (otherwise known as the cohort), which included patients who had a full plasma lipid profile at follow-up (n=2404) and was the population used for the analysis. Associations between qualitative variables were analyzed by the χ^2 test. Associations between quantitative variables were analyzed by the paired Student *t* test. Univariate effects were analyzed by means of hazard ratios and their 95% confidence intervals with a clustered Cox model in which the cluster was the family (a family for each index case).[25] A clustered Cox model was adjusted by introducing those variables with a value of $P<0.05$ and confounding variables, and a risk equation was derived (SAFEHEART-RE). Patient data at enrollment were used for the analysis. To simplify the use of the equation and to introduce the variables in the model in a more parsimonious way, continuous variables were transformed into categorical variables. Cut points for LDL-C and Lp(a) were selected on the basis of currently used levels to establish clinical decisions. Cut points for body mass index were selected according the definition of overweight and obesity. In the case of age, the cut points correspond to the inferior and superior quintiles of the age distribution in the analyzed population. We evaluated the ability of the risk prediction model to discriminate individuals who experienced incident ASCVD from those who did not using an overall C statistic,[26,27] extending a previous suggestion by Harrell et al.[28] This C statistic is analogous to the area under the receiver-operating characteristic curve. The performance of the model was also evaluated with respect to their discrimination and calibration ability on the basis of the Hosmer-Lemeshow type χ_2 statistic. For internal validation of the model, the degree of overoptimism resulting from model assessment on the same data on which it was developed was estimated with bootstrap resampling of the original set (100 randomized samples) as recommended by TRIPOD.[15] To estimate the probability of an event, we used the Kaplan-Meier estimator to obtain the 5-year and 10-year risk according the method described by D'Agostino et al.[29,30] Risk estimation based on the Framingham equation and American College of Cardiology/American Heart Association (ACC/AHA) ASCVD Pooled Cohort Risk Equations[31] was carried out for each individual without previous ASCVD, and Harrell C indexes were obtained. Interequation risk agreement was evaluated by the intraclass correlation coefficient by use of the rate obtained for each individual according the different scores. To compare Harrell C indexes in patients without previous ASCVD (patients with ASCVD before enrollment were excluded for this analysis), the method described by Newson[32] was used. Two-tailed tests were used, and a value of $P<0.05$ was considered significant.

RESULTS

A total of 4141 subjects were recruited. Of them, 787 patients were index cases (19.0%). Of the total population, 3749 were ≥18 years of age, of whom 2746 were FH cases, and 2404 subjects were followed up and had a full plasma lipid profile (Figure 1). This was the population analyzed. One thousand five hundred patients

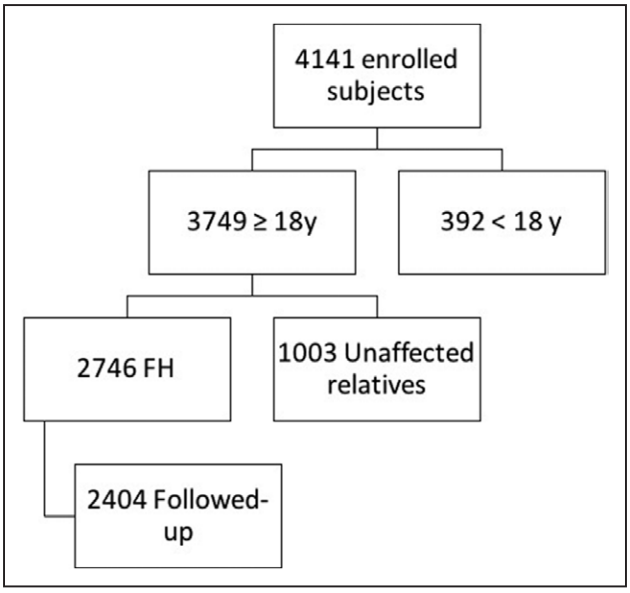

Figure 1. Flowchart of case recruitment in the SAFEHEART study (Spanish Familial Hypercholesterolemia Cohort Study).
FH indicates familial hypercholesterolemia.

