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ORIGINAL RESEARCH

Vendor Independent Coronary Calcium Scoring Improves Individual Risk Assessment

MESA (Multi-Ethnic Study of Atherosclerosis)

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ABSTRACT

BACKGROUND Substantial variation in Agatston scores (AS) acquired with different computed tomography (CT) scanners may influence patient risk classification.

OBJECTIVES This study sought to develop a calibration tool for state-of-the-art CT systems resulting in vendor-neutral AS (vnAS), and to assess the impact of vnAS on coronary heart disease (CHD) event prediction.

METHODS The vnAS calibration tool was derived by imaging 2 anthropomorphic calcium containing phantoms on 7 different CT and 1 electron beam tomography system, which was used as the reference system. The effect of vnAS on CHD event prediction was analyzed with data from 3,181 participants from MESA (Multi-Ethnic Study on Atherosclerosis). Chi-square analysis was used to compare CHD event rates between low (vnAS $<$100) and high calcium groups (vnAS $\geq$100). Multivariable Cox proportional hazard regression models were used to assess the incremental value of vnAS.

RESULTS For all CT systems, a strong correlation with electron beam tomography-AS was found (R^2 $>$0.932). Of the MESA participants originally in the low calcium group (n = 781), 85 (11%) participants were reclassified to a higher risk category based on the recalculated vnAS. For reclassified participants, the CHD event rate of 15% was significantly higher compared with participants in the low calcium group (7%; $P = 0.008$) with a CHD HR of 3.39 (95% CI: 1.82-6.35; $P = 0.001$).

CONCLUSIONS The authors developed a calibration tool that enables calculation of a vnAS. MESA participants who were reclassified to a higher calcium category by means of the vnAS experienced more CHD events, indicating improved risk categorization. (J Am Coll Cardiol Img 2023;16:1552–1564) © 2023 by the American College of Cardiology Foundation.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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Major coronary artery calcium (CAC) scoring outcome studies with long follow-up time have shown that computed tomography (CT) CAC measurements improve risk stratification for both coronary heart disease (CHD) and atherosclerotic cardiovascular disease (ASCVD) in asymptomatic individuals beyond traditional risk factors.[1-7] Due to its risk reclassification potential, CAC is an increasingly important tool to support the decision to initiate or defer statin therapy in individuals at low-to-intermediate risk.[8] CAC assessment is therefore recommended in both American and European guidelines, with statin therapy initiation for individuals at intermediate ASCVD risk with a CAC score of ≥100. In addition, as proposed by the National Lipid Association, intensive statin therapy for individuals with a CAC score ≥300 should be considered.[9-11] Moreover, the National Lipid Association recommends a follow-up CAC assessment, guided by ASCVD risk assessment, as a way of monitoring atherosclerotic disease and the effectiveness of current treatment decisions.[9,12]

Clinically, CAC assessment is performed according to the Agatston method.[13] This method was developed in 1990 using now obsolete electron beam tomography (EBT). A unique feature of EBT when compared with currently used multidetector CT (MDCT) systems is the high temporal resolution of approximately 50 ms. Large longitudinal cohort studies found that CAC adds incremental prognostic value to commonly known cardiovascular risk factors, including the Framingham Risk score for prediction of future cardiovascular events.[1,5-7,14] Notably, current guidelines are based on evidence derived from these studies, almost all of which used EBT scanners.[1-3,15]

Nowadays, MDCT systems are used in clinical practice. For these systems, however, it has been shown that CAC detection and quantification differs substantially not only from EBT systems, but also between different CT manufacturers, and between different CT systems from the same manufacturer, with differences in median Agatston score (AS) of up to 44%.[16,17] One potential reason for these observed differences could be the lower temporal resolution of modern MDCT systems with values ranging between 68 ms for the fastest dual-source system to up to 200 ms for previous generation wide-detector MDCT systems. Clinically, variations in AS may translate into risk misclassification and improper treatment in up to 6.5% of asymptomatic individuals.[16] Despite these variations, there are presently no tools or methods to convert MDCT-derived AS, as obtained with modern CT systems, to EBT-derived AS.

We therefore sought to: 1) develop a calibration tool for current state-of-the-art CT systems, allowing for calculation of a vendor-neutral Agatston score (vnAS), which would be equal to the AS an individual would have had if scanned on an EBT system; 2) assess whether the proposed vnAS improves event prediction for both CHD and ASCVD for participants

ABBREVIATIONS AND ACRONYMS

AS = Agatston score

ASCVD = atherosclerotic cardiovascular disease

CAC = coronary artery calcium

CHD = coronary heart disease

CT = computed tomography

EBCT = electron beam computed tomography

EBT = electron beam tomography

MDCT = multidetector computed tomography

NNT = number needed to treat

vnAS = vendor-neutral Agatston score

TABLE 1 Acquisition and Reconstruction Parameters for the Electron Beam Tomography Reference Standard and CT Systems

