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ORIGINAL RESEARCH

Coronary Artery Calcium Score to Refine the Use of PCSK9i in Asymptomatic Individuals: A Multicohort Study

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BACKGROUND: The value of coronary artery calcium (CAC) in the allocation of PCSK9i (proprotein convertase subtilisin/kexin type 9 inhibitors) among individuals without clinically evident atherosclerotic cardiovascular disease (ASCVD) is unknown for indications that do not require confirmed familial hypercholesterolemia. We aimed to assess the ability of CAC to stratify ASCVD risk under 3 non–familial hypercholesterolemia PCSK9i allocation paradigms.

METHODS AND RESULTS: We included participants without clinically evident ASCVD from MESA (Multi-Ethnic Study of Atherosclerosis), CARDIA (Coronary Artery Risk Development in Young Adults) study, DHS (Dallas Heart Study), and HNR (Heinz Nixdorf Recall) study. Three PCSK9i eligibility scenarios were defined: a broad scenario informed only by high low-density lipoprotein cholesterol levels (N=567), a restrictive one combining higher low-density lipoprotein cholesterol levels and presence of ≥2 additional risk factors (N=127), and a high-risk scenario where individuals with subclinical organ damage or high estimated risk would be treated to achieve low-density lipoprotein cholesterol <55 mg/dL (N=471). The high-risk scenario had the highest ASCVD event rates (27.8% at 10 years). CAC=0 was observed in 35% participants in the broad scenario, 25% in the restrictive scenario, and 16% in the high-risk scenario. In all, CAC=0 was associated with the lowest incident ASCVD rates at 5 and 10 years, and CAC burden was independently associated with ASCVD events adjusting for traditional risk factors.

CONCLUSIONS: CAC may be used to refine the allocation of PCSK9i, potentially leading to a more conservative use if CAC=0. The value of CAC testing is greater in scenarios that use low-density lipoprotein cholesterol levels and/or traditional risk factors to define PCSK9i eligibility (CAC=0 present in 1 of 3–4 patients), whereas its prevalence is lower when allocation is informed by presence of noncoronary subclinical organ damage.

Key Words: atherosclerosis ■ cardiovascular disease ■ coronary artery calcium ■ PCSK9i ■ primary prevention ■ risk

Cumulative exposure to high low-density lipoprotein cholesterol (LDL-C) levels is a powerful causal factor of atherosclerotic cardiovascular disease (ASCVD).[1,2] Consequently, there is growing interest in using pharmacotherapies that can achieve large reductions in "LDL-C years," as means to expand the lifespan free of clinical ASCVD and the burden of disease in the general population.[3,4]

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CLINICAL PERSPECTIVE

What Is New?

- The burden of coronary artery calcium had not been described among individuals who may qualify for PCSK9i (proprotein convertase subtilisin/kexin type 9 inhibitor) therapy for primary prevention indications other than familial hypercholesterolemia.
- Across 3 scenarios for PCSK9i allocation in primary prevention, coronary artery calcium (CAC) stratified atherosclerotic cardiovascular disease risk and was independently associated with atherosclerotic cardiovascular disease events.

What Are the Clinical Implications?

- CAC may be used to further refine the allocation of PCSK9i in this setting, potentially leading to a more conservative use if CAC=0.
- The value of CAC testing for identifying CAC=0 is greater in scenarios that use low-density lipoprotein cholesterol levels and/or traditional risk factors to define PCSK9i eligibility (present in 1 of 3–4 patients), whereas the prevalence of CAC=0 is lower when allocation is informed by presence of noncoronary subclinical organ damage.

Nonstandard Abbreviations and Acronyms

ACC	American College of Cardiology
AHA	American Heart Association
CARDIA	Coronary Artery Risk Development in Young Adults
DHS	Dallas Heart Study
ESC	European Society of Cardiology
FH	familial hypercholesterolemia
HNR	Heinz Nixdorf Recall
MESA	Multi-Ethnic Study of Atherosclerosis
MS	Multi-Society
PCSK9i	proprotein convertase subtilisin/kexin type 9 inhibitors

Besides individuals with familial hypercholesterolemia (FH), different paradigms have been proposed to identify additional good candidates for large LDL-C reductions with PCSK9i (proprotein convertase subtilisin/kexin type 9 inhibitors) and similar therapies among individuals without clinically evident ASCVD. A first, broader paradigm would use high LDL-C levels as the main allocation criterion.[3] A second, more restrictive approach would prioritize these therapies among individuals with either extremely high LDL-C levels or high levels plus several other risk factors for ASCVD. This second paradigm resembles the 2018 American Heart Association/American College of Cardiology/Multi-Society (AHA/ACC/MS) recommendations for consideration of PCSK9i among individuals without confirmed FH.[5] A third paradigm was proposed in the 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society Dyslipidemia Guidelines, where consideration of PCSK9i therapy was recommended among individuals with no confirmed FH or clinical ASCVD but who are at high risk of ASCVD events (typically on the basis of subclinical target organ damage) and who have on-treatment LDL-C levels ≥55 mg/dL.[6]

The coronary artery calcium (CAC) score is endorsed across multiple guidelines for personalized allocation of statin therapy in primary prevention.[5–7] CAC has also been recently proposed as a tool that may help inform a targeted allocation of several other interventions.[8–11] In contrast, the value of CAC in refining the allocation of PCSK9i among non-FH potential candidates for therapy is unknown. Defining this is important: in a context of limited resources, PCSK9i remain underused,[12–14] and moving forward, identifying potential candidates at lower absolute risk can enrich shared decision-making discussions and inform a more cost-effective allocation of these therapies.

To fill this knowledge gap, we pooled a multiethnic, geographically diverse cohort of potential PCSK9i candidates without clinically evident ASCVD from the general population. The aims of the present study were to (1) assess the ability of the CAC score to stratify ASCVD risk in the context of 3 different PCSK9i allocation paradigms among middle-aged or older individuals without clinically evident ASCVD and (2) evaluate the independent associations between CAC and incident ASCVD events in this setting.

METHODS

A detailed description of the research methods used is presented below. Requests to access the study data sets from qualified researchers trained in human subject confidentiality protocols may be sent to the respective Coordinating Centers of each study. The analyses that support the findings of the present study are available from the corresponding author on reasonable request.

Study Design and Cohorts

This was a pooled cohort study combining individual-level data from 4 large prospective cohort studies of adults without a history of ASCVD at baseline, from the United States (MESA [Multi-Ethnic Study of Atherosclerosis],[15] CARDIA [Coronary Artery Risk Development in Young Adults] study,[16] and DHS [Dallas Heart Study])[17] and Europe (HNR [Heinz Nixdorf Recall]

study).[18] Details of each of these cohorts have been published previously,[15–18] and a summary is provided in Data S1. The 4 studies were approved by institutional review committees, and all participants provided written informed consent before enrollment.

