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Density of calcium in the ascending thoracic aorta and risk of incident cardiovascular disease events

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Abstract

Background and aims—The volume and density of coronary artery calcium (CAC) both independently predict cardiovascular disease (CVD) beyond standard risk factors, with CAC density inversely associated with incident CVD after accounting for CAC volume. We tested the hypothesis that ascending thoracic aorta calcium (ATAC) volume and density predict incident CVD events independently of CAC.

Methods—The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study of participants without clinical CVD at baseline. ATAC and CAC were measured from baseline cardiac computed tomography (CT). Cox regression models were used to estimate the associations of ATAC volume and density with incident coronary heart disease (CHD) events and CVD events, after adjustment for standard CVD risk factors and CAC volume and density.

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Conflict of interest

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

Author contributions

Study design: ICT, RLM, EDM, MAA, NIF, WTL, WSP, NDW, MJB, MHC; Data Analysis: ICT, RLM; Manuscript Preparation and Critical Revision: ICT, RLM, EDM, MAA, NIF, WTL, WSP, NDW, MJB, MHC.

Results—Among 6811 participants, 234 (3.4%) had prevalent ATAC and 3395 (49.8%) had prevalent CAC. Over 10.3 years, 355 CHD and 562 CVD events occurred. One-standard deviation higher ATAC density was associated with a lower risk of CHD (HR 0.48 [95% CI 0.29–0.79], $p<0.01$) and CVD (HR 0.56 [0.37–0.84], $p<0.01$) after full adjustment. ATAC volume was not associated with outcomes after full adjustment.

Conclusions—ATAC was uncommon in a cohort free of clinical CVD at baseline. However, ATAC density was inversely associated with incident CHD and CVD after adjustment for CVD risk factors and CAC volume and density.

Keywords

Density; Calcified atherosclerosis; Thoracic aorta; Ascending thoracic aorta; Coronary artery calcium; Cardiovascular disease; Cardiac computed tomography

Introduction

The presence and extent of arterial calcification is a reliable marker of atherosclerotic plaque burden[1] and a robust predictor of cardiovascular disease (CVD) outcomes in multiple vascular beds beyond the coronary arteries.[2–4] For instance, calcium in the thoracic aorta has previously been observed to be associated with coronary heart disease (CHD) and CVD events.[2,5,6]

Recent findings from the Multi-Ethnic Study of Atherosclerosis (MESA) have demonstrated that components of coronary artery calcium (CAC), i.e. volume and density, are separately and independently associated with CVD outcomes, with higher CAC density being associated with lower risk of incident disease after accounting for CAC volume.[7] Whether the same associations are true of calcium in the ascending thoracic aorta are unknown. Because of its close proximity with the coronary and carotid arteries, ascending thoracic aorta calcium (ATAC) may have strong associations with incident coronary heart disease (CHD) and stroke. Given this, we conducted a study to evaluate the independent associations and incremental predictive value of ATAC volume and density for incident CHD and CVD events in a cohort free of clinical CVD at baseline.

Materials and methods

MESA study design

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study of 6814 individuals aged 45 to 84 years without known clinical CVD at recruitment and enrolled from six field centers: Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY; and St. Paul, MN. Specific ethnic groups enrolled were Non-Hispanic White, African-American, Hispanic, and Chinese. Baseline examinations were conducted from 2000 to 2002. Institutional Review Boards at each participating center approved the study, and all participants provided written informed consent. Details of the study design have been described previously.[8]

Baseline medical history and laboratory data for the present study were taken from the first examination of the MESA cohort (2000–2002). Smoking status was classified as current, former, or never, with current defined as having smoked a cigarette in the last 30 days. Resting blood pressure was measured three times in the seated position, and the average of the 2nd and 3rd readings was recorded. Total and high-density lipoprotein cholesterol (HDL-C), as well as plasma glucose, was measured from blood samples obtained after a 12-hour fast. Diabetes mellitus was defined as a fasting glucose ≥126 mg/dL or use of hypoglycemic medications. Participant variables were used to calculate the American College of Cardiology/American Heart Association 2013 Pooled Cohort Atherosclerotic Cardiovascular Disease (ASCVD) Risk Score and the Global Framingham Risk Score (GFRS).[9,10]

