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Coronary computed tomographic angiography findings and their therapeutic implications in asymptomatic patients with familial hypercholesterolemia. Lessons from the SAFEHEART study

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BACKGROUND: Familial hypercholesterolemia (FH) confers an increased risk of premature atherosclerotic disease. Coronary computed tomographic angiography (CTA) can assess preclinical coronary atherosclerosis.

OBJECTIVES: To describe coronary CTA findings in asymptomatic molecularly defined FH individuals, to identify those factors related to its presence and extension, and to assess the impact of these results in patients' care and estimated risk.

METHODS: Four hundred and forty individuals with FH, without clinical cardiovascular disease, were consecutively enrolled and underwent a coronary CTA that was used to analyze coronary atherosclerosis based on coronary calcium score (CCS), sum of stenosis severity, and plaque composition sum (PCS). For FH patients, cardiovascular risk was estimated using the specific SAFEHEART risk equation. Follow-up was performed using a standardized protocol.

RESULTS: Mean age was 46.4 years (231 women, 52%). Coronary calcium was present in 55%, mean CCS was 130.9, 46% had a plaque with lumen involvement, and mean PCS was 1.1. During follow-up, there were 17 (4%) nonfatal events and 2 (1%) fatal events. CCS was independently associated to the estimated risk and low-density lipoprotein-cholesterol life-years, sum of stenosis severity to the estimated risk, and PCS to the estimated risk and low-density lipoprotein-cholesterol life-years. CTA findings induced a positive change in patients' care and in their estimated risk.

CONCLUSION: Coronary artery atherosclerosis is highly prevalent in asymptomatic patients with FH and it is independently associated to cardiovascular risk. More advanced disease on CTA was associated with subsequent intensification of therapy and reduction of estimated risk. Further longitudinal studies are required to know if these findings might improve the risk stratification in patients with FH.

Introduction

Heterozygous familial hypercholesterolemia (FH) is the most common genetic disorder associated with premature atherosclerotic cardiovascular disease (ASCVD).[1] Patients with FH have 3- to 13-fold greater risk of premature ASCVD compared with non-FH individuals.[2–4] However, risk of cardiovascular disease in FH can be highly variable.[5]

Vascular imaging is a useful tool to define the natural history of the atherosclerotic disease process, as the atherosclerotic plaque is the pathological substrate underlying the occurrence of ischemic cardiovascular events.[6] In this sense, coronary computed tomographic angiography (CTA) is able to detect and quantify the calcium in the coronary artery wall and the luminal stenosis, as well as to analyze the plaque composition characteristics. These 3 aspects have been related to patients' prognosis[7] and might provide an added value for identification of factors contributing to atherogenesis in individuals with FH and to better classify their cardiovascular risk.[5,8]

Although the coronary involvement detected by coronary CTA in patients with FH has been described, the findings have been based on small cohorts of patients. However, the diagnosis and prognostic value of coronary CTA in FH patients remain inconclusive.[9–14] The SAFEHEART registry (Spanish Familial Hypercholesterolemia Cohort Study) provides a unique opportunity to approach this entity in patients enrolled in a dedicated longitudinal registry.[15,16]

Our aims were to describe the coronary involvement using coronary CTA in molecularly defined and asymptomatic FH subjects, to identify which factors are related to the presence, extension, and characteristics of their coronary atherosclerosis and to assess the impact of coronary CTA results in patients' management, care, and estimated risk.

Methods

Study design and population

SAFEHEART is a multicentre, nationwide, long-term prospective cohort study in a molecularly defined population of patients with heterozygous FH in Spain.[15,16] Of them, for this study, data were obtained from 440 individuals (aged 20 to 70 years), without clinical cardiovascular disease, consecutively enrolled in the registry in 6 university hospitals, who voluntarily underwent a coronary CTA between January 2013 and December 2016. Patients with contraindications for coronary CTA were refused. All patients were managed according to the indications of their treating physician and followed-up on a yearly base through a standardized protocol. Cardiovascular events

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

Clinical measurements

Demographic and clinical characteristics were recorded as described elsewhere.[15] Venous blood samples were taken after a 12-hour fast. Lipid profile and lipoprotein (a) [Lp(a)] levels were determined as previously described.[17,18] DNA was isolated from whole blood, and the genetic diagnosis of FH was made.[19] Low-density lipoprotein-cholesterol (LDL-C) life-years was calculated as previously described.[2] Estimated cardiovascular risk at 5- and 10-years was obtained by using the SAFEHEART risk equation (SAFEHEART-RE),[5] which estimates the likelihood to occur the first one of the following: Fatal or nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, coronary revascularization, peripheral artery revascularization, and cardiovascular death (any death related to cardiovascular disease or derived of cardiovascular therapeutic procedures not described in the previous definitions).