In MESA, HNR, and DHS, CAC was quantified for the first time at the respective baseline study visits (between years 2000 and 2002 in MESA and DHS, and between years 2000 and 2003 in HNR).[15–18] In CARDIA study, CAC was measured for the first time at the year 15 follow-up visit (years 2000–2001). For this pooled analysis, the study baseline was defined for each participant at the time of his/her first study CAC scan.

Study Population and PCSK9i Eligibility Scenarios

Three scenarios were defined, aimed at assessing the potential value of CAC for refining the allocation of PCSK9i therapy in the context of 3 different allocation paradigms. Details on the calculations used to define the LDL-C thresholds in each of these scenarios are described in Data S1.[19]

The "LDL-C–based broad" scenario was defined aimed at assessing the value of CAC when consideration of PCSK9i therapy is driven solely by LDL-C levels, regardless of burden of traditional risk factors and/or subclinical disease. To make this scenario as broad as possible, we used an on-treatment LDL-C threshold ≥97 mg/dL among statin users to define PCSK9i eligibility and did not require pretreatment with ezetimibe. These 2 features were inspired by the recent 2021 Canadian Dyslipidemia guidelines, which used this on-treatment threshold for consideration of PCSK9i in patients with FH and did not require pretreatment with ezetimibe.[7] The on-treatment threshold of LDL-C ≥97 mg/dL is lower than the ≥100- and ≥130-mg/dL thresholds used in the AHA/ACC/MS guideline,[5] and both the AHA/ACC/MS and the ESC/European Atherosclerosis Society guidelines required pretreatment with both statins and ezetimibe before considering PCSK9i therapy in candidates with and without FH.[5,6] The specific calculations performed are summarized in Data S1; all participants with either LDL-C ≥194 mg/dL (statin naïve) or LDL-C ≥136 mg/dL on a statin were included in this scenario.

The "restrictive" scenario aimed at evaluating the value of CAC when either extremely high LDL-C levels or the combination of high LDL-C and traditional risk factor burden drive the consideration of PCSK9i therapy. This scenario was inspired by non-FH indications in the 2018 AHA/ACC/MS guidelines,[8] and included (1) participants with either baseline LDL-C levels of ≥371 mg/dL or LDL-C levels of ≥184 mg/dL and prevalent statin use; and (2) participants with either LDL-C levels ≥286 or ≥142 mg/dL and prevalent statin use, and "multiple factors that increase subsequent risk of ASCVD events."[5] We defined the latter as having ≥2 of the following: age ≥55 years in men or ≥65 years in women, hypertension, diabetes, obesity, active smoking, and estimated glomerular filtration rate <60 mL/min per 1.73 m^2.

The "high-risk" scenario evaluated the utility of CAC when PCSK9i are used to achieve low LDL-C levels (<55 mg/dL) in high-risk individuals without clinically evident ASCVD.[6] This scenario was inspired by the high-risk recommendation in non-FH individuals included in the 2019 ESC/European Atherosclerosis Society guidelines, and included participants with either LDL-C ≥158 mg/dL (statin naïve) or LDL-C ≥78 mg/dL and prevalent statin use, who had any of the following "high-risk" characteristics: (1) diabetes and albuminuria; (2) diabetes and estimated glomerular filtration rate <60 mL/min per 1.73 m^2; (3) diabetes plus ≥3 additional "major risk factors"; (4) estimated glomerular filtration rate <30 mL/min per 1.73 m^2; (5) ankle-brachial index <0.9 (evaluated in MESA and HNR); (6) carotid stenosis ≥50% (evaluated using carotid ultrasound in MESA and HNR); and (7) estimated 10-year ASCVD risk ≥30% using the Pooled Cohort Equations (as a proxy of a SCORE (Systematic Coronary Risk Evaluation)-based estimated risk ≥10% for fatal events).[6] From now on and for the sake of brevity, we will refer to features 1, 2, and 4 to 6 as "subclinical organ damage."

In all scenarios, we excluded participants with clinical ASCVD at baseline, those with missing CAC scores, and those with missing information on incident ASCVD events. In HNR, we also excluded participants who had not fasted for ≥8 hours before the baseline blood tests were performed.

Measurements and Definitions of Risk Factors

Levels of LDL-C were calculated using the Friedewald equation,[20] except in HNR, where they were measured using enzymatic methods.[18] Diabetes was defined as self-report, use of diabetes medications, fasting plasma glucose levels ≥126 mg/dL, or glycosylated hemoglobin levels ≥6.5%.[21] The latter was only available in HNR at the time of the CAC scan.[22] Hypertension was defined as blood pressure ≥130 mm Hg systolic or ≥80 mm Hg diastolic or use of antihypertensive medications.[23] Obesity was defined as a body mass index ≥30 kg/m^2. Albuminuria was defined as urine albumin levels of either ≥30 mg/24 h or ≥30 μg/mg urine creatinine,[21] and was measured in all cohorts except for DHS. The ankle-brachial index and presence and degree of carotid stenosis using ultrasound imaging were measured at baseline in both HNR and MESA using standard procedures.[24–26] Because most participants were from the United States, the 10-year risk of having an ASCVD event was estimated in all participants using the Pooled Cohort Equations.[8]

CAC Scores

Per inclusion criteria, all participants in the present analysis had undergone baseline CAC scanning. The Agatston method was used in all 4 cohorts for CAC quantification.[27] Scores were categorized as CAC=0, CAC >0 to ≤100, and CAC >100.

Study Outcomes

Follow-up and event ascertainment methods were similar across cohorts and have been reported previously.[15–18] For the present analysis, the outcome of interest was defined as a composite ASCVD end point including cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, unstable angina, and coronary revascularization.[28]

Statistical Analysis

The baseline characteristics of the participants included in each of the PCSK9i eligibility scenarios were described. Categorical variables were summarized using number (percentage), and continuous variables were summarized using mean (±SD) for normally distributed variables and median (interquartile range) otherwise. Normality was inspected graphically. We also described the prevalence of CAC categories in each subpopulation. Baseline characteristics further stratified by CAC burden were reported as well.

We used Kaplan-Meier survival functions to generate 5- and 10-year cumulative incidence estimates of ASCVD events. These were computed overall in each of the 3 scenarios, and by baseline CAC strata in each of them. Crude incidence rates were also computed (expressed per 1000 person-years and with 95% CIs) using all person-time data available for each participant.

Cox regression models were used to evaluate the associations between higher CAC scores (compared with CAC=0) and incident ASCVD events. We used 3 progressively adjusted models: model 1 was unadjusted; model 2 adjusted for age, sex, race and ethnicity, and study cohort; and model 3 further adjusted for systolic and diastolic blood pressure, hypertension medication use, tobacco use, LDL-C, high-density lipoprotein cholesterol, statin use, other cholesterol medication use, and diabetes. This analysis was not pursued in the restrictive scenario as it was expected to include a small number of participants.