	Reference Standard	CT-A	CT-B	CT-C	CT-D	CT-E	CT-F	CT-G
Manufacturer	Imatron	Philips	Philips	Siemens	GE	Canon	GE	Siemens
CT system	C-150	Iqon	Brilliance iCT	SOMATOM Force	Revolution	Aquilion one	Lightspeed	Volume Zoom
Acquisition mode	Axial	Axial	Axial	Axial	Axial	Axial	Axial	Axial
Tube voltage, kVp	130	120	120	120	120	120	120	140
Tube current time product, mAs	Small: 63 Large: 63	Small: 40 Large: 48	Small: 50 Large: 60	Small: 44 Large: 194	Small: 30 Large: 161	SD = 55	Small: 106 Large: 132	Small: 50 Large: 63
AEC	Off	Off	Off	Off	Off	On	Off	Off
Collimation, mm	–	64 x 0.625	128 x 0.625	160 x 0.6	224 x 0.625	280 x 0.5	16 x 0.625	4 x 2.5
Field of view, mm	250	250	250	250	250	250	220	250
Rotation time, s	–	0.27	0.27	0.25	0.28	0.275	0.5	0.5
Slice thickness, mm	3.0	3.0	3.0	3.0	2.5	3.0	2.5	2.5
Increment, mm	3.0	3.0	3.0	1.5	2.5	3.0	2.5	2.5
Reconstruction kernel	Sharp R62	XCA	XCA	Qr36d	Standard	FC12	Standard	B35f
Matrix size, pixels	512 x 512	512 x 512	512 x 512	512 x 512	512 x 512	512 x 512	512 x 512	512 x 512
Reconstruction	FBP	iDose-level 0 (FBP)[a]	FBP	FBP	FBP	FBP	FBP	FBP

[a]For CT-A, iDose level 0 is the iterative reconstruction technique which matches FBP the closest.
AEC = automatic exposure control; CT = computed tomography; FBP = filtered back projection.

CENTRAL ILLUSTRATION Schematic of Vendor-Neutral Agatston Score Calculator

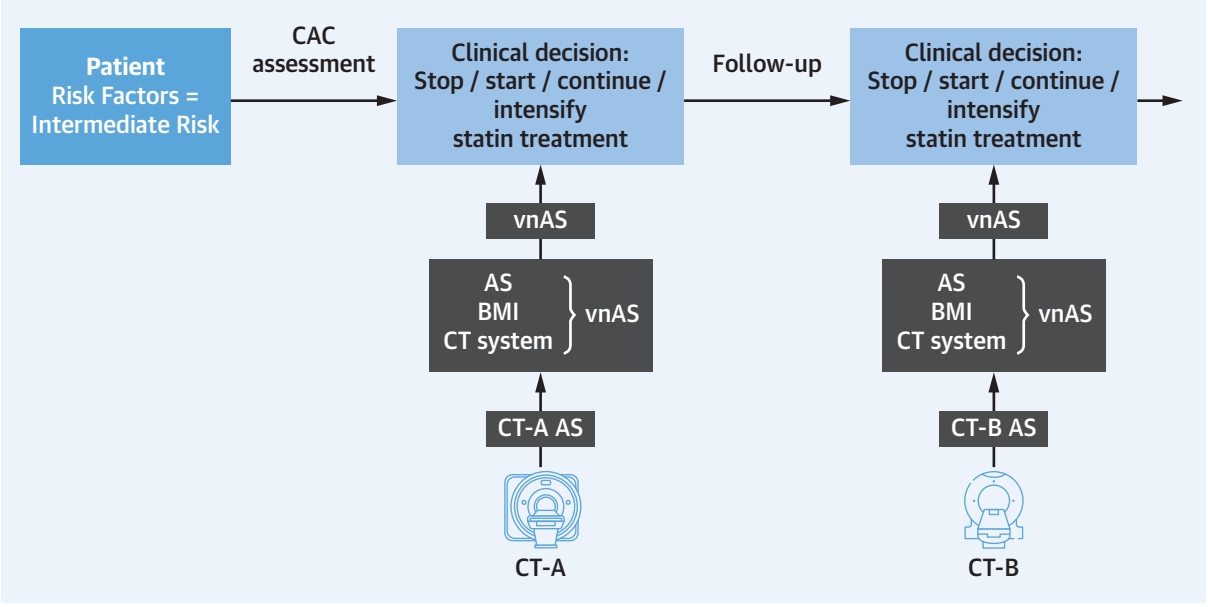

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Illustration of the use of the vendor-neutral Agatston score (vnAS) calculator, which converts a multidetector computed tomography (MDCT)-specific Agatston score (AS) (CT-A AS or CT-B AS) into a vnAS based on patient and computed tomography (CT)-specific parameters. The vnAS can subsequently be used for clinical decisions on statin treatment for patients at intermediate atherosclerotic cardiovascular disease risk, both initially and in follow-up assessments. BMI = body mass index; CAC = coronary artery calcium.

of MESA (Multi-Ethnic Study of Atherosclerosis); and 3) determine the influence of vnAS on initiation or deferral of statin therapy.

METHODS

CALIBRATION TOOL DEVELOPMENT. Phantom. The vnAS calibration tool was derived from scans of 2 static CAC containing inserts, placed at the center of an anthropomorphic chest phantom (QRM thorax; PTW). Both phantom inserts contained cylindrical calcifications composed of hydroxyapatite with a variety of sizes and densities to mimic the large variety of in vivo CAC. An extension ring was used to increase phantom size.

Data acquisition. Chest CT examinations were performed using routine clinical CAC protocols on 5 state-of-the-art MDCT systems. In addition, we acquired data on 2 older MDCT systems that were used to scan participants of the MESA (**Table 1**).[18] Reference standard acquisitions were obtained on an EBT C-150 system (Imatron).

