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Association of calcium density in the thoracic aorta with risk factors and clinical events

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Abstract

Objectives In the ascending aorta, calcification density was independently and inversely associated with cardiovascular disease (CVD) risk prediction. Until now, the density of thoracic aorta calcium (TAC) was estimated as the Agatston score divided by the calcium area (D_{AG}). We thought to analyze TAC density in a full Hounsfield unit (HU) range and to study its association with TAC volume, traditional risk factors, and CVD events.

Methods Non-enhanced CT images of 1426 patients at intermediate risk were retrospectively reviewed. A calcium density score was estimated as the average of the maximum HU attenuation in all calcified plaques of the entire thoracic aorta (D_{AV}).

Results During a mean 4.0 years follow-up, there were 26 events for a total of 674 patients with TAC > 0. TAC volume and D_{AV} were positively correlated ($R = 0.72$). The median D_{AV} value was 457 HU (IQ 323–603 HU) and was exponentially related to D_{AG} ($R = 0.86$). D_{AV} was inversely associated with systolic pressure ($p < 0.05$), pulse pressure ($p < 0.01$), hypertension ($p < 0.05$), and 10-year FRS ($p < 0.001$) after adjusting for TAC volume. When TAC volume and D_{AV} were included in a logistic model, a significant improvement was shown in CVD risk estimation beyond coronary artery calcium (CAC) (AUC = 0.768 vs 0.814, $p < 0.05$). In multivariable Cox models, TAC volume and D_{AV} showed an independent association with CVD.

Conclusions In intermediate risk patients, TAC density was inversely associated with several risk factors after adjustment for TAC volume. A significant improvement was observed over CAC when TAC volume and density were added into the risk prediction model.

Key Points

• *Calcifications in the aorta can be non-invasively assessed using CT images*
• *A higher calcium score is associated with a higher cardiovascular risk*
• *Measuring the calcifications size and the density separately can improve the risk prediction*

Keywords Thoracic aorta · Calcium · Atherosclerosis · Cardiovascular diseases

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Abbreviations

AS	Agatston score
CAC	Coronary artery calcium
CHD	Coronary heart disease
CI	Confidence intervals
CVD	Cardiovascular disease
DAG	Calcium density score based on Agatston
DAV	Calcium density score based on average attenuation
FRS	Framingham risk score
HU	Hounsfield units
IQ	Interquartile range
maxHU	Maximum HU attenuation value
MSCT	Multislice computed tomography

TA   Thoracic aorta
TAC   Thoracic aorta calcium

Introduction

Coronary artery calcium (CAC) is accepted as a strong predictor of cardiovascular disease (CVD) events [1, 2]. Although less studied, thoracic aorta calcification (TAC) detected in the visible parts of the thoracic aorta during CAC examination was also associated with CVD events and death [3–5]. The quantification of CAC and TAC using the Agatston score (AS) is based on the size of lesions positively weighted by a categorical factor of the calcium density [6]. Recently, the separation of calcium volume and density from the AS showed that the CAC volume was positively associated with occurrence of CVD when CAC density was inversely related to such occurrence [7]. This result was assumed to be related to the lower vulnerability of very dense calcified plaques of coronary artery lesions [8, 9]. The negative relation between CAC density and CVD risk was further extended recently to the thoracic aorta [10, 11]. Although calcifications in the ascending thoracic aorta are infrequent, when present, the risk of CVD events is elevated when the calcium volume increases and when the density drops [11]. Nevertheless, the incorporation of the TAC volume and density of calcifications of the ascending aorta to the model did not provide a significant improvement in CVD risk prediction over CAC. Two limitations were mentioned to explain this lack of improvement. First, the proposed calculation of density was approximated because it is based on the estimation of the simple ratio AS over the calcium area, giving a value within a limited range from 1 to 4 [8]. Second, the very frequent calcifications of the aortic arch were not taken into account due to insufficient aorta coverage in these studies, which were mainly focused on CAC [12, 13].

