Circulation

ORIGINAL RESEARCH ARTICLE

Very High Coronary Artery Calcium (≥1000) and Association With Cardiovascular Disease Events, Non–Cardiovascular Disease Outcomes, and Mortality

Results From MESA

BACKGROUND: There are limited data on the unique cardiovascular disease (CVD), non-CVD, and mortality risks of primary prevention individuals with very high coronary artery calcium (CAC; ≥1000), especially compared with rates observed in secondary prevention populations.

METHODS: Our study population consisted of 6814 ethnically diverse individuals 45 to 84 years of age who were free of known CVD from MESA (Multi-Ethnic Study of Atherosclerosis), a prospective, observational, community-based cohort. Mean follow-up time was 13.6±4.4 years. Hazard ratios of CAC ≥1000 were compared with both CAC 0 and CAC 400 to 999 for CVD, non-CVD, and mortality outcomes with the use of Cox proportional hazards regression adjusted for age, sex, and traditional risk factors. Using a sex-adjusted logarithmic model, we calculated event rates in MESA as a function of CAC and compared them with those observed in the placebo group of stable secondary prevention patients in the FOURIER clinical trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk).

RESULTS: Compared with CAC 400 to 999, those with CAC ≥1000 (n=257) had a greater mean number of coronary vessels with CAC (3.4±0.5), greater total area of CAC (586.5±275.2 mm^2), similar CAC density, and more extensive extracoronary calcification. After full adjustment, CAC ≥1000 demonstrated a 4.71- (3.63–6.11), 7.57- (5.50–10.42), 4.86-(3.32–7.11), and 1.94-fold (1.57–2.41) increased risk for all CVD events, all coronary heart disease events, hard coronary heart disease events, and all-cause mortality, respectively, compared with CAC 0 and a 1.65- (1.25–2.16), 1.66- (1.22–2.25), 1.51- (1.03–2.23), and 1.34-fold (1.05–1.71) increased risk compared with CAC 400 to 999. With increasing CAC, hazard ratios increased for all event types, with no apparent upper CAC threshold. CAC ≥1000 was associated with a 1.95- (1.57–2.41) and 1.43-fold (1.12–1.83) increased risk for a first non-CVD event compared with CAC 0 and CAC 400 to 999, respectively. CAC 1000 corresponded to an annualized 3-point major adverse cardiovascular event rate of 3.4 per 100 person-years, similar to that of the total FOURIER population (3.3) and higher than those of the lower-risk FOURIER subgroups.

CONCLUSIONS: Individuals with very high CAC (≥1000) are a unique population at substantially higher risk for CVD events, non-CVD outcomes, and mortality than those with lower CAC, with 3-point major adverse cardiovascular event rates similar to those of a stable treated secondary prevention population. Future guidelines should consider a less distinct stratification algorithm between primary and secondary prevention patients in guiding aggressive preventive pharmacotherapy.

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Clinical Perspective

What Is New?

- Individuals with coronary artery calcium (CAC) ≥1000 constitute a unique population at substantially higher risk for cardiovascular disease events, non–cardiovascular disease outcomes, and mortality than those with lower CAC.
- Those with CAC ≥1000 had a much more extensive pattern of extracoronary calcification, a significantly increased CAC area, yet almost identical CAC density compared with those with CAC 400 to 999.
- CAC 1000 corresponded to an annualized 3-point major adverse major adverse cardiovascular event rate of 3.4 per 100 person-years, similar to that of the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) stable treated secondary prevention population (3.3) and higher than that of lower-risk FOURIER subgroups.

What Are the Clinical Implications?

- There is a risk continuum according to atherosclerotic burden; the cardiovascular disease risk of some asymptomatic primary prevention patients such as those with CAC ≥1000 is the same as or higher than that of traditional secondary prevention patients.
- Aggressive prevention with pharmacological agents such as statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 inhibitors will be important for these high-risk primary prevention patients.
- Future guidelines should incorporate recommendations on this unique group of individuals with CAC ≥1000.

Coronary artery calcium (CAC), a crude measure of atherosclerotic burden, has evolved into a clinical decision aid in the past decade. Increased CAC scores are strongly associated with a higher risk of cause-specific cardiovascular mortality and all-cause mortality in both younger and older adults.[1–3] Higher CAC scores have also been linked to non–cardiovascular disease (CVD)–related outcomes, including dementia and cancer.[4–8] Consistent with its usefulness as a predictor of CVD- and non–CVD-related outcomes, the CAC score has been shown to significantly improve on traditional risk factors and risk scores such as the MESA (Multi-Ethnic Study of Atherosclerosis) Coronary Heart Disease (CHD) Risk Score and the Pooled Cohort Equations, with meaningful reclassification of patients particularly in the borderline- to intermediate-risk range.[9–13] One recent study in an asymptomatic primary prevention population found that combining CAC with the Pooled Cohort Equations resulted in significantly better risk discrimination for future CVD death, improving the concordance or C statistic in middle-aged adults from 0.71 to 0.75.[14]

CAC scores >300 or >400 are generally considered to represent the highest-risk group in clinical practice.[15] However, there is increasing interest in the unique group of individuals with very high CAC scores. A recent clinical study investigated individuals with CAC scores ≥1000 and found secondary prevention–level CVD mortality rates in this population; however, the authors used a retrospective clinical database of referred patients and were able to explore only long-term cause-specific and all-cause mortality.[3] In addition, this study was not able to investigate non-CVD outcomes, yet CAC is known to be a marker of not only atherosclerosis but also biological age and chronic disease.[5,16–20] More data on the unique group of individuals with CAC ≥1000 are needed, especially with regard to non-CVD outcomes and CVD outcomes, including whether such patients truly experience secondary prevention–level risk.

MESA is a National Heart, Lung, and Blood Institute–sponsored community-based prospective cohort study of diverse adults free of known CVD with long-term follow-up for nonfatal CVD and physician-adjudicated non-CVD end points.[21,22] We sought to use MESA to expand on the few previous studies exploring very high CAC scores (CAC ≥1000), investigating for the first time both CVD and non-CVD event rates in apparently healthy individuals. We also sought to conduct a more formal comparison of CVD event rates in individuals with CAC ≥1000 and recent trials in stable secondary prevention (such as FOURIER [Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk]), including establishing the CAC score cutoffs that correspond to the event rates found in these trials.

METHODS

The study data set is made available through the MESA website or can be obtained via BioLINCC. Qualified researchers trained in human subject confidentiality protocols may also request to access the data set from the Collaborative Health Studies Coordinating Center, University of Washington, at chsccweb@u.washington.edu. The corresponding author can provide the analyses that support the findings of this study on reasonable request.