More details about the phantom and data acquisition are listed in the Supplemental Methods.

vnAS calculator specification and processing. ASs were calculated for all CT reconstructions with vendor-specific CAC scoring parameters using a previously validated Python script, as it is well-known that CAC scores can vary somewhat between software.[19] For the EBT, vendor-specific CAC scoring software (AccuImage, Diagnostic Corporation) was used. Next, for each combination of phantom size and CT system, linear regression was used to convert the obtained AS to a vnAS for all repeated measurements. Regression

TABLE 2 Cohort 1 Group Definition for CHD and ASCVD Event Prediction Based on AS and vnAS

Group Definition	MDCT-AS	vnAS	Number of MESA Participants
0 coronary calcium	0	0	1,576
Low coronary calcium	<100	<100	696
Reclassified	<100	≥100	85
High coronary calcium	≥100	≥100	824

AS = Agatston Score; vnAS = vendor-neutral Agatston Score; MDCT = multidetector computed tomography; MESA = Multi-Ethnic Study of Atherosclerosis.

TABLE 3 Cohort 2 Group Definition for Statin Therapy Assessment Based on AS and vnAS

Group Definition	MDCT-AS	vnAS	Number of Participants	ASCVD Events, %
Group 0	0	0	374	10.7
Group 1	<100	<100	233	17.6
Reclassified group 1	<100	≥100	30	23.3
Group 2	100-299	100-299	87	27.6
Reclassified group 2	100-299	≥300	34	38.2
Group 3	≥300	≥300	131	32.8

For each group, the percentage of atherosclerotic cardiovascular (ASCVD) events is indicated.
Abbreviations as in Table 2.

model fit was assessed using both R^2 and the analysis of variance methodology. The resulting regression model was used in a calculator, where the 3 input parameters (CT system, patient size, and AS) were used to calculate the vnAS (Central Illustration). Within MESA, phantom-adjusted ASs were used to account for intersystem variation. However, in our study, we used the clinically relevant phantom-unadjusted AS, as in clinical practice phantoms are never used to unify AS. The vnAS calculator will be made publicly available.

VALIDATION STUDY: MESA POPULATION. Data sharing. Data from the MESA was requested via the MESA website[20] following a described data request procedure. MESA data were shared based on a signed data sharing agreement (denoted 21-090/C).

Study population. MESA is a multicenter, cohort (n = 6,814) study involving 6 centers (Forsyth County, North Carolina, USA; Bronx and Northern Manhattan, New York, USA; Baltimore City and County, Maryland, USA; St. Paul, Minnesota, USA; Chicago, Illinois, USA; and Los Angeles County, California, USA).[2] The rationale for the multicenter prospective, observational cohort study was to determine the underlying factors of cardiovascular diseases; the study design and methods have been previously described in detail elsewhere.[2] In brief, investigators included 6,814 asymptomatic individuals between 45 and 84 years of age. At baseline, demographic data were collected from each participant and 2 immediate subsequent

TABLE 4 Characteristics of 3,181 Individuals (Cohort 1) of the MESA Study With MDCT Scans on CT-F or CT-G, Stratified by Calcium Group

	0 Calcium (n = 1,576)	Low Calcium (n = 696)	Reclassified Individuals (n = 85)	High Calcium (n = 824)	*P* Value[a]
Age, y	58 ± 9	63 ± 9	67 ± 8	69 ± 9	<0.001
Race/ethnicity					<0.001
White	735 (46.6)	368 (52.9)	40 (47.1)	549 (66.6)	
Black	572 (36.3)	232 (33.3)	37 (43.5)	190 (23.1)	
Hispanic	269 (17.1)	96 (13.8)	8 (9.4)	85 (10.3)	
Gender					<0.001
Female	998 (63.3)	336 (48.3)	34 (40.0)	303 (36.8)	
Male	578 (36.7)	360 (51.7)	51 (60.0)	521 (63.2)	
Diabetes mellitus	142 (9.0)	86 (12.4)	20 (23.5)	135 (16.4)	<0.001
Systolic blood pressure	124 ± 21	126 ± 21	134 ± 22	134 ± 22	<0.001
Hypertension medication	500 (31.7)	283 (40.7)	45 (52.9)	421 (51.1)	<0.001
HDL	52 ± 15	49 ± 14	48 ± 13	49 ± 14	<0.001
LDL	116.4 ± 32	119 ± 32	113 ± 31	117 ± 30	0.175
Total cholesterol	194 ± 36	194 ± 37	185 ± 33	192 ± 33	0.086
Triglycerides	108 (76.0-159.0)	113.0 (80.0-162.0)	105.0 (78.0-160.0)	134.2 (77.2-166.0)	0.078
Any lipid-lowering therapy	200 (12.7)	137 (19.7)	28 (32.9)	193 (23.4)	<0.001
Cigarette smoking	244 (15.5)	696 (15.4)	7 (8.2)	116 (14.1)	0.266
Family history of heart attack	614 (39.0)	334 (48.0)	36 (42.4)	439 (53.3)	<0.001
Coronary calcium score					
vnAS	0.0	30.5 (14.1-56.7)	117.1 (105.3-126.1)	801.6 (243.0-910.1)	
MDCT-AS	0.0	22.4 (10.2-42.4)	87.2 (78.1-94.2)	619.2 (186.2-736.9)	
Risk calculators					
ASCVD risk	5.5 (2.4-11.6)	13.9 (5.7-19.6)	20.4 (11.3-25.7)	22.1 (11.3-29.3)	<0.001
Events					
CHD	54 (3.4)	49 (7.0)	13 (15.3)	152 (18.4)	<0.001
ASCVD	138 (8.8)	127 (18.2)	20 (23.5)	290 (35.2)	<0.001

