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Thoracic extra-coronary calcification for the prediction of stroke: The Multi-Ethnic Study of Atherosclerosis

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ABSTRACT

Background and aims: Atherosclerosis is a systemic disease. We examined whether the cumulative burden of thoracic extra-coronary calcification (ECC) improves prediction of stroke, transient ischemic attack (TIA), and stroke mortality beyond traditional risk factors and coronary artery calcium (CAC).
Methods: We followed a total of 6805 participants (mean age 62.1 ± 10.2 years, 47.2% male) from the Multi-Ethnic Study of Atherosclerosis (MESA) over a median of 12.1 years. The presence or absence of calcification at 4 thoracic ECC sites (mitral valve annulus, aortic valve, aortic root, and thoracic aorta) was determined from baseline cardiac-gated non-contrast CT scans. A multisite thoracic ECC score, ranging 0–4, was calculated by summing the 4 individual sites, which were treated as binary variables. Multivariable Cox proportional hazards regression models, controlled for traditional risk factors and CAC, were used to estimate hazard ratios for ischemic (primary endpoint) and hemorrhagic stroke, total stroke, TIA, and stroke mortality with increasing thoracic ECC.
Results: With an increasing number of thoracic ECC sites, there was a significant ($p < 0.05$) multivariable adjusted step-wise increase in the risk for ischemic stroke (n = 184), total stroke (n = 235), and TIA (n = 85), but not hemorrhagic stroke (n = 32) and stroke mortality (n = 42). Thoracic ECC increased the c-statistic and net reclassification index beyond traditional risk factors and CAC, but the results were not significant ($p > 0.10$).
Conclusions: Although multisite thoracic ECC is independently associated with ischemic stroke, total stroke, and TIA, the incremental predictive value of thoracic ECC beyond traditional risk factors and CAC appears to be minimal.

1. Introduction

Atherosclerosis is a systemic process [1]. Detection of subclinical atherosclerosis using imaging, particularly coronary artery calcium (CAC) from computed tomography (CT) scans, has proven to be

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superior to traditional risk factors for prediction of coronary heart disease (CHD) [2]. The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines placed an emphasis on the prediction of both CHD *and* stroke events [3]. However, CAC is a stronger predictor of CHD [2] than stroke [4,5]. Therefore, further risk information, in particular other imaging data, may be needed beyond CAC to enhance prediction of stroke.

Extra-coronary calcification (ECC) can be visualized on a variety of imaging modalities, including routine non-gated and cardiac-gated non-contrast chest CT scans, plain radiography, and echocardiography [6–8] and, as such, its identification does not require additional cost or radiation exposure. Of these modalities, CT scanning has a superior sensitivity for identifying vascular calcification and allows for a more quantitative assessment of ECC. Previous studies have demonstrated the association between individual sites of thoracic ECC, including aortic or mitral valve [6], ascending aorta [7], thoracic aorta [8], abdominal aorta [10], and carotid arteries [9], and the risk for CVD. In the Multi-Ethnic Study of Atherosclerosis (MESA), thoracic aortic [11] and aortic valve [12] calcification have been shown to predict CHD and CVD events beyond CAC.

ECC may reflect the manifestation of CVD risk factors, such as hypertension and diabetes, on the systemic vasculature [13]. Previous studies have shown that individual thoracic ECC sites herald the presence or risk of atherosclerotic calcification at other vascular sites [6,10]. As such, thoracic ECC sites may be suitable for prediction of cerebrovascular events, such as ischemic stroke and TIA, as these sites are more proximal to the cerebrovascular circulation, compared with CAC and ECC sites outside the thoracic region [13]. In MESA, Tison et al. suggested a strong association of an ordinal multisite thoracic ECC score with total CVD and mortality rather than with CHD [14]. No further studies have evaluated the utility of a multisite thoracic ECC score for predicting the risk for total and individual stroke types.

In this study, we sought to evaluate the discrimination and reclassification ability of thoracic ECC, including mitral valve calcification (MVC), aortic valve calcification (AVC), aortic root calcification (ARC), and thoracic aorta calcification (TAC), for the prediction of ischemic and hemorrhagic stroke, total stroke, TIA, and stroke mortality.