(46.6%) were followed up in a primary care setting. Mean follow-up was 5.5 years (SD 3.2 years). Mean characteristics of the cohort and the population without follow-up are given in Table 1. Statistically significant differences between both groups were found for active smoking, total cholesterol, LDL-C, calculated LDL-C, triglycerides, non–high-density lipoprotein cholesterol, patients on maximum statin dose, patients on ezetimibe, patients on

Table 1. Baseline Clinical and Laboratory Characteristics of the Population Divided Into Those With Follow-Up (Cohort) and Those Without Follow-Up

	Patients With FH With Follow-Up	Patients With FH Without Follow-Up	*P* Value
n	2404	342	
Male, n (%)	1087 (45.2)	171 (50.0)	0.10
Age, y	45.5 (15.4)	45.4 (17.6)	0.9
History of ASCD before enrollment, n (%)	307 (12.8)	53 (15.5)	0.16
Premature familial ASCD history, n (%)	826 (41.2)	76 (39.4)	0.62
Type 2 diabetes mellitus, n (%)	104 (4.3)	15 (4.4)	0.94
Hypertension, n (%)	341 (14.2)	56 (16.4)	0.25
Active tobacco smoker, n (%)	615 (25.6)	110 (32.4)	0.02
Xanthomas, n (%)	335 (13.9)	42 (12.3)	0.44
Corneal arcus, n (%)	792 (32.9)	123 (36.0)	0.22
Body mass index, kg/m^2	26.5 (4.8)	26.3 (5.1)	0.46
Waist circumference, cm	86.9 (14.2)	87.4 (14.9)	0.56
Total cholesterol, mg/dL	247.4 (65.0)	267.7 (73.0)	<0.001
LDL-C, mg/dL	177.8 (60.4)	196.2 (68.9)	<0.001
Calculated pretreatment LDL-C, mg/dL	238.8 (77.6)	251.1 (83.8)	0.007
HDL-C, mg/dL	50.1 (12.8)	49.7 (13.1)	0.58
Triglycerides, mg/dL	97.6 (54.5)	109.2 (64.5)	<0.001
Non–HDL-C, mg/dL	197.3 (64.1)	218.0 (72.6)	<0.001
APOAI, mg/dL	137.3 (28.1)	135.7 (29.9)	0.36
APOB, mg/dL	115.0 (36.4)	125.5 (42.0)	<0.001
Lipoprotein(a), mg/dL	38.2 (40.6)	34.4 (38.3)	0.13
C-reactive protein, mg/L	2.2 (4.9)	2.5 (4.0)	0.22
Patients on maximum statin dose, n (%)	943 (39.2)	102 (29.8)	0.001
Patients on ezetimibe, n (%)	902 (37.5)	95 (27.8)	<0.001
Patients on maximum combined therapy, n (%)	547 (22.8)	51 (14.9)	0.001
Patients on maximum lipid-lowering therapy, n (%)	1248 (51.9)	138 (40.4)	<0.001
Time on statins, y	12.9 (8.2)	10.0 (8.6)	<0.001
Time on ezetimibe, y	3.3 (4.5)	2.2 (3.9)	<0.001
LDL-C–y	9945.0 (4703.1)	10 771.5 (6065.7)	0.004
Lipid-lowering therapy potency*	6.3 (1.7)	6.0 (1.7)	0.012

Values are mean (SD) when appropriate. ASCVD indicates atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol. Maximum statin dose: atorvastatin 40 to 80 mg/d, rosuvastatin 20 to 40 mg/d. Maximum combined therapy: maximum statin dose combined with ezetimibe 10 mg/d. Maximum lipid-lowering therapy: treatment considered giving at least a 50% reduction in LDL-C pretreatment levels: simvastatin 20, 40, or 80 mg/d combined with ezetimibe 10 mg/d, pravastatin 40 mg/d combined with ezetimibe 10 mg/d, fluvastatin 80 mg/d combined with ezetimibe 10 mg/d, atorvastatin 40 or 80 mg/d with or without ezetimibe 10 mg/d, atorvastatin 10 or 20 mg/d combined with ezetimibe 10 mg/d, rosuvastatin 20 or 40 mg/d with or without with ezetimibe 10 mg/d, rosuvastatin 10 mg/d combined with ezetimibe 10 mg/d, pitavastatin 4 mg/d combined with ezetimibe 10 mg/d.