Values are mean ± SD, n (%), or median (IQR), unless otherwise indicated. Reclassified individuals are those with AS <100 and vnAS ≥100. [a]Chi-square test.
ASCVD = atherosclerotic cardiovascular disease; CHD = coronary heart disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; vnAS = vendor-neutral Agatston score; other abbreviations as in Table 2.

TABLE 5 Characteristics of 889 Individuals (Cohort 2) of the MESA Study With CT Scans on CT-F or CT-G and at Intermediate Cardiovascular Risk, Stratified by Statin Therapy Group

	Group 0 (AS = 0) (n = 374)	Group 1 (AS = 1-99) (n = 233)	Reclassified Group 1 (vnAS ≥100) (n = 30)	Group 2 (AS = 100-299) (n = 87)	Reclassified Group 2 (vnAS ≥300) (n = 34)	Group 3 (AS ≥300) (n = 131)
Age, y	64 ± 7	65 ± 7	67 ± 6	67 ± 7	67 ± 7	64 ± 8
Race/Ethnicity						
White	133 (35.6)	118 (50.6)	14 (46.7)	60 (69.0)	20 (58.8)	94 (71.8)
Black	186 (49.7)	87 (37.3)	14 (46.7)	22 (25.3)	14 (41.2)	24 (18.3)
Hispanic	55 (14.7)	28 (12.0)	2 (6.7)	5 (5.7)	0 (0.0)	13 (9.9)
Gender						
Female	197 (52.7)	101 (43.3)	14 (46.7)	51 (58.6)	12 (35.3)	42 (32.1)
Male	177 (47.3)	132 (56.7)	16 (53.3)	51 (58.6)	22 (64.7)	89 (67.9)
Diabetes mellitus						
Systolic blood pressure	132.6 ± 18.4	129.3 ± 17.4	132.7 ± 19.8	126.2 ± 17.9	134.5 ± 23.2	127.6 ± 16.6
Hypertension medication	151 (40.4)	88 (37.8)	17 (56.7)	42 (48.3)	16 (47.1)	46 (35.1)
HDL	51.3 ± 15.5	49.1 ± 14.8	48.7 ± 12.1	50.3 ± 15.5	44.3 ± 11.2	49.5 ± 13.4
LDL	121 ± 26	121 ± 27	110.3 ± 23.8	120.5 ± 27.1	120.1 ± 23.1	120.9 ± 26.5
Total cholesterol	198.5 ± 30.1	195.8 ± 31.8	179.3 ± 27.3	194.1 ± 27.8	194.5 ± 27.4	196.7 ± 28.3
Triglycerides	112.0 (83.0-158.2)	112.0 (79.0-161.0)	91.0 (67.5-114.7)	102.0 (68.0-143.0)	122.5 (77.7-201.2)	116.0 (84.0-162.0)
Any lipid-lowering therapy	65 (17.4)	37 (15.9)	9 (30.0)	22 (25.3)	7 (20.6)	35 (26.7)
Cigarettes smoking	74 (19.8)	41 (17.6)	2 (6.7)	7 (8.0)	9 (26.5)	18 (13.7)
Family history of heart attack	145 (38.8)	112 (48.1)	17 (56.7)	48 (55.2)	15 (44.1)	75 (57.3)
Coronary calcium score						
vnAS	0.0	39.5 (14.7-64.7)	117.1 (110.2-127.1)	198.6 (160.4-239.4)	338.9 (322.6-368.5)	825.1 (533.3-1,586.8)
MDCT-AS	0.0	30.2 (10.3-49.3)	87.2 (81.8-94.9)	154.2 (128.9-181.5)	253.5 (241.0-274.1)	674.1 (413.9-1,263.3)
ASCVD risk						
Risk calculators	11.1 ± 3.3	12.5 ± 3.5	14.1 ± 3.8	12.7 ± 3.7	13.8 ± 3.3	14.1 ± 3.3
Events	13 (3.5)	17 (7.3)	3 (10.0)	15 (17.2)	8 (23.5)	20 (15.3)
CHD	40 (10.7)	41 (17.6)	7 (23.3)	24 (27.6)	13 (38.2)	43 (32.8)
ASCVD	374	233	30	87	34	131