Coronary CTA performance, image reconstruction, and evaluation

Using a tomographic scanner, 3-mm-thick slices were obtained during a breath holding protocol, and the Agatston coronary calcium score (CCS) was calculated.[20] Coronary CTA was performed using 64–detector row scanners or higher with prospective or retrospective electrocardiographic gating. Eighty to 100 mL of intravenous contrast, followed by 50 to 80 mL of saline, was administered at a rate of 5 mL/s via a power injector through an antecubital vein. Scanning parameters included heart rate–dependent pitch (0.20 to 0.45), 330-ms gantry rotation time, 100- or 120-kVp tube voltage, and 350- to 800-mA tube current.

Coronary CTAs were reconstructed using the following parameters: 0.5- to 0.75-mm slice thickness, 0.3-mm slice increment, 160- to 250-mm field of view, 512 × 512 matrix, and a standard kernel. Optimal phase reconstruction was assessed by comparison of different phases, if available, and the phase with the least amount of coronary artery motion was chosen for analysis. Multiple phases were used for image interpretation if minimal coronary artery motion differed among the various arteries.

Every coronary CTA was analyzed by 2 independent experienced readers, blinded to the clinical characteristics of the subjects, in a central laboratory. In case of discrepancy, a third reader was consulted. Coronary CTA analysis was performed on dedicated workstations (Philips Extended Brilliance TM Workspace 4.5 equipped with the software Comprehensive Cardiac Analysis; Philips Medical Systems Nederland). CTs were evaluated by using different techniques, including axial, multiplanar reformat, maximum intensity projection, and cross-sectional views.

Table 1 Main characteristics of the study population

Variable	Mean (SD)/n (%)
N	440
Female	231 (53%)
Age (y)	46.4 (10.5)
Index cases	204 (46%)
Premature familial CVD history	197 (45%)
Type 2 diabetes	5 (1%)
Hypertension	38 (9%)
Active tobacco smoker	120 (27%)
Xanthomas	77 (18%)
Corneal arcus	152 (35%)
BMI (kg/m^2)	26.0 (4.8)
Waist circumference (cm)	85.9 (13.1)
Total cholesterol (mg/dL)	246.8 (68.1)
LDL-C (mg/dL)	176.2 (62.8)
HDL-C (mg/dL)	50.6 (13.5)
TG (mg/dL)	99.1 (56.0)
Lp(a) (mg/dL)	39.2 (40.9)
LDLR null mutation	64 (15%)
Patients on maximum statin dose	194 (44%)
Patients on ezetimibe	193 (44%)
Patients on maximum combined therapy	124 (28%)
Patients on maximum LLT	245 (56%)
LDL-C life-years (decades)	955.2 (375.9)
Time of statin use (y)	11.9 (7.9)
LLT potency*	6.0 (1.6)
5-y SAFEHEART-RE (%) [median (interquartile range)]	0.6 (0.3–12)
10-y SAFEHEART-RE (%) [median (interquartile range)]	1.3 (0.7–2.6)

BMI, body mass index; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LDLR, LDL receptor; LLT, lipid-lowering therapy; Lp(a), lipoprotein (a); TG, triglycerides.

5- and 10-y SAFEHEART-REs: 5- and 10-y risk estimated by means of the SAFEHEART risk equation, which estimates the likelihood to occur the first one of the following: Fatal or nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, coronary revascularization, peripheral artery revascularization, and cardiovascular death (any death related to cardiovascular disease or derived of cardiovascular therapeutic procedures not described in the previous definitions).