All statistical analyses were conducted using Stata software, version 16.

RESULTS

Study Participants

The study included 944 participants without clinically evident ASCVD who would meet eligibility criteria in at least 1 of the 3 scenarios evaluated. MESA contributed 469 participants (49.7%), 65 were CARDIA study participants (6.9%), 41 were from DHS (4.3%), and 369 were from HNR study (39.1%). A total of 567 participants were included in the LDL-C–based broad scenario, 127 individuals were included in the restrictive scenario, and 471 were included in the high-risk scenario (not mutually exclusive).

Table S1 displays the number of participants from each cohort included in each of the 3 allocation scenarios. Table S2 confirms that the characteristics of HNR participants who were excluded because of nonfasting at the time of the blood tests were roughly similar to those who were fasting.

Baseline Characteristics

Median age ranged from 59 years (LDL-C–based broad scenario) to 69 years (high-risk scenario; Table 1). The proportion of women was slightly higher than men, and non-Hispanic White individuals comprised most participants. The highest baseline use of statins was observed in the restrictive scenario (97.6%; mean LDL-C level, 169 mg/dL) and the lowest in the LDL-C–based broad scenario (36%; mean LDL-C level, 195 mg/dL). Individuals in the high-risk subpopulation had the highest prevalence of diabetes (53.5%), hypertension (90%), and obesity (43.5%), whereas the mean LDL-C levels were the lowest across the 3 scenarios (147 mg/dL).

Compared with higher CAC scores, a CAC score of 0 was associated with younger age and female sex, and with a lower burden of some traditional risk factors (eg, diabetes) in some but not all scenarios (Tables S3 through S5).

Interplay Between PCSK9i Eligibility and CAC

Of 3 participants in the LDL-C–based broad scenario, 1 had CAC=0 at baseline, and this was 1 of 4 in the restrictive scenario (Figure 1). In the high-risk scenario, the CAC=0 stratum was smallest, although this finding was still observed in 15.9% of participants. The latter was the scenario with the largest CAC >100 stratum (51.8%) as well as with any CAC.

Incident ASCVD Events

The results for cumulative incidence of ASCVD events at 5 and 10 years and crude event rates per 1000 person-years using all follow-up data available all yielded consistent qualitative trends. At 5 years, the overall incidence of ASCVD events ranged from 7.7% to 15.6% across subpopulations, with the highest being observed in the high-risk scenario (Figure 2). In all 3 scenarios, higher CAC scores were consistently

Table 1. Baseline Characteristics of the Participants Included in Each of the 3 Scenarios Evaluated

Characteristic	LDL-C–based broad scenario	Restrictive scenario	High-risk scenario
Total No.	567	127	471
Age, y	59 (50–66)	64 (56–70)	69 (63–75)
Women	297 (52.4)	66 (52.0)	237 (50.3)
Race and ethnicity			
Non-Hispanic White*	365 (64.4)	53 (41.7)	253 (53.7)
Asian (American)	18 (3.2)	4 (3.2)	26 (5.5)
Black (American)	125 (22.1)	51 (40.2)	126 (26.8)
Hispanic (American)	59 (10.4)	19 (15.0)	66 (14.0)
BMI, kg/m^2	28.6±5.1	29.8±5.5	29.8±5.4
Obesity	176 (31.0)	53 (41.7)	205 (43.5)
Current smoking	134 (23.6)	28 (22.1)	98 (20.8)
Diabetes	84 (14.8)	34 (26.8)	252 (53.5)
Fasting glucose, mg/dL	107±33	107±30	124±44
Total cholesterol, mg/dL	273±38	247±38	226±50
LDL-C, mg/dL	195±35	169±33	147±44
HDL-C, mg/dL	52±14	51±13	50±14
Triglycerides, mg/dL	150±68	144±69	153±88
Use of statins	200 (36.0)	124 (97.6)	238 (51.0)
Hypertension	378 (66.7)	109 (85.8)	424 (90.0)
Systolic blood pressure, mm Hg	129±21	133±21	143±24
Diastolic blood pressure, mm Hg	78±11	76±11	77±13
Hypertension medication use	187 (33.0)	80 (63.0)	296 (62.9)
eGFR, mL/min per 1.73 m^2	79±20	74±18	71±21

Data presented as number (percentage), mean±SD if normally distributed, or median (interquartile range) otherwise. BMI indicates body mass index; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.

*Includes White participants from CARDIA (Coronary Artery Risk Development in Young Adults) study, non-Hispanic White participants from MESA (Multi-Ethnic Study of Atherosclerosis) and DHS (Dallas Heart Study), and all participants from HNR (Heinz Nixdorf Recall) study (Germany).

associated with a higher incidence, and ranged from 0% to 2.7% among those with CAC=0.

Similar trends were observed at 10 years of follow-up, with the overall incidence of ASCVD events ranging from 13.5% to 27.8% and being highest in the high-risk scenario (Figure 3). Among those with CAC=0, this ranged from 2.6% to 6.4%, whereas the incidence was 4.9- to 10.3-fold higher in participants with CAC >100.

Consistent patterns were observed in analyses of incidence rates per 1000 person-years (Table 2).

Associations Between CAC and ASCVD Events

Cox regression analyses adjusting for baseline demographics and risk factors demonstrated strong associations between CAC >0 to 100, CAC >100, and incident ASCVD events compared with CAC=0, consistently across scenarios (Table 3). In fully adjusted models, the hazard ratio of ASCVD events comparing CAC >0 to 100 versus CAC=0 ranged from 2.74 to 4.81, and it ranged from 6.62 to 7.48 comparing CAC >100 versus CAC=0.

DISCUSSION

In the coming years, pursuit of progressively lower LDL-C targets in increasingly broader populations will likely continue to expand the recommendation to use PCSK9i, as well as other novel lipid-lowering therapies that yield dramatic reductions in LDL-C levels. This includes among individuals without clinically evident ASCVD but expected to derive large absolute benefit from this intervention. Although there are no published randomized trials of PCSK9i in primary prevention populations free of FH, current ACC/AHA and ESC/European Atherosclerosis Society guidelines already recommend consideration of this therapy in some asymptomatic populations without FH.[5–7] These recommendations are based on the benefits that are expected to be achieved through LDL-C reduction, regardless of the specific drug used for this purpose, and extrapolate the benefits observed in primary prevention with statins[28] to other LDL-C–lowering options, such as ezetimibe and PCSK9i.

