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Association of thoracic aortic calcium with incident cardiovascular disease and all-cause mortality across the spectrum of coronary artery calcium burden

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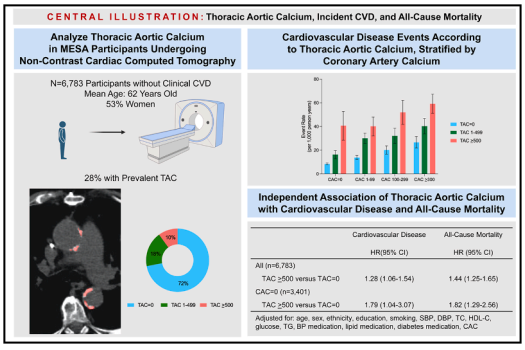
GRAPHICAL ABSTRACT



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ABSTRACT

Background: Calcification of the ascending and/or descending thoracic aorta is easily measured via non-contrast cardiac computed tomography (CT), commonly performed for quantification of coronary artery calcium (CAC).

Abbreviations: CAC, coronary artery calcium; CAC-DRS, CAC Data and Reporting System; CT, computed tomography; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MESA, multi-ethnic study of atherosclerosis; TAC, thoracic aortic calcium.

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Vascular calcification
Computed tomography
Atherosclerosis
Coronary artery calcium
Cardiovascular disease

We assessed whether thoracic aortic calcium (TAC) further improves long-term cardiovascular disease (CVD) risk stratification beyond CAC alone.

Methods: Cardiac CT was performed among 6,783 asymptomatic Multi-Ethnic Study of Atherosclerosis participants at baseline. Cox proportional hazards regression assessed the association of TAC with incident CVD and all-cause mortality over a median follow-up of 17.7 years, adjusting for CVD risk factors and CAC.

Results: The mean age was 62.1 years old, 53% were female, and 28% had TAC. Over a median follow-up of 17.7 years, 48% of participants with TAC ≥500 experienced CVD and 72% died. Compared to TAC=0, TAC ≥500 was significantly associated with an increased risk of CVD (HR=1.28, 95% CI: 1.06-1.54) and all-cause mortality (HR=1.44, 95% CI: 1.25–1.65), with the strongest association among persons with CAC=0 (CVD HR=1.79, 95% CI: 1.04–3.07; all-cause mortality HR=1.82, 95% CI: 1.29–2.56). The addition of TAC to traditional risk factors and CAC did not improve CVD discrimination (ΔC-statistic=+0.002, p=0.12), but incrementally improved prediction of all-cause mortality (CVD: ΔC-statistic=+0.002, p=0.02).

Conclusions: Participants with TAC ≥500 had a high long-term risk for CVD and all-cause mortality. TAC primarily improved risk stratification among persons with CAC=0.

1. Introduction

The total burden of coronary atherosclerosis is recognized as the most important risk factor for predicting cardiovascular disease (CVD) events [1] and a greater number of vascular beds with atherosclerosis is also associated with a strong increase in CVD risk [2]. Thoracic aortic calcium (TAC) of the ascending and/or descending thoracic aorta is an important, but often underappreciated form of subclinical atherosclerosis that is easily measured from non-contrast cardiac computed tomography (CT) scans performed for the assessment of coronary artery calcium (CAC) [3]. TAC is associated with CVD mortality [4–8] along with an approximate two-fold higher risk for both coronary heart disease and cerebrovascular disease events, independent of traditional CVD risk factors [4,9]. Additionally, among persons with CAC=0, presence of TAC is associated with an approximately 40% increased risk for incident CAC [10], which suggests it may provide important complementary CVD risk prediction information.

However, a majority of previous studies assessing the role of TAC in CVD risk have been limited by reporting TAC only as a binary (presence/absence) variable [11], not examined outcomes beyond CVD mortality [12], have been conducted among predominantly White participants [9], and have not incorporated long durations of follow-up. It is uncertain whether 1) evaluating the burden of TAC can further improve long-term CVD risk prediction beyond CAC alone and 2) whether the addition of TAC burden to the CAC-Data and Reporting System (CAC-DRS) [13] provides additional CVD risk stratification. Therefore, TAC is not recommended as a routine part of CVD risk assessment and often not reported as a part of clinical CAC score results.

We sought to assess the association of TAC burden with incident CVD, individual CVD outcomes, and all-cause mortality in the Multi-Ethnic Study of Atherosclerosis (MESA) in order to further refine our understanding of TAC and how it may improve long-term CVD risk stratification beyond CAC in a diverse, population-based sample.

2. Methods

2.1. Study population

MESA is a community-based prospective cohort study whose specific details on its design and rationale have previously been reported [14]. Briefly, MESA enrolled 6,814 adults aged 45-84 years old who were free of known clinical CVD, including White, Black, Hispanic, and Chinese participants. We included the participants who underwent cardiac CT at baseline (MESA Visit 1). After excluding individuals who did not undergo CT scans at Visit 1 (n=2), were missing follow-up information (n=3) or who had a CVD event or death (n=26), there were 6,783 MESA participants for the current analysis.

All study participants provided written informed consent at each study visit and study protocols were approved at each MESA participating institution's local Institutional Review Board (IRB) and sponsored by the National Heart, Lung, and Blood Institute (http://www.mesa-nhlbi.org).