In the present work, the main objective was to calculate a calcium density score in a continuous HU scale and to study its association with the full calcium volume of the whole thoracic aorta, with traditional risk factors and with CVD events after taking the CAC score into account.

Methods

Study subjects

All study subjects were recruited in the same unit of the Hôpital Européen Georges Pompidou (Paris, France) over 3 years between 2009 and 2012. In this Cardiovascular Preventive Medicine unit, all consecutive primary prevention patients at intermediate risk for cardiovascular disease undergone an extended non-enhanced multislice computed

tomography (MSCT) scan for CAC assessment in view of cardiovascular risk stratification program according to the current guidelines [14]. Thus, only subjects with at least one traditional risk factor and free of clinical overt CVD were likely to be included in the present study. All subjects accepting a voluntary monitoring follow-up program of their cardiovascular status every 6 months were included in the present study ($n = 1426$). Participants without TAC at baseline ($n = 495$) as well as patients that did not come to their first follow-up consultation at 6 months ($n = 193$) or because of the absence of full follow-up until the end of 2015 ($n = 64$) were excluded from this follow-up analysis. A diagram with the final patient group is shown in Fig. 1. In January 2016, the clinical history of all the remaining included patients ($n = 674$) was revised by an expert (AS) using the hospital database to look for documented presence or absence of occurrence of CV event.

Blood pressure, hypertension, cholesterol, and blood glucose were determined as described elsewhere [12, 14]. The Framingham risk score (FRS) was calculated in all subjects after recalibration for the French population. Patients during their hospitalization were informed of the use of their medical data for research purposes and all the institution received authorization from the National Commission for Informatics and Freedom after checking that the researches carried out was in accordance with the Helsinki Declaration.

Image acquisition

All prospective ECG-gated non-enhanced images of the heart and of the thoracic aorta were obtained in the same breath hold with a 64-MSCT (Light-speed VCT; GE Health care) from the top of the aortic arch to the level of the diaphragm [12]. Acquisitions were performed at 120 kVp, with tube current adapted to the patient weight. All images were reconstructed with a thickness of 2.5 mm and a field of view of 250 mm before being analyzed using a custom software designed in our laboratory and previously used to detect and calculate the size and position of calcifications in the thoracic aorta (TA) [12, 14, 15]. As previously assessed, the effective radiation dose of our acquisition protocol was 1.23 ± 0.14 mSv (range 0.92–2.1 mSv) [14]. All measurements were made by the same expert, blinded to clinical parameters.

TA calcification assessment

A single automated algorithm developed by biomedical engineers in the Favaloro University was employed to segment the TA and to calculate the calcium scores. Details about the segmentation process can be found in previous reports [12, 14, 16]. Briefly, the algorithm extracted a list of ≈ 150 centerline points of the TA with the corresponding diameters, detected and quantified the aortic calcifications. The area in mm^2 and

Assessed for eligibility with TAC score in the whole thoracic aorta (n=1426)
→Excluded participants with TAC score = 0 (n=495)
Potential participants (n=931)
→Excluded participants that did not come to the 1st planned consultation at 6 months (n=193) or that stopped their follow-up before January 2015 (n=64)
Final patient group (n=674)

the maximum attenuation values in HU (maxHU) were assessed for each lesion to calculate the calcium scores:

- The Agatston score of a lesion was calculated using a categorical weighted value from 1-to-4 depending on the maxHU obtained in each calcification (1 = 130–199 HU, 2 = 200–299 HU, 3 = 300–399 HU, and 4 ≥ 400 HU) multiplied by the lesion area. For each participant, the TAC Agatston score was calculated as the sum of the detected lesions scores.
- The TAC volume score was calculated as the lesion area multiplied by the slice thickness (2.5 mm). For each participant, the TAC volume score was calculated as the sum of all the detected lesions scores
- The raw TAC density score (D_{AV}) was calculated as the average of the maxHU values of all the detected lesions: D_{AV} = mean (maxHU). For comparison purposes, a categorical density score (D_{AG}) employed in the MESA study reports [8] was calculated as the TAC Agatston score divided by the sum of calcifications area. Whereas D_{AV} values result in a continuous HU range, D_{AG} values are restricted from 1-to-4.