Study Design and Study Population

This analysis includes 6814 ethnically diverse participants (age, 45–84 years) from MESA, which is a prospective, observational cohort of participants recruited from the general population from 6 US cities: Baltimore, MD; Chicago, IL; Los Angeles, CA; New York, NY; St. Paul, MN; and Winston-Salem, NC. All participants were free of any baseline CVD, were not receiving active cancer treatment, and underwent baseline

CAC scans at time of recruitment. Details on the data collection and design of MESA have been published elsewhere.[21] Briefly, MESA is an ongoing study that collected baseline data from July 2000 to September 2002, with follow-up until December 2017 used for this analysis. Institutional Review Board approval was obtained from each field center, and all study participants provided informed consent.

Computed Tomography Data

Three study sites used cardiac-gated electron-beam computed tomography (CT) scans, whereas the other 3 sites used multidetector CT scans. Each participant was scanned twice at baseline examination, with mean Agatston score used for analysis.[23] All scans were phantom adjusted and read by 2 trained CT image analysts at a central MESA CT reading center, with high reproducibility and comparability between electron beam CT and multidetector CT scanning.[24–26] Detailed information on CT scan methods and interpretation has been given previously.[24]

CAC area and density were derived from total Agatston and volume scores, which were provided in the original MESA data set. The methods for this derivation are described in a previous article.[27] Data on the total number of vessels with CAC 0 to 4 were available in 6543 participants (96%); aortic root calcium scores in 6812 participants (>99%), thoracic aortic calcium scores in 6812 participants (>99%), aortic valve calcium scores in 6812 participants (>99%), and mitral valve calcium scores in 6814 participants (100%). Data on CAC density and area could be calculated in 6543 participants (96%).

Measurement and Definition of Baseline Characteristics and Risk Factors

Participants had baseline anthropometric measurements, vital signs, lifestyle characteristics, risk factors, and laboratory data collected at the time of their initial examination. Missing data are summarized in Table I in the Data Supplement. Obesity was defined as body mass index ≥30 kg/m^2. Hypertension was defined as systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg. Diabetes was defined as a fasting blood glucose level ≥126 mg/dL or previous diagnosis of diabetes (treated or untreated). Cigarette smoking was defined as having smoked cigarettes in the past 30 days. Family history of myocardial infarction (MI) included parents, siblings, and children regardless of age. Metabolic syndrome was defined per National Cholesterol Education Program Adult Treatment Panel III criteria.[28] Ten-year atherosclerotic CVD (ASCVD) risk scores were calculated using Pooled Cohort Equations scoring method described in the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guideline on the assessment of cardiovascular risk.[29]

Outcome Ascertainment and Follow-Up

Telephone interviews and chart reviews were performed for all participants at 9- to 12-month intervals to collect information about any hospital admissions, outpatient diagnoses or procedures, and deaths. Self-reported diagnoses were verified with medical records, death certificates, and next-of-kin interviews for the case of out-of-hospital deaths. Follow-up time was measured from baseline examination to first occurrence of specified outcome, loss to follow-up, death, or December 31, 2017. Mean follow-up time was 13.6±4.4 years (median, 15.7 years; first–third quartile, 12.2–16.5 years).

CVD Events and All-Cause Mortality

Our CVD outcomes of interest included all CVD events, defined as MI, resuscitated cardiac arrest, stroke, adjudicated angina, and cardiovascular death (secondary to stroke, CHD, other atherosclerotic death, or other CVD death); hard CVD events, defined as MI, resuscitated cardiac arrest, stroke, and cardiovascular death (secondary to stroke, CHD, other atherosclerotic death, or other CVD death); all CHD events, defined as MI, resuscitated cardiac arrest, adjudicated angina, and coronary death; hard CHD events, defined as MI, resuscitated cardiac arrest, and coronary death; and all-cause mortality. Presence of angina was defined as definite or probable angina, both of which were distinct from MI diagnoses. Definite angina required objective evidence of obstructive coronary artery disease or reversible myocardial ischemia, and probable angina was followed by revascularization. The final adjudication of each end point was done by the MESA Morbidity and Mortality Committee.[30] The number of all CVD events, hard CVD events, all CHD events, hard CHD events, and all-cause mortalities in each CAC group is summarized in Table II in the Data Supplement.

Non-CVD Events

Other outcomes of interest included non-CVD events, which were extracted from inpatient records with the use of 9th and 10th revisions of the *International Classification of Diseases* codes and were analyzed as noncompeting events. For the purposes of this analysis, we included cancer, chronic kidney disease or other indicators of end-stage renal disease, pneumonia, chronic obstructive pulmonary disease, deep vein thrombosis/pulmonary embolism, dementia, and hip fracture as non-CVD events.[5] An aggregate non-CVD event variable was created from these individual events defined as time to any first non-CVD event. Table III in the Data Supplement summarizes a breakdown of cancer type by CAC group. A full list of codes used can be found in Table IV in the Data Supplement. The number of each specific non-CVD event type and aggregate non-CVD events in each CAC group is summarized in Table V in the Data Supplement.

Statistical Methods

CAC scores were categorized as CAC 0, CAC 1 to 399, CAC 400 to 999, and CAC ≥1000. Baseline characteristics were stratified by CAC groups, with number (percentage) and means (SD) reported as appropriate.

Hazard ratios were calculated using unadjusted and multivariable-adjusted Cox regression models to assess the relative hazards of CAC groups for CVD events, all-cause mortality, and non-CVD events compared with a reference group of CAC score of 0. For the purposes of specific comparison, the same models were also used to compare the CAC ≥1000 group with a reference group of CAC 400 to 999. We chose to include 2 models: model 1, which was unadjusted, and model 2, which was fully adjusted for covariates. The covariates we used for the fully adjusted model were age, sex, race/

ethnicity, obesity, hypertension, total cholesterol, high-density lipoprotein cholesterol, triglycerides, smoking status, diabetes, family history of MI, antihypertensive medications, and cholesterol medications at baseline.

In a multivariable model adjusted for the same covariates listed above, cubic splines with knots placed at CAC 100 and CAC 1000 were used to study the dose-response relationship between CAC score and event outcomes (CVD, CHD, non-CVD, and all-cause mortality) to graphically examine risks around the CAC 1000 threshold.