CT image acquisition

Cardiac computed tomography (CT) was performed on all participants to measure CAC at the baseline examination.[11] With the participant supine, a minimum of 35 contiguous images were obtained starting above the left main coronary artery, superiorly, and extending to the bottom of both ventricles, inferiorly. Chicago, Los Angeles, and New York Field Centers used a cardiac-gated electron-beam CT scanner. Baltimore, Forsyth County and St. Paul Field Centers used a four-slice multi-detector CT system. The nominal section thickness was 3.0 mm for electron-beam CT and 2.5 mm for four-detector row CT. A radiologist or cardiologist read all scans at a central reading center (Los Angeles Biomedical Research Institute at Harbor-UCLA in Torrance, CA).

In an ancillary study, calcium in the thoracic aorta was retrospectively evaluated on the images obtained from the original cardiac CT scans. ATAC was defined as calcium in the ascending thoracic aorta extending from the lower edge of the pulmonary artery, superiorly, to the aortic annulus, inferiorly.[12] The aortic arch was not visualized on these scans.

Volume and density scoring of calcium

ATAC was quantified using the same lesion definition as for CAC.[11] Calcified plaque within the vascular territory of interest was identified as attenuation greater than 130 Hounsfield units (HU) with a minimum size of 5.5 mm^3 (electron beam CT) or 4.6 mm^3 (multi-detector CT). The Agatston score was computed by multiplying individual calcified plaque areas by a density factor of 1, 2, 3, or 4, corresponding to the maximum attenuation within each plaque (130–199 HU=1, 200–299 HU=2, 300–399 HU=3, 400+ HU=4).[13] The scores for all calcified plaque were then summed to produce the total Agatston score. The volume score was computed by summing the products of all calcified plaque areas (mm^2) multiplied by the CT scan slice thickness (3.0 mm for electron beam CT or 2.5 mm for multidetector CT).

For this study, ATAC and CAC *density* scores were calculated using a method previously described.[7] Specifically, the volume score for each vascular territory was divided by the CT scan slice thickness, resulting in the total area of calcified plaque. This total area was then divided into the total Agatston score, resulting in the density score, which reflects the average density factor of all calcified plaques and is a unitless value that theoretically ranges from 1 to 4, though actual values extend slightly outside of the expected range due to minor software differences in measuring the Agatston and volume scores.[7]

CVD outcomes surveillance

Follow-up began at the time of the first examination and continued until the first CVD event, death, loss to follow-up, or December 2013. Details of CVD event ascertainment have been previously reported.[14] Briefly, participants or their next of kin (if participants were unavailable) were contacted at intervals of 9–12 months by telephone, and trained interviewers inquired about interim hospital admissions, cardiovascular outpatient diagnoses, and death. Medical records and death certificates were requested for verification. Two physicians independently classified events and assigned incidence dates. A mortality and morbidity review committee adjudicated disagreements.

Incident outcomes evaluated in this study were: CHD (myocardial infarction, resuscitated cardiac arrest, or CHD-related death); stroke (fatal and non-fatal ischemic, hemorrhagic, and unknown type stroke); and CVD (CHD plus fatal and non-fatal stroke). End points such as angina and revascularization were not included.

Statistical analysis

In the MESA, 6811 participants had available calcium scoring of both the ascending thoracic aorta and coronary arteries. Of these, 234 had ATAC volume scores greater than zero and were able to have a density score computed. Ten had ATAC density scores outside of the standard range (five between 0.6 and 0.9 and five between 4.1 and 4.9). When these participants were excluded, no significant change was observed in the results. Therefore, these participants are included in the results that follow.

ATAC and CAC volume scores were natural logarithm (*ln*) transformed [*ln*(ATAC volume +1) and *ln*(CAC volume +1)] to adjust for skewness. Descriptive statistics are presented as means (± standard deviations) for continuous variables and frequencies (%) for categorical variables. Student's *t*-test and Pearson's Chi-squared test were performed to evaluate differences in participant characteristics among those with and without ATAC. Spearman correlation coefficients (ρ) were computed between *ln*ATAC and *ln*CAC volume and between ATAC and CAC density scores (for participants with prevalent ATAC and CAC).

