

Aortic Calcification Onset and Progression: Association With the Development of Coronary Atherosclerosis

Hagen Kälsch, MD; Nils Lehmann, PhD; Susanne Moebus, PhD; Barbara Hoffmann, PhD; Andreas Stang, PhD; Karl-Heinz Jöckel, PhD; Raimund Erbel, MD; Amir A. Mahabadi, MD

Background—Thoracic aortic calcification (TAC) and coronary artery calcification (CAC) are markers of subclinical atherosclerosis and are associated with incident major cardiovascular events. We investigated major determinants for incidence and progression of TAC and the association between TAC and CAC incidence and progression.

Methods and Results—In a population-based cohort study, 3270 participants (aged 45–74 years, 53.1% women) received cardiac computed tomography at baseline and after a mean follow-up of 5.1 ± 0.3 years for quantification of calcification of the ascending (ATAC) and descending thoracic aorta (DTAC) and CAC. Multivariable relative risk regression analysis was used to investigate associations of cardiovascular risk factors with incident TAC, of baseline TAC with incident CAC, and of baseline CAC with incident TAC. Of 1243 participants with baseline TAC of 0, 517 (41.6%) revealed incident TAC after 5 years. Incidence of descending TAC was higher (34.5%) than ascending TAC (23.3%). Incident TAC after 5 years was associated with age (relative risk 1.26 [95% CI 1.21–1.33], per 5 years), blood pressure (relative risk 1.06 [95% CI 1.03–1.10], per 10 mm Hg), low-density lipoprotein cholesterol (relative risk 1.08 [95% CI 1.04–1.12], per 20 mg/dL), and smoking (relative risk 1.28 [95% CI 1.07–1.53]). Among the 1185 participants without CAC at baseline, the risk of developing CAC was 28.3% when baseline TAC was present compared with 22.2% among those without baseline TAC (excess risk 6.1% [95% CI 1.2–11.0%]). The point estimate of excess risk for incident CAC was higher for ascending TAC (10.8% [95% CI 4.8–16.7%]) and low for descending TAC (1.8% [95% CI –3.2% to 6.7%]). Excess risk for developing ascending and descending TAC with present baseline CAC was 16.4% (95% CI 12.7–20.0%) and 15.6% (95% CI 10.8–20.4%), respectively.

Conclusion—TAC and CAC share similar major determinants for incident calcification. Participants with TAC, especially ascending TAC, are at elevated risk for development of CAC. (*J Am Heart Assoc.* 2017;6:e005093. DOI: 10.1161/JAHA.116.005093.)

Key Words: aortic disease • calcification • cardiac CT • computed tomography • coronary artery calcification • thoracic aortic calcification

Thoracic aortic calcification (TAC) and coronary artery calcification (CAC) are markers of subclinical atherosclerosis and can be quantified from noncontrast cardiac

computed tomography (CT).^{1,2} Prevalence of TAC is associated with risk factors similar to those for CAC and is closely related to coronary atherosclerosis, consistent with a common underlying systemic vascular atherosclerotic process.^{3,4} With rising TAC and CAC scores, the probability of future coronary and cardiovascular events increases. Both CAC and aortic calcification predict vascular morbidity and mortality^{5–8}; therefore, quantification of vascular calcification is currently regarded as the best single test for risk assessment in asymptomatic patients at intermediate risk for cardiovascular events. For those without CAC, excellent cardiovascular prognosis is well documented.^{9,10}

Corresponding to overall atherosclerosis burden, the extent of vascular calcification changes over time. The incidence or progression of TAC and CAC can be investigated by repetitive CT examinations.¹¹ New onset or rapid CAC progression is associated with an enhanced risk for future coronary heart disease events and all-cause mortality.^{2,12} The likelihood of subsequent CAC incidence has

From the Department of Cardiology and Vascular Medicine, West-German Heart and Vessel Center Essen (H.K., A.A.M.) and Institute of Medical Informatics, Biometry, and Epidemiology (N.L., S.M., A.S., K.-H.J., R.E.), University Duisburg-Essen, Essen, Germany; IUF-Leibniz Research Institute for Environmental Medicine and University of Düsseldorf, Germany (B.H.).

Accompanying Tables S1 through S4 and Figure S1 are available at <http://jaha.ahajournals.org/content/6/4/e005093/DC1/embed/inline-supplementary-material-1.pdf>

Correspondence to: Hagen Kälsch, MD, Department of Cardiology and Vascular Medicine, West-German Heart and Vessel Center Essen, University of Duisburg-Essen, Hufelandstrasse 55, 45122 Essen, Germany. E-mail: hagen.kaelsch@uk-essen.de

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recently been shown to increase with rising TAC scores, suggesting that a TAC score >100 could serve as an independent predictor of CAC incidence.¹³ So far, this finding is not confirmed in a population-based setting. TAC burden varies between ascending and descending thoracic aorta,^{1,14} with different impact of thoracic aortic segment calcifications on cardiovascular events.¹⁵ Furthermore, presence of calcification in the descending thoracic aortic (descending TAC [DTAC]) has been demonstrated to be associated with CAC independent of cardiovascular risk factors.¹⁴ To date, neither the impact of different TAC scores on CAC progression nor the influence of TAC progression on CAC has been reported.

The aim of this study was to assess the main determinants of TAC incidence and progression and the predictive value of baseline TAC (TAC_{bi}) scores on CAC incidence and progression for the overall thoracic aorta and for aortic segments separately, as quantified from cardiac CT in a population-based cohort.

Methods

Study Population

The Heinz Nixdorf Recall study is a population-based prospective cohort study designed to assess the predictive value of novel markers for risk stratification in addition to traditional cardiovascular risk factors. Between December 2000 and August 2003, a total of 4814 persons were contacted on the basis of a random sample of men and women aged 45 to 74 years who were registered in mandatory citizen registries in the German cities of Bochum, Essen, and Mülheim/Ruhr. Details of recruitment and study design were published previously.^{2,5} Those with prior coronary artery disease (coronary artery bypass grafting and/or interventional revascularization procedures and history of prior myocardial infarction) were excluded from this analysis (n=327). Of the remaining participants (n=4487), 3916 participated in the follow-up examination after 5 years. Of those, 3446 participants had information on TAC_{bi} (both ascending TAC [ATAC] and DTAC), baseline CAC (CAC_{bi}), and follow-up. Also excluded were participants with stent implantation, bypass surgery, or myocardial infarction during the 5-year follow-up period, (n=141); participants outside the study age range (45–74 years at baseline, 50–79 years at 5-year follow-up; n=10); or participants with missing information on Framingham risk factors (n=25). A total of 3270 eligible participants (53.1% women) remained for the present analysis (Figure S1). All participants provided written informed consent, and the study was approved by the ethics committee of the University Clinic Essen, Germany.

