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Coronary artery Calcium predicts Cardiovascular events in participants with a low lifetime risk of Cardiovascular disease: The Multi-Ethnic Study of Atherosclerosis (MESA)

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ABSTRACT

Aims: Patients with a low lifetime risk of coronary heart disease (CHD) are not completely free of events over 10 years. We evaluated predictors for CHD among "low lifetime risk" participants in the population-based Multi-Ethnic Study of Atherosclerosis (MESA).

Methods: MESA enrolled 6814 men and women aged 45–84 years who were free of baseline cardiovascular disease. Using established criteria of non-diabetic, non-smokers with total cholesterol ≤200 mg/dL, systolic BP ≤ 139 mmHg, and diastolic BP ≤ 89 mmHg at baseline, we identified 1391 participants with a low lifetime risk for cardiovascular disease. Baseline covariates were age, gender, ethnicity, HDL-C, C-reactive protein, family history of CHD, carotid intima-media thickness and coronary artery calcium (CAC). We calculated event rates and the number needed to scan (NNS) to identify one participant with CAC>0 and > 100.

Results: Over 10.4 years median follow-up, there were 33 events (2.4%) in participants with low lifetime risk. There were 479 participants (34%) with CAC>0 including 183 (13%) with CAC>100. CAC was present in 25 (76%) participants who experienced an event. In multivariable analyses, only CAC>100 remained predictive of CHD (HR 4.6; 95% CI: 1.6–13.6; p = 0.005). The event rates for CAC = 0, CAC>0 and CAC>100 were 0.9/1,000, 5.7/1,000, and 11.0/1000 person-years, respectively. The NNS to identify one participant with CAC>0 and > 100 were 3 and 7.6, respectively.

Conclusions: While 10-year event rates were low in those with low lifetime risk, CAC was the strongest predictor of incident CHD. Identification of individuals with CAC = 0 and CAC>100 carries significant potential therapeutic implications.

1. Introduction

Cardiovascular risk estimation in asymptomatic patients is the basis for primary preventive efforts against cardiovascular disease (CVD), the leading cause of death in developed nations [1]. Traditionally, risk factors captured at one office visit are used to estimate the absolute risk of CVD over the ensuing 10-years, guiding eligibility for preventive therapies [2,3]. However, concerns exist over the uncertainty of these intermediate-term predictive models and the predilection to miss a significant portion of those truly at risk, especially in younger individuals [4].

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Lifetime risk estimates are now available based on traditional risk factors and have been incorporated into US risk-assessment guidelines [3,5]. These estimates may identify younger individuals with low short-term but high lifetime risks, who may still benefit from intensive lifestyle modification. Additionally, a low lifetime risk may provide reassurance. However, although occurring at a considerably lower rate, cardiovascular events still ensue in some middle-aged adults with low lifetime risk.

Subclinical atherosclerosis detection and burden by coronary artery calcium (CAC) has consistently provided incremental risk prediction across varying subgroups, suggesting significant potential therapeutic implications. This finding extends to those identified as low risk based on traditional risk factors [6–8].

Low lifetime risk patients have a low burden of traditional risk factors. We analyzed asymptomatic participants with a low lifetime risk of CVD from the Multi-Ethnic Study of Atherosclerosis (MESA) to determine which risk factors predict coronary heart disease (CHD) events. We hypothesized that subclinical atherosclerosis burden independently predicts CHD events over the intermediate term.

2. Methods

2.1. Study participants

The methods and objectives of MESA have been described [9]. A total of 6814 participants aged 45–84 years and free of CVD were recruited at 6 field centers (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; and St. Paul, Minnesota). Ethnic diversity was emphasized to include participants identifying themselves as white, black, Hispanic, or Chinese. The protocols were approved at each site's institutional review board and all participants provided informed written consent.