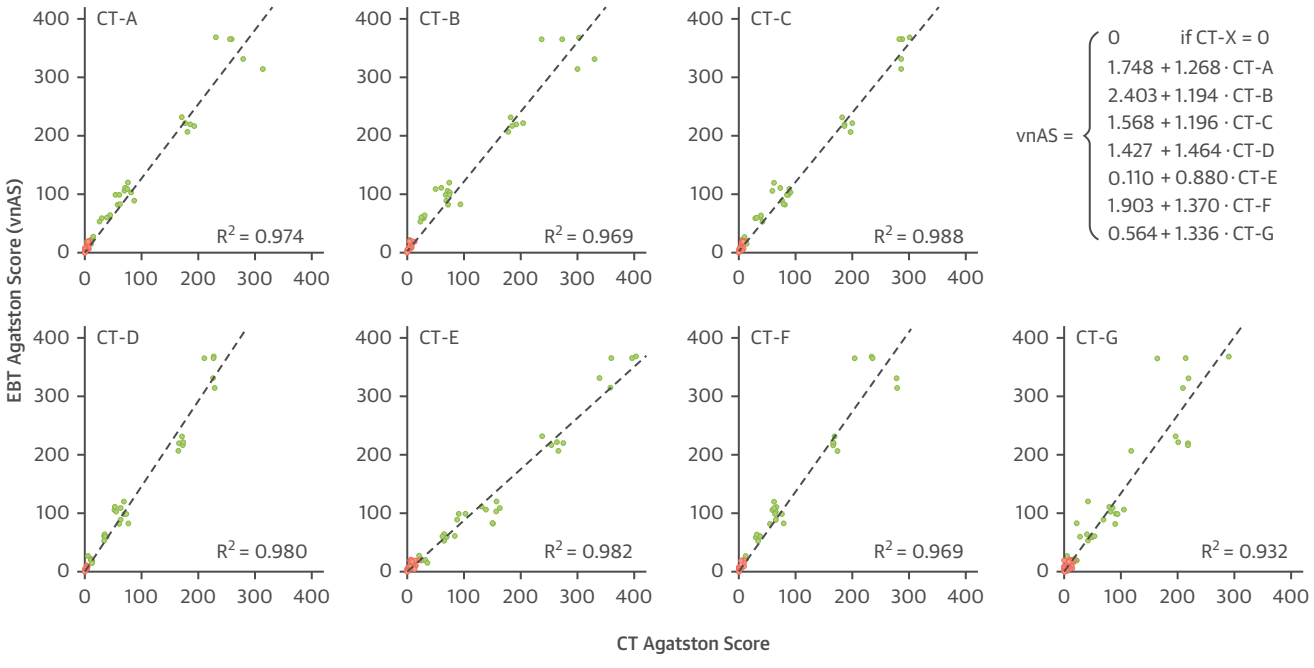
Values are mean ± SD, n (%), or median (IQR), unless otherwise indicated.
Abbreviations as in Tables 1 and 4.

CT scans were performed. Institutional review boards at each of the 6 centers approved the study protocols, and all subjects undergoing examinations provided written informed consent.

Findings presented in the current analysis represent both baseline data as collected between July 2000 and September 2002, and follow-up information about CHD and ASCVD events from follow-up contacts every 9 to 12 months from 2000 through December 2018. CHD events were defined as myocardial infarction, resuscitated cardiac arrest, fatal CHD, or revascularization. ASCVD events were defined as nonfatal or fatal myocardial infarction, resuscitated cardiac arrest, probable angina, definite angina followed by revascularization, nonfatal or fatal stroke, other atherosclerotic death, or other cardiovascular death.[5] Within MESA, participants were scanned on several CT systems, including CT-F and CT-G. Participants who were not scanned on either of these 2 systems were excluded from the current study. We were unable to acquire phantom data for other CT systems used in the MESA study because those systems were no longer operational. Also, subjects for whom follow-up or risk factor data were missing were excluded, which resulted in a total of 3,181 (1,077 and 2,152 on CT-F and CT-G, respectively) included individuals for the current analysis on CHD and ASCVD event prediction in cohort 1 (Supplemental Figure 1). To assess the influence of vnAS on the initiation or deferral of statin therapy, a subcohort of participants who were at intermediate cardiovascular risk was formed.[9,11] For this cohort 2, 889 individuals were included (Supplemental Figure 1).[9,11] Intermediate cardiovascular risk was defined as individuals with an ASCVD risk between 7.5% and 19.9 %, without diabetes, low-density lipoprotein cholesterol 70 to 189 mg/dL, and without previous ASCVD events.[10,11,21]

vnAS CALCULATION. For all included MESA participants, a vnAS was calculated based on the patient size specific regression models from either CT-F or CT-G, as appropriate. A body mass index cutoff value of 25 kg/m^2 was used to differentiate between average and large-sized participants.

FIGURE 1 Large Phantom Conversion Factors



Large phantom multidetector computed tomography (MDCT)-specific Agatston scores (AS) vs electron beam tomography (EBT) AS for both the CCI (light-gray) and D100 (dark gray) insert. For each combination of MDCT system and EBT, the coefficient of determination (R^2) and linear regression model parameters are indicated. CT-X refers to the AS of any computed tomography (CT), CT-A is the AS of CT-A, and so on. The dashed line shows the linear regression model which is used to calculate the vendor-neutral Agatston score (vnAS).

COHORT 1: ASSOCIATIONS WITH CHD AND ASCVD EVENTS. Based on baseline MDCT-AS, participants from cohort 1 (n = 3,181) were assigned to 0, low, or high coronary calcium groups, defined as MDCT-AS = 0, MDCT-AS 1-99, or MDCT-AS ≥100, respectively (Table 2). Participants with MDCT-AS 1-99 but vnAS ≥100 were considered reclassified individuals (Table 2). For all 4 groups (0, low, high, reclassified) CHD and ASCVD event rates were compared.