Risk Factor Analyses

Cardiovascular risk factors were assessed at the time of each noncontrast CT scan (baseline and after 5 years). The methodology was published previously.⁵ Smoking behavior was assessed in detail.¹⁶ Body mass index (kg/m²) was calculated using standardized height and weight measurements. Total cholesterol, high-density lipoprotein cholesterol, triglycerides, and low-density lipoprotein cholesterol (LDL-C) were measured with the standard enzymatic methods. Use of lipid-lowering medication was documented. Blood pressure was measured using an oscillometric method (Omron), according to a standard protocol. The mean value of the second and third of 3 measurements taken at least 2 minutes apart was used. Hypertension was defined as systolic or diastolic blood pressure ≥ 140 or ≥ 90 mm Hg, respectively, or documented use of antihypertensive medication. Blood fasting glucose was measured after overnight fasting 9.7–4.9 hours (median 12 hours). Participants were classified as diabetic when glucose was ≥ 126 mg/dL or use of insulin or oral hypoglycemic agents was reported.¹⁷

CT Scan Protocol

CT scans were performed for quantification of CAC with a C-100 and C-150 scanner (GE Imatron) in 2 independent radiology institutions at baseline. Follow-up imaging was performed after a mean of 5.1 ± 0.3 years (median 5.1 years, interquartile range [IQR] 5.0–5.2 years) with an identical scanning protocol, using an Imatron C-150 scanner.

The CTs were operated in the single-slice mode with an image acquisition time of 100 ms. A slice thickness of 3 mm was chosen. Prospective ECG triggering was performed at 80% of the R-R interval. Contiguous slices from the right pulmonary artery down to the apex of the heart were obtained, sufficient to include the entire heart as well as the ascending aorta and descending thoracic aorta. TAC and CAC were defined as a focus of at least 4 contiguous pixels with a CT density > 130 Hounsfield units and quantified using the Agatston method.¹⁸

TAC included calcification scored from segments of the ascending and descending portions of the thoracic aorta visible in the coronary CT scan and was classified using the standard CAC categories (TAC 0, 1–99, 100–399, and ≥ 400), as described previously.^{1,3} The aortic arch and the infrarenal abdominal aorta were not included in the scan. Calcification in the aortic root (eg, above the aortic valve) was included in ATAC. Participants and physicians remained unaware of the CAC and TAC scoring results of the baseline examination.

Statistical Analyses

Means and standard deviations were calculated for continuous measures with the exception of TAC and CAC, for which medians and IQRs were calculated due to the skewed nature; frequencies were given as number (percentage). Demographics and risk factors at baseline were estimated for each TAC score category at baseline (TAC_{bi}). To statistically evaluate the relationship between TAC groups and continuous data, we used a Spearman correlation test for trend with TAC groups. For frequencies, we used the Mantel-Haenszel χ^2 or Cochran–Armitage test as a trend test.

Incidence of overall TAC within 5 years and of ATAC and DTAC separately was modeled using the robust variance version¹⁹ of relative risk regression. These models with CAC_{bi} (on the log-scale) as exposure were calculated crude (and univariate for each cardiovascular risk factor) and adjusting the influence of CAC_{bi} for all cardiovascular risk factors. Results are given as relative risk with 95% CI.

For graphical representation, the sex-specific 50th, 75th, and 90th percentiles per 5-year age group of TAC distribution for baseline and 5-year follow-up data were analyzed, investigating ATAC and DTAC separately. These observed data points were plotted together with linear quantile regression fits of the form $\log(TAC+1)=I+b \text{ age}$ for the 50th, 75th, and 90th percentiles.

To operationalize 5-year TAC progression as a continuous end point, we let $y=[((TAC_f)+1)/(TAC_{bi}+1)]^{(5/T)}$ denote TAC change in 5 years, explicitly taking the actual time (T) in years between scans (5.1 ± 0.3 years) into account. Then, in a given subgroup, $100\cdot[y-1]\%$ is the 5-year TAC progression in that subgroup, represented as median percentage (IQR). Furthermore, β denoted the regression coefficient of TAC change in 5 years in the framework of linear regression of $\log(y)$ on x (known as exponential regression), where x is a potential risk factor. Then the 5-year change in TAC progression related to an increase in x by 1 is given as $100\cdot[\exp(\beta)-1]\%$. The results are given crude and, with addition of cardiovascular risk factors, adjusted for TAC_{bi} (as $\log[TAC_{bi}+1]$) and are reported with their 95% CIs.

In the next step, as primary outcome, we estimated the excess risk of incident CAC (CAC_i) by contrasting participants with versus without TAC_{bi} as risk differences with their 95% CIs. This calculation was also carried out for excess risk of incident CAC depending on the presence of ATAC and DTAC separately. Secondary outcomes were all other combinations: incident ATAC depending on presence of CAC_{bi} or DTAC at baseline ($DTAC_{bi}$) and incident DTAC depending on ATAC as well as CAC_{bi} . We also computed relative risk regressions for CAC_i with TAC_{bi} , baseline ATAC ($ATAC_{bi}$) or $DTAC_{bi}$ (on the log scale) as exposure, crude, and fully adjusted for cardiovascular risk factors.

For both sexes, we calculated CAC percentiles at baseline as functions of age from linear quantile regression on the log scale, $\log(CAC_{bi}+1)$. CAC at follow up (CAC_f) was predicted exponentially extrapolating along the participant's percentile by the time T between measurements. A predefined acceptance band nominally covers 20% of observed values around the individually predicted value. CAC progression was classified as CAC function within band (expected progression), above band (fast progression), or below band (slow progression). Overall, 68% of the participants lay within the acceptance band.^{20,21} We found that this approach could not be transferred to progression of thoracic aortic calcium.

We further calculated and reported confidence intervals to assess the precision of our estimates. Reported *P* values are to be understood as additional but purely descriptive information. Our primary goal was estimation, not significance testing, and to avoid publication bias by preferential reporting of significant results. The value of our estimates will be discussed with a focus on precision and validity.

Results

Baseline Parameter

The baseline demographics of the cohort of 3270 participants, who underwent baseline and 5-year follow-up CT, are given in Table 1 for men and women. Both cohorts are subdivided by TAC score categories at baseline (TAC_{bi}) (Table 1). All baseline risk factors showed a strong association with TAC except for high-density lipoprotein cholesterol.