Participants were excluded due to missing data regarding blood pressure, cholesterol, relevant medications, diabetic or smoking status for this analysis. Based on established criteria [5], low lifetime risk was defined as participants with all optimal or suboptimal risk factors, but no elevated or major risk factors. Optimal and suboptimal risk factors were non-current smoking and non-diabetic status, untreated total cholesterol (TC) $\leq$200 mg/dL, and untreated systolic and diastolic blood pressure (SBP, DBP) < 140 mmHg and <90 mmHg, respectively. We excluded those with elevated and major risk factors consisting of smoking, diabetes, antihypertensive treatment, lipid-lowering treatment, untreated TC > 200 mg/dL, and untreated SBP and DBP $\geq$140 mmHg and $\geq$90 mmHg, respectively.

We excluded 38 participants due to missing data leaving 1391 participants with low lifetime risk among whom 499 (36%) had all optimal risk factors and 892 (64%) had at least one suboptimal risk factor (Fig. 1).

Elevated risk factors were untreated TC 200–239 mg/dL, untreated SBP 140–159 mmHg, or untreated DBP 90–99 mmHg. Major risk factors were smoking, diabetes, treated blood pressure, SBP >160 mmHg, DBP >100 mmHg, treated lipids, or TC > 240 mg/dL. Optimal risk factors were TC < 180 mg/dL, untreated SBP and DBP <120/80 mmHg, non-smoking and non-diabetic status. Suboptimal risk factors were TC 180–200 mg/dL, untreated SBP 120–139 mmHg, or untreated DBP 80–89 mmHg. CHD—Coronary Heart Disease.

2.2. Subclinical atherosclerosis imaging

Computed tomography (CT) methods for CAC scanning and interpretation have been described [10]. CAC scanning was performed at each study site and the Agatston score was interpreted at a single MESA reading center (LA Biomedical Research Institute at Harbor-UCLA, Torrance, California) [11].

Carotid intima-media thickness (CIMT) was obtained at each study site using ultrasonography of bilateral internal and common carotid arteries. Maximal IMT was the mean of the maximum IMT from each anatomical site at a single MESA reading center (Tufts Medical Center, Boston, Massachusetts).

2.3. Clinical variables

At baseline each field center collected socioeconomic and demographic data, smoking status, diabetes status, anthropometric measurements, family history, and blood pressure measurements. Three measures of seated blood pressure were obtained with a uniform automated cuff, and the average of the last two measurements was reported. Fasting blood samples were sent to a central laboratory (University of Vermont, Burlington, Vermont) for TC, triglycerides, high-density lipoprotein cholesterol (HDL-C), high-sensitivity C-reactive protein (hsCRP), and glucose measurements.

Diabetes mellitus was either fasting glucose >125 mg/dL or the use of diabetes medications. Elevated hsCRP was hsCRP $\geq$2 mg/L; "low" HDL-C was HDL-C <40 mg/dL in men and <50 mg/dL in women. Family history of CHD was any immediate member (parent, sibling, or child) who had a myocardial infarction (MI), coronary angioplasty, or coronary artery bypass surgery at any age.

2.4. Event follow-up

CHD events were fatal and nonfatal MI, definite angina, probable angina resulting in revascularization, or resuscitated cardiac arrest. MI was diagnosed using a combination of symptoms, cardiac biomarkers, and electrocardiogram findings. Interviewers contacted participants or family members at 9- to 12-month intervals to determine interim hospital admissions, diagnoses of CHD, and deaths. Medical records were obtained for verification in >95% of cases.

Deaths were verified by hospital records, interviews with family members and collection of death certificates. If the death occurred in the 28 days following a MI, the patient had chest pain within the 72 h prior to death, or there was a history of CHD and no other identifiable cause of death, it was considered a CHD death. Angina was identified as definite, probable or absent by adjudicators. Definite angina required demonstration of reversibility of symptoms through revascularization, the presence of obstructive CAD by angiography, or inducible ischemia on stress testing. Supplemental analyses using CVD as the outcome included CHD death, MI, and fatal and nonfatal strokes (Supplement).

Two physicians of the MESA Morbidity and Mortality committee independently reviewed events and in cases of disagreement, the entire committee adjudicated the event. CHD events were collected over a median follow-up of 10.4 years (Interquartile Range 9.8–10.8 years). Full details of follow-up methods and adjudication are available at http://www.mesa-nhlbi.org.

