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Original Research



Age- and sex-based heterogeneity in coronary artery plaque presence and burden in familial hypercholesterolemia: A multi-national study

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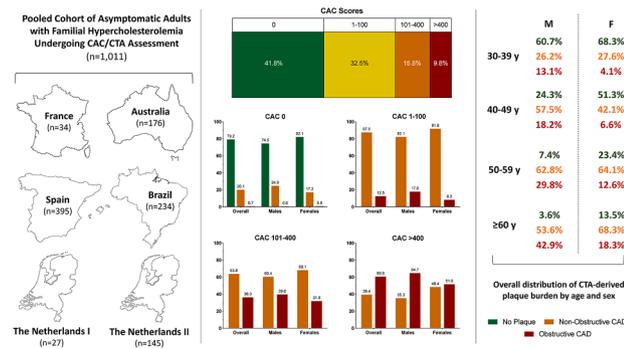
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HIGHLIGHTS

- The absence of coronary artery calcification (CAC) is a robust negative risk marker in the primary prevention of coronary artery disease (CAD) and is heterogeneous in familial hypercholesterolemia (FH).
- Pooling data from 1011 treated individuals with FH who were free of established CAD across 5 countries, more than 2 in every 5 patients had CAC=0 (~1 in 2 in female patients).
- Females had a lower prevalence of obstructive CAD across all CAC ranges >0. Among those aged 50–59 years, ~1 in 4 female patients had no plaque (< 1 in 14 in males).
- Among individuals without CAC, nearly 1 in 5 had non-obstructive CAD.
- These findings provide evidence for the less pronounced increase in coronary atherosclerosis among female patients with FH, however, further assessment of the long-term prognostic implications among asymptomatic patients with FH and an absence of CAC is needed.

GRAPHICAL ABSTRACT



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Key Words:

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ABSTRACT

Objectives: Individuals with familial hypercholesterolemia (FH) are at an increased risk for coronary artery disease (CAD). While prior research has shown variability in coronary artery calcification (CAC) among those with FH, studies with small sample sizes and single-center recruitment have been limited in their ability to characterize CAC and plaque burden in subgroups based on age and sex. Understanding the spectrum of atherosclerosis may result in personalized risk assessment and tailored allocation of costly add-on, non-statin lipid-lowering therapies. We aimed to characterize the presence and burden of CAC and coronary plaque on computed tomography angiography (CTA) across age- and sex-stratified subgroups of individuals with FH who were without CAD at baseline.

Methods: We pooled 1,011 patients from six cohorts across Brazil, France, the Netherlands, Spain, and Australia. Our main measures of subclinical atherosclerosis included CAC ranges (i.e., 0, 1–100, 101–400, >400) and CTA-derived plaque burden (i.e., no plaque, non-obstructive CAD, obstructive CAD).

Results: Ninety-five percent of individuals with FH (mean age: 48 years; 54% female; treated LDL-C: 154 mg/dL) had a molecular diagnosis and 899 (89%) were on statin therapy. Overall, 423 (42%) had CAC=0, 329 (33%) had CAC 1–100, 160 (16%) had CAC 101–400, and 99 (10%) had CAC >400. Compared to males, female patients were more likely to have CAC=0 (48% [n = 262] vs 35% [n = 161]) and no plaque on CTA (39% [n = 215] vs 26% [n = 120]). Among patients with CAC=0, 85 (20%) had non-obstructive CAD. Females also had a lower prevalence of obstructive CAD in CAC 1–100 (8% [n = 15] vs 18% [n = 26]), CAC 101–400 (32% [n = 22] vs 40% [n = 36]), and CAC >400 (52% [n = 16] vs 65% [n = 44]). Female patients aged 50–59 years were less likely to have obstructive CAD in CAC >400 (55% [n = 6] vs 70% [n = 19]).

Conclusion: In this large, multi-national study, we found substantial age- and sex-based heterogeneity in CAC and plaque burden in a cohort of predominantly statin-treated individuals with FH, with evidence for a less pronounced increase in atherosclerosis among female patients. Future studies should examine the predictors of resilience to and long-term implications of the differential burden of subclinical coronary atherosclerosis in this higher risk population.

Abbreviations and acronyms

ASCVD atherosclerotic cardiovascular disease
 CAC coronary artery calcium
 CAD coronary artery disease
 CHD coronary heart disease
 CTA computed tomography angiography
 FH familial hypercholesterolemia
 LDL-C low-density lipoprotein cholesterol
 MACE major adverse cardiac event
 PCSK9 proprotein convertase subtilisin/kexin type 9

SCCT Society of Cardiovascular Computed Tomography

1. Introduction

Heterozygous familial hypercholesterolemia (FH) is the leading genetic cause of premature atherosclerotic cardiovascular disease (ASCVD) worldwide [1,2]. Early initiation of lipid-lowering therapies including statins and ezetimibe is critical for preventing ASCVD in patients diagnosed with FH [3–5]. Compared to unaffected individuals, those with FH experience a greater and earlier risk of coronary artery disease (CAD) if left untreated [6]. However, FH remains largely

undetected and undertreated in the general population both in the United States and worldwide [1,2,7]. Despite the increased risk of CAD, many individuals with FH never experience a major adverse cardiac event (MACE), while others do despite intensive and prolonged lipid-lowering [8,9].

