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The Added Value of Coronary Calcium Score in Predicting Cardiovascular Events in Familial Hypercholesterolemia

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on behalf of the REFERCHOL and SAFEHEART investigators

ABSTRACT

OBJECTIVES This study aimed at investigating the additional contribution of coronary artery calcium (CAC) score to SAFEHEART (Spanish Familial Hypercholesterolemia Cohort Study) risk equation (SAFEHEART-RE) for cardiovascular risk prediction in heterozygous familial hypercholesterolemia (HeFH).

BACKGROUND Common cardiovascular risk equations are imprecise for HeFH. Because of the high phenotype variability of HeFH, CAC score could help to better stratify the risk of atherosclerotic cardiovascular disease (ASCVD).

METHODS REFERCHOL (French Registry of Familial Hypercholesterolemia) and SAFEHEART are 2 ongoing national registries on HeFH. We analyzed data from primary prevention HeFH patients undergoing CAC quantification. We used probability-weighted Cox proportional hazards models to estimate HRs. Area under the receiver-operating characteristic curve (AUC) and net reclassification improvement (NRI) were used to compare the incremental contribution of CAC score when added to the SAFEHEART-RE for ASCVD prediction. ASCVD was defined as coronary heart disease, stroke or transient ischemic attack, peripheral artery disease, resuscitated sudden death, and cardiovascular death.

RESULTS We included 1,624 patients (mean age: 48.5 $\pm$ 12.8 years; men: 45.7%) from both registries. After a median follow-up of 2.7 years (interquartile range: 0.4-5.0), ASCVD occurred in 81 subjects. The presence of a CAC score of >100 was associated with an HR of 32.05 (95% CI: 10.08-101.94) of developing ASCVD as compared to a CAC score of 0. Receiving-operating curve analysis showed a good performance of CAC score alone in ASCVD prediction (AUC: 0.860 [95% CI: 0.853-0.869]). The addition of log(CAC + 1) to SAFEHEART-RE resulted in a significantly improved prediction of ASCVD (AUC: 0.884 [95% CI: 0.871-0.894] for SAFEHEART-RE + log(CAC + 1) vs AUC: 0.793 [95% CI: 0.779-0.818] for SAFEHEART-RE; $P < 0.001$). These results were confirmed also when considering only hard cardiovascular endpoints. The addition of CAC score was associated with an estimated overall net reclassification improvement of 45.4%.

CONCLUSIONS CAC score proved its use in improving cardiovascular risk stratification and ASCVD prediction in statin-treated HeFH. (J Am Coll Cardiol Img 2021;■:■-■) © 2021 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

AUC = area under the receiver-operating characteristic curve

AVR = aortic valve replacement

CAC = coronary artery calcium

HeFH = heterozygous familial hypercholesterolemia

LDL-C = low-density lipoprotein cholesterol

LLT = lipid-lowering treatment

MI = myocardial infarction

NRI = net reclassification improvement

PCSK9 = proprotein convertase subtilisin kexin 9

Q = quartile

RE = risk equation

SAFEHEART-RE = Spanish Familial Hypercholesterolemia Cohort Study risk equation

Heterozygous familial hypercholesterolemia (HeFH) is an underdiagnosed and undertreated disorder associated with an increased risk of cardiovascular morbidity and mortality (1-4). It is caused by a reduced low-density lipoprotein cholesterol (LDL-C) clearance depending on mutations on the LDL-C catabolism pathway involving LDL receptor, apolipoprotein B, or proprotein convertase subtilisin kexin 9 (PCSK9) (5). HeFH is characterized by a high phenotypic variability, with some forms entirely silent, being undiagnosed in subjects with a normal life expectancy, to more severe cases overlapping with homozygous FH clinical phenotype and high incidence of atherosclerotic cardiovascular disease (ASCVD) (6). The association of common cardiovascular risk factors leads to a 3- to 5-fold higher risk of ASCVD in HeFH (7); however, because of the high cardiovascular risk associated with the genetic nature of HeFH, common cardiovascular risk equations (REs) are obsolete for HeFH risk stratification. SAFEHEART (Spanish Familial Hypercholesterolemia Cohort Study) allowed the development of a specific RE (8), initially validated in a mixed population of primary and secondary prevention HEFH patients. We recently extended the validation of the SAFEHEART-RE in REFERCHOL (French Registry of Familial Hypercholesterolemia) (9), specifically in primary prevention HeFH patients.

A potential drawback of currently available REs is the lack of information on the presence of subclinical atherosclerosis derived from noninvasive vascular exploration. The coronary artery calcium (CAC) score is an easy-to-use reproducible diagnostic tool that helps in further stratifying cardiovascular risk in the general population (10-14). Current guidelines recommend its use in intermediate-risk subjects and suggest it in low-risk subjects (15). Several studies have investigated the prevalence of CAC in HeFH (16-20), but there is still no consensus on the clinical use of coronary imaging to improve cardiovascular risk stratification in patients with HeFH. Recent evidence has highlighted the absence of CAC in middle-age asymptomatic HeFH (21). The clinical implication of this finding is yet to be explored (22). Early detection of the most severe forms of FH would be helpful to prevent early cardiovascular events in patients with HeFH and propose a personalized therapeutic approach (23).

We aimed to investigate the contribution of CAC score on top of SAFEHEART-RE for cardiovascular risk prediction in HeFH adults on primary prevention.

METHODS

STUDY DESIGN AND POPULATION. In this multicentric, cross-sectional investigation, we analyzed data from 2 national registries of HeFH: the REFERCHOL and SAFEHEART cohorts.

