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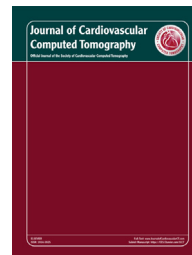
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Original Research Article

Multisite extracoronary calcification indicates increased risk of coronary heart disease and all-cause mortality: The Multi-Ethnic Study of Atherosclerosis

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ABSTRACT

Background: Cardiovascular calcification outside of the coronary tree, known as extracoronary calcification (ECC), is highly prevalent, often occurs concurrently in multiple sites, and yet its prognostic value is unclear.

Objective: To determine whether multisite ECC is associated with coronary heart disease (CHD) events, CHD mortality, and all-cause mortality.

Methods: We evaluated 5903 participants from the Multi-Ethnic Study of Atherosclerosis without diabetes who underwent CT imaging for calcification of the aortic valve, aortic root, mitral valve, and thoracic aorta. Participants were followed for 10.3 years. Multivariable adjusted hazard ratios estimated risk of outcomes for increasing numbers of ECC sites (0, 1, 2, 3, and 4), and receiver operator characteristic analysis assessed model discrimination.

Conflict of interest: Matthew J. Budoff is a consultant for General Electric, and Nathan Wong is a consultant for Reengineering Healthcare, Inc. The other authors declare no conflicts of interest.

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Mortality
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Cardiovascular imaging

Results: Prevalence of any ECC was 45%; median age was 62 years. Compared with those without ECC, those with ECC in 4 sites had increased hazards of 4.5, 7.1 and 2.3 for CHD events, CHD mortality, and all-cause mortality, respectively, independent of traditional risk factors (TRF; all $P \leq .05$), and had ≥ 2 -fold increased hazards for outcomes independent of coronary artery calcification (CAC). Each additional site of ECC was positively associated with each outcome in a graded fashion. When added to TRF, ECC significantly increased the area under the receiver operator characteristic curve for all outcomes and modestly increased the area under the curve for mortality beyond TRF + CAC (0.799 to 0.802; $P = .03$).
Conclusion: Increasing multisite ECC has a graded association with higher CHD and mortality risk, contributing information beyond TRF. Multisite ECC incidentally identified on imaging can be used to improve individualized risk prediction.

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1. Introduction

Despite vigorous prevention efforts, 2 times as many coronary heart disease (CHD) events occur as first-time, rather than recurrent, events,¹ highlighting the need for improved CHD risk assessment and earlier intervention. The existence of cardiovascular calcification has been identified for decades in various extracoronary sites, such as the aortic valve, mitral valve,² or aorta,³ and is thought to be driven by a systemic calcific process.⁴ However, extracoronary calcification (ECC) is rarely given consideration in clinical practice to inform individualized risk profiling. The preferential development of atherosclerosis in different cardiovascular locations among different patient populations invokes the possibility to improve subclinical CHD detection by measuring ECC.⁵ Although studies have correlated individual sites of ECC with outcomes such as CHD events and mortality,^{2,3,6} the significance of multisite ECC concurrently present in a given individual is not well characterized.

ECC has the advantage of being identifiable on the same CT scan as CAC, as well as on noncardiac CT scans and a wide variety of imaging modalities, including plain radiography, dual-energy X-ray absorptiometry, echocardiography, and ultrasonography.^{2,6–8} Although calcification outside of the coronary tree (such as ECC) a priori is not expected to predict CHD events more effectively than coronary calcification, ECC represents readily available information—particularly when found incidentally—which can be used to inform clinical decision making beyond traditional risk scores. Determining the prognostic value of ECC may thus allow the use of ECC information from various sources, possibly even without additional cost or harm to the patient, to direct primary prevention and improve cardiovascular risk prediction. The aim of this study is to use a simple, clinically applicable assessment of ECC to evaluate the hypothesis that multisite ECC is associated with and incrementally improves risk prediction for CHD events, CHD mortality, and all-cause mortality.

2. Materials and methods

2.1. Study population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a longitudinal, population-based cohort study of 6814 people, free of

clinical cardiovascular disease at baseline, aged 45 to 84 years from 6 US centers. Details of its design have been reported.⁹ All participants gave informed consent, and the study protocol was approved by the institutional review board at each site in accordance with the Health Insurance Portability and Accountability Act. Approximately 53% of the cohort participants are female, and the ethnic distribution is 38% Caucasian, 12% Chinese, 28% African American, and 22% Hispanic. Participants were enrolled between August 2000 and July 2002, when a baseline examination was performed. For this study, to allow comparison with the Framingham risk score, we excluded all participants with diabetes, those missing ECC measurements and follow-up, for a total study population of 5903.

