Thoracic Aorta Calcification and Noncardiovascular Disease–Related Mortality

The Multi-Ethnic Study of Atherosclerosis

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Objective—Arterial calcification is highly correlated with underlying atherosclerosis. Arterial calcification of the thoracic aorta is evident in many older individuals at high susceptibility to aging-related diseases and non-cardiovascular disease (CVD)–related mortality. In this study, we evaluated the association of thoracic aorta calcification (TAC) with non-CVD morbidity and mortality.

Approach and Results—We analyzed data from participants in the Multi-Ethnic Study of Atherosclerosis, a prospective cohort study of subclinical atherosclerosis, in which participants underwent cardiac computed tomography at baseline and were followed longitudinally for incident CVD events and non-CVD events. Using modified proportional hazards models accounting for the competing risk of CVD death and controlling for demographics, CVD risk factors, coronary artery calcium, and CVD events, we evaluated whether TAC was independently associated with non-CVD morbidity and mortality. Among 6765 participants (mean age, 62 years), 704 non-CVD deaths occurred for a median follow-up of 12.2 years. Compared with no TAC, the highest tertile of TAC volume was associated with a higher risk of non-CVD mortality (hazard ratio, 1.56; 95% confidence interval, 1.23–1.97), as well as several non-CVD diagnoses, including hip fracture (2.14; 1.03–4.46), chronic obstructive pulmonary disease (2.06; 1.29–3.29), and pneumonia (1.79; 1.30–2.45), with magnitudes of association that were larger than for those of coronary artery calcium.

Conclusions—TAC is associated with non-CVD morbidity and non-CVD mortality, potentially through a pathway that is unrelated to atherosclerosis. TAC may be a general marker of biological aging and an indicator of increased risk of non-CVD and death. **(*Arterioscler Thromb Vasc Biol*. 2018;38:00-00. DOI: 10.1161/ATVBAHA.118.310850.)**

Key Words: aging ■ aorta, thoracic ■ atherosclerosis ■ mortality ■ tomography

Aging is a process involving cellular senescence, tissue degeneration, and declining organ function, ultimately resulting in heightened disease susceptibility and death. With an aging global population, the worldwide burden of disease is expected to rise exponentially in the coming decades.[1,2] Moving beyond chronological age, or the time elapsed since birth, to biological measures of aging may help identify individuals at risk of developing aging-related diseases.

Arterial calcification detected by computed tomography (CT) has been proposed as a potential biological measure of aging because of the strong association of arterial calcification with atherosclerosis.[3] Atherosclerosis is itself viewed as a disease process closely linked to aging,[4] manifesting at its earliest stage in childhood and characterized by lipid accumulation, inflammation and, frequently, calcification of the arterial wall later in life.[5] However, it is unknown whether arterial calcification also reflects a broader process of aging that extends beyond atherosclerosis. If so, arterial calcification would be expected to reflect a heightened susceptibility to diseases not causally-related to atherosclerosis, such as incident cancer, as well as non-cardiovascular disease (CVD)–related mortality.

Indeed, coronary artery calcification (CAC) has been associated with several types of non-CVD morbidities,[6] suggesting a potential dual significance of arterial calcification. As visualized in the conceptual framework of Figure 1, the well-established pathway of atherosclerosis, atherosclerotic calcification, and CVD events is complemented by a hypothetical parallel pathway of biological aging, aging-associated calcification, and non-CVD events. This latter pathway, if it exists, can be difficult to distinguish from the former because arterial calcification is strongly associated with CVD events,

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Nonstandard Abbreviations and Acronyms	
CAC	coronary artery calcium
COPD	chronic obstructive pulmonary disease
CT	computed tomography
CVD	cardiovascular disease
HR	hazard ratios
TAC	thoracic aorta calcium

and the morbidity associated with CVD events can increase susceptibility to non-CVD mortality, creating an indirect pathway that can confound a direct relationship between arterial calcification and non-CVD mortality.

Given this, we tested the possible direct relationship between arterial calcification in the thoracic aorta (thoracic aorta calcium [TAC]) and both non-CVD morbidity and mortality. Although indicative of systemic atherosclerosis,[7] TAC may also occur independently of the atherosclerotic process and has a robust association with mortality.[8–12] Thus, by evaluating TAC and attempting to disentangle its association with atherosclerosis via adjustment for CVD risk factors, CAC, and CVD events, we sought to derive insight into arterial calcification as a possible prognostic indicator of biological aging.