REFERCHOL. The national French Registry was established in 2015 by the Nouvelle Société Francophone d'Athérosclérose, as previously described (24). In the present study, the population was prospectively enrolled between November 2015 and March 2021. We included 1,196 adults with both a molecular diagnosis of HeFH in primary prevention and a CAC score.

SAFEHEART. SAFEHEART is an open, multicenter, nationwide, long-term prospective cohort study in a molecularly defined FH population (25). Data analyzed of 428 adults with a CAC score were obtained between January 2013 and December 2016.

For both cohorts, only patients >18 years of age on primary prevention (without ASCVD at baseline) and with a CAC score at baseline were included in the analysis. We therefore selected 1,624 patients, as shown in the flowchart (**Figure 1**).

COLLECTION OF PATIENT DATA. Demographic and clinical characteristics at the enrollment visit (baseline) were used in this study. The maximum statin dose was defined as previously described (atorvastatin 40 or 80 mg/d, rosuvastatin 20 or 40 mg/d, or simvastatin 80 mg/d) (14). The maximum combined lipid-lowering therapy (LLT) was defined as the maximum statin dose plus ezetimibe 10 mg/day. Bitherapy was defined as statin with either ezetimibe or anti-PCSK9. A family history of early 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 first-degree relatives.

Assessment of biological parameters, including a plasma lipid profile, was performed in the clinical laboratory attached to each lipid clinic, using assay

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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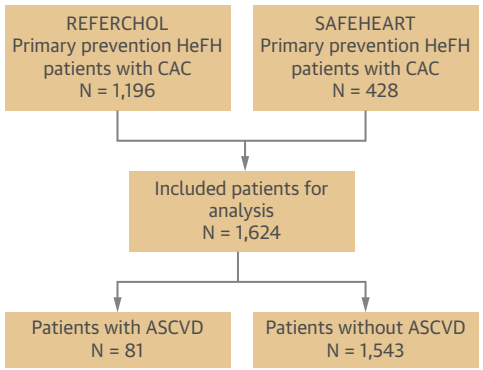
FIGURE 1 Patient Flowchart Showing the Recruitment of Patients in the REFERCHOL and SAFEHEART Registries



We selected subjects >18 years of age on primary prevention (without ASCVD at baseline) and with a CAC score at baseline from the REFERCHOL (French Registry of Familial Hypercholesterolemia) (n = 1,196) and SAFEHEART (Spanish Familial Hypercholesterolemia Cohort Study) (n = 428) cohorts. We therefore selected 1,624 patients. After a median 2.7 years of follow-up, 81 subjects experienced ASCVD, whereas 1,543 remained free from ASCVD. ASCVD was defined as a composite of fatal or nonfatal acute coronary syndromes, fatal or nonfatal stroke or transient ischemic attack, peripheral artery disease, aortic valve replacement, resuscitated sudden death, and cardiovascular death. ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; HeFH = heterozygous familial hypercholesterolemia.

methods subject to quality control. The LDL-C-year-score was calculated as previously described (9) according to the following formula: [LDL-C max × (age at diagnosis/initiation of statin)] + [LDL-C at inclusion × (age at inclusion − age at diagnosis/initiation of statin therapy)].

CAC MEASUREMENT. CAC score was performed at the baseline visit. CAC was quantified by means of the previously described Agatston scoring method over the entire epicardial coronary tree (26). Briefly, coronary calcium was defined as a lesion above a threshold of 130 HU, with an area of ≥3 adjacent pixels (at least 1 mm^2). The CAC score was computed from the product of the attenuation factor and the area of calcification (in square millimeters), with the total CAC score of each coronary artery being equal to the sum CAC of all calcified plaques from that artery. The total calcium score was calculated by summing CAC scores from the left main, left anterior descending, left circumflex, and right coronary arteries.

DEFINITION OF CARDIOVASCULAR OUTCOMES. ASCVD events were defined as fatal or nonfatal acute coronary syndromes, including myocardial infarction (MI) and unstable angina requiring revascularization, defined according to international guidelines (27,28); elective myocardial revascularization performed by percutaneous coronary intervention or coronary artery bypass graft (29), as indicated by the treating physician, caused by stable angina or inducible ischemia after stress testing; and aortic valve replacement (AVR); fatal or nonfatal stroke or transient ischemic attack, peripheral artery disease, resuscitated sudden death, and cardiovascular death (15,17,18,30). The duration of follow-up was defined as the time from the enrollment visit to the last available visit at the lipid clinic. The lipid clinic specialist performed endpoints assessment during the follow-up visits. For the REFERCHOL cohort, all cardiovascular events were cross-matched with the national health system database.

This research was conducted in accordance with good clinical practices.

REFERCHOL cohort. The cohort was declared to the French National Agency for Medicines Safety and received a declarant number (a unique number identifying a particular research protocol, issued by the French National Agency for Medicines Safety in France): 2014-A01549-38. Two separate committees assessed the protocol of this study: the French Advisory Committee on the Processing of Information for Medical Research and the National Commission for Computer Technology and Freedom in May and November 2015, respectively.

SAFEHEART cohort. This study was approved by the local ethics committees, and all eligible subjects gave written informed consent.

STATISTICAL ANALYSIS. Data are expressed as mean ± SD for continuous parametric variables, median (interquartile range [IQR]) for continuous nonparametric variables, and percentages for categorical variables.

Probability estimation of ASCVD within 5 years was obtained according to the method described by D'Agostino et al (31,32).