However, in a context of finite resources, a further enhanced identification of subgroups of potential candidates likely to derive the smallest and largest absolute

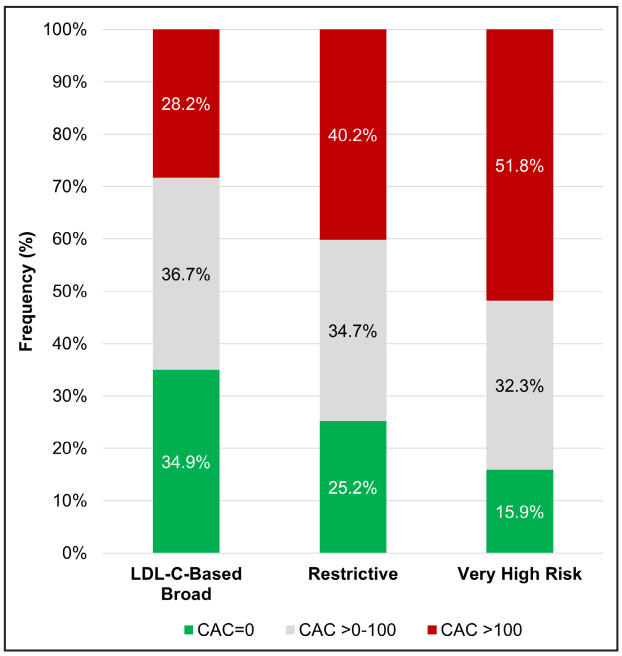

Figure 1. Distribution of coronary artery calcium (CAC) scores in each scenario.
LDL-C indicates low-density lipoprotein cholesterol.

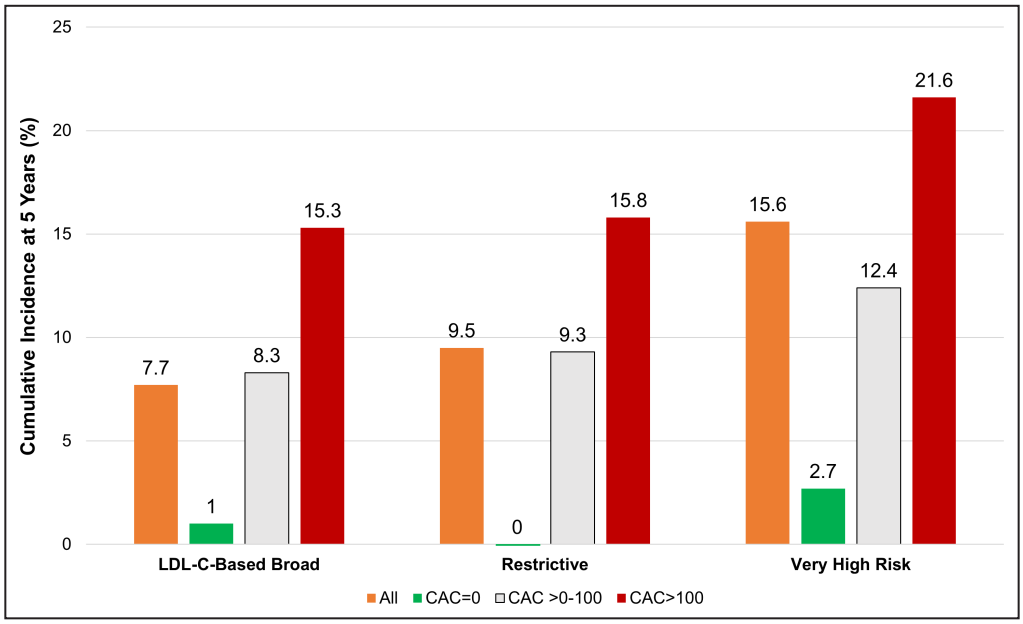

Figure 2. Cumulative incidence (percentage) of atherosclerotic cardiovascular disease events at 5 years in each scenario, overall and by coronary artery calcium (CAC) scores.
LDL-C indicates low-density lipoprotein cholesterol.

benefit from aggressive LDL-C lowering with PCSK9i can help inform shared decision-making discussions with patients, and a most targeted, cost-effective allocation. In this context, the value of the CAC score was unknown in this setting. Our study yields 3 novel findings: (1) a PCSK9i allocation paradigm aimed at achieving low LDL-C levels among individuals with subclinical organ damage identifies a large target population with high ASCVD event rates; (2) CAC stratifies ASCVD risk across non-FH indications for PCSK9i allocation in primary prevention, and is independently associated with ASCVD events in this setting; and (3) the

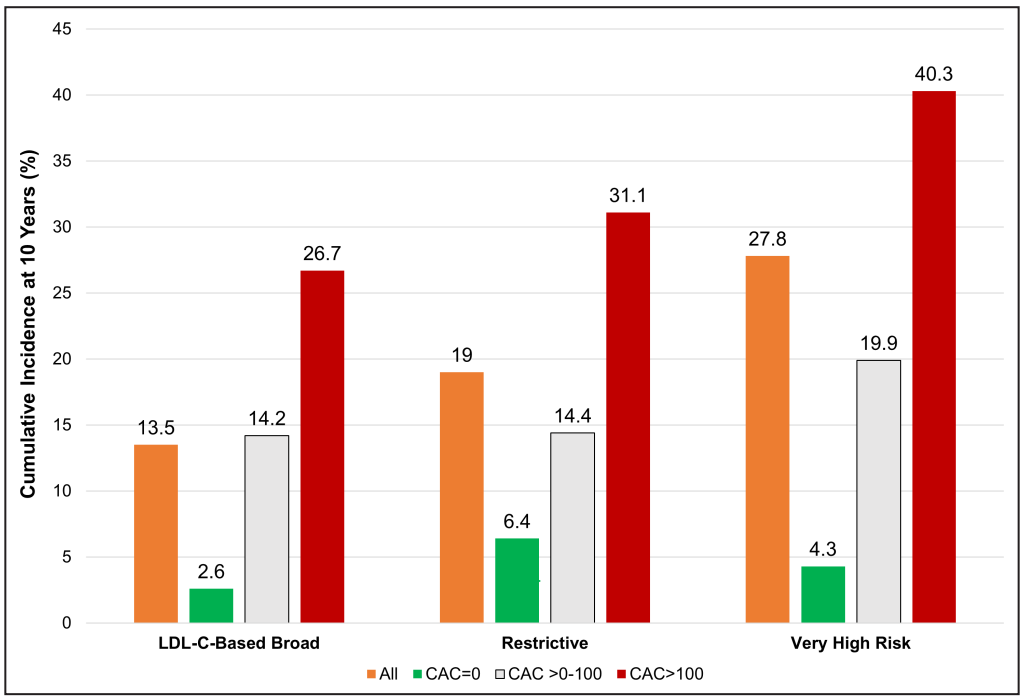

Figure 3. Cumulative incidence (percentage) of atherosclerotic cardiovascular disease events at 10 years in each scenario, overall and by coronary artery calcium (CAC) scores.
LDL-C indicates low-density lipoprotein cholesterol.

