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Coronary plaque burden, plaque characterization and their prognostic implications in familial hypercholesterolemia: A computed tomographic angiography study

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ABSTRACT

Background and aims: Heterozygous familial hypercholesterolemia (FH) is associated with premature atherosclerotic cardiovascular disease. Semi-automated plaque characterization (SAPC) by coronary computed tomographic angiography (CTA) provides information regarding coronary plaque burden and plaque characterization. Our aim was to quantify and characterize the coronary plaque burden of patients with FH using SAPC analysis and to identify which factors are related to plaque burden and plaque characteristics. A second aim was to analyse the prognostic implications of these parameters.

Methods: Two hundred and fifty-nine asymptomatic individuals with molecularly determined FH were enrolled in this follow-up cohort study and underwent a coronary CTA analysed with SAPC.

Results: Mean follow-up time after coronary CTA was 3.9 ± 2 years. Mean age was 46.9 (10.7) years (130 women, 50.2%). Median plaque burden was 25.0% (19.0–29.0), non-calcified plaque burden 22.83% (17.94–26.88), calcified plaque-burden 1.12% (0.31–2.86) and CCS 8.9 (0–93). Five-year risk was independently related to plaque burden, non-calcified plaque burden, calcified plaque burden and coronary calcium score (B:3.75, 95% CI:2.92–4.58; $p < 0.001$, B:2.9, 95%CI:2.15–3.66; $p < 0.001$, B:0.75, 95%CI 0.4–1.1; $p < 0.001$ and B:82.2, 95% CI:49.28–115.16; $p < 0.001$ respectively). During follow-up, there were 15 (5.81%) nonfatal events and 1 (0.4%) fatal event. Plaque burden was significantly related to event-free survival during follow-up (HR:1.11; 95% CI:1.05–1.18; $p < 0.001$).

Conclusions: Coronary atherosclerosis and its qualitative components may be quantified by means of SAPC in patients with FH. Plaque burden, calcified plaque burden and non-calcified plaque burden were independently related to the estimated cardiovascular risk. Plaque burden was also related to prognosis.

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1. Introduction

Heterozygous familial hypercholesterolemia (FH) is the most common genetic disorder characterized by life-long exposure to highly elevated cholesterol levels and associated with premature atherosclerotic cardiovascular disease (ASCVD) [1]. However, risk of cardiovascular disease in FH can be highly variable [2].

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. Coronary computed tomographic angiography (coronary CTA) is able to quantify calcium in the coronary artery wall and luminal stenosis, as well as to analyse plaque characteristics [3]. These three aspects have been related to patients' prognosis and might provide an added value for the identification of factors contributing to atherogenesis in individuals with FH and to better classify their cardiovascular risk [4,5]. Thus, coronary CTA has aroused as an accessible and accurate tool for coronary tree anatomical evaluation, avoiding the inconvenience and risk of invasive studies. Nevertheless, the atherosclerotic disease evaluation when analysing coronary CT images is rather subjective and non-automatic.

Recently, new automatic tools for coronary atherosclerotic disease have appeared. Among them, those that provide a global evaluation of coronary lumen involvement and coronary wall characteristics have acquired a predominant and promising role. Semi-automated plaque characterization (SAPC) is a diagnostic tool that incorporates medical image processing algorithms for automatic coronary tree evaluation [6]. It can provide information regarding coronary lumen and wall, including plaque burden and its characterization, based on coronary CT data. It has been shown to be an accurate and reproducible diagnostic tool [7,8].

Our aim was to quantify and characterize the coronary plaque burden of molecularly defined and asymptomatic ASCVD patients with FH based on SAPC analysis and to identify which factors are related to plaque burden and to each one of its components derived from plaque characterization analysis. A second aim was to analyse the prognostic implications of these parameters.

2. Patients and methods

2.1. Study design and population

The authors will make the data, methods used in the analysis and materials used to conduct the research available to any researcher for purposes of reproducing the results or replicating the procedure.