Methods

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be requested by contacting research personnel from the MESA (Multi-Ethnic Study of Atherosclerosis). Details can be found at http://www.mesa-nhlbi.org.

Study Participants

We conducted analyses using data from of the MESA, a prospective, population-based cohort study of the natural history of subclinical atherosclerosis performed at 6 centers across the Unites States. Details on the overall study design, recruitment methods, examination components, and data collection have been reported.[13] The study was approved by institutional review boards at each site, and all participants provided written informed consent. A total of 6814 men and women aged 45 to 84 years and free of clinical CVD at recruitment underwent cardiac CT scans for CAC at the MESA baseline examination conducted between 2000 and 2002. In a subsequent ancillary study, these CT scan images were evaluated for calcification in several extracoronary sites visible on cardiac CT, including in the thoracic aorta.

Arterial Calcium Measurement

TAC was defined as the presence of calcium within the boundaries of the descending thoracic aorta visualized on cardiac CT studies, measuring from the level of the pulmonary artery bifurcation superiorly to the level of the apex of the heart inferiorly. The ascending thoracic aorta is also visualized on these scans. However, we have previously observed ascending TAC to be uncommon (≈3% of participants) but strongly associated with CVD events.[14] Therefore, we did not include TAC found in the ascending aorta in this analysis, and our definition of TAC included only the descending segment.

Both TAC and CAC lesions had a minimum volume of 5.5 mm^3 when measured on electron beam CT or 4.6 mm^3 when measured on multidetector CT and a density (attenuation) of >130 Hounsfield units. Detailed methods of calcium measurement have been previously reported.[15,16] At the time of ascertainment, TAC and CAC Agatston and volume scores were measured and recorded. For this study, we used TAC and CAC volume and density scores. We

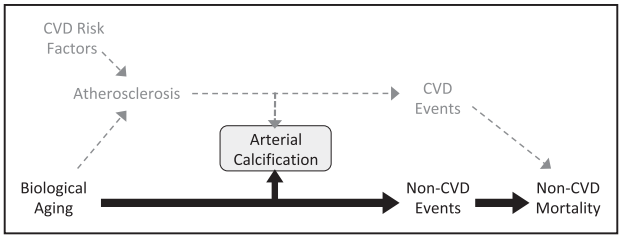

Figure 1. Conceptual framework for the associations of biological aging, arterial calcification, and non-cardiovascular disease (CVD) mortality. Calcification of the arterial wall is a well-recognized consequence of atherosclerosis. We hypothesized that biological aging may also result in arterial calcification through a parallel pathway. Although atherosclerosis leads to CVD events, biological aging may lead to an increased susceptibility to non-CVD events (eg, cancer), leading to non-CVD–related mortality. Aging is also a risk factor for atherosclerosis, which in turn leads to CVD events that can also increase an individual's susceptibility to non-CVD mortality (eg, heightened cancer mortality among individuals with a history of clinical CVD).

calculated density scores for each participant using the following formula as reported in prior studies: density score=Agatston score×CT slice thickness/volume score.[17] Calcium density has been reported to be inversely associated with CVD events after adjustment for natural log-transformed calcium volume in prior studies.[14,17,18]

Mortality and Non-CVD Event Ascertainment

Follow-up began at the baseline examination and continued until death, loss to follow-up, or through the end of calendar year 2013, whichever occurred first. Details on event ascertainment and adjudication have been previously reported.[13] Briefly, at intervals of 9 to 12 months, each participant and their next of kin (if participants were unavailable) were contacted via telephone by trained interviewers to inquire about interim hospital admissions, cardiovascular outpatient diagnoses, and deaths. Medical records and copies of death certificates were requested. A physician review committee assigned cause of death for potential CVD-related deaths. CVD-related deaths were classified as because of atherosclerotic coronary heart disease, stroke, other atherosclerotic disease (noncoronary/nonstroke), or other CVD. Non-CVD deaths were defined as deaths not meeting the above classifications or a likely cause of death that was not related to coronary heart disease.

