American Journal of Preventive Cardiology 17 (2024) 100611

Contents lists available at ScienceDirect

American Journal of Preventive Cardiology

journal homepage: www.journals.elsevier.com/american-journal-of-preventive-cardiology

Original Research

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

Khurram Nasir [a,1,*], Reed Mszar [b,1], Miguel Cainzos-Achirica [c], Gowtham R. Grandhi [d], Tycho R. Tromp [e], Rodrigo Alonso [f,g], Márcio S. Bittencourt [h], Eric Bruckert [i], José Luis Díaz-Díaz [j], Antonio Gallo [i], G. Kees Hovingh [e], Marcio H. Miname [k], Ovidio Muñiz-Grijalvo [l], Jing Pang [m], Leopoldo Perez de Isla [n], Eric J.G. Sijbrands [o], Gerald F. Watts [m], Pedro Mata [g,2], Raul D. Santos [k,p,2]

[a] Houston Methodist DeBakey Heart & Vascular Center, Houston, TX, USA
[b] Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, CT, USA
[c] Department of Cardiology, Hospital del Mar / Parc de Salut Mar, Barcelona, Spain
[d] Virginia Commonwealth University Health Pauley Heart Center, Richmond, VA, USA
[e] Department of Vascular Medicine, Amsterdam UMC, location AMC, Amsterdam, the Netherlands
[f] Center for Advanced Metabolic Medicine and Nutrition, Santiago, Chile
[g] Fundación Hipercolesterolemia Familiar, Madrid, Spain
[h] Division of Internal Medicine, University Hospital, University of São Paulo, São Paulo, Brazil
[i] Sorbonne Université, INSERM UMR1166, Lipidology and Cardiovascular Prevention Unit, Department of Nutrition, APHP, Hôpital Pitié-Salpètrière, Paris, France
[j] Complejo Hospitalario Universitario, Hospital Abente y Lago, A Corūna, Spain
[k] Heart Institute (INCOR), University of São Paulo Medical School Hospital, São Paulo, Brazil
[l] Internal Medicine Department, Hospital Virgen del Rocío, Sevilla, Spain
[m] School of Medicine, University of Western Australia, Department of Cardiology, Royal Perth Hospital, Western Australia, Australia
[n] Cardiology Department, Hospital Clinico San Carlos, IDISSC, Facultad de Medicina, Universidad Complutense, Madrid, Spain
[o] Department of Internal Medicine, Section Pharmacology, Vascular and Metabolic Diseases, Erasmus University Medical Center, Rotterdam, the Netherlands
[p] Hospital Israelita Albert Einstein, São Paulo, Brazil

* Corresponding author at: Division of Cardiovascular Prevention and Wellness, Houston Methodist DeBakey Heart and Vascular Center, Center for Outcomes Research, Houston Methodist, 6550 Fannin St, Suite 1801, Houston, TX, 77030.
E-mail address: knasir@houstonmethodist.org (K. Nasir).
[1] Dr. Nasir and Mr. Mszar are co-first authors.
[2] Drs. Mata and Santos are co-senior authors.

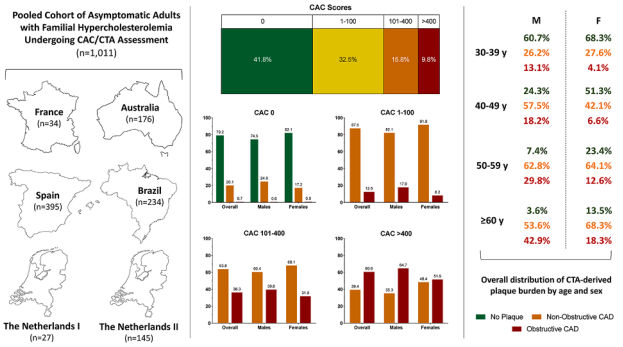
https://doi.org/10.1016/j.ajpc.2023.100611

Available online 23 November 2023

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 heterogenous 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



ARTICLE INFO

Key Words:
Atherosclerotic cardiovascular disease
Coronary artery calcium
Familial hypercholesterolemia
Low-density lipoprotein cholesterol
Plaque burden