SAFEHEART is a multicentre, nationwide, long-term prospective cohort study in a molecularly defined population of patients with heterozygous FH in Spain [9]. For this study, 440 individuals (20–70 years old) without clinical ASCVD, were consecutively enrolled in the registry at 6 university hospitals and they underwent coronary CTA between January 2013 and December 2016. Patients with contraindications for coronary CTA were not enrolled [10]. Those studies that did not fulfil the required quality (motion artefacts, suboptimal definition of the coronary arteries …) to evaluate the three major epicardial coronary arteries and the left main coronary artery in their whole length using this new software were excluded.

2.2. Clinical measurements

Demographic and clinical characteristics were recorded as described elsewhere [9]. Venous blood samples were taken after a 12 h fast. Lipid profile and lipoprotein (a) [Lp(a)] levels were determined as previously described [11]. LDL-*C*-life years was calculated as previously described [12]. DNA was isolated from whole blood and the genetic diagnosis of FH was made. Estimated cardiovascular risk at 5 and 10 years was obtained using the SAFEHEART-Risk equation (SAFEHEART-RE), which estimates the likelihood to occur the first one for the following: fatal or non-fatal myocardial infarction, fatal or non-fatal ischemic stroke, coronary revascularization, peripheral artery revascularization and cardiovascular death (any death related to cardiovascular disease or derived from cardiovascular therapeutic procedures not described in the previous definitions) [2].

2.3. Coronary CTA performance and image reconstruction

Using a tomographic scanner, 3-mm thick slices were obtained during a breath holding protocol and Agatston coronary calcium score (CCS) was calculated. Coronary CTA was performed using 64–detector row scanners or higher with prospective or retrospective electrocardiographic gating. Eighty to 100 ml intravenous contrast, followed by 50–80 ml of saline, was administered at a rate of 5 ml/s via a power injector through an antecubital vein. Scanning devices and reconstruction parameters are described in Supplemental Material. 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 utilized for image interpretation if minimal coronary artery motion differed among the various arteries.

2.4. SAPC

SAPC [QAngio CT (Research Edition V2.1.16.1; Medis Specials)] was the tool used for coronary atherosclerotic plaque quantification and characterization. It incorporates medical image processing algorithms for automatic coronary tree extraction, as well as lumen and vessel contour detection. SAPC provides information regarding vessel morphology, intensities, and plaque burden and characterization in coronary CT data. The analysis workflow allows a fully automatic extraction of the complete coronary tree, semi-automatic editing of coronary tree, automatic labeling of the segments in the coronary tree with anatomical names, a two-step contour detection approach per vessel for both lumen and vessel contour: longitudinal detection, transversal detection and edit contour in longitudinal and transversal images simultaneously. In addition, this software can realize lumen and plaque statistics, including degree of stenosis, lesion length, plaque burden, plaque volume, as well as an adaptive thresholding for plaque characterization (Fig. 1). In this way, the plaque is split in four well differentiated components: fibrous, fibro-fatty, necrotic and calcified and to exclude the media volume [13,14]. Non-calcified plaque was defined as the sum of fibrous, fibro-fatty and necrotic components. Thus, it allows us to approach the qualitative composition of the plaque [15,16]. The adaptive mode that modifies Hounsfield units ranges based on the measured intensities in the lumen was used to balance for different kilovoltages in plaque analysis. Media border exclusion was used to subtract a fixed region from the outer border from the plaque. Normalization was not used to avoid increased variability in the results and due to the fact that plaque burden is a relative measure and this correction would also not have a large influence on the results. SAPC measurements were done by a blinded operator, unaware of any clinical or biochemical data.