Incidence of TAC

At the time of repeated CT scan, 517 (41.6%) of the 1243 participants without TAC_{bi} developed overall incident TAC (TAC_i ; incident ATAC: 448 [23.3%]; incident DTAC: 502 [34.5%]). Regression analysis revealed systolic blood pressure, smoking, LDL-C, and CAC_{bi} score in addition to age and sex as determinants significantly associated with TAC_i in fully adjusted models, similar to incident ATAC, whereas incident DTAC was significantly associated with systolic blood pressure, intake of antihypertensive medication, diabetes mellitus, smoking, and CAC_{bi} score (Table 2).

Progression of TAC

The fitted percentile curves as a function of age for the TAC distribution at follow-up in either sex showed little overlap with their counterparts at baseline. This holds especially for the 75th and 90th percentiles (Figure 1A). This phenomenon was even more pronounced in DTAC percentiles (Figure 1C), whereas ATAC percentiles showed curvature nearly

Table 1. Baseline Characteristics by TAC Categories in Men and Women

	TAC ₀ Categories at Baseline for Men (n=1533)				TAC ₀ Categories at Baseline for Women (n=1737)				P for Trend
	TAC ₀ 0 (n=558)	TAC ₀ 1–99 (n=537)	TAC ₀ 100–399 (n=254)	TAC ₀ ≥400 (n=184)	TAC ₀ 0 (n=685)	TAC ₀ 1–99 (n=665)	TAC ₀ 100–399 (n=252)	TAC ₀ ≥400 (n=135)	
Age, y	56.3±7.0	58.0±7.2	61.7±6.6	64.8±6.3	56.4±7.1	58.6±7.1	63.2±7.2	65.9±6.3	<0.0001*
Diabetes mellitus, %	10.6	13.6	19.7	25.0	6.6	7.5	9.5	17.0	0.0003†
Systolic BP, mm Hg	134.0±17.8	135.7±17.8	140.3±18.4	148.5±20.2	123.3±18.8	127.0±20.4	133.3±20.8	137.1±20.7	<0.0001*
Diastolic BP, mm Hg	83.9±10.5	84.1±10.2	85.2±10.0	85.4±10.4	77.5±10.0	79.2±10.6	79.8±10.5	80.3±10.5	<0.0001*
Hypertension, %	38.0	41.0	50.0	70.7	21.2	28.3	42.1	43.0	<0.0001†
Antihypertensive med., %	26.0	22.9	38.6	50.5	23.4	27.1	44.4	57.8	<0.0001†
Former smoking, %	40.1	48.6	47.6	52.2	27.9	21.5	22.2	21.5	0.033‡
Present smoking, %	26.2	22.2	22.0	27.7	18.2	22.9	16.7	20.7	
LDL-C, mg/dL	144.9±33.7	146.1±34.8	152.3±37.7	149.7±38.4	140.1±34.9	144.8±34.7	154.3±35.2	158.6±39.4	<0.0001*
HDL-C, mg/dL	52.0±14.2	51.9±13.1	51.6±15.5	51.5±15.7	66.3±17.4	66.8±17.2	64.1±16.0	63.9±15.0	0.16*
Lipid-lowering med., %	6.7	5.8	10.4	20.9	7.4	9.0	14.9	20.8	<0.0001†
Framingham risk, %	12.7±6.8	13.8±8.0	18.0±10.1	22.7±10.4	6.2±4.4	7.3±4.9	9.1±5.0	10.6±6.2	<0.0001*
CAC ₀ -score, median (IQR)	14 (0–104)	21 (1–112)	118 (25–345)	288 (106–823)	0 (0–8)	0 (0–9)	11 (0–86)	83 (6–267)	<0.0001*

Values are mean±SD or percentages unless otherwise stated. BP indicates blood pressure; CAC₀, coronary artery calcification at baseline; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; med., medications; TAC₀, thoracic aortic calcification at baseline.

*Spearman correlation test.

†Cochran–Armitage test.

‡ χ^2 test.

Table 2. Relative Risk Regression Analysis of TAC, ATAC, and DTAC Incidence at 5 Years (Crude and Fully Adjusted)

Parameters at Baseline	TAC Incidence (n=1243, 517 With Incidence)		ATAC Incidence (n=1924, 448 With Incidence)		DTAC Incidence (n=1456, 502 With Incidence)	
	Crude RR (95% CI)	Fully Adjusted RR (95% CI)	Crude RR (95% CI)	Fully Adjusted RR (95% CI)	Crude RR (95% CI)	Fully Adjusted RR (95% CI)
Age (5 years)	1.33 (1.28–1.39)*	1.26 (1.21–1.33)*	1.28 (1.22–1.35)*	1.14 (1.07–1.21)*	1.41 (1.35–1.47)*	1.35 (1.29–1.42)*
Sex (female vs male)	0.95 (0.83–1.08)	1.18 (1.01–1.37)*	0.96 (0.81–1.12)	1.40 (1.15–1.71)*	0.98 (0.85–1.13)	1.23 (1.04–1.46)*
BMI, kg/m ²	1.03 (1.02–1.04)*	1.00 (0.98–1.02)	1.05 (1.04–1.07)*	1.01 (0.99–1.03)	1.03 (1.01–1.04)*	0.99 (0.98–1.01)
Diabetes mellitus, yes vs no	1.33 (1.10–1.61)*	1.19 (0.98–1.44)	1.41 (1.12–1.78)*	1.12 (0.88–1.42)	1.54 (1.28–1.86)*	1.25 (1.03–1.51)*
Systolic BP (10 mm Hg)	1.12 (1.09–1.16)*	1.06 (1.03–1.10)*	1.16 (1.12–1.20)*	1.09 (1.05–1.14)*	1.13 (1.10–1.17)*	1.07 (1.03–1.11)*
Antihypertensive medication, yes vs no	1.43 (1.25–1.63)*	1.06 (0.92–1.22)	1.66 (1.41–1.95)*	1.14 (0.96–1.36)	1.59 (1.38–1.83)*	1.19 (1.02–1.37)*
Former smoking vs never	0.92 (0.79–1.08)	1.03 (0.88–1.20)	0.91 (0.76–1.10)	1.01 (0.83–1.23)	0.91 (0.78–1.08)	1.04 (0.87–1.23)
Present smoking vs never	0.99 (0.84–1.18)	1.28 (1.07–1.53)*	0.92 (0.75–1.14)	1.15 (0.92–1.43)	1.06 (0.89–1.27)	1.50 (1.24–1.82)*
HDL-C (5 mg/dL)	0.99 (0.97–1.01)	1.00 (0.98–1.02)	0.97 (0.94–0.99)	0.98 (0.95–1.01)	0.97 (0.95–1.00)	0.98 (0.96–1.01)
LDL-C (20 mg/dL)	1.10 (1.06–1.15)*	1.08 (1.04–1.12)*	1.14 (1.09–1.19)*	1.11 (1.06–1.16)*	1.06 (1.02–1.11)*	1.03 (0.99–1.07)
Lipid-lowering medication, yes vs no	1.27 (1.02–1.59)*	1.06 (0.85–1.32)	1.53 (1.16–2.01)*	1.27 (0.96–1.68)	1.32 (1.06–1.64)*	1.02 (0.82–1.26)
Baseline CAC _{bl} score [†]	1.14 (1.12–1.17)*	1.08 (1.05–1.12)*	1.20 (1.17–1.24)*	1.15 (1.11–1.20)*	1.14 (1.11–1.17)*	1.07 (1.03–1.10)*

ATAC indicates ascending thoracic aortic calcification; BMI indicates body mass index; BP, blood pressure; CAC, coronary artery calcification; CAC_{bl}, coronary artery calcification at baseline; DTAC, descending thoracic aortic calcification; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; RR, relative risk; TAC, thoracic aortic calcification.