Non-CVD morbidity diagnoses were abstracted from inpatient medical records via *International Classification of Diseases*, *Ninth Revision* codes and verified by review of hospital records and death certificates.[6] *International Classification of Diseases*, *Ninth Revision* codes relating to the following broader groups were included: chronic kidney disease and indicators of end-stage renal failure, any malignant neoplasm, dementia, hip fracture, deep vein thrombosis or pulmonary embolism, pneumonia, and chronic obstructive pulmonary disease (COPD). For this report, participants with a history of a non-CVD diagnosis at the baseline examination were excluded from the longitudinal analysis of that non-CVD diagnosis.

Covariates

Full details on MESA examination components have been previously reported.[13] Participant variables including demographics, medical and social history, and physical and laboratory data were collected at the baseline examination of the cohort. In this analysis, continuous CVD risk factors were total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, body mass index, and natural log-transformed C-reactive protein. Categorical CVD risk factors were hypertension medication use, smoking status, diabetes mellitus, and statin medication use. We also adjusted for incident nonfatal CVD events occurring during follow-up. Nonfatal CVD events were defined as incident coronary heart disease events (definite and probable myocardial infarction, resuscitated cardiac arrest, and definite angina) and stroke (nonfatal).

Statistical Analysis

Descriptive statistics for baseline characteristics are presented stratified by level of TAC volume. We used Spearman correlation coefficients to evaluate the bivariate associations between TAC and CAC volume and density scores. We divided participants with detectable TAC into tertiles of TAC volume. Participants with no detectable TAC (TAC volume=zero) served as the reference category in regression models. We also evaluated TAC volume ($\log_e$ TAC volume+1) as a continuous variable.

We used Kaplan-Meier survival curves and modified proportional hazards models accounting for the competing risk of CVD death as described by Fine and Gray[19] to estimate the risks of non-CVD mortality and non-CVD adverse events. Hierarchical models adjusted for age, sex, race/ethnicity (model 1), CVD risk factors (model 2), and tertiles of CAC volume (model 3), and incident nonfatal CVD events (model 4). Sub-hazard ratios (HR) and 95% confidence intervals are reported.

We evaluated the association of the density of TAC and CAC with non-CVD mortality using modified proportional hazards models with similar hierarchical adjustment as above. As the density score is only available among participants with detectable calcium, these analyses were restricted to participants with TAC and CAC volume scores >0. For the analysis of TAC with non-CVD morbidity, we excluded participants with a history of the diagnosis of interest based on participant report at the baseline examination.

No significant multiplicative interactions were observed between TAC volume and sex (P=0.13) or race/ethnicity (P=0.43). Missing covariate data (<0.1%) were imputed using sample variable means. In a sensitivity analysis, we including ascending TAC volume in the models and found that the results were materially unchanged; therefore, we present results reflective of only the descending thoracic aorta segment. Analyses were performed using R Statistical Software (version 3.2.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

We excluded 4 participants with missing TAC volume scores, 5 participants who died of unknown causes, and 40 participants

Table 1. Baseline Characteristics of Participants by Level of Thoracic Aortic Calcification in the Multi-Ethnic Study of Atherosclerosis