2. Patients and methods

2.1. Study population

MESA is a longitudinal study of 6814 White, Black, Hispanic, or Chinese Americans aged 45–84 years old free of known CVD at baseline, enrolled from 6 US centers between 2000 and 2002. Participants were excluded if they had a confirmed diagnosis of myocardial infarction, stroke, TIA, heart failure, angina, atrial fibrillation, or any history of cardiovascular procedures, weight >300 pounds, pregnancy, or any medical conditions that could prevent long-term participation. Exam 2 was held from Fall 2002 to Winter 2004, Exam 3 from Spring 2004 to Fall 2005, Exam 4 from Fall 2005 to Spring 2007, and the fifth exam between Spring 2010 and Winter 2012. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board at each site in accordance with the Health Insurance Portability and Accountability Act. Details regarding protocol and design of MESA were reported elsewhere [15].

2.2. Data collection

Baseline data were collected using self-administered questionnaires and obtained clinical and laboratory data. Total cholesterol, high-density lipoprotein cholesterol, triglyceride and blood glucose measurements were performed after a 12-h fast. Diabetes was defined as fasting blood glucose ≥7.0 mmol/l (126 mg/dl), self-reported diabetes, or use of hypoglycemic drugs. The definition of hypertension was untreated systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive medication. Metabolic syndrome was defined according to the modified National Cholesterol Education Program Adult Treatment Panel III definition [16]. Smoking status was considered as never, former, and current use of cigarettes. Self-reported education and income level were assessed as parameters of socioeconomic status.

2.3. Measuring coronary and extra-coronary calcium

The details of the MESA cardiac CT protocol have been published elsewhere [17]. Briefly, CAC and ECC were measured by Agatston method by two consecutive baseline non-contrast cardiac CT scans, which were EKG-gated to the R-R interval. To assess CAC, all participants underwent two consecutive noncontrast cardiac-gated CT scans. A minimum of 35 images was obtained starting above the left main coronary artery to the bottom of both ventricles during a single breath hold. To reconstruct raw image data, a slice thickness of 3 mm, field of view of 35 cm, and a matrix of 512 × 512 was used. Three sites used an electron beam CT scanner (GE–Imatron C–150XL, San Francisco, CA), and three sites used a 4-slice multidetector CT scanner. The nominal section thicknesses were 3.0 for electron beam scanner and 2.5 mm for multidetector scanner. Spatial resolution was described as 1.38 mm^3 for electron beam scanner (0.68 × 0.68 × 3.00 mm) and 1.15 mm^3 for multidetector scanner (0.68 × 0.68 × 2.50 mm).

Axial datasets of CT scans were also reviewed for the presence of calcification at 4 non-coronary sites: 1) the level of mitral annulus (MVC), 2) from aortic valve to just before aortic root (AVC), 3) the level of aortic root (ARC), 4) and ascending or descending thoracic aorta (TAC). Ascending aortic calcification was measure from the aortic annulus to the lower edge of pulmonary artery. Descending aortic calcification was measured from the lower edge of pulmonary artery to the cardiac apex. Therefore, aortic arch was not visualized on scans. We excluded participants with at least one thoracic ECC site information missing.

Due to the heterogeneity in Agatston scores across different extra-coronary vascular sites [18], and to increase the generalizability of results, we used a binary variable for each of 4 individual thoracic ECC sites based on presence (1) or absence (0) of any calcifications. The presence of CAC or ECC was defined as any measured Agatston scores higher than zero. The integrated multisite thoracic ECC score was the sum of individual ordinal binary scores at each calcification site.

2.4. Follow-up and ascertainment of events

During a median follow-up of 12.1 years, new cases of stroke, TIA, and stroke mortality were recorded using interviews to document interim hospital admissions, outpatient diagnoses, and deaths. Two neurologists adjudicated independently all events. Stroke endpoints were classified by their type comprising ischemic and hemorrhagic (subarachnoid and intra-parenchymal hemorrhage). TIA was defined as having symptoms that lasted less than 24 h and negative imaging. Primary endpoint was ischemic stroke. Detailed description of follow-up of MESA participants is available online (www.mesa-nhlbi.org).

2.5. Statistical analyses

For comparison of discrete or normally distributed continuous

variables across the four thoracic ECC groups, Pearson's Chi-square test or ANOVA were performed, respectively. For skewed variables, medians and interquartile ranges were reported and Kruskal-Wallis tests performed for comparison. We ran logistic regression models to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for CAC>0 based on thoracic ECC score.