2.2. Data collection

Participants completed a self-administered questionnaire during the baseline examination, and clinical and laboratory data were obtained. Total and high-density lipoprotein cholesterol, as well as glucose levels were measured from blood samples after a 12-hour fast. Blood pressure was measured in a seated position 3 times with a Dinamap Pro-100 automated oscillometric sphygmomanometer (Critikon, Wipro GE Healthcare, Waukesha, WI); the average of the last 2 measurements was used in the analysis. Current smoking was defined as having smoked a cigarette in the last 30 days. Diabetes was defined as either a fasting glucose level ≥ 126 mg/dL or use of diabetes medication.

2.3. CT and ECC measures

After providing informed consent, all participants underwent 2 consecutive baseline noncontrast cardiac CT scans that were electrocardiographically gated to the R-R interval.¹⁰ Three sites used the Imatron C-150XL CT scanner (GE Imatron, San Francisco, CA), and 3 sites used multidetector CT scanners (4 slices). The participant was supine for imaging, and a minimum of 35 contiguous images were obtained with a 2.5- or 3-mm slice thickness, starting above the left main coronary artery to the bottom of both ventricles. Each scan was obtained in a single breathhold. A section thickness of 3 mm, field of view of 35 cm, and a matrix of 512×512 were used to reconstruct raw image data. The nominal section thickness was 3.0 mm for electron-beam CT and 2.5 mm for 4-detector row CT. Spatial resolution can be described by the smallest volume element, or voxel, for

the protocol of each system: 1.15 mm³ for 4-detector row CT (0.68 mm × 0.68 mm × 2.50 mm) and 1.38 mm³ for electron-beam CT (0.68 mm × 3.00 mm).¹¹

The CT scans were analyzed for the presence of calcification at 4 sites where ECC is commonly found: aortic valve calcification (AVC), mitral valve calcification, thoracic aorta calcification (TAC), and aortic root calcification (Fig. 1). We decided a priori that given the differential prevalence and wide variation in the range of Agatston scores for calcification in different vascular sites^{12,13} (also seen in the MESA cohort), and in the absence of information on how to integrate such data, determining a weighting or standardization scheme for Agatston scores of various ECC sites would be both difficult to interpret and difficult to generalize. Simply combining the continuous Agatston scores from each ECC site would likely over-represent sites such as TAC, which have up to 5-fold higher Agatston scores than other sites. Thus, we aimed with this study to use a simple, clinically applicable ordinal score of multisite ECC to explore its correlation with and contribution to predicting outcomes: we considered the total number of ECC sites that had any calcium for each participant, from 0 to 4. This ordinal scoring also serves to mimic the amalgamation of available ECC information from various imaging sources to inform a patient's risk in a clinical setting.

According to a previously described method,^{11,14} any calcified focus seen extending from the aortic valve to the

aortic root was deemed AVC, and mitral valve calcification was assessed on every level of the mitral annulus. TAC included both the ascending and descending thoracic aorta, which ranged from the lower edge of the pulmonary artery bifurcation to the cardiac apex. Aortic root calcification was measured at the level of the aortic ring. Total calcium score for CAC was analyzed as a continuous covariate such that ECC could be compared against the best available measure of CAC.

2.4. Event surveillance

Incident CHD and mortality were recorded over a median follow-up of 10.3 years. The outcomes examined in this study included all CHD events, CHD mortality, and all-cause mortality. At intervals of 9 to 12 months, an interviewer contacted each participant or a family member to inquire about interim hospitalizations, cardiovascular procedures, diagnoses, and deaths. MESA successfully obtained medical records for 99% of hospitalizations and 97% of outpatient encounters. Two physicians from the MESA-coordinating center independently classified events; if there were disagreements, a full committee review was made. CHD events were myocardial infarction, resuscitated cardiac arrest, death from CHD, definite angina, or probable angina followed by revascularization. Death investigation included examination of death certificates and next-of-kin interviews. CHD death is defined as death ascertained due to atherosclerotic CHD. Full details of MESA follow-up methods, investigators, and institutions are available at the MESA Web site (www.mesa-nhlbi.org).

2.5. Statistical methods

Multiplicative interaction between diabetes and ECC was found to be significant for the outcome of CHD events ($P = .004$). In light of this interaction and diabetes being considered a CHD equivalent,¹⁵ those with diabetes were excluded from the present analysis. Several descriptive and unadjusted analyses were performed to describe the distribution of ECC in the MESA population. Baseline characteristics were tabulated for the cohort and stratified by the number of calcified ECC locations (0, 1, 2, 3, and 4; Table 1). The distribution of ECC was plotted according to baseline CAC score and Framingham 10-year CHD risk (Fig. 2A,B). Kaplan-Meier curves were plotted for outcomes by increasing sites of ECC (Fig. 4).