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 (≥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 (± 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 ≥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 ($n = 1007$)	961 (95.1)	437 (94.0)	524 (96.0)
LDLR	893 (88.3)	411 (88.4)	482 (88.3)
APOB	63 (6.2)	24 (5.2)	39 (7.1)
PCSK9	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

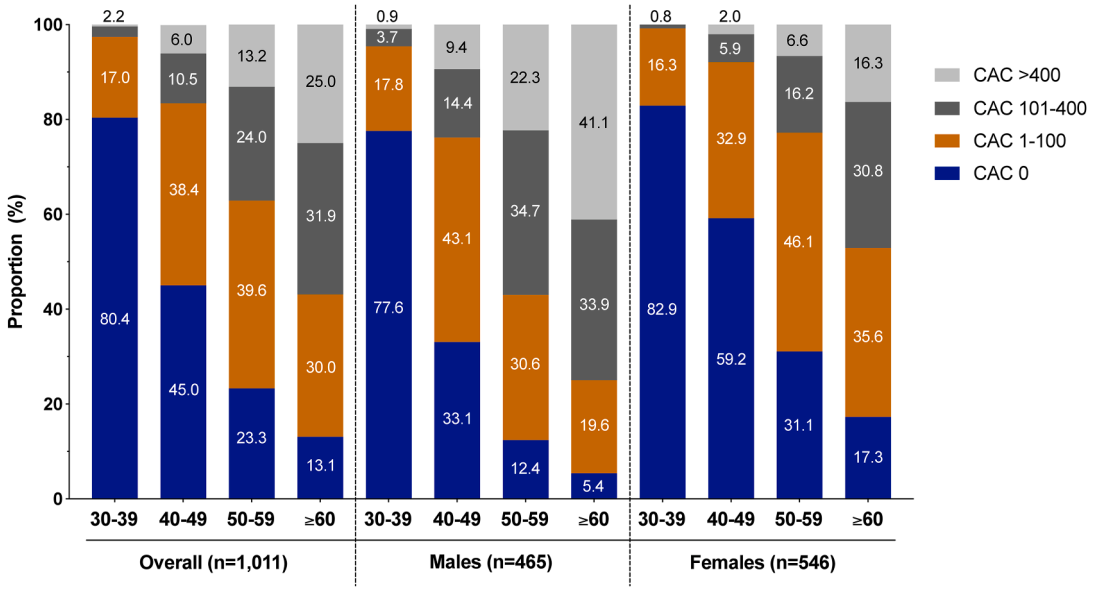


Fig. 1. Distribution of CAC scores across age- and sex-stratified subgroups of individuals with heterozygous familial hypercholesterolemia free of clinical ASCVD at baseline (n = 1011).
Abbreviations: CAC, coronary artery calcium

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.

Funding

None.

Declaration of Competing Interest

Dr. Nasir is supported by the Katz Academy for Translational Research. Dr. Santos received honoraria for consulting, speaker activities and research from Abbott, Ache, Amgen, Astra Zeneca, EMS, Hypera, Libbs, Esperion, Kowa, Getz pharma, PTC therapeutics, Novo-Nordisk, Novartis, Merck, MSD, Pfizer, and Sanofi, he also receives a research scholarship from Conselho Nacional de Pesquisa e Desenvolvimento Tecnológico, Brazil, (CNPq) #303734/2018-3. Dr. Watts has received honoraria related to consulting, research and/or speaker activities from: Amgen, Arrowhead, AstraZeneca, Esperion, Kowa, Novartis, and Sanofi/Regeneron. Dr. Hovingh reports research grants from the Netherlands Organization for Scientific Research (vidi 016.156.445), CardioVascular Research Initiative, European Union and the Klinkerpad fonds, institutional research support from Aegerion, Amgen, AstraZeneca, Eli Lilly, Genzyme, Ionis, Kowa, Pfizer, Regeneron, Roche, Sanofi, and The Medicines Company; speaker's bureau and consulting fees from Amgen, Aegerion, Sanofi, and Regeneron until April 2019 (fees paid to the academic institution); and part-time employment at Novo-Nordisk A/S, Denmark since April 2019. Dr. Gallo has received grants and personal fees from Amgen, Sanofi and Regeneron, Mylan Viatris, MSD, Akcea Therapeutics, Amryt, Novartis, Servier, Eli Lilly, Ultragenyx. Dr. Sijbrands has received a research grants from Amgen and the European Union. Dr. Bruckert has received honoraria from Amgen, Genfit, MSD, Sanofi-Regeneron, Novartis,

