Early Coronary Calcifications are Related to Cholesterol Burden in Heterozygous Familial Hypercholesterolemia

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TITLE: Early coronary calcifications are related to cholesterol burden in heterozygous familial hypercholesterolemia.

SHORT TITLE: Early atherosclerosis in hypercholesterolemia.

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ABSTRACT

Background. The identification of high-risk patients with Heterozygous Familial Hypercholesterolemia (HeFH) that may benefit from early treatment is challenging. Coronary Artery Calcification (CAC) score accounts for coronary atherosclerotic burden. It has proven its accuracy in cardiovascular risk (CVR) assessment in the general population but data in HeFH are lacking.

Objective. The aim of our study was to assess CAC prevalence and its relationship with lifelong cholesterol exposure, calculated by Total Cholesterol Burden (TCB) in patients with HeFH.

Methods. 112 HeFH patients (50% males, median age 45) regularly followed-up since diagnosis were prospectively recruited at Pitié-Salpêtrière Hospital, Paris, France. CAC score was assessed using non contrast multi-detector computed tomography. TCB was calculated as total cholesterol (TC) x age at diagnosis plus annually assessed TC.

Results. The prevalence of CAC was 58%. Patients without CAC showed lower TCB than patients with CAC (298±110 vs 417.9±89 mmol-years/l, p<0.001). Among patients <45 (n=56), 39% exhibited CAC and a higher TCB compared to patients without CAC (352±71 vs 255±88 mmol-years/l, p<0.001) due to higher TC levels at diagnosis (10.2±2 vs 8.7±2 mmol/l, p=0.01). Multivariate analysis indicated that TCB was independently associated to
CAC.

Conclusions. Asymptomatic HeFH subjects exhibit early coronary atherosclerosis directly associated with TCB. Cholesterol burden and CAC score may be useful to identify higher risk HeFH patients who can benefit
from earlier and more aggressive treatment.

Keywords: Familial Hypercholesterolemia; Cardiovascular disease prevention; Calcium Score; Coronary Artery Calcification; Cholesterol burden.

Introduction

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In Western countries, one over 200 people is affected by Heterozygous Familial Hypercholesterolemia (HeFH) (1,2). In this autosomal dominant genetic disorder the early and prolonged elevation of atherogenic lipoprotein particles triggers the development of premature coronary artery disease (CAD) (3); nevertheless HeFH phenotype varies among patients, some being more severe than others (4). The identification of HeFH patients at high cardiovascular risk (CVR) is crucial for early treatment initiation as a 100-fold increase in coronary heart disease (CHD) risk has been observed in 20-39 years old untreated HeFH patients (5). As recently pointed out, the characterization of severe FH phenotypes is crucial for targeting a more aggressive treatment since younger age (6). Common risk score calculators are inadequate as they underestimate FH young patients CVR by not accounting for lifelong elevated cholesterol levels s. Furthermore, currently recommended imaging techniques for the detection of asymptomatic atherosclerosis suffer from various drawbacks limiting their applicability in young populations.

Coronary Artery Calcium (CAC) Score measures atherosclerotic burden and predicts cardiovascular events in young patients and in patients with familial history of cardiovascular disease (7,8). Lifelong exposure to cholesterol can be estimated by the addition of yearly-obtained Total Cholesterol (TC) levels to calculate Total Cholesterol Burden (TCB).

Our aim was to use CAC score to evaluate coronary atherosclerotic burden in patients with genetically diagnosed HeFH and to study the relationship between CAC and TCB.

Methods

Study population

Patients were consecutively recruited between May and December 2015 at the Cardiovascular Prevention Unit at Pitié-Salpêtrière Hospital in Paris, France.

Inclusion criteria were: genetically confirmed HeFH, age between 20 and 60 years, no symptoms or electrocardiographic signs of ischemia, no personal history of CHD, regular follow-up since diagnosis.

Exclusion criteria were: no affiliation to a healthcare system, informed consent refusal, contra-indication to computed tomography (CT), personal history of cardiovascular disease and myocardial infarction, diabetes mellitus, uncontrolled hypertension or triglycerides (TG) > 4.5 mmol/l. We

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included only index cases; relatives were excluded. The local institutional review board approved the study and informed consent was obtained from all included patients.