The detection of coronary artery calcium (CAC) by non-contrast cardiac computed tomography (CT) has been recognized as a safe and inexpensive surrogate of subclinical atherosclerosis and offers a guideline-recommended method for tailored risk assessment [10]. Improved accuracy in the stratification of risk afforded by CAC can lead to more personalized allocation of pharmacotherapies among borderline and intermediate risk individuals from the general primary prevention population [11]. Absence of CAC (CAC=0) is a *negative risk marker* that can accurately predict low MACE risk in primary prevention settings [12,13]. Furthermore, many patients with FH have CAC=0, [14] which has a favorable prognosis in the short-term [15,16]. As a result, utilization of CAC scoring may be an effective strategy for identifying patients who are at increased ASCVD risk and would likely derive the greatest benefit from novel but costly add-on, non-statin therapies, such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors used in addition to maximally tolerated statin therapy and/or in combination with ezetimibe [17,18,19]. However, individual studies have provided limited insights into the prevalence and severity of coronary plaque and calcification across different subgroups stratified by age and sex. This information may result in improvements in personalizing risk stratification and informing shared decision-making practices between patients with FH and their physicians.

Accordingly, the purpose of our study was to evaluate potential differences in coronary calcification and plaque burden on CT angiography (CTA) across age- and sex-stratified subgroups of patients with heterozygous FH. We pooled cross-sectional data from six cohorts across five countries to characterize CAC and CTA-derived plaque burden, as well as luminal obstruction among individuals with FH free of clinical ASCVD at baseline.

2. Methods

2.1. Study population and study design

This was a cross-sectional study in which we pooled data from patients with FH who were referred to specialized lipid clinics or who were identified through cascade screening programs. Upon enrollment, all patients were without known coronary heart disease (CHD, defined broadly as asymptomatic adults without a history of ASCVD or CHD, prior revascularization procedures, or symptoms suggestive of ischemia) at the baseline study visit. Included patients had CAC and CTA imaging data and were enrolled at sites from five different countries that have each previously reported on the atherosclerotic plaque burden of patients with FH (i.e. Spain [20], the Netherlands [2 cohorts, 21,22] Brazil [15,23] Australia [24], and France [25]). Individuals were included if they 1) were free of clinical ASCVD at baseline (i.e., time of initial CAC and CTA assessment), 2) underwent cardiac CT tests to assess coronary artery plaque burden, and 3) received a clinical or genetic diagnosis of heterozygous FH. The rationale for performing cardiac imaging varied by site, however, patients enrolled at most sites, including those in Spain and Brazil, underwent CAC and CTA assessment to quantify the presence and burden of coronary plaque burden in FH independent of determining treatment goals or success.

Patient enrollment periods for the participating cohorts varied as follows: Australia (Lipid Disorders Clinic at Royal Perth Hospital): March 2007 – September 2019 [24,26,27]; Brazil (Lipid Clinic at the Heart Institute (InCor), University of São Paulo Medical School Hospital): September 2006 – September 2019 [28]; France (Cardiovascular Prevention Unit at Pitié-Salpêtrière Hospital): June 2018 – January 2020 [25]; the Netherlands I (Amsterdam Medical Center): September 2014 – September 2020; the Netherlands II (Erasmus Medical Center,

Rotterdam): February 2008 – June 2011 [29]; and Spain (SAFEHEART Registry from six university hospitals): January 2013 – December 2016 [30]. Detailed information on each of the participating multi-national cohorts including participants' baseline characteristics, eligibility criteria, and CAC/CTA imaging data are presented in Supplemental Tables 1–4.

Lead investigators at all sites were contacted and provided with the study objectives and a standard data collection form to gather pooled baseline demographic and clinical information of enrolled patients with FH, along with their CAC and CTA imaging results. Given that our pooled analysis sought to collect de-identified data from participating sites in aggregate, it was deemed exempt of individual informed consent by the Yale University Institutional Review Board. Each site's separate ethical review information and participant informed consent processes can be found in Supplemental Table 4.