*Maximum statin dose, maximum combined therapy, maximum lipid-lowering therapy, and LLT potency have been calculated according the method described in reference.[5]

In each coronary artery segment, coronary atherosclerosis was defined as tissue structures ≥1 mm^2 that existed either within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself. Angiographic analysis by coronary computed tomography was performed according to a 17-segment American Heart Association classification.[21]

The stenosis severity was visually evaluated. A lesion severity score was defined as follows: 0 = no stenosis; 1 = mild diameter stenosis (<50%); 2 = moderate (50% to 70%); and 3 = severe diameter stenosis (>70%). Sum of

stenosis severity (SSS) was defined as the sum of the lesion severity in all segments.[22]

Plaque composition was classified as follows, according to a new score system designed for this assessment: 0 = no plaque; 1 = calcified plaque (highly attenuating tissue for >70% of the plaque volume, which could be clearly separated from the contrast enhanced coronary lumen); 2 = mixed plaque (containing both calcified and noncalcified tissue); and 3 = noncalcified plaque (low-attenuating lesions that could be clearly separated from the coronary lumen and the surrounding epicardial fat or myocardium). Vessel segments <1.5 mm in diameter were excluded from analysis. For each patient, the plaque composition sum (PCS), defined as the sum of all the plaque composition values in all segments, was calculated.

Statistical analysis

Statistical analyses were carried out using SPSS, version 18.0 (SPSS Inc, Chicago, Illinois). Variables were analyzed for a normal distribution with the Kolmogorov-Smirnov test. Quantitative data were expressed as mean (standard deviation) and qualitative data as absolute number (percentage). Comparisons of frequencies between qualitative variables were carried out using the chi-square test. Changes in binary variables before and after coronary CTA were analyzed by McNemar's test. Mean values of quantitative variables were compared with the *t*-test. A forward linear regression analysis was conducted, to determine the variables independently associated with CCS, SSS, and PCS. We included variables that were statistically significant in univariate analyses, excluding those variables showing collinearity. Differences were considered statistically significant with a P value <.05.

Results

Four hundred and forty individuals (231 women, 53%) underwent a coronary CTA between January 2013 and December 2016. Mean age was 46.4 years. Main characteristics including lipid-lowering therapy and lipid plasma levels are shown in Table 1. All subjects were on lipid-lowering therapy (LLT), and 56% were on maximum LLT. Median 5- and 10-year cardiovascular risk according SAFEHEART-RE were 0.6% and 1.3%, respectively, and mean LDL-C was 176.2 mg/dL.

Coronary CTA findings

Coronary calcium was found in more than a half of patients (56%), and an atherosclerotic plaque compromising the arterial lumen was found in 46% patients (Table 2). Analyzing these results by gender, coronary calcium was found in 108 (52%) women and 136 (71%) men, and coronary artery stenosis of any severity was found in 94 (41%) women and 110 (53%) men. Mean plaque composition score was 1.1, which means that the plaque composition is predominantly calcium. Only 1 patient had at least one stenosis 50% or greater with zero CCS. Figure 1 depicts the three main global parameters (CCS, SSS, and PCS) stratified by gender, age, and estimated

Table 2 Main coronary CTA characteristics of the study population

Variable	Mean (SD)/n (%)
Number of nonanalyzed segments	1.7 (1.7)
Presence of coronary calcium	244 (56%)
CCS	130.9 (324.6)
Atherosclerotic plaque with lumen involvement	204 (46%)
Patients with at least 1 moderate coronary stenosis (50–70%)	71 (16%)
Patients with at least 1 severe coronary stenosis (>70%)	26 (6%)
SSS	2.4 (4.1)
PCS	17.1 (5.8)
Mean number of segments with any stenosis (per patient)	1.9 (2.6)
Mean number of segments with stenosis >50% (per patient)	0.4 (1.2)
Mean number of segments with stenosis >70% (per patient)	0.2 (0.9)
Mean number of segments with noncalcified plaques (per patient)	0.7 (1.7)
Mean number of segments with mixed plaques (per patient)	1.6 (2.3)
Mean number of segments with calcified plaques (per patient)	12.1 (4.1)
Mean number of segments with calcified or mixed plaques (per patient)	13.7 (3.1)
Mean number of proximal segments with calcified plaques (per patient)	2.8 (1.4)
Mean number of proximal segments with mixed plaques (per patient)	0.7 (1.0)
Mean number of proximal segments with calcified or mixed plaques (per patient)	3.5 (0.9)
Mean number of proximal segments with stenosis >50% (per patient)	1.0 (1.3)

CTA, computed tomographic angiography; CCS, coronary calcium score; PCS, plaque composition sum; SD, standard deviation; SSS, sum of stenosis severity in 17 defined segments.

See text for more details.