CAC measurements

Each patient underwent a multi-detector CT scan (Definition Flash, Siemens, Erlangen, Germany) for a total radiation exposure of 1 to 3mSv. Coronary arteries were imaged without contrast using helicoidal computed tomography with prospective ECG gating. Monophasic mesodiastolic imaging (75% of cardiac cycle) was performed when the heart rate was under 85 bpm and replaced by systolic imaging (40% of cardiac cycle) when heart rate was over 85 bpm to avoid right coronary artery motion artifacts. Radiation dose was automatically adjusted to patient morphology scout. Default voltage was 100kV and 120kV in overweight patients and tube current was automatically adapted according to patient morphology (average 100 to 200 mAs) to minimize radiation dose. Slice thickness reconstruction was 0.75mm every 0.7mm. Typical total breatholding time was from 10 to 15s. CAC was quantified by means of the previously described Agatston scoring method (9). The presence of CAC was evaluated by semi-automated Calcium Scoring software SyngoVia (Siemens, Erlangeen, Germany) over the entire epicardial coronary tree. Briefly, coronary calcium was defined as a lesion above a threshold of 130 Hounsfield units, 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 (mm^2), 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. All CT scans were quantified in an expert central reading center and supervised by a senior cardiovascular radiologist (A.R.) who was blinded to patients FH status and TCB.

Total Cholesterol burden calculation

Lifelong cholesterol exposure was calculated as TCB (mmol-years/l) according to Schmidt HH et al. (10). TCB is the addition of cholesterol burden at diagnosis (dCB) and post-diagnosis cholesterol burden (pdCB). dCB was obtained by multiplying the initial serum TC value (before treatment initiation) by the age of the patient at diagnosis. pdCB was calculated by adding the TC values annually measured during follow-up (on statin treatment) using patients' medical records. For patients who were already on treatment when genetic diagnosis was obtained, TCB was calculated by

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multiplying the highest TC value before the onset of statin treatment by patient's age at clinical diagnosis. Missing TC values during follow-up were replaced by the mean of all available TC values.

Risk factors assessment

Body Mass Index (BMI) was measured as weight (kilograms) divided by measured height (meters squared). Arterial hypertension was defined as Systolic Blood Pressure (SBP) ≥140 mmHg, Diastolic Blood Pressure (DBP) ≥90 mmHg and/or use of antihypertensive medication. Diabetes mellitus was defined as Fasting Plasma Glucose (FPG) levels ≥7.0 mmol/L or HbA_{1C}>6.5% and/or use of antidiabetic treatment. Current smoking was defined as having smoked at least one cigarette in the last 30 days.

Statistical analysis

Data are reported as mean ± standard deviation (SD) for continuous parametric and median (Interquartile Range-IQR) for continuous non-parametric variables, and as frequency (percentage) for categorical variables. Normality of continuous variables distribution was tested using Shapiro-Wilk's test. Differences between groups were evaluated by ANOVA. Distribution of categorical variables between groups was evaluated using the χ^2 test. Correlations between two variables were assessed using a linear regression model and Pearson's correlation coefficient (r) or Spearman's rho (for non-parametric variables) were provided. CAC score was further studied for its associations with TCB, SBP, sex (male =1), FPG, High-density Lipoprotein-cholesterol (HDL-C), TG, smoking status (current smoking = 1) and statin treatment (yes=1) using multivariate regression model. Age was not considered separately as already included in the TCB equation. The cubic root of CAC score was used for parametrical tests (10). Study population was stratified by age according to median age of 45 years. Statistical analyses were performed using SAS® software and a p-value <0.05 was considered significant.