		TAC Volume Tertiles			
	TAC=Zero	T1: 1–93 mm³	T2: 94–435 mm³	T3: 436–22 376 mm³	*P* Value
n	4933	608	613	611	
Age, y	58.9 (9.1)	67.5 (8.3)	71.0 (7.2)	73.7 (6.7)	<0.01
Women	52.1%	51.3%	56.0%	58.1%	0.01
Ethnicity					<0.01
Non-Hispanic white	36.0%	40.6%	45.0%	49.3%	
Hispanic	22.8%	19.9%	19.4%	19.5%	
Black	30.2%	26.8%	19.9%	17.8%	
Chinese	11.0%	12.7%	15.7%	13.4%	
Total cholesterol, mg/dL	194 (35)	197 (38)	193 (35)	195 (36)	0.30
HDL cholesterol, mg/dL	51 (15)	50 (14)	51 (14)	52 (15)	0.37
SBP, mm Hg	123 (20)	133 (21)	136 (23)	140 (23)	<0.01
Hypertension medication	31.6%	46.1%	50.6%	60.0%	<0.01
Smoking status					0.01
Current	13.6%	11.3%	11.1%	12.3%	
Former	35.4%	37.3%	39.5%	42.3%	
Diabetes mellitus	11.0%	15.3%	15.9%	19.2%	<0.01
Statin medication	14.3%	16.5%	17.2%	16.2%	0.10
Body mass index, kg/m²	28.6 (5.6)	27.9 (5.0)	27.8 (5.1)	27.4 (5.0)	<0.01
C-reactive protein, mg/L	3.7 (5.7)	3.4 (5.0)	4.1 (7.0)	4.1 (6.8)	0.08
TAC volume, mm³	0 [0, 0]	35 [19, 57]	219 [140, 315]	979 [626, 1823]	<0.01
TAC density	…	2.99 (0.78)	3.50 (0.40)	3.57 (0.41)	…
CAC >0	38.8%	68.3%	79.0%	89.7%	<0.01
CAC volume, mm³	0 [0, 29]	32 [0, 145]	87 [8, 311]	196 [46, 568]	<0.01
CAC density	2.60 (0.73)	2.71 (0.66)	2.78 (0.63)	2.92 (0.57)	<0.01
Follow-up time, y	12.4 [11.8, 12.8]	12.1 [11.6, 12.7]	11.9 [11.5, 12.6]	11.7 [9.2, 12.4]	<0.01
CVD mortality	109 (2.2%)	21 (3.5%)	36 (5.9%)	62 (10.1%)	<0.01
Non-CVD mortality	342 (6.9%)	81 (13.3%)	117 (19.1%)	164 (26.8%)	<0.01

Values presented are number and percentages, means (SDs), or medians [interquartile ranges]. CAC indicates coronary artery calcium; CVD, cardiovascular disease; HDL, high-density lipoprotein; SBP, systolic blood pressure; and TAC, thoracic aorta calcium.