* $P < 0.05$. Fully adjusted: for age, sex, BMI, diabetes mellitus, systolic BP, antihypertensive medication, smoking, HDL-C, LDL-C, lipid-lowering medication, and CAC_{bl} score.

[†] $\log(\text{CAC}+1)$.

indistinguishable from the baseline results except for men in the highest percentile (Figure 1B).

Regression analysis revealed systolic blood pressure, diabetes mellitus, smoking, LDL-C, and presence of lipid-lowering and/or antihypertensive medication besides age as the determinants significantly associated with TAC progression in fully adjusted analysis (Table 3).

CAC_i by Presence of TAC_{bl}

In the absence of TAC_{bl}, 22.1% of participants developed CAC_i after 5 years, mostly low CAC burden (Table 4). With rising TAC_{bl} scores, this trend increased to 65.4% of CAC_i when TAC_{bl} scores were ≥ 400 . Furthermore, the portion of high CAC_i burden increased with rising TAC_{bl} scores.

Regarding aortic segments separately, similar results were found. When ATAC_{bl} was absent (n=881), only 22.5% of participants developed CAC_i, and 24.4% developed CAC_i when DTAC_{bl} was absent (n=635). However, with rising ATAC_{bl} and DTAC_{bl} scores, portion of CAC_i increased up to 83.3% (ATAC_{bl}

scores ≥ 400 , n=6) and 65% (DTAC_{bl} ≥ 400 , n=20). Similar to overall TAC_{bl}, CAC_i scores increased with rising ATAC_{bl} and DTAC_{bl} scores (Table S1).

Besides age, systolic blood pressure, smoking, LDL-C, and presence of lipid-lowering regression analysis showed a significant association of present ATAC_{bl} with CAC_i in fully adjusted models. Nevertheless, the presence of overall TAC_{bl} or DTAC_{bl} was not significantly associated with CAC_i after 5 years (Table 5).

Correspondingly, the presence of ATAC_{bl} was associated with a high excess risk of CAC_i (10.8%, IQR 4.8–16.7%, $P=0.0002$). Reciprocally the presence of CAC_{bl} was associated with a high excess risk of ATAC_i (excess risk 16.4%, IQR 12.7–20.0%, $P < 0.0001$). DTAC_{bl} was not associated with a high excess risk of CAC_i (1.8%, IQR –3.2–6.7%, $P=0.48$) (Figure 2).

TAC_i by Presence of CAC_{bl}

To investigate the influence of CAC_{bl} on 5-year incident TAC as a secondary outcome, we calculated TAC_i for different

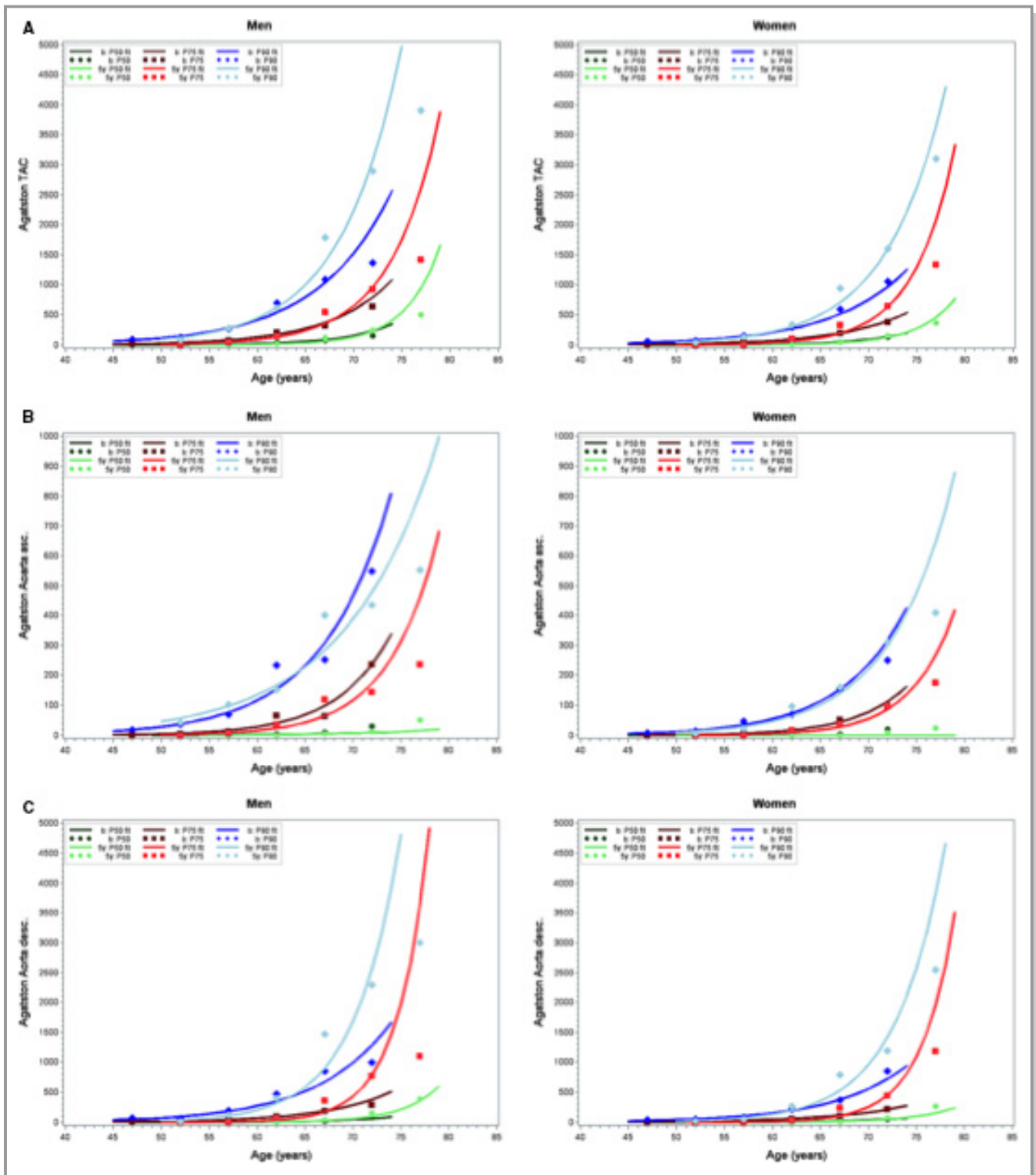


Figure 1. Observed and fitted 50th, 75th, and 90th percentiles (P50, P75, and P90, respectively) of thoracic aortic calcification (TAC) distribution for (A) overall TAC, (B) ascending (asc.) TAC and (C) descending (desc.) TAC by age categories in men and women. Dark colors show baseline values when participant age was between 45 and 74 years, and light colors show 5-year follow-up data.