Kaplan-Meier curves were generated to estimate rates of stroke, TIA, and stroke mortality events. Three Cox proportional hazard models were built to estimate hazard ratios (HRs) with 95% CIs with increasing thoracic ECC sites. The first model was unadjusted, and the second model also included traditional CVD risk factors and other potential confounders including age, gender, race/ethnicity, education, estimated glomerular filtration rate, LDL-C, HDL-C, total cholesterol, diabetes mellitus, hypertension, cigarette smoking status (never, former, current), any lipid-lowering medications, anti-hypertensive medications, aspirin use, and family history of heart attack or stroke. In addition, third model also included the continuous CAC score, which was calculated by natural logarithmic transformation of CAC+1 (Log_eCAC). For each model, trend analysis was conducted to test whether stroke or mortality increased linearly with increasing number of thoracic ECC sites. Two-sample log-rank test was used to compare the survival experiences between the four thoracic ECC groups. The proportional hazards assumption was assessed by Schoenfeld residuals and plotting log-log survival.

We assessed discrimination by calculating and comparing area under the Receiver Operating Characteristic (ROC) curves for models with and without thoracic ECC. The base model included traditional CVD risk factors and CAC, and the second model also included multisite thoracic ECC. We compared the two models using the likelihood ratio test. Integrated discrimination improvement (IDI) was also calculated [19].

Thresholds of Framingham risk score for stroke were calculated using sex-specific calibration factors for individual CVD as reported previously [20]. The ability of thoracic ECC to reclassify risk beyond traditional risk factors with or without CAC was assessed by calculating the net reclassification improvement (NRI). Information is insufficient on how to justify categories of NRI for stroke. Therefore, we calculated the category-less, continuous NRI that is independent of risk thresholds and has more statistical power [21].

We performed secondary analysis for individual thoracic ECC sites can significantly predict stroke events and stroke mortality. Thus, we added MVC, AVC, ARC, and TAC as binary (presence or absence of calcification) or continuous (Agatston score) covariates into models. Subgroup analyses were performed by restricting the analysis to participants with no CAC (CAC = 0), CAC>100, and CAC>75th percentile in the population. We used multivariable adjusted competing risk regression considering competing risk from total mortality and stroke mortality. Moreover, we adjusted for atrial fibrillation, all interim non-stroke CVD events, and change in lipid-lowering and aspirin use prior to incident stroke in Cox regression models. We tested for interaction between thoracic ECC score and age, sex, gender, and estimated glomerular filtration rate

Table 1
Baseline characteristics of asymptomatic participants without a history of cardiovascular disease in Multi-Ethnic Study of Atherosclerosis by the number of thoracic extra-coronary calcification sites.