CAC Equivalent Risk Model

To study the CAC scores in primary prevention individuals associated with a CVD event risk equivalent to that of secondary prevention patients in clinical trials, we compared event rates in MESA with those observed in the placebo group of FOURIER.[31,32] The rationale for choosing the secondary prevention population of FOURIER was that it is a modern study of individuals with stable CVD. Specifically, the population consists of patients who had a median time of >3 years since their last atherothrombotic event and had been stable in the interim versus other recent trials in which patients had acute coronary syndrome in the past 1 to 12 months.[33] We chose a MESA population with clinical indication for CAC scoring under new 2019 CVD Primary Prevention Clinical Practice Guidelines[34] (ie, ASCVD risk ≥7.5%). This produced a population with an age and sex distribution nearly identical to that of FOURIER.

First, we used a logarithmic model to graph sex-adjusted annualized hard CVD event rate (per 100 person-years) as a function of total CAC score in MESA, using methods similar to those used in a previous study in the literature.[35] To facilitate comparison with common end points in clinical trials, we defined hard CVD events in this model as the familiar 3-point major adverse cardiovascular event (MACE) outcome, that is, MI, stroke, and cardiovascular death. In this model, cardiovascular death was defined as death attributable to any atherosclerotic disease, stroke, or CVD. This slightly expanded definition of cardiovascular death compared with the standard MESA definition of hard CVD death (which includes only death secondary to CHD or stroke) was used to mirror the definition used in FOURIER.

Annual placebo group event rates were then extracted from publications summarizing the FOURIER population. Additional attention was placed on so-called low-risk groups in FOURIER as defined by Sabatine et al.[31,32] These were (1) no multivessel disease, (2) only 1 previous MI, and (3) no high-risk features (ie, recent MI <2 years ago, >1 previous MI, or multivessel disease). The FOURIER low-risk subgroups with the percentage of the FOURIER placebo arm they represent, 3-year Kaplan-Meier rate as reported by FOURIER, and annualized event rate are summarized in Table VI in the Data Supplement.

Finally, using the equation derived from our CAC-CVD event rate logarithmic model in MESA, we calculated the CAC score in MESA that gives the same event rate as that observed in FOURIER. Equivalency with the total FOURIER population and the low-risk subgroups was then expressed graphically.

A 2-sided value of $P<0.05$ was considered statistically significant. All analyses were performed with Stata/SE 14.0 (StataCorp LP, College Station, TX).

RESULTS

Baseline Characteristics

Participants with CAC ≥1000 made up 3.8% (257 participants) of the total MESA study population. These participants with CAC ≥1000 were older (mean, 71.7±7.5 years), more likely to be male (80.9%) and non-Hispanic White (52.9%), and had a higher mean estimated 10-year ASCVD risk using the Pooled Cohort Equations (27.5±14.0%) than those with lower CAC (Table 1). Compared with those with lower CAC, a higher percentage of participants with CAC ≥1000 were also taking antihypertensive medication (54.1%) or cholesterol medication (31.9%), had a positive family history of MI (57.4%), and had albuminuria (20.6%).

The proportion of men increased with increasing CAC score. In those with CAC 0, 1 to 399, 400 to 999, and ≥1000, 36.6%, 54.7%, 63.6%, and 80.9%, respectively, were men. The percentage of participants in the high-risk group for 10-year ASCVD risk (≥20%) also increased with higher CAC scores, with 10.9% in the CAC 0 group, 32.1% in the CAC 1 to 399 group, 55.8% in the CAC 400 to 999 group, and 66.9% in the CAC ≥1000 group.

Several traditional CVD risk factors such as diabetes, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, cigarette smoking, family history of MI, body mass index, and metabolic syndrome were similar between the CAC ≥1000 group and the CAC 400 to 999 group. The distribution of specific risk factors can be found in Table 1.

Imaging Characteristics

Table 2 details the imaging characteristics across CAC score groups, including extracoronary calcification. In those with CAC ≥1000, the mean number of coronary vessels with CAC was 3.4±0.5, of which 53.3% had 3-vessel CAC and 44.7% had 4-vessel CAC. Compared with those with CAC 400 to 999, a greater number of participants with CAC ≥1000 had calcium (80.1% versus 67.9%), thoracic artery calcium (77.3% versus 61.4%), aortic valve calcium (47.3% versus 32.7%), and mitral valve calcium (37.0% versus 18.1%).

The specific distribution of extracoronary calcium by CAC score group is shown in Table 2. Although the CAC ≥1000 group had an average CAC density similar to that of the CAC 400 to 999 group (3.2±0.3 versus 3.1±0.4), this extensive CAC group had a substantially greater total area of CAC than the CAC 400 to 999 group (586.5±275.2 mm^2 versus 198.1±56.3 mm^2).

Multivariable-Adjusted Hazard Ratios

CVD Events

After adjustment for traditional cardiovascular risk factors (listed in Table 3), those with CAC ≥1000

Table 1. Baseline Characteristics According to CAC Score Group

Demographic characteristics	CAC 0 (n=3416)	CAC 1–399 (n=2721)	CAC 400–999 (n=420)	CAC ≥1000 (n=257)
Age, mean (SD), y	58.0 (9.1)	65.3 (9.6)	69.8 (7.9)	71.7 (7.5)
Male, %	36.6	54.7	63.6	80.9
Race/ethnicity, %				
White	33.0	42.0	51.2	52.9
Chinese	11.7	12.9	9.0	5.4
Black	31.4	24.6	22.1	23.0
Hispanic	23.9	20.4	17.6	18.7
Diabetes,* %	9.3	14.3	22.9	22.7
Systolic blood pressure, mean (SD), mm Hg	122.4 (20.5)	129.8 (21.5)	135.2 (22.3)	134.3 (20.9)
Diastolic blood pressure, mean (SD), mm Hg	71.3 (10.3)	72.3 (10.2)	73.9 (10.4)	72.8 (10.4)
Antihypertensive medication, %	26.3	37.8	48.3	54.1
Statin medication,* %	9.6	18.5	24.3	30.0
LDL cholesterol,* mean (SD), mg/dL	116.0 (30.7)	119.0 (32.1)	118.9 (32.9)	110.8 (31.4)
HDL cholesterol,* mean (SD), mg/dL	52.5 (15.0)	49.6 (14.4)	49.3 (14.9)	47.7 (14.1)
Triglycerides,*, mean (SD), mg/dL	126.8 (84.9)	136.1 (93.8)	139.0 (89.6)	135.8 (80.1)
Total cholesterol,* mean (SD), mg/dL	193.7 (35.0)	195.3 (36.2)	195.7 (36.9)	185.9 (37.4)
Cholesterol medication, %	10.7	20.1	25.7	31.9
Cigarette smoking,* %	13.3	13.0	11.7	12.9
Family history of MI,* %	37.2	46.5	55.5	57.4
Body mass index, mean (SD), kg/m^2	28.3 (5.7)	28.3 (5.3)	28.7 (5.2)	28.3 (4.8)
Metabolic syndrome,* %	30.8	40.2	45.1	47.1
ASCVD Risk Score,* mean (SD), %	8.5 (9.5)	17.1 (13.9)	24.5 (15.2)	27.5 (14.0)
Low (<5%)	49.6	16.9	3.6	2.0
Borderline (5%–<7.5%)	12.2	11.9	6.2	2.4
Intermediate (≥7.5%–<20%)	27.3	39.1	34.4	28.7
High (≥ 20%)	10.9	32.1	55.8	66.9
Creatinine,* mean (SD), mg/dL	0.9 (0.2)	1.0 (0.3)	1.0 (0.3)	1.1 (0.6)
eGFR (MDRD),* mean (SD), mL·min^{-1}·m^{-2}	83.4 (16.7)	79.5 (20.1)	77.9 (18.1)	75.6 (20.0)
Albuminuria* (≥30 mg/g), %	7.0	10.7	16.6	20.6
CRP,* mean (SD), mg/L	3.8 (5.5)	3.8 (6.1)	4.0 (7.0)	3.5 (7.1)