Multivariable-adjusted hazard ratios for increasing ECC scores were estimated using 2 Cox proportional hazards models (Tables 2 and 3). The first model was adjusted for traditional risk factors (TRF), including age, sex, race, total cholesterol, high-density lipoprotein, smoking status, cigarette pack-years, systolic blood pressure, hypertension medication use, and creatinine; the second model additionally adjusted for continuous CAC score as $\log(\text{CAC} + 1)$ in addition to TRF. Proportional hazards assumptions were tested by the Schoenfeld residuals and were not violated. A significance test for linear trend for increasing ECC was performed for each model. A P value of $\leq .05$ was deemed to be statistically significant. In sensitivity analysis, we additionally analyzed ECC as a binary variable and performed sensitivity analysis in the

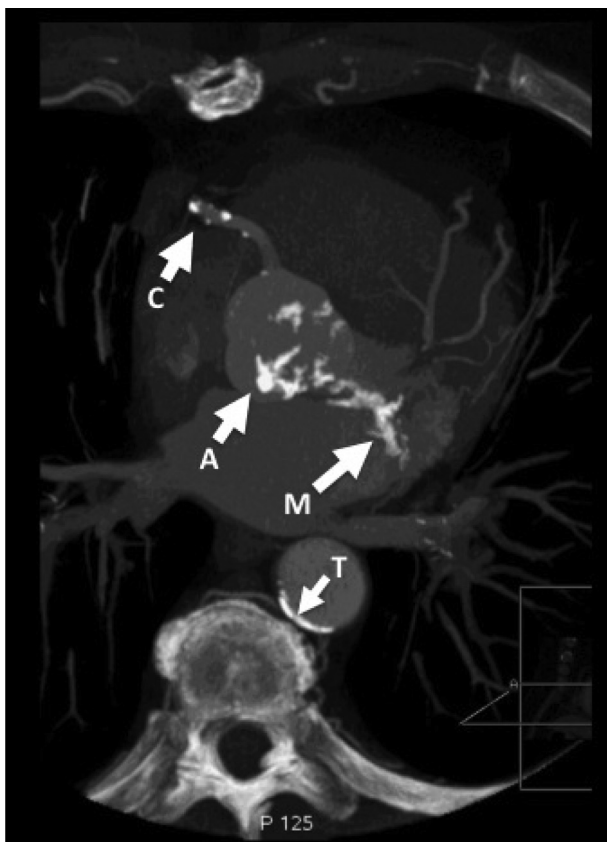


Fig. 1 – Example CT image showing extracoronary calcification. A, aortic valve calcification; C, coronary artery calcification; M, mitral annular calcification; T, thoracic aortic calcification.

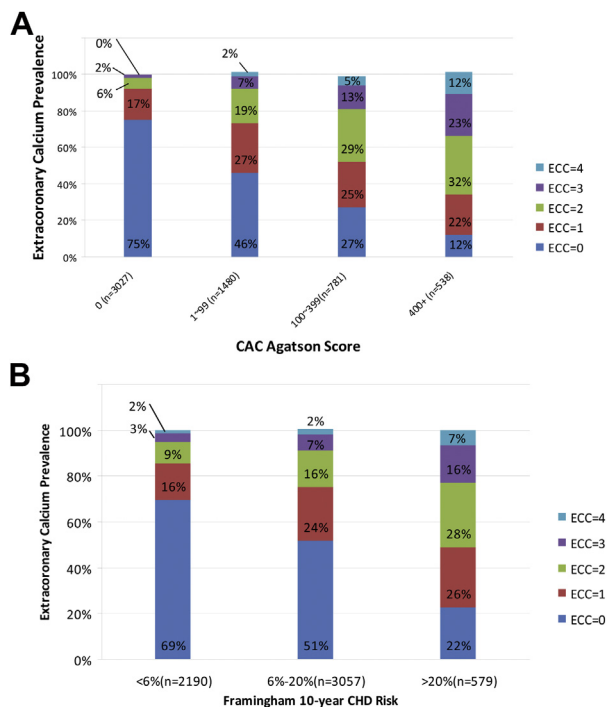


Fig. 2 – Unadjusted prevalence by CAC and Framingham risk strata. (A) Prevalence of extracoronary calcification (ECC) by coronary artery calcification (CAC) score categories in the Multi-Ethnic Study of Atherosclerosis (MESA). (B) Prevalence of ECC by Framingham 10-year coronary heart disease risk in MESA.

subgroup of participants with intermediate CAC scores 1 to 1399. To assess discrimination, receiver operator characteristic (ROC) analysis was performed, and area under the curve (AUC) was compared between models with and without ECC. In addition, we performed net reclassification index analysis¹⁶ for the outcome of CHD events using 10-year Framingham risk categories as cut-points and present the results separately for those participants who did and did not experienced events in the MESA cohort.

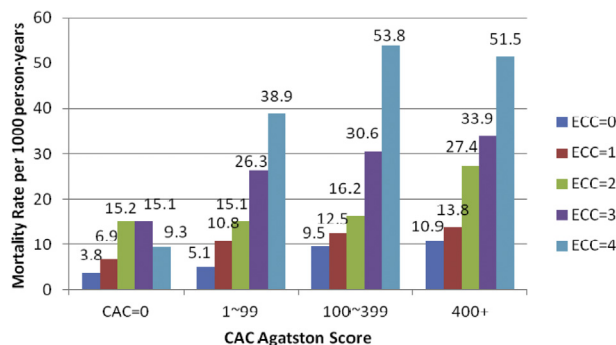


Fig. 3 – Unadjusted all-cause mortality rates per 1000 person years for extracoronary calcium categories according to coronary artery calcium score categories in the Multi-Ethnic Study of Atherosclerosis.