2.2. Measurement of coronary artery calcium and thoracic aortic calcium

Half of the MESA field centers used electron beam computed tomography (EBCT) (MESA: Chicago, Los Angeles, New York), while the other half used multidetector computed tomography (MDCT) (MESA: Baltimore, Forsyth County, St. Paul) to measure CAC [15]. CAC scores computed using the Agatston method and derived from EBCT and MDCT scanners have excellent agreement (interobserver κ=0.93, and intraobserver κ=0.90) [16,17]. Similarly, there is strong agreement in TAC Agatston scores between a first and second repeat scan on both EBCT and MDCT scanners (κ=0.95) [18]. Standardization of CAC scans among field centers was achieved using calcium phantoms scanned alongside participants [15,19]. The phantom had 4 bars of known calcium density and was used to calibrate the level of brightness between study subjects and sites. Two consecutive CT scans were performed, and they were processed and interpreted at a centralized MESA reading center.

Using the Agatston method, each participant's burden of TAC at MESA Visit 1 (2000–02) was quantified as the sum of provide plaque present in portions of the ascending aorta (aortic annulus to the lower edge of pulmonary artery) plus the sum of calcified plaque present in the descending aorta (lower edge of pulmonary artery to the cardiac apex). This quantification process uses the same Agatston scoring methodology and imaging software as use for CAC scoring. We then categorized TAC into the following groups: TAC=0, TAC 1–499, TAC ≥500. These TAC categories were chosen based on the fact that the aorta has a much larger surface area compared to the coronary arteries.

We created a revised CAC DRS score [13] (CAC-DRS+) by adding a third component that included TAC burden. In addition to the four-level Agatston CAC score (A0: CAC=0, A1: CAC 1–99, A2: CAC 100–299, A3: CAC ≥300) and coronary artery involvement score (N0: none, N1: one artery, N2: two arteries, N3: three or more arteries), we constructed a three-level Agatston TAC score variable for the CAC-DRS (T0: TAC=0, T1: TAC 1–499, T2: TAC ≥500).

Table 1
Baseline characteristics of 6,783 multi-ethnic study of atherosclerosis participants who underwent non-contrast cardiac computed tomography, stratified by TAC burden.

	All (n=6,783)	TAC=0 (n=4,886)	TAC 1-499 (n=1,212)	TAC ≥500 (n=685)	*p*-value
Age, mean ± SD, years	62.1 ± 10.2	58.9 ± 9.1	69.0 ± 8.1	73.5 ± 6.7	<0.001
Female, %	52.8	52.1	52.9	58.3	0.01
Race					<0.001
White	38.5	36.1	41.4	50.0	
Chinese	11.8	11.1	14.0	12.9	
Black	27.7	29.9	24.5	18.1	
Hispanic	22.0	22.9	20.1	19.0	
Income ≥$35,000, %	53.2	57.8	43.2	38.4	<0.001
Post-High School Education, %	63.6	67.2	55.5	52.0	<0.001
Body Mass Index, mean ± SD, kg/m^2	28.3 ± 5.5	28.6 ± 5.6	27.8 ± 5.1	27.5 ± 5.0	<0.001
Pack-Years of Cigarette Smoking, pack-years	0.0 (0.0, 19.0)	0.0 (0.0, 12.5)	0.0 (0.0, 21.0)	2.6 (0, 27.5)	<0.001
Systolic Blood Pressure, mean ± SD, mmHg	126.6 ± 21.5	122.8 ± 19.7	134.7 ± 22.3	139.1 ± 23.3	<0.001
Diastolic Blood Pressure, mean ± SD, mmHg	71.9 ± 10.3	72.0 ± 10.2	72.0 ± 10.4	70.9 ± 10.6	0.02
Antihypertensive Medication, %	33.3	27.7	44.8	53.1	<0.001
Total Cholesterol, mean ± SD, mg/dL	194.1 ± 35.7	193.7 ± 35.4	196.0 ± 37.0	193.5 ± 35.9	0.12
HDL-Cholesterol, mean ± SD, mg/dL	51.0 ± 14.8	51.0 ± 15.0	50.4 ± 14.0	51.5 ± 15.3	0.38
LDL-Cholesterol, mean ± SD, mg/dL	117.2 ± 31.5	117.1 ± 31.4	118.7 ± 31.7	115.4 ± 31.3	0.09
Triglycerides, median (IQR), mg/dL	111.0 (78.0, 161.0)	109.0 (76.0, 159.0)	117.0 (83.0, 165.0)	117.0 (84.0, 162.0)	<0.001
Lipid-Lowering Medication, %	16.3	13.2	22.1	27.7	<0.001
Fasting Blood Glucose, mean ± SD, mg/dL	97.3 ± 30.3	96.4 ± 30.2	99.7 ± 31.1	100.2 ± 28.6	<0.001
Glucose-Lowering Medication, %	9.7	8.0	12.5	16.4	<0.001
ACC/AHA 10-Year ASCVD Risk, %	9.3 (3.7, 19.5)	6.4 (2.8, 13.2)	18.1 (10.2, 27.9)	25.0 (16.4, 37.7)	<0.001
Coronary Artery Calcium, median (Q1, Q3), AU	0 (0, 87)	0 (0, 26)	44 (0, 244)	198 (38, 617)	<0.001
Thoracic Aortic Calcium, median (Q1, Q3), AU	0 (0, 23)	0 (0, 0)	102 (34, 240)	1184 (754, 2337)	<0.001