ASCVD indicates atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MDRD, Modification of Diet in Renal Disease; and MI, myocardial infarction.

*Data available in only a subset of the study population in Demographic Characteristics. Detailed data on number of participants in each subgroup can be found in Table I in the Data Supplement.

had a 4.71- (95% CI, 3.63–6.11), 3.18- (95% CI, 2.31–4.36), 7.57- (95% CI, 5.50–10.42), 4.86- (95% CI, 3.32–7.11), and 1.94-fold (95% CI, 1.57–2.41) increased risk for all CVD events, hard CVD events, all CHD events, hard CHD events, and all-cause mortality, respectively, compared with those with CAC 0 (Table 3).

In the same fully adjusted model compared with a reference group of CAC 400 to 999, participants with CAC ≥1000 had a 1.65- (95% CI, 1.25–2.16), 1.33- (95% CI, 0.94–1.86), 1.66- (95% CI, 1.22–2.25), 1.51- (95% CI, 1.03–2.23), and 1.34-fold (95% CI, 1.05–1.71) increased risk for all CVD events, hard CVD events, all CHD events, hard CHD events, and all-cause mortality, respectively (Table 3).

Non-CVD Events

The risk distribution of non-CVD events by specific event type is shown in Table 4 and stratified by CAC score group. After adjustment for traditional cardiovascular risk factors, those with CAC ≥1000 had almost double the risk (hazard ratio, 1.95 [95% CI, 1.57–2.41]) for a first non-CVD event compared with participants in the CAC 0 group. Specific events driving this association included cancer, chronic kidney disease, pneumonia, chronic obstructive pulmonary disease, dementia, and

Table 2. Imaging Characteristics According to CAC Score Group

Imaging characteristics	CAC 0	CAC 1–399	CAC 400–999	CAC ≥1000
Imaging characteristics 1, n	3282	2618	397	246
Vessels with CAC, mean (SD), n	0 (0)	1.9 (0.9)	3.2 (0.6)	3.4 (0.5)
0, %	100.0	0.0	0.0	0.0
1, %	0.0	41.0	0.8	0.0
2, %	0.0	30.0	8.3	2.0
3, %	0.0	23.6	57.9	53.3
4, %	0.0	5.4	33.0	44.7
Imaging characteristics 2, n	3416	2721	420	255
TAC, %	11.9	38.4	61.4	77.3
TAC 1–399, %	9.2	23.0	25.5	28.6
TAC 400–999, %	1.8	7.9	13.6	18.8
TAC ≥1000, %	0.9	7.5	22.4	29.8
Imaging characteristics 3, n	3416	2721	419	256
AVC, %	4.9	17.9	32.7	47.3
AVC 1–399, %	4.5	16.4	29.4	37.5
AVC 400–999, %	0.3	0.8	2.6	6.3
AVC ≥1000, %	0.1	0.8	0.7	3.5
Imaging characteristics 4, n	3416	2721	420	257
MVC, %	4.3	12.0	18.1	37.0
MVC 1–399, %	3.5	9.6	12.9	26.5
MVC 400–999, %	0.4	1.1	1.7	5.1
MVC ≥1000, %	0.4	1.3	3.6	5.5
Imaging characteristics 5, n	3415	2721	420	256
ARC, %	16.4	45.8	67.9	80.1
ARC 1–399, %	15.9	40.6	52.1	55.5
ARC 400–999, %	0.4	3.9	13.1	16.4
ARC ≥1000, %	0.1	1.4	2.6	8.2
Imaging characteristics 6, n	3282	2618	397	246
Estimated total area, mean (SD), mm²	0 (0)	32.7 (34.1)	198.1 (56.3)	586.5 (275.2)
Average CAC density, mean (SD)	0	2.6 (0.7)	3.1 (0.4)	3.2 (0.3)

ARC indicates aortic root calcium; AVC, aortic valve calcium; CAC, coronary artery calcium; MVC, mitral valve calcium; and TAC, thoracic artery calcium.

hip fracture; those with CAC ≥1000 had significantly increased risk for developing these outcomes versus those with CAC 0 (Table 4). Compared with those with CAC 400 to 999 in the same multivariable-adjusted model, participants with CAC ≥1000 had a 1.43-fold (95% CI, 1.12–1.83) increased risk for a first non-CVD event (Table 4).

Figure 1 depicts the association between CAC score and multivariable-adjusted risk of all CVD events, all CHD events, non-CVD events, and all-cause mortality. With rising CAC, the hazard ratios increased for all types of events, including all-cause mortality. Although the slope of increase for hazard ratios becomes slightly less steep above a CAC score of 1000 for CVD events, CHD events, and non-CVD events, it still continues to increase with no clear upper CAC threshold. Figure I in the Data Supplement uses the same model to depict the curves for hard CVD events (equivalent to Pooled Cohort Equations definition of ASCVD) and hard CHD events.