2.2. CAC/CTA data

At each site, CAC burden was quantified using the Agatston method [31] and the extent of CAD was determined based on CTA findings and according to guidelines from the Society of Cardiovascular Computed Tomography (SCCT) [32]. Participants' CAC scores were stratified into CAC=0, CAC 1–100, 101–400, and CAC >400 ranges, as classified in prior studies and widely-used multi-society guidelines [10,33]. We further stratified participants' CAD burden and stenosis severity into obstructive CAD ($\geq 50\%$ stenosis), non-obstructive CAD ($< 50\%$ stenosis), and no plaque or stenosis. Pooled data were obtained from the standardized data extraction form in the form of aggregate frequencies and percentages. We coalesced these data, along with previously published information (e.g., eligibility criteria, CAC/CTA imaging information, and study sample characteristics) corresponding with each site, to produce pooled estimates of our study variables.

2.3. Covariates

Demographic and clinical characteristics were collected in aggregate from each of the participating sites. Demographic information included age and sex, while clinical characteristics included the frequency and proportion of patients on statin, ezetimibe, and/or PCSK9i therapy, along with their pre-treatment and treated LDL-C levels. Additionally, we collected participants' personal history of diabetes mellitus and hypertension along with their current/former smoking status and the presence of xanthomas at the time of their most recent hospital visit. Two participating sites had missing data on pre-treatment LDL-C levels and one site lacked information on participants' presence of xanthomas.

2.4. Statistical analysis

We presented dichotomous and categorical variables as counts and percentages and continuous variables as mean (\pm standard deviation [SD]). Given our collection of pooled data in aggregate from each of the participating clinical sites, we ascertained distribution of CAC scores as well as CTA-derived plaque burden (obstructive CAD, non-obstructive CAD, and no plaque) both overall and across the pre-specified CAC ranges. Additionally, we conducted subgroup analyses of CAC and plaque burden stratified by sex and across distinct age subgroups (i.e., 30–39y, 40–49y, 50–59y, and $\geq 60y$).

3. Results

A total of 1011 patients with heterozygous FH who underwent CAC and CTA assessment were evaluated, of which 961 (95.1%) had a molecular diagnosis (mean age 48.3 [SD 10.3] years; 54.0% female; 88.8% on statin therapy; treated LDL-C 155.1 [SD 58.7] mg/dL) (Graphical Abstract and Table 1). Most patients were heterozygous carriers of a variant in *LDLR* (88.3%), followed by *APOB* (6.2%) and *PCKS9* (0.4%).

Table 1

Baseline demographic, clinical, and laboratory characteristics among individuals with heterozygous familial hypercholesterolemia free of clinical ASCVD at baseline ($n = 1011$).

| Study Characteristics | Overall ($n = 1011$) | Males ($n = 465$) | Females ($n = 546$) |
|---|---------------------------|------------------------|--------------------------|
| Demographic Characteristics | | | |
| Age, y (mean [SD]) | 48.3 (10.3) | — | — |
| Age, y | | | |
| 30 – 39 | 230 (22.7) | 107 (23.0) | 123 (22.5) |
| 40 – 49 | 333 (32.9) | 181 (38.9) | 152 (27.8) |
| 50 – 59 | 288 (28.5) | 121 (26.0) | 167 (30.6) |
| ≥ 60 | 160 (15.8) | 56 (12.0) | 104 (19.0) |
| Sex (female) | 546 (54.0) | — | — |
| Country Cohort | | | |
| Australia | 176 (17.4) | 74 (15.9) | 102 (18.7) |
| Brazil | 234 (23.1) | 74 (15.9) | 160 (29.3) |
| France | 34 (3.4) | 19 (4.1) | 15 (2.7) |
| The Netherlands I (Amsterdam) | 27 (2.7) | 14 (3.0) | 13 (2.4) |
| The Netherlands II (Rotterdam) | 145 (14.3) | 93 (20.0) | 52 (9.5) |
| Spain | 395 (39.1) | 191 (41.1) | 204 (37.4) |
| Clinical Characteristics | | | |
| Hypertension | 178 (17.6) | 76 (16.3) | 102 (18.7) |
| Diabetes mellitus | 44 (4.4) | 16 (3.4) | 28 (5.1) |
| Current or former smoking status | 313 (31.0) | 148 (31.8) | 165 (30.2) |
| Xanthomas ($n = 984$) | 173 (17.6) | 81 (18.0) | 92 (17.3) |
| Pre-treatment LDL-C, mg/dL (mean [SD]) ($n = 589$) | 277.9 (75.3) | 274.3 (75.4) | 278.2 (76.6) |
| Treated LDL-C, mg/dL (mean [SD]) ($n = 1011$) | 155.1 (58.7) | 146.7 (53.0) | 157.6 (62.5) |
| Lipid-lowering therapies | | | |
| Statin | 899 (88.8) | 418 (89.9) | 480 (87.9) |
| Ezetimibe | 538 (53.2) | 265 (57.0) | 273 (50.0) |
| PCSK9i | 14 (1.4) | 7 (1.5) | 7 (1.3) |
| Age at start of statin treatment, yr (mean [SD]) ($n = 905$) | 38.1 (11.2) | 37.0 (10.3) | 39.1 (11.7) |
| Duration of statin use, yr (mean [SD]) ($n = 808$) | 11.1 (7.8) | 10.5 (7.1) | 15.0 (10.4) |
| Age at start of ezetimibe treatment, yr (mean [SD]) ($n = 663$) | 46.6 (11.1) | 42.2 (10.0) | 51.5 (9.8) |
| Duration of ezetimibe use, yr (mean [SD]) ($n = 663$) | 4.0 (3.0) | 5.0 (3.3) | 3.1 (2.2) |
| Molecular diagnosis of FH ($n = 1007$) | | | |
| LDLR | 961 (95.1) | 437 (94.0) | 524 (96.0) |
| APOB | 893 (88.3) | 411 (88.4) | 482 (88.3) |
| PCSK9 | 63 (6.2) | 24 (5.2) | 39 (7.1) |
| Other [†] | 4 (0.4) | 2 (0.4) | 2 (0.4) |
| Other [†] | 1 (0.1) | 0 (0) | 1 (0.2) |