To include participants without density scores (i.e. participants with ATAC/CAC volume scores of zero and, thus, no calcium density), conditional density scores of zero were assigned to these participants, and multivariable models included ATAC presence and CAC presence terms to allow for the discontinuity. Volume and density scores were centered among those with prevalent ATAC and CAC so that the presence terms could be interpreted. For example, the hazard ratio for ATAC presence is interpreted as the relative hazard for participants with ATAC of average volume and density compared to participants without ATAC. This model allows for the separation of the qualitative association of ATAC and CAC presence from the quantitative associations of the continuous volume and density variables.[15] Cox proportional regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CI) per standard deviation in the predictor variable for time to first CHD or CVD event in multivariable models as follows:

- Model 1: Age, gender, race/ethnicity, CT scanner type, ATAC presence (yes/no), *ln*ATAC volume, and ATAC density

- Model 2: Model 1 + CVD risk factors [systolic blood pressure, blood pressure medication, total cholesterol, HDL-C, diabetes status, current smoker] and statin use
- Model 3: Model 2 + CAC presence (yes/no), *ln*CAC volume, and CAC density.

The incremental values of *ln*ATAC volume and ATAC density scores for the prediction of incident CHD and CVD were evaluated by changes in the area under the receiver operating characteristic curve (AUC) in the following models:

- Model A: Age, gender, race/ethnicity, CVD risk factors (as above), statin use, and CT scanner type
- Model B: Model A + CAC presence, *ln*CAC volume, and CAC density
- Model C: Model B + ATAC presence, *ln*ATAC volume, and ATAC density.

AUC analyses were also performed in models restricted to participants with prevalent ATAC (excluding the ATAC presence variable from Model C) and reported separately. Analyses were also performed stratified by gender, with no significant interactions observed. Analyses were performed using SPSS Statistics version 22.0 (IBM Corporation, Armonk, NY). Statistical significance was defined as a two-tailed *p*-value of less than 0.05.

Results

Sample characteristics

Table 1 summarizes the unadjusted characteristics of participants without ATAC (volume=0) and participants with ATAC (volume >0). Of the total cohort, 234 (3.4%) participants had prevalent ATAC at baseline. Compared to participants without ATAC, participants with ATAC had significantly higher mean age, LDL-C, SBP, ASCVD risk score, and GFRS, and a higher proportion were male, on hypertension treatment, currently smoking, and had diabetes mellitus. Among the total cohort, 355 CHD events and 562 CVD events occurred over a mean follow-up period of 10.3 years. Participants with ATAC had a higher unadjusted proportion of CHD (29 events, 12.4%), CVD (41 events, 17.6%), and stroke (15 events, 6.4%).

Calcium distribution and correlations

Among participants with prevalent ATAC, the mean ATAC volume was 216 ± 591 mm^3 and density of 2.82 ± 0.95. ATAC density ranged from 0.61 to 4.96. CAC was present in 82.9% of participants with ATAC, with a mean CAC volume score of 411.5 ± 628.0 mm^3 and density score of 2.89 ± 0.57. The proportion of those with CAC, as well as mean CAC volume and density scores, was higher in those with ATAC compared to those without ATAC.

Fig. 1 displays scatterplots for the values of *ln*ATAC and *ln*CAC volumes for the full cohort, as well as ATAC and CAC densities for each participant with prevalent ATAC and CAC. *Ln*ATAC volume had a modest correlation with *ln*CAC volume (ρ= 0.16), while ATAC density had little to no correlation with CAC density (ρ= −0.04). *Ln*ATAC volume was

moderately correlated with ATAC density (ρ= 0.66), as was *ln*CAC volume with CAC density (ρ= 0.56).

Risk of CHD and CVD with ATAC presence, volume and density

Standardized HRs and 95% CIs for incident CHD and CVD are summarized in Table 2. Compared to the absence of ATAC, the presence of ATAC alone was not significantly associated with incident CHD or CVD in any of the models. In participants with ATAC present, *ln*ATAC *volume* was associated with an increased hazard for CHD in Model 1 (HR 1.769 [95% CI 1.14–2.81]) and Model 2 (HR 1.66 [1.06–2.60]) that was attenuated in Model 3 (HR 1.54 [0.97–2.45]). *Ln*ATAC *volume* was associated with CVD in Model 1 (HR 1.50 [1.02–2.21], but the association was attenuated in Model 2 (HR 1.34 [0.91–1.97]) and Model 3 (1.25 [0.85–1.85]).