Multivariable-Adjusted Logarithmic Model of Annualized Event Rates

A sex-adjusted logarithmic model graphing annualized 3-point MACE rates as a function of CAC score is shown in Figure 2. In this logarithmic model (R^2=0.93), the annualized 3-point MACE rate rises with a steep slope below a CAC score of ≈200 and begins to level off above that CAC score, although still increasing. A CAC score of 1000 corresponded to an annualized 3-point MACE rate of 3.4 per 100 person-years. The

Table 3. Hazard Ratios for CVD Events by CAC Score Group

CAC score	CVD event type and all-cause mortality, HR (95% CI)				
	All CVD	Hard CVD	All CHD	Hard CHD	All-cause mortality
CAC 0 as reference group					
Model 1, unadjusted HRs					
0	REF	REF	REF	REF	REF
1–399	3.31 (2.84–3.85)	3.00 (2.52–3.57)	4.18 (3.41–5.11)	3.70 (2.94–4.65)	2.41 (2.15–2.71)
400–999	6.88 (5.59–8.48)	5.68 (4.45–7.24)	9.76 (7.55–12.62)	7.69 (5.68–10.41)	4.23 (3.56–5.02)
≥1000	10.95 (8.76–13.68)	7.78 (5.92–10.21)	15.53 (11.83–20.37)	11.72 (8.48–16.21)	6.65 (5.53–7.99)
Model 2, fully adjusted* HRs					
0	REF	REF	REF	REF	REF
1–399	2.06 (1.74–2.43)	1.80 (1.49–2.19)	2.77 (2.22–3.45)	2.24 (1.74–2.88)	1.20 (1.05–1.37)
400–999	3.12 (2.46–3.97)	2.51 (1.90–3.32)	4.92 (3.66–6.61)	3.42 (2.41–4.85)	1.48 (1.22–1.80)
≥1000	4.71 (3.63–6.11)	3.18 (2.31–4.36)	7.57 (5.50–10.42)	4.86 (3.32–7.11)	1.94 (1.57–2.41)
CAC 400–999 as reference group					
Model 1, unadjusted HRs					
400–999	REF	REF	REF	REF	REF
≥1000	1.57 (1.23–2.00)	1.36 (1.00–1.84)	1.57 (1.19–2.08)	1.51 (1.07–2.14)	1.57 (1.27–1.95)
Model 2, fully adjusted* HRs					
400–999	REF	REF	REF	REF	REF
≥1000	1.65 (1.25–2.16)	1.33 (0.94–1.86)	1.66 (1.22–2.25)	1.51 (1.03–2.23)	1.34 (1.05–1.71)

CAC indicates coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio; and REF, referent.

*Adjusted for age, sex, race/ethnicity, obesity, hypertension, total cholesterol, high-density lipoprotein cholesterol, triglycerides, smoking, diabetes, family history of myocardial infarction, antihypertensive medications, and cholesterol medications.

annualized 3-point MACE rate of those in the FOURIER trial (3.3 per 100 person-years) corresponded to a CAC score of ≈900 in our model.

In the low-risk subpopulations of FOURIER, for example, those with no multivessel disease, only 1 previous MI, and no high-risk features (ie, recent MI <2 years ago, >1 previous MI, or multivessel disease), the annualized 3-point MACE rate corresponded to a CAC score of ≈550, 350, and 300, respectively. The CAC equivalency to low-risk subgroups in FOURIER is shown in Figure 2.

DISCUSSION

Our study describes in detail those with very high CAC scores (≥1000) in the most diverse and generalizable population of these individuals that currently exists in the literature. We demonstrate that those with CAC ≥1000 are primarily older, White, and male with a much more extensive pattern of coronary and extracoronary calcification compared with those with lower CAC. These individuals also have a substantially greater total area of CAC while remaining at a similar average CAC density compared with lower CAC score groups. Moreover, we show that CAC scores >1000 are associated with a markedly greater risk for CVD, CHD, and non-CVD events, in addition to all-cause mortality, than those with lower CAC.

These individuals with CAC ≥1000 are at an almost 2 times increased risk for all CVD and all CHD events and an almost 1.5 times increased risk for non-CVD events compared with those with CAC 400 to 999. With higher CAC scores, the risk for CVD events, CHD events, non-CVD events, and all-cause mortality seems to increase without a notable upper CAC threshold. Furthermore, this distinct group of primary prevention individuals with CAC ≥1000 taken from the US general population has a 3-point MACE rate similar to that of stable treated secondary prevention patients from the placebo arm in the FOURIER trial (3.4 versus 3.3 per 100 person-years).

In the previous limited body of literature on those with CAC ≥1000, authors have investigated either only mortality events or only CHD events in their respective study cohorts and with less extensive descriptive characteristics on these individuals.[3,36,37] For example, although a previous study by Shaw et al[38] showed higher risk for all-cause mortality in asymptomatic patients with CAC ≥1000, the study did not focus on this population of individuals with CAC ≥1000 and thus provided limited descriptive characteristics on this group. In a different study that explored patients with CAC ≥1000, the authors investigated only all-cause mortality and found decreased survival with increasing CAC scores and no upper CAC threshold for mortality risk.[37] In addition, the only reference categories used were those with either CAC 1 to 1000 or CAC 0.

Table 4. Hazard Ratios for Non-CVD Events by CAC Score Group

CAC score	Non-CVD event type and aggregate non-CVD, HR (95% CI)							
	Cancer	CKD	Pneumonia	COPD	DVT/PE	Dementia	Hip fracture	Aggregate non-CVD
CAC 0 as reference group								
Model 1, unadjusted HRs								
0	REF	REF	REF	REF	REF	REF	REF	REF
1–399	1.76 (1.53–2.02)	2.17 (1.85–2.54)	1.85 (1.51–2.26)	2.23 (1.72–2.90)	1.63 (1.25–2.12)	2.99 (2.36–3.80)	4.03 (2.33–6.99)	2.11 (1.90–2.35)
400–999	2.68 (2.13–3.37)	3.61 (2.81–4.64)	3.64 (2.70–4.91)	3.66 (2.43–5.49)	1.68 (1.01–2.82)	5.96 (4.27–8.33)	5.86 (2.68–12.79)	3.41 (2.88–4.05)
≥1000	4.51 (3.55–5.74)	6.64 (5.12–8.62)	5.89 (4.28–8.10)	6.02 (3.92–9.26)	3.10 (1.86- 5.19)	9.09 (6.38–12.96)	9.65 (4.29–21.67)	5.68 (4.73–6.83)
Model 2, fully adjusted* HRs								
0	REF	REF	REF	REF	REF	REF	REF	REF
1–399	1.11 (0.95–1.29)	1.12 (0.94–1.33)	1.11 (0.88–1.39)	1.29 (0.96–1.72)	1.03 (0.77–1.39)	1.38 (1.06–1.79)	1.84 (1.00–3.38)	1.21 (1.07–1.36)
400–999	1.34 (1.04–1.73)	1.19 (0.90–1.57)	1.60 (1.14–2.24)	1.69 (1.07–2.66)	0.75 (0.42–1.34)	1.72 (1.18–2.51)	2.03 (0.86–4.79)	1.41 (1.17–1.71)
≥1000	1.80 (1.36–2.40)	2.01 (1.49–2.70)	2.22 (1.53–3.22)	2.16 (1.32–3.54)	1.49 (0.83–2.67)	2.15 (1.41–3.26)	3.35 (1.33–8.44)	1.95 (1.57–2.41)
CAC 400–999 as reference group								
Model 1, unadjusted HRs								
400–999	REF	REF	REF	REF	REF	REF	REF	REF
≥1000	1.68 (1.25–2.26)	1.82 (1.33–2.50)	1.60 (1.10–2.35)	1.61 (0.96–2.71)	1.79 (0.91–3.50)	1.57 (1.05–2.34)	1.68 (0.68–4.13)	1.66 (1.33–2.07)
Model 2, fully adjusted* HRs								
400–999	REF	REF	REF	REF	REF	REF	REF	REF
≥1000	1.35 (0.97–1.88)	1.70 (1.19–2.43)	1.33 (0.88–2.02)	1.32 (0.75–2.34)	1.68 (0.78–3.64)	1.25 (0.79–1.99)	2.45 (0.91–6.58)	1.43 (1.12–1.83)