Results

Table 1 summarizes the main clinical and biochemical characteristics of the 112 patients, according to gender. Mean time between age of HeFH diagnosis and CT scan was 25 years and 82.1% of patients were under statin treatment. Median overall CAC score was 9.1 (0-148) and males had a higher CAC score compared to females (median 59.7 vs 0.0 respectively, p<0.01). The overall prevalence of CAC

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was 58.1%, being higher in males than in females (p=0.04). No differences were found between genders in terms of age, TCB, BMI as well as xanthomas, mutation type, smoke and hypertension prevalence. Higher TC, HDL-C and Apolipoprotein-A1 (Apo-A1) levels, as well as lower TG were observed in females, whereas a higher proportion of males were under lipid-lowering treatment. Main characteristics of the study population, stratified by presence or absence of CAC, are shown in Table 2. Patients with CAC exhibited higher TCB than patients without CAC (417.9 ± 89 vs. 298.0 ± 110 mmol-years/l, p<0.001). Patients with CAC were more likely to be males and older, with a higher prevalence of xanthomas and hypertension. At diagnosis, they also presented with a higher age and TC. Compared to patients without CAC they had higher LDL-C (p<0.05), TC, Apo-B and TG (p<0.02) levels. Among patients with LDLR mutations, 47 (45.2%) had a null mutation, and 57 (54.8%) a defective mutation. No differences were found in CAC prevalence according to the residual LDLR function. Lp(a) was not associated to TCB or CAC, either as a dichotomous and a continuous variable.

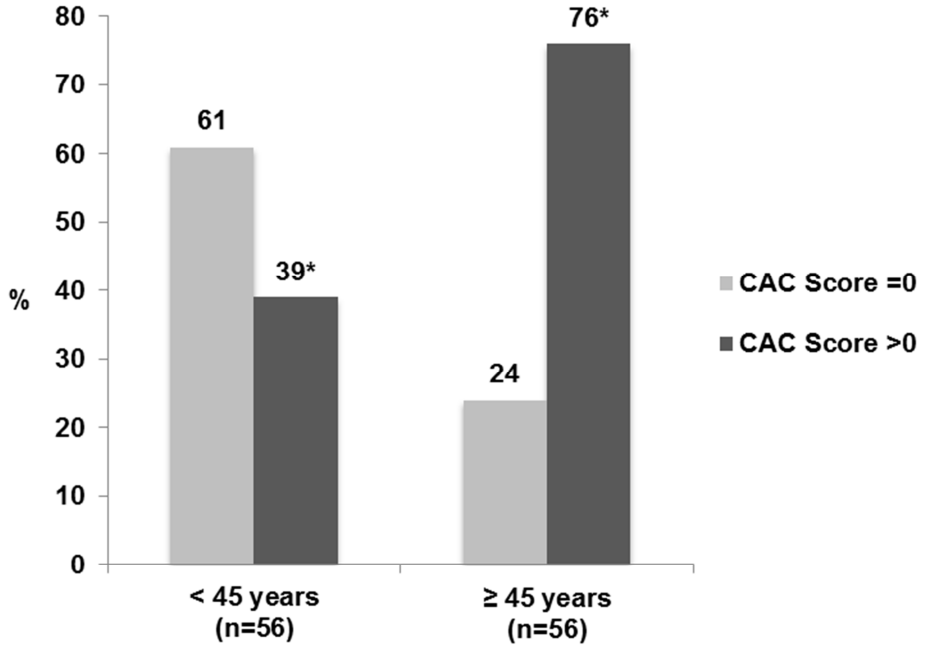
TBC was significantly related with all three commonly used scores for clinical diagnosis of FH (DLCN, Simon-Broome or MEDPED), even though the Simon-Broome showed the strongest association (R^2=0,645, p=0.00001. Additional Table 1). Conversely, the CAC score levels were significantly associated only with DLCN scores (R^2=0.193, p=0.014) in a model that included age.

Noteworthy, according to all three CVR scores the cohort was at low risk (median [IQR], SCORE 0.0% [0.0-1.1]; Framingham 2.1% [0.375- 6.05]; ASCVD 2.2% [1.0- 4.9]). CAC was present in about half of patients identified as low CVR by common CVR equations (Additional Table 2). To this regard, about 20% of HeFH patients classified as at low risk patients had CAC > 100. This was observed also in the young subgroup (Additional Table 3).

When stratified according to the median age of 45 years, patients below 45 years of age exhibited a 39% prevalence of CAC (Figure 1).