*Lipid-lowering therapy potency has been calculated according the method described in Penning-van Beest et al[21] modified by Masana et al.[22] As a reference point, the potency of atorvastatin 40 mg is 6.

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maximum combined therapy, patients on maximum LLT, years on statins, years on ezetimibe, LDL-C–years, and LLT potency.

Molecular Diagnosis

Two hundred nine different functional mutations in the *LDLR* (97.0%) and *APOB* (3.0%) genes were identified. In the cohort, 856 patients (35.6%) had *LDLR*-null mutations, 1092 (45.4%) had defective mutations, and 384 (16.0%) had unclassified mutations.

LLT, LDL-C Plasma Levels, and Attainment of LDL-C Goals at Inclusion and Follow-Up

At entry, 2025 patients (84.2%) with FH were receiving LLT. Of them, 943 patients with FH (39.2%) were receiving maximum statin dose, and this increased to 1326 (55.2%) at follow-up. The use of ezetimibe, maximum combined therapy, and maximum LLT increased at follow-up from 902 (37.5%) to 1419 (59.0%), from 547 (22.8%) to 973 (40.5%), and from 1248 (51.9%) to 1728 (71.9%), respectively. Plasma LDL-C concentration decreased by 19.1%, reaching a mean value 143.9 mg/dL (SD 45.0 mg/dL) at follow-up (Table 2). LDL-C goals (LDL-C <70 mg/dL for patients with previous ASCVD and <100 mg/dL for patients without) were reached by 79 patients (3.3%) at inclusion and 195 (8.1%) during follow-up. LDL-C level <100 mg/dL was reached by 110 subjects (4.6%) at enrollment and by 252 (10.5%) at follow-up.

Predictors of Incident ASCVD

At entry, 307 patients (12.8%) in the cohort had an established diagnosis of ASCVD before enrollment. Nonfatal incident ASCVD occurred in 122 subjects (5.1%; 62 nonfatal myocardial infarctions, 42 coronary artery revascularization procedures, 13 nonfatal strokes, and 5 peripheral artery revascularizations) during follow-up; among them, 64 patients (52.5%) had an established diagnosis of ASCVD before enrollment. Fatal incident ASCVD occurred in 12 patients (0.5%; 3 fatal acute myocardial infarctions, 2 fatal strokes, and 7 cardiovascular deaths). Ten of these 12 patients had nonfatal incident ASCVD (3 fatal acute myocardial infarctions, 2 fatal strokes, and 5 cardiovascular deaths, all of them after enrollment). Only the first event during follow-up was considered for analysis.

Table 2. Plasma Lipid and Lipoprotein Concentrations of the Study Cohort at Baseline and Follow-Up

	Cohort at Baseline, mg/dL	Cohort at Follow-Up, mg/dL	*P* Value
Total cholesterol	247.4 (65.0)	217.2 (48.4)	<0.001
LDL-C	177.8 (60.4)	143.9 (45.0)	<0.001
HDL-C	50.1 (12.8)	53.6 (13.8)	<0.001
Triglycerides	97.6 (54.5)	99.0 (53.2)	0.16
Non–HDL-C	197.3 (64.1)	163.4 (47.7)	<0.001

Values are mean (SD).

HDL-C indicates high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.