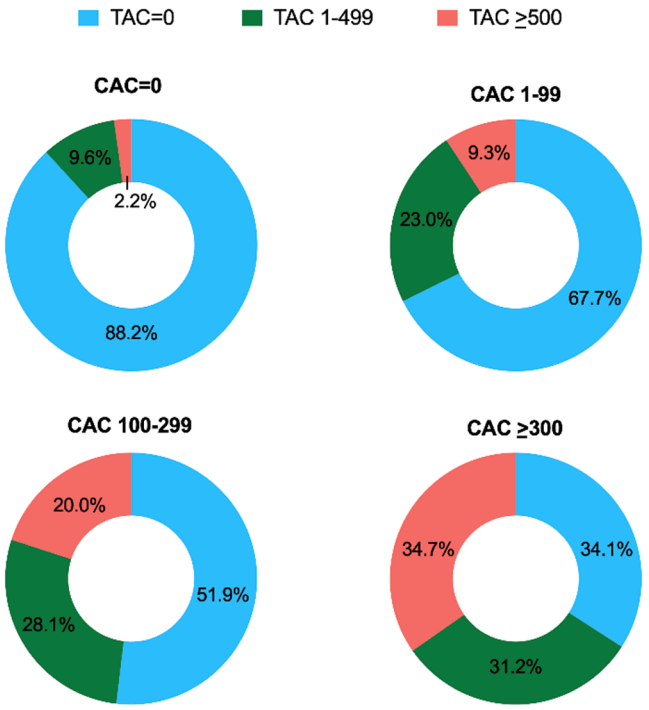

Fig. 1. Proportion of individuals with absent, mild, and high TAC, stratified by CAC burden.

2.3. Ascertainment of ASCVD outcomes

MESA participants and/or family members of participants were contacted by study staff via telephone every nine to twelve months to ascertain hospital admissions, outpatient ASCVD diagnoses, and deaths. Events were adjudicated independently by two separate MESA physicians on the Morbidity and Mortality Review Committee using standardized definitions [14]. Disagreements were resolved by the full review committee. Incident CVD events were defined by definite or probable myocardial infarction, resuscitated cardiac arrest, fatal coronary heart disease (CHD), fatal and non-fatal stroke, and other atherosclerotic or cardiovascular death. CHD events were defined as definite/probable angina, myocardial infarction, resuscitated cardiac arrest, or fatal CHD. Cerebrovascular events were defined as fatal and non-fatal stroke, and transient ischemic attack. Heart failure was defined by a constellation of persistent symptoms, such as shortness of breath and edema, as well as objective criteria including, a physician diagnosis of heart failure, pulmonary edema or congestion on chest x ray, and/or abnormal ventricular function on echocardiography [20]. A further description [14] of the adjudication protocol and categorization of events is available on the MESA website (www.mesa-nhlbi.org).

2.4. General clinical examination and measurement of CVD risk factors

Standardized survey methods were used to collect demographic and clinical information, including sex, race/ethnicity, education status, income, smoking status, and medication use history [14]. Smoking status was defined through cigarette smoking pack-years.

Blood pressure was measured in triplicate from the brachial artery while participants were in a seated resting position and the average of the second and third readings was recorded. Fasting blood glucose was measured using a hexokinase/glucose-6-phosphate dehydrogenase method [21]. Type 2 diabetes was defined as a fasting blood glucose concentration ≥126 mg/dL or the use of glucose-lowering medications. Total cholesterol and high-density lipoprotein-cholesterol (HDL-C) were measured enzymatically [21], and low-density lipoprotein-cholesterol (LDL-C) values were calculated using the Friedewald equation [22]. Fasting plasma triglycerides were quantified using a glycerol-blanked enzymatic method [23].

Table 2
Cardiovascular disease event rates, stratified by TAC burden.

Outcome	All (n=6,783)		TAC=0 (n=4,886)		TAC 1-499 (n=1,212)		TAC ≥500 (n=685)	
	Events (%)	Event rate (95% CI)[a]	Events (%)	Event rate (95% CI)[a]	Events (%)	Event rate (95% CI)[a]	Events (%)	Event rate (95% CI)[a]
Cardiovascular Disease	1202 (17.7)	12.5 (11.8-13.2)	656 (13.4)	8.9 (8.2-9.6)	321 (26.5)	21.0 (18.7-23.3)	225 (32.9)	30.7 (26.7-34.7)
Coronary Heart Disease	770 (11.4)	7.9 (7.3-8.4)	432 (8.8)	5.8 (5.3-6.3)	196 (16.2)	12.5 (10.7-14.2)	142 (20.7)	19.1 (15.9-22.2)
Stroke/TIA	474 (7.0)	4.8 (4.4-5.2)	261 (5.3)	3.5 (3.0-3.9)	131 (10.8)	8.2 (6.8-9.6)	82 (12.0)	10.7 (8.4-13.1)
Heart Failure	431 (6.4)	4.3 (3.9-4.7)	221 (4.5)	2.9 (2.5-3.3)	119 (9.8)	7.4 (6.0-8.7)	91 (13.3)	11.8 (9.4-14.2)
All-Cause Mortality	1899 (28.0)	17.6 (16.8-18.4)	943 (19.3)	11.6 (10.9-12.4)	513 (42.3)	28.4 (26.0-30.9)	443 (64.7)	50.4 (45.7-55.1)

[a] Per 1,000 person-years.

2.5. Statistical analyses

Study sample characteristics were presented as mean ± standard deviation (SD) for continuous variables, and categorical variables were presented as percentages. Normality of continuous variables was assessed via the Kolmogorov-Smirnov test. Continuous variables that were not normally distributed were presented as median (Q1, Q3). Differences between normally and non-normally distributed variables were assessed through the Student's t-test and Wilcoxon signed-rank test, respectively. Differences between categorical variables were evaluated through the chi-square test.