All analyses were conducted with R 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria) and SAS 9.2 (SAS Institute Inc, Cary, NC).

3. Results

3.1. Total population analysis

Forty-five percent of this cohort had baseline calcification in ≥ 1 extracoronary site, and 9 percent had concurrent calcification in ≥ 3 sites. Participants with calcification in more vascular sites tended to be older and white, had higher systolic blood pressure, higher waist circumference, more metabolic syndrome, and more hypertension medication use, were former smokers, and had higher CAC scores and Framingham and Pooled Cohort Equation risk scores¹⁷ (Table 1). Chinese were less likely than other ethnicities to have multi-site ECC.

Although ECC was correlated with CAC ($r = 0.51$; $P < .001$), there remained significant differences between the measures. Twenty-five percent of those with no CAC had ECC in ≥ 1 location, whereas more than two-thirds of participants with CAC ≥ 400 had ECC in ≥ 2 locations in addition to CAC, suggesting a state of generalized cardiovascular calcification (Fig. 2A). About half of the individuals in the expanded intermediate Framingham risk group had some ECC at baseline, whereas nearly 10% had ECC in ≥ 3 sites (Fig. 2B); 36% of those in the Pooled Cohort Equation intermediate risk score group had some ECC at baseline. For those with ECC in 1 site, 52% had calcification in the aortic root, 34% had TAC, 9% had AVC, and 5% had mitral valve calcification. For those with ECC in 2 sites, 61% had calcification in the aortic root + TAC and 16% had aortic root + AVC. For those with ECC in 3 sites, 54% had aortic root + AVC and TAC.

3.2. Clinical outcomes

Over a median of 10.3 years (interquartile range, 1.0 year) of follow-up in MESA, there were 348 CHD events, 65 subjects who died from CHD and 572 subjects who died of any cause. Figure 3 shows unadjusted all-cause mortality rates for increasing numbers of ECC sites, stratified by baseline CAC score categories. For those with nonzero CAC, a positive and graded relationship is observed between increasing ECC and all-cause mortality, with ECC in 4 locations having the highest mortality (Fig. 3). In Figure 4, the Kaplan-Meier curves for the outcomes of CHD events, CHD death, and all-cause mortality all demonstrate separation between the curves for increasing sites of ECC, indicating that an increased burden of ECC is associated with increased risk for these outcomes.

3.3. Survival analysis

Cox proportional hazards models were used to estimate multivariable-adjusted hazard ratios of increasing ECC after adjustment for TRF alone and TRF + CAC for 3 outcomes (Table 2). When added to TRF alone, increasing ECC was significantly positively associated with all outcomes in a graded fashion, with ECC in 4 sites conferring statistically