2.5. Statistical analysis

Statistical analyses were carried out using SPSS version 18.0 (SPSS Inc., Chicago, Illinois). Variables were analysed for a normal distribution with the Kolmogorov-Smirnov test. Quantitative data were expressed as mean (standard deviation) or median (interquartile range) and qualitative data as absolute numbers (percentage). T test or Mann-Whitney test were used to compare quantitative variables and Chi-square test to compare proportions. A multivariate forward linear regression analysis was conducted, to determine the variables independently associated with plaque burden, calcified plaque burden, non-calcified plaque

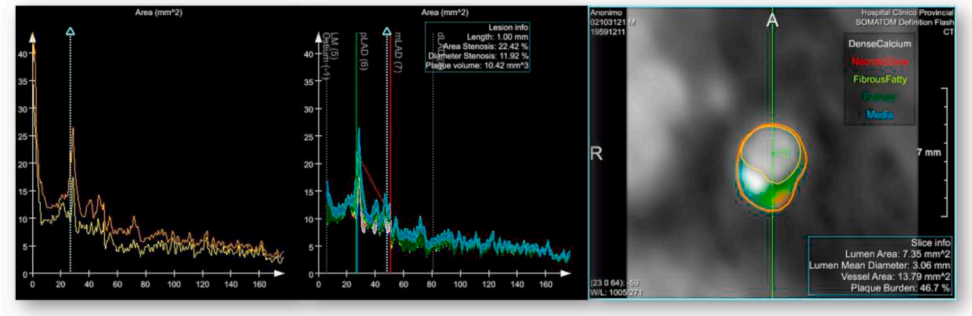

Fig. 1. Example of a coronary artery analysed by SAPC.
(From left to right) Plaque burden analysis (the area between the yellow line and the orange line represents the volume of arterial media and atherosclerotic plaque), plaque characterization (blue color, dark green, light green, red and white represents media, fibrous plaque, fibro-fatty plaque, necrotic plaque and calcified plaque respectively) and cross-section of the artery. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

burden and CCS. We included in the multivariate analysis those variables that were statistically significant in univariate analyses, excluding those variables included in the SAFEHEART-RE, in case it should be included, and those showing statistical collinearity. Cox proportional hazards uni- and multivariate analysis was carried out. We included in the multivariate analysis those variables that were statistically significant in univariate analyses but excluding those variables included in the SAFEHEART-RE, in case it should be included, and those showing statistical collinearity. Kaplan-Meier curves were constructed for survival analysis. To analyse inter-observer variability of plaque burden quantification, two blinded observers analysed 20 randomly selected studies. To examine the intra-observer variability, the first reader re-analysed the same studies in a similar blinded fashion. Inter and intra-observer agreement was evaluated by means of the intra-class correlation coefficient. ROC curves were constructed to analyse diagnostic accuracy. Differences were considered statistically significant with a p value < 0.05.

3. Results

Two hundred and fifty-nine individuals were included (130 women; 50.2%) between January 2013 and December 2016. Mean age was 46.9 ± 10.7 years. Main characteristics including lipid lowering therapy and lipid plasma levels are shown in Table 1. All subjects were on lipid lowering treatment (LLT). One hundred and twenty-one patients (46.7%) were on treatment with high potency, high dose statins, 158 (61.0%) patients were on ezetimibe and 2 (0.8%) were on PCSK9 inhibitors immediately before coronary CTA. Mean 5- and 10-year cardiovascular risk according to SAFEHEART-RE was 0.8 ± 0.9% and 1.8 ± 1.9% respectively, and mean LDL-C was 151.7 ± 52.7 mg/dL.

3.1. Coronary SAPC findings

Supplementary Table 1 describes the SAPC findings. Median coronary length was 270.25 (173.44–354.19) mm. Median plaque burden was 25.0% (19.0–29.0). Its distribution according to plaque characterization analysis results is shown in the Table. In summary, median calcified plaque burden was 1.12 (0.31–2.86) and non-calcified plaque burden 22.83% (17.94–26.88). CCS results are also shown. Intra and inter-observer intraclass correlation coefficients for plaque burden were 0.96 (95% CI 0.88–0.99) and 0.87 (95% CI: 0.53–0.96), respectively.