Briefly, a 6-step conception of the risk prediction model was performed:

1) We specified the ASCVD outcomes as specified.
2) We selected the population of HeFH subjects, at high-risk but without ASCVD at baseline.
3) We selected a follow-up time of 5 years.
4) We selected specific cardiovascular risk factors already embedded in SAFEHEART-RE, such as age, male sex, history of ASCVD before enrollment, high blood pressure, increased body mass index,

TABLE 1 Baseline Clinical and Laboratory Characteristics of the Study Population

	Patients With ASCVD (n = 81)	Patients Without ASCVD (n = 1,543)	*P* Value
Male	49 (60.49)	692 (44.94)	0.01
Age, y	55.60 ± 10.13	48.11 ± 12.85	<0.0001
History of premature familial ASCVD	34 (45.33)	503 (39.05)	0.28
Type 2 diabetes	6 (7.50)	28 (1.86)	<0.0001
Hypertension	28 (35.44)	288 (19.12)	0.0004
Current smoking	16 (20.25)	287 (19.16)	0.60
BMI ≥25 kg/m^2	40 (49.39)	592 (38.39)	0.01
Lipid profile at baseline			
TC, mg/dL	258.26 (87.17)	255.27 (76.68)	0.74
LDL-C, mg/dL	185.84 (80.27)	181.51 (75.11)	0.62
HDL-C, mg/dL	50.46 (16.35)	54.54 (15.69)	0.04
TG, mg/dL	57.01 (9.20)	56.20 (9.13)	0.71
Lp(a), mg/dL	36 (16-79)	22 (10-53)	0.01
Lipid profile at last visit			
TC, mg/dL	232.71 (81.80)	244.44 (75.49)	0.21
LDL-C, mg/dL	170.01 (85.53)	171.63 (84.83)	0.87
HDL-C, mg/dL	53.16 (24.83)	54.66 (15.65)	0.06
TG, mg/dL	59.37 (9.47)	56.54 (8.71)	0.23
LDL-c year score, mg/dL-year	14,695 (5,118)	11,448 (4,997)	<0.0001
Lipid-lowering treatment at baseline			0.15
None	11 (15.07)	352 (23.75)	
Statin therapy	62 (76.5)	1130 (73.2)	
Bitherapy	33 (45.21)	538 (36.30)	
High-potency statins	40 (49.38)	460 (29.81)	0.0002
Lipid-lowering treatment at last visit			0.03
None	10 (12.20)	267 (18.15)	
Statin therapy	72 (88.9)	1,204 (82.9)	
Bitherapy	52 (63.41)	716 (48.67)	
High-potency statins	50 (58.14)	537 (34.80)	<0.0001
Age at start of statins, y	40.81 (12.79)	34.05 (13.00)	<0.0001
Treatment exposure, y	12.0 (4.0-15.0)	10 (1.0-18.0)	0.74
CAC score, HU	387 (146-879)	8 (0-109)	<0.0001
CAC category			<0.0001
0	3 (3.70)	627 (40.64)	
1-100	11 (13.58)	512 (33.18)	
>100	67 (82.72)	404 (26.18)	

Values are n (%), mean ± SD, or median (interquartile range).

ASCVD = atherosclerotic subclinical cardiovascular disease; BMI = body mass index; CAC = coronary artery calcium; HDL-C = high-density lipoprotein cholesterol; HU = Hounsfield U; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); TC = total cholesterol; TG = triglycerides.

active smoking, LDL-C, and Lp(a), previously validated in the REFERCHOL population (9).

5) We selected the following standard Cox model for time-to-event analysis and risk estimation: $1 - S_0(t)\exp(\Sigma\beta X - m)$.
6) We tested the ability of the model to produce absolute and relative risk estimates.

The natural logarithm of the Agatston score log(CAC + 1) was used according to previous studies (10). In addition, the HR for predefined CAC score categories were considered (0, 1-100, and >100). Patients were stratified by risk group based on the empirical distribution of the 5-year risk computed from the SAFEHEART-RE (below median: low risk; median to quartile [Q] 3: intermediate risk; >Q3: high risk). As a result, SAFEHEART-RE was designed according to the following cutoffs: low risk (0 to median [0%-2%]), intermediate risk (median to Q3 [2%-5%]), and high risk (>Q3 [5%]). SAFEHEART-RE with log(CAC + 1) was designed according to the following cutoffs: low risk (0 to median [0%-2%]), intermediate risk (median to Q3 [0%-12%]), high risk (>Q3). A univariate Cox proportional hazards regression model was used to estimate the HR for the CAC score and SAFEHEART-RE alone and combined prediction of ASCVD. The number of total ASCVD events was counted in the study cohort, and the incidence rate was expressed as the number of events per 1,000 patient-years.

We assessed the improvement in discrimination by comparing the area under the receiver-operating characteristic curves (AUC) in models with CAC score alone, SAFEHEART-RE alone, and combined with log(CAC + 1) (33). We assessed the classification of risk using the net reclassification improvement (NRI) formula (34): NRI = [*Prob* (being correctly upward reclassified/event) − *Prob* (being incorrectly downward reclassified/event)] + [*Prob* (being correctly downward reclassified /nonevent) − *Prob* (being incorrectly classified to an upward category/nonevent)].

As a subgroup analysis, Cox proportional hazards regression model, AUC, and NRI were computed for only hard cardiovascular endpoints. These were defined as fatal or nonfatal acute coronary syndromes, stroke, and peripheral artery disease.

RESULTS

BASELINE CHARACTERISTICS OF PATIENTS WITH HeFH. Table 1 shows the main clinical and laboratory baseline characteristics of the study population (n = 1,624; mean age: 48.5 ± 12.8 years; males: 45.7%), with or without ASCVD. Subjects who developed ASCVD were more likely to be men, older, diabetic, hypertensive, and overweight. They also exhibited higher Lp(a) levels and LDL-C year score, lower high-density lipoprotein cholesterol, had a later onset of LLT, and exhibited a higher prevalence of CAC. Clinical and laboratory findings of the study cohort stratified according to CAC categories are presented in Supplemental Table 1.