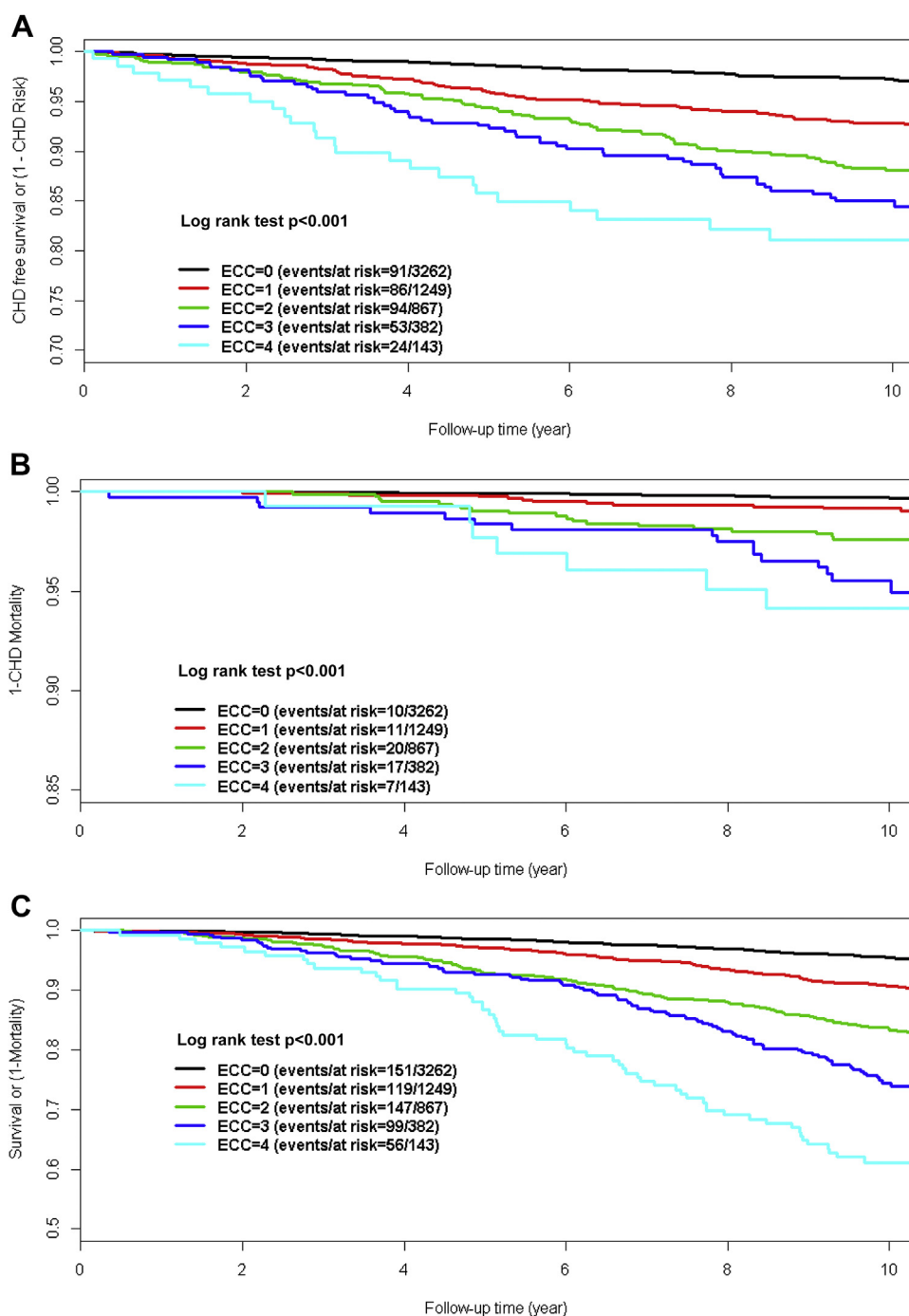


Fig. 4 – Survival curves for incident coronary heart disease (CHD) events, CHD mortality, and all-cause mortality by increasing number of extracoronary calcification (ECC) sites. (A) Kaplan-Meier curves for incident CHD events by increasing number of ECC sites in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort. (B) Kaplan-Meier curves for CHD mortality by increasing number of ECC sites in the MESA cohort. (C) Kaplan-Meier curves for all-cause mortality by increasing number of ECC sites in the MESA cohort.

significant hazard ratios of 4.5, 7.1, and 2.3 for CHD events, CHD mortality, and all-cause mortality, respectively. In models additionally adjusted for CAC, hazard ratios were attenuated but remained graded and statistically significant, with ≥ 2 -fold increased hazard of events for ECC = 4. Statistical

significance for the hazard ratios of individual strata is reflected in the 95% confidence intervals (Table 2), and a significance test for linear trend across increasing ECC of 1 to 4 was significant for all models ($P \leq .01$). Heterogeneity by sex and ethnicity was tested and not found to be significant.

Table 1 – Baseline demographic characteristics and risk factors by number of ECC sites in MESA.