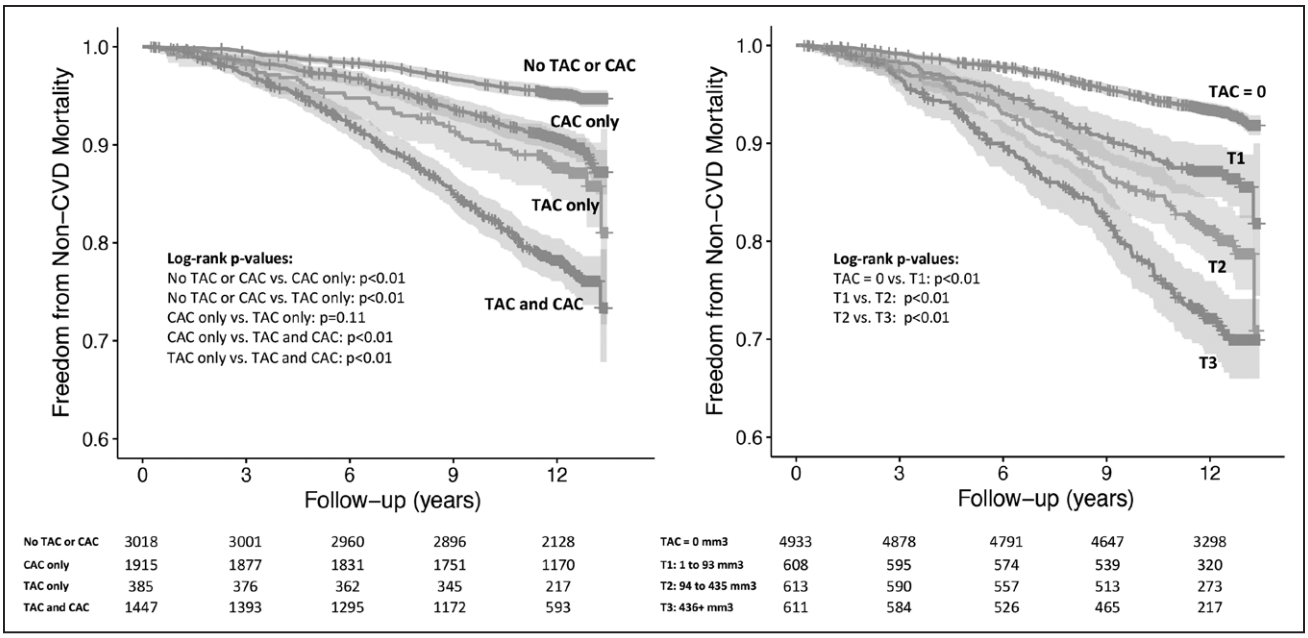

Figure 2. Kaplan-Meier estimates of freedom from non-cardiovascular disease (CVD) mortality stratified by prevalence of thoracic aorta calcium (TAC), coronary artery calcium (CAC), neither, or both (**left**) and TAC volume tertile (**right**).

whose deaths were not adjudicated for cause at the time of this analysis, leaving a final analytic sample of 6765 participants. Seven-hundred four non-CVD deaths occurred for a median follow-up of 12.2 years.

Baseline characteristics of the sample stratified by presence and tertile of prevalent TAC volume are presented in Table 1. Across tertiles, participants with prevalent TAC were on average older and more often female and non-Hispanic white. CVD risk factors, such as higher systolic blood pressure, use of hypertension medication, and diabetes mellitus, were more common among participants with TAC while body mass index was somewhat lower. Both non-CVD and CVD mortality more commonly occurred across higher tertiles of TAC. Several incident non-CVD diagnoses, such as COPD and cancer, were also more common across TAC tertiles (Table I in the online-only Data Supplement). CAC was present in 38.8% of participants without TAC and in 79.0% of participants with TAC. Notably, TAC volume scores were only moderately correlated with CAC volume scores (r=0.44), and TAC density scores showed no correlation with CAC density scores (r=−0.04; Table II in the online-only Data Supplement).

Figure 2 displays Kaplan-Meier survival curves for non-CVD mortality stratified by baseline prevalence of TAC or CAC and among tertiles of TAC volume. Survival probability decreased with the presence of TAC or CAC and was decreased further in the presence of both. Survival also decreased with ascending tertiles of TAC volume, with significant differences observed between tertiles (P<0.01).

In modified proportional hazards models, we observed a higher risk of non-CVD mortality in higher tertiles of TAC volume. As summarized in Table 2, and after controlling for age, sex, and race/ethnicity in model 1, the HR for TAC tertiles 2 and 3, compared with no TAC, were 1.49 (1.18, 1.88) and 1.89 (1.51, 2.36), respectively. The HR for tertile 1 was smaller at 1.17 (0.91, 1.50). With additional adjustment for CVD risk factors in model 2, and further adjustment for tertile

Table 2. Association of TAC Volume With Non-CVD–Related Mortality

TAC	Model 1: Age, Sex, Race/ Ethnicity	Model 2: Model 1+CVD Risk Factors	Model 3: Model 2+CAC Volume Tertile	Model 4: Model 3+CVD Events
TAC=0	ref	ref	ref	ref
Tertile 1	1.17 (0.91, 1.50)	1.14 (0.89, 1.47)	1.10 (0.86, 1.42)	1.10 (0.86, 1.42)
Tertile 2	1.49 (1.18, 1.88)*	1.38 (1.09, 1.74)*	1.31 (1.04, 1.67)*	1.30 (1.03, 1.65)*
Tertile 3	1.89 (1.51, 2.36)*	1.70 (1.35, 2.13)*	1.56 (1.23, 1.97)*	1.56 (1.24, 1.97)*
TAC volume (per log-unit)	1.09 (1.06, 1.12)*	1.07 (1.04, 1.11)*	1.06 (1.03, 1.09)*	1.06 (1.03, 1.09)*

Values presented are subhazard ratios (95% confidence intervals) from modified proportional hazards models accounting for the competing risk of CVD death for tertiles of TAC volume scores compared with a reference group of zero and for the continuous natural log-transformed TAC volume. CVD risk factors were gathered at baseline and are total cholesterol, HDL cholesterol, systolic blood pressure, hypertension medication, smoking, diabetes mellitus, statin medication, body mass index, and C-reactive protein. Nonfatal CVD events were defined as incident coronary heart disease (CHD) events (definite and probable myocardial infarction, resuscitated cardiac arrest, and definite angina) and stroke (nonfatal). CAC indicates coronary artery calcium; CVD, cardiovascular disease; HDL, high-density lipoprotein; and TAC, thoracic aorta calcium.