Variable	Entire cohort	Thoracic extra-coronary calcification sites				*p* value
	(N = 6805)	0, N = 3617	1, N = 1474	2, N = 1052 (%)	3–4, N = 662	
Age	62.1 ± 10.2	56.6 ± 8.3	65.0 ± 8.4	69.9 ± 7.4	72.5 ± 7.0	**<0.001**
Male, n (%)	3209 (47.2)	1685 (46.6)	713 (48.4)	491 (46.7)	320 (48.3)	0.61
Race, n (%)						**<0.001**
White	2615 (38.4)	1277 (35.3)	559 (37.9)	451 (42.9)	328 (49.6)	
African American	1892 (27.8)	1065 (29.4)	424 (28.8)	266 (25.3)	137 (20.7)	
Hispanics	1495 (22.0)	802 (22.2)	330 (22.4)	215 (20.4)	148 (22.4)	
Chinese American	803 (11.8)	473 (13.1)	161 (10.9)	120 (11.4)	49 (7.4)	
High school education, n (%)	4323 (63.7)	2503 (69.5)	900 (61.3)	572 (54.4)	348 (52.9)	**<0.001**
Income ≥ $40,000	3503 (51.5)	2083 (57.6)	712 (48.3)	442 (42.0)	266 (40.2)	**<0.001**
Body mass index, kg/m^2	28.3 ± 5.5	28.4 ± 5.7	28.4 ± 5.3	28.1 ± 5.3	28.4 ± 4.9	0.34
Waist circumference, cm	98.1 ± 14.4	96.9 ± 14.8	99.2 ± 14.2	98.9 ± 13.8	101.3 ± 13.1	**<0.001**
Metabolic syndrome, n (%)	2444 (36.0)	1080 (29.9)	581 (39.6)	458 (43.5)	325 (49.4)	**<0.001**
Triglycerides (mg/dL)	111 (78, 161)	107 (74, 157)	113 (81, 163)	118 (80, 163)	120 (86, 169)	**<0.001**
Total cholesterol, mg/dL	194.1 ± 35.7	192.2 ± 34.7	197.0 ± 36.3	195.3 ± 36.2	196.5 ± 38.3	**<0.001**
HDL cholesterol, mg/dL	51.0 ± 14.8	51.2 ± 15.0	50.9 ± 14.2	50.9 ± 15.4	50.2 ± 14.1	0.48
Systolic blood pressure, mmHg	126.6 ± 21.5	120.7 ± 19.0	129.8 ± 21.1	134.9 ± 21.7	138.4 ± 23.9	**<0.001**
Estimated GFR, mL/min/1.73 m^2	81.2 ± 18.5	83.7 ± 16.6	81.1 ± 12.4	77.5 ± 18.3	73.6 ± 18.3	**<0.001**
Hypertension, n (%)	3055 (44.9)	1188 (32.8)	759 (51.5)	651 (61.9)	457 (69.0)	**<0.001**
Diabetes, n (%)	858 (12.6)	334 (9.2)	212 (14.4)	180 (17.1)	132 (19.9)	**<0.001**
Hypertension medication, n (%)	2532 (37.2)	987 (27.3)	628 (42.6)	533 (50.7)	384 (58.0)	**<0.001**
Lipid-lowering medication, n (%)	1096 (16.1)	380 (10.5)	278 (18.9)	237 (22.6)	201 (30.3)	**<0.001**
Smoking status, n (%)						**<0.001**
Never	3415 (50.4)	1889 (52.4)	734 (50.0)	492 (46.8)	300 (45.5)	
Former	2482 (36.6)	1212 (33.6)	551 (37.5)	425 (40.4)	294 (44.6)	
Current	886 (13.1)	503 (14.0)	184 (12.5)	134 (12.8)	65 (9.9)	
Pack-year	11.3 ± 20.9	8.7 ± 16.8	12.7 ± 23.6	14.6 ± 24.0	16.9 ± 26.5	**<0.001**
CAC score, n (%)						**<0.001**
0	3414 (50.2)	2526 (69.8)	591 (40.1)	216 (20.5)	81 (12.2)	
>0–100>	1793 (26.4)	785 (21.7)	498 (33.7)	349 (33.2)	161 (24.3)	
≥100-400	926 (13.6)	233 (6.4)	231 (15.7)	279 (26.5)	183 (27.6)	
≥400	672 (9.9)	73 (2.0)	154 (10.5)	208 (19.8)	237 (35.8)	
ASCVD risk for MESA						**<0.001**
<7.5%	2919 (42.9)	2317 (64.1)	440 (29.9)	136 (12.9)	26 (3.9)	
≥7.5% and <15.0%	1539 (22.6)	774 (21.4)	412 (28.0)	250 (23.8)	103 (15.6)	
≥15.0%	2295 (33.7)	499 (13.8)	607 (41.2)	664 (63.1)	525 (79.3)	

ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; ECC, extra-coronary calcification; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; MESA, Multi-Ethnic Study of Atherosclerosis; SD, standard deviation.
p values less than 0.05 were considered significant and are shown in bold.

as well as hypertension and diabetes status, as they are different mechanistic roles in ischemic and hemorrhagic strokes [22]. A p of <0.05 was considered significant. All analyses were performed using Stata (version 13.0, College Station, TX, USA).

3. Results

3.1. Baseline characteristics

A total of 6805 participants were included in the final analyses. The mean age was 62.1 ± 10.2 years and 47% were male. Characteristics of the participants by number of ECC sites are provided in Table 1. Participants with higher number of thoracic ECC sites were older and more likely to be White, hypertensive, diabetic, and have higher waist circumference, pack-years of smoking, systolic blood pressure, triglyceride, and total cholesterol levels. Use of lipid-lowering and anti-hypertensive medications at baseline was higher among participants with higher thoracic ECC scores. ARC had the highest prevalence within each thoracic ECC score group, followed by TAC, AVC, and MVC (Fig. 1A).

An increase in thoracic ECC sites was associated with step-wise increase in baseline $\log_e$CAC. Prevalence of CAC was 30% (1091 participants) among 3617 participants without thoracic ECC, and 88% (581 participants) among 662 participants with 3–4 thoracic ECC sites (Fig. 1B). At baseline, compared with participants without thoracic ECC, there were higher odds of CAC>0 for participants with 1 (OR = 2.27 [1.96, 2.64]), 2 (OR = 4.57 [3.75, 5.58]), and 3–4 (OR = 6.1 [4.60, 8.08]) thoracic ECC sites, after adjusting for potential confounders. Among 3414 participants with CAC = 0, about 26% had calcifications in at least one thoracic extra-coronary site.