Table 1
Main characteristics of the study population.

	Before CTA	End of follow-up
	Mean (SD)/n (%)	Mean (SD)/n (%)
n	259	–
Female	130 (50.2%)	–
Age (years)	46.9 (10.7)	50.3 (10.7)
Premature familial ASCVD history	97 (37.5%)	–
Type 2 diabetes	5 (1.9%)	11 (4.3%)
Hypertension	18 (6.9%)	30 (11.6%)
Active tobacco smoker	68 (26.3%)	41 (15.8%)
BMI (kg/m^2)	26.0 (4.3)	26.1 (4.1)
Total cholesterol (mg/dl)	224.7 (58.9)	189.7 (53.0)
LDL-C (mg/dl)	151.7 (52.7)	116.8 (50.8)
HDL-c (mg/dl)	52.7 (13.4)	54.4 (14.8)
TG (mg/dl)	99.7 (64.5)	94.0 (45.8)
Lp(a) (mg/dl)	39.6 (40.8)	–
Patients on high potency, high dose statins[a]	121 (46.7%)	137 (52.9%)
Patients on ezetimibe	158 (61.0%)	207 (79.9%)
Patients on PCSK9 inhibitors	2 (0.8%)	40 (15.4%)
LDL-C life years (decades)	921.2 (360.3)	963.0 (321.3)
Time of statin use (years)	12.2 (7.1)	16.1 (7.4)
Time of ezetimibe use (years)[b]	5.2 (3.7)	8.4 (4.2)
5-y SAFEHEART-RE (%) [median (interquartile range)]	0.8 (0.9)	1.3 (1.9)
10-y SAFEHEART-RE (%) [median (interquartile range)]	1.8 (1.9)	2.8 (4.0)

5- and 10-y SAFEHEART-RE: 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 non-fatal myocardial infarction, fatal or non-fatal 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).
BMI: body mass index; ASCVD: cardiovascular disease; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; LLT: Lipid lowering therapy; Lp(a): lipoprotein (a); TG: triglycerides.
[a] High dose, high potency statins: atorvastatin 40 or 80 mg per day or rosuvastatin 20 or 40 mg per day.
[b] Estimated in patients on ezetimibe.

Table 2
Association of different variables with plaque burden (uni- and multivariate analysis; per patient analysis).

	B	R^2	95%CI	*p*
UNIVARIATE ANALYSIS				
Age (years)	0.14	0.05	0.07–0.22	<0.001
Male	0.79	0.003	−0.87–2.46	0.348
Premature familiar ASCVD history	1.03	0.006	−0.72–2.78	0.251
Diabetes mellitus	2.84	0.003	−3.20–8.88	0.352
High blood pressure	7.13	0.072	3.98–10.28	<0.001
BMI (kg/m^2)	0.26	0.028	0.07–0.45	0.007
Active smoking	0.30	0.0	−1.59–2.19	0.758
Total cholesterol (mg/dl)	0.023	0.039	0.009–0.037	0.001
LDL-C (mg/dl)	0.022	0.03	0.007–0.038	0.005
HDL-C (mg/dl)	0.005	0.01	−0.012–0.11	0.123
TG (mg/dl)	0.008	0.006	−0.005–0.021	0.210
Lp(a) (mg/dl)	0.024	0.021	0.003–0.045	0.022
Patients on high potency, high dose statins[a]	0.012	0.008	−0.005–0.028	0.164
Patients on ezetimibe	0.003	0.001	−0.014–0.02	0.74
Patients on PCSK9 inhibitors	0.05	0.005	−0.013–0.028	0.28
LDL-C life years (decades)	0.004	0.05	0.002–0.006	0.001
SAFEHEART-RE 5 years (%)	3.75	0.25	2.92–4.58	<0.001
SAFEHEART-RE 10 years (%)	1.79	0.25	1.40–2.19	<0.001
MULTIVARIATE ANALYSIS				
SAFEHEART-RE 5 years (%)	3.75	0.25	2.92–4.58	<0.001

[a] High dose, high potency statins: atorvastatin 40 or 80 mg per day or rosuvastatin 20 or 40 mg per day.