Abbreviations: APOB, apolipoprotein B; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; PCSK9(i), proprotein convertase subtilisin/kexin type 9 (inhibitor).

Values presented as either n (%) or mean (SD).

[†] Other molecular diagnosis of FH includes an identified mutation in *APOE*.

The majority of patients without genetically confirmed FH ($n = 46$, 4.5%) received a clinical diagnosis of FH based on a “probable” or “definite” score according to the Dutch Lipid Clinics Network diagnostic criteria. Participants’ mean age at the start of their statin treatment was 38.1 (SD 11.2) years and the average duration of statin use was 11.1 (SD

7.8) years.

3.1. Overall coronary calcification and plaque burden

Overall, 423 (41.8%) individuals had CAC=0, while 329 (32.5%) had CAC 1–100, 160 (15.8%) had CAC 101–400, and 99 (9.8%) had CAC >400 (Fig. 1 and Table 2). The proportion of female patients with CAC=0 was higher compared to males (48.0% vs 34.6%), whereas 14.6% of males and 5.7% of females had CAC >400.

In terms of plaque burden on CTA, 355 (33.1%) individuals had no plaque, 514 (50.8%) had non-obstructive CAD, and 162 (16.0%) had obstructive CAD (Fig. 2). Female patients were more likely to have no plaque compared with males (39.4% vs 25.8%), and had a lower likelihood of having obstructive CAD (10.1% vs 23.0%). Male and female patients had a similar proportion of non-obstructive CAD (50.5% vs 51.2%).

3.2. Plaque burden across cac scores

Among individuals with CAC=0, 20.8% had non-calcified plaque (20.1% with non-obstructive CAD and 0.7% with obstructive CAD) (Table 2). Females were less likely to have obstructive CAD than male patients with CAC 1–100 (8.2% vs 17.9%), CAC 101–400 (31.9% vs 39.6%), and CAC >400 (51.6% vs 64.7%). Table 3 shows plaque burden across CAC ranges stratified by age and sex.

Among individuals aged 40–49 years with CAC=0, 12.2% of female patients and 26.7% of males had detectable plaque. These proportions increased to 25.0% in females and 40.0% in males aged 50–59 years with CAC=0. In patients with CAC 1–100, 7.8% and 2.7% of females aged 50–59 years and ≥ 60 years had obstructive CAD, respectively (males: 16.2% [50–59 years] and 9.1% [≥ 60 years]). Among those with CAC >400, females aged 50–59 years had a lower likelihood of obstructive CAD compared with men of the same age group (54.5% vs 70.4%). Supplemental Table 5 shows plaque burden across CAC ranges between statin and non-statin users.

3.3. Age- and sex-based differences in CAC/CTA

Female patients had a higher proportion of CAC=0 across all age groups (Fig. 1). For instance, 59.2% and 31.1% of females aged 40–49 and 50–59 years had CAC=0, respectively, compared with 33.1% and 12.4% among males. Females also had a lower likelihood of CAC 101–400 and CAC >400 across age groups compared with males. Specifically, 5.9% of female patients aged 40–49 years had CAC 101–400 compared to 14.4% among men of the same age. Moreover, 6.6% of females 50–59 years of age had CAC >400, compared to 22.3% in males.

While the proportion of individuals with obstructive CAD increased with age, females had a lower likelihood of obstructive CAD at ≥ 60 years (18.3% vs 42.9%) (Fig. 2). Female patients also had a higher proportion of no plaque at younger age ranges compared with males (68.3% vs 60.7% [30–39 years] and 51.3% vs 24.3% [40–49 years]). These variations in the absence of plaque by sex were also found among older age groups (23.4% vs 7.4% [50–59 years] and 13.5% vs 3.6% [≥ 60 years], respectively).