Table 3 shows univariate and multivariate predictors of incident ASCVD in the study cohort. Age, male sex, history of ASCVD before enrollment, high blood pressure, increased body mass index, active smoking, and LDL-C and Lp(a) levels were independent predictors of incident ASCVD development during follow-up. It is of note that the Harrell C index for this model was 0.85. The Hosmer-Lemeshow $\chi^2(8)$ was 1.64; probability>χ^2 = 0.99. With the use of continuous rather than categorical variables for age, body mass index and LDL-C yielded similar discrimination (Harrell C index=0.85). Figure I in the online-only Data Supplement presents the expected and observed distribution of the number of events in the cohort calibrated by deciles. From these findings, the incident ASCVD risk for an individual with FH can be estimated by using the SAFEHEART-RE (examples in Table 3). Thus, the 5-year risk can be calculated as $1-0.9532^{\exp(\Sigma\beta^{X-5.4078})}$, where β is the regression coefficient and X is the level for each risk factor; the 10-year risk is given as $1-0.9025^{\exp(\Sigma\beta^{X-5.4078})}$. The 5-year median risk of the population was 3.59% (IQR, 1.94%–10.63%), and 10-year median risk was 7.53% (IQR,4.11%–21.39%). Figures 2 and 3 show examples of the 5- and 10-year estimated cardiovascular risk provided by the SAFEHEART-RE.

Internal Validation

The bootstrap resampling of the original set (100 randomized samples) showed a degree of overoptimism of 0.003, which represents the deviation from the mean of the standard error of the estimation in these 100 samples.

Framingham Risk Equation and ACC/AHA ASCVD Pooled Cohort Risk Equations Compared With SAFEHEART-RE in Patients Without Previous ASCVD

The SAFEHEART-RE Harrell C index for patients without an established diagnosis of ASCVD before enrollment in the registry was 0.81. Individual risk was estimated for each person without an established diagnosis of ASCVD before enrollment in the registry by use of the modified Framingham risk equation. The 10-year estimated median risk of the enrolled population was 7.17% (IQR, 2.93%–14.48%) with the use of the Framingham

Table 3. Univariable and Multivariable Predictors of Atherosclerotic Cardiovascular Disease

	Univariable Analysis			Multivariable Analysis		
	Hazard Ratio	95% CI	*P* Value	Hazard Ratio	95% CI	*P* Value
Age, y						
<30	Referent					
30–59	5.88	2.22–15.59	<0.001	2.92	1.14–7.52	0.026
≥60	12.81	4.83–34.01	<0.001	4.27	1.60–11.48	0.004
Male	2.76	1.89–4.02	<0.001	2.01	1.33–3.04	0.001
History of ASCVD	6.64	4.52–9.76	<0.001	4.15	2.55–6.75	<0.001
Premature familial ASCVD history	2.66	1.76–4.05	<0.001			
Diabetes mellitus	3.45	2.03–5.86	<0.001			
High blood pressure	3.38	2.29–4.98	<0.001	1.99	1.26–3.15	0.003
Waist circumference	1.04	1.03–1.06	<0.001			
Body mass index						
Normal weight	Referent					
Overweight	4.69	2.71–8.12	<0.001	2.40	1.36–4.23	0.002
Obesity	6.12	3.51–10.70	<0.001	2.67	1.47–4.85	0.001
Active smoking	1.77	1.20–2.6	0.004	1.62	1.08–2.44	0.02
Years smoking	1.04	1.03–1.05	<0.001			
LDLR-null mutation	1.48	0.96–2.27	0.074			
Total cholesterol	1.002	1.00006–1.005	0.05			
LDL-C, mg/dL						
<100	Referent					
100–159	1.66	0.49–5.57	0.83	2.50	0.60–10.53	0.21
≥160	2.06	0.63–6.72	0.23	4.80	1.15–20.01	0.032
Calculated pretreatment LDL-C, mg/dL						
<100	Referent					
100–159	1.15	0.12–11.01	0.90			
≥160	2.47	0.30–20.42	0.40			
HDL-C	0.97	0.96–0.98	<0.001			
Non–HDL-C	1.003	1.001–1.005	0.004			
Triglycerides	1.004	1.003–1.006	<0.001			
APOAI	0.99	0.985–0.997	0.003			
APOB	1.007	1.003–1.01	<0.001			
Lipoprotein(a) >50 mg/dL	2.14	1.51–3.04	<0.001	1.52	1.05–2.21	0.028
C-reactive protein	1.03	1.01–1.04	0.001			
Patient on maximum statin dose	2.08	1.48–2.93	<0.001			
Patient on ezetimibe	3.42	2.38–4.92	<0.001			
Patient on maximum combined therapy	2.97	2.04–4.34	<0.001			
Patient on maximum lipid-lowering therapy	2.88	2.002–4.15	<0.001			
Years on statins	1.04	1.01–1.07	0.002			
Years on ezetimibe	1.14	1.10–1.18	<0.001			