3.2. Factors related to plaque burden and its components

Table 2 shows the association of different variables with plaque burden. It is of note that age, high blood pressure, BMI, total cholesterol, LDL-C, Lp(a), and LDL-*C*-life years were significantly and positively related to plaque burden in univariate analysis. Furthermore, the estimated cardiovascular risk based on SAFEHEART-RE was significantly related to plaque burden. Supplementary Tables 2 and 3 show the association of different variables with non-calcified and calcified plaque burden, respectively. High blood pressure, BMI, total cholesterol, LDL-C, HDL-C, LDL-C life years and estimated cardiovascular risk were significantly related to the non-calcified component of plaque burden. On the other hand, age, high blood pressure, Lp(a), LDL-C life years and estimated cardiovascular risk were significantly related to the calcified component of plaque burden.

3.3. Factors related to CCS

Table 3 shows the association of different variables with CCS. It is of note that age, male gender, diabetes mellitus, high blood pressure, BMI, use of ezetimibe, and use of PCSK9 inhibitors were significant and positively related to CCS. The estimated cardiovascular risk based on SAFEHEART-RE was also significantly related to CCS.

3.4. Multivariate analysis results

The multivariate analysis results (Tables 2 and 3 and Supplementary Tables 2 and 3) showed that SAFEHEART-RE (5-year equation results are shown but the independent association was similar to the 10-year equation) was the only factor independently related to plaque burden (B: 3.75; 95%CI: 2.92–4.58; R Square: 0.25; $p < 0.001$), non-calcified plaque burden (B: 2.90; 95%CI: 2.15–3.66; R Square: 0.19; $p < 0.001$)

Table 3
Association of different variables with CCS (uni and multivariate analysis; per patient analysis).

	B	R^2	95%CI	*p*
UNIVARIATE ANALYSIS				
Age (years)	7.78	0.087	4.52–11.04	<0.001
Male	112.4	0.039	40.30–184.56	0.002
Premature familiar ASCVD history	37.19	0.004	−42.14–116.53	0.361
Diabetes mellitus	272.83	0.019	20.34–525.32	0.034
High blood pressure	341.86	0.091	202.64–481.08	<0.001
BMI (kg/m^2)	10.47	0.025	1.97–18.97	0.016
Active smoking	−60.94	0.009	−144.04–22.17	0.153
Total cholesterol (mg/dl)	−0.27	0.003	−0.89–0.35	0.387
LDL-C (mg/dl)	−0.24	0.002	−0.94–0.45	0.491
HDL-C (mg/dl)	−1.75	0.007	−4.44–0.94	0.201
TG (mg/dl)	0.014	0.001	−0.54–0.57	0.961
Lp(a) (mg/dl)	−0.088	0.001	−0.85–0.68	0.823
Patients on high potency, high dose statins[a]	69.73	0.015	−3.4–142.9	0.062
Patients on ezetimibe	96.6	0.026	19.92–169.29	0.013
Patients on PCSK9 inhibitors	863.31	0.077	478.65–1247.98	<0.001
LDL-C life years (decades)	0.11	0.016	−0.011–0.24	0.074
SAFEHEART-RE 5 years (%)	83.63	0.10	50.24–117.02	<0.001
SAFEHEART-RE 10 years (%)	40.43	0.10	24.44–56.42	<0.001
MULTIVARIATE ANALYSIS				
Diabetes mellitus	271.80		72.38–471.21	0.008
SAFEHEART-RE 5 years (%)	82.22		49.28–115.16	<0.001

[a] High dose, high potency statins: atorvastatin 40 or 80 mg per day or rosuvastatin 20 or 40 mg per day.