Baseline characteristics	Number of ECC sites					Entire cohort, N = 5903
	0, n = 3262 (55%)	1, n = 1249 (21%)	2, n = 867 (15%)	3, n = 382 (7%)	4, n = 143 (2%)	
Age, y, mean (SD)	56.4 (8.3)	64.9 (8.6)	70.2 (7.3)	72.8 (6.9)	76.2 (4.8)	61.8 (10.3)
Male gender, n (%)	1489 (45.9)	597 (47.9)	393 (45.4)	184 (48.3)	67 (47.5)	2730 (46.5)
Race, n (%)						
White	1218 (37.5)	523 (42.1)	408 (47.2)	205 (53.8)	82 (58.2)	2436 (41.4)
Chinese American, n (%)	427 (13.2)	137 (11.0)	95 (11.0)	30 (7.9)	5 (3.5)	694 (11.8)
African American	894 (27.5)	328 (26.4)	207 (23.9)	67 (17.6)	29 (20.6)	1525 (25.9)
Hispanics	708 (21.8)	255 (20.5)	155 (17.9)	79 (20.7)	25 (17.7)	1222 (20.8)
Body mass index, kg/m ² , mean (SD)	28.1 (5.6)	27.9 (5.1)	27.8 (5.2)	27.9 (4.6)	27.7 (5.0)	28.0 (5.4)
Waist circumference, cm, mean (SD)	96.2 (14.6)	97.9 (13.9)	98.0 (13.3)	100.1 (13.1)	99.8 (11.2)	97.2 (14.1)
Metabolic syndrome, n (%)	724 (22.2)	361 (28.9)	281 (32.4)	149 (39)	52 (36.4)	1567 (26.5)
Systolic blood pressure, mm Hg, mean (SD)	120.0 (18.8)	128.9 (20.9)	134.6 (21.8)	138.4 (23.8)	138.0 (23.4)	125.7 (21.3)
Triglycerides, mg/dL, mean (SD)	125.4 (80.9)	129.7 (78.8)	125.8 (63.9)	135.0 (70.9)	131.0 (76.8)	127.1 (77.5)
Total cholesterol, mg/dL, mean (SD)	193.0 (34.5)	198.0 (35.7)	196.4 (34.8)	198.2 (36.6)	196.4 (37.9)	195.0 (35.1)
HDL cholesterol, mg/dL, mean (SD)	51.8 (15.2)	51.7 (14.4)	51.9 (15.5)	50.6 (14.1)	51.9 (14.9)	51.7 (15.0)
Hypertension medication, n (%)	793 (24.4)	481 (38.7)	410 (47.4)	201 (52.8)	76 (53.9)	1961 (33.4)
Cigarette pack per year	8.5 (16.6)	13.4 (30.0)	14.3 (23.1)	17.0 (27.1)	20.0 (27.8)	11.2 (22.3)
eGFR using CKD-EPI equation, mean (SD)	81.6 (14.6)	76.4 (15.5)	71.4 (15.0)	68.2 (15.1)	66.6 (15.3)	77.8 (15.7)
Log(CAC + 1), mean (SD)	1.1 (1.9)	2.5 (2.4)	3.8 (2.4)	4.5 (2.9)	5.4 (2.3)	2.1 (2.5)
CAC score, n (%)						
0	2287 (70.1)	513 (41.1)	178 (20.5)	54 (14.1)	12 (8.4)	3044 (51.6)
1–99	699 (21.4)	419 (33.5)	292 (33.7)	102 (26.7)	25 (17.5)	1537 (26.0)
100–399	213 (6.5)	197 (15.8)	227 (26.2)	104 (27.2)	42 (29.4)	783 (13.3)
400+	63 (1.9)	120 (9.6)	170 (19.6)	122 (31.9)	64 (44.8)	539 (9.1)
Framingham 10-year CHD risk, n (%)						
<6%	1533 (47.2)	360 (29.0)	209 (24.2)	76 (19.9)	37 (26.2)	2215 (37.7)
6%–20%	1584 (48.8)	730 (58.7)	492 (56.9)	212 (55.6)	64 (45.4)	3082 (52.4)
>20%	130 (4.0)	153 (12.3)	164 (19.0)	93 (24.4)	40 (28.4)	580 (9.9)
Pooled Cohort Equation 10-year risk, n (%)						
<5%	1785 (54.7)	256 (20.5)	54 (6.2)	13 (3.4)	2 (1.4)	2110 (35.7)
≥5% and <7.5%	466 (14.3)	176 (14.1)	73 (8.4)	12 (3.1)	2 (1.4)	729 (12.3)
≥7.5%	1011 (31.0)	817 (65.4)	740 (85.4)	357 (93.5)	139 (97.2)	3064 (51.9)

CAC, coronary artery calcification; CHD, coronary heart disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ECC, extracoronary calcification; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; MESA, Multi-Ethnic Study of Atherosclerosis; SD, standard deviation.

To evaluate whether the presence of “any ECC” is associated with increased clinical risk, similar to when ECC is found incidentally, ECC was modeled as a binary predictor. Because detailed ECC information can and should be obtained from cardiac CT scans themselves when CAC is available, the analysis of binary ECC is not relevant to models that include CAC and was not performed. When added to a model including TRF alone, any ECC was found to be associated with >2-fold higher risk of CHD events, and CHD mortality, but did not reach statistical significance for all-cause mortality (Table 2). Given the strong negative predictive value of CAC = 0 for CHD and the positive predictive value of high CAC ≥400,^{18,19} we performed sensitivity analysis and confirmed that the associations of ECC with all outcomes were as strongly positive in the intermediate CAC group (CAC = 1–399) as in the whole MESA population (data not shown).

3.4. Model comparison

In ROC analysis, ECC significantly improved the AUC for both CHD events and all-cause mortality when added to TRF alone and had borderline significance for CHD mortality, increasing

the AUC from 0.822 to 0.841 ($P = .05$; Table 3). When ECC was added to a model adjusted for TRF and CAC, only the AUC for all-cause mortality was modestly however significantly increased from 0.799 to 0.802 ($P = .03$). When net reclassification index analysis was performed, we observed an improvement among those participants who experienced CHD events when ECC is added to a model adjusted for TRF (Supplementary Table 1); reclassification was not improved in models containing CAC.

4. Discussion

In this population-based, prospective cohort study, we demonstrate that multisite ECC is associated with increased risk of, and incrementally improves prediction for, CHD events, CHD mortality, and all-cause mortality when added to traditional cardiac risk factors. The results of our prospective study support the use of ECC information to improve clinical risk assessment and may be applicable to the common clinical scenario whereby ECC is identified in multiple concurrent sites in a given patient through various imaging modalities.

Table 2 – Hazard ratios by ECC for CHD events, CHD mortality, and all-cause mortality in the MESA cohort.