4. Discussion

In this cross-sectional study, we present the largest pooled CAC/CTA analysis of more than one thousand patients with heterozygous FH who were without clinical ASCVD at baseline. We found evidence of age- and sex-based heterogeneity in CAC scores and CTA-derived plaque burden. Overall, 42% of patients had CAC=0 and 33% had no detectable plaque on CTA. These findings varied by age and sex with nearly 1 in 4 female patients aged 50–59 years having no coronary plaque as compared to fewer than 1 in 14 males older than 50 years of age. Importantly, among individuals without CAC, approximately 1 in 5 had non-obstructive CAD

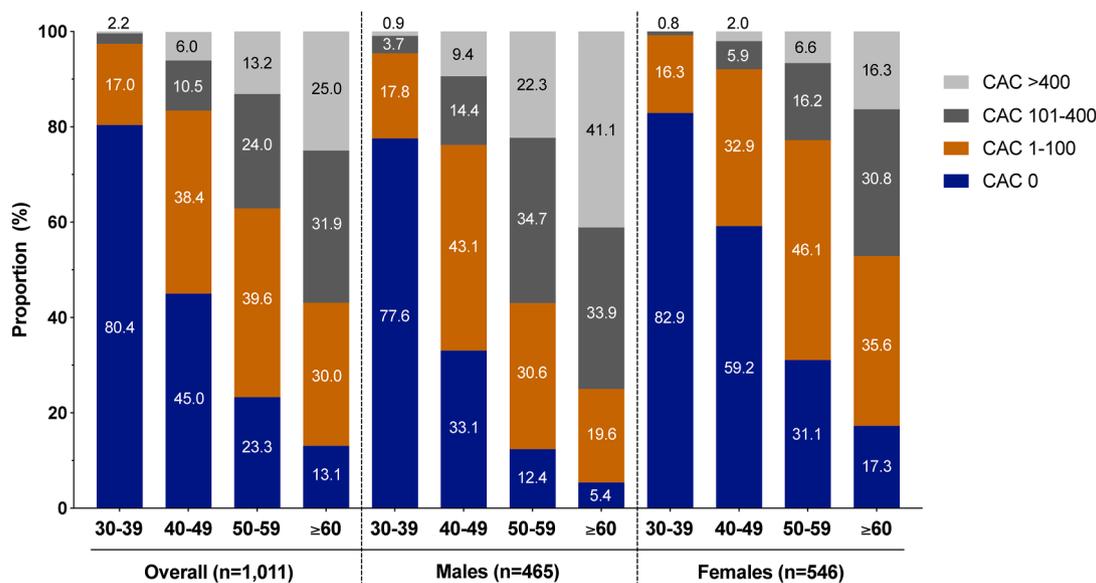


Fig. 1. Distribution of CAC scores across age- and sex-stratified subgroups of individuals with heterozygous familial hypercholesterolemia free of clinical ASCVD at baseline ($n = 1011$).

Abbreviations: CAC, coronary artery calcium

on CTA.

Previous CAC/CTA studies have assessed subclinical coronary atherosclerosis and CAD risk among adults with heterozygous FH [15, 20,21,25]. However, most of these studies were conducted in relatively small cohorts, which limits their accuracy and reliability in ascertaining the prevalence of CAC=0 between male and female patients and across different age groups. As a result, prevalence estimates of CAC=0 have varied from as low as 27% (mean age: 47 years) [34] to as high as 69% (mean age: 36 years) [35]. While a recent pooled analysis of 9 such studies ($n = 1176$) found a CAC=0 prevalence of 45% (mean age: 47 years; 53% women) [14], additional studies were deemed necessary to further stratify CAC scores by age and sex, as well as to analyze the distribution of plaque burden across CAC scores.

A recent study conducted in more than 25,000 individuals without known CHD in the general population found that any CCTA-detected atherosclerosis was present in 42.1% of individuals and that the prevalence of atherosclerosis increased with increasing CAC scores, results concurrent with the findings in our analysis. Moreover, 59.8% of the sample had CAC=0, and among those with an absence of CAC, 94.5% had no CCTA-detected atherosclerosis [36]. Similarly, in a US population of asymptomatic individuals (Miami Heart Study), the prevalence of any plaque among those with CAC zero was nearly 16% [37]. In our population, up to 20% of patients with CAC=0 had plaque on CCTA, a difference in proportions among those with CAC zero (20% in our cohort vs 5–16% in the general population) that is likely attributable to population-level differences (i.e., general population vs. patients with molecularly confirmed FH). To date, there is minimal information on the prognostic value of CAC zero in patients with FH. However, in a recently published study of nearly 622 patients (mean age: 54 years) with genetically confirmed FH and baseline mean LDL of 229 mg/dL, a similar prevalence of CAC zero (46%) was noted [38]. In this longitudinal study with a median follow-up of 13.2 years (IQR 9.8–18.4 years), the CVD event rate per 1000 person years among patients with CAC zero was reassuringly low at 1.2, with the vast majority of events occurring in those with CAC>0. While further studies will illuminate the prognostic value of those with minimal plaque in the absence of CAC among those with FH, we can extrapolate from existing data. For example, among patients with an absence of CAC and non-obstructive plaque, a recent study conducted in more than 23,000 symptomatic patients from the Western Denmark Heart Registry found that 46.2% of individuals with

severe hypercholesterolemia (LDL>190 mg/dL) had CAC=0 and, in this subgroup, the presence of non-calcified plaque was not significantly associated with higher CVD risk [39]. These emerging data are critical in further enhancing our understanding of the interplay between CAC, plaque, and adverse outcomes in this uniquely high-risk group, including whether further disease phenotyping can provide a more precision based approach for key treatment-related decisions.