Table 4
Cox proportional hazards univariate and multivariate analysis results regarding cardiovascular events during follow-up.

	HR	95%CI	*p*
UNIVARIATE ANALYSIS			
Age (years)	1.060	1.008–1.116	0.024
Male	4.578	1.304–16.076	0.018
Premature familiar ASCVD history	2.283	0.812–6.422	0.118
Diabetes mellitus	10.056	2.252–44.904	0.002
High blood pressure	6.680	2.316–19.270	<0.001
BMI (kg/m^2)	1.112	1.002–1.274	0.045
Active smoking	1.242	0.431–3.577	0.688
Total cholesterol (mg/dl)	1.005	0.998–1.012	0.137
LDL-C (mg/dl)	1.006	0.999–1.014	0.103
HDL-C (mg/dl)	0.990	0.951–1.030	0.619
TG (mg/dl)	1.002	0.996–1.008	0.487
Lp(a) (mg/dl)	1.008	0.999–1.017	0.090
Patients on high potency, high dose statins[a]	0.88	0.33–2.37	0.80
Patients on ezetimibe	3.06	0.87–10.75	0.082
Patients on PCSK9 inhibitors	0.049	−0.001–1.5	0.82
LDL-C life years (decades)	1.000	1.000–1.001	0.006
SAFEHEART-RE 5 years (%)	1.843	1.493–2.274	<0.001
SAFEHEART-RE 10 years (%)	1.350	1.218–1.496	<0.001
Plaque burden (%)	1.117	1.058–1.180	<0.001
MULTIVARIATE ANALYSIS			
Diabetes mellitus	6.79	1.51–30.57	0.013
Plaque burden (%)	1.11	1.05–1.18	<0.001

[a] High dose, high potency statins: atorvastatin 40 or 80 mg per day or rosuvastatin 20 or 40 mg per day.

and calcified plaque burden (B: 0.75; 95%CI: 0.40–1.10; R Square: 0.07; $p < 0.001$). Multivariate analysis also showed that diabetes mellitus (B: 271.80 95%CI: 72.38–471.25; $p = 0.008$) and SAFEHEART-RE (B: 82.22 95%CI: 49.28–115.16; $p < 0.001$) were independently related to CCS.

3.5. Follow-up (events)

Mean follow-up time after coronary CTA was 3.9 ± 2 years. Table 1 shows the increase in LLT intensity, including an increased use of PCSK9 inhibitors, and the reduction in LDL-c at the end of follow-up. During follow-up, there were 15 (5.8%) no-fatal events (4 acute coronary syndromes, 10 coronary revascularizations and 1 aortic valve replacement) and 1 (0.4%) fatal event (1 acute coronary syndrome). The reason for coronary revascularization in stable patients was the presence of myocardial ischemia showed by means of a stress test. The management of every patient was decided by his/her treating physician, regardless of the SAFEHEART registry. Mean follow-up time to first event was 1.6 ± 1.6 years. Median plaque burden was 28.5 (26.5–34.75) and 25.0 (19.0–29.0) for patients with and without an event during follow-up, respectively ($p = 0.003$). Calcified plaque burden was 3.5 (2.3–5.4) and 1.0 (0.3–2.6) for patients with and without an event during follow-up respectively ($p < 0.001$). Non-calcified plaque burden was 24.2 (21.6–28.3) and 21.8 (13.8–26.7) for patients with and without an event during follow-up respectively ($p < 0.001$). Regarding survival analysis, univariate Cox proportional hazards analysis results (Table 4) showed a statistically significant association between plaque burden and cardiovascular events during follow-up (HR: 1.117; 95%CI: 1.058–1.180; $p < 0.001$). In multivariate analysis (Table 4), plaque burden and diabetes mellitus were independent predictors of cardiovascular events (HR: 1.11; 95%CI: 1.05–1.18; $p < 0.001$ and HR: 6.79; 95%CI: 1.51–30.57; $p = 0.013$). Survival curves for plaque burden tertiles are depicted in Fig. 2. ROC curves analysis results showed an area under the curve of 0.89 (95% CI 0.84–0.95; $p < 0.001$) and 0.72 (0.61–0.83; $p = 0.003$) for plaque burden and CCS, respectively.