Figure 1.

Prevalence of CAC in patients below and over 45 years of age.



*p<0.001 vs absence of CAC. CAC, Coronary Artery Calcium; HeFH, Heterozygous Familial Hypercholesterolemia.

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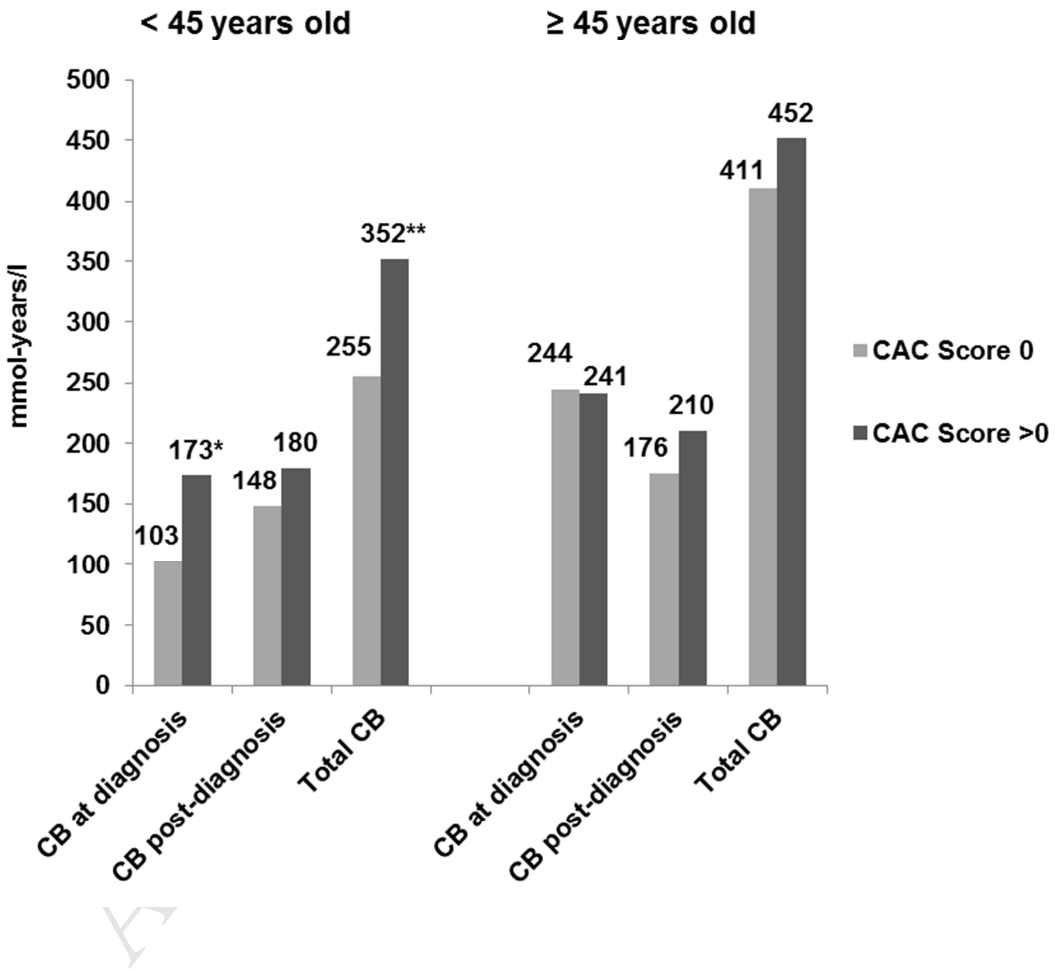
Furthermore, HeFH patients below 45 years with CAC had a higher dCB and TCB compared to patients without CAC in the same age range (Figure 2).

Figure 2.

Cholesterol burden in patients below 45 years old (left) and greater than or equal to 45 years old (right) with or without CAC.



*p<0.02;**p<0.001 vs absence of CAC.