As shown in prior observational studies, the extent of subclinical coronary atherosclerosis is accelerated and occurs up to three decades earlier among individuals with the FH phenotype compared to the general population [40]. Our results will facilitate the discussion whether inclusion of CAC to further stratify patients' ASCVD risk provides an opportunity for personalized risk assessment on top of LDL-C levels in order to guide the allocation of emerging and advanced therapies beyond statins [17]. In particular, data from the study by Miname et al. showed that no adverse cardiovascular events occurred over 3.7 years follow-up among statin-treated patients with an absence of CAC (constituting nearly 50% of the overall study population) and, among those with CAC 1–100 and CAC >100, patients with FH had annualized event rates of 26.4 and 44.1, respectively [15]. Although the prognostic value of CAC=0 was not assessed in the current study, we can place our findings in the context of recently published data. Conducted in more than 1600 patients with FH from the REFERCHOL and SAFEHEART national clinical registries, Gallo et al. found that the addition of CAC to the SAFEHEART risk equation downgraded risk in nearly 41% of intermediate and high-risk subjects, and was associated with an overall net reclassification improvement of approximately 45% [16]. Despite evidence of risk heterogeneity among affected individuals, current recommendations highlight the importance of early and robust cholesterol-lowering with statins and/or ezetimibe in patients with FH [10,41,42]. Incorporating long-term follow-up, as well as investigating the prognostic value of CAC=0 in younger adults, represent key research priorities that merit further investigation.

Age- and sex-specific distributions in CAC and coronary plaque have been well-established in various groups including the general population and those at-risk of adverse cardiovascular events, with an increased risk of coronary calcification and plaque burden being found consistently among older, males. However, in terms of patients with FH specifically, prior studies have been limited in their ability to perform stratified demographic analyses due to relatively smaller sample sizes,

Table 2

Overall distribution of and sex-based differences in coronary artery calcification, plaque burden, and plaque characteristics among individuals with heterozygous familial hypercholesterolemia.

| CAC/CTA Findings | Overall (n = 1011) | Males (n = 465) | Females (n = 546) |
|---|-----------------------|--------------------|----------------------|
| CAC Scores | | | |
| CAC 0 | 423 (41.8) | 161 (34.6) | 262 (48.0) |
| No Plaque | 335 (79.2) | 120 (74.5) | 215 (82.1) |
| Non-Obstructive CAD | 85 (20.1) | 40 (24.8) | 45 (17.2) |
| Obstructive CAD | 3 (0.7) | 1 (0.6) | 2 (0.8) |
| CAC 1–100 | 329 (32.5) | 145 (31.2) | 184 (33.7) |
| Non-Obstructive CAD | 288 (87.5) | 119 (82.1) | 169 (91.8) |
| Obstructive CAD | 41 (12.5) | 26 (17.9) | 15 (8.2) |
| CAC 101–400 | 160 (15.8) | 91 (19.6) | 69 (12.6) |
| Non-Obstructive CAD | 102 (63.8) | 55 (60.4) | 47 (68.1) |
| Obstructive CAD | 58 (36.3) | 36 (39.6) | 22 (31.9) |
| CAC >400 | 99 (9.8) | 68 (14.6) | 31 (5.7) |
| Non-Obstructive CAD | 39 (39.4) | 24 (35.3) | 15 (48.4) |
| Obstructive CAD | 60 (60.6) | 44 (64.7) | 16 (51.6) |
| Plaque Burden | | | |
| No Plaque | 355 (33.1) | 120 (25.8) | 215 (39.4) |
| Non-Obstructive CAD | 514 (50.8) | 238 (51.2) | 276 (50.5) |
| Obstructive CAD | 162 (16.0) | 107 (23.0) | 55 (10.1) |
| Plaque Characteristics | | | |
| No. of Vessels Compromised (n = 1001) | | | |
| 1 | 138 (13.8) | 59 (12.8) | 79 (14.7) |
| 2 | 125 (12.5) | 54 (11.7) | 71 (13.2) |
| ≥3 | 275 (27.5) | 151 (32.7) | 124 (23.0) |
| Right Coronary Artery (RCA) (n = 1001) | 341 (34.1) | 181 (39.2) | 160 (29.7) |
| Left Main (n = 1001) | 207 (20.7) | 99 (21.4) | 108 (20.0) |
| Left Anterior Descending (LAD) (n = 1001) | 442 (44.2) | 209 (45.2) | 233 (43.2) |
| Left Circumflex (LCX) (n = 1001) | 231 (23.1) | 124 (26.8) | 107 (19.9) |
| Posterior Descending Artery (n = 974) | 53 (5.4) | 36 (8.0) | 17 (3.2) |
| Diagonals (n = 974) | 149 (15.3) | 83 (18.5) | 66 (12.5) |
| Obtuse Marginals (n = 974) | 82 (8.4) | 47 (10.5) | 35 (6.7) |
| Other (n = 940) | 57 (6.1) | 38 (8.9) | 19 (3.7) |