Statistical analysis

Histograms of the TAC volume and density scores were constructed and box-plots indicating the median, interquartile range (IQ), and 10th-to-90th percentiles were calculated. Calcium scores were log-transformed (lnVolume and lnDensity) to reduce skewness and linear associations between them were evaluated with a Pearson correlation. The association of the TAC density scores (D_{AV} and D_{AG}) was evaluated using an exponential regression model.

Patients with and without CVD events were compared using a t test (p threshold < 0.05). Two multivariable linear regressions models were performed to evaluate the associations of several exposure variables with TAC volume and density scores as the outcome variables after adjustment for age, BSA, and male gender. For regression analyses, β-coefficients for continuous variables were expressed per SD change in the exposure variables. In a third multivariable linear regression, the TAC density model was further adjusted for TAC volume score.

Four logistic models were calculated to evaluate the association of incident CVD events with calcium scores, accounting for 10-year FRS. Model 1 only included lnCAC score as a cofactor. In models 2 and 3, lnTAC Agatston or lnTACVolume scores were incorporated. Model 4 included lnCAC, lnTAC volume, and lnDensity scores. Odds ratio were expressed per 1-SD change in the exposure variables. The area under the receiver operating characteristic curve (AUC) and the 95th confidence intervals (CI) were calculated for each model. The incremental value of each variable across the models for the prediction of CVD events was evaluated by the increase in the AUC [17].

Finally, Cox proportional hazard regression was used to estimate hazard ratios (HRs) for time to CVD events for both lnTACVolume and lnTACdensity scores adjusted for 10-year FRS and lnCAC score. HRs were expressed per 1-SD change in the covariates. All statistical calculations were performed with JMP 10 software (SAS institute) or MedCalc (version 14).

Results

Patients with and without CVD events

Demographics, clinical characteristics, and aortic measurements of the study participants are shown in Table 1. The mean follow-up was 4.0 ± 0.8 years (range 2.3–6.2 years). The 26 identified patients with CVD events were as follows: 11 with occurrence of CAD treated with stents and optimal medical treatment, 12 with arterial diseases that have benefited from surgery and/or interventional procedure aortic disease, 1 heart failure, 2 patients with occurrence of symptomatic brain vascular disease (1 ischemic attack and 1 vertebrobasilar insufficiency). FRS, CAC score, TAC Agatston score, and TAC volume score at baseline were higher in patients with CVD events than those without (all $p < 0.001$ except $p < 0.01$ for FRS). The TAC density score D_{AV} was not different between groups ($p = 0.36$).

Histograms of TAC volume and density

The distribution of TAC volume and density scores is shown in Fig. 2. The median volume score value was 159 mm³ (IQ 48–500 mm³). The median D_{AV} value was 457 HU (IQ 323–603 HU). Sixty-one percent of the patients had a density score above 400 HU. Patients with higher volume of TA calcium showed also higher density values ($R = 0.72$, Fig. 3). Most of patients with CV events relied below the TAC volume vs D_{AV}

Table 1 Demographics, clinical characteristics, and aortic calcium measurements of participants with TAC > 0