Patients < 45 years old: CAC=0 (n=34); CAC>0 (n=22)

Patients ≥45 years old: CAC=0 (n=13); CAC>0 (n=43)

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The higher dCB was explained by higher TC at diagnosis (10.2 ± 2 vs 8.7 ± 2 mmol/l, p=0.01) while age at diagnosis was not different (11 vs 15 years, p=0.09). Post-diagnosis CB was not different between the two subgroups. No differences in TCB, dCB and pdCB were found between patients ≥45 years of age with CAC versus patients without CAC.

Univariate analysis showed that CAC presence was associated with TCB (R^2= 0.330, p<0.001), pdCB (R^2= 0.248, p<0.001) and dCB (adjusted R^2=0.156, p=0.001). When considered separately, both age and TCB were found to be positively correlated to CAC (Spearman's rho= 0.462 and 0.500, respectively. p <0.001). Multivariate analysis (Table 3) indicated that TCB was associated to CAC score levels independently from gender, smoking status, statin treatment, HDL-C, TG, FPG and SBP levels (p<0.001).

Discussion

In this study asymptomatic genetically determined HeFH patients were found to have a high prevalence of CAC. Lifelong cholesterol accumulation, measured by the total cholesterol burden, was independently associated to this premature CAC detection.

These findings are in line with two previous reports of early calcified coronary plaques in clinically diagnosed HeFH evaluated by electron-beam tomography (11) and CT (12). In the latter study, the prevalence of HeFH patients with CAC was below 50% which is comparable to our results.

Presence of CAC has been associated to a higher risk of CHD in asymptomatic patients with dyslipidemia (13) or with family history of CHD (8). The prevalence of CAC in our cohort was much higher than that found in the CARDIA study, where only 9.9% of 2832 patients aged 33 to 45 years of age exhibited coronary calcifications (14). Furthermore, the presence of CAC in about a half of patients classified as at low risk by common CVR equations suggest that CAC evaluation could have a real incremental value beyond risk algorithms. However, the final incremental value could only be determined with long term prospective trial.

Typically CAC scanning is not used for individuals <45 years of age because most atherosclerotic plaques are not calcified in younger individuals, but in our high risk population, 39% of individuals with HeFH aged <45 already had CAC. The large reference Multi-Ethnic Study of Atherosclerosis

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(MESA) only enrolled individuals >45, therefore presence of CAC would be a high-risk score for MESA adults aged 45-50 years (15).

The absence of CAC has been associated with a low risk of CHD (16). In the Dallas Heart Study cohort of young patients with a family history of CHD, the overall absence of CAC (47%) was associated to a 0.4-1.9% CHD rate. However, in this study the presence of HeFH, often associated with a family history of CHD, was not assessed (8). In a cohort of 140 clinically diagnosed HeFH asymptomatic patients (mean age 52 years, known genetic disorder in 66% of the cohort, diabetes prevalence 6%); only 21% were found without CAC. They underwent CT angiography and no plaques were found, while 69% of patients with a CAC score > 400 exhibited obstructive CAD (17). Apart from CAC, some clinical parameters have shown to be useful in HeFH patients for CVD risk refinement. Among them Lp(a) has been associated with early CHD also in FH (18) and can be used for risk reclassification (19). Contrarily, while a null mutation has been associated with an increased prevalence of premature CVD and recurrence of CV events compared to a defective LDLR mutation (20), no significant associations were found between mutation type and aortic/carotid plaque presence (21).

Our results in HeFH with an established genetic diagnosis reinforce the concept of an association between early, lifelong cholesterol exposure and premature atherosclerosis shown in non-HeFH subjects of the Framingham offsprings cohort (22). Here, in HeFH subjects, we showed an independent association between TCB and calcified coronary atherosclerotic burden that expands previous results on arterial stiffening and thickening (23). In young patients under 45 years we report the high prevalence of CAC presence in correlation with the cholesterol burden at diagnosis suggesting a potential role of early exposure to elevated cholesterol levels. The strength of our study is the inclusion of HeFH who have been genetically diagnosed, early treated and regularly followed in our unit since diagnosis. This enabled us to limit potential bias in cholesterol burden calculation and to present results in a very well characterized population.