CARDIOVASCULAR ENDPOINTS. After a median follow-up of 2.7 years (IQR: 0.4-5.0 years), 81 ASCVD

TABLE 2 Follow-Up and ASCVD in the Study Population (N = 1,624)

Follow-up, y	2.7 (0.4-5.0)
Total ASCVD	81 (4.99)
Nonfatal ACS	23 (28.40)
MI	12 (52.20)
UA	11 (47.80)
Elective myocardial revascularization	45 (55.55)
AVR	5 (6.17)
Stroke	5 (6.17)
PAD	1 (1.23)
CV death	2 (2.47)

Values are median (interquartile range) or n (%).

ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; AVR = aortic valve replacement; CV = cardiovascular; MI = myocardial infarction; PAD = peripheral artery disease; UA = unstable angina.

events were recorded for an estimated 19.44 events per 1,000 patients/year. More than one-half of the events were elective myocardial revascularizations (n = 45; 55.5%). There were 2 cardiovascular deaths and 34 (41.9%) nonfatal ASCVD events (Table 2).

CAC-RELATED CARDIOVASCULAR OUTCOMES. Univariate regression analysis showed that a unit increase in log(CAC + 1) was associated with a 1.8-fold higher risk of ASCVD (95% CI: 1.6-2.1; $P < 0.001$).

Compared with HeFH subjects without CAC, the HR for ASCVD was 4.28 (95% CI: 1.19-15.33) among subjects with a CAC score of 1 to 100 and 32.05 (95% CI: 10.08-101.94) among subjects with a CAC score of >100 (log-rank $P < 0.0001$), as shown in Figure 2A (Supplemental Table 2).

EFFECT OF THE ADDITION OF CAC TO SAFEHEART-RE IN ASCVD PREDICTION. Subjects at intermediate and high risk according to SAFEHEART-RE had a significant increase in ASCVD (HR: 2.83 [95% CI: 1.65-4.86] and 3.73 [95% CI: 2.17-6.41], respectively) as compared to HeFH subjects with a SAFEHEART-RE low risk (log-rank $P < 0.0001$), as shown in Figure 2B (Supplemental Table 2). When CAC score was added to SAFEHEART-RE, the HR for incident ASCVD was significantly higher in both intermediate- and high-risk groups (HR: 5.43 [95% CI: 2.47-11.92] and HR: 15.34 [95% CI: 7.54-31.23], respectively) compared to the low-risk group (log-rank $P < 0.0001$) (Figure 2C, Supplemental Table 2).

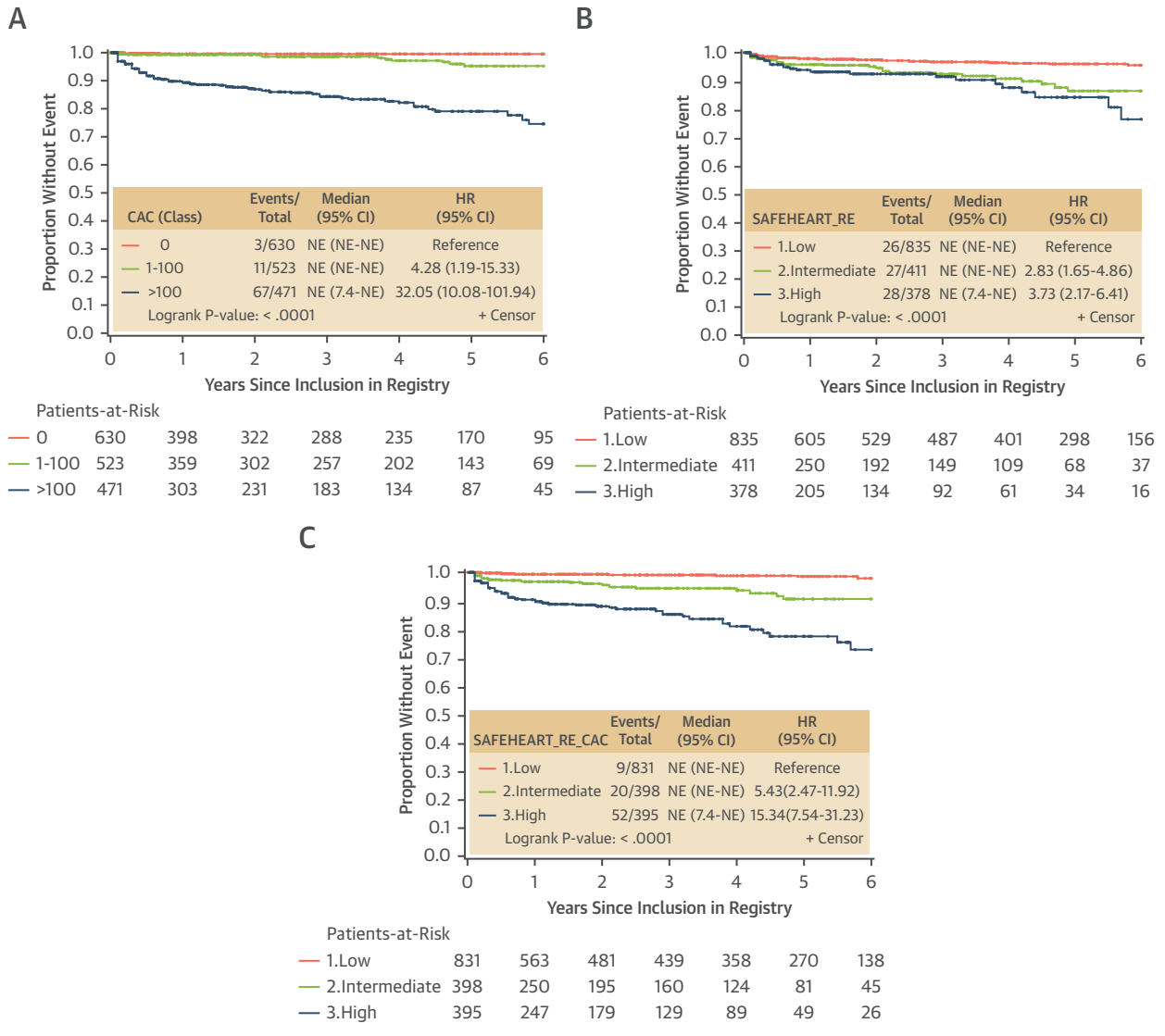
The addition of CAC score also allowed improving the redistribution of patients' risk according to incident ASCVD: Supplemental Figure 1 shows the Kaplan-Meyers curves for ASCVD (only hard endpoints) according to CAC category and SAFEHEART-RE, alone and combined for hard endpoints only (see also Supplemental Table 3 for the number of ASCVD—hard endpoints only—according to each risk category).