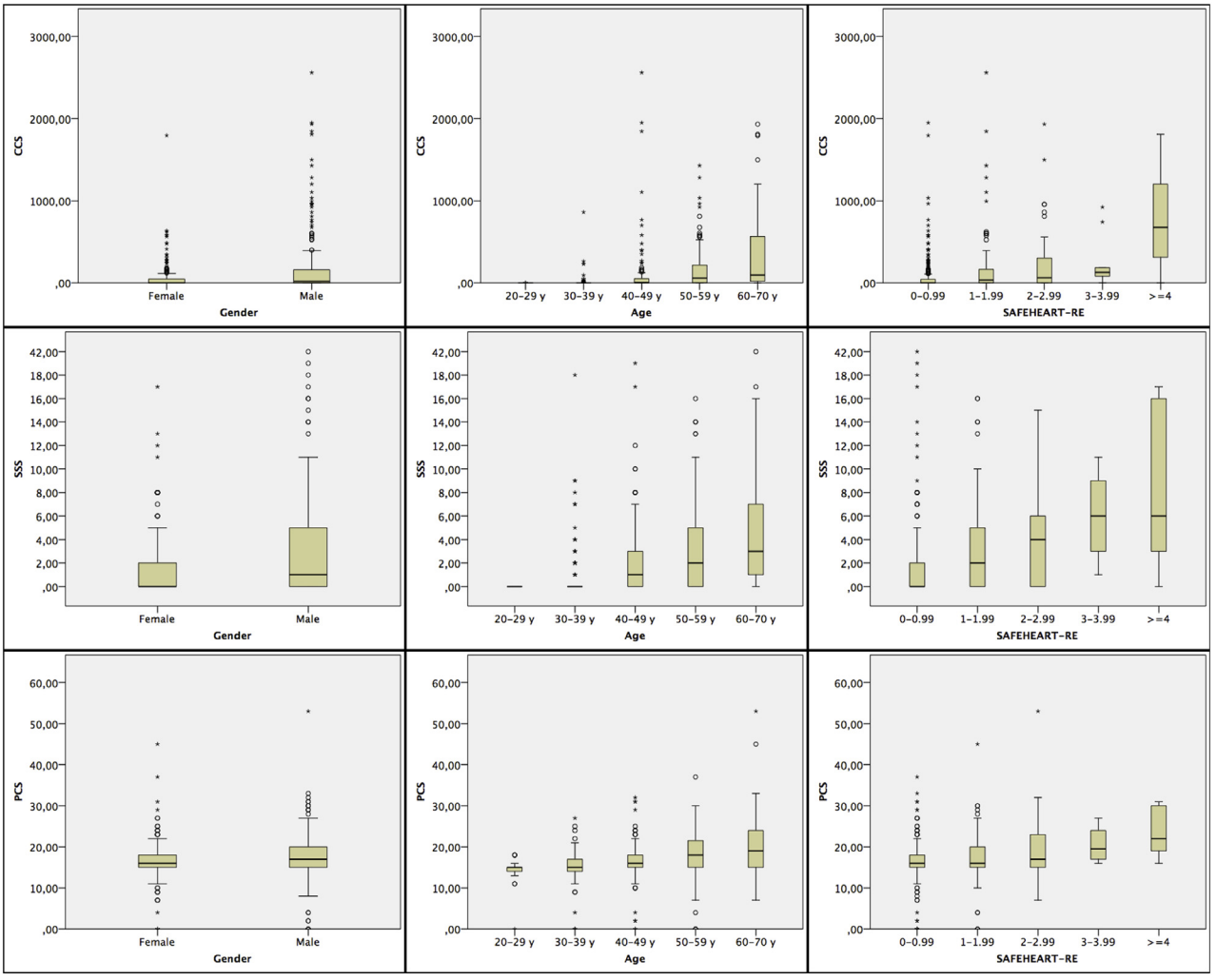

Figure 1 Coronary involvement evaluated by means of CCS (top), SSS (middle), and PCS (bottom). The graphs show CCS, SSS, and PCS vs gender, age (shown in decades from 20 to 70 years), and SAFEHEART-RE 5-y estimated risk. CCS, coronary calcium score; SSS, sum of stenosis severity; PCS, plaque composition sum.

cardiovascular risk. As can be seen, the coronary involvement under 30 years, especially in women, is almost absent. Mean estimated radiation dose for coronary CTAs was 3.8 mSv.