*P<0.05.

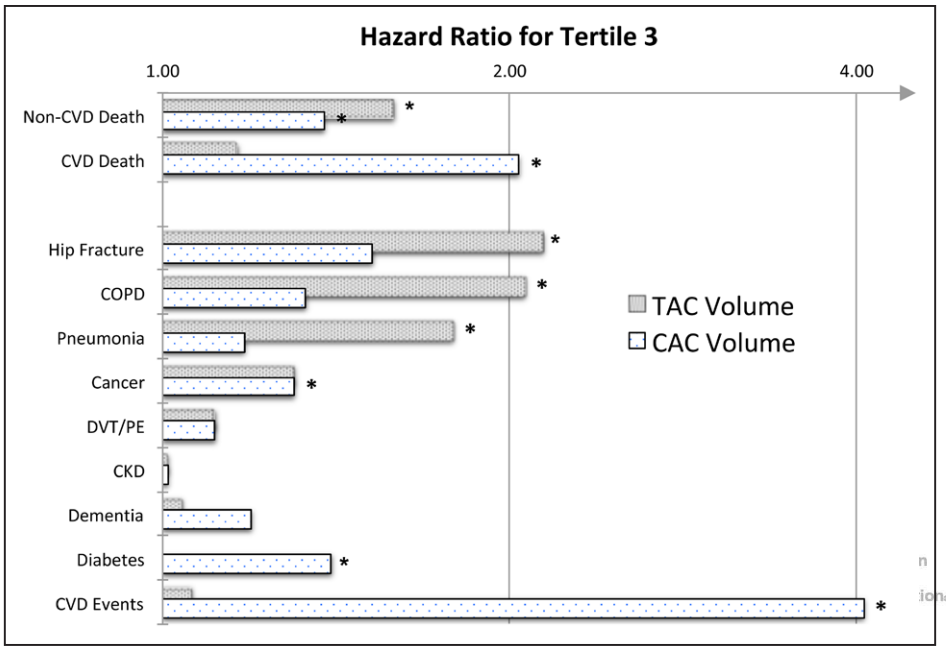

Figure 3. Associations of thoracic aorta calcium (TAC) and coronary artery calcium (CAC) with mortality and incident morbidities. Causes of death were adjudicated by physician committee. Morbidities were abstracted from inpatient medical records via *International Classification of Diseases, Ninth Revision* codes. Subhazard ratios are plotted for tertile 3 of TAC volume and CAC volume compared with a reference of no TAC and CAC volume, respectively. Associations are adjusted for age, sex, race/ethnicity, cardiovascular disease (CVD) risk factors (total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, hypertension medication, smoking, diabetes mellitus, statin medication, and body mass index) and mutually-adjusted for TAC and CAC volume tertile, and nonfatal CVD events. Participants reporting a history of a given morbidity at the baseline examination were excluded from the analysis of that morbidity. *P<0.05. CKD indicates chronic kidney disease; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; and PE, pulmonary embolism.

of CAC volume and nonfatal CVD events in models 3 and 4, the HR were attenuated slightly but remained statistically significant.

Log-transformed TAC volume scores were significantly associated with non-CVD mortality, with an HR of 1.06 (1.03, 1.09) per mm^3 in model 4. In models evaluating calcium density, TAC and CAC density scores were not significantly associated with non-CVD mortality after adjusting for corresponding volume scores (Table III in the online-only Data Supplement).

Figure 3 displays the associations of TAC and CAC volume with incident non-CVD morbidity with adjustment for model 3 variables, which included mutual adjustment for TAC and CAC tertiles. In these analyses, TAC was significantly associated with an increased risk of several incident non-CVD morbidities, including hip fracture (HR, 2.14 [1.03, 4.46]), COPD (HR, 2.06 [1.29, 3.29]), and pneumonia (HR, 1.79 [1.30, 2.45]). TAC had a larger magnitude of association for non-CVD mortality and these non-CVD diagnoses than CAC while CAC had a larger magnitude of association for diabetes mellitus, CVD death, and CVD events.