SAFEHEART-RE and CAC score separately discriminated for incident ASCVD (AUC: 0.793 [95% CI: 0.779-0.869] and AUC: 0.860 [95% CI: 0.853-0.869], respectively; $P = 0.009$). The discrimination for incident ASCVD was improved when SAFEHEART-RE and CAC score were combined (AUC: 0.884 [95% CI: 0.871-0.894]) versus SAFEHEART-RE alone ($P < 0.001$), although it was not different from the performance of CAC score alone ($P = 0.2503$) (Figure 3A).

A similar trend was observed when the 36 encountered hard cardiovascular endpoints were included in the analysis. CAC score and SAFEHEART-RE alone improved the prediction of ASCVD in the study population (AUC: 0.815 [95% CI: 0.803-0.826] and AUC: 0.776 [95% CI: 0.766-0.787], respectively; $P = 0.161$]. When CAC was combined with SAFEHEART-RE, the discrimination was significantly improved (AUC: 0.859 [95% CI: 0.845-0.873]) vs SAFEHEART-RE alone; $P = 0.0439$) although CAC score alone performed as well as combined with SAFEHEART-RE ($P = 0.2845$) (Figure 3B).

RECLASSIFICATION OF ASCVD RISK. Once stratified according to SAFEHEART-RE, we explored for each risk category the rate of upward or downward risk reclassification by adding log(CAC + 1) to SAFEHEART-RE (Table 3). In the low-risk SAFEHEART patients with ASCVD, 21 subjects (80.7%) were correctly upward reclassified. In the intermediate SAFEHEART risk category, 20 (74.1%) of the 27 patients with ASCVD were appropriately reclassified to the higher risk category, with 3 patients (11.1%) being incorrectly downgraded. In the high-risk SAFEHEART category, only 1 (3.6%) of the 28 patients was incorrectly downgraded. Among HeFH subjects without ASCVD, adding log(CAC + 1) to the SAFEHEART-RE determined a correct downgrade of 159 over 384 (41.4%) intermediate-risk subjects and 145 over 350 (41.2%) high-risk subjects. Applying the NRI formula that considers both those correctly reclassified and those incorrectly reclassified, a net 45.7% of the events group was reclassified upward appropriately, whereas a net −0.3% of the nonevents group was appropriately downgraded into the low-risk group by the addition of CAC score to SAFEHEART-RE. The NRI for the addition of CAC score to SAFEHEART-RE was therefore 45.4%. Even without embedding CAC as a continuous variable into SAFEHEART-RE but considering the CAC categories (0, 1-100, and >100), we found a 41.5% overall reclassification of ASCVD prediction (Supplemental Table 4). Finally, up to one-third of hard endpoints were reclassified by adding

FIGURE 2 **Kaplan-Meier ASCVD-Free Survival According to CAC Score and SAFEHEART-RE, Alone and Combined**



(A) CAC score was classified according to the following categories: CAC = 0, CAC = 1-100, and CAC of >100. **(B)** SAFEHEART-RE categories were designed according to the following cutoffs: low risk (0 to median [0%-2%]), intermediate risk (median to Q3 [2%-5%]), and high risk (>Q3 [5%]). **(C)** SAFEHEART-RE with log(CAC + 1) was designed according to the following cutoffs: low risk (0 to median [0%-2%]), intermediate risk (median to Q3 [0%-12%]) and high risk (>Q3). NE = not estimable; Q = quartile; SAFEHEART-RE = Spanish Familial Hypercholesterolemia Cohort Study risk equation; other abbreviations as in Figure 1.

CAC score to the SAFEHEART-RE (Supplemental Table 5).

DISCUSSION

The goal of this study was to assess the improvement in discrimination obtained through the addition of CAC score to HeFH-specific SAFEHEART-RE in a cross-national cohort. Our study, which is the largest so far, showed that CAC score improves the discrimination for ASCVD in HeFH.