2.5. Statistical analysis

The pre-specified analysis consisted of chi-square testing for categorical variables, analysis of variance for continuous variables, and Kruskal–Wallis testing of medians for non-normal distributions to compare independent variables among participants with and without incident CHD. Analogous analyses were performed using CVD as the outcome (Supplement).

Independent variables for adjustments in this sample of non-diabetic, non-smokers were age (by decade), gender, ethnicity,

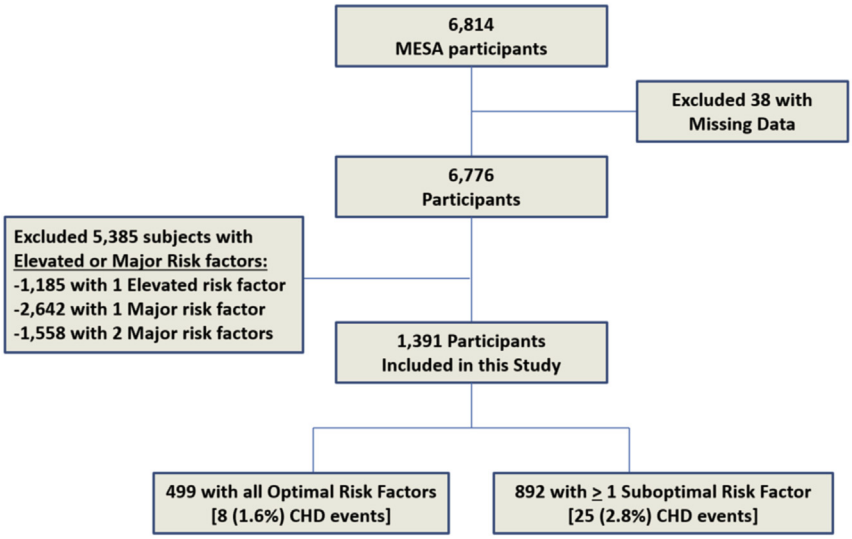

Fig. 1. Study entry flowchart.

family history of CHD at any age, low HDL-C (gender-based), elevated hsCRP, CIMT and CAC. CIMT was categorized above and below the 75th percentile value for the sample. CAC was categorized in Agatston score categories of 0, 1–100, and >100. Clinically relevant categorizations were used for continuous variables (age, HDL-C, CRP) to simulate clinical practice.

Cox proportional hazards regression models to estimate hazard ratios (HR) for events were created after verifying proportional hazards assumptions. Model 1 consisted of unadjusted analyses of independent variables. Model 2 was the primary analysis and consisted of multivariable analysis of all significant variables ($p < 0.1$) from Model 1. Supplementary analyses included Model 3 consisting of Model 2 without imaging variables. The area under the receiver operating curve (AUC) from Model 2, inclusive of significant imaging variables, was compared with the AUC from Model 3 for the prediction of CHD. Similar analyses were performed using CVD as the outcome (Supplement).

Unadjusted CHD event rates per 1000 person years across CAC categories were determined. In a sensitivity analysis, we calculated event rates across age categories: <55 years, 55–65 years, and >65 years. The numbers needed to scan (NNS) to identify one participant with CAC >0 and CAC >100 were calculated.

With the release of the 2013 ACC/AHA pooled atherosclerotic cardiovascular disease (ASCVD) estimator [3], we modified the statistical analysis plan to include a sensitivity analysis comparing the baseline 10-year CVD risk using chi-square testing between those going on to experience incident CHD versus those who did not. Cox models inclusive of 10-year CVD risk estimates were created to compare models with and without imaging (CAC, CIMT) parameters using ROC analysis. The net reclassification improvement using a model inclusive of CAC when added to ASCVD risk was estimated compared to a baseline model of ASCVD risk estimate. Event rates were calculated across categories of 10-year ASCVD risk: low (<5%), intermediate (5–7.5%), and high (≥7.5%).

All statistical analyses were performed using STATA 13.1 (StataCorp LP, College Station, TX).