Values presented as n (%).

Abbreviations: CAC, coronary artery calcium; CAD, coronary artery disease; CTA, computed tomography angiography.

but have found similar trends nonetheless. To our knowledge, there have been few, if any, multi-national studies conducted in more than 1000 patients with FH that have examined both CAC and CTA-derived plaque burden. Future largescale studies utilizing data from longitudinal cohorts and prospective registries are needed to assess differences in subclinical coronary atherosclerosis over time and whether the short-term favorable prognosis of CAC zero in patients with FH can be maintained in the long term. Also, the findings of this study can allow further deliberation among stakeholders on the issue of considering advanced lipid-lowering therapies beyond statins and ezetimibe among those with an absence of CAC (CAC=0), especially in circumstances where cost of medications may not be an issue.

Notably, our findings illustrate large differences in residual CAD risk among patients with treated FH. Given the costs and limited access to novel therapies such as PCSK9 inhibitors [43,44], it is essential to ensure those who are at higher ASCVD risk (those with CAC>0) and possibly those with non-obstructive, non-calcified plaques have access to add-on, non-statin lipid-lowering therapies. These findings may also be applied to shared decision-making efforts across different subgroups in which CTA results can be considered in select circumstances to ensure non-calcified plaques are ruled out prior to the consideration of more

flexible treatment goals.

4.1. Study limitations

Our study has several limitations. First, we lacked patient-level information pertaining to the individualized management of FH, including time of diagnosis, lipoprotein(a) levels, and other lipid concentrations (e.g., HDL-C, total cholesterol, and triglycerides). Moreover, the pooled data that were obtained in aggregate from participating sites precluded our ability to evaluate demographic and clinical characteristics associated with an absence of CAC and plaque burden/severity, beyond presenting descriptive statistics. Second, all patients included in this analysis were referred to specialized centers that offered CAC/CTA imaging and may not represent the general population with FH, a large group that remains largely undiagnosed and undertreated globally. Third, we used cross-sectional data, therefore, we could not assess incident MACE, temporal trends in atherosclerotic progression, and longitudinal changes in CAD risk. Fourth, changes in the sensitivity of CT imaging over time may have led to underestimates in the proportion of individuals with non-obstructive CAD at the clinical sites with earlier enrollment periods. Future studies are urgently needed to investigate the “warranty period” for CAC testing among asymptomatic and treated patients with FH, as well as to examine differences in plaque progression over time and cost-effectiveness considerations for the use of CAC testing to add on pharmacologic therapies such as PCSK9i.

5. Conclusion

In this large, multi-national study of predominantly genetically confirmed individuals with FH who were free of clinical CAD at baseline, we found significant age- and sex-based heterogeneity in coronary calcification and plaque burden. Of importance, in those without CAC, non-obstructive plaques were encountered in 20% of individuals. Future studies should investigate the determinants of relative resilience to and long-term prognostic implications of the varying burden of subclinical coronary atherosclerosis among patients with FH.

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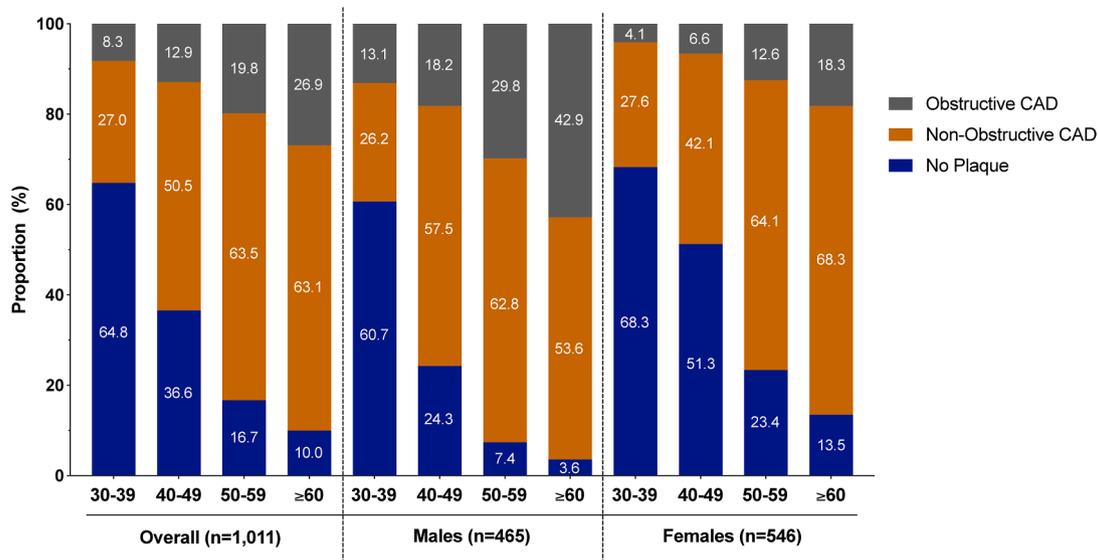