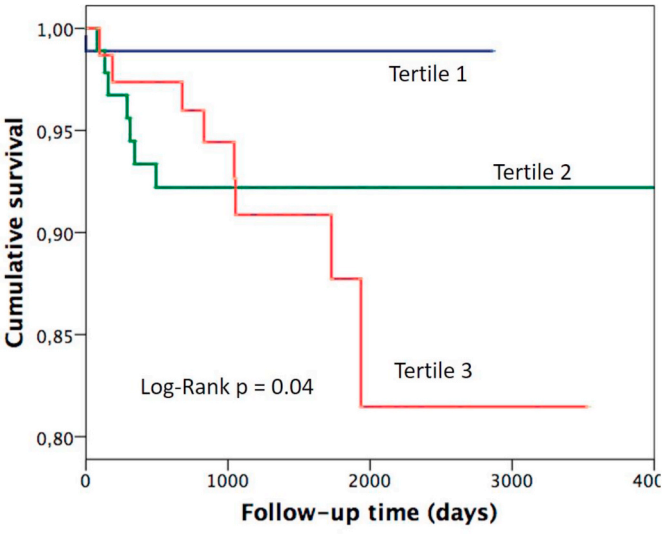

Fig. 2. Kaplan-Meier survival curves showing the incidence of cardiac events according the coronary plaque burden tertiles (cut-off points for tertiles: 21% and 28%).

4. Discussion

This study shows for the first time the results of a detailed quantitative analysis of coronary atherosclerotic involvement in a cohort of molecularly defined FH individuals without clinical ASCVD. For that purpose, a non-invasive technique of global assessment of the coronary tree wall was assessed using SAPC. Our findings confirm the relevant atherosclerotic involvement of the coronary tree, beyond calcium quantification and subjective evaluation, and remark the high prevalence and wide extension of coronary atherosclerosis in asymptomatic FH individuals despite lipid lowering treatment. Furthermore, our results show an independent and significant association between the estimated cardiovascular risk, assessed by SAFEHEART-RE, and coronary plaque burden, as well as a relationship between ASCVD incidence and plaque burden during follow-up.

Cardiovascular imaging techniques have the ability to detect the presence of atherosclerosis in the arteries and, due to its characteristics, coronary CTA might be considered the reference technique to evaluate the coronary tree [3]. In a recent publication, patients with FH had a higher frequency and severity of coronary atherosclerotic plaques [17]. Furthermore, atherosclerotic burden evaluated by CT angiography

improves the prediction of cardiac outcome in patients with presumably stable coronary artery disease [18].

It is now well known that there is a direct relationship between volume of atherosclerotic plaque present in the coronary arteries and the likelihood of developing a coronary event based on intra-vascular ultrasounds [19]. Therefore, it is not only important to know whether or not atherosclerotic plaques are present in the coronary arteries, but also to quantify them, a concept that is gaining a decisive role. Among the different parameters obtained from the quantitative evaluation, probably the most important one is the percentage of atherosclerotic volume or plaque burden [19]. The software used in the present study is also able to provide a plaque characterization analysis. The results of the present study may lead to a new paradigm for managing patients with FH centred on preventing the development of atherosclerotic events by targeting plaque burden.