Factors related to coronary atherosclerosis

Tables 3–5 show the results of the univariate regression analysis. CCS and PCS were independently associated to SAFEHEART-RE estimated risk (B: 114.9; 95% CI: 73.8–156.0; $P \leq .001$ and B: 1.0; 95% CI: 0.26–1.74; $P = .008$, respectively) and LDL-C life-years (B: 0.14; 95% CI: 0.04–0.24; $P = .006$ and B: 0.005; 95% CI: 0.003–0.007; $P < .001$). SSS is independently associated only to SAFEHEART-RE estimated risk (B: 1.6; 95% CI: 1.1–2.1; $P < .001$). Proportion of variance (R^2) and final n were 0.4 and 297 for the CCS model, 0.5 and 297 for the SSS model, and 0.4 and 304 for the PCS model, respectively.

The number of proximal segments with calcified plaques showed a significant inverse association with the SAFEHEART-RE result (B: −0.19; 95% CI: −0.25 to −0.13; $P < .001$). Nevertheless, the number of proximal segments with mixed plaques (B: 0.18; 95% CI: 0.10–0.26; $P < .001$), the number of proximal segments with noncalcified plaques (B: 0.13; 95% CI: 0.08–0.18; $P < .001$), and the number of proximal segments with a stenosis >50% (B: 0.20; 95% CI: 0.14–0.26; $P < .001$) showed a direct positive association with the result of the SAFEHEART-RE.

Follow-up

Mean follow-up time after coronary CTA was 2.7 years. During follow-up, there were 17 (4%) nonfatal events (2 acute coronary syndromes and 15 coronary revascularizations) and 2 (1%) fatal events (1 acute coronary syndrome and 1 cardiovascular death). The reason for coronary revascularization in stable patients was the presence of myocardial ischemia demonstrated by means of a stress test. Mean follow-up time to first event was 0.5 years. CCSs were 706.3 and 102.4 for patients with and without an event during follow-up, respectively ($P < .001$). SSS scores were

Table 3 Predictive value of different variables for CCS (per patient analysis)

	Univariate analysis		
Variable	B	95% CI	*P*
Age (y)	9.8	6.9 to 12.7	<.001
Female	−144.5	−206.7 to −82.4	<.001
Premature familiar ASCVD history	45.7	−2.7 to 94.1	.064
Diabetes mellitus	259.1	−27.3 to 545.5	.076
High blood pressure	282.1	169.3 to 394.8	<.001
Waist circumference (cm)	4.0	1.5 to 6.5	.002
BMI (kg/m^2)	9.6	3.0 to 16.2	.005
Active smoking	−15.7	−87.3 to 55.8	.67
LDLR null mutation	26.3	−63.7 to 116.3	.57
Xanthomas	−0.41	−80.8 to 80.0	.99
Corneal arcus	49.4	−16.1 to 114.9	.14
Total cholesterol (mg/dL)	0.07	−0.4 to 0.5	.79
LDL-C	0.08	−0.4 to 0.59	.77
HDL-C	−1.1	−3.5 to 1.25	.35
TG	0.22	−0.4 to 0.8	.46
Lp(a)	1.1	0.4 to 1.8	.004
Patient on maximum statin dose	11.4	−52.9 to 75.7	.73
Patient on ezetimibe	9.3	−55.1 to 73.7	.78
Patients on maximum combined therapy	18.9	−52.3 to 90.2	.6
Patient on maximum LLT	9.5	−54.5 to 73.6	.6
LDL-C life-years (decades)	0.25	0.16 to 0.34	<.001
LLT potency	3.0	−24.3 to 30.2	.83
SAFEHEART-RE 5 y (%)	122.7	88.3 to 157.2	<.001
SAFEHEART-RE 10 y (%)	58.4	42.0 to 74.9	<.001

CCS, coronary calcium score; BMI, body mass index; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LDLR, LDL receptor; LLT, lipid-lowering therapy; Lp(a), lipoprotein (a); TG, triglycerides.

8.6 and 2.2 for patients with and without an event during follow-up, respectively ($P < .001$). Finally, PCS scores were 26.7 and 16.7 for patients with and without an event during follow-up, respectively ($P < .001$).

Management of patients after coronary CTA

Table 6 shows the changes in patients' management and care after knowing coronary CTA results. Impressively, there was a significant increase in intensity of treatment, decrease in LDL-C levels, and reduction of smoking habit. Twenty-nine patients (7%) started treatment with PCSK9 inhibitors, being one of the first subjects to use these antibodies after their approval in our country. Interestingly, there is a significantly more intense change in maximum combined therapy and maximum LLT use and a higher reduction in LDL-C levels and predicted risk in those patients with coronary disease demonstrated in the computed tomography. The reduction in smoking habit was more intense among patients without coronary disease.