	No CVD event (*n* = 648)	CVD event (*n* = 26)	*p* value
Age, mean (SD)	61 ± 8	63 ± 9	0.09
Male gender, N (%)	483 (75)	24 (92)	0.02
Body surface area, m^2	1.89 ± 0.21	1.99 ± 0.13	0.02
Systolic pressure, mmHg	125 ± 13	123 ± 10	0.55
Diastolic pressure, mmHg	73 ± 9	73 ± 8	0.87
Pulse pressure, mmHg	51 ± 9	50 ± 9	0.50
Hypertension, N (%)	378 (59)	16 (61)	0.76
Antihypertensive therapy, N (%)	351 (51)	16 (61)	0.46
Hypercholesterolemia, N (%)	564 (87)	24 (92)	0.40
Lipid-lowering therapy, N (%)	437 (67)	21 (81)	0.14
Total cholesterol, mmol/l	5.02 ± 1.08	4.40 ± 0.99	0.005
HDL Cholesterol, mmol/l	1.35 ± 0.39	1.20 ± 0.31	0.06
LDL Cholesterol, mmol/l	3.02 ± 0.92	2.51 ± 0.79	0.01
Triglycerides, mmol/l	1.40 ± 0.79	1.50 ± 0.75	0.53
Diabetes mellitus, N (%)	52 (8)	3 (12)	0.55
Current smoking, N (%)	100 (15)	9 (35)	0.02
Framingham risk score at 10 years, %	11.0 ± 7.9	15.4 ± 11.0	0.01
Calcium measurements			
Ln CAC Agatston Score	3.69 ± 2.52	5.81 ± 1.55	< 0.001
Ln TAC Agatston Score	5.24 ± 1.96	6.62 ± 1.64	< 0.001
Ln TAC volume score	4.98 ± 1.74	6.31 ± 1.47	< 0.001
Ln TAC density score	6.10 ± 0.42	6.18 ± 0.42	0.36

regression line (*n* = 19 of 26, 73%). The relationship between the continuous (D_{AV}) and categorical (D_{AG}) density estimations showed an exponential association ($R = 0.86$, $p < 0.001$, Fig. 1 in supplementary material).

Association of TAC volume and density with risk factors

Both TAC volume and density scores were positively associated with age ($\beta = 0.1100$/years, $p < 0.001$, $R = 0.48$ and $\beta = 0.0185$/years, $p < 0.001$, $R = 0.33$ for *ln*TACVolume and *ln*TACDensity, respectively). TAC density score was inversely associated with male gender (6.08 ± 0.41 vs 6.18 ± 0.44, $p < 0.001$) and BSA ($\beta = -0.2404$/m^2, $p < 0.01$, $R = 0.14$). Associations between TAC volume and density scores with several exposure variables are shown in Table 2. Thus, TAC volume score was positively associated with pulse pressure ($p < 0.01$), hypertension ($p < 0.01$), hypertensive therapy ($p < 0.001$), lipid-lowering therapy ($p < 0.001$), current smoking ($p < 0.001$), highly correlated to CAC score ($R = 0.56$, $p < 0.001$), and negatively associated with LDL cholesterol ($p < 0.05$). In contrast, TAC density score was only positively associated with lipid-lowering therapy ($p < 0.001$), current smoking ($p < 0.05$), and CAC score ($p < 0.001$). However, after adjustment for TAC volume (Table 3), such TAC density D_{AV} was inversely associated with systolic

pressure ($p < 0.05$), pulse pressure ($p < 0.01$), hypertension ($p < 0.05$), and 10-year FRS ($p < 0.001$). Furthermore, TAC density score was positively associated with total and HDL cholesterol ($p < 0.05$).