The total number of events was divided by person-years to calculate CVD, CHD, cerebrovascular, and heart failure event rates (per 1,000-year follow-up). Event rates were calculated for the overall sample and stratified by CAC burden. Cumulative incidence curves were computed for CVD, CHD, cerebrovascular events, and heart failure according to categorized TAC burden. Differences in incidence among TAC burden categories were assessed by the log rank test.

Multivariable Cox proportional hazards regression was used to estimate the hazard of overall CVD, and the individual CVD outcomes of 1) CHD, 2) cerebrovascular, and 3) heart failure events associated with TAC burden in the overall cohort adjusted for CAC as a continuous variable and also stratified by CAC (0, 1–99, 100–299, and ≥300). Additionally, we evaluated all-cause mortality as an outcome. The proportional hazards assumption was satisfied and was tested by assessing the significance of time-dependent independent variables concurrently. The association of TAC with CVD events and all-cause mortality was evaluated after adjusting for age, race, sex, educational attainment, income, body mass index, total cholesterol, high-density lipoprotein-cholesterol, fasting blood glucose, systolic blood pressure, diastolic blood pressure, pack years of cigarette smoking, and lipid-, blood pressure- and glucose-lowering medications.

To compare whether TAC improved the discrimination of CVD outcomes we calculated C-Statistic models with differences between models assessed using the approach developed by Uno et al. [24]. The base model for calculating concordance statistics included demographics, traditional risk factors, and CAC. We then evaluated the magnitude of C-statistic improvement when adding TAC to the base model for overall CVD, individual CVD outcomes (CHD, cerebrovascular, heart failure), and all-cause mortality.

3. Results

The mean age was 62.1 years old, 53% were female, 39% were White, 28% were Black, 12% were Chinese, and 22% were Hispanic. More than one-half (53.2%) and approximately two-thirds (63.6%) of participants had post-high school education and had a total family income ≥$35,000, respectively. Persons with higher TAC burden had a generally higher traditional CVD risk factor burden, except for total cholesterol and HDL-C (Table 1). While individuals with TAC=0 on average had a borderline baseline 10-year predicted CVD risk (median 6.4%), persons with TAC 1-499 had intermediate estimated CVD risk (median 18.1%) and those with TAC ≥500 had high estimated CVD risk (median 25.0%). CAC scores were higher across higher TAC scores. A total of 28% of participants had TAC, which was more common in women compared to men (29% versus 27%, p=0.04). The prevalence of TAC ≥500 was 10%, with a graded increase in TAC ≥500 across higher CAC burden (Fig. 1).

Over a median of 17.7 years follow-up, there was a total of 1,202 (17.7%) CVD events, with 770, attributable to CHD, 474 to cerebrovascular disease, and 431 to heart failure. All-cause mortality occurred among 28.0% (n=1899) participants (Table 2). There was an increased CVD event rate across CAC groups, which generally occurred in a stepwise pattern with higher TAC scores (Central Illustration, Fig. 2A-C). Individuals with TAC ≥500 and CAC ≥300 had the highest burden of CVD events (43.2 per 1,000 person-years). Cumulative incidence curves showed significant differences by TAC burden for total CVD, CHD, stroke, and heart failure (Fig. 3A-C).

There was a generally stepwise higher observed CVD event rate using the revised CAC-DRS+ (Fig. 4A-B). For individuals categorized in T0A0 and T2A3N3, the incidence of CVD ranged from 4.8 to 39.7 per 1,000 person-years and incidence of all-cause mortality ranged from 8.4 per 1,000 person-years to 56.6 per 1,000 person-years, respectively. Within CAC groups, the largest difference in the event rates based on TAC occurred among participants with CAC=0.

After adjusting for traditional CVD risk factors and CAC, there was a 1.3-fold higher hazard for incident CVD with TAC ≥500 (HR=1.28, 95% CI: 1.06–1.54) (Table 3). Among persons with CAC=0, TAC ≥500 was associated with a 79% higher hazard for CVD (HR=1.79, 95% CI: 1.04–3.07). Within CVD event subgroups, TAC ≥500 was significantly associated only with incident heart failure when CAC ≥300 (HR 1.81, 95% CI: 1.05–3.10).

There was a robust stepwise increase in total mortality by TAC groups within each CAC group (Central Illustration, Fig. 5B). Cumulative incidence curves for mortality were significantly different by TAC group and participants with TAC ≥500 had an extremely high probability of long-term mortality of 72% over a median 17.7 years follow up (Fig. 5B). Overall, TAC ≥500 conferred a 44% higher hazard for all-cause mortality (HR=1.44, 95% CI: 1.25–1.65) compared to persons with TAC=0. Among participants with CAC=0 and TAC ≥500, there was a nearly two-fold higher hazard of all-cause mortality (HR=1.82, 95% CI: 1.29–2.56) and there was a stepwise higher HR for total mortality with higher CAC scores.

The addition of TAC to traditional risk factors and CAC did not improve CVD discrimination (ΔC-statistic=+0.002, p=0.12), but incrementally improved prediction of all-cause mortality (CVD: ΔC-statistic=+0.002, p=0.02) (Table 4). There were no C-statistic improvements for heart failure or stroke when TAC was added to models including traditional risk factors and CAC.