CAC indicates coronary artery calcium; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DVT, deep vein thrombosis; HR, hazard ratio; PE, pulmonary embolism; and REF, referent.

*Adjusted for age, sex, race/ethnicity, obesity, hypertension, total cholesterol, high-density lipoprotein cholesterol, triglycerides, smoking, diabetes, family history of myocardial infarction, anti-hypertensive medications, and cholesterol medications.

In terms of non-CVD events, no existing literature explores those with CAC ≥1000. Although Handy et al[5] in a previous study found an association among multiple types of non-CVD events with increased CAC scores in the MESA population, the highest CAC group investigated in that study had CAC >400. In our study, we found that those with CAC ≥1000 had almost double the risk for a first non-CVD event compared with those with CAC 0 and almost 1.5-fold increased risk compared with those with CAC 400 to 999. These findings are supported by the idea that CAC is a marker of not only atherosclerosis but also biological age and subclinical organ injury.[16–20] Although CAC may not have a direct causal relationship with non-CVD outcomes, it reflects an individual's vulnerability to risk factors and can help predict the risk of developing future chronic disease such as cancer and chronic kidney disease, in addition to its usefulness as a risk predictor for CVD events.[5,16,19,20]

Most notably, in a previous 2011 study by Coylewright et al[36] that used the MESA population to investigate CHD events and individual coronary end points such as MI and angina, the authors found that very high CAC ≥1000 was not associated with hard CHD end points (such as CHD death, MI, and resuscitated cardiac arrest) compared with those with CAC 400 to 999, although these individuals did have a higher risk for angina. Although these findings are in contrary to results from our analysis, they were seen as consistent with the idea that individuals with more dense CAC could have a risk profile similar to that of individuals with lower CAC scores or even benefit from a protective effect, given that CAC density has been shown to be inversely associated with CHD and CVD risk at any level of CAC volume.[27] Indeed, some have postulated that those with extensive CAC have increased calcification density rather than more plaque burden, perhaps even lessening an individual's risk for ASCVD events.[39–44] Because of this notion, those with extensive CAC were not necessarily interpreted as being such a distinctly high-risk population in the past.

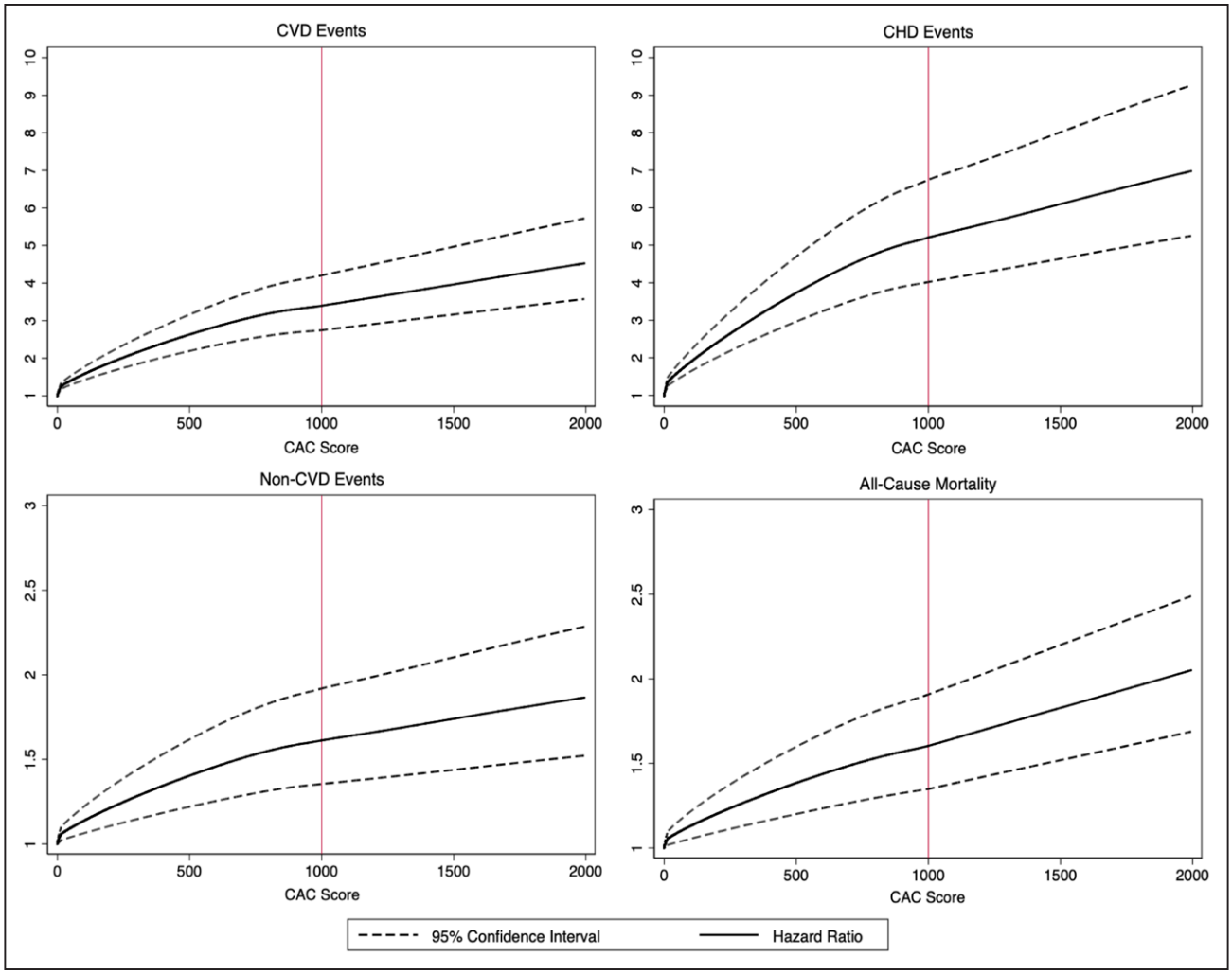

Figure 1. Multivariable-adjusted hazard ratios and 95% CIs for cardiovascular disease (CVD) events, coronary heart disease (CHD) events, non-CVD events, and all-cause mortality as a function of coronary artery calcium (CAC) score.
Cubic splines were used in the multivariable model with knots placed at CAC 100 and CAC 1000. Hazard ratios were adjusted for age, sex, race/ethnicity, obesity, hypertension, total cholesterol, high-density lipoprotein cholesterol, triglycerides, smoking, diabetes, family history of myocardial infarction, antihypertensive medications, and cholesterol medications.