Association of TAC volume and density with CVD events

Logistic regression models combining CAC and TAC scores to predict CVD events are shown in Table 4. The base model 1 using CAC Agatston score resulted in an AUC of 0.768 (0.734–0.800). When either the TAC volume or TAC density scores were separately added to the initial model 1, AUCs increased to 0.786 (0.754–0.817) and 0.769 (0.735–0.801), respectively, but these increments did not reach significance. Only when TAC volume and density scores were both included into the basic model, the AUC increased significantly to 0.814 (0.782–0.842) ($p < 0.05$). As shown in Table 5, in the Cox regression model adjusted for 10-year FRS and *ln*CAC score, the *ln*TACVolume was a high significant predictor of CVD event with HR of 2.42 (95% CI 1.31 to 4.36; $p < 0.01$), whereas each SD increase in *ln*TACdensity was significantly associated with a 51% reduction (HR 0.49; 95% CI 0.27 to 0.93; $p < 0.05$).
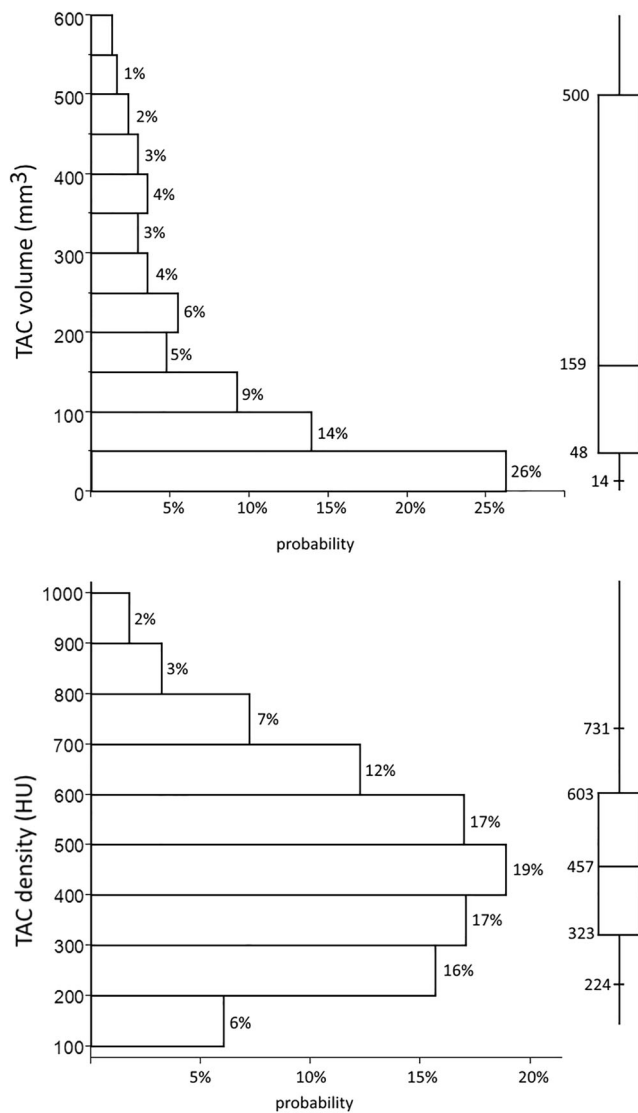
Fig. 2 Histograms of TAC volume and density scores (*n* = 674 patients)

Fig. 3 Linear correlation between TAC volume and TAC density scores (*n* = 674 patients, *R* = 0.72). TAC volume and density values were log-transformed. Crosses indicate patients with cardiovascular events (*n* = 26) and 73% of them (*n* = 19) rely below the regression line

Discussion

In our study, we found that when both the volume and density of TAC were incorporated with the CAC score in a logistic model, the prediction of the CV risk improved with respect to using CAC alone. In multivariable Cox models, both TAC volume and density scores showed an independent association with time to CVD events beyond CAC. Our results reinforce the idea that quantifying calcium throughout the entire thoracic aorta can add information complementary to CAC [13].