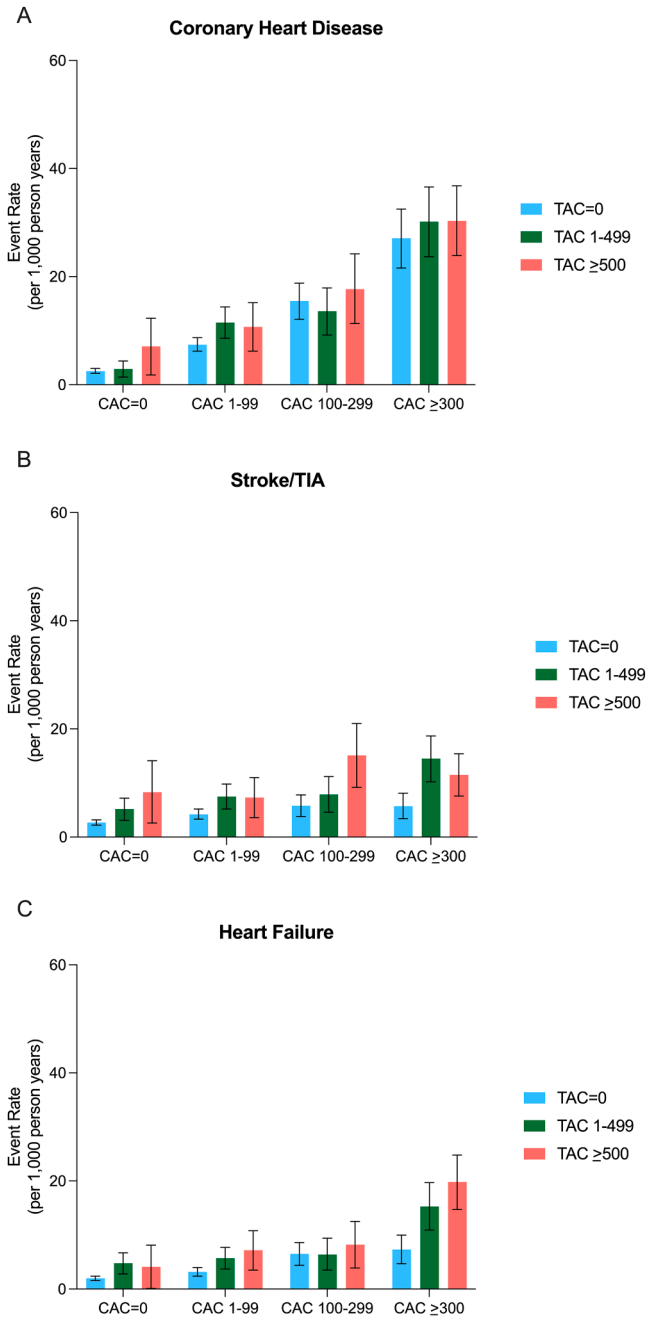

Fig. 2. Cardiovascular disease event rates according to TAC, stratified by CAC burden.

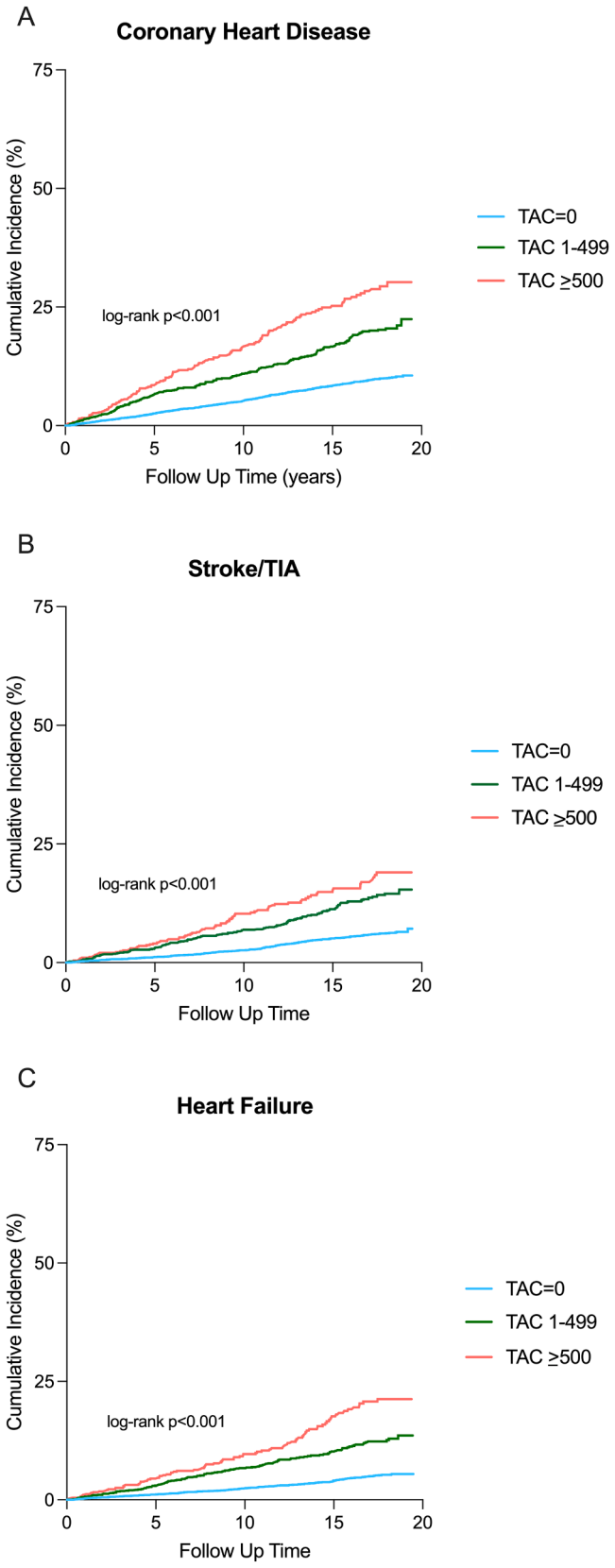

Fig. 3. Cumulative incidence plots for cardiovascular disease according to TAC burden.