(*Continued*)

Table 3. Continued

	Univariable Analysis			Multivariable Analysis		
	Hazard Ratio	95% CI	*P* Value	Hazard Ratio	95% CI	*P* Value
LDL-C–y	1.003	1.001–1.005	0.002			
Lipid-lowering therapy potency	1.82	1.50–2.21	<0.001			
Managed in specialized setting	2.86	1.86–4.14	<0.001			

ASCVD indicates atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.

The following examples illustrate the application of the formulas to estimate the 5-year and 10-year risk of developing incident ASCVD. Risks are expressed as percentages.

Case 1: a 20-year-old woman with normal blood pressure and no previous ASCVD, who is not a current smoker, and who has a normal body mass index, LDL-C of 90 mg/dL, and lipoprotein(a) of 33 mg/dL. The risk estimate based on the model is computed as follows:

5-year risk = $1-0.9532^{\exp[(0.70\times0+1.07\times0+1.45\times0+0.69\times0+1.42\times0+0.48\times0+0.88\times0+0.98\times0+0.92\times0+1.57\times0+0.42\times0)-5.4078]}=0.0002148\approx0.02\%$

10-year risk = $1-0.9025^{\exp[(0.70\times0+1.07\times0+1.45\times0+0.69\times0+1.42\times0+0.48\times0+0.88\times0+0.98\times0+0.92\times0+1.57\times0+0.42\times0)-5.4078]}=0.0004598\approx0.05\%$

Case 2: a 63-year-old man who is hypertensive, has previous myocardial infarction, is a current smoker, is obese, and has an LDL-C of 182 mg/dL and lipoprotein(a) of 64 mg/dL. The risk estimate based on the model is computed as follows:

5-year risk=$1-0.9532^{\exp[(0.70\times1+1.07\times0+1.45\times1+0.69\times1+1.42\times1+0.48\times1+0.88\times0+0.98\times1+0.92\times0+1.57\times1+0.42\times1)-5.4078]}=0.3808\approx38.1\%$

10-year risk=$1-0.9025^{\exp[(0.70\times1+1.07\times0+1.45\times1+0.69\times1+1.42\times1+0.48\times1+0.88\times0+0.98\times1+0.92\times0+1.57\times1+0.42\times1)-5.4078]}=0.6415\approx64.15\%$

The numbers 0.9532 and 0.9025 are the 5- and 10-year baseline cumulative probabilities of suffering an incident ASCVD. They are obtained from the Kaplan-Meier curves.

risk equation. The Harrell C index for this model was 0.78. SAFEHEART-RE versus Framingham risk equation for the 10-year risk intraclass correlation coefficient was 0.55 (95% confidence interval, 0.52–0.58). The Harrell C indexes were significantly different between the 2 methods of risk estimation (*P*=0.023). Risk was also estimated for each individual without an established diagnosis of ASCVD before enrollment in the registry with the ACC/AHA ASCVD Pooled Cohort Risk Equations. Ten-year estimated median risk of the enrolled population was 6.0% (IQR, 0.07%–41.48%) with the ACC/AHA ASCVD Pooled Cohort Risk Equations. The Harrell C index