Our work shows that the relationships between systolic blood pressure, pulse pressure, presence of hypertension, and 10-year FRS were positively related to the TAC volume and negatively related to the TAC density after adjusting for calcification volume. Thus, this latter finding suggests that in presence of calcification along the thoracic aorta, beyond the volume, the density of such calcification is negatively related
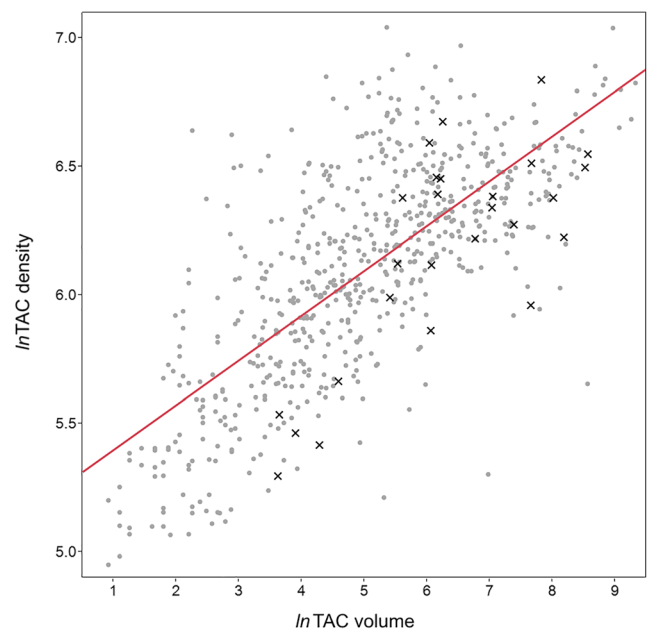
to some conventional cardiovascular risk factors (Table 3). This is in line with a recent study that estimated TAC density in the ascending aorta and showed that, even if the ascending TAC was uncommon, the density of the ascending aorta calcifications was negatively and independently associated with CHD and CVD after adjustment for CAC volume [11]. Other prospective studies comparing volume and density on CAC showed that CAC density was inversely related to CHD and CVD risk at any level of CAC volume and that many CVD risk factors, including male gender, diabetes, BMI, and non-Hispanic white race, were also inversely associated with CAC density score after adjustment for CAC volume [7]. More importantly, a risk model including the CAC volume score and the CAC density score as separate cofactors was more predictive than the use of the Agatston CAC score as a single factor, providing the highest correct reclassification [8, 9].

At the coronary artery site, the influence of the density of calcifications on CV risk prediction may be explained by the fact that a low density in atheromatous plaques within the arterial wall may reflect a greater vulnerability of such plaques [18]. At the aortic level, the hypothesis that can be proposed might not be the same. Since arterial stiffening is directly related to blood pressure and age [19], it was not surprising to see that TAC volume was directly related to hypertension. The inverse relationship between density and both systolic and pulse pressure levels suggests that TAC volume and TAC density exert a differential effect on arterial hemodynamics.

In our study, the lipid-lowering therapy and the current smoking status were positively associated with both TAC

Table 2 Multivariable linear regression analyses performed to evaluate the associations of the exposure variables with TAC volume and density adjusted for age, male gender, and BSA. β-coefficients were expressed per 1-SD change