Fig. 2. Distribution of CTA-derived plaque burden scores across age- and sex-stratified subgroups of individuals with heterozygous familial hypercholesterolemia free of clinical ASCVD at baseline (n = 1011).
Abbreviations: CAD, coronary artery disease; CTA, computed tomography angiography

Table 3

Plaque burden across coronary artery calcification ranges stratified by age and sex among patients with heterozygous familial hypercholesterolemia.

| CAC Scores | Plaque Burden | Males (n = 465) | | | | Females (n = 546) | | | |
|------------------------------|---------------------|-----------------|------------|-----------|-----------|-------------------|-----------|------------|-----------|
| | | 30–39 y | 40–49y | 50–59 y | ≥60 | 30–39 y | 40–49y | 50–59 y | ≥60 |
| Overall (n = 1011) | No Plaque | 65 (60.7) | 44 (24.3) | 9 (7.4) | 2 (3.6) | 84 (68.3) | 78 (51.3) | 39 (23.4) | 14 (13.5) |
| | Non-Obstructive CAD | 28 (26.2) | 104 (57.5) | 76 (62.8) | 30 (53.6) | 34 (27.6) | 64 (42.1) | 107 (64.1) | 71 (68.3) |
| | Obstructive CAD | 14 (13.1) | 33 (18.2) | 36 (29.8) | 24 (42.9) | 5 (4.1) | 10 (6.6) | 21 (12.6) | 19 (18.3) |
| CAC 0 (n = 423) | No Plaque | 65 (78.3) | 44 (73.3) | 9 (60.0) | 2 (66.7) | 84 (82.4) | 78 (86.7) | 39 (75.0) | 14 (77.8) |
| | Non-Obstructive CAD | 18 (21.7) | 15 (25.0) | 6 (40.0) | 1 (33.3) | 18 (17.6) | 11 (12.2) | 13 (25.0) | 3 (16.7) |
| | Obstructive CAD | 0 (0) | 1 (1.7) | 0 (0) | 0 (0) | 0 (0) | 1 (1.1) | 0 (0) | 1 (5.6) |
| CAC 1–100 (n = 329) | No Plaque | — | — | — | — | — | — | — | — |
| | Non-Obstructive CAD | 8 (42.1) | 70 (89.7) | 31 (83.8) | 10 (90.9) | 16 (80.0) | 46 (92.0) | 71 (92.2) | 36 (97.3) |
| | Obstructive CAD | 11 (57.9) | 8 (10.3) | 6 (16.2) | 1 (9.1) | 4 (20.0) | 4 (8.0) | 6 (7.8) | 1 (2.7) |
| CAC 101–400 (n = 160) | No Plaque | — | — | — | — | — | — | — | — |
| | Non-Obstructive CAD | 2 (50.0) | 12 (46.2) | 31 (73.8) | 10 (52.6) | 0 (0) | 4 (44.4) | 18 (66.7) | 25 (78.1) |
| | Obstructive CAD | 2 (50.0) | 14 (53.8) | 11 (26.2) | 9 (47.4) | 1 (100.0) | 5 (55.6) | 9 (33.3) | 7 (21.9) |
| CAC >400 (n = 99) | No Plaque | — | — | — | — | — | — | — | — |
| | Non-Obstructive CAD | 0 (0) | 7 (41.2) | 8 (29.6) | 9 (39.1) | 0 (0) | 3 (100.0) | 5 (45.5) | 7 (41.2) |
| | Obstructive CAD | 1 (100.0) | 10 (58.8) | 19 (70.4) | 14 (60.9) | 0 (0) | 0 (0) | 6 (54.5) | 10 (58.8) |

Values presented as n (%).

Abbreviations: CAC, coronary artery calcium; CAD, coronary artery disease.

Danone, Amarin, Akcea, Servier, MYLAN, Silence Therapeutic. Dr. Miname has received honoraria for speaker activities from Amgen. Other authors report no disclosures.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.ajpc.2023.100611](https://doi.org/10.1016/j.ajpc.2023.100611).

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