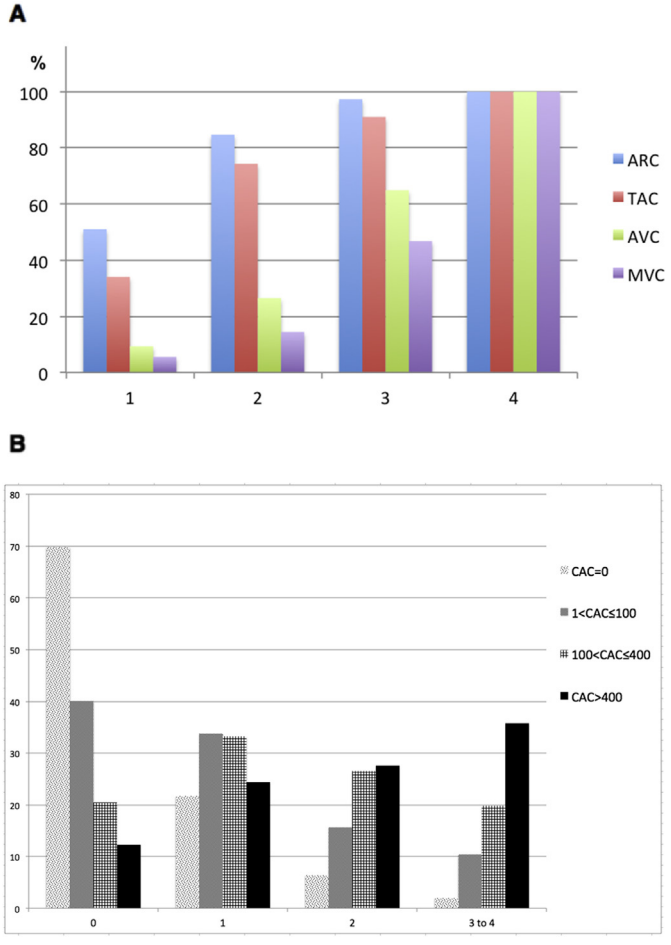

Fig. 1. Individual thoracic calcification sites and coronary artery calcium (CAC) by multisite thoracic extra-coronary calcification (ECC) in MESA.
(A) Prevalence of aortic root calcification (ARC), thoracic aorta calcification (TAC), aortic valve calcification (AVC), mitral valve calcification (MVC) by number of multisite thoracic ECC; All 4 thoracic extra-coronary calcification sites were involved in 183 participants (not shown). (B) Prevalence of CAC, stratified into 4 categories, by the number of multisite thoracic ECC. Scale, 1.5:1.

3.2. Survival analyses

Over a median of 12.1 years of follow-up, there were 184 ischemic strokes, 32 hemorrhagic strokes, 235 total strokes, 85 TIAs, and 42 deaths due to stroke (Table 2). Incidence rates per 1000 person-years for stroke outcomes are shown on Fig. 2.

The results of the Cox models are shown in Table 2. An increase in the number of thoracic ECC sites was associated with a graded increase in HRs for ischemic and total stroke in all three models. HRs were attenuated in Models 2 and 3 but results remained significant for 3–4 thoracic ECC score. Hemorrhagic stroke events were not associated with thoracic ECC in any of three models. For TIA, the HRs were attenuated in models 2 and 3, but results remained significant in all models and across all thoracic ECC score groups. An increase in the number of thoracic ECC sites was associated with a step-wise increase in the rate of stroke mortality only in the unadjusted models. Supplementary Fig. 1 shows cumulative incidence of stroke events by thoracic ECC score.

3.3. Discrimination and reclassification

Adding thoracic ECC to traditional cardiovascular risk factors, other potential confounders, and CAC increased the area under the ROC curve for all endpoints, but results were not statistically significant (Supplementary Table 1). IDI was only statistically significant for ischemic stroke (0.0023; $p = 0.005$), but not hemorrhagic stroke (−0.0000; $p = 0.927$), total stroke (0.0012; $p = 0.058$), TIA (0.0013; $p = 0.101$), and stroke mortality (0.0000; $p = 0.990$). Thoracic ECC improved continuous NRI but results were not statistically significant (Table 3).