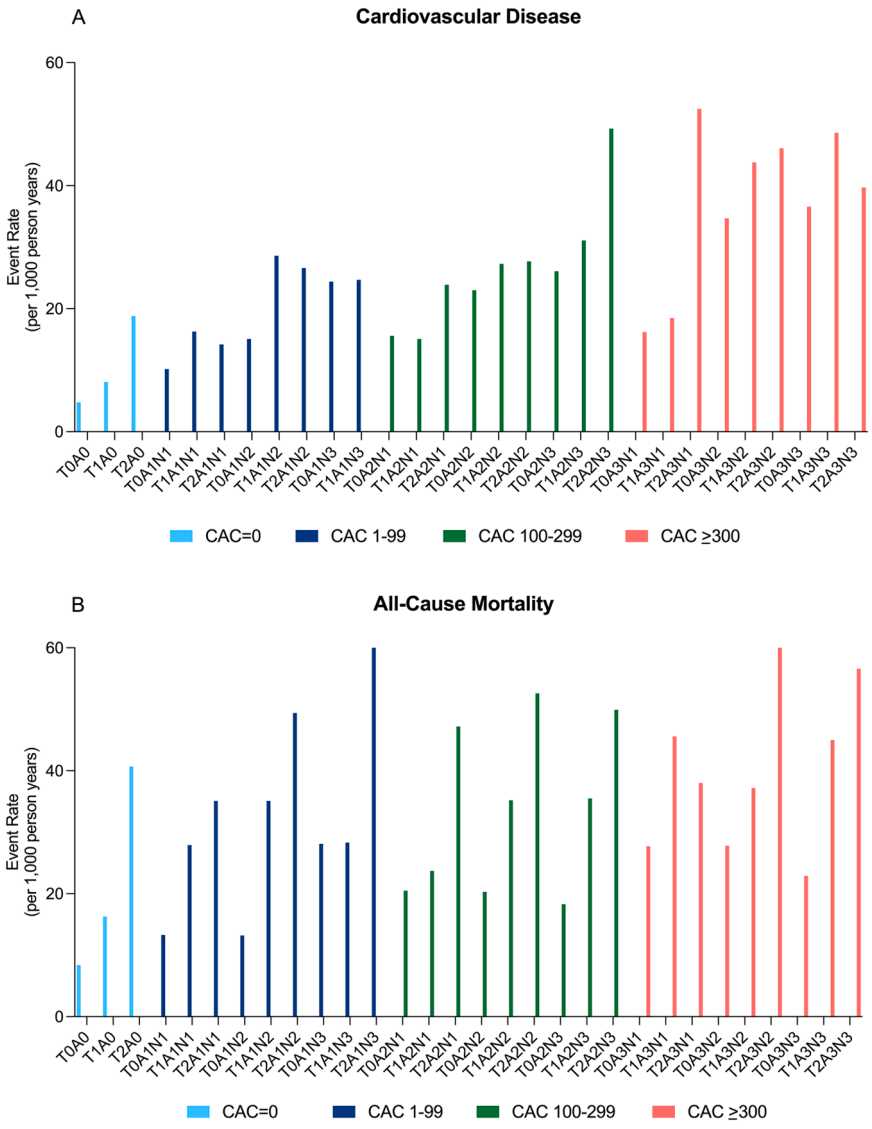

Fig. 4. Cardiovascular disease (A) and all-cause mortality (B) event rates according to a revised CAC-DRS score including TAC burden.
*T=three-level Agatston score (T0: TAC=0, T1: TAC 1-499, T2: TAC ≥500); A=four-level Agatston Score (A0: CAC=0, A1: CAC 1-99, A2: CAC 100-299, A3: CAC ≥300); coronary artery involvement score (N0: none, N1: one artery, N2: two arteries, N3: three or more arteries).
*There were no cardiovascular disease events among individuals with CAC 1-99, three involved vessels and TAC ≥500 (A1N3T2).

Table 3
Association of Thoracic Aortic Calcium with Cardiovascular Disease Events and All-Cause Mortality, Stratified by Coronary Artery Calcium Burden