Discussion

In this study, we evaluated calcification in the descending thoracic aorta and found that, after controlling for CVD risk factors, CAC, and CVD events, the volume of TAC was associated with non-CVD mortality, as well as incident non-CVD diagnoses, such as COPD, hip fracture, and pneumonia. Taken together, these findings suggest that arterial calcification may identify individuals at increased susceptibility to non-CVD morbidity and subsequent non-CVD–related mortality.

We found that TAC volume scores had only a moderate correlation with CAC volume scores, and TAC density scores had no correlation with CAC density scores. Furthermore, TAC had stronger associations with non-CVD morbidity and mortality than those of CAC. These findings suggest that TAC and CAC may represent different underlying pathophysiologic processes relevant to different diseases. In their review of thoracic aorta calcification, Abramowitz et al[20] posit that calcification in the thoracic aorta can be the result of both atherosclerotic and nonatherosclerotic processes, with the former occurring in the tunica intima of the vessel wall and the latter occurring in the tunica media. Importantly, the nonatherosclerotic processes resulting in medial calcification may reflect biological aging. In a necropsy study of 58 thoracic aortas, Elliot and McGrath[21] reported that while medial calcification concentration increased with age, intimal calcification concentrations did not. These differences in medial and intimal calcification may account for the discrepancy in the associations of TAC and CAC with non-CVD mortality as medial calcification is common in the aorta and uncommonly reported in the coronary arteries.[21–23] Identifying the layer of the artery wall involved with calcium may provide useful information on both biological aging and CVD risk. However, current CT imaging is unable to definitively distinguish medial from intimal calcification although this is an area of ongoing research.[24]

Prior studies have also suggested a link between arterial calcification and aging. Systemic inflammation is viewed as central to the aging process and has been implicated in the calcification of cardiovascular structures.[25,26] Inflammation contributes to intimal atherosclerosis and calcification of the coronary arteries and also seems to be a key contributor

to the emerging epidemic of calcific aortic valve disease.[27] Furthermore, animal models suggest that inflammation is the shared mechanism underlying the association between vascular calcification and osteoporosis,[28] and inflammation is implicated in COPD, cancer, and even infection via concurrent maladaptive immune system modulation.[29–31] Adjusting chronological age by levels of CAC to determine an individual's arterial age has been shown to provide superior CVD prognostication in several studies.[3,32–35] Defects in the expression of the *klotho* gene in mice lead to several abnormalities associated with aging, including a shortened lifespan, emphysema, osteoporosis and, notably, calcification of the medial layer of the aorta.[36,37]

Strengths of our study include its longitudinal design, as well as the inclusion of several CVD risk factors, assessment of arterial calcification in >1 vascular bed, and CVD and non-CVD event ascertainment performed in a multiethnic, community-based prospective cohort study of the natural history of subclinical atherosclerosis. This allowed for adjustment for several potential confounders in our assessment of the independent association of TAC with non-CVD events and mortality. However, non-CVD event ascertainment was based on inpatient medical records, and thus only captured diagnoses associated with a hospitalization and were not independently adjudicated by physician committee. Furthermore, adjustment for medication use and changes in CVD risk factor status after the baseline examination were not performed in our analysis. Finally, although we attempted to control for the association of atherosclerosis with arterial calcification and any possible downstream effects on non-CVD mortality, our results could still be prone to residual confounding.

If validated in additional studies, our findings would support the use of TAC as a marker of increased risk of non-CVD–related morbidity and mortality and lend credence to arterial calcification representing a broader process of biological aging that extends beyond atherosclerosis. TAC can be assessed on diagnostic and screening chest CT that are performed routinely in the clinical setting, as well as cardiac CT for CAC that were used in this study. As the global burden of disease is expected to rise exponentially with the aging population, the early identification of accelerated aging via markers, such as TAC, may provide opportunities for effective targeting of screening and prevention efforts.

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Disclosures

None.

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Highlights

- In a community-based cohort free of baseline clinical cardiovascular disease, calcification of the thoracic aorta was associated with a greater risk of noncardiovascular disease–related morbidities and mortality.
- The magnitudes of these associations were larger for calcification of the thoracic aorta compared with calcification of the coronary arteries.
- Calcification of the thoracic aorta could be a general marker of biological aging and an indicator of increased risk of noncardiovascular diseases and death.