COHORT 2: POTENTIAL BENEFIT OF STATIN THERAPY. In addition to studying event rates, the potential benefit from statin therapy was assessed for MESA participants at intermediate cardiovascular risk (cohort 2, n = 889). The impact of using the vnAS was quantitatively expressed as change in the number needed to treat (NNT).

To calculate the NNT, cohort 2 was divided into 4 groups based on 3 thresholds: MDCT-AS = 0, MDCT-AS ≥100 for statin therapy initiation, or MDCT-AS ≥300 for intensive statin therapy initiation (Table 3).[4,9] The resulting groups were MDCT-AS = 0, MDCT-AS 1-99, MDCT-AS ≥100, and MDCT-AS ≥300, which were designated group 0 to 3, respectively (Supplemental Figure 1, Table 3). Based on vnAS, 2 additional groups were formed: reclassified group 1 with MDCT-AS 1-99 but vnAS ≥100, and reclassified group 2 with MDCT-AS <300 but vnAS ≥300 (Supplemental Figure 1, Table 3).

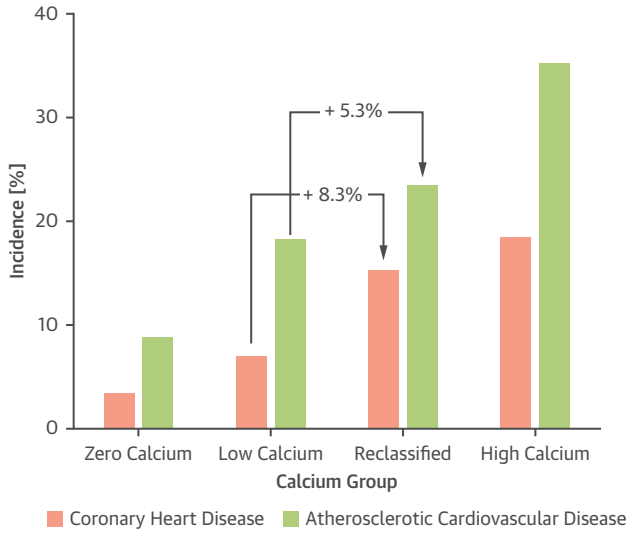
STATISTICAL ANALYSIS. Study population characteristics were stratified according to calcium score groups (Table 4) and statin therapy group (Table 5) for cohorts 1 and 2, respectively. For continuous variables, either mean ± SD or median (IQR) were calculated. Normality was visually assessed based on histograms and Q-Q plots. To compare variables between groups, chi-square test, Kruskal-Wallis test, and 1-way analysis of variance were used, as appropriate.

TABLE 6 Example vnASs for an MDCT-AS of 100 for Both Small (BMI <25 kg/m²) and Large (BMI ≥25 kg/m²) Patients

Patient Size	CT-A	CT-B	CT-C	CT-D	CT-E	CT-F	CT-G
Small	105	107	94	112	93	120	102
Large	129	122	121	148	88	139	123

BMI = body mass index; other abbreviations as in Tables 1 and 4.

FIGURE 2 CHD and ASCVD Event Rates



Coronary heart disease (CHD) and atherosclerotic cardiovascular disease (ASCVD) event rates during 18 years of follow-up as per recommended by the European Society of Cardiology and American College of Cardiology for all calcium groups: 0 calcium (AS = 0), low calcium (AS = 1-99, vnAS = 1-99), reclassified individuals (MDCT-AS = 1-99; vnAS ≥100), high calcium group (AS ≥300). Reclassified individuals experienced more CHD (+8.3%; $P = 0.008$) and ASCVD (+5.3%; $P = 0.24$) events in comparison with the baseline low calcium group. Abbreviations as in Figure 1.

Differences in both CHD and ASCVD events among the 4 coronary calcium groups were assessed with Kaplan-Meier curves and log-rank tests. The association of age, race, gender, systolic blood pressure, antihypertensive medication, high-density lipoprotein, total cholesterol, lipid-lowering medication, cigarette smoking status, diabetes, and coronary calcium group (0, low, reclassified individuals, high) with first-ever CHD or ASCVD event was assessed using univariable Cox proportional hazard regressions models. Only the first CHD or ASCVD event was included, within 18 years of follow-up data. Next, all parameters were simultaneously used for a multivariable Cox proportional hazard regression model.

All statistical analyses were conducted using SPSS 27 (IBM) or MedCalc 15.8 (MedCalc Software). Statistical significance was defined as $P < 0.05$.

RESULTS

DERIVATION OF vnAS: PHANTOM STUDY. Irrespective of the MDCT system, a high degree of correlation with EBT-derived AS was found (R^2 ≥0.932) for both the small and large phantoms, respectively (Supplemental Figure 2, Figure 1). For all MDCT systems, the linear regression models, which predicted EBT-AS, were statistically significantly (all $P < 0.001$). These prediction models, or vnAS, convert MDCT-AS to AS acquired on EBT. For the small phantom size, vnASs were lower than noncorrected AS for CT-C and CT-E, whereas for the large phantom size, only CT-E showed lower vnAS than AS.

For example, for a patient with a body mass index >25 kg/m^2 and an MDCT-derived AS of 100, the vnAS varied between 88 and 148 depending on the specific CT system that was used (Table 6). For patients with an AS of 0, vnAS was always 0.