Table 2. Crude Incidence Rates of ASCVD Events per 1000 Person-Years

Scenario	No. of events	Person-years	Event rates
LDL-C–based broad			
All	101	6911	14.61 (12.03–17.76)
CAC=0	9	2833	3.18 (1.65–6.11)
CAC >0–100	41	2430	16.87 (12.42–22.92)
CAC >100	51	1648	30.95 (23.52–40.72)
Restrictive			
All	31	1478	20.97 (14.75–29.82)
CAC=0	2	456	4.38 (1.10–15.73)
CAC >0–100	8	515	15.54 (7.77–31.08)
CAC >100	21	508	41.37 (26.98–63.46)
High risk			
All	156	4675	33.37 (28.53–39.04)
CAC=0	8	944	8.47 (4.24–16.94)
CAC >0–100	36	1625	22.15 (15.98–30.71)
CAC >100	112	2105	53.20 (44.21–64.02)

Data presented as incidence rates per 1000 person-years and 95% CIs. ASCVD indicates atherosclerotic cardiovascular disease; CAC, coronary artery calcium; and LDL-C, low-density lipoprotein cholesterol.

value of CAC testing for identifying CAC=0 is greater in scenarios that use LDL-C levels and/or traditional risk factors to define PCSK9i eligibility, whereas the value of CAC diminishes (lower prevalence of CAC=0) when allocation is informed by the presence of noncoronary subclinical organ damage.

The LDL-C–based broad and restrictive scenarios evaluated the potential utility of CAC for personalized allocation of PCSK9i when this is informed by LDL-C levels with or without consideration of burden of traditional risk factors. Despite a respective median age of 59 and 64 years, 35% and 25% participants in these scenarios had CAC=0, respectively, and this finding was associated with low ASCVD event rates. Interestingly, the high prevalence of CAC=0 observed in the LDL-C–based broad scenario is consistent with the observations from cohorts of patients with genetically confirmed FH.[29–33] Indeed, several studies have suggested that CAC can be useful in ASCVD risk stratification in populations with genetically confirmed FH, a key is another key population of asymptomatic candidates for PCSK9i therapy. Among 206 Brazilians with genetically proven heterozygous FH without clinical ASCVD (mean age, 45 years), Miname et al observed a 49% prevalence of CAC=0, and baseline CAC burden was associated with incident events at 3 years.[29] In a Spanish cohort of 440 patients with genetically proven heterozygous FH without clinical ASCVD (mean age, 46 years), Pérez de Isla et al reported a 45% prevalence.[30] A high prevalence of CAC=0 has also been reported in older populations with FH described by Galaska (mean age, 50.2 years; 47% prevalence of CAC=0)[31] and Shipman (mean age, 50.4 years; 50% prevalence of CAC=0).[32] A study-level meta-analysis combining these and 5 other FH studies (n=1176; mean age, 47 years) reported an overall prevalence of CAC=0 of 45%.[33] Finally, in a recent study combining the REFERCHOL (Registre Français des Hypercholestérolémies Familiales) and SAFEHEART (Spanish Familial Hypercholesterolemia Cohort Study) clinical registries, which pooled 1543 patients with confirmed FH without clinical ASCVD (mean age, 48 years) followed up for a median of 2.7 years, the baseline prevalence of CAC=0 was 41%, and CAC improved ASCVD risk prediction.[34]

The high-risk scenario included 3.7-fold more participants than the restrictive scenario, and the overall ASCVD event rates were higher than in the other 2 scenarios. Event rates across the 3 study scenarios should be compared cautiously, because the background use of statin therapy was markedly different. However, the large number of participants included in the high-risk scenario together with the high event rates observed in this group lend support to current ESC guideline

Table 3. Associations Between CAC and ASCVD Events

Scenario	Model 1	Model 2	Model 3
LDL-C–based broad (n=567)			
CAC=0	1 (Ref.)	1 (Ref.)	1 (Ref.)
CAC >0–100	5.35 (2.59–11.03)	5.53 (2.57–11.88)	4.81 (2.18–10.60)
CAC >100	9.81 (4.82–19.99)	9.34 (4.27–20.45)	7.48 (3.31–16.90)
High risk (n=471)			
CAC=0	1 (Ref.)	1 (Ref.)	1 (Ref.)
CAC >0–100	2.64 (1.23–5.68)	2.68 (1.24–5.82)	2.74 (1.26–5.97)
CAC >100	6.45 (3.14–13.24)	6.60 (3.14–13.86)	6.62 (3.15–13.91)

Data presented as hazard ratios from Cox proportional hazard models and 95% CIs. Model 1 was unadjusted; model 2 adjusted for age, sex, race and ethnicity, and study cohort; and model 3 further adjusted for systolic blood pressure, hypertension medication use, tobacco use, low-density lipoprotein and high-density lipoprotein cholesterol levels, statin use, and diabetes. This analysis was not pursued in the restrictive scenario because the numbers of participants and events were small. ASCVD indicates atherosclerotic cardiovascular disease; CAC, coronary artery calcium; LDL-C, low-density lipoprotein cholesterol; and Ref., reference group.

recommendations for the allocation of PCSK9i in asymptomatic individuals, which not only considered a high LDL-C paradigm, but also a high ASCVD risk one, which used significantly lower on-treatment LDL-C thresholds and made greater emphasis on the presence of high-risk features (such as diabetes with end-organ damage, severe renal dysfunction, or a high estimated 10-year risk).

In this setting, the prevalence of CAC=0 was lower in the high-risk than in the other scenarios, suggesting that the utility of CAC may be more limited in this indication. However, we also noted that the absolute number of individuals with CAC=0 identified in this scenario (75 participants) was larger than in the restrictive one.[32] Moreover, despite using a rather inclusive definition of ASCVD events, the incidence of ASCVD among those with CAC=0 was remarkably low also in this scenario, and much lower than among peers with higher CAC scores. This finding is consistent with prior studies, where CAC accurately stratified ASCVD risk among individuals with high-risk features such as diabetes.[35] Of note, the median age of the population included in the high-risk scenario was 69 years. The prevalence of CAC=0 would be expected to be higher in younger populations,[36] and their event rates, even lower.

What are the clinical implications? Our results suggest that among middle-aged and older individuals who may be considered candidates for PCSK9i therapy in primary prevention on the basis of high LDL-C levels with or without multiple traditional risk factors, or noncoronary subclinical disease, relatively inexpensive CAC scanning can help make a more personalized treatment decision involving PCSK9i initiation. Although there are no trials of PCSK9i in this setting guided by CAC scores, the observed event rates suggest that the absolute risk reduction in ASCVD events with PCSK9i among individuals with CAC=0 would be expected to be small. CAC testing may be most informative among individuals already treated with statins and potentially ezetimibe who have on-treatment LDL-C levels close to the relevant guideline target and are unsure about the absolute benefit of further LDL-C reductions.