In participants with ATAC present, ATAC *density* was inversely associated with incident CHD in Model 1 (HR 0.46 [0.28–0.74]), with an association that was not significantly attenuated with additional adjustment in Model 2 (HR 0.46 [0.28–0.76]) and Model 3 (HR 0.48 [0.29–0.79]). A similar inverse association was seen with incident CVD in Model 1 (HR 0.53 [0.35–0.79]), Model 2 (HR 0.54 [0.36–0.82]), and Model 2 (HR 0.56 [0.37–0.84]).

ATAC presence, volume, and density were not significantly associated with incident stroke (see Supplementary Data).

Prediction of CHD and CVD

Table 3 displays the ROC analyses for prediction of incident CHD and CVD among all participants. For *CHD*, the AUC for the base Model A (AUC 0.735 [0.711–0.759]) increased significantly with the addition of CAC presence, *ln*CAC *volume* and CAC density (Model B: 0.773 [0.750–0.796], $p<0.001$ *vs.* Model A). Adding ATAC presence, *ln*ATAC volume and ATAC density (Model C) increased the AUC slightly (0.775 [0.752–0.798], $p=0.212$ *vs.* Model B), but this was not statistically significant. Models of *CVD* prediction had a similar trend, with the AUC in Model A (0.735 [0.715–0.755]) increasing significantly in Model B (0.761 [0.742–0.780], $p<0.001$ *vs.* Model A), with a slight but non-significant increase in Model C (0.763 [0.744–0.783], $p=0.101$ *vs.* Model B).

Table 4 displays AUCs for prediction of CHD and CVD, restricted to participants with prevalent ATAC (n=234). For *CHD,* the AUC of the base Model A′ (0.696 [0.587–0.805]) increased in Model B′ (0.737 [0.641–0.833], $p=0.201$ *vs.* Model A′) and Model C′ (0.779 [0.679–0.878], $p=0.074$ *vs.* Model A′, $p=0.184$ vs, Model B′). A similar trend was seen for CVD, with the AUC in Model A′ (0.674 [0.585–0.762]) increasing in Model B′ (0.692 [0.605–0.779], $p=0.468$ *vs.* Model A′), with a quantitatively larger increase in Model C′ (0.741 [0.655–0.827], $p=0.070$ *vs.* Model A′, $p=0.072$ *vs.* Model B′). However, none of these increases reached statistical significance.

Discussion

In this study we observed that: 1) ATAC was uncommon in a cohort free of clinical CVD at baseline; 2) ATAC volume and density scores had little to no correlation with CAC volume

and density scores; 3) ATAC density was independently and inversely associated with CHD and CVD even after adjustment for CAC volume and density; and 4) the incorporation of ATAC volume and density provided a non-significant improvement in CVD risk prediction.

Among participants with prevalent ATAC in this cohort, ATAC volume and density scores had little to no correlation with CAC volume and density scores, despite what is presumed to be a shared pathophysiology. This divergence may be related to developmental anatomy: calcification of smooth muscle cells differs based on embryologic origin,[16] and neural crest-derived smooth muscle cells found in the proximal ascending thoracic aorta extend only partially into the proximal coronary arteries, and most coronary artery smooth muscle cells derive from a distinct embryological origin.[17] Additionally, calcification of the coronary artery primarily involves only the intimal layer, whereas calcification of the thoracic aorta involves both the intima and media.[18] Moreover, after the take-off of the coronary arteries, the ascending thoracic aorta is devoid of arterial branches, which are frequently associated with the development of atherosclerosis.[19] The possibility that calcification develops differently in these vascular territories merits further investigation.

In the MESA, CAC density has been shown to be associated with a lower risk for incident CHD and CVD after accounting for CAC volume. CAC volume and density also provided for superior risk prediction among the subset of participants that had CAC present.[7] In this study, ATAC density had strong inverse associations with CHD and CVD. Moreover, the inverse hazards of ATAC density were both independent of CAC volume and density.