	LnTAC volume score			LnTAC density score		
	β (SE)	p value	Model R	β (SE)	p value	Model R
Systolic pressure (/12.9983 mmHg)	0.0840 (0.0598)	0.16		− 0.0117 (0.0156)	0.46	
Diastolic pressure (/8.9870 mmHg)	− 0.0647 (0.0597)	0.28		− 0.0162 (0.0153)	0.32	
Pulse pressure (/9.3349 mmHg)	0.1804 (0.0617)	0.004	0.49	− 0.0015 (0.0161)	0.92	
Hypertension	0.1889 (0.0608)	0.004	0.49	0.0055 (0.0163)	0.74	
Antihypertensive therapy	0.2277 (0.0601)	< 0.001	0.50	0.0151 (0.0160)	0.35	
Hypercholesterolemia	0.1230 (0.0888)	0.17		0.0393 (0.0231)	0.09	
Lipid-lowering therapy	0.2568 (0.0638)	< 0.001	0.50	0.0502 (0.0168)	< 0.001	0.36
Total cholesterol (/1.0797 mmol/l)	− 0.1085 (0.0604)	0.07		0.0051 (0.0166)	0.76	
HDL cholesterol (/0.3844 mmol/l)	− 0.0103 (0.0608)	0.87		0.0272 (0.0172)	0.11	
LDL cholesterol (/0.9236 mmol/l)	− 0.1338 (0.0630)	0.03	0.49	− 0.0044 (0.0164)	0.79	
Triglycerides (/0.7928 mmol/l)	0.0442 (0.0606)	0.46		0.0013 (0.0178)	0.93	
Diabetes mellitus	0.0678 (0.1088)	0.53		− 0.0142 (0.0284)	0.62	
Current smoking	0.3878 (0.0805)	< 0.001	0.51	0.0477 (0.0211)	0.02	0.35
Calcium measurements						
lnCAC Agatston Score (/2.5191)	0.5014 (0.0584)	< 0.001	0.56	0.0953 (0.0163)	< 0.001	0.40
lnTAC Agatston Score (/1.9699)	1.7328 (0.0090)	< 0.001	0.99	0.3379 (0.0116)	< 0.001	0.78
LnTAC volume score (/1.7527)	–	–	–	0.3108 (0.0128)	< 0.001	0.73
LnTAC density score (/0.4238)	1.1073 (0.0463)	< 0.001	0.76	–	–	–

volume and density, but this association was not statistically significant when D_{AV} was adjusted for TAC volume. The positive association between lipid-lowering therapy and

TAC density in the univariate model (Table 2) might be driven by the strong volume-density relation (Fig. 3). Some studies have shown that statins may increase calcified coronary

Table 3 Multivariable linear regression analyses performed to evaluate the associations of the exposure variables with TAC density adjusted for TAC volume, age, male gender, and BSA. β-coefficients were expressed per 1-SD change

	LnTAC density score		
	β (SE)	p value	Model R
Systolic pressure (/12.9983 mmHg)	− 0.0244 (0.0115)	0.03	0.73
Diastolic pressure (/8.9870 mmHg)	− 0.0022 (0.0118)	0.85	
Pulse pressure (/9.3349 mmHg)	− 0.0034 (0.0687)	0.004	0.73
Hypertension	− 0.0265 (0.0119)	0.03	0.73
Hypercholesterolemia	0.0173 (0.0170)	0.31	
Lipid-lowering therapy	0.0056 (0.0125)	0.66	
Total cholesterol (/1.0797 mmol/l)	0.0229 (0.0120)	0.05	0.73
HDL cholesterol (/0.3844 mmol/l)	0.0248 (0.0125)	0.04	0.73
LDL cholesterol (/0.9236 mmol/l)	0.0194 (0.0119)	0.10	
Triglycerides (/0.7928 mmol/l)	− 0.0048 (0.0115)	0.68	
Diabetes mellitus	− 0.0221 (0.0206)	0.28	
Current smoking	− 0.0231 (0.0158)	0.14	
10-year Framingham risk score (/8.1428)*	− 0.0409 (0.0123)	< 0.001	0.73
Calcium measurements			
lnCAC Agatston Score (/2.5191)	− 0.0017 (0.0130)	0.89	
lnTAC Agatston Score (/1.9699)	1.6880 (0.0698)	< 0.001	0.87

*adjusted for LnTAC volume score and body surface area

Table 4 Logistic regression models for CVD risk prediction. Models were adjusted for 10-year FRS. Odds ratio are expressed per 1-SD change