We know that the higher the atherosclerotic burden the worse the prognosis [19]. Its absolute volume and, especially, plaque burden, are variables related to the prognosis of the patients. Furthermore, the treatment used in different studies support the existence of a relationship between the decrease of LDL cholesterol, the reduction of the volume of atherosclerotic plaque and the decrease of coronary events. This relationship has been demonstrated with statins, ezetimibe and PCSK9 inhibitors [20–23]. In addition, it has been confirmed that intensive treatments with lipid-lowering drugs are able to reduce the coronary atherosclerotic plaque. It is noteworthy that these studies have been performed with invasive techniques, unlike the present study that uses non-invasive CT images.

Studies of patients with FH who underwent a coronary CTA have been published, providing crucial information regarding the potential use of coronary CTA to stratify the cardiovascular prognosis in patients with FH [4,5]. In view of our study, we can say that coronary atherosclerosis is highly prevalent in asymptomatic patients with FH and that plaque burden and its different components are independently associated with the cardiovascular risk, estimated according the pragmatic SAFEHEART-RE [2]. But, in order to assess if coronary involvement may improve risk stratification in patients with FH, further studies are required. It is of interest that among the different variables related to the estimated risk, plaque burden obtains the best model fit, with R Square 0.25. Furthermore, area under the curve obtained from ROC analysis was higher for plaque burden than for CCS.

In this study, the non-calcified component of the atherosclerotic plaque is more related to the adverse prognosis than the calcified component. The non-calcium component is more related to plaque instability, so it would be logical if it was associated with a worse prognosis. Nevertheless, this finding should be nuanced, considering two crucial aspects: first, the long-time on treatment with high-potency statins at high doses that the patients included in the study had been taking; secondly, the fact that the software used does not differentiate coronary microcalcifications, a finding related to an increase in the probability of cardiovascular events, from coronary macrocalcifications, a parameter that indicates plaque stability. Thus, this finding requires further studies.

The presence and degree of coronary artery calcium predict coronary events in asymptomatic, middle aged FH patients treated with statins [5] and this is partly mediated by associations with risk factors, particularly the burden of cholesterol-life years. However, coronary artery calcium is less responsive to cholesterol lowering and may increase with statin therapy [24], so that its utility in patients already treated with statins is questionable. Finally, the extent of plaque burden on coronary CTA in a subgroup of FH patients from the SAFEHEART study is directly related to the number of circulating microvesicles and may be effectively employed to intensify therapy [4,25]. Thus, clinical events, cardiovascular risk, cardiovascular imaging and biochemical markers run in parallel in patients with FH. On the other hand, the factors associated with CCS and calcification evaluated by SAPC are not equal. This is probably due to the differences in techniques, SAPC being technically much more precise because of its much higher spatial resolution.

4.1. Study limitations

The patients were nor randomly selected from the SAFEHEART registry population. Furthermore, not every patient's data could be completely analysed. Nevertheless, although the sample size is not large, the sample is well balanced for gender and the results are robust. One hundred and eighty-one patients were excluded. Although this aspect is a limitation of the study, it is of note that the exclusion of patients was done exclusively based on image quality criteria and never on clinical or biochemical criteria, so the potential bias was limited. Furthermore, it would be a much greater limitation to introduce partial data from the coronary tree of those patients not included in the analysis. The different plaque types may overlap in their signal intensities due to partial volume artefacts. Nevertheless, until a new technological development is reached, this is currently the best we can do using intensity-based tissue characterization. Another limitation is the fact that SAPC is not widely available and, so far, its results cannot be used in daily clinical practice.

4.2. Conclusion

Coronary atherosclerosis and its qualitative components may be quantified by means of SAPC based on CTA images. Coronary atherosclerosis is highly prevalent in asymptomatic patients with FH. Plaque burden, calcified plaque burden and non-calcified plaque burden are independently related to the estimated cardiovascular risk and cardiovascular clinical prognosis at follow-up, being plaque burden the most related. Further studies are required to understand if coronary involvement, assessed by SAPC, may improve the risk re-stratification in patients with FH.

Author contributions

All authors contributed in design, patient enrolment, analysis and redaction of the manuscript.

Trial registration

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2020.11.012.

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