We found the prevalence of ATAC to be very low in the MESA cohort, consistent with findings from other population-based studies of chest CT from individuals without clinical CVD, where prevalent ATAC was similarly observed in less than 5% of the subjects.[20,21] This stands in contrast to the Heinz-Nixdorf Recall Study, where ATAC was present in 43% of subjects.[22] Nonetheless, due to low ATAC prevalence, the findings of our study do not support widespread imaging of the ascending thoracic aorta. This was reflected in the marginal and non-significant increase in the AUC beyond that provided by both CVD risk factors and CAC when evaluated in the full cohort. Conversely, when evaluating only participants with prevalent ATAC, the addition of ATAC volume and density resulted in more substantial increases in the AUCs for CHD and CVD prediction. These improvements over CVD risk factors and CAC were of borderline statistical significance likely due to the small sample size. Nonetheless, these trends suggest that among those with prevalent ATAC, CHD and CVD prediction may possibly be enhanced by ATAC volume and density score assessment.

In a previous study in the MESA, investigators found that after adjusting for CVD risk factors and ascending categories of CAC Agatston scores, the presence of calcium in the thoracic aorta, in comparison to no calcium, was associated with incident CHD in women.[6] Other studies have demonstrated independent associations of TAC Agatston scores with stroke,[23] CHD and CVD events,[24] that were attenuated to non-significance with inclusion of CAC scores. Our study adds to these findings, demonstrating that after adjusting for calcium volume, the density of calcium in the segment of the ascending aorta that is evaluated on

cardiac scans has a strong inverse association with CHD and CVD events that are independent of CAC.

If observed in additional cohorts, these findings would suggest that when ATAC is present, its volume and density are important metrics of CHD and CVD risk that may provide added discrimination beyond CVD risk factors and CAC volume and density scores. Such a conclusion would have potential clinical implications. For patients undergoing standard chest CT, consideration could be given toward evaluating the ascending thoracic aorta for ATAC.[25] If ATAC were present, the predictive value of standard CVD risk factors may possibly be enhanced by inclusion of ATAC volume and density scoring. Similarly, when a cardiac-gated CT scan was performed and scored for CAC, ATAC volume and density scores could be included if ATAC were present, and they might be important metrics of CHD and CVD risk in that patient.

Our study has important limitations. First, our study only evaluates the ascending thoracic aorta, a relatively short segment of the thoracic aorta. Prior studies have demonstrated the important role of calcification in the aortic arch and descending thoracic aorta.[3,23] Furthermore, many associations that were observed were of borderline or no statistical significance, possibly due to the small sample size of participants with ATAC and insufficient statistical power. Second, in the Agatston method, density scores are arbitrarily capped at a maximum value of 4, potentially underestimating the inverse association of ATAC density with CHD and CVD in plaques of attenuation in excess of 400 HU. Additionally, the density score was not determined during the original scoring of ATAC, but rather was calculated from the recorded Agatston score and volume score. Errors or imprecision in either of these variables will be reflected in the density score, and may explain the scores that were observed outside of the range of 1 to 4. These outliers do not appear to have biased our results, as excluding them from the analysis does not change the results significantly. Finally, to our knowledge this is the first study to evaluate ATAC density, and it is unknown whether these observations extend beyond the MESA cohort. As a result, these findings should be taken with a note of caution.

In conclusion, ATAC was uncommon in a cohort free of clinical CVD. However, ATAC density was inversely associated with CHD and CVD, independently of CAC. When ATAC is present, ATAC volume and density scores may provide clinically useful prognostic information beyond standard CVD risk factors and CAC. Further study is needed to validate these findings and investigate the determinants of ATAC volume and density.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- The density of coronary artery calcium (CAC) has previously been shown to be inversely associated with cardiovascular disease (CVD) events.
- The density of ascending thoracic aorta calcium (ATAC) is also inversely associated with CVD events, independently of CAC.
- These findings deepen our understanding of the relationship between arterial calcium density and CVD risk.
- Although uncommon, ATAC density may provide added prognostic information when present.