	Odds ratio (95% CI)	p value	AUC (95% CI)
Base model			0.768 (0.734–0.800)
LnCAC Agatston score	3.11 (1.65–5.86)	< 0.001	
Base + volume			0.786 (0.754–0.817)
LnCAC Agatston score	2.55 (1.34–4.86)	< 0.01	
LnTAC volume score	1.60 (1.00–2.56)	0.05	
Base + density			0.769 (0.735–0.801)
LnCAC Agatston score	3.23 (1.70–6.15)	< 0.001	
LnTAC density score	0.94 (0.60–1.48)	0.80	
Base + volume + density			0.814 (0.782–0.842)*
LnCAC Agatston score	2.48 (1.31–4.70)	< 0.01	
LnTAC volume score	2.55 (1.37–4.75)	< 0.01	
LnTAC density score	0.48 (0.25–0.91)	< 0.05	

*vs base model $p = 0.04$

plaques [20, 21] but the effect on aortic calcification was not reported. Since our population consists of intermediate-risk patients, statins are intensively prescribed to patients at higher risk and it might be a major confounding factor. Since the HCT treatment is a better marker of lipid disease than LDL in our patients, it is not surprising that this treatment was positively related to the TAC volume. Recent reports have shown that CAC and TAC incidence and progression shared similar determinants and both CAC and TAC increase under statin intake, supporting the hypothesis of a plaque-stabilizing effect [22, 23]. Our adjusted regression model has shown that TAC density was not associated with lipid-lowering therapy after accounting for TAC volume [10]. The same effect was observed in smoking patients. Smokers might have more density and volume of calcium because of the pro-atherosclerotic effect of tobacco on the arterial wall, but further studies including TAC volume and density progression in smokers and patients on statins are needed to confirm these results.

Strength and limitations of the study

To our knowledge, our study is the first to report a raw TAC density score where the calcifications volume and density scores were independently quantified. Calcium density score D_{AG} was typically estimated as the quotient between the Agatston score and the calcium area, where a residual linear dependence with calcium area could not be completely disregarded. Until now, no other density estimations have been informed, probably because the size and the attenuation intensities were not registered for each calcification. Even if the 4-point scale categories adopted in the Agatston method would be insufficient to characterize the intensity of the TA calcified lesions, a linear correlation with the categorical estimation was still observed in our results ($R = 0.77$, $p < 0.001$). This association might partially justify the use of the D_{AG} as a surrogate of D_{AV}. Measurement of calcifications done along the whole thoracic aorta pathway with inclusion of the aortic arc is another strength of our study, together with the possibility of accounting for precise geometric descriptors of the aorta [15].

The first limitation to mention is the observational and retrospective nature of the study, together with the lack of measurement of the density of coronary calcification. Since our study was based on previous automated measurements of thoracic aorta geometry and calcium, automated detection and calcium quantification of coronary lesions were not included in our software and CAC score could not be separated into calcium volume and density. Due to the spatial resolution of non-enhanced CT images, we were not able to distinguish intimal or medial seat from calcifications of the thoracic aorta. Finally, the participants in this study were not retrieved from a general population and the extrapolation of our findings should be made with caution.

Conclusion

In a cohort of patients at intermediate risk of CVD, our study showed that some CVD risk factors were inversely associated with TAC density score after adjustment for TAC volume score, including 10-year FRS, systolic pressure, pulse pressure, and hypertension. The use of both TAC volume and

Table 5 Multivariable hazard ratios (HRs) for TAC volume, TAC density, and CAC score adjusted for 10-year FRS. HRs are expressed per 1-SD change

	HR (95% CI)	p value
10-year FRS, per SD = 8.14%	1.08 (0.74–1.51)	0.67
LnCAC Agatston score, per SD = 2.52	2.33 (1.32–4.53)	0.003
LnTAC volume score, per SD = 1.75	2.42 (1.31–4.36)	0.005
LnTAC density score, per SD = 0.42	0.49 (0.27–0.93)	0.03

TAC density as separate variables improved the risk prediction of CVD events beyond the CAC score.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Dr. Damian Craiem.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap Some study subjects have been previously reported in previous articles of the research team, included in References 12, 14, 15, and 16.

Methodology
• Retrospective
• Cross-sectional study
• Performed at one institution

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