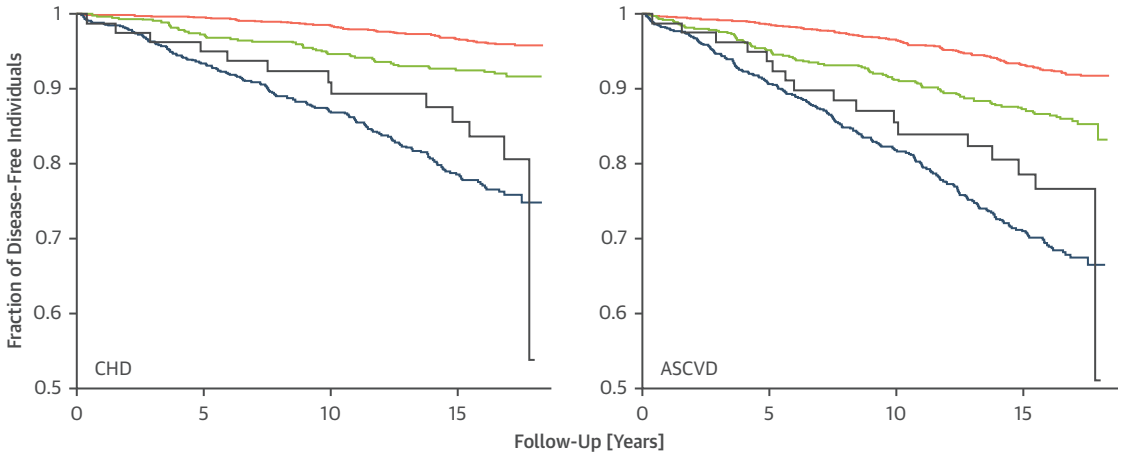
VALIDATION STUDY: MESA PARTICIPANTS. Cohort 1: Associations with CHD and ASCVD events. The mean age of cohort 1 participants (n = 3,181) was 62 ± 10 years, 52.5% were women, and 46.8% of participants were of non-Caucasian ethnicity (Table 4). For both CT-F and CT-G, vnAS was higher than AS, with increases of up to 39%. This resulted in a total of 85 (85/[696 + 85] = 11%) reclassified individuals, who were reclassified from the low to the high coronary calcium group (Table 2).

Of the reclassified individuals, 13 (13 of 85 = 15.3%) and 20 (20 of 85 = 23.5%) experienced a CHD or ASCVD event during 16.7 (IQR: 4.8) years of follow-up (Figure 2). In comparison with the low coronary calcium group, reclassified individuals' event rate was 8.3% ($P = 0.008$) higher for CHD and 5.3% ($P = 0.24$) higher for ASCVD. This was also reflected in the Kaplan-Meier curves, which confirmed substantial differences in CHD event rates between the reclassified and low calcium groups ($P = 0.004$), whereas there was no substantial difference in event rate between the reclassified individuals and the high coronary calcium group ($P = 0.319$) (Figure 3). For ASCVD, the opposite was true, with nonsignificant differences between reclassified individuals and the low coronary calcium group ($P = 0.116$), but significant differences between reclassified individuals and the high coronary calcium group ($P = 0.025$).

Based on multivariable Cox regression, the HR of CHD for reclassified individuals was 3.39 (95% CI: 1.82-6.35; $P = 0.001$) (Figure 4, Table 7). The HR of ASCVD for reclassified individuals was 1.97 (95% CI: 1.22-3.18) (Supplemental Figure 3, Supplemental Table 1). The univariable Cox regression is depicted in Supplemental Table 2.

Cohort 2: Potential benefit of statin therapy. The mean age of cohort 2 participants (n = 889) was 64 ± 7 years, 47% were women, and 51% of participants were of non-White ethnicity (Table 5). The vnAS calculation increased AS for the used CT systems,

FIGURE 3 CHD and ASCVD Kaplan-Meier Survival Estimates



Number at Risk For Years of Follow Up

Calcium Group	Coronary Heart Disease 0	5	10	15	Cardiovascular Disease 0	5	10	15
Zero	1,576	1,479	1,352	1,164	1,576	1,464	1,328	1,127
Low	696	632	552	460	696	612	525	429
Reclassified	85	75	61	44	85	71	54	38
High	824	691	539	348	824	639	471	406

Zero Calcium Group — Low Calcium Group — Reclassified Individuals — High Calcium Group

Kaplan-Meier survival estimates (fraction of disease-free ranging from 0.5 to 1.0) for all coronary calcium groups, for both CHD (upper left) and ASCVD (upper right). Total number of participants at risk are indicated in the table (bottom) for each coronary calcium group for 0, 5, 10, and 15 years of follow-up. Abbreviations as in Figure 2.

which resulted in 30 (30 of 263 = 11%) and 34 (34 of 121 = 28%) reclassified individuals from the baseline groups 1 and 2 into reclassified groups 1 and 2, respectively (Table 3). For reclassified groups 1 and 2, ASCVD event rates were 5.7% and 10.6% higher, respectively (Table 3).