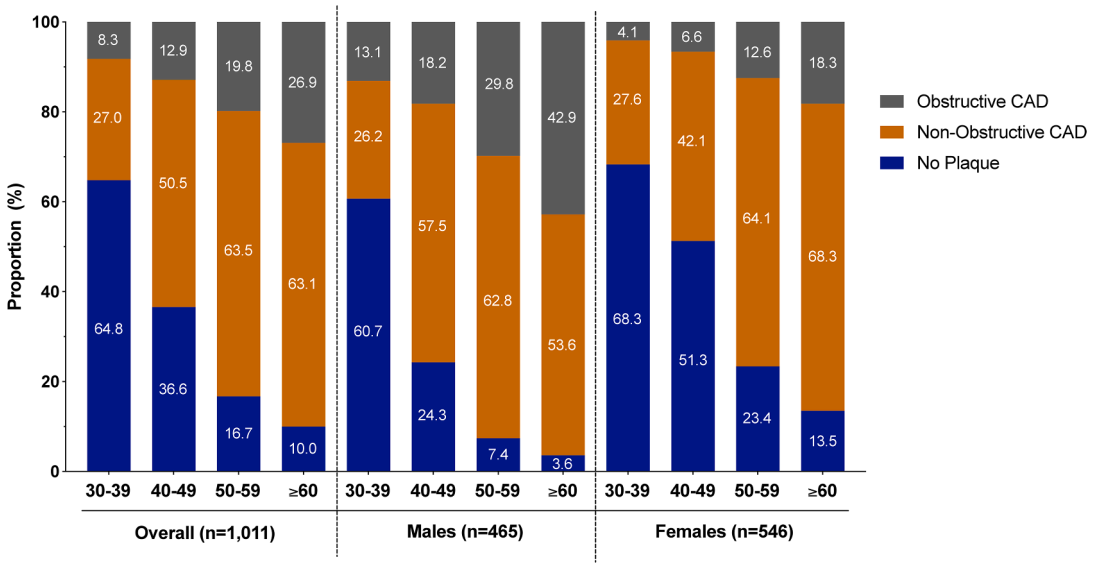


Fig. 2. Distribution of CTA-derived plaque burden scores across age- and sex-stratified subgroups of individuals with heterozygous familial hypercholesterolemia free of clinical ASCVD at baseline ($n = 1011$).
Abbreviations: CAD, coronary artery disease; CTA, computed tomography angiography

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.

References

[1] Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, Wiklund O, Hegele RA, Raal FJ, Defesche JC, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J 2013;34:3478–3490a.

[2] Gidding SS, Champagne MA, de Ferranti SD, Defesche J, Ito MK, Knowles JW, McCrindle B, Raal F, Rader D, Santos RD, et al. The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association. Circulation 2015;132:2167–92.

[3] Perez-Calahorra S, Laclaustra M, Marco-Benedi V, Lamiquiz-Moneo I, Pedro-Botet J, Plana N, Sanchez-Hernandez RM, Amor AJ, Almagro F, Fuentes F, et al. Effect of lipid-lowering treatment in cardiovascular disease prevalence in familial hypercholesterolemia. Atherosclerosis 2019;284:245–52.

[4] Versmissen J, Oosterveer DM, Yazdanpanah M, Defesche JC, Basart DC, Liem AH, Heeringa J, Witteman JC, Lansberg PJ, Kastelein JJ, et al. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. BMJ 2008;337:a2423.