3. Results

3.1. Baseline characteristics

The baseline characteristics (Table 1) demonstrate the population was middle-aged, evenly distributed by gender, slightly overweight, and had well-controlled traditional cardiovascular risk factors. The 75th percentile value for CIMT was 0.942 mm. There were 479 (34%) participants with CAC>0, including 183 (13%) who had CAC>100.

3.2. Events

Over the 10.4-year median follow-up, there were 33 (2.4%) CHD events, including 4 CHD deaths and 18 MIs. Comparing baseline characteristics (Table 1), those with CHD were older, and had higher proportions of men and family history of CHD. The prevalence of any CAC and CIMT >75th percentile was higher in those experiencing CHD. Among 33 participants experiencing CHD, CAC was present in 25 (76%).

3.3. Predictors of CHD

In unadjusted models (Table 2), increasing decade of age, male gender, family history, CIMT>75th percentile, and CAC categories of 1–100 and > 100 were significant predictors of CHD. There were trends toward higher risk of CHD ($p < 0.1$) for white ethnicity (relative to African American ethnicity) and elevated hsCRP. CIMT >75th percentile and elevated CAC >100 and were associated with the highest HRs at 4.0 and 12.6, respectively.

In the primary multivariable analysis (Model 2) including categorical CAC and CIMT (Table 2), only CAC >100 was a significant, independent predictor of CHD with a HR of 4.6. In multivariable analyses without imaging variables (Model 3), increasing decade of age, male gender, and family history of CHD significantly predicted CHD (Supplement). Similar results were seen when examining CVD as the outcome (Supplement).

In ROC analysis to predict CHD, the AUC increased from 0.775 (95% CI: 0.701, 0.849) to 0.806 (95% CI: 0.724, 0.888) when adding CAC categories to Model 3 (traditional risk factors), though this difference did not reach significance (p 0.14).

3.4. Event rates

The cumulative incidence of CHD in the MESA low lifetime risk sample increases with increasing burden of subclinical atherosclerosis (Fig. 2). The 10-year event rates in those with CAC 0, >0,

Table 1
Baseline Characteristics in MESA participants with Low Lifetime Risk and in those with incident CHD vs. No CHD at 10.4 years median follow-up.

Variable	Entire sample	CHD	No CHD	p-value[a]
Number	1391	33 (2.4%)	1358 (97.6%)	
Demographics				
Age (years)	58.6 (10.2)	**66.6 (10.0)**	**58.4 (10.1)**	**<0.001**
Male	715 (51%)	**24 (73%)**	**691 (51%)**	**0.01**
Ethnicity				**0.10**
White	573 (41%)	20 (61%)	553 (41%)	
Black	277 (20%)	3 (9%)	274 (20%)	
Hispanic	305 (22%)	7 (21%)	298 (22%)	
Asian	236 (17%)	3 (9%)	233 (17%)	
Former smoker	565 (41%)	17 (52%)	548 (41%)	0.20
Family History of CHD	438 (33%)	**16 (53%)**	**422 (33%)**	**0.02**
Measurements				
BMI (kg/m^2)	27.0 (5.0)	28.0 (4.6)	27.0 (5.0)	0.22
Systolic BP (mmHg)	113.8 (13.0)	117.2 (13.0)	113.7 (13.0)	0.12
Diastolic BP (mmHg)	68.6 (8.7)	66.7 (7.8)	68.7 (8.7)	0.21
Biomarkers				
LDL-C (mg/dL)	102.3 (19.3)	104.5 (18.4)	102.3 (19.3)	0.51
HDL-C (mg/dL)	48 (40, 59)	45 (36, 52)	48 (40, 59)	0.07
Low HDL-C[b]	501 (36%)	14 (42%)	487 (36%)	0.44
Total Cholesterol (mg/dL)	173.7 (19.0)	174.5 (15.2)	173.7 (19.1)	0.83
Triglycerides (mg/dL)	91 (66, 131)	99 (77, 154)	91 (66, 131)	0.14
NonHDL-C (mg/dL)	123.3 (21.4)	128.8 (18.2)	123.1 (21.4)	0.13
CRP (mg/L)	1.3 (0.6, 3.3)	2.0 (0.8, 5.9)	1.3 (0.6, 3.3)	0.11
High CRP (>2 mg/L)	513 (37%)	17 (52%)	496 (37%)	0.08
Subclinical Atherosclerosis				
CAC (Agatston's Score)	0 (0, 20)	**126 (3, 427)**	**0 (0,15)**	**<0.001**
CAC Categories				**<0.001**
0	912 (66%)	**8 (24%)**	**904 (67%)**	
1–100	296 (21%)	**7 (21%)**	**289 (21%)**	
>100	183 (13%)	**18 (55%)**	**165 (12%)**	
Carotid IMT (mm)	0.81 (0.17)	**1.17 (0.61)**	**0.87 (0.42)**	**<0.001**
Carotid IMT (>75th percentile[c])	340 (25%)	**18 (56%)**	**322 (24%)**	**<0.001**