The association of common cardiovascular risk factors as well as some genetic modulation determine an overlap of differently severe HeFH phenotypes. In the SAFEHEART-RE, age, male sex, history of cardiovascular disease before enrollment, high blood pressure, increased body mass index, active smoking, and LDL-C and Lp(a) levels were independent

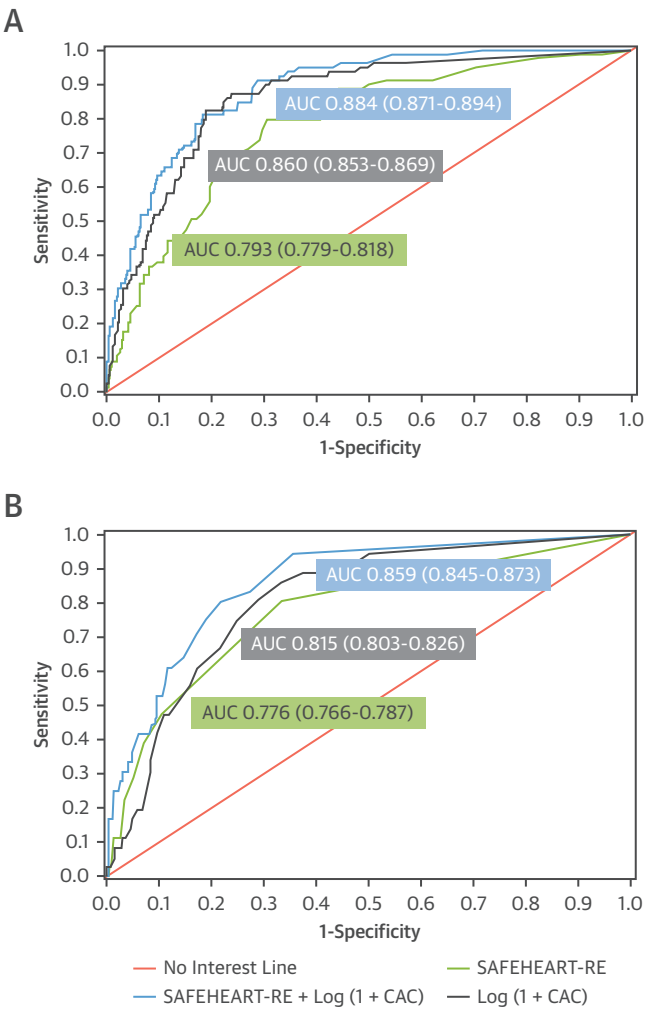
predictors of incident major adverse cardiac events (8,35). The SAFEHEART-RE, like many equations used in medicine, is very accurate, but it is not perfect. The SAFEHEART-RE has demonstrated its strong ability to discriminate patients at high risk of cardiovascular events (C-index: 0.85). We think that the CAC score is a valuable tool to cover this lack of precision of the SAFEHEART-RE. Indeed, CAC score alone performed as well as combined with SAFEHEART-RE in the prediction of ASCVD in the study population. We observed that more than one-half (50.6%) of the HeFH subjects at low and intermediate risk according to the SAFEHEART-RE developing ASCVD were upward-reclassified by the addition of CAC score. This finding suggests that CAC score has an important place for the early discrimination of more severe forms of HeFH despite the absence of traditional additional risk factors and that it may represent an optimal tool to refine cardiovascular risk when information on other clinical markers is not available.

The primary endpoint of our study was a composite of coronary and peripheral carotid/femoral vascular events, and in our study, 5 patients underwent AVR. Initially thought of as being a homozygous FH prerogative, aortic calcifications are a recurrent finding in HeFH, showing a significantly increased prevalence as compared to the non-FH population (36). Aortic valve stenosis has been recently shown to lead to 4.36 times more AVR in HeFH compared to nonaffected relatives, making AVR a cardiovascular endpoint to be accounted for in this specific population (37). HeFH mainly targets the coronary territory: as confirmed in our study, the great majority of the ASCVD events involved the coronary arteries. CAC score led to unmasking of coronary artery disease in a high percentage of asymptomatic HeFH subjects: of interest, almost one-half of the elective myocardial revascularization procedures consisted of coronary artery bypass graft, with an indication to surgery being established because of the severity of the detected atherosclerotic coronary burden.

CAC score has also shown a positive predictive power for other-than-coronary events: a meta-analysis of 13,362 asymptomatic subjects has shown that the presence of CAC was associated with a 2.85-fold increased risk of stroke compared to subjects without CAC (38). On the other side, the absence of CAC has not proven to fully rule out the presence of peripheral atherosclerosis in non-FH asymptomatic subjects (39).

Nearly 40% of patients from our cohort did not exhibit any CAC. Mszar et al (21) have recently highlighted a similar prevalence (45%) from a cumulative analysis of 9 studied on asymptomatic HeFH subjects, with a mean age of 36 to 51 years. If these findings were expected in the general population, as recently reported from the MESA (Multi-ethnic Study of Atherosclerosis) cohort (40), they are quite challenging in a traditionally believed at-high-risk population like HeFH. Our findings confirm on a larger scale previous findings by Miname et al (18), where the absence of CAC occurred in 50% of studied patients and was associated with no ASCVD events during follow-up despite the persistence of elevated residual LDL-C levels (150 mg/dL). According to

FIGURE 3 ROC Curves Comparing SAFEHEART-RE, Log(CAC + 1) Alone and Combined for the 5-Year Risk Prediction Of ASCVD



(A) ASCVD included both soft and hard endpoints. **(B)** ASCVD included only hard endpoints. ROC curves for SAFEHEART-RE alone are highlighted in blue, ROC curves for log(CAC + 1) alone are highlighted in green, and ROC curves for SAFEHEART-RE plus log(CAC + 1) score are highlighted in red. AUC = area under the curve; ROC = receiver-operating characteristic; other abbreviations as in Figures 1 and 2.