ECC	Number of events/number at risk [†]	Model with TRF* + ECC		Model with TRF* + log(CAC + 1) + ECC	
		HR (95% CI)	P value (trend)	HR (95% CI)	P value (trend)
CHD events					
ECC = 0 (reference)	90/3214				
ECC = 1	83/1228	1.72 (1.25–2.38)	≤.001	1.33 (0.96–1.84)	≤.001
ECC = 2	93/855	2.38 (1.68–3.38)		1.55 (1.08–2.20)	
ECC = 3	53/380	3.04 (2.03–4.55)		1.66 (1.09–2.52)	
ECC = 4	24/138	4.54 (2.67–7.70)		2.15 (1.25–3.70)	
Any ECC vs no ECC (binary)		2.04 (1.53–2.72)	<.001		
CHD mortality					
ECC = 0 (reference)	10/3214				
ECC = 1	11/1228	1.67 (0.68–4.13)	≤.001	1.55 (0.63–3.86)	.002
ECC = 2	20/855	3.51 (1.47–8.40)		3.04 (1.24–7.42)	
ECC = 3	17/380	5.56 (2.17–14.26)		4.54 (1.70–12.10)	
ECC = 4	7/138	7.13 (2.27–22.44)		5.60 (1.71–18.41)	
Any ECC vs no ECC (binary)		2.66 (1.25–5.70)	.012		
All-cause mortality					
ECC = 0 (reference)	149/3214				
ECC = 1	117/1228	1.01 (0.78–1.31)	≤.001	0.97 (0.75–1.26)	≤.001
ECC = 2	142/855	1.26 (0.96–1.64)		1.16 (0.88–1.52)	
ECC = 3	98/380	1.65 (1.22–2.24)		1.49 (1.09–2.03)	
ECC = 4	53/138	2.30 (1.60–3.31)		2.00 (1.37–2.93)	
Any ECC vs no ECC (binary)		1.21 (0.97–1.51)	.096		

CAC, coronary artery calcification; CHD, coronary heart disease; CI, confidence interval; ECC, extracoronary calcification; HR, hazard ratio; MESA, Multi-Ethnic Study of Atherosclerosis.

Bold values highlight statistical significance.

* TRF = traditional risk factors (includes age, total cholesterol, high-density lipoprotein, smoking status, systolic blood pressure) and sex, hypertension medication, race, and creatinine.

† Excludes those with missing covariates.

Thus, as a risk marker to supplement traditional risk factors, ECC information has the “practical advantage”²⁰ of potentially being identifiable without additional cost or radiation exposure, underscoring its clinical value to supplement traditional cardiac risk assessment.

Our results advance the findings from prior studies that had begun to explore how combinations of atherosclerosis markers in concurrent vascular sites affect hard outcomes, although most studies identifying multisite ECC used echocardiography. The Rotterdam study combined multiple surrogates of atherosclerosis including carotid intima-media thickness, radiographic aortic calcification, and ankle-arm index, to demonstrate that more severe extracoronary atherosclerosis increased risk of myocardial infarction.²¹ The Cardiovascular Health Study used echocardiography to identify valvular calcification in 3 sites in an elderly population

and demonstrated increased incident cardiovascular and all-cause mortality with increasing sites of valvular calcification.² One limitation of the Cardiovascular Health Study is its lack of thoracic aortic calcification assessment, which is one of the most common sites of ECC and is strongly and independently associated with events.^{22,23} Neither the Cardiovascular Health Study nor the Rotterdam study examined improvement in discrimination beyond traditional risk factors, as we present in this study.

In a historical cohort study, Allison et al³ used CT to measure calcification in the carotid artery, thoracic aorta, abdominal aorta, and iliac artery and demonstrated that the addition of ECC measures to models with TRF + CAC significantly increased the AUC for total mortality but not for cardiovascular disease or noncardiovascular disease mortality. Our prospective results corroborate and expand on these

Table 3 – Receiver operator curve analysis for extracoronary calcification and outcomes in the MESA cohort.

Entire cohort	Model with TRF*	Model with TRF* + ECC (ordinal)	P value	Model with TRF* + CAC	Model with TRF* + CAC + ECC (ordinal)	P value
CHD events	0.741	0.756	<.01	0.794	0.796	.36
CHD mortality	0.822	0.841	.05	0.828	0.842	.07
All-cause mortality	0.797	0.801	.01	0.799	0.802	.03

CAC, coronary artery calcification; CHD, coronary heart disease; ECC, extracoronary calcification; MESA, Multi-Ethnic Study of Atherosclerosis.