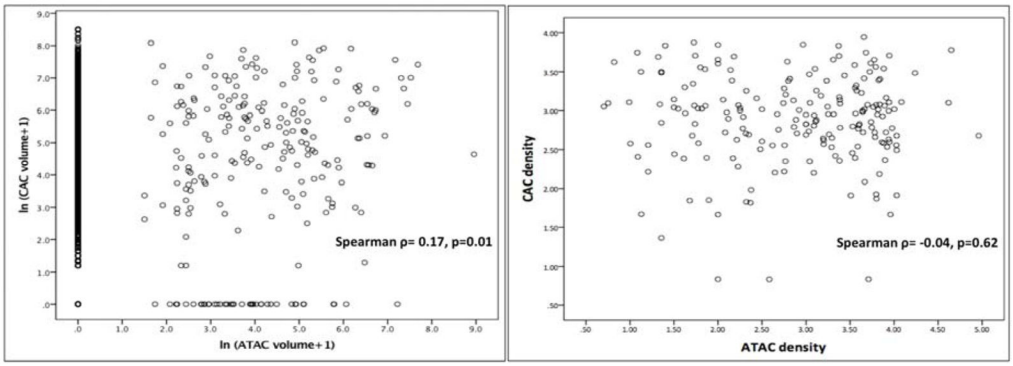

Fig. 1.

Scatterplots of the volume scores of ATAC and CAC in the full cohort (left panel, n=6811) and density scores of ATAC and CAC in participants with prevalent ATAC and CAC (right panel, n=194).

Spearman correlation coefficients are inset. Volume scores are natural logarithm transformed [*ln*(CAC volume +1) and *ln*(ATAC volume+1)] to adjust for skewness.

Table 1

Characteristics of participants by presence of ascending thoracic aorta calcium in the Multi-Ethnic Study of Atherosclerosis

	ATAC >0 (n=234)	ATAC =0 (n=6577)	*p*
Age (years)	71.3 ± 8.1	61.8 ± 10.1	<0.01
Female gender	45.7%	53.1%	0.03
Ethnicity			0.01
Non-Hispanic White	34.2%	38.6%	
Hispanic	23.5%	21.9%	
African-American	35.5%	27.5%	
Chinese	6.8%	12.0%	
Clinical characteristics			
Total cholesterol, mg/dL	198 ± 41	194 ± 36	0.18
HDL cholesterol, mg/dL	50 ± 14	51 ± 15	0.20
Systolic BP, mm Hg	140 ± 23	126 ± 21	<0.01
Hypertension treatment	57.7%	36.5%	<0.01
Smoking (current)	18.9%	12.9%	<0.01
Diabetes mellitus	17.9%	12.5%	0.01
Statin therapy	16.8%	14.8%	0.40
Risk scores			
ASCVD, 10-year CVD risk	26.7% ± 15.9%	13.1% ± 12.8%	<0.01
GFRS, 10-year CVD risk	23.1% ± 8.2%	14.2% ± 9.5%	<0.01
Calcium scores			
CAC>0	194 (82.9%)	3201 (48.7%)	0.07
CAC=0	40 (17.1%)	3376 (51.3%)	
CAC volume, mm^3	412 ± 628	118 ± 331	<0.01
CAC density	2.89 ± 0.57	2.68 ± 0.70	<0.01
ATAC volume, mm^3	216 ± 591	0.00 ± 0.00	<0.01
ATAC density	2.82 ± 0.95	--	--
Events			
CHD	29 (12.4%)	326 (5.0%)	<0.01
CVD	41 (17.6%)	521 (7.9%)	<0.01
Stroke	15 (6.4%)	221 (3.4%)	0.01
Death, any cause	88 (37.8%)	885 (13.5%)	<0.01

Values presented are percentages or means ± standard deviations.

ASCVD, atherosclerotic cardiovascular disease risk score; ATAC, ascending thoracic aorta calcium; BP, blood pressure; CAC, coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease; GFRS, global Framingham risk score; HDL, high-density lipoprotein.