CAC_{bl} categories. When CAC_{bl} was absent, only 32% of participants developed TAC_i after 5 years (mostly low TAC_i burden), whereas this trend increased with up to 85% of TAC_i

when CAC_{bl} scores were ≥ 400 (Table S2). Furthermore, the portion of high TAC_i burden increased with rising CAC_{bl} scores ($P < 0.0001$ for trend). When CAC_{bl} was absent, 14% and 25%

Table 3. Regression Analysis for TAC, ATAC, and DTAC Progression After 5 Years (Crude and Full Model, Given as Percentage Change in [TAC+1] depicted as β -estimates [95% CI])

Parameters at Baseline	TAC Progression Percentage Change in (TAC+1)		ATAC Progression Percentage Change in (ATAC+1)		DTAC Progression Percentage Change in (DTAC+1)	
	Crude	Full Model	Crude	Full Model	Crude	Full Model
Age (5 years)	46.1 (38.7–53.8)*	83.6 (73.9–94)*	9.3 (5.1–13.7)*	23.2 (18–28.7)*	57.4 (49.2–66)*	86.3 (76.1–97.1)*
Sex (female vs male)	-1.6 (-16.3 to 15.7)	11.9 (-5.4 to 32.3)	-6.6 (-17.1 to 5.3)	-2.4 (-14.8 to 11.7)	-5.2 (-19.9 to 12.1)	19.6 (0.3–42.6)*
BMI, kg/m ²	3.5 (1.6–5.5)*	0.1 (-1.7 to 2)	0.8 (-0.6 to 2.2)	0.2 (-1.2 to 1.8)	3.4 (1.4 to 5.4)*	-1.1 (-3 to 0.8)
Diabetes mellitus, yes vs no	62.9 (26.3–110)*	56.9 (24.2–98.2)*	43.1 (18.5–72.7)*	50.2 (24.4–81.3)*	67.5 (28.6–118.2)*	44 (12.7–83.9)*
Systolic BP (10 mm Hg)	17.7 (13.1–22.4)*	16 (11.5–20.7)*	6.5 (3.4–9.6)*	7.3 (3.9–10.7)*	21 (16.2–26.1)*	17.3 (12.5–22.2)*
Antihypertensive medication, yes vs no	89.9 (59.5–126)*	62.1 (37.2–91.6)*	22 (7.2–39)*	18.9 (3.9–35.9)*	108.5 (74–149.9)*	72.2 (44.6–105.1)*
Former smoking, vs never	-5.1 (-21 to 14.1)	24.9 (5.5–47.9)*	4.3 (-9 to 19.5)	18.9 (3.8–36.3)*	-1.4 (-18.6 to 19.4)	23.5 (3.5–47.4)*
Present smoking, vs never	22 (-1.2 to 50.6)	137 (94.9–188.2)*	30 (11.2–52)*	68.4 (43.7–97.2)*	14.2 (-8.3 to 42.2)	120.7 (79.9–170.9)*
HDL-C (5 mg/dL)	-3.3 (-5.5 to -1)	-2.2 (-4.6 to 0.3)	-2.1 (-3.8 to -0.4)	-0.8 (-2.8 to 1.2)	-3.8 (-6.1 to -1.4)	-3.1 (-5.6 to -0.5)
LDL-C (20 mg/dL)	13.2 (8.2–18.4)*	15.2 (10.5–20)*	6.7 (3.1–10.3)*	12 (8.3–15.8)*	10.2 (5.2–15.5)*	8.2 (3.6–12.9)*
Lipid-lowering medication, yes vs no	59 (19.4–111.6)*	68.4 (31.3–116.1)*	30.9 (5.8–61.8)*	81.6 (48.2–122.5)*	71.2 (27.1–130.5)*	40.8 (8.5–82.7)*
Baseline CAC score (log [CAC+1])	21.9 (17.9–26.1)*		9.7 (6.9–12.4)*		24.4 (20.2–28.8)*	
Baseline TAC score (log [TAC+1]) in the respective vessels	-23.8 (-26.2 to -21.4)	-39.2 (-41.2 to -37.2)	-21.2 (-23.4 to -19)	-30.3 (-32.4 to -28.1)	-25.6 (-28.1 to -22.9)	-39 (-41.1 to -36.8)

ATAC indicates ascending thoracic aortic calcification; BMI indicates body mass index; BP, blood pressure; CAC, coronary artery calcification; DTAC, descending thoracic aortic calcification; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TAC, thoracic aortic calcification.

* $P < 0.05$. Full model containing age, sex, BMI, diabetes mellitus, systolic BP, antihypertensive medication, smoking, HDL-C, LDL-C, lipid-lowering medication, and respective baseline TAC score as $\log(\text{TAC}_{\text{Cr}+1})/\log(\text{ATAC}_{\text{Cr}+1})/\log(\text{DTAC}_{\text{Cr}+1})$.

Table 4. Amount of CAC_i After 5 Years Distributed in Different CAC_i Categories Depending on TAC_{bl}

Baseline TAC _{bl} Score (n=1185)	Amount of CAC _i After 5 Years			P for Trend
	CAC _i 0 (n=886, 75%)	CAC _i 1–99 (n=290, 24%)	CAC _i 100–399 (n=9, 1%)	
TAC _{bl} 0 (n=587, 50%)	457 (78%)	127 (21%)	3 (1%)	<0.0001*
TAC _{bl} 1–99 (n=491, 41%)	367 (75%)	120 (24%)	4 (1%)	
TAC _{bl} 100–399 (n=81, 7%)	53 (65%)	26 (32%)	2 (3%)	
TAC _{bl} ≥400 (n=26, 2%)	9 (35%)	17 (65%)	0 (0%)	

CAC_i indicates amount of incident coronary artery calcification; TAC_{bl}, thoracic aortic calcification at baseline.