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Cholesterol burden at diagnosis can be easily calculated and may be helpful beyond single TC levels to identify higher risk HeFH patients who could benefit from a more aggressive lipid lowering treatment (e.g. high-dose statin+ezetimibe, PCSK9 inhibitors and/or lomitapide).

The dCB calculation (TC levels at diagnosis x age at diagnosis) assumes that TC levels are a constant throughout early life which may rise some doubts. However, during the 27 years of follow-up of the Bogalusa Heart Study, 66.2% of the dyslipidemic subjects in the two highest quintiles for non-HDL cholesterol levels remained in the same quintiles during adulthood (24).

The early appearance of calcified plaques in HeFH can be explained by several mechanisms. First, the LDL-Receptor (LDL-R) itself may have a potential role in determining a higher prevalence of calcifications in young HeFH patients. A crosstalk between LDL-R and LDL-Related Protein 5/6 may take place that would allow the nuclear translocation of beta-catenin in the osteocyte, determining calcium deposition in the vascular wall (25). Our results also confirm previously data published by Borholt-Petersen et al. where no influence of the type of LDL-R mutation (null versus defective) was associated with a more severe vascular phenotype (26).Statins have been shown to prevent atherosclerotic plaques development but also to enhance their calcifications (27). 80% of our patients were under statin treatment: on the one hand, this may have explained the relatively high prevalence of calcified plaques in our younger subgroup of HeFH patients; on the other hand an early treatment initiation may have accounted for the 61% prevalence of zero CAC in the younger. However, in the multivariate analysis statin treatment was not associated with CAC. Novel recommendations suggest for HeFH a treatment goal LDL-C <1.8 mmol/l for patients at high risk due to the evidence of CVD or a severe FH phenotype (28) suggestive of a delayed diagnosis and/or treatment .CAC scanning could be a useful tool in HeFH patients upward CVR reclassification, to identify those individuals who could benefit from a statin-ezetimibe combination or PCSK9 antibodies therapy. Moreover, in this age of electronic medical records, a measure of total cholesterol burden could be generated as a tool for clinicians to identify high risk individuals that might warrant early and more intensified prevention.

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Our study exhibits some limitations. First, it is a cross-sectional study on a small genetically selected population. However, it enabled accurate phenotyping and TCB calculation.

The concept of TCB may be considered controversial in FH patients because they are exposed to very high cholesterol levels since birth. However, even in our cohort genetically classified, early treated and regularly followed-up HeFH patients, we were able to observe that treatment initiation has an effect in reducing TCB.

CT Angiography, the gold standard for coronary plaque detection, was not performed. Although this may have allowed hypodense non-calcified plaques detection, CT angiography requires contrast injection and a higher radiation exposure. In terms of risk reclassification, it did not lead to an improvement when compared to a model based on standard risk factors and CAC in a registry of asymptomatic non HeFH (29) or HeFH subjects with other cardiovascular risk factors (12,17). Finally, we did not compare HeFH to a control group. However, we used the same age non-HeFH CARDIA study cohort to compare the prevalence of CAC. Furthermore, validated age and gender-adjusted nomograms from the MESA were used in which young patients with CAC > 0 fall in the 75th percentile to postulate that having CAC under the age of 45 indicates high cardiovascular risk (15).

In conclusion, young asymptomatic HeFH subjects exhibit early calcified coronary atherosclerosis in association with lifelong exposure to high cholesterol levels. Total cholesterol burden calculation at the time of diagnosis may be useful to identify more severe phenotypes of HeFH patients who could benefit from a more aggressive lipid lowering therapy as advocated by recent guidelines. . In this accurately selected population of genetically confirmed HeFH patients, CAC score may therefore contribute to tailor more aggressive LDL-C lowering strategies aiming at reaching LDL-C target..

AUTHORS' CONTRIBUTIONS

All authors contributed to conception, design, drafting and final revision and approval of the article. AG, PG, EB and DR provided to data collection and analysis; AC performed genetic analysis; AR analyzed all CT images for CAC Score calculation; RB provided lipid and biochemical profiling.