[5] Humphries SE, Cooper JA, Seed M, Capps N, Durrington PN, Jones B, McDowell IFW, Soran H, Neil HAW. Simon Broome Familial Hyperlipidaemia Register G. Coronary heart disease mortality in treated familial hypercholesterolaemia: update of the UK Simon Broome FH register. Atherosclerosis 2018;274:41–6.

[6] Umans-Eckenhausen MA, Sijbrands EJ, Kastelein JJ, Defesche JC. Low-density lipoprotein receptor gene mutations and cardiovascular risk in a large genetic cascade screening population. Circulation 2002;106(24):3031–6.

[7] Wilemon KA, Patel J, Aguilar-Salinas C, Ahmed CD, Alkhnifsawi M, Almahmeed W, Alonso R, Al-Rasadi K, Badimon L, Bernal LM, et al. Reducing the Clinical and Public Health Burden of Familial Hypercholesterolemia. JAMA Cardiol 2020;5:217–29.

[8] Besseling J, Hovingh GK, Huijgen R, Kastelein JJP, Hutten BA. Statins in Familial Hypercholesterolemia: consequences for Coronary Artery Disease and All-Cause Mortality. J Am Coll Cardiol 2016;68(3):252–60.

[9] Santos RD, Gidding SS, Hegele RA, Cuchel MA, Barter PJ, Watts GF, Baum SJ, Catapano AL, Chapman MJ, Defesche JC, et al. Defining severe familial hypercholesterolaemia and the implications for clinical management: a consensus

statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel. Lancet Diabet Endocrinol 2016;4(10):850–61.
[10] Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a Report of the American College of Cardiology/American Heart association task force on clinical practice guidelines. Circulation 2019;139:e1082–143.
[11] Miname MH, Bittencourt MS, Nasir K, Santos RD. Subclinical coronary atherosclerosis and cardiovascular risk stratification in heterozygous familial hypercholesterolemia patients undergoing statin treatment. Curr Opin Lipidol 2019;30(2):82–7.
[12] Mortensen MB, Falk E, Li D, Nasir K, Blaha MJ, Sandfort V, Rodriguez CJ, Ouyang P, Budoff M. Statin trials, cardiovascular events, and coronary artery calcification: implications for a trial-based approach to statin therapy in MESA. J Am Coll Cardiol Img 2018;11(2 Pt 1):221–30.
[13] Sarwar A, Shaw LJ, Shapiro MD, Blankstein R, Hoffmann U, Cury RC, Abbara S, Brady TJ, Budoff MJ, Blumenthal RS, et al. Diagnostic and prognostic value of absence of coronary artery calcification. J Am Coll Cardiol Img 2009;2(6):675–88.
[14] Mszar R, Grandhi GR, Valero-Elizondo J, Virani SS, Blankstein R, Blaha M, Mata P, Miname MH, Al Rasadi K, Krumholz HM, et al. Absence of coronary artery calcification in middle aged familial hypercholesterolemia patients without atherosclerotic cardiovascular disease. J Am Coll Cardiol Img 2020;13:1090–2.
[15] Miname MH, Bittencourt MS, Moraes SR, Alves RIM, Silva PRS, Jannes CE, Pereira AC, Krieger JE, Nasir K, Santos RD. Coronary artery calcium and cardiovascular events in patients with familial hypercholesterolemia receiving standard lipid-lowering therapy. J Am Coll Cardiol Img 2019;12:1797–804.
[16] Gallo A, Perez de Isla L, Charriere S, Vimont A, Alonso R, Muniz-Grijalvo O, Diaz-Diaz JL, Zambon D, Moulin P, Bruckert E, et al. The added value of coronary calcium score in predicting cardiovascular events in familial hypercholesterolemia. JACC Cardiovasc Imaging 2021.
[17] Mszar R, Nasir K, Santos RD. Coronary Artery Calcification in Familial Hypercholesterolemia: an Opportunity for Risk Assessment and Shared Decision Making With the Power of Zero? Circulation 2020;142(15):1405–7.
[18] Gallo A, Mszar R, Miname MH. Updates on the use of subclinical atherosclerosis to predict risk of cardiovascular events in heterozygous familial hypercholesterolemia. Curr Atheroscler Rep 2022;24(6):407–18.
[19] Cainzos-Achirica M, Quispe R, Mszar R, Dudum R, Al Rifai M, Erbel R, et al. Coronary Artery Calcium Score to Refine the Use of PCSK9i in Asymptomatic Individuals: A Multicohort Study. J Am Heart Assoc 2022;11(16):e025737.
[20] Perez de Isla L, Alonso R, Muniz-Grijalvo O, Diaz-Diaz JL, Zambon D, Miramontes JP, Fuentes F, Gomez de Diego JJ, Gonzalez-Estrada A, Mata N, et al. Coronary computed tomographic angiography findings and their therapeutic implications in asymptomatic patients with familial hypercholesterolemia. Lessons from the SAFEHEART study. J Clin Lipidol 2018;12:948–57.
[21] Vongpromek R, Bos S, Ten Kate GR, Bujo H, Jiang M, Nieman K, Schneider W, Roeters van Lennep JE, Verhoeven AJM, Sijbrands EJG, et al. Soluble LR11 associates with aortic root calcification in asymptomatic treated male patients with familial hypercholesterolemia. Atherosclerosis 2017;265:299–304.
[22] Bos S, Duvekot MH, Ten Kate GR, Verhoeven AJ, Mulder MT, Schinkel AF, Nieman K, Watts GF, Sijbrands EJ, Roeters van Lennep JE. Carotid artery plaques and intima medial thickness in familial hypercholesteraemic patients on long-term statin therapy: a case control study. Atherosclerosis 2017;256:62–6.
[23] Santos R, Meneghelo R, Chacra A, Martinez T, Ramires J, Carvalho J. Detection of subclinical atherosclerosis by electron beam tomography in females with heterozygous familial hypercholesterolaemia. Heart 2004;90(1):92–4.
[24] Pang J, Abraham A, Vargas-Garcia C, Bates TR, Chan DC, Hooper AJ, Bell DA, Burnett JR, Schultz CJ, Watts GF. An age-matched computed tomography angiographic study of coronary atherosclerotic plaques in patients with familial hypercholesterolaemia. Atherosclerosis 2020;298:52–7.
[25] Gallo A, Giral P, Carrie A, Carreau V, Beliard S, Bittar R, Maranghi M, Arca M, Cluzel P, Redheuil A, et al. Early coronary calcifications are related to cholesterol burden in heterozygous familial hypercholesterolemia. J Clin Lipidol 2017;11(3):704–11. e702.