Values listed as number (%), mean (standard deviation), or median (25th, 75 t h percentiles) as appropriate.
[a] p-value for heterogeneity between those with incident vs. those without incident CHD over study follow-up.
[b] Low HDL-C defined as <50 mg/dL in women and <40 mg/dL in men.
[c] 75th percentile CIMT = 0.942 mm; CIMT available in 1365 participants.

Table 2
Unadjusted and adjusted hazard ratios for CHD in MESA participants with low lifetime risk.

Variable	Unadjusted (95% CI)	p-value	Adjusted Model 2 (95% CI)[a]	p-value
Age (per 10 yrs)	2.2 (1.6–3.1)	**<0.001**	1.3 (0.9–2.0)	0.22
Male	2.6 (1.2–5.6)	**0.01**	1.6 (0.7–3.9)	0.29
Ethnicity				
White	1 (ref)	–	1 (ref)	–
Chinese-American	0.4 (0.1–1.2)	0.11	0.9 (0.3–3.3)	0.91
African-American	0.3 (0.1–1.1)	**0.08**	0.6 (0.2–2.1)	0.43
Hispanic	0.7 (0.3–1. 7)	0.43	1.2 (0.5–3.0)	0.73
Low HDL-C[b]	1.3 (0.7–2.6)	0.44	–	–
CRP>2 mg/dL	1.8 (0.9–3.6)	**0.08**	2.1 (1.0–4.6)	0.06
Family History of CHD	2.3 (1.1–4.6)	**0.03**	1.8 (0.8–3.7)	0.13
Carotid IMT>75th Percentile[c]	4.0 (2.0–8.1)	**<0.001**	2.1 (0.9–4.7)	0.08
CAC Categories				
0	1 (ref)	–	1 (ref)	–
1–100	2.9 (1.0–7.9)	**0.04**	1.5 (0.5–4.7)	0.46
>100	12.6 (5.5–28.9)	**<0.001**	**4.6 (1.6–13.6)**	**0.005**

[a] Multivariable Model 2 includes variables with p < 0.1 in unadjusted analysis.
[b] Low HDL-C defined as <50 mg/dL in women and <40 mg/dL in men.
[c] 75 t h percentile CIMT = 0.942 mm; CIMT available in 1365 participants.

and >100 consistently increases in a similar fashion across age categories as well (Table 3).

Event rates increase across increasing burdens of subclinical atherosclerosis measured by coronary artery calcium (CAC) and carotid intima media thickness (CIMT) percentiles.

3.5. Number needed to scan

In order to identify one low lifetime risk individual with any CAC (CAC >0), the NNS was 3. In order to identify one low lifetime risk individual with CAC >100, the only significant predictor of CHD in multivariable analysis, the NNS was 7.6. Among those with 10-year ASCVD risk of <5%, the NNS to identify CAC>0 and > 100 were 5.8 and 26.5, respectively. Among those with ASCVD risk 5–7.5%, the NNS to identify CAC>0 and > 100 were 2.3 and 7.6, respectively. Among those with ASCVD risk >7.5%, the NNS to identify CAC>0 and > 100 were 1.5 and 3.1, respectively.