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DISCLOSURE STATEMENT

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Table 1

Patient characteristics according to gender

	All (n=112)	Males (n=56)	Females (n=56)
Age - *years*	44.5 (38-52)	44 (36-51)	46.5 (38-55)
BMI - Kg/m²	24.4 (21-27)	25.4 (23-28)	23.4 (20-27)
Subclinical atherosclerosis burden			
CAC Score 0 – n (%)	58 (51.8)	23 (41.1)	35 (62.5) ‡
CAC Score 1-100 – *n (%)*	22 (19.6)	10 (17.8)	12 (21.4)
CAC >100 – *n (%)*	32 (28.6)	23 (41.1)	9 (16.1) *
Cholesterol burden			
Cholesterol Burden at diagnosis - *mmol-years/l*	187.6 ± 118	186.9 ± 134	188.4 ± 100
Cholesterol Burden post-diagnosis - *mmol-years/l*	182.0 ± 87	175.3 ± 87	188.7 ± 88
Total Cholesterol Burden - *mmol-years/l*	363.7 ± 114	359.6 ± 132	374.5 ± 94
FH History			
Mutation type (LDLR/ ApoB/PCSK9) - (*n)*	104 / 7 / 1	51 / 4 / 1	53 / 3 / -
Age of diagnosis - *years*	18.0 (11-27)	16 (10-29)	18 (12-23)
TC at diagnosis - *mmol/l*	9.6 (8-11)	9.0 (7.9-11.6)	9.8 (8.3-10.6)
Xanthomas - *n(%)*	27 (24.1)	13 (23.2)	14 (25)
Cardiovascular Risk Factors			
Current smoking - *n (%)*	34 (30.4)	19 (34)	15 (26.7)
Arterial Hypertension - *n(%)*	11 (9.8)	7 (12.5)	4 (7.1)
Lipid profile			
TC - *mmol/l*	6.2 (5-7)	5.6 (5-6.6)	6.6 (6-7)‡
TG - *mmol/l*	1.0 (0.7-1.3)	1.1 (1-1.5)	0.9 (0.7-1.3)*
HDL-C - *mmol/l*	1.3 (1-1.6)	1.2 (1-1.4)	1.5 (1-2)§
LDL-C - *mmol/l*	4.1 (3.6-5)	3.9 (4-5)	4.2 (4-5.5)
ApoB - *mg/dl*	116.0 (103-137)	116.0 (101.5-137)	117.0 (103-214)

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ApoA1 - *mg/dl*	145.0 (131-163)	140.0 (126-152)	149.5 (137-166)*
Lp(a) - *mg/dl*	26.0 (12-51)	21.5 (9-45)	27.0 (13-53)
Current lipid-lowering treatment			
Overall - *n(%)*	92 (82.1)	53 (94.6)	39 (69.6)*
Statins - *n(%)*	90(80.3)	52 (92.8)	38 (67.8)*
Ezetimibe - *n(%)*	38 (33.9)	24 (42.8)	14 (25)†

Data are expressed as mean ± SD or median (IQR).*p<0.01;†p<0.05;‡p<0.02;§p<0.001; males vs female.

Cholesterol Burden at diagnosis was calculated as Age x TC at diagnosis; Cholesterol Burden post-diagnosis was calculated as the sum of one value of TC/year since diagnosis; Total Cholesterol Burden is the sum of Cholesterol Burden at diagnosis and Cholesterol Burden post-diagnosis.

ApoA1, Apolipoprotein A1; ApoB, Apolipoprotein B; BMI, Body Mass Index; CAC, Coronary Artery Calcium; FH, Familal Hypercholesterolemia; HDL-c, High-Density Lipoprotein cholesterol; LDL-C, Low-Density Lipoprotein cholesterol; LDLR, Low-Density Lipoprotein cholesterol receptor; Lp(a), Lipoprotein (a); SBP, Systolic Blood Pressure; TC, total cholesterol; TG, triglycerides