Arteriosclerosis, Thrombosis, and Vascular Biology

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Thoracic Aorta Calcification and Noncardiovascular Disease–Related Mortality: The Multi-Ethnic Study of Atherosclerosis

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Online Supplemental Material

Supplementary Table I: Incident Non-CVD and CVD Diagnoses Over Follow-up Across Tertiles of TAC volume

	TAC Volume Tertiles				
	TAC = Zero	T1: 1 - 93 mm3	T2: 94 - 435 mm3	T3: 436-22,376 mm3	p-value
COPD	98 (2.0%)	22 (3.5%)	29 (5.3%)	53 (8.1%)	<0.01
Hip Fracture	22 (0.4%)	12 (1.9%)	10 (1.8%)	26 (4.0%)	<0.01
Pneumonia	200 (4.1%)	35 (5.6%)	54 (9.9%)	90 (13.7%)	<0.01
Cancer	500 (10.1%)	96 (15.8%)	128 (20.9%)	144 (23.6%)	<0.01
DVT/PE	158 (3.2%)	17 (2.8%)	34 (5.5%)	39 (6.4%)	<0.01
CKD/ESRD	317 (6.4%)	65 (10.7%)	65 (10.6%)	97 (15.9%)	<0.01
Dementia	85 (1.7%)	17 (2.8%)	43 (7.0%)	54 (8.8%)	<0.01
Diabetes	533 (10.8%)	99 (16.3%)	101 (16.5%)	115 (18.8%)	<0.01
Coronary Heart Disease	145 (3.0%)	29 (4.8%)	29 (4.9%)	50 (8.5%)	<0.01
Stroke	110 (2.2%)	25 (4.1%)	28 (4.6%)	34 (5.7%)	<0.01

Values listed are the number and percentage of study participants in each tertile with a non-CVD morbidity diagnosis or non-fatal CVD event. Non-CVD morbidity diagnoses were abstracted from inpatient medical records via ICD-9 codes. Nonfatal CVD events were adjudicated by physician committee and defined as incident coronary heart disease (CHD) events (definite and probable myocardial infarction, resuscitated cardiac arrest, and definite angina) and stroke. Abbreviations: CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disease, CVD=cardiovascular disease, DVT=deep venous thrombosis, ESRD=end stage renal disease, PE=pulmonary embolism, TAC=thoracic aorta calcium

Supplementary Table II: Correlation Matrix for TAC and CAC Volume and Density Scores

	TAC Volume	TAC Density	CAC Volume	CAC Density
TAC Volume	1	0.39	0.44	0.17
TAC Density	0.39	1	0.06	-0.04
CAC Volume	0.44	0.06	1	0.56
CAC Density	0.17	-0.04	0.56	1

Spearman correlation coefficients for TAC and CAC volume scores (n=6,765) and density scores (n=1,832)

Supplementary Table III: The Association of TAC and CAC Density with Non-CVD Mortality

	TAC Density	CAC Density
Model A: Corresponding calcium (TAC or CAC) volume score	0.92 (0.81, 1.04)	0.93 (0.78, 1.09)
Model B: Model A + age, sex, race/ethnicity	0.95 (0.83, 1.09)	0.97 (0.82, 1.15)
Model C: Model B + CVD risk factors, CAC or TAC density score, and CVD events	0.95 (0.83, 1.09)	0.94 (0.79, 1.12)

Values presented are sub-hazard ratios (95% confidence intervals) per standard deviation (0.61 and 0.70 density-units for TAC and CAC, respectively). Due to the nature of the exposure variable (TAC and CAC density), only participants with prevalent calcium (TAC and CAC > 0, n=1,447) are included. TAC and CAC volume are log-transformed to adjust for skewness. Bolded text indicates $p<0.05$. CVD risk factors are total cholesterol, HDL-cholesterol, systolic blood pressure, hypertension medication, smoking, diabetes mellitus, statin medication, body mass index, and C-reactive protein. CAC=coronary artery calcium, CVD=cardiovascular disease, TAC=thoracic aorta calcium