3.6. 10-year risk estimates

The mean estimated 10-year ASCVD risk was 6.5 ± 7.3%. There were 7 CHD events (0.9%) among 822 participants with estimated 10-year risk <5%, 3 events (1.9%) among 159 participants with risk between 5 and 7.5%, and 23 events (5.7%) among 404 participants with risk >7.5%. Those developing CHD had higher average 10-year risk compared to those without incident CHD (13.2 ± 9.0% vs. 6.3 ± 7.1%; p < 0.001). In multivariable models of 10-year risk and CAC and CIMT (supplemental material), CAC>100 remained significant with HR 5.2 (95% CI: 1.9–14.2; p = 0.001), as did an ASCVD risk > 7.5% with a HR 2.8 (95% CI: 1.0–7.7; p = 0.04). Similar results were seen when examining CVD as the outcome of interest, although only CAC>100 was significantly predictive of CVD in multivariable analysis with HR 4.0 (95% CI: 1.5–10.5; p = 0.006; Supplement).

In ROC analysis, the AUC increased significantly when adding

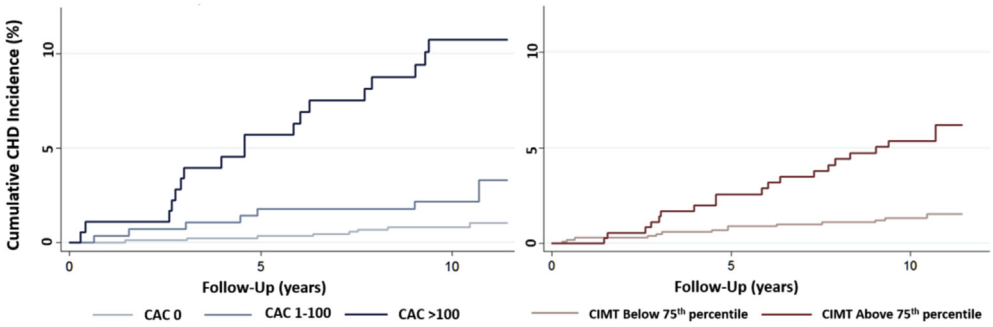

Fig. 2. Event rates across subclinical atherosclerosis Categories.

Table 3
10-year CHD Event Rates per 1000 person-years among CAC categories for MESA participants with Low Lifetime Risk across baseline age and 10-year CVD risk categories.[a]

Category	Event rates if CAC = 0	Event rates if CAC>0	Event rates if CAC>100
All Participants (n = 1391)	0.9 (n = 912)	5.7 (n = 479)	11.0 (n = 183)
Age Categories			
<55 years (n = 611)	0.8 (n = 520)	1.1 (n = 91)	7.6 (n = 14)
55–64 years (n = 362)	0.9 (n = 231)	4.7 (n = 131)	9.1 (n = 15)
≥65 years (n = 418)	1.3 (n = 161)	8.1 (n = 257)	12.2 (n = 124)
Risk Categories[a]			
<5% (n = 822)	0.9 (n = 681)	0.7 (n = 141)	3.3 (n = 31)
5–7.5% (n = 159)	0 (n = 90)	4.4 (n = 69)	15.3 (n = 21)
≥7.5% (n = 404)	1.6 (n = 136)	9.0 (n = 268)	12.4 (n = 130)

[a] Categories of 10-year CVD risk based on the 2013 AHA/ACC pooled CVD risk calculator.

imaging variables to ASCVD risk categories from 0.718 to 0.795 (p = 0.003). When adding CAC scores to ASCVD risk, among those experiencing a CHD event, 24% were correctly reclassified. Among those not experiencing a CHD event, 9.7% were correctly reclassified yielding a net reclassification improvement of 33.9% (p = 0.03). Event rates across categories of 10-year CVD risk demonstrate the low risk associated with a 0 CAC score and increased risk with any CAC (Table 3).