	Overall (n=6,783)	CAC=0 (n=3,401)	CAC 1-99 (n=1,788)	CAC 100-299 (n=754)	CAC ≥300 (n=840)
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
CVD					
TAC=0	Ref	Ref	Ref	Ref	Ref
TAC 1-499	1.20 (1.03, 1.40)	0.99 (0.69, 1.43)	1.26 (0.97, 1.64)	0.85 (0.60, 1.20)	1.10 (0.83, 1.47)
TAC ≥500	1.28 (1.06, 1.54)	1.79 (1.04, 3.07)	0.94 (0.62, 1.41)	1.08 (0.73, 1.61)	1.12 (0.81, 1.54)
CHD					
TAC=0	Ref	Ref	Ref	Ref	Ref
TAC 1-499	1.11 (0.92, 1.36)	0.73 (0.41, 1.32)	1.26 (0.90, 1.76)	0.78 (0.50, 1.20)	1.00 (0.72, 1.39)
TAC ≥500	1.24 (0.98, 1.57)	1.56 (0.70, 3.51)	1.07 (0.64, 1.81)	0.98 (0.59, 1.63)	1.03 (0.71, 1.48)
Stroke/TIA					
TAC=0	Ref	Ref	Ref	Ref	Ref
TAC 1-499	1.30 (1.02, 1.65)	1.04 (0.65, 1.67)	1.29 (0.85, 1.97)	0.72 (0.39, 1.32)	2.05 (1.19, 3.55)
TAC ≥500	1.31 (0.97, 1.79)	1.36 (0.61, 3.02)	1.01 (0.53, 1.94)	1.21 (0.64, 2.29)	1.55 (0.83, 2.91)
Heart Failure					
TAC=0	Ref	Ref	Ref	Ref	Ref
TAC 1-499	1.16 (0.90, 1.50)	1.20 (0.72, 1.98)	1.17 (0.72, 1.90)	0.56 (0.29, 1.07)	1.60 (0.97, 2.64)
TAC ≥500	1.28 (0.95, 1.73)	0.82 (0.29, 2.31)	1.20 (0.62, 2.32)	0.54 (0.26, 1.15)	1.81 (1.05, 3.10)
All-Cause Mortality					
TAC=0	Ref	Ref	Ref	Ref	Ref
TAC 1-499	1.09 (0.97, 1.23)	0.94 (0.74, 1.22)	1.22 (0.99, 1.50)	1.01 (0.75, 1.34)	1.00 (0.77, 1.30)
TAC ≥500	1.44 (1.25, 1.65)	1.82 (1.29, 2.56)	1.27 (0.97, 1.68)	1.41 (1.03, 1.94)	1.38 (1.05, 1.81)

Adjusted for: age, sex, ethnicity, education, cigarette smoking pack years, systolic pressure, diastolic pressure, total cholesterol, HDL-cholesterol, glucose, triglycerides, antihypertensive medication, lipid-lowering medication, glucose-lowering medication, and continuous Agatston CAC score

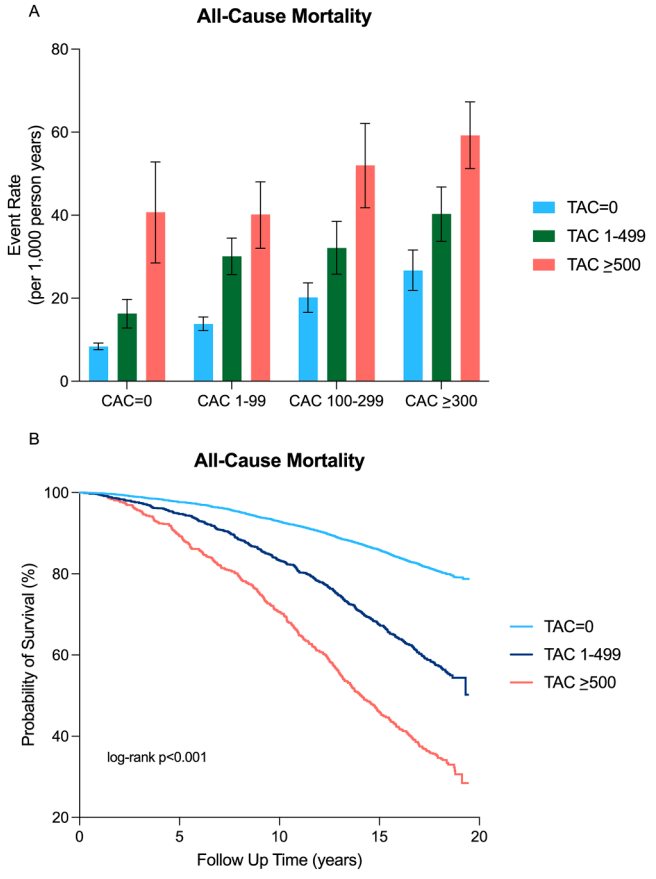

Fig. 5. All-cause mortality event rates (A) and cumulative incidence plots (B) for TAC burden.

4. Discussion

In this ethnically diverse cohort, we observed a stepwise higher incidence of CVD and all-cause mortality across a higher burden of TAC independent of traditional risk factors and CAC. The prevalence of any TAC conferred a 1.3-fold higher risk of CVD compared to TAC=0 and within CAC groups, TAC ≥500 had the strongest association for CVD among persons with CAC=0. Furthermore, there was a stepwise higher event rate for all-cause mortality for increasing TAC burden across all CAC score groups, and we also found that adding TAC to the CAC-DRS further refined CVD and total mortality risk stratification. In summary, over nearly two decades follow-up, TAC primarily improved CVD risk stratification among persons with CAC=0 and had a strong association with all-cause mortality across all CAC scores.

Our study is the first show a significant association of TAC burden with CVD outcomes as well as total mortality in an ethnically diverse cohort. While we focused on multivariable Cox regression models rather than formal risk prediction to examine for statistical significance, the addition of TAC to the CAC-DRS provides important further risk stratification beyond measures of CAC. Furthermore, the addition of TAC to the CAC-DRS to create a modified CAC-DRS+ is an important finding from this study, as the adoption of the CAC-DRS+ can be easily accomplished in clinical practice. Additionally, the use of TAC was found to be especially clinically relevant among individuals with CAC=0, where there was an approximate doubling in CVD event rates across each higher TAC burden category in the CAC DRS+ and individuals with CAC=0 and TAC ≥500 experienced CVD events approaching 20 per 1,000 person years.