*Mantel-Haenszel test.

of participants developed ATAC_i and DTAC_i, respectively; however, with higher CAC_{bl} scores, incidence of ATAC and DTAC markedly increased ($P<0.0001$ for trend) (Table S3).

Prediction of CAC Progression by TAC_{bl}

In the absence of TAC_{bl}, 15.5% of participants revealed slow CAC progression, 67.1% had expected progression, and 17.4% had fast progression. With rising TAC_{bl} scores, the portion of fast CAC progression increased up to 24.1% (TAC_{bl} ≥400, $P<0.0001$ for trend) (Table 6).

Regarding aortic segments separately, data corresponded with findings to overall TAC_{bl}; when ATAC_{bl} was absent (n=1924), 13.6% of participants revealed slow CAC progression, 67.5% had expected progression, and 18.9% fast progression. In the absence of DTAC_{bl} (n=1456), 14.4% had slow CAC progression, 66.6% had expected progression, and 19.0% had fast progression. With rising ATAC_{bl} and DTAC_{bl} scores, the proportion of fast CAC progression increased

respectively to 28.1% (ATAC_{bl} ≥400, n=96) and 23.9% (DTAC_{bl} ≥400, n=222; $P<0.0001$ for trend) (Table S4).

Discussion

In this study, we investigated the interaction of both TAC_i and CAC_i with progression over 5 years in the general population. We found that the thoracic aorta and coronary arteries share similar major determinants for incidence and progression of calcification. In addition, participants with high extent of TAC, especially in the ascending aorta, reveal considerably elevated risk of incidence and accelerated progression of coronary calcification.

CT scanning for detection and quantification of CAC and TAC was previously demonstrated to show important prognostic information for the management of patients at intermediate cardiovascular risk.^{5–8} Furthermore, repetitive calcification scanning after 5 years is recommended because ≈20% of participants without initial CAC develop subsequent CAC after 4 years.¹¹ New-onset or extensive CAC progression is associated with an enhanced risk of future coronary heart disease events and all-cause mortality.^{2,12} Previous studies demonstrated systolic blood pressure, diabetes mellitus, smoking, and lipid-lowering medication as the main confounders for accelerated CAC progression.^{21–25}

Similar to CAC, TAC, which is closely related to coronary atherosclerosis, can easily be measured and categorized with a noncontrast CT scan.^{3,4,6,7,13} Taking the strong association of thoracic aortic with coronary calcification into account, the identification of main determinants for TAC incidence and progression may play a pivotal role in cardiovascular prevention. In a multiethnic population-based cohort, Youssef et al found age, systolic blood pressure, intake of antihypertensive medication, and smoking to be associated with TAC_i, thus not discriminating between the ascending and descending thoracic aorta.²⁶ Accordingly, our results reveal—aside from age and sex—systolic blood pressure and LDL-C as the main determinants of TAC_i, especially in the ascending aorta.

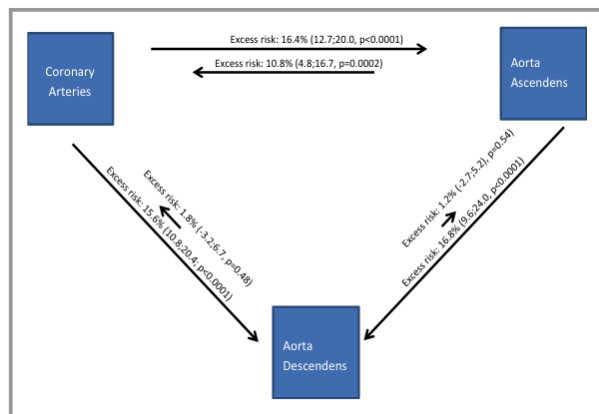


Figure 2. Five-year progression of calcification with relations between vascular beds. Lengths of arrows indicate excess risk of 5-year onset in the artery where the arrow points and contrasting presence and absence of baseline calcification where the arrow originates, IQR indicates interquartile range.

Table 5. Relative Risk Regression for Incidence of CAC by Amount of TAC, ATAC, and DTAC at Baseline (Fully Adjusted)

Parameters at Baseline	Incidence of CAC as a Function			
	Crude	Fully Adjusted Models		
	RR (95% CI)	TAC at Baseline RR (95% CI)	ATAC at Baseline RR (95% CI)	DTAC at Baseline RR (95% CI)
Age (5 years)	1.25 (1.17–1.33)*	1.17 (1.08–1.26)*	1.16 (1.08–1.25)*	1.18 (1.1–1.27)*
Sex (female vs male)	0.76 (0.62–0.93)*	0.89 (0.7–1.15)	0.9 (0.7–1.15)	0.9 (0.7–1.15)
BMI, kg/m ²	1.04 (1.01–1.06)*	1 (0.98–1.03)	1 (0.97–1.02)	1 (0.98–1.03)
Diabetes mellitus, yes vs no	1.53 (1.1–2.13)*	1.19 (0.83–1.69)	1.18 (0.83–1.68)	1.18 (0.83–1.68)
Systolic BP (10 mm Hg)	1.18 (1.14–1.23)*	1.11 (1.06–1.17)*	1.11 (1.06–1.17)*	1.11 (1.06–1.17)*
Antihypertensive medication, yes vs no	1.47 (1.19–1.81)*	1.15 (0.91–1.44)	1.14 (0.91–1.43)	1.15 (0.92–1.44)
Former smoking vs never	1.04 (0.84–1.28)	1.17 (0.92–1.48)	1.17 (0.93–1.48)	1.17 (0.93–1.48)
Present smoking vs never	1.11 (0.87–1.4)	1.37 (1.05–1.77)*	1.35 (1.04–1.76)*	1.38 (1.06–1.8)*
HDL-C (5 mg/dL)	0.96 (0.93–0.99)*	0.98 (0.94–1.02)	0.98 (0.94–1.02)	0.98 (0.94–1.02)
LDL-C (20 mg/dL)	1.11 (1.04–1.17)*	1.09 (1.03–1.15)*	1.08 (1.02–1.15)*	1.09 (1.03–1.15)*
Lipid-lowering medication, yes vs no	1.69 (1.22–2.35)*	1.47 (1.08–2.01)*	1.43 (1.06–1.94)*	1.48 (1.08–2.02)*
Baseline TAC score (log[TAC _{bl} +1])	1.09 (1.04–1.14)*	1.03 (0.98–1.08)		
Baseline ATAC score (log[ATAC _{bl} +1])	1.16 (1.1–1.22)*		1.07 (1.01–1.13)*	
Baseline DTAC score (log[DTAC _{bl} +1])	1.05 (1–1.11)*			1 (0.95–1.05)

ATAC indicates ascending thoracic aortic calcification; BMI, body mass index; BP, blood pressure; CAC, coronary artery calcification; DTAC, descending thoracic aortic calcification; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TAC, thoracic aortic calcification.