TABLE 3 Net Reclassification Improvement for ASCVD Prediction With the Addition of CAC Quantification to SAFEHEART-RE in Asymptomatic HeFH Subjects

Classification According to SAFEHEART Risk	Classification According SAFEHEART + log(CAC + 1)			
	Low	Intermediate	High	Total
Low risk (<2%)				
Nonevents	611	171	27	809
Events	5	16	5	26
NRI, %				
Nonevents		−24.5		
Events		80.8		
Overall		56.3		
Intermediate risk (2%-5%)				
Nonevents	159	114	111	384
Events	3	4	20	27
NRI, %				
Nonevents		12.5		
Events		77.8		
Overall		90.3		
High risk (>5%)				
Nonevents	52	93	205	350
Events	1	0	27	28
NRI, %				
Nonevents		41.4		
Events		3.6		
Overall		45.0		
Total				
Nonevents	822	378	343	1,543
Events	9	20	52	81
NRI, %				
Nonevents[a]		−0.3		
Events[b]		45.7		
Overall		45.4		

Values are n, unless otherwise indicated. We assessed the classification of risk using the NRI index: NRI = [*Prob* (being correctly upward reclassified/event) − *Prob* (being incorrectly downward reclassified/event)] + [*Prob* (being correctly downward reclassified /nonevent) − *Prob* (being incorrectly classified to an upward category/ nonevent)]. Therefore. [a][(159 + 52 + 93) -(171 + 27 + 111)/1,543]. [b][(16 + 5 + 20) - (3 + 1 + 0)/81].

ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; HeFH = heterozygous familial hypercholesterolemia; NRI = net reclassification improvement; SAFEHEART-RE = Spanish Familial Hypercholesterolemia Cohort Study risk equation.

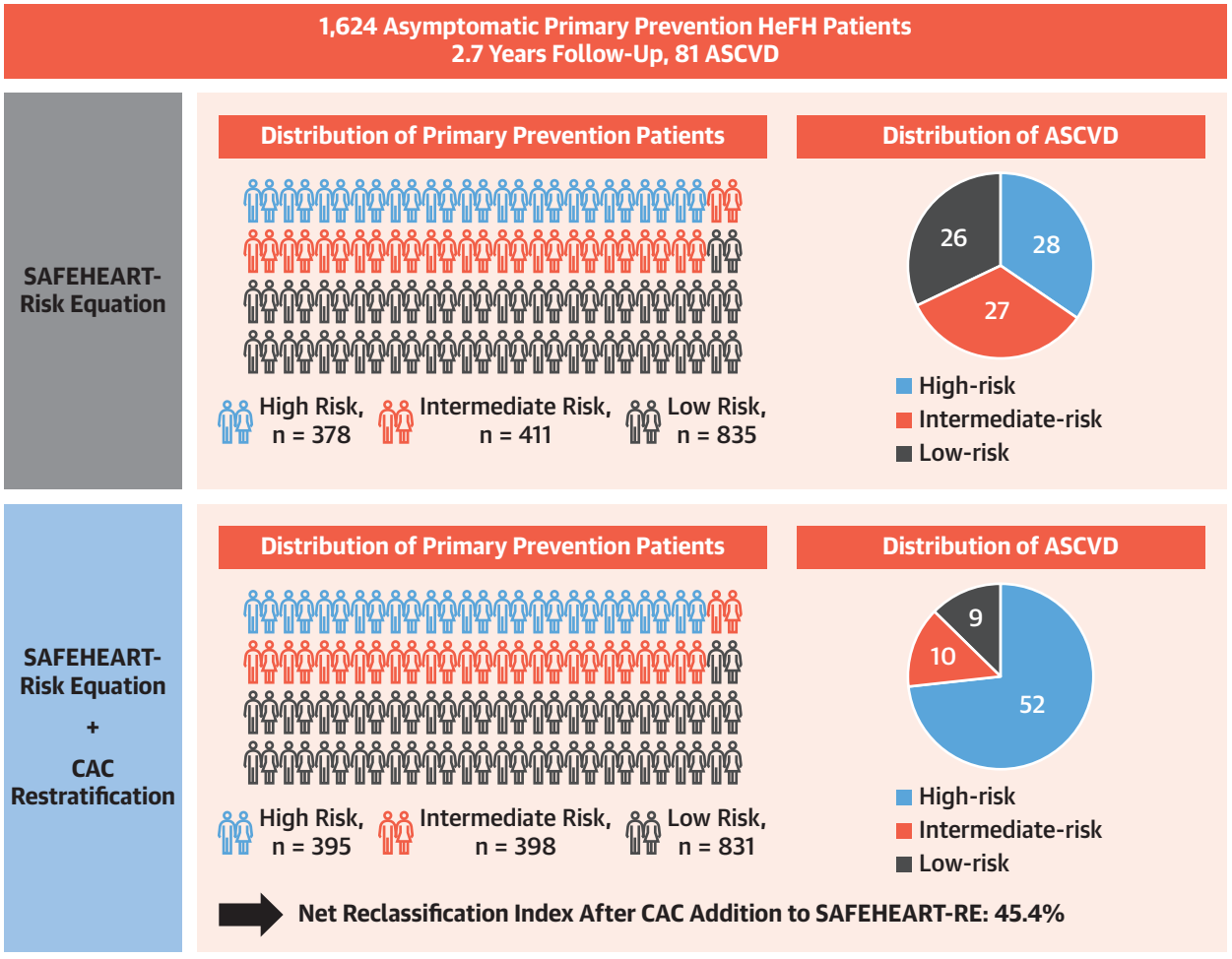
current guidelines, all patients with HeFH need to be treated with a high-intensity LLT for ≥50% reduction from baseline LDL-C (15). Cardiovascular noninvasive imaging may, however, help in targeting a more personalized approach, by choosing which patients should have easier access to the most recent medical innovations, ie, PCSK9 inhibitors, in a cost-sustainable balance for health care systems (22). We observed a late onset of LLT in our study population, with a range from 34 to 40 years of age; this finding highlights the underdiagnosis and undertreatment of this condition and the need to improve awareness of the disease in the general population.