3.4. Secondary, subgroup, and sensitivity analyses

Compared with other thoracic ECC sites, MVC was a better predictor for ischemic stroke and total stroke in all 3 models, while TAC could better predict TIA in models 1 and 2 (Supplementary Table 2). The results were largely unchanged after restricting the analyses to participants with CAC = 0, CAC>100, and CAC>75th percentile in the population (Supplementary Tables 3–5). The results were unchanged after considering competing risk from total mortality and stroke mortality, as well as further adjustment for atrial fibrillation, all CVD events, and change in lipid-lowering and aspirin use in Cox regression models. There was no interaction between age, sex, race, body mass index, body weight, estimated glomerular filtration rate, and hypertensive status and thoracic ECC score for any outcomes. The interaction was borderline significant between diabetes and thoracic ECC for TIA ($p = 0.060$), such that all estimates were significant among participants without diabetes and no endpoints were significant for participants with diabetes (Supplementary Table 6 and 7).

4. Discussion

In this study, we demonstrated that with increasing number of thoracic ECC sites there is a step-wise increase in the risk for ischemic stroke, total stroke, and TIA, but not hemorrhagic stroke,

Table 2
Hazard ratios with 95% confidence intervals by multisite thoracic extra-coronary calcification for stroke endpoints, transient ischemic attack, and stroke mortality.

Thoracic ECC						
		n = 0 (reference)	n = 1	n = 2	n = 3–4	*p* value (trend)
Ischemic stroke	Events/total at risk (%)	52/3617 (1.44)	37/1474 (2.51)	50/1052 (4.75)	45/662 (6.80)	
	Model 1	1.00	**1.87 (1.23–2.86)**	**3.72 (2.52–5.49)**	**5.92 (3.97–8.83)**	<0.001
	Model 2	1.00	1.22 (0.76–1.96)	**1.97 (1.22–3.17)**	**2.35 (1.37–4.02)**	<0.001
	Model 3	1.00	1.15 (0.70–1.76)	**1.76 (1.09–2.92)**	**2.02 (1.15–3.58)**	0.001
Hemorrhagic stroke	Events/total at risk (%)	14/3617 (0.39)	10/1474 (0.68)	5/1052 (0.47)	3/662 (0.45)	
	Model 1	1.00	1.86 (0.82–4.18)	1.35 (0.49–3.75)	1.43 (0.41–4.98)	0.62
	Model 2	1.00	1.13 (0.45–2.83)	0.68 (0.21–2.14)	0.64 (0.15–2.72)	0.33
	Model 3	1.00	1.12 (0.44–2.86)	0.66 (0.20–2.22)	0.64 (0.14–2.85)	0.36
Total stroke	Events/total at risk (%)	70/3617 (1.94)	50/1474 (3.40)	60/1052 (5.70)	55/662 (8.31)	
	Model 1	1.00	**1.88 (1.31–2.70)**	**3.32 (2.35–4.69)**	**5.39 (3.78–7.68)**	<0.001
	Model 2	1.00	1.18 (0.79–1.78)	**1.65 (1.08–2.52)**	**2.00 (1.25–3.22)**	<0.001
	Model 3	1.00	1.11 (0.73–1.68)	1.47 (0.95–2.27)	**1.71 (1.04–2.81)**	0.01
TIA	Events/total at risk (%)	21/3617 (0.58)	26/1474 (1.76)	26/1052 (2.47)	12/662 (1.81)	
	Model 1	1.00	**3.27 (1.84–5.81)**	**4.82 (2.71–8.57)**	**3.86 (1.89–7.84)**	<0.001
	Model 2	1.00	**2.82 (1.46–5.44)**	**3.67 (1.77–7.57)**	**3.00 (1.24–7.25)**	<0.01
	Model 3	1.00	**2.63 (1.35–5.11)**	**3.21 (1.52–6.80)**	**2.54 (1.02–6.33)**	0.02
Stroke mortality	Events/total at risk (%)	10/3617 (0.28)	5/1474 (0.34)	14/1052 (1.33)	13/662 (1.96)	
	Model 1	1.00	1.29 (0.44–3.77)	**5.35 (2.38–12.06)**	**8.59 (3.76–19.63)**	<0.001
	Model 2	1.00	0.36 (0.11–1.23)	1.00 (0.48–2.63)	1.02 (0.35–2.98)	0.24
	Model 3	1.00	0.34 (0.10–1.18)	0.90 (0.32–2.48)	0.89 (0.29–2.79)	0.36

Model 1 includes multisite thoracic ECC
Model 2 includes thoracic ECC and traditional cardiovascular risk factors and other potential confounders including age, gender, race/ethnicity, estimated glomerular filtration rate, LDL-C, HDL-C, total cholesterol, diabetes mellitus, hypertension, cigarette smoking status (never, former, current), any lipid-lowering medications, anti-hypertensive medications, aspirin use, family history of heart attack or stroke, and education
Model 3 includes log (CAC+1) and all factors in Model 2
Significant results are shown in bold.
CAC, coronary artery calcification; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ECC, extra-coronary calcification; TIA, transient ischemic attack.