*P<0.05. Fully adjusted for age, sex, BMI, diabetes mellitus, systolic BP, antihypertensive medication, smoking, HDL-C, LDL-C, and lipid-lowering medication.

Incidence of DTAC was triggered by systolic blood pressure, intake of antihypertensive medication, diabetes mellitus, and smoking. In both aortic segments, CAC score was markedly associated with the atherosclerotic process. For TAC progression, we identified systolic blood pressure, diabetes mellitus, smoking, LDL-C, and presence of lipid-lowering and/or antihypertensive medication, in addition to age, as the main determinants. This is in line with the population-based findings of Youssef et al, who investigated this link across 4 different ethnicities. They found age, systolic blood pressure, intake of lipid-lowering medication, diabetes mellitus, and smoking to be associated with TAC progression.²⁶ In contrast to TAC progression, we did not observe a relevant association of incident TAC with the intake of lipid-lowering medication; however, the duration and extent of medical intake was not

included into the analysis. Because atherosclerosis is an ongoing disease, this may have biased our results. Dykun et al reported enhanced CAC progression under statin intake.²⁷ Our corresponding results for TAC progression may support the hypothesis of a plaque-stabilizing effect of statins, which might be reflected by an increase in TAC. This may influence expectations of clinicians when monitoring statin therapy by repetitive TAC scores. Further studies using CT angiography including lesion-specific information over time and higher number of participants with statins are needed to confirm our results.

In contrast, the risk of CAC_i was recently shown to increase with rising TAC burden, suggesting that a TAC score >100 could serve as an independent predictor of future CAC conversion.¹³ Until now, this finding had not been

Table 6. CAC Progression in 5 Years Distributed by Slow, Expected, and Fast Progression Depending on TAC_{bl}

Baseline TAC _{bl} Score (n=3270)	CAC Progression in 5 Years			P for Trend
	Slow (n=395, 12%)	Expected (n=2238, 68%)	Fast (n=637, 20%)	
TAC _{bl} 0 (n=1243, 38%)	192 (16%)	834 (67%)	217 (17%)	<0.0001*
TAC _{bl} 1–99 (n=1202, 37%)	133 (11%)	828 (69%)	241 (20%)	
TAC _{bl} 100–399 (n=506, 15%)	55 (11%)	349 (69%)	102 (20%)	
TAC _{bl} ≥400 (n=319, 10%)	15 (5%)	227 (71%)	77 (24%)	

CAC indicates coronary artery calcification; TAC_{bl}, thoracic aortic calcification at baseline.

*Mantel-Haenszel test.

investigated in a population-based setting and the commonly accepted calcification score categories had not been utilized, especially with regard to high calcification burden with scores ≥ 400 . Consideration of high calcification burden appears relevant, given the proportion of participants in the overall population with high TAC scores (11.7%).^{1,3} We were able to demonstrate that the rate of CAC_i increased up to 65.4% after 5 years in participants with TAC scores ≥ 400 at baseline. In addition, the portion of high CAC incidence/burden increased with rising TAC scores at baseline.

It was previously demonstrated that the prevalence and extent of TAC burden varies considerably between the ascending and descending thoracic aortic segments, displaying higher prevalence and extent of calcifications in the descending than in the ascending aorta. Both are included in the standard coronary calcification scan.^{1,14} Importantly, the risk of cerebrovascular events (eg, stroke) is significantly higher in participants with DTAC.¹⁵ Interestingly, the rate of CAC conversion was more closely related to ATAC than DTAC. This divergent finding underscores the hypothesis that stroke events seem primarily associated with aortic atherosclerosis but not with coronary atherosclerosis.

Longitudinal assessment of CAC burden allows the quantification of progression of coronary artery disease.^{11,21} An annual score increase of 15% is associated with an enhanced risk of myocardial infarction.^{28,29} Major risk factors such as LDL-C, family history of coronary heart disease, and hypertension showed only weak association with CAC progression. In addition, risk-modifying medical therapy, known to reduce risk for CV events,³⁰ was not associated with a reduction or attenuation of CAC.^{27,31,32} Furthermore, it was demonstrated previously that the rate of CAC progression is proportional to preexisting CAC.³³ Neither the impact of different TAC scores on CAC progression, especially stratified by different aortic segments, nor the influence of TAC progression on the progression of coronary atherosclerosis has been reported.

In our study, ATAC was associated with high excess risk of CAC progression, whereas DTAC was not. With rising TAC scores at baseline, the portion of fast CAC progression increased up to 24.1% when TAC was ≥ 400 , whereas the portion of slow CAC progression was 4.7%. Evaluating the association for aortic segments separately, data corresponded with findings for overall TAC. Because patients with TAC scores ≥ 400 have considerably elevated cardiovascular event rates,⁷ our results suggest this finding may be explained by accelerated CAC onset or CAC progress in this TAC category.

Clinical Implications

Noncontrast cardiac CT is performed for the assessment of CAC score, which independently predicts future coronary

mortality and morbidity.^{1,2,5} Once CT examinations are performed, information on TAC score is readily available. This study demonstrates that TAC_{b1} is associated with the incidence and progression of CAC. Consequently, our results support the implementation of TAC assessment as an adjunct measurement of primary indication in a clinical workup, with noncontrast cardiac CT looking for CAC to improve the prognostic value of this imaging technology. Cardiac CT is considered appropriate for patients in the intermediate-risk group only, which may limit the clinical value of our findings.

Strengths and Limitations of the Study

The strength of our study is the population-based design with close follow-up over 5 years. Traditional cardiovascular risk factors were measured using highly standardized protocols, and both CAC and TAC were quantified using a reproducible method. The CT scans were repeated with the same scanner technology and identical scanning protocols, so we avoided the use of any correction factors. Moreover, a potential bias by therapy was eradicated because participants and their physicians were blinded to the results of calcification scoring at the baseline examination.

A 5-year follow-up period may appear short but offers extrapolation to longer time intervals based on the exponential percentile curvature, which remained constant over time.

As a further limitation, we excluded those participants with revascularization during the 5-year period, given uncertainties in the calcification score analysis; this approach may have biased our results toward the null. Because we studied mainly participants of white ethnicity, our results may not be generalizable to other ethnic groups; however, no interaction between TAC and ethnicity was observed in an ethnically diverse population.³⁴

Finally, in this study, the aorta was examined in the available location on initially performed CAC scanning, excluding the aortic arch and the infrarenal abdominal aorta, 2 locations with noted higher prevalence of calcification.^{1,3} Consequently, our TAC scores did not evaluate the potential importance of aortic arch or abdominal aorta calcification in the prediction of CAC incidence or progression.