Discussion

This study describes the presence of atherosclerotic coronary disease, coronary lumen involvement, and plaque composition in a wide cohort of molecularly defined FH without clinical cardiovascular disease by using coronary CTA. Our findings confirm the high prevalence and wide extension of coronary atherosclerosis in asymptomatic FH individuals despite LLT. Our results show an independent and significant association between the estimated risk evaluated by the SAFEHEART-RE and CCS, SSS, and PCS and between LDL-C life-years and CCS and PCS. This is the largest and most detailed study of subclinical coronary atherosclerosis, based on coronary CTA, in FH, and it provides us with several lessons on subclinical atherosclerosis in this group of patients. Furthermore, patients' management and care improve when the physician knows about the presence and extension of atherosclerotic coronary disease.

Comparing this study with other previously published studies, there are several differences that can be addressed. Our cohort is 100% molecularly defined, index cases and nonindex cases were included in a consecutive manner, the proportion of female and male patients is similar, and they present a better age stratification. Furthermore, the way to analyze the coronary involvement is more extensive and more complex, approaching the coronary atherosclerosis from several points of view.[9,10] Nevertheless, the prevalence of coronary involvement in our study is similar to other previously published studies.[9,12–14,23,24] For instance,

Table 4 Predictive value of different variables for sum of stenosis severity in 17 defined segments (SSS) (per patient analysis)

	Univariate analysis		
Variable	B	95% CI	*P*
Age (y)	0.1	0.09 to 0.17	<.001
Female	−1.9	−2.7 to 1.1	<.001
Premature familiar ASCVD history	0.1	−0.5 to 0.8	.44
Diabetes mellitus	7.7	4.1 to 11.3	<.001
High blood pressure	1.6	0.9 to 3.1	.04
Waist circumference (cm)	0.1	0.04 to 0.1	<.001
BMI (kg/m^2)	0.17	0.09 to 0.25	<.001
Active smoking	−0.6	−1.6 to 0.3	.17
LDLR null mutation	−0.4	−1.6 to 0.8	.52
Xanthomas	1.6	0.6 to 2.7	.002
Corneal arcus	0.6	0.2 to 1.5	.13
Total cholesterol (mg/dL)	0.01	0.001 to 0.02	.03
LDL-C	0.01	0.001 to 0.012	.08
HDL-C	−0.02	−0.05 to 0.01	.27
TG	0.01	0.002 to 0.02	.013
Lp(a)	0.004	−0.006 to 0.02	.41
Patient on maximum statin dose	1.0	0.2 to 1.8	.014
Patient on ezetimibe	0.9	0.06 to 1.7	.04
Patients on maximum combined therapy	1.2	0.3 to 2.1	.008
Patient on maximum LLT	1.1	0.3 to 1.9	.009
LDL-C life-years (decades)	0.004	0.003 to 0.005	<.001
LLT potency	0.28	−0.006 to 0.6	.06
SAFEHEART-RE 5 y (%)	1.43	0.97 to 1.9	<.001
SAFEHEART-RE 10 y (%)	0.7	0.46 to 0.9	<.001

BMI, body mass index; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LDLR, LDL receptor; LLT, lipid-lowering therapy; Lp(a), lipoprotein (a); TG, triglycerides.

Neefjes et al[10] reported coronary involvement, evaluated by means of CCS, in 80% of a 140 asymptomatic FH population, 66% of them molecularly diagnosed. This higher prevalence may be explained by the fact that their group is older and the proportion of male patients is higher. In other recently published studies, in a 100% molecularly diagnosed FH index cases, mean age 45 years and 50% women, the prevalence of coronary involvement (CCS) was 58%,[24] similar to our study. In that work, coronary involvement was associated to total cholesterol burden, a parameter related to LDL-C life-years, the variable used in our work, which was found to be an independent factor associated to coronary involvement. It is of note that the ideal age to start coronary screening in individuals with FH is unknown. Our results suggest that it should be around the fourth decade of life because presence of coronary disease is present in subjects older than 30 years, especially in men. Nevertheless, imaging methods not requiring either radiation or intravenous contrast might be used in young adults with FH, such as carotid ultrasound to evaluate the presence of atherosclerotic plaques and carotid intima-media thickness.[1]