[26] Bell DA, Pang J, Burrows S, Bates TR, van Bockxmeer FM, Hooper AJ, O'Leary P, Burnett JR, Watts GF. Effectiveness of genetic cascade screening for familial hypercholesterolaemia using a centrally co-ordinated clinical service: an Australian experience. Atherosclerosis 2015;239(1):93–100.
[27] Chan DC, Pang J, Hooper AJ, Bell DA, Bates TR, Burnett JR, Watts GF. A comparative analysis of phenotypic predictors of mutations in familial hypercholesterolemia. J Clin Endocrinol Metab 2018;103(4):1704–14.
[28] Jannes CE, Santos RD, de Souza Silva PR, Turolla L, Gagliardi AC, Marsiglia JD, Chacra AP, Miname MH, Rocha VZ, Filho WS, et al. Familial hypercholesterolemia in Brazil: cascade screening program, clinical and genetic aspects. Atherosclerosis 2015;238(1):101–7.
[29] Ten Kate GJ, Neefjes LA, Dedic A, Nieman K, Langendonk JG, Galema-Boers AJ, Roeters van Lennep J, Moelker A, Krestin GP, Sijbrands EJ, et al. The effect of LDLR-negative genotype on CT coronary atherosclerosis in asymptomatic statin treated patients with heterozygous familial hypercholesterolemia. Atherosclerosis 2013;227(2):334–41.
[30] Perez de Isla L, Alonso R, Gomez de Diego JJ, Muniz-Grijalvo O, Diaz-Diaz JL, Zambon D, Miramontes JP, Fuentes F, de Andres R, Werenitzky J, et al. Coronary plaque burden, plaque characterization and their prognostic implications in familial hypercholesterolemia: a computed tomographic angiography study. Atherosclerosis 2021;317:52–8.
[31] Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15(4):827–32.
[32] Leipsic J, Abbara S, Achenbach S, Cury R, Earls JP, Mancini GJ, Nieman K, Pontone G, Raff GL. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. J Cardiovasc Comput Tomogr 2014;8(5):342–58.
[33] Nasir K, Bittencourt MS, Blaha MJ, Blankstein R, Agatson AS, Rivera JJ, Miedema MD, Sibley CT, Shaw LJ, Blumenthal RS, et al. Implications of coronary artery calcium testing among statin candidates according to American College of Cardiology/American Heart Association cholesterol management guidelines: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2015;66(15):1657–68.
[34] Descamps OS, Gilbeau J-P, Luwaert R, Heller FR. Impact of genetic defects on coronary atherosclerosis in patients suspected of having familial hypercholesterolaemia. Eur J Clin Invest 2003;33(1):1–9.
[35] Ye Z-X, Cheng H-M, Chiou K-R, Huang P-H, Lin S-J, Charng M-J. Relation of coronary artery calcium to flow-mediated dilation and C-reactive protein levels in asymptomatic patients with heterozygous familial hypercholesterolemia. Am J Cardiol 2007;100(7):1119–23.
[36] Bergstrom G, Persson M, Adiels M, Bjornson E, Bonander C, Ahlstrom H, Alfredsson J, Angeras O, Berglund G, Blomberg A, et al. Prevalence of subclinical coronary artery atherosclerosis in the general population. Circulation 2021;144(12):916–29.
[37] Nasir K, Cainzos Achirica M, Valero-Elizondo J, Ali SS, Havistin R, Lakshman S, Blaha MJ, Blankstein R, Shapiro MD, Arias L, et al. Coronary atherosclerosis in an asymptomatic US Population: Miami Heart Study of Baptist Health South Florida. JACC Cardiovasc Imaging 2022 (In-Press).
[38] Tada H, Kojima N, Yamagami K, Nomura A, Nohara A, Usui S, Sakata K, Hayashi K, Fujino N, Takamura M, et al. Coronary artery calcium among patients with heterozygous familial hypercholesterolaemia. Eur Heart J Open 2023;3(3):oead046.
[39] Mortensen MB, Cainzos-Achirica M, Steffensen FH, Botker HE, Jensen JM, Sand NPR, Maeng M, Bruun JM, Blaha MJ, Sorensen HT, et al. Association of coronary plaque with low-density lipoprotein cholesterol levels and rates of cardiovascular disease events among symptomatic adults. JAMA Netw Open 2022;5(2):e2148139.
[40] Perak AM, Ning H, de Ferranti SD, Gooding HC, Wilkins JT, Lloyd-Jones DM. Long-term risk of atherosclerotic cardiovascular disease in US adults with the familial hypercholesterolemia phenotype. Circulation 2016;134(1):9–19.
[41] Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41(1):111–88.
[42] Luirink IK, Wiegman A, Kusters DM, Hof MH, Groothoff JW, de Groot E, Kastelein JJP, Hutten BA. 20-year follow-up of statins in children with familial hypercholesterolemia. N Engl J Med 2019;381(16):1547–56.
[43] Baum SJ, Toth PP, Underberg JA, Jellinger P, Ross J, Wilemon K. PCSK9 inhibitor access barriers-issues and recommendations: improving the access process for patients, clinicians and payers. Clin Cardiol 2017;40(4):243–54.
[44] Myers KD, Farboodi N, Mwamburi M, Howard W, Staszak D, Gidding S, Baum SJ, Wilemon K, Rader DJ. Effect of access to prescribed PCSK9 inhibitors on cardiovascular outcomes. Circ Cardiovasc Qual Outcomes 2019;12:e005404.