Conversely, we show that those with extensive CAC (≥1000) are a unique population of individuals who are at substantially higher risk than those with CAC 400 to 999 for CVD, CHD, and non-CVD events, in addition to all-cause mortality. These high-risk individuals also are distinct in their burden of extracoronary calcium, with higher aortic root calcium, aortic valve calcium, mitral valve calcium, and thoracic artery calcium than those with lower CAC, similar to results found by the CAC Consortium.[3] We show that these individuals with CAC ≥1000 have significantly increased CAC area compared with those with CAC 400 to 999 yet almost identical CAC density.

Although our results may seem contradictory to the Coylewright et al[36] previous study on the same population of MESA participants, this could be explained by the fact that our analysis now uses almost 10 more years of follow-up data than the previous study. It is likely that this previous MESA study was underpowered because of its shorter follow-up time for event end points compared with our study, which has a median of 15.7 years of follow-up. For example, at the time of the study by Coylewright et al, there were only 45 CHD events in the CAC ≥1000 group and 53 events in the CAC 400 to 999 group[36]; our study has 90 CHD events in the CAC ≥1000 group and 109 events in the CAC 400 to 999 group. A tipping-point analysis (Table VII and Figure II in the Data Supplement) performed on the MESA data set shows that the *P* value for log rank becomes significant for CHD events only after a follow-up time between 6 and 7 years, whereas the Coylewright et al study had between 5 and 6 years of follow-up time.

When examining the extracoronary calcification specifically in the CAC ≥1000 group, a univariate analysis (Figure III in the Data Supplement) shows a trend that more extracoronary calcification adds graded risk for all-cause mortality. However, a multivariate analysis (Table VIII in the Data Supplement), when adjusted for

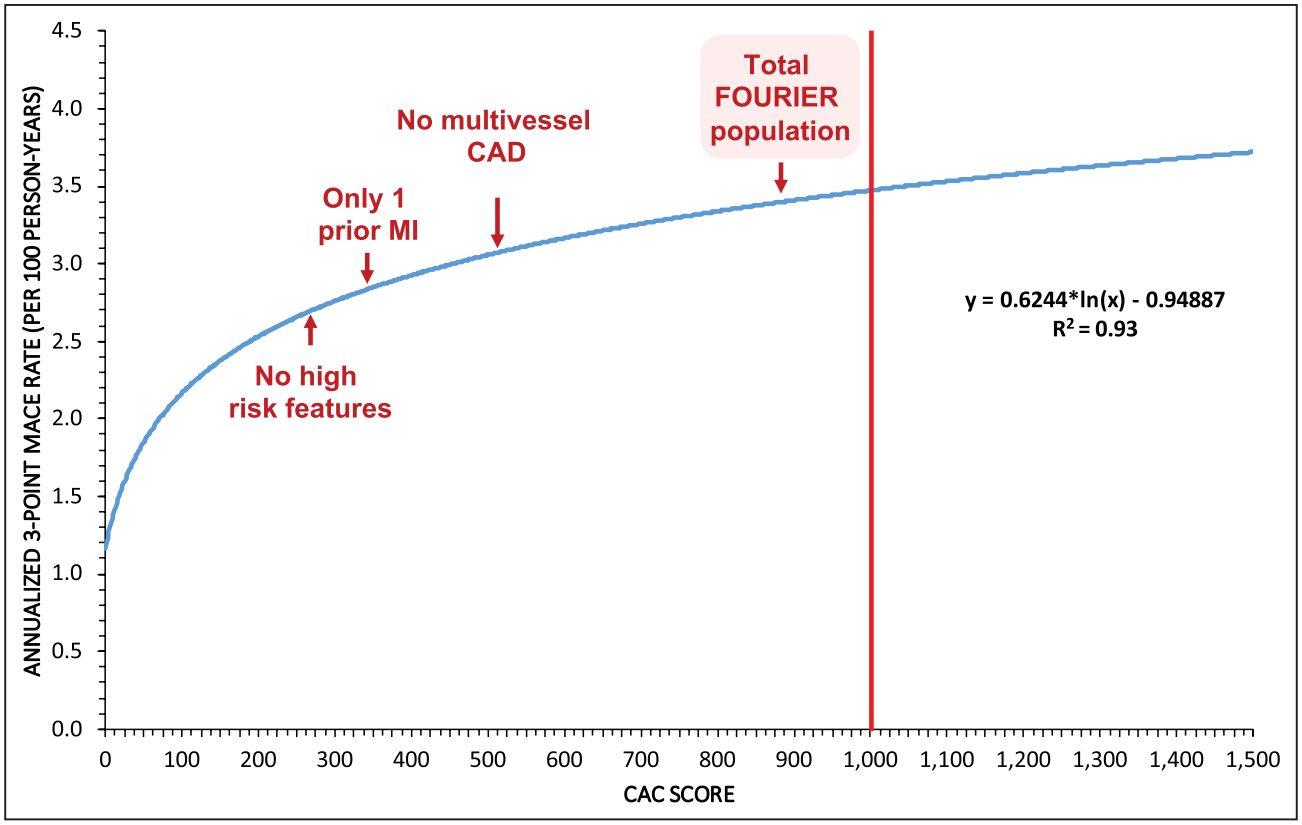

Figure 2. Annualized 3-point major adverse cardiovascular event (MACE) rate (per 100 person-years) as a function of coronary artery calcium (CAC) score.