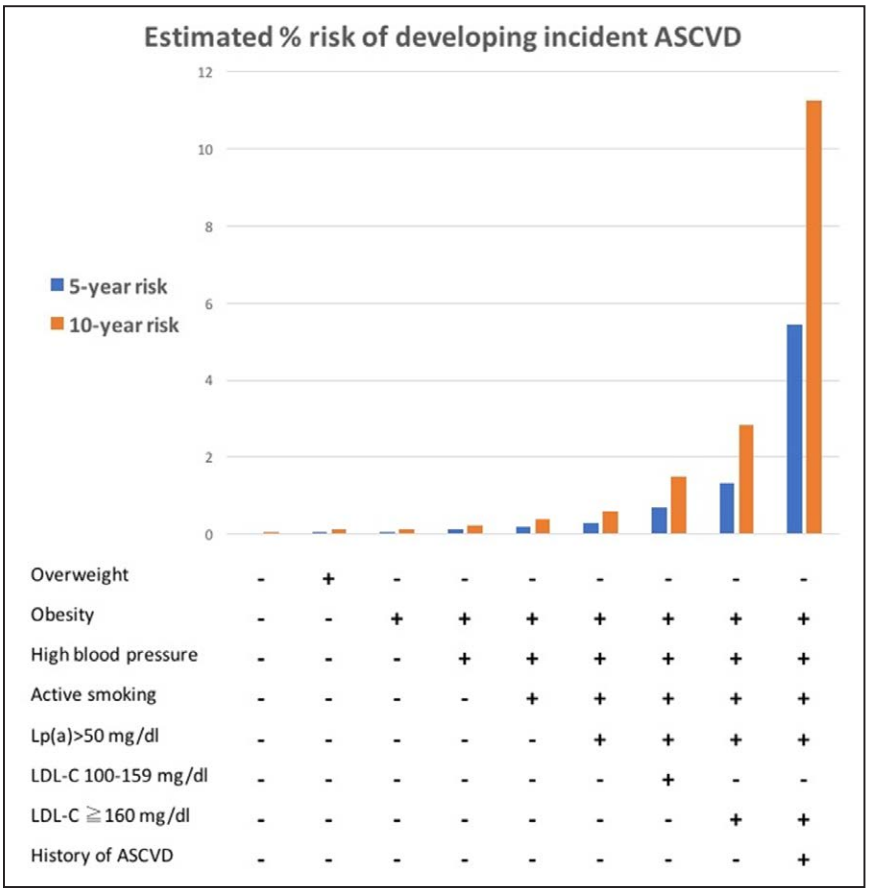

Figure 2. Five- vs 10-year risk of developing incident atherosclerotic cardiovascular disease (ASCVD) for 20-year-old women with familial hypercholesterolemia and low-density lipoprotein cholesterol (LDL-C) <100 mg/dL.
Changes in risk profile can be observed according the modifications in the risk factors. Lp(a) indicates lipoprotein(a).