Another important finding of the present study is the strong association between CAC burden and incident ASCVD events observed in a context of high baseline statin use. This is consistent with prior analyses among cohorts of statin users, regardless of the indication.[29,34,35,37,38] This confirms that despite the calcium density paradox that occurs with statin therapy,[39] the Agatston CAC score and particularly a CAC score of 0 (which is a relatively frequent finding also in this setting[29,34,35,37,38]) remain highly informative in statin users, and can be useful for informing a personalized allocation of add-on therapies.

It could be argued that the analyses of incident ASCVD events at 5 years may be insufficient, and that a longer time frame would be more informative, as the effect of LDL-C-years on ASCVD events may not be linear and risk reduction with LDL-C–lowering therapies may increase over time.[40,41] Nevertheless, our results at 10 years of follow-up as well as using all follow-up data available were also rather reassuring for the subgroups with CAC=0. This is particularly true in a context of low use of high-intensity statin therapy and no availability of ezetimibe in the early 2000s baseline, the use of which would have further reduced ASCVD event rates in all groups, including among those with CAC=0. Finally, although the current cost of some LDL-C–lowering therapies is high, recent price reductions and the potential future availability of relatively cheap treatments based on modified small interfering RNA[42] may make the cost of these therapies a less important factor in clinical decision making, particularly once such treatments become available in generic forms.

Study Limitations

Despite pooling >18 000 participants from 4 large, carefully phenotyped cohorts, the number of participants included in some of the scenarios, particularly the restrictive scenario, was small. However, the consistent qualitative trends by CAC observed across scenarios and analyses as well as the consistency with the published FH-CAC literature are reassuring. Of note, our interpretation of the AHA/ACC/MS guideline risk factor criteria ("multiple factors that increase subsequent risk of ASCVD events")[5] was rather liberal, and a more restrictive definition would have resulted in an even smaller population of PCSK9i candidates in that scenario.

Information on statin type or dose was not available. However, most commercially available statins in the period of 2000 to 2003 were low intensity. Also, many nonusers of statins at baseline may have started therapy during follow-up (eg, triggered by the detection of high LDL-C levels [or CAC itself] as part of the study examination). This could not be accounted for in our multivariable regression analyses because information on medication use during follow-up was recorded inconsistently across studies. Similarly, adherence over time to lipid-lowering medications remains an issue and could not be accounted for in the analyses.

We explored the possibility of computing the number needed to treat for 5 years with PCSK9i to prevent one ASCVD event in each of the study scenarios, overall and by CAC scores.[11] However, we disregarded this analysis, as it would have involved several assumptions and the need to extrapolate efficacy estimates from studies like the meta-analysis by Silverman et al to more extreme LDL-C reductions not evaluated by the authors. Nonetheless, our analysis of incident ASCVD events at 5 years is informative. Specifically, it suggests that the absolute risk reduction in ASCVD events

with PCSK9i would be small among participants with CAC=0 in all 3 scenarios, even if the relative risk reduction was as high as the 15% observed in the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial in a high-risk secondary prevention population.[43] Those small absolute risk reductions would translate into high numbers needed to treat, ≈250 in the high-risk scenario if CAC=0, and ≈670 in the LDL-C–based broad scenario if CAC=0.

Finally, all participants included in this study underwent CAC scanning and LDL-C measurement ≈20 years ago, and ASCVD event rates would be expected to be significantly lower nowadays.[44] This means that ASCVD event rates may have been overestimated, including among participants with CAC=0, whose true rates would be even lower than those observed in our study.

CONCLUSIONS

A PCSK9i allocation paradigm aimed at achieving low LDL-C levels among individuals with subclinical organ damage identifies a large target population with high ASCVD event rates. Across non-FH scenarios for PCSK9i allocation in primary prevention, CAC stratified ASCVD risk and was independently associated with ASCVD events. The value of CAC testing for identifying CAC=0 is greater in scenarios that use LDL-C levels and/or traditional risk factors to define PCSK9i eligibility (present in 1 of 3–4 patients), whereas the prevalence of CAC=0 is lower when allocation is informed by presence of noncoronary subclinical organ damage.

ARTICLE INFORMATION

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Supplemental Material

Data S1
Tables S1–S5

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Supplemental Material

Data S1.

Supplemental Methods

Description of study cohorts

The Multi-Ethnic Study of Atherosclerosis (MESA) is a US, NIH/NHLBI-funded, community based, prospective cohort study of men and women free of clinical cardiovascular disease at baseline. The study was started in year 2000 and recruited 6,814 participants aged 45 to 84 years from 4 racial/ethnic groups (non-Hispanic White, non-Hispanic Black, Hispanic, and Chinese American) from 6 US sites: Columbia University, New York (NY); Johns Hopkins University, Baltimore (MD); Northwestern University, Chicago (IL); UCLA, Los Angeles (CA); University of Minnesota, Twin Cities (MN); and Wake Forest University, Winston Salem (NC).[18] Study website: https://www.mesa-nhlbi.org/

The Coronary Artery Risk Development in Young Adults (CARDIA) study is also a US, NIH/NHLBI-funded, community based, prospective cohort study of young adults free of clinical cardiovascular disease at baseline. The study was started in year 1985 and enrolled 5,115 Black and White men and women aged 18 to 30 years of age from four US cities: Birmingham (AL), Chicago (IL), Minneapolis (MN) and Oakland (CA).[19] Of those, 3,672 were evaluated in the study visit at Year 15, in which cardiac CT scanning for CAC quantification was conducted for the first time in CARDIA. Study website: https://www.cardia.dopm.uab.edu/

The Dallas Heart study (DHS) is a US, population- and probability-based prospective cohort study of 3,072 participants (age range 30 to 65 years) from the Dallas County (TX) started in year 2000. The study included a multi-ethnic population with intentional oversampling of

African Americans to compose approximately 50% of the cohort.[20] Study website: https://www.utsouthwestern.edu/research/translational-medicine/doing-research/dallas-heart/

The Heinz Nixdorf Recall Study (HNR) study is a German, population-based prospective cohort study of 4,814 White participants from the metropolitan area of the city Ruhr, in Germany.[21] Participants were aged 45–75 years at enrollment and did not have a history of clinical coronary artery disease. The study was initiated in year 2000 and was aimed at evaluating the prognostic value of CAC beyond traditional and other novel risk factors. Study website: https://www.uni-due.de/recall-studie/

Definition of study subpopulations and calculations used

The "LDL-C-Based Broad" scenario was defined broadly, used the on-treatment LDL-C target levels ≥97 mg/dL described in the 2021 Canadian Dyslipidemia guidelines for consideration of PCSK9i among individuals with FH, and pre-treatment with ezetimibe was not modeled:[7]

Strong	Use of a PCSK9 inhibitor (alirocumab or evolocumab) recommended to lower LDL-C in patients with heterozygous FH without clinical ASCVD whose LDL-C remains above the target (i.e., LDL-C ≥2.5 mmol/L or < 50% reduction from baseline; or Apo-B ≥0.85 mg/dL or non-HDL-C ≥3.2 mmol/L) despite maximally tolerated statin therapy with or without ezetimibe therapy.