In this study, CAC score helped in reclassifying downward more than 40% of patients from the high-risk SAFEHEART-RE subgroup, who did not experience ASCVD during follow-up (**Central Illustration**). The role of CAC score in downgrading risk stratification is still a matter of debate in the general population, and our findings in high-risk subjects need to be interpreted with caution. In our study, 3 events occurred among subjects with a CAC score of 0 at baseline: the first was a cerebrovascular event in a statin-treated 49-year-old woman (untreated total cholesterol [TC]: 290 mg/dL; follow-up: 2.5 years); the second was a coronary revascularization in a 46-year-old statin-intolerant woman (TC: 400 mg/dL; follow-up: 6.3 years) who presented with unstable angina; the third was a coronary revascularization in a 45-year-old man following a diagnosis of silent ischemia (untreated TC: 289 mg/dL; follow-up: 4.5 years). Although these findings suggest a very low risk in subjects with HeFH without CAC, CAC score does not allow the detection of soft, vulnerable plaque, and in specific cases, it is not a predictor of other-than-coronary vascular disease. The absence of CAC has been associated with a very low incidence of ASCVD (41-43); however, targeted studies are still lacking, and it is still unclear what the timing is of the eventual development of ASCVD to guide therapeutic management. Our analysis also included younger subjects, for whom the presence of CAC may be less influenced by common unmodifiable risk factors, such as age. A 12.5-year follow-up analysis from the CARDIA (Coronary Artery Risk Development in Young Adults) study has confirmed a role of CAC as an independent predictor of cardiovascular morbidity and mortality in subjects aged 32 to 46 years (11). This has not yet been confirmed in HeFH young adults.

STUDY LIMITATIONS. The first limitation is the cumulative analysis of 2 separate cohorts with possible different backgrounds in terms of genetic, diagnostic and cardiovascular outcomes as well as therapeutic profile. However, the validation of SAFEHEART-RE derived from the Spanish registry confirmed its prognostic value in the REFERCHOL cohort.

Second, a selection bias cannot be excluded for both SAFEHEART and REFERCHOL patient selection based on CAC score indication and availability. Patients received a prescription for a computed tomography scan based on the management of each treating physician. In both registries, however, patients were consecutively enrolled, and only subjects with a molecular diagnosis were selected. We performed an analysis on the REFERCHOL cohort by selecting patients without a CAC score, respecting the same other eligibility criteria for this study. We found that those not having a CAC score were more likely to be

CENTRAL ILLUSTRATION **The Added Value of Coronary Artery Calcium Score on Top of SAFEHEART Risk Equation for Atherosclerotic Cardiovascular Disease Prediction in Asymptomatic Heterozygous Familial Hypercholesterolemia**



Gallo, A. et al. J Am Coll Cardiol Img. 2021;■(■):■–■.

This study aimed at evaluating the contribution of coronary artery calcium (CAC) score in the improvement of risk stratification through the SAFEHEART (Spanish Familial Hypercholesterolemia Cohort Study) risk equation in heterozygous familial hypercholesterolemia (HeFH). Over a median 2.7 y of follow-up, atherosclerotic cardiovascular disease occurred in 81 out of 1,624 subjects from the French and Spanish HeFH registries. The addition of CAC score improved risk stratification, leading to a correct upward/downward reclassification of nearly half of previously incorrectly classified patients. Our findings suggest that CAC sore is a useful tool to improve the accuracy of currently available risk equations for patients with HeFH.

younger, smokers, and less intensely treated with LLT, suggesting that patients with a late onset treatment might have been more likely proposed a CAC score. However, they showed a lower prevalence of familial premature ASCVD, hypertension, and overweight and had been treated earlier that those with a CAC score (Supplemental Table 6).

Third, this analysis was first intended to evaluate a wide spectrum of ASCVD, including soft endpoints as elective coronary revascularizations. These represented most of the ASCVD on follow-up, which might overestimate the predictive power of CAC. Nevertheless, CAC score proved a good predictive power when elective coronary revascularizations were excluded from the analysis (**Figure 3B,** Supplemental Table 3).

CONCLUSIONS

The addition of CAC score to the SAFEHEART-RE improved discrimination and refining of risk assessment in asymptomatic patients with HeFH. The

optimization of treatment based on CAC score will be a challenge for the future.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: This study has strong clinical implications for the management of HeFH: CAC score has an important place for the early discrimination of more severe forms of HeFH despite the absence of traditional additional risk factors and on top of SAFEHEART-RE stratification. The results of our study can translate into an improvement and personalized intensification of LLT through currently available novel pharmacological options.

TRANSLATIONAL OUTLOOK: Cardiovascular imaging represents a promising tool to overcome major challenges represented by cardiovascular risk stratification in HeFH. Further work is needed to provide a better understanding of the physiopathologic process underlying coronary calcifications in this genetic disease and explaining the high phenotype variability.

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KEY WORDS cardiovascular disease, coronary artery calcium, coronary imaging, familial hypercholesterolemia, genetic disease, risk prediction

APPENDIX For supplemental tables and a figure, please see the online version of this paper.