4. Discussion

In this multi-ethnic population with a low lifetime risk of CVD, while CHD event rates over 10-years were low (2.5%), elevated CAC>100 was the most significant predictor of incident CHD. The 10-year event rates in those with any CAC>0 and elevated CAC>100 was 5.7/1000 and 11/1000 person years, respectively. In contrast, the event rate in those with CAC = 0 was very low at 0.9/1000 person years. Our findings have several important implications for risk prediction and public health.

In this population with a low burden of traditional risk factors, there is surprising heterogeneity in risk for CHD. This heterogeneity is most closely associated with either a lack of (CAC = 0) or high burden (CAC>100) of subclinical atherosclerosis. Given this heterogeneity, our study suggests a need for further investigation into the value of CAC scanning across a wide spectrum of cardiovascular risk. Additionally, the presence of subclinical atherosclerosis in this population without traditional risk factors supports the utility of CAC to identify unrecognized risk factors and biomarkers that may contribute to atherosclerosis in future studies. Moreover, our findings raise important questions about preventive measures in those with well-controlled modifiable risk factors.

Finally, among those with low lifetime risk, three individuals would need to undergo CAC scanning to identify one with any CAC and 7 to 8 individuals would need to be scanned to identify one with high burdens of CAC (>100). The public health implications of these values merit further attention.

4.1. CAC and cardiovascular risk

The finding of CAC as the most significant predictor of CHD events in this novel analysis of a low-lifetime risk population is not unexpected. CAC is a specific marker of atherosclerosis, the necessary intermediate phenotype for CHD events. As such, several studies have shown CAC to be a superior predictor across a spectrum of cardiovascular risk estimated by traditional risk factors.

In the intermediate risk group (10–20% 10-year Framingham risk) from the Heinz–Nixdorf Recall Study, CAC led to significant reclassification above traditional risk estimation [12]. Greenland et al. also found the greatest utility of CAC in reclassifying the intermediate Framingham 10-year risk group [13]. However, Greenland et al. found no impact of CAC on risk stratification in the low risk group, perhaps due to the low event rate and small sample size of one event in 98 patients with low (<10%) 10-year Framingham risk [13]. In the entire MESA population there is a substantial improvement in risk stratification when adding CAC to traditional risk factors [14].

Expanding on this prior work, we analyzed groups with lower traditional risk factor burdens and demonstrated improved risk prediction by CAC in participants with LDL cholesterol levels <130 mg/dL[7]. Shaw et al. demonstrated improved prediction for mortality across CAC categories in 1302 participants with low Framingham risk [15]. In more than 18,000 participants without traditional risk factors, our group demonstrated incremental increases in all-cause mortality with increasing CAC scores [6].

The present study expands upon prior work 10-year risk estimates by extending the analysis to those with a low lifetime risk for CVD [5]. Lifetime risk assessments can provide guidance for earlier therapeutic intervention in the atherosclerotic disease process and emphasize the importance of achieving simple risk factor control.

Despite a low burden of traditional risk factors, those with a low

lifetime risk were not event-free and CAC was the strongest predictor of events. Notably, enhancing risk prediction among a population with very low risk at baseline is challenging, and could only be accomplished by a marker with significant prognostic value. Our findings add to those of prior studies in persons without risk factors and support the ability of CAC to integrate risk factors (e.g. genetic, dietary, lifestyle factors) that are uncaptured by traditional models of risk estimation [6,7,15]. Improved risk prediction with CAC is a consistent outcome across the spectrum of cardiovascular risk in asymptomatic patients [16].

4.2. CAC in low risk groups

Emerging evidence has addressed the value of CAC detection in traditionally low risk groups. Nasir et al studied a cohort of 44,052 asymptomatic, self-referred individuals who underwent CAC testing and were followed for all-cause mortality over 5.6 years [6]. Individuals with 0 risk factors (i.e., low lifetime risk) and elevated CAC, a feature seen in nearly 15% of this population, had a mortality rate of 16.9/1000 person-years. However, this study was limited due to self-reported risk factors, potential referral bias, and lack of CHD-specific mortality. Our findings confirm these results in a prospective cohort with verified risk factors and well-characterized outcomes in those with low lifetime risk.