Although atherosclerotic disease may affect cerebrovascular and peripheral artery territories, coronary artery disease is the most frequent location in patients with FH.[3] It is well known that subclinical atherosclerotic disease is also prevalent in asymptomatic non-FH individuals. In a recently published study carried out in 4184 asymptomatic middle-aged (40 to 54 years) individuals in Spain, the presence and extension of atherosclerosis in the carotid, abdominal aortic, and iliofemoral territories were assessed.[25] Coronary calcium was found in 5% women and 25% men. Our results show the much higher prevalence of individuals with calcium in their coronary arteries in spite of a similar mean age in both groups. These findings confirm the higher prevalence of accelerated atherosclerotic disease in a population exposed to high levels of LDL-C from birth. In our study, 56% of the enrolled population had coronary calcifications. Analyzing by gender, coronary calcium was found in 52% women and 71% men. As can be seen, these results show the higher prevalence of coronary artery involvement in subjects with FH when compared with nonselected subjects with similar mean age in the same country. These findings have been confirmed in other studies and even in other arterial territories.[14,23,26]

In the present study, atherosclerotic coronary involvement was evaluated from three different points of view: the CCS, the SSS, and the PCS. The CCS, a surrogate marker of the coronary plaque burden, has become a useful and widely available variable to identify individuals at increased risk for coronary event, even if they are otherwise considered as low-risk patients according to clinical

Table 5 Predictive value of different variables for plaque characterization—plaque composition sum (PCS) (per patient analysis)

	Univariate analysis		
Variable	B	95% CI	*P*
Age (y)	0.18	0.13 to 0.23	<.001
Female	−1.2	−2.3 to −0.01	.043
Premature familiar ASCVD history	−0.15	−1.005 to 0.71	.74
Diabetes mellitus	7.8	2.8 to 12.9	.002
High blood pressure	0.73	−1.3 to 2.8	.49
Waist circumference (cm)	0.08	0.04 to 0.13	<.001
BMI (kg/m^2)	0.15	0.04 to 0.13	<.001
Active smoking	−0.44	−1.7 to 0.8	.49
LDLR null mutation	−0.87	−2.5 to 0.74	.29
Xanthomas	1.6	0.19 to 3.1	.027
Corneal arcus	1.4	0.29 to 2.6	.014
Total cholesterol (mg/dL)	0.009	0.001 to 0.02	.028
LDL-C	0.007	−0.002 to 0.02	.12
HDL-C	0.004	−0.04 to 0.05	.85
TG	0.01	0.004 to 0.023	.004
Lp(a)	0.02	0.001 to 0.03	.031
Patient on maximum statin dose	1.15	0.03 to 2.3	.044
Patient on ezetimibe	0.85	−0.27 to 1.98	.14
Patients on maximum combined therapy	0.84	−0.41 to 2.08	.19
Patient on maximum LLT	1.3	0.18 to 2.41	.024
LDL-C life-years (decades)	0.005	0.004 to 0.007	<.001
LLT potency	0.39	−0.02 to 0.8	.06
SAFEHEART-RE 5 y (%)	1.48	0.84 to 2.12	<.001
SAFEHEART-RE 10 y (%)	0.71	0.4 to 1.01	<.001

BMI, body mass index; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LDLR, LDL receptor; LLT, lipid-lowering therapy; Lp(a), lipoprotein (a); TG, triglycerides.

assessment. Our results show an independent and statistically significant association with the estimated cardiovascular risk[5] and with the LDL-C life-years, which reflects both the phenotypic expression and the treatment efficacy. The second variable, the SSS, shows the coronary lumen involvement. Although coronary atherosclerosis is a disease of the vessel wall, the presence or absence of coronary lumen stenosis is the most frequent approach to assess coronary heart disease in our daily clinical practice.[7] Our results show that atherosclerotic plaque with lumen involvement could be found in 46%. Furthermore, 16% patients had >50% lumen diameter stenosis, a smaller proportion than reported (ie, 24%).[10] In our work, the only variable independently associated to the stenosis severity was the estimated cardiovascular risk.[5] Finally, the PCS is a newly designed variable that reflects the composition as a surrogate marker of coronary atherosclerotic plaques stability, although it has not been definitively validated. This finding has not been previously described. Noncalcified composition is associated to unstable plaques, and calcified plaques are usually stable plaques unless the calcification is spotty.[27,28] Thus, the greater the PCS, the higher the noncalcified composition and the higher the likelihood for being responsible of an acute coronary syndrome. Once more, the presence of unstable plaque characteristics was independently associated to the estimated cardiovascular risk according the SAFEHEART-RE. In this case, there was another parameter independently associated to PCS, the LDL-C life-years. These results show the important relationship between atherosclerotic coronary involvement, evaluated by using different approaches, and the cardiovascular prognosis of patients with FH, reinforcing the already known relationship between atherosclerotic burden and cardiovascular events.[24,29] This relationship can be clearly seen in our work as the CCS, SSS, and PCS are higher in those patients with an event during follow-up, although these results should be cautiously interpreted due to the low number of events in this study. Importantly, to reinforce our findings, the 3 analyzed coronary CTA-derived parameters are related to the development of clinical ASCVD. These findings may improve the risk stratification and could be used to guide therapy, including the novel PCSK9 inhibitors, in patients with FH, whose residual ASCVD risk remains high despite current lipid-lowering therapy. Interestingly, the number of proximal segments with calcified plaques was inversely associated to the SAFEHEART-RE result, and the number of proximal segments with mixed or noncalcified plaques was directly associated to the prognosis estimated by the equation, reinforcing 2 concepts: Plaque composition is related to patient prognosis, and calcification may suggest plaque stability.