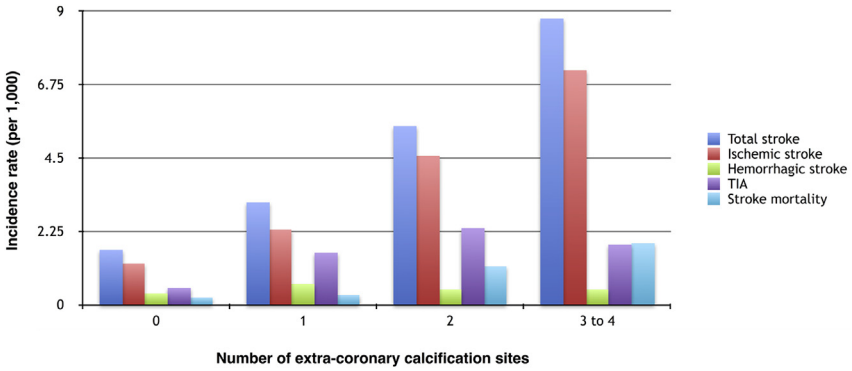

Fig. 2. Incidence rate per 1000 person-years for stroke outcomes by number of extra-coronary calcification sites.
Scale, 2:1. TIA, transient ischemic attack.

and stroke mortality. In addition, we showed that multisite thoracic ECC minimally improves global risk prediction for ischemic stroke over traditional risk factors and CAC. However, the increase in risk discrimination and reclassification was not significant for other stroke-related outcomes.

Although, a quantitative assessment of ECC can be more robust from methodological perspective, it cannot be replicated clinically in general chest CT imaging. Our study is amongst the few that devised and utilized a novel multisite thoracic ECC score for more pragmatic and comprehensive clinically relevant risk stratification. The clinical significance of our findings is rooted in the widespread use of various imaging methods on which thoracic ECC data can be easily obtained and is often reported. Calcification outside the coronary beds can be found incidentally on several imaging modalities, such as gated CT, non-gated chest CT scans, plain radiography, ultrasonography, echocardiography, magnetic resonance imaging, and dual energy X-ray absorptiometry (DEXA). ECC may appear earlier or in the absence of CAC, and therefore, may be a more sensitive marker for CHD and cardiovascular disease (CVD) risk assessment [6,8]. As such, the benefits of multisite ECC scoring regarding improving current risk assessment strategies, altering treatment decisions, and improving clinical outcomes has been hypothesized to outweigh healthcare expenses in the absence of additive radiation exposure [23].

A few previous studies have shown the role of extra-coronary calcifications for predicting CHD risk. Van der Meer et al. combined carotid plaque and carotid intima-media thickness as early markers of atherosclerosis with abdominal aortic calcification to create a score for predicting myocardial infarction in Rotterdam Study population. In this study, the HRs for moderate and severe atherosclerosis according to composite atherosclerosis score were 1.71 (1.06–2.76) and 2.77 (1.70–4.52), respectively, as compared with no atherosclerosis [24]. Munter et al. combined MVC, AVC, and abdominal aortic calcification along with age and history of dialysis

Table 3
Net reclassification improvement (NRI) with 95% confidence intervals for stroke endpoints after adding thoracic extra-coronary calcium (ECC) score to models adjusted for traditional risk factors (TRF) and coronary artery calcium (CAC) score.

Endpoint	TRF/confounders *vs.* TRF/confounders + thoracic ECC			TRF/confounders + CAC *vs.* TRF/confounders + CAC + thoracic ECC		
	Continuous event NRI	Continuous non-event NRI	Continuous NRI	Continuous event NRI	Continuous non-event NRI	Continuous NRI
Ischemic stroke	0.060 (−0.074, 0.179)	**0.079 (0.002, 0.152)**	0.139 (−0.047, 0.305)	0.048 (−0.113, 0.176)	0.047 (−0.026, 0.125)	0.095 (−0.118, 0.292)
Hemorrhagic stroke	0.267 (−0.473, 0.483)	0.053 (−0.015, 0.174)	0.320 (−0.460, 0.607)	0.133 (−0.448, 0.429)	0.065 (−0.018, 0.178)	0.198 (−0.427, 0.555)
Total stroke	0.023 (−0.085, 0.135)	0.061 (−0.000, 0.123)	0.085 (−0.067, 0.239)	−0.014 (−0.157, 0.115)	0.024 (−0.028, 0.090)	0.010 (−0.168, 0.191)
TIA	0.038 (−0.169, 0.218)	**0.115 (0.014, 0.204)**	0.153 (−0.127, 0.390)	0.013 (−0.212, 0.208)	0.074 (−0.015, 0.187)	0.087 (−0.181, 0.348)
Stroke mortality	−0.243 (−0.488, 0.406)	−0.006 (−0.111, 0.281)	−0.249 (−0.447, 0.488)	−0.189 (−0.485, 0.355)	−0.021 (−0.107, 0.279)	−0.210 (−0.466, 0.461)