The scenario included all participants meeting the following LDL-C thresholds: either LDL-C ≥194 mg/dL (statin-naïve) or LDL-C ≥136 mg/dL on a statin.

The ≥194 mg/dL LDL-C threshold was defined assuming that a 50% reduction with high-intensity statin therapy would yield on-treatment LDL-C levels ≥97 mg/dL (≥2.5 mml/L).[6] The effect of ezetimibe was not modeled, as pre-treatment with ezetimibe was not required in the Canadian Dyslipidemia guidelines to consider addition of PCSK9i.[7] The scenario also included prevalent statin users with baseline LDL-C levels ≥136 mg/dL, as those would both have fulfilled the requirement of LDL-C levels ≥194 mg/dL if they were not treated with statins (136/0.7 = 194 mg/dL), and have on-treatment LDL-C levels ≥97 mg/dL even after doubling the statin dose twice (136*0.925*0.925 = 116 mg/dL).

The "Restrictive" scenario was inspired by the two non-FH indications for PCSK9i therapy in the 2018 AHA/ACC/MS guidelines:[5]

IIb	In patients 40 to 75 years of age with baseline LDL-C ≥220 mg/dL and who achieve an on-treatment LDL-C ≥130 mg/dL while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9i may be considered.
N/A	In patients with severe primary hypercholesterolemia (LDL-C level ≥190 mg/dL [≥4.9 mmol/L]), (…) if the LDL-C level on statin plus ezetimibe remains ≥100 mg/dL and the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9i may be considered, although the long-term safety (>3 years) is uncertain and economic value is uncertain at mid-2018 list prices.

The scenario included 1) participants with either baseline LDL-C levels of ≥371 mg/dL, or LDL-C levels of ≥184 mg/dL and prevalent statin use; and 2) participants with either LDL-C

levels ≥286 mg/dL, or ≥142 mg/dL and prevalent statin use, and "multiple factors that increase subsequent risk of ASCVD events".[1]

The ≥371 mg/dL LDL-C threshold was defined assuming that a 65% LDL-C reduction with high-intensity statins plus ezetimibe[6] would result in on-treatment levels ≥130 mg/dL.[5] The ≥184 mg/dL LDL-C threshold was defined assuming that prevalent statin users in the study (all of whom were evaluated between years 2000 and 2003) would be using low/intermediate intensity statins, and that after LDL-C reductions of 7.5% with a first doubling of the statin dose, additional 7.5% with a second doubling, and a 17.5% LDL-C reduction with ezetimibe,[19] the on-treatment LDL-C levels would remain ≥130 mg/dL.[5]

The ≥286 mg/dL LDL-C threshold was defined assuming that a 65% LDL-C reduction with high-intensity statins plus ezetimibe[6] would result in on-treatment levels ≥100 mg/dL.[5] The ≥142 mg/dL LDL-C threshold was defined assuming that prevalent statin users in the study would be using low/intermediate intensity statins, and that after LDL-C reductions of 7.5% with a first doubling of the statin dose, additional 7.5% with a second doubling, and a 17.5% LDL-C reduction with ezetimibe,[19] the on-treatment LDL-C levels would remain ≥100 mg/dL.[5]

The "Very High-Risk" scenario was inspired by the non-FH recommendation for PCSK9i therapy included in the ESC/EAS guidelines:[6]

IIb	For primary prevention patients at very high risk, but without FH, if the LDL-C goal (<55 mg/dL) is not achieved on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9i may be considered. Very high risk was defined in this setting as: diabetes with target organ damage or at least three major risk factors; early onset of type 1 diabetes of long duration (>20 years); severe chronic kidney disease

	(eGFR <30 mL/min/1.73m2); SCORE ≥10% for 10-year risk of fatal CVD; unequivocally documented ASCVD on imaging, which "includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or computed tomography scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound".

The scenario included participants with either LDL-C ≥158 mg/dL (statin-naïve), or LDL-C ≥78 mg/dL and prevalent statin use, who had at least on "very high-risk" characteristic.

The ≥158 mg/dL LDL-C threshold was defined assuming that these participants would have LDL-C levels ≥55 mg/dL even after a 65% LDL-C reduction with high-intensity statins plus ezetimibe; and the ≥78 mg/dL LDL-C threshold for prevalent statin user was defined assuming that their on-treatment LDL-C levels would remain ≥55 mg/dL even if the statin dose was doubled twice and ezetimibe was used subsequently.

Table S1. Number of participants from each cohort included in each of the study scenarios.

	LDL-C-Based		Very High	Total
	Broad	Restrictive	Risk	
N	**567**	**127**	**471**	**944**
MESA	210 (37.0%)	74 (58.3%)	305 (64.8%)	469
CARDIA	61 (10.8%)	11 (8.7%)	6 (1.3%)	65
Heinz Nixdorf Recall	36 (6.4%)	14 (11.0%)	8 (1.7%)	41
Dallas Heart Study	260 (45.9%)	28 (22.1%)	152 (32.3%)	369

Data presented as number (column %)

CARDIA, Coronary Artery Risk Development in Young Adults; LDL-C, low-density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis; N, number

Table S2. Baseline characteristics of Heinz Nixdorf Recall participants without established ASCVD and with CAC data (N = 3,813), by fasting status.

	Non-fasting	Fasting	P value
N	1,497 (39.3%)	2,316 (60.7%)	—
Age, years	59 (IQR: 53, 64)	59 (IQR: 52, 65)	0.299
Women	46.4%	46.6%	0.910
White race	100%	100%	—
Diabetes	16.0%	14.4%	0.193
Active smokers	23.6%	23.8%	0.857
Obesity	24.0%	26.8%	0.054
CAC scores			0.767
=0	33.0%	33.9%	
>0 - 100	41.1%	41.1%	
>100	25.9%	24.9%	
Would have qualified for the study scenarios?			
LDL-C-Based Broad	11.0%	11.8%	0.469
Restrictive	1.9%	1.3%	0.117
Very High Risk	6.3%	6.9%	0.478

Non-fasting was defined as having had any food < 8 hours before the blood test.

Data presented as n (%) or median (IQR).

ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; N, number

Table S3. Baseline characteristics of the study participants by baseline CAC score, LDL-C-Based Broad scenario.