Conclusion

The thoracic aorta and coronary arteries share similar major determinants of incidence of calcification. Participants with TAC, especially in the ascending aorta, are at elevated risk of development of CAC and reciprocally, participants with CAC reveal elevated risk for the development of thoracic aortic calcification.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Amount of incident CAC (CAC_i) after 5 yrs, distributed in different CAC-categories depending on baseline amount of TAC in separate aortic segments.

Baseline ATAC _{bl} - / DTAC _{bl} -score (n=1185)	Amount of incident CAC _i after 5 yrs			p for trend
	CAC _i =0 (n=886, 75%)	CAC _i 1 to 99 (n=290, 24%)	CAC _i 100 to 399 (n=9, 1%)	
ATAC _{bl} =0 (n=881, 74%)	683 (78%)	193 (21%)	5 (1%)	<0.0001
ATAC _{bl} 1 to 99 (n=272, 23%)	188 (69%)	81 (30%)	3 (1%)	
ATAC _{bl} 100 to 399 (n=26, 2%)	14 (54%)	11 (42%)	1 (4%)	
ATAC _{bl} ≥400 (n=6, 1%)	1 (17%)	5 (83%)	0 (0%)	
DTAC _{bl} =0 (n=635, 53%)	480 (76%)	151 (23%)	4 (1%)	0.008
DTAC _{bl} 1 to 99 (n=469, 40%)	359 (76%)	106 (23%)	4 (1%)	
DTAC _{bl} 100 to 399 (n=61, 5%)	40 (65%)	20 (33%)	1 (2%)	
DTAC _{bl} ≥400 (n=20, 2%)	7 (35%)	13 (65%)	0 (0%)	
Abbreviations: CAC _i = incidence of coronary artery calcification, in ascending aorta, ATAC _{bl} = calcification at baseline in ascending aorta, DTAC _{bl} = calcification at baseline in descending thoracic aorta.				

Table S2. Amount of incident TAC (TAC_i) after 5 yrs distributed in different TAC_i -categories depending on baseline amount of CAC (CAC_{bl}).

Baseline CAC_{bl} -score (n=1243)	Amount of incident TAC_i after 5 yrs				p for trend
	$TAC_i=0$ (n=726, 58%)	TAC_i 1 to 99 (n=320, 26%)	TAC_i 100 to 399 (n=141, 11%)	$TAC_i \geq 400$ (n=56, 5%)	
$CAC_{bl}=0$ (n=587, 47%)	401 (68%)	136 (23%)	39 (7%)	11 (2%)	<0.0001 §)
CAC_{bl} 1 to 99 (n=466, 37%)	257 (55%)	126 (27%)	66 (14%)	17 (4%)	
CAC_{bl} 100 to 399 (n=145, 12%)	61 (42%)	44 (30%)	24 (17%)	16 (11%)	
$CAC_{bl} \geq 400$ (n=45, 4%)	7 (15%)	14 (31%)	12 (27%)	12 (27%)	
Abbreviations: CAC_{bl} = coronary artery calcification at baseline, TAC_i = amount of incident thoracic aortic calcification. §) = Mantel-Haenszel test					

Table S3. Amount of incident calcification in separate aortic segments after 5 yrs distributed in different categories depending on baseline amount of CAC.

Amount of incident ATAC _i / DTAC _i after 5 yrs	Baseline CAC _{bl} score (n=1243)				p for trend
	CAC _{bl} =0 (n=587, 47%)	CAC _{bl} 1 to 99 (n=466, 37%)	CAC _{bl} 100 to 399 (n=145, 12%)	CAC _{bl} ≥400 (n=45, 4%)	
ATAC _i =0 (n=959, 77%)	505 (86%)	345 (74%)	92 (63%)	17 (37%)	<0.0001
ATAC _i 1 to 99 (n=238, 19%)	72 (12%)	106 (23%)	43 (30%)	17 (38%)	
ATAC _i 100 to 399 (n=40, 3%)	10 (2%)	15 (3%)	7 (5%)	8 (18%)	
ATAC _i ≥400 (n=6, 1%)	0 (0%)	0 (0%)	3 (2%)	3 (7%)	
DTAC _i =0 (n=845, 68%)	442 (75%)	315 (68%)	74 (51%)	14 (31%)	<0.0001
DTAC _i 1 to 99 (n=243, 19%)	107 (19%)	86 (18%)	38 (26%)	12 (27%)	
DTAC _i 100 to 399 (n=112, 9%)	30 (5%)	49 (11%)	22 (15%)	11 (24%)	
DTAC _i ≥400 (n=43, 4%)	8 (1%)	16 (3%)	11 (8%)	8 (18%)	
Abbreviations: ATAC _i = incident calcification in ascending aorta, DTAC _i = incident calcification in descending aorta, CAC _{bl} = coronary artery calcification at baseline.					

Table S4. CAC-Progression in 5 yrs distributed in slow, expected and fast progression depending on baseline amount of TAC in in separate aortic segments.

Baseline ATAC _{bl} - / DTAC _{bl} -score (n=3270)	CAC-Progression in 5 yrs			p for trend
	Slow Progression (n=395, 12%)	Expected Progression (n=2238, 68%)	Fast Progression (n=637, 20%)	
ATAC _{bl} =0 (n=1924, 59%)	261 (14%)	1298 (68%)	365 (18%)	0.0002
ATAC _{bl} 1 to 99 (n=993, 30%)	111 (11%)	693 (70%)	189 (19%)	
ATAC _{bl} 100 to 399 (n=257, 8%)	21 (8%)	180 (70%)	56 (22%)	
ATAC _{bl} ≥400 (n=96, 3%)	2 (2%)	67 (70%)	27 (28%)	
DTAC _{bl} =0 (n=1456, 44%)	209 (14%)	969 (67%)	278 (19%)	0.0009
DTAC _{bl} 1 to 99 (n=1230, 38%)	136 (11%)	858 (70%)	236 (19%)	
DTAC _{bl} 100 to 399 (n=362, 11%)	39 (11%)	253 (70%)	70 (11%)	
DTAC _{bl} ≥400 (n=222, 7%)	11 (5%)	158 (71%)	53 (24%)	
Abbreviations: ATAC _{bl} = calcification at baseline in ascending aorta, DTAC _{bl} = calcification at baseline in descending thoracic aorta CAC = coronary artery calcification.				

Figure S1. Flow diagram of the original study participants and steps of exclusion, resulting in participants eligible for final analysis.