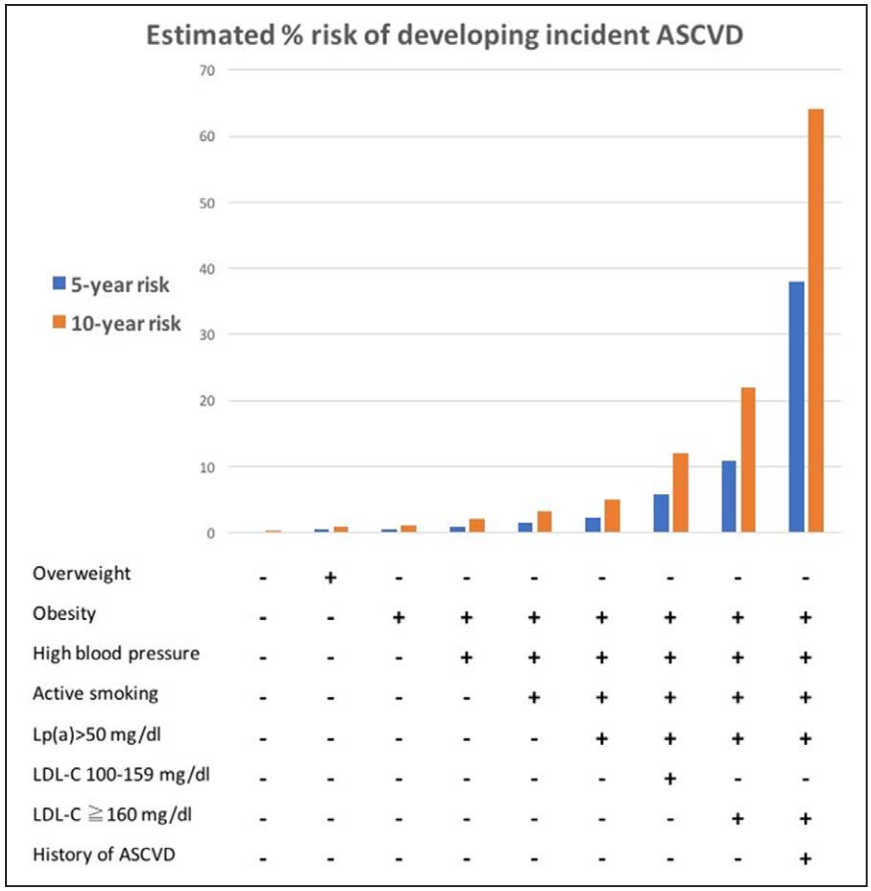

Figure 3. Five- vs 10-year risk of developing incident atherosclerotic cardiovascular disease (ASCVD) for 66-year-old men with familial hypercholesterolemia and low-density lipoprotein cholesterol (LDL-C) <100 mg/dL.
Changes in risk profile can be observed according to the modifications in the risk factors. Lp(a) indicates lipoprotein(a).

for this model was 0.80. SAFEHEART-RE versus ACC/AHA ASCVD Pooled Cohort Risk Equations for 10-year risk intraclass correlation coefficient was 0.13 (95% confidence interval, 0.09–0.17). The Harrell C indexes were significantly different between the 2 methods of risk estimation (P=0.045).

DISCUSSION

This study identifies increased age, male sex, history of ASCVD, high blood pressure, increased body mass index, active smoking, and LDL-C and Lp(a) levels as independent prospective predictors of increased risk of incident ASCVD in patients with FH, which were subsequently used to develop the SAFEHEART-RE. To the best of our knowledge, this is the first report of an equation to predict cardiovascular events in patients with FH. These results are simple, highly accurate, and widely applicable in primary and specialist care settings.

Unlike the general population for which robust risk prediction models are available, risk stratification in patients with FH has been based mostly on retrospective and cross-sectional observations.[13] The prospective SAFEHEART study, which enrolled only patients with molecularly proven FH undergoing contemporary LLT, allowed for the first time the development of a new prospective model for predicting incident ASCVD in FH. Even more, SAFEHEART-RE is a pragmatic approach to patients with FH because it reproduces real-life circumstances: The patient is initially evaluated by means of simple variables present in the first medical contact, and his/her prognosis is assessed, taking into account the LLT optimization that the patient will receive according to his/her clinical and biochemical characteristics during follow-up, similar to what occurred in the SAFEHEART registry.

LDL-C levels >309 mg/dL before therapy have been previously used to identify a more severe FH phenotype in a Dutch cohort.[33] This definition is not based on prospective data, however. A more rigorous approach to defining incident ASCVD risk in patients with FH is provided by the present study, with implications for more rational use of diagnostic and screening services and, in particular, more cost-effective prescription of newer and expensive LDL-C–lowering treatments such as proprotein convertase subtilisin/kexin type 9 inhibitors.[1,13,34]

Previous evidence identifying ASCVD risk factors in an FH population presenting a high rate of established cardiovascular disease has been published, although the study was cross-sectional, the sample size was relatively small, and molecular diagnosis was confirmed in only 62% of cases. Therefore, this evidence has limited value compared with our prospective data.[35] In the present study, we present a new equation that is able to prospec-

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tively assess incident ASCVD risk over 5 and 10 years in patients with FH. Based on a limited number of variables, the equation estimates the likelihood of developing fatal or nonfatal incident ASCVD. Furthermore, the accuracy of the SAFEHEART-RE is high and significantly better than that offered by both the Framingham risk equation and the ACC/AHA ASCVD Pooled Cohort Risk Equations in those patients with FH without ASCVD at baseline. This model could afford clinical services for patients with FH an invaluable tool to evaluate incident ASCVD risk and consequently to establish a more cost-effective design of healthcare systems that could improve the quality of life[36] and the life expectancy of patients. Nevertheless, the cutoff point to define high risk needs to be established according to scientific, economic, and political criteria, acknowledging that moderate statin therapy can reduce ASCVD mortality by 70%[9] and that recent data suggest a 44% reduction in ASCVD events with statins with the possible addition of ezetimibe.[37]