Beyond risk stratification, especially for individuals with CAC=0, our study findings are hypothesis-generating with respect to clinical management considerations. Given the crude and multivariable estimates observed in the current study for individuals with CAC=0 and very-high TAC (≥500 Agatston Units), this subgroup of individuals may benefit from a risk-benefit discussion regarding initiation of primary prevention therapies, including statin and/or aspirin therapy. In MESA the prevalence of CAC=0 and TAC ≥500 was approximately 2–3%. Further studies are required to better evaluate the underlying pathophysiology of these patients with discordant CAC and TAC.

In the overall sample, TAC ≥500 conferred a 44% higher risk for all-cause mortality independent of traditional risk factors and CAC over nearly two decades of follow-up. Additionally, TAC ≥500 had an even stronger association (82% higher risk) with all-cause mortality among individuals with CAC=0. Among individuals with CAC=0, the presence of high TAC (≥500) can thus identify those at higher risk of mortality and could be considered to help guide the interval of repeat cardiac CT.

Table 4
AUC Analysis for CVD Events and All-Cause Mortality for the Addition of TAC

	C-Statistic	Change in C-Statistic	C-Statistic Contrast P-Value
CVD			
Demographics* + Traditional Risk Factors† + Baseline CAC	0.743	-	-
Demographics* + Traditional Risk Factors† + Baseline CAC + TAC	0.745	0.002	0.12
CHD			
Demographics* + Traditional Risk Factors†† + Baseline CAC	0.745	-	-
Demographics* + Traditional Risk Factors† + Baseline CAC + TAC	0.746	0.001	0.47
Stroke/TIA			
Demographics* + Traditional Risk Factors† + Baseline CAC	0.723	-	-
Demographics* + Traditional Risk Factors† + Baseline CAC + TAC	0.725	0.002	0.56
HF			
Demographics* + Traditional Risk Factors† + Baseline CAC	0.784	-	-
Demographics* + Traditional Risk Factors† + Baseline CAC + TAC	0.785	0.001	0.37
All-Cause Mortality			
Demographics* + Traditional Risk Factors† + Baseline CAC	0.775	-	-
Demographics* + Traditional Risk Factors† + Baseline CAC + TAC	0.777	0.002	0.02

* age, sex, race, education
† cigarette smoking pack years, systolic blood pressure, diastolic blood pressure, total cholesterol, HDL-cholesterol, fasting blood glucose, body mass index, antihypertensive medication, lipid-lowering medication, glucose-lowering medication

In particular, individuals with high TAC burden and CAC=0 are likely to benefit from a shorter time between CT scans to guide risk stratification and primary prevention management. We have previously shown that absence of TAC is one of the strongest predictors for long-term CAC=0 in several different patient populations, therefore it is thought that calcific atherosclerosis of the two anatomical sites is closely correlated [25,26]. Therefore, association between TAC and all-cause mortality may be due to a combination of both atherosclerotic and all-cause mortality.

Individuals with CAC ≥300 and TAC ≥500 experienced very high all-cause mortality rates approaching 60 per 1,000 person years, suggesting that this group of individuals has accelerated biologic aging. Additionally, we found that TAC ≥500 was associated with a near doubling in the risk for heart failure among persons with CAC ≥300. There have been no previous reports regarding TAC and incident heart failure. However, TAC is strongly associated with aortic stiffness and systolic hypertension [27], which are both risk factors for heart failure. Likewise, CAC may be especially predictive of ischemic heart failure, while TAC may share an association with both ischemic heart failure and potentially heart failure with preserved ejection fraction (HFpEF) since hypertension is a key risk factor for diastolic dysfunction and HFpEF.

Our study should be interpreted in the setting of certain limitations and strengths. The most notable limitation of our study may be related to the large number of categories in our newly created CAC-DRS+ scoring system, which may have had limited power to detect event rates in all subgroups of the CAC-DRS+. Additionally, our findings may be limited in that MESA did not include a reproducibility measurement protocol for TAC. Furthermore, in order to stay consistent with prior MESA studies, we presented absolute event rates over a median 17-year follow-up, which is the average event rate and does not account for an increased event rate over time as the mean participant age increases. The major strengths of this study include the measurement of TAC and CAC among an ethnically diverse cohort with a nearly 20-year follow up. We are also the first study to assess the association of TAC burden across CAC groups for both CVD and non-CVD outcomes over nearly two decades of follow up period.

In conclusion, a higher burden of TAC identified persons at increased risk of CVD and all-cause mortality beyond traditional risk factors and CAC with differences in CVD and all-cause mortality event rates that were most notable among persons with CAC=0. Persons with TAC ≥500 and CAC ≥300 were also at a particularly high risk for all-cause mortality. Thus, reporting of TAC should be considered to improve risk stratification for CVD and all-cause mortality.

CRediT authorship contribution statement

Alexander C. Razavi: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Omar Dzaye:** Writing – review & editing, Methodology. **Miguel Cainzos-Achirica:** Writing – review & editing, Methodology. **Zeina Dardari:** Writing – review & editing, Methodology. **Marly Van Assen:** Writing – review & editing, Methodology. **Arshed A. Quyyumi:** Writing – review & editing, Methodology. **Khurram Nasir:** Writing – review & editing, Methodology. **J. Jeffrey Carr:** Writing – review & editing, Methodology. **Matthew J. Budoff:** Writing – review & editing, Methodology, Funding acquisition, Data curation. **Roger S. Blumenthal:** Writing – review & editing, Project administration, Methodology. **Paolo Raggi:** Writing – review & editing, Methodology. **Carlo N. De Cecco:** Writing – review & editing, Methodology. **Laurence S. Sperling:** Writing – review & editing, Methodology. **Michael J. Blaha:** Writing – review & editing, Project administration, Methodology, Funding acquisition. **Seamus P. Whelton:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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