A logarithmic model was used. The annualized 3-point MACE rates (per 100 person-years) of the total FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) population along with low-risk subgroups of the FOURIER population are indicated on the graph with their corresponding equivalent CAC scores. For the total FOURIER population, the annualized 3-point MACE rate was 3.3 with an equivalent CAC score of 902. The annualized 3-point MACE rate for the low-risk subgroups of FOURIER with no multivessel disease, only 1 previous myocardial infarction (MI), and no high-risk features and the corresponding equivalent CAC score for each were as follows: 3.0 with CAC 529, 2.7 with CAC 364, and 2.6 with CAC 294, respectively. CAD indicates coronary artery disease.

age, sex, and race/ethnicity, does not show a consistent independent risk between extracoronary calcification and risk for CVD events or all-cause mortality. Given the small sample size (n=257) for the CAC ≥1000 group, we believe that the multivariate analysis is underpowered to show additive risk of extracoronary calcification in this group. An interesting finding is that, in the univariate analysis (Figure III in the Data Supplement), once there is at least 1 site of extracoronary calcification, the risk becomes >2 per 100 person-years and >5 per 100 person-years for all CVD events. The outlier, with considerably lower event rates, is zero sites of extracoronary calcification. Those with CAC ≥1000 who have no extracoronary calcification may represent a unique phenotype in need of further study.

With a growing body of literature on the importance of CAC as a tool in CVD and non-CVD risk assessment, major guidelines have now incorporated the use of CAC in risk stratification.[45–48] For example, the 2019 CVD Primary Prevention Clinical Practice Guidelines recommend statin use in select adults with CAC >100 or above the 75th percentile for age/sex/race; this is an update from the 2013 ACC/AHA guidelines that state that CAC ≥300 could inform decision making in starting statin therapy in those with unclear risk.[15,34] For these primary prevention individuals, the guidelines recommend either nonpharmacological or statin therapy, depending on their risk level.[34,49] More intense low-density lipoprotein cholesterol lowering with the addition of nonstatin drugs such as ezetimibe and proprotein convertase subtilisin/kexin type 9 inhibitors is not indicated in this group except in rare instances such as in those with familial hypercholesterolemia, for whom guidelines state that these drugs may be considered as add-on treatment to maximally tolerated statin therapy.[49]

On the other hand, for secondary prevention patients, the 2018 Cholesterol Clinical Practice Guideline recommends more intensive low-density lipoprotein cholesterol lowering with the addition of nonstatin therapy (ie, ezetimibe and proprotein convertase subtilisin/kexin type 9 inhibitors) in these individuals if they fall in the high-risk category or very high-risk category, with category criteria described in the guidelines.[49,50] However, we demonstrate that primary prevention individuals with extensive CAC (≥1000) actually had an

annualized rate for hard CVD events (ie, 3-point MACE) similar to that of stable treated high-risk secondary prevention patients such as those in FOURIER.[31,32] Our results argue for a less distinct risk stratification algorithm between primary and secondary prevention patients because we show that their risk for CVD events could overlap or the risk could be even higher in certain primary prevention populations.

These findings are in agreement with a previous study using the CAC Consortium population of primary prevention patients, showing CVD mortality event rates in their study population equivalent to those in secondary prevention patients from FOURIER. The authors found a CVD mortality annualized event rate of 0.80%/y in their study population versus 0.77%/y in FOURIER.[3] Our study expands on this previous study in many ways, notably by also comparing event rates of those with CAC ≥1000 with lower-risk groups as defined by Sabatine et al.[31] In addition, the CAC Consortium population of individuals with CAC ≥1000 was almost 90% White in ethnicity, whereas in our study, Black and Hispanic individuals make up almost half of those with CAC ≥1000, with a similar ethnicity distribution across all other CAC score groups.[3] Furthermore, MESA enrolled participants from the general population, allowing more generalizability than the CAC Consortium study, which enrolled patients who were referred for CAC scans.[22] Studies with referred patients likely have a greater number of individuals with atypical symptoms or with higher pretest probability for CVD events. Although more generalizable, our estimates in MESA likely underestimate events in the clinical population, which would potentially make our results more impactful in clinical practice.

Conclusions

These results establish a need for future guidelines to recognize the risk continuum according to atherosclerotic burden, that is, that some asymptomatic primary prevention patients have a CVD risk that is the same as or higher than that for traditional secondary prevention patients (with a previous event) and thus should have the opportunity to receive the same aggressive treatment regimen, with the addition of ezetimibe or proprotein convertase subtilisin/kexin type 9 inhibitors to maximally tolerated statin therapy. Although some may pose the argument that aggressive prevention may be too late, we believe that those with CAC ≥1000 are certainly high-risk but not of sufficiently high absolute risk that aggressive prevention could not provide considerable benefit. For example, in our CAC ≥1000 subset, 1-year survival was 98.4%, 3-year survival was 92.6%, and 5-year survival was 87.5%. Even at 10 years, the survival rate was 65.9%, and by the end of our 17.5 years of follow-up, the survival was still 38.4%. This provides a long latency for prevention, for example, for statins or other pharmacological agents to modulate plaque and prevent events. Therefore, we feel that aggressive prevention would still be very beneficial for those with CAC ≥1000, despite their high-risk status. We expect future guidelines to incorporate specific recommendations for this high-risk group. The implications from our findings also open the door for future studies to consider recruiting this high-risk primary prevention group into secondary prevention clinical trials.

Study Limitations

Our study has several limitations. First, our primary study population of participants with CAC ≥1000 was still relatively few in number (n=257), and one of our main comparative groups (CAC 400–999) had only 420 participants. The relatively small sample size may cause our results to be underpowered in detecting significant differences between event rates for certain outcomes of interest such as the less common non-CVD end points. Because of the relatively small sample size, the limited number of events could influence the CAC threshold in terms of designating CAC 1000 as a cut point for the distinct high-risk group. However, CAC 1000 is a well-established, extensively studied cut point.

Another limitation in our study is that we did not account for change in therapy after baseline. However, previous studies in MESA showed limited impact of knowledge of CAC score on downstream behavior, and in the limited instances of imbalanced initiation of aspirin, antihypertensive therapy, or statins, this would bias our results toward the null, increasing the impact of our results for those with CAC ≥1000. A fourth limitation is the choice of a logarithmic model to graph CVD event rates as a function of CAC score, which might underestimate event rates at extremely high values. In our spline curves (Figure 1), the graph of hazard ratios for CVD events continued to increase past CAC scores of 1000 with no apparent risk plateau, whereas our logarithmic model graph (Figure 2) by its nature plateaus earlier. Thus, our CAC scores producing stable secondary prevention level risk may be somewhat conservative. Finally, non-CVD diagnoses in MESA were obtained using inpatient hospitalization *International Classification of Diseases* coding, which would overlook mild cases managed exclusively in the outpatient setting. This could potentially underestimate our observed associations between CAC score and certain non-CVD outcomes (ie, dementia or pneumonia).

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Supplemental Materials

Data Supplement Tables I–VIII
Data Supplement Figures I–III

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