The role that Lp(a) plays in the prediction of incident ASCVD in patients with FH is noteworthy. In the present prospective analysis, we confirm our previous association between high Lp(a) levels and cardiovascular disease in patients with FH.[17] This mandates the value of routinely estimating Lp(a) concentrations in patients with FH, with possible implications for the use of new Lp(a)-lowering therapies.[1]

It is noteworthy that some expected risk factors were not included in the final predictive model. The reason was that they did not enhance the accuracy of the equation in predicting incident ASCVD. Type, potency, and length of treatment against a background of LDL-C life-years are key aspects of the management of patients with FH. Statins and drugs that reduce cholesterol absorption have been widely used to treat FH.[1,7,24] Usually, individuals with higher LDL-C levels need several medications to reduce LDL-C to targets recommended by expert guidelines.[2,16] However, we found that type of treatment was not independently associated with the risk of incident ASCVD, implying that the level of LDL-C attained is more important than the type of drug used to treat FH. Furthermore, the presence of diabetes mellitus was not a predictor of incident ASCVD risk, which may relate to the low prevalence and the low mean age of our FH cohort. This low prevalence of type 2 diabetes mellitus among patients with FH, significantly lower than among unaffected relatives, has previously been reported.[38] Type of *LDLR* mutation (null/defective) was also not selected as a risk predictor, implying that LDL-C concentrations are more important in predicting outcomes in FH than type of molecular defect, as has been previously suggested.[13] This reinforces the concept that phenotype is more important than genotype in managing patients with FH.[13,39] Hence, a patient with a null mutation but low LDL-C could have less risk than a patient with a defective mutation but high LDL-C level.

Strengths and Limitations

This is the largest longitudinal study of a molecularly characterized heterozygous FH population that reflects real-life clinical care of patients by both general practitioners and specialists. These results emphasize the potential of a well-organized registry in assessing treatment monitoring and outcomes, as well as national trends in the care of FH. Nevertheless, there are some limitations. For instance, the study uniquely used national registry data, and children and adolescents were excluded from this analysis. Furthermore, a pretreatment lipid profile for every patient was lacking, but a recognized estimation was provided. Although in this work the internal validation was carried out according the TRIPOD recommendations,[15] further studies and recalibration are needed to validate the SAFEHEART-RE in other FH populations. Nevertheless, in our population, there are >200 different mutations, and most of these mutations are shared with many European and American countries, which underscores the generalizability of our risk-estimating equation. Unfortunately, at present, there is no patient cohort comparable to SAFEHEART in terms of number of patients enrolled, quality of the diagnosis, and duration of follow-up to externally validate our risk equation. Last, because our mean follow-up period was only 5.5 years, risk predictions made over 10 years should be viewed cautiously.

Conclusions

The risk of incident ASCVD may be estimated in patients with FH using simple clinical estimates, including age, sex, history of ASCVD, blood pressure, body mass index, smoking, and plasma LDL-C and Lp(a) levels. The SAFEHEART-RE is an accurate tool to implement these predictors in daily clinical practice. These findings may improve risk stratification and could be used to guide therapy in patients with HF and to assist with clinical research.

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Dr Perez de Isla has received honoraria for consulting, speaker, or researcher activities from Merck, Sharp and Dohme, AstraZeneca, Esteve, Amgen, and Sanofi. Dr Alonso reports personal fees from Amgen, Aegerion, and Ionis. Dr Santos has received honoraria for consulting, speaker, or researcher activities from AstraZeneca, Amgen, Akcea, Aegerion, Boehringer-Ingelheim, Cerenis, Eli-Lilly, Genzyme, Kowa, Pfizer, Sanofi/Regeneron, Torrent, Procaps and Unilever. Dr Watts has received honoraria for advisory boards and received research grants from Amgen and Sanofi. Dr Mata has received honoraria for advisory boards and received research grants from Amgen and Sanofi. The other authors report no conflicts.

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FOOTNOTES

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