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Table 2

Characteristics of patients with and without CAC

	CAC 0 (n=47)	**CAC >0 (n=65)**
Gender - *n male/n female*	18/29	38/27*
Age - *years*	38 (28-46)	48.5 (43-53)†
BMI - *kg/m²*	22.6 (20-27)	25.6 (23-28)
CAC score	0	161.75(32-375)
Cholesterol burden		
Cholesterol Burden at diagnosis - *mmol-years/l*	145.5 ± 111	217.3 ± 114†
Cholesterol Burden post-diagnosis - *mmol-years/l*	155.6 ± 78	199.6 ± 89†
Total Cholesterol Burden - *mmol-years/l*	298 ± 110	417.9 ± 89†
FH History		
Mutation type (LDLR/ ApoB/PCSK9) – *n*	45/2/-	59/5/1
Age of diagnosis – *years*	15 (8-22)	20 (15-30)*
TC at diagnosis - *mmol/l*	8.4(7-10)	10.3(8-12)†
Xanthomas - *n(%)*	7 (14.9)	20 (30.7)‡
Cardiovascular Risk Factors		
Current smoking - *n (%)*	13 (27.7)	21 (32.3)
Arterial Hypertension - *n(%)*	1 (2.1)	10 (15.4)*
Lipids levels		
TC - *mmol/l*	5.7 (5-7)	6.4 (6-7.3)§
TG - mmol*/l*	0.9(0.7-1.2)	1.1 (0.8-1.5)§
HDL-C - *mmol/l*	1.2 (1-1.5)	1.3 (1.2-1.6)
LDL-C - *mmol/l*	3.9 (3.6-5)	4.2 (3.8-5.4)*
ApoB -m*g/dl*	110.0 (101-124)	121.0 (105-147)§
ApoA1 - m*g/dl*	136.0 (127-157)	149.0 (132-163)

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Lp(a) - *mg/dl*	26.0 (12-50)	25.0 (9-51)
Current lipid treatment		
Statin - *n(%)*	35 (74.5)	55 (84.6)
Ezetimibe - *n(%)*	7 (14.9)	31 (47.7)†

*p<0.05; †p<0.001;‡p<0.01; §p<0.02 vs CAC 0.

Cholesterol Burden at diagnosis was calculated as Age x TC at diagnosis;

Cholesterol Burden post-diagnosis was calculated as the sum of one cholesterol/year since diagnosis. Total Cholesterol Burden is the sum of Cholesterol Burden at diagnosis and Cholesterol Burden post-diagnosis.

ApoA1, Apolipoprotein A1; ApoB, Apolipoprotein B; BMI, Body Mass Index; CAC, Coronary Artery Calcium; FH, Familal Hypercholesterolemia; HDL-c, High-Density Lipoprotein cholesterol; LDL-c, Low-Density Lipoprotein cholesterol; LDLR, Low-Density Lipoprotein cholesterol receptor; Lp(a), Lipoprotein (a); SBP, Systolic Blood Pressure; TC, total cholesterol; TG, triglycerides.

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Table 3

Multivariate analysis of CAC score determinants.

	Calcium Score		
	R^2	**β**	**p**
Overall Model	0.29		0.0001
Gender - *(male =1)*		1.98 ± 0.7	0.005
Total cholesterol burden - *mmol-years/l*		0.01 ± 0.003	0.0001
Current smoking - *(yes=1)*		0.5 ± 0.64	0.42
Statin treatment - *(yes=1)*		0.38 ± 0.81	0.64
HDL-C - *mmol/l*		0.1 ± 0.7	0.9
TG - *mmol/l*		0.33 ± 0.5	0.5
FPG - *mmol/l*		0.29 ± 0.63	0.65
SBP – *mmHg*		-0.002 ± 0.031	0.98

FPG, Fasting Plasma Glucose; HDL-C, high-density lipoprotein cholesterol; SBP, Systolic Blood Pressure; TG, triglycerides.

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HIGHLIGHTS

- Cholesterol burden makes risk evaluation challenging in hypercholesterolemia
- CAC Score is a validated method predicting cardiovascular events in young subjects
- A high CAC prevalence was found in young asymptomatic hypercholesterolemic patients
- CAC Score was higher when a higher cholesterol burden at diagnosis was present
- Cholesterol burden and CAC Score at diagnosis may target higher risk patients

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