* TRF = traditional risk factors (includes age, total cholesterol, high-density lipoprotein, smoking status, systolic blood pressure) and sex, hypertension medication, race, and creatinine.

retrospective findings and contribute evidence to the growing concept that diffuse plaque burden, more than focal atherosclerosis intensity, may be more predictive of outcomes.²⁴ In our study, calcification at the aortic root and thoracic aorta appear to show the highest prevalence of calcification compared with other ECC locations examined, both when present in 1 location or multiple locations. Other cohorts have identified thoracic aortic calcification as being highly prevalent,^{3,25} although ours additionally demonstrates the importance of aortic root calcification and confirms that both sites are commonly involved when ECC is concurrently present in multiple locations.

With the increased clinical use of imaging, interest has grown in the implications of incidentally found ECC, which has been identified using a variety of imaging modalities including plain radiography, dual-energy X-ray absorptiometry, echocardiography, and ultrasonography.^{2,6–8} Investigators from the PROVIDI study have published several retrospective reports showing that incidentally found valvular and aortic calcification were independent predictors of cardiovascular events.^{8,26} The ECC detected in MESA can be considered “incidentally found” because the primary intent in obtaining the CT scans was to assess CAC, and studies were over-read to measure ECC. This study is thus among the larger prospective studies to show that incidentally found ECC increases the future risk of incident CHD and mortality outcomes. Our findings should be generalizable to ECC found using other imaging modalities (such as radiographs or non-gated CT), as these modalities require a higher calcium burden to identify positive ECC compared to CT. Similarly, our findings may generalize to ECC identified by echocardiography, although echocardiography may tend to overestimate calcification compared to CT by identifying fibrosis as calcification.

In modeling ECC, we decided to use a simple ordinal quantification of ECC for several reasons. Foremost, the simplicity of ordinal scoring of ECC has direct clinical applicability: ECC that is identified by imaging modalities such as plain radiography or echocardiography is most commonly denoted as present or absent at each site. Thus, ordinal scoring can most easily be applied to ECC that is identified by less-sensitive imaging modalities than CT. Furthermore, it achieves the goal of examining whether higher extracoronary atherosclerotic burden increases risk for CHD and mortality outcomes. Although simpler, our approach has the limitation that ordinal ECC fails to capture the intensity of calcification at any given site or the wide variation in calcific burden between extracoronary sites.¹³ It is well documented that thoracic aortic calcification often exhibits several-fold higher absolute Agatston scores compared with other locations.^{12,13} A recent study analyzing CAC density demonstrated an inverse relationship of higher CAC density and events.²⁷ Therefore, future analysis should use quantitative ECC measures and explore differential, weighted adjustment by ECC site.

Because CAC is one of the most robust markers for overall coronary atherosclerotic burden, which pathophysiologically is most proximally responsible for CHD events,²⁸ calcification outside of the coronary tree a priori would not be expected to predict CHD events more effectively than CAC. Thus, the lack of improvement in discrimination when ECC is added to TRF + CAC for the outcomes of CHD events and CHD mortality is not

unexpected (Table 3; Supplementary Table 1). Multisite ECC, on the other hand, appears to be representative of a more generalized process of whole-body atherosclerosis, whose diffuse nature may explain its ability to improve prediction for all-cause mortality beyond TRF + CAC (although the increase in AUC is modest at best); this improvement was also identified in the study by Allison et al³ using a different cohort. The correlation of ECC with age may also contribute to its association with all-cause mortality—although all present analyses were age adjusted. Prior investigators have reported that atherosclerotic plaque throughout the cardiovascular system orchestrates systemic proinflammatory pathways which predispose to numerous sequelae.²⁹ To the degree that ECC acts as a marker for diffuse atherosclerosis, this may contribute independent predictive information for all-cause mortality.

4.1. Limitations

One limitation of our study is the relatively few cases of CHD mortality in our cohort at the time of analysis, resulting in wide confidence intervals and possibly exaggerated point estimates. Other limitations include the lack of CT measurement of calcification in other vascular locations in the full cohort, such as the iliac arteries or aortic arch (which is a common site of ECC⁶), and the need to exclude participants missing ECC measures, although this was <1% of the total cohort. The MESA cohort also lacks non-CT ECC imaging information with which to test the generalizability of our findings to other imaging modalities, including echocardiography. To compare models with and without ECC, we present both ROC analysis and net reclassification index, realizing that each comparison method has its own limitations.^{16,30} Thus, the significant increase in AUC for all-cause mortality when ECC is added does not confirm its clinical relevance. Future research directions should include the longitudinal follow-up of individuals with truly incidentally found ECC in other cohorts, as well as methodologies exploring how best to incorporate continuous calcification information from multiple ECC sites.

5. Conclusions

The importance of our findings lies in the widespread prevalence of ECC (45% in the asymptomatic MESA population) and in the potential ability to obtain information about ECC from a variety of imaging studies, possibly even from existing patient records. Thus, ECC can offer the powerful value proposition to better understand CHD and overall mortality risk without additional studies, cost or radiation exposure. Our findings support the hypothesis that calcification in multiple extracoronary vascular locations is associated with significantly increased CHD and mortality risk and can be used in addition to traditional risk scores to improve risk prediction of these outcomes.

Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jcct.2015.03.012>.

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