Due to the selection criteria, the low lifetime risk group has a low burden of traditional risk factors. The average participant in the present analysis was non-diabetic, non-smoking, and middle aged with normal lipids and blood pressure yielding a median ASCVD risk<5%. However, more than a third had atherosclerosis as measured by CAC and one in 7.5 participants had a high burden of CAC>100. This dichotomy of atherosclerosis in the absence of traditional risk factors raises important questions about mechanisms of atherogenesis, treatment implications, and public health consequences. Our findings clearly demonstrate that one cannot reliably equate the absence of risk factors to a low risk of CHD. This heterogeneity of risk suggests that future guidelines should consider identifying underlying atherosclerotic burden for earlier preventive strategies in traditionally low risk groups.

Our findings highlight uncertainty over treatment implications in those with low traditional risk factor burden. In addition to lifestyle modifications, pharmacotherapies including statins, aspirin, and antihypertensive medications have become mainstays in preventing CVD events. The St. Francis Heart Study demonstrated a benefit from low-dose statin therapy in those with high burdens of CAC [17]. Whether these therapies carry a similar benefit in a population with well-controlled lipids and blood pressure, but with CAC, remains unknown. However, a Cholesterol Treatment Trialists meta-analysis suggests statins benefit those with already low LDL-C levels [18].

Our analysis carries significant public health implications for CAC scanning as CAC outperformed 10-year ASCVD risk estimations in multivariable models. Currently, CAC assessment is given a IIb recommendation to be considered in asymptomatic individuals in whom the decision to start statin therapy remains uncertain after risk discussion [3]. Our findings support the use of CAC scanning to identify those at higher risk, but also highlight an important and often overlooked aspect of CAC scanning: the prognostic power of a zero CAC score [19,20].

Among any risk category, a zero CAC score in those with low lifetime risk translated to the lowest 10-year event rates. In particular, those with >7.5% 10-year ASCVD risk and a zero CAC score had an event rate of less than 2%, though current guidelines would suggest foregoing a CAC scan and prescribing high-dose statin therapy in many of these individuals. It is questionable whether a population with such a low event rate would derive an overall net benefit from interventions beyond low-risk lifestyle modifications. This prognostic power of a zero score in higher risk subgroups, coupled with studies showing the high event rates in those with elevated CAC and low burdens of traditional risk factors [6–8,21], suggests that the impact of CAC scanning across the cardiovascular risk spectrum warrants further evaluation.

Finally, while CAC measurement leads to improved risk discrimination [22], there are concerns over radiation exposure, costs of population-based screening, and incidental findings. In low lifetime risk patients, the NNS are 3 and 7.6 to identify one patient with any CAC and elevated CAC>100, respectively. The public health implications of these NNS are unknown due to the uncertainty regarding the concerns about radiation, cost and incidental findings. The average radiation dose in MESA was 0.9 mSv, and with modern technology, it can be even lower. The cost of a CAC scan is now commonly less than $100. There was no difference in downstream medical testing in a prospective randomized trial of CAC scanning [23].

4.3. Limitations

The study is primarily limited by a low event-rate in this low risk population, requiring the inclusion of soft CHD endpoints. However, the power to detect an association between subclinical atherosclerosis burden and events was adequate, and persisted in an analysis of hard CVD (supplement). Although MESA provides the opportunity to study multiple ethnicities, the low event rate limits our ability to evaluate these findings within ethnic subgroups. Notably, the impact of lifestyle factors such as diet and physical activity were not assessed in this analysis.

5. Conclusion

While 10-year event rates are very low at 2.4% in those with low lifetime risk, a high burden of CAC strongly predicts incident CHD. The NNS to identify one individual with CAC >0 and > 100 are 3 and 7.6, respectively. Those without CAC had the lowest 10-year risk for events, regardless of their 10-year risk estimate. Whether standard primary prevention therapies including aspirin, statins, and antihypertensive medications are beneficial in those with a low burden of traditional risk factors, but with CAC>0 is unclear. A large-scale trial assessing the utility of CAC testing to guide primary prevention therapies across the cardiovascular risk spectrum is needed.

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Disclosures

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2016.01.017.

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