Table 6 Impact of coronary CTA results in patients' management and care

Variable	Coronary disease (−)*, N = 174 (39.5%)				Coronary disease (+)*, N = 266 (60.5%)				Δ Coronary disease (+) vs Δ Coronary disease (−)
	Before	After	Δ	*P*	Before	After	Δ	*P*	*P*
LDL-C (mg/dL)†	174.3 (59.6)	136.9 (49.3)	37.4 (61.1)	<.001	181.3 (63.1)	123.6 (44.4)	57.7 (71.3)	<.001	.005
Patients on maximum statin dose	60 (35%)	128 (74%)	68 (39%)	.03	134 (50%)	218 (82%)	84 (32%)	<.001	.06
Patients on ezetimibe	60 (35%)	89 (51%)	29 (17%)	.001	133 (50%)	184 (69%)	51 (19%)	<.001	.37
Patients on maximum combined therapy	33 (19%)	63 (36%)	30 (17%)	<.001	91 (34%)	155 (58%)	64 (24%)	<.001	.02
Patients on maximum LLT	80 (46%)	97 (56%)	17 (10%)	.06	165 (62%)	207 (78%)	42 (16%)	<.001	.01
Patients on PCSK9 inhibitors		2 (1%)				27 (10%)			
Active smoking	56 (39%)	30 (21%)	26 (18%)	<.001	48 (21%)	29 (13%)	19 (9%)	<.001	<.001
Coronary revascularization		0				15 (6%)			
SAFEHEART-RE 5 y (%)	0.7 (0.7)	0.5 (0.5)	0.2 (0.4)	<.001	1.1 (0.9)	0.7 (0.8)	0.4 (0.6)	<.001	<.001
Use of aspirin	23 (13%)	25 (14%)	2 (1%)	.760	24 (9%)	44 (17%)	20 (8%)	.001	<.001

Δ, absolute change (% change); After, after coronary CTA n (%) or mean (SD); Before, before coronary CTA n (%) or mean (SD); CTA, computed tomographic angiography; LLT, lipid-lowering therapy; LDL-C, low-density lipoprotein cholesterol.

*Coronary disease is defined as the presence of calcium or a stenosis (any severity) in the coronary tree.

†Analyzed in 365 patients with LDL-C assessment before and after coronary CTA.

Finally, coronary CTA results were associated to several changes in patients' management and estimated risk. Lipid-lowering therapy potency increased with the subsequent decrease in LDL-C levels. Also, smoking habit significantly decreased, although more intensively in patients without coronary artery disease. We think this surprising result might be due to variables different to the coronary CTA or to the relatively low number of patients. Nevertheless, we have to keep in mind the fact that in these FH patients with and without coronary disease, there was a reduction in the percentage of smokers. Furthermore, some of these patients benefited from the use of PCSK9 inhibitors. Besides, these changes induced an improvement in the estimated risk. All these findings and modifications might show the importance of coronary CTA results in the perception of the severity and the therapeutic management carried out by the physician responsible for these patients.

Conclusion

Coronary atherosclerosis is highly prevalent in asymptomatic patients with FH. CCS, SSS, and PCS are independently associated to the cardiovascular risk estimated according the SAFEHEART-RE and might be related to the prognosis in the follow-up. More advanced disease on CTA was associated with subsequent intensification of therapy and reduction of estimated risk. Further longitudinal studies are required to know if the coronary involvement, assessed by coronary CTA, may improve the risk stratification in patients with FH.

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