	CAC=0	CAC>0 - 100	CAC>100
N	**198**	**209**	**160**
Age, years	53 (IQR 44, 61)	59 (IQR 52, 65)	65 (IQR 57, 71)
Women	120 (60.6%)	106 (50.7%)	71 (44.4%)
Race/ethnicity			
Non-Hispanic White*	106 (53.5%)	145 (69.4%)	114 (71.3%)
Asian (American)	8 (4.0%)	7 (3.4%)	3 (1.9%)
Black (American)	67 (33.8%)	34 (16.3%)	24 (15.0%)
Hispanic (American)	17 (8.6%)	23 (11.0%)	19 (11.9%)
BMI, kg/m^2	28.6 ± 5.4	28.5 ±4.9	28.7 ±5.0
Obesity	56 (28.3%)	67 (32.1%)	53 (33.1%)
Current smoking	37 (18.7%)	63 (30.1%)	34 (21.3%)
Diabetes	17 (8.6%)	34 (16.3%)	33 (20.6%)
Fasting glucose, mg/dL	101 ± 28	107 ± 35	114 ± 36
Total cholesterol, mg/dL	268 ± 35	277 ± 37	276 ± 43
LDL cholesterol, mg/dL	190 ± 32	200 ± 35	194 ± 38
HDL cholesterol, mg/dL	52 ± 13	52 ± 14	53 ± 15
Triglycerides, mg/dL	142 ± 69	151 ± 66	160 ± 70
Use of statins	74 (38.1%)	63 (30.9%)	63 (39.9%)
Hypertension	102 (51.5%)	146 (69.9%)	130 (81.3%)
Systolic blood pressure, mmHg	122 ± 18	130 ± 21	136 ± 22

Diastolic blood pressure, mmHg	76 ± 9	78 ± 11	79 ± 11
Hypertension medication use	57 (28.8%)	68 (32.7%)	62 (38.3%)
EGFR, mL/min/1.73m^2	84 ± 20	77 ± 18	76 ± 20

*Includes White participants from CARDIA, non-Hispanic White participants from MESA and Dallas Heart Study, and all participants from Heinz Nixdorf Recall (Germany).

Data presented as n (%), mean (± standard deviation) or median (IQR).

BMI, body mass index; CAC, coronary artery calcium; EGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; N, number

Table S4. Baseline characteristics of the study participants by baseline CAC score, Restrictive scenario.

	CAC=0	CAC>0 - 100	CAC>100
N	**32**	**44**	**51**
Age, years	51 (IQR 44, 65)	63 (IQR 57, 69)	68 (IQR 62, 73)
Women	20 (62.5%)	25 (56.8%)	21 (41.2%)
Race/ethnicity			
Non-Hispanic White*	10 (31.3%)	16 (36.4%)	27 (52.9%)
Asian (American)	0 (0%)	2 (4.6%)	2 (3.9%)
Black (American)	20 (62.5%)	18 (40.9%)	13 (25.5%)
Hispanic (American)	2 (6.3%)	8 (18.2%)	9 (17.7%)
BMI, kg/m^2	31.5 ± 5.8	28.8 ± 5.8	29.6 ± 4.9
Obesity	16 (50.0%)	15 (34.1%)	22 (43.1%)
Current smoking	7 (21.9%)	14 (31.8%)	7 (13.7%)
Diabetes	7 (21.9%)	11 (25.0%)	16 (31.4%)
Fasting glucose, mg/dL	100 ± 17	103 ± 18	116 ± 41
Total cholesterol, mg/dL	240 ± 27	249 ± 36	251 ± 45
LDL cholesterol, mg/dL	163 ± 19	172 ± 31	169 ± 41
HDL cholesterol, mg/dL	51 ± 14	51 ± 12	52 ± 14
Triglycerides, mg/dL	132 ± 62	131 ± 60	161 ± 78
Use of statins	32 (100%)	43 (97.7%)	49 (96.1%)
Hypertension	29 (90.6%)	36 (81.8%)	44 (86.3%)
Systolic blood pressure, mmHg	130 ± 24	132 ± 20	135 ± 20

Diastolic blood pressure, mmHg	75 ± 10	76 ± 11	77 ± 10
Hypertension medication use	21 (65.6%)	27 (61.4%)	32 (62.8%)
EGFR, mL/min/1.73m^2	83 ± 18	74 ± 19	68 ± 16

*Includes White participants from CARDIA, non-Hispanic White participants from MESA and Dallas Heart Study, and all participants from Heinz Nixdorf Recall (Germany).

Data presented as n (%), mean (± standard deviation) or median (IQR).

BMI, body mass index; CAC, coronary artery calcium; EGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; N, number

Table S5. Baseline characteristics of the study participants by baseline CAC score, Very High-Risk scenario.

	CAC=0	CAC>0 - 100	CAC>100
N	**75**	**152**	**244**
Age, years	66 (IQR 57, 73)	68 (IQR 61, 75)	72 (IQR 66, 77)
Women	52 (69.3%)	82 (54.0%)	103 (42.2%)
Race/ethnicity			
Non-Hispanic White*	25 (33.3%)	88 (57.9%)	140 (57.4%)
Asian (American)	4 (5.3%)	10 (6.6%)	12 (4.9%)
Black (American)	34 (45.3%)	36 (23.7%)	56 (23.0%)
Hispanic (American)	12 (16.0%)	18 (11.8%)	36 (14.8%)
BMI, kg/m^2	31.3 ± 5.7	30.1 ± 5.6	29.2 ± 5.0
Obesity	39 (52.0%)	73 (48.0%)	93 (38.1%)
Current smoking	15 (20.0%)	25 (16.5%)	58 (23.8%)
Diabetes	44 (58.7%)	85 (55.9%)	123 (50.4%)
Fasting glucose, mg/dL	123 ± 44	127 ± 47	123 ± 43
Total cholesterol, mg/dL	225 ± 49	231 ± 50	223 ± 50
LDL cholesterol, mg/dL	145 ± 43	152 ± 44	145 ± 45
HDL cholesterol, mg/dL	52 ± 13	51 ± 16	50 ± 13
Triglycerides, mg/dL	139 ± 67	155 ± 82	155 ± 96
Use of statins	35 (46.7%)	72 (48.0%)	131 (54.1%)
Hypertension	65 (86.7%)	132 (86.8%)	227 (93.0%)
Systolic blood pressure, mmHg	145 ± 25	141 ± 24	144 ± 24

Diastolic blood pressure, mmHg	78 ± 11	77 ± 13	77 ± 13
Hypertension medication use	51 (68.0%)	88 (57.9%)	157 (64.3%)
EGFR, mL/min/1.73m^2	72 ± 18	71 ± 24	70 ± 20

*Includes White participants from CARDIA, non-Hispanic White participants from MESA and Dallas Heart Study, and all participants from Heinz Nixdorf Recall (Germany).

Data presented as n (%), mean (± standard deviation) or median (IQR).

BMI, body mass index; CAC, coronary artery calcium; EGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; N, number