Significant results are shown in bold.
CAC, coronary artery calcium; ECC, extra-coronary calcium; NRI, net reclassification improvement; TRF, traditional.

to create a “cardiovascular calcification index”, which was significantly predictive of CAC [25]. Tison et al. reported that a multisite thoracic ECC score, consisting of TAC, MVC, MVC, ARC, can improve risk prediction for CHD events, CHD mortality, and all-cause mortality when combined with traditional risk factors. However, when CAC was added to the model, thoracic ECC significantly predicted all-cause mortality, but not CHD events or CHD mortality [13]. Our results support the ability of thoracic ECC, regardless of the presence of CAC, for prediction of stroke, TIA, and stroke mortality, in addition to CHD and other mortality endpoints. However, thoracic ECC does not improve measured of global discrimination above that provided by CAC.

New guidelines have recommendations for the risk assessment of atherosclerotic CVD, which includes fatal and nonfatal stroke events in addition to CHD [3]. CAC has already been shown to be a stronger predictor of CHD than stroke [4,5]. The fact that more patients have CT scans with thoracic ECC than CAC, make thoracic ECC scoring a valuable method to be studied and utilized for patient risk assessment. Although CAC = 0 is deemed to predict lower CVD risk [26], Wong et al. showed that more than 55% of MESA participants had extra-coronary calcification that may put them at high risk for CVD events [27]. In this regard, our results demonstrated that thoracic ECC is predictive of stroke beyond traditional risk factors when CAC was not in the model (Model 2). Therefore, thoracic ECC can stratify patients for stroke, and consequently, may help physicians make decisions about starting appropriate lifestyle or pharmacological primary prevention measures when CAC is not available.

This study has limitations. The Agatston score was developed in early 1990s in order to quantify calcification in coronary vessels. Due to the heterogeneity of calcification in extra-coronary vascular beds, the utility of thoracic ECC as a continuous score for the prediction of CVD events is questionable. To address this problem, we used an ordinal multisite thoracic ECC score that only considered presence of calcification at locations outside coronary beds, in order to refrain from the bias that results from outliers and difference in Agatston score across thoracic ECC sites. Volume and density of calcification were also not measured in this study. Moreover, although individual thoracic ECC, such as TAC and MVC, were treated the same in the calculation of thoracic ECC score, they may be associated with different clinical outcomes [6,9]. However, the rationale to create a multisite score in this study was to reduce reliance on individuals ECC sites, increase the generalizability of results, and simplify stroke risk prediction for clinicians. Another limitation of our study might be the low number of events for stroke endpoints, as compared with the total population. Small numbers resulted in wide confidence intervals for sensitivity analyses that included evaluati on of individual stroke types, individual thoracic ECC sites, and race-based risk. Finally, the MESA cohort lacks CT measurement for other calcification sites, such as carotid arteries, aortic arch, and iliac arteries, which may potentially provide more complete CVD risk prediction [8].

In conclusion, our study shows that multisite thoracic ECC is associated with increased risk of ischemic stroke, total stroke, and TIA and minimally improves global risk prediction for all stroke-related outcomes independent of traditional risk factors and CAC. Although significant associations between thoracic ECC and stroke events may be useful for predictive purposes, this study was not designed to show their causal relationships. However, while incidentally found calcifications on various imaging modalities may provide some prognostic information without further cost or radiation exposure, their value to global risk prediction is limited in comprehensive models. More studies with larger number of stroke events are needed to show if particular subgroups defined by age, sex, race, or comorbid conditions might benefit from thoracic ECC-based stroke risk prediction.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Author contributions

Sina Kianoush, Mahmoud Al Rifai, and Michael J. Blaha contributed to the literature search, study design, data interpretation, and writing and editing of the manuscript. Sina Kianoush contributed to the statistical analyses. All other co-authors contributed to the study design, data interpretation, and editing of the manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.atherosclerosis.2017.10.010.

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