Table 2

Hazard ratios of ATAC volume and density for CHD and CVD

	Model 1			Model 2			Model 3		
Coronary heart disease event	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
ATAC presence (yes/no)	1.45	0.94–2.25	0.09	1.23	0.79–1.91	0.36	1.04	0.67–1.62	0.86
*ln*ATAC volume, per 1.48 ln-units	**1.79**	**1.14–2.81**	**0.01**	**1.66**	**1.06–2.60**	**0.03**	1.54	0.97–2.45	0.07
ATAC density, per 0.95 density units	**0.46**	**0.28–0.74**	**<0.01**	**0.46**	**0.28–0.76**	**<0.01**	**0.48**	**0.29–0.79**	**<0.01**
Cardiovascular disease event									
ATAC presence (yes/no)	1.37	0.96–1.94	0.08	1.13	0.80–1.61	0.48	0.99	0.70–1.41	0.96
*ln*ATAC volume, per 1.48 ln-units	**1.50**	**1.02–2.21**	**0.04**	1.34	0.91–1.97	0.13	1.25	0.85–1.85	0.26
ATAC density, per 0.95 density units	**0.53**	**0.35–0.79**	**<0.01**	**0.54**	**0.36–0.82**	**<0.01**	**0.56**	**0.37–0.84**	**<0.01**

n=6811 at risk. 355 CHD events and 562 CVD events. ATAC volumes are natural logarithm transformed to adjust for skewness. Bolded text indicates 2-tailed *p*-value <0.05. HR and CI rounded to nearest hundredth, and reflect one standard deviation change in predictor. Model 1 adjusts for age, gender, race/ethnicity, CT scanner type, and ATAC presence, lnATAC volume, and ATAC density. Model 2 adjusts for Model 1 variables and systolic blood pressure, blood pressure medication use, total cholesterol, HDL cholesterol, diabetes status, and current smoking. Model 3 adjusts for Model 2 variables and CAC presence, lnCAC volume, and CAC density. Coronary heart disease (CHD) is the composite of myocardial infarction, resuscitated cardiac arrest, and CHD death. Cardiovascular disease (CVD) is the composite of CHD, stroke, or stroke death.

Abbreviations as in Table 1.

Table 3

Areas under the ROC curves for prediction of CHD and CVD (n=6811)

	CHD (355 events)			CVD (562 events)		
	AUC	**95% CI**	***p***	**AUC**	**95% CI**	***p***
Model A (Age, gender, race/ethnicity, CVD risk factors, statin use, CT scanner type)	0.735	0.711–0.759		0.735	0.715–0.755	
Model B (Model A+ CAC presence, *ln*CAC volume, CAC density)	0.773	0.750–0.796	<0.001[a]	0.761	0.742–0.780	<0.001[a]
Model C (Model B+ ATAC presence, *ln*ATAC volume, ATAC density)	0.775	0.752–0.798	<0.001[a] 0.212[b]	0.763	0.744–0.783	<0.001[a] 0.101[b]

[a] *vs.* Model A.

[b] *v.s* Model B. CHD is the composite of myocardial infarction, resuscitated cardiac arrest, and CHD death; CVD is the composite of CHD, stroke, or stroke death. CVD risk factors are systolic blood pressure, blood pressure medication, total cholesterol, HDL cholesterol, diabetes status, and current smoking.

AUC, area under the curve; ROC, Receiver Operating Characteristics; other abbreviations as in Table 1.

Table 4

Areas under the ROC curves for prediction of CHD and CVD in participants with prevalent ATAC (n=234)

	CHD (29 events)			CVD (41 events)		
	AUC	**95% CI**	***p***	**AUC**	**95% CI**	***p***
Model A′ (CVD risk factors, race/ethnicity, statin use, CT scanner type)	0.696	0.587–0.805		0.674	0.585–0.762	
Model B′ (Model A′ + volume, CAC presence, *ln*CAC CAC density)	0.737	0.641–0.833	0.201[a]	0.692	0.605–0.779	0.468[a]
Model C′ (Model B′ + *ln*ATAC volume, ATAC density)	0.779	0.679–0.878	0.074[a] 0.184[b]	0.741	0.655–0.827	0.070[a] 0.072[b]

[a] *vs.* Model A.

[b] *vs.* Model B. CHD is the composite of myocardial infarction, resuscitated cardiac arrest, and CHD death; CVD is the composite of CHD, stroke, or stroke death. CVD risk factors are age, gender, systolic blood pressure, blood pressure medication, total cholesterol, HDL cholesterol, diabetes status, and current smoking.

AUC, area under the curve; ROC, Receiver Operating Characteristics; other abbreviations as in Table 1.