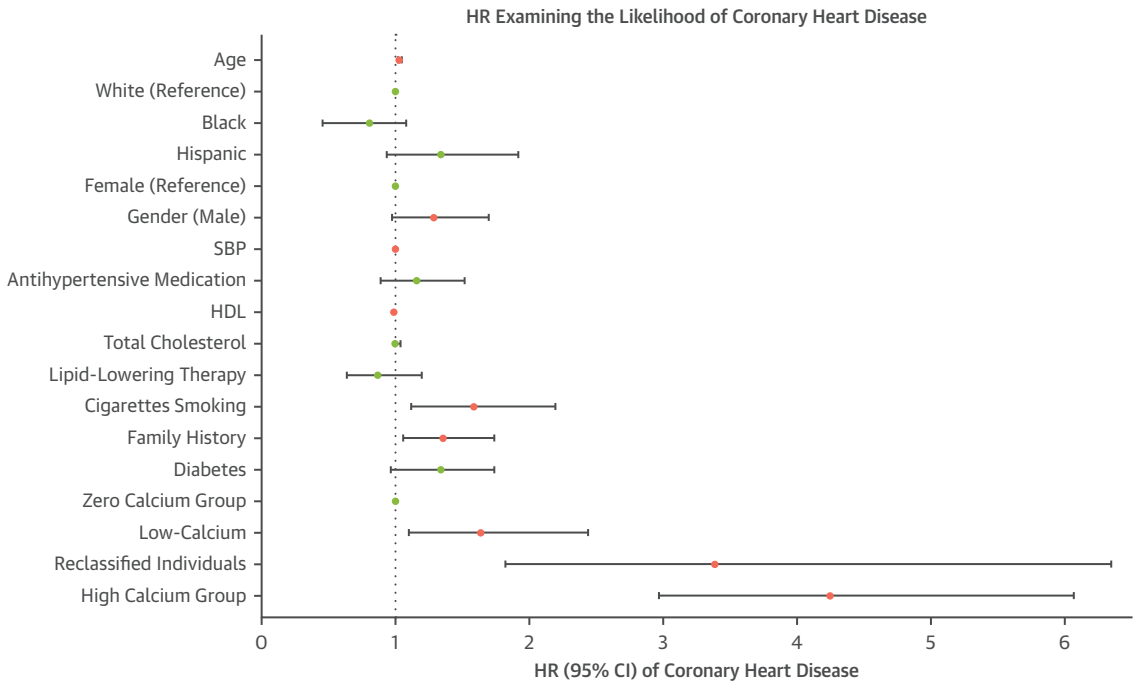
In comparison with their baseline group, the statin therapy NNT reduced from 12 to 7 and from 15 to 2 for reclassified groups 1 and 2, respectively (Figure 5). As a result of limited sample sizes, these differences were nonsignificant.

DISCUSSION

There is substantial variation in AS between different modern MDCT scanners. We developed a calibration tool that allows for calculation of a vnAS. Based on the proposed vnAS, a substantial proportion of MESA participants were reclassified from a low to a high calcium group and a significantly higher proportion of these subjects experienced CHD and ASCVD events when compared with nonreclassified participants. This indicates that vnAS provides an improved risk categorization compared with AS. Moreover, the proposed vnAS can also reduce the NNT of patients at intermediate ASCVD risk assigned to AS-based initiation of or intensification of statin therapy according to current guidelines. Therefore, our proposed vendor-neutral CAC assessment may improve patient risk classification and subsequent patient management.

This study showed large differences in AS between different CT manufacturers, but also between different CT systems from the same manufacturer. To place the variability in AS between different systems and vendors in perspective, it is important to consider the interscan variability for EBT. Achenbach et al[22] previously found that scan-rescan repeatability with EBT is 5.7%, which is significantly lower compared with the reclassification rate we found. It is therefore reasonable to conclude that differences in AS obtained with different modern MDCT scanners do matter. To overcome these differences between MDCT systems we created a vendor-neutral calibration tool, which converts the vendor-specific AS to the gold-standard EBT-AS. This calibration tool has

FIGURE 4 Cox Regression Model for CHD Events



Summary of the Cox regression model for the prediction of CHD events. The red dots depict a significant association between a variable and an event. HDL = high-density lipoprotein; SBP = systolic blood pressure; other abbreviation as in Figure 2.

been validated in large, long-term follow-up cohorts. Since the introduction of the EBT-derived AS in 1990, CT technology has dramatically changed. Despite the present-day use of advanced MDCT systems in clinical practice, current clinical guidelines and risk calculators are based on studies that almost exclusively used EBT systems to study the relation between the presence and amount of coronary calcium and subsequent cardiovascular events. This approach was correct from a methodological point of view, with EBT serving as the gold standard. However, it does not reflect current clinical practice.

Other studies also assessed the vendor dependency of AS, with contradictory findings. Mao et al[17] showed that the difference between EBT-AS and MDCT-AS was approximately 8.3% for 102 patients and was considered clinically insignificant. In addition, Ghadri et al[23] showed that there were no substantial differences in CAC scores acquired on single-source and dual-source CT scanners. Importantly, neither of these studies included information about patients' follow-up. On the other hand, in a study performed by Willemink and colleagues,[16] it was shown that differences in AS acquired with scanners from different vendors resulted in risk category reclassifications in up to 6.5% of individuals. This is in agreement with our phantom analysis, in which we compared EBT with both older and state-of-the-art MDCT systems, and showed underestimations of AS up to 48% on CT with respect to EBT. Importantly, in our study we were able to use the exact same phantom setup for both EBT and MDCT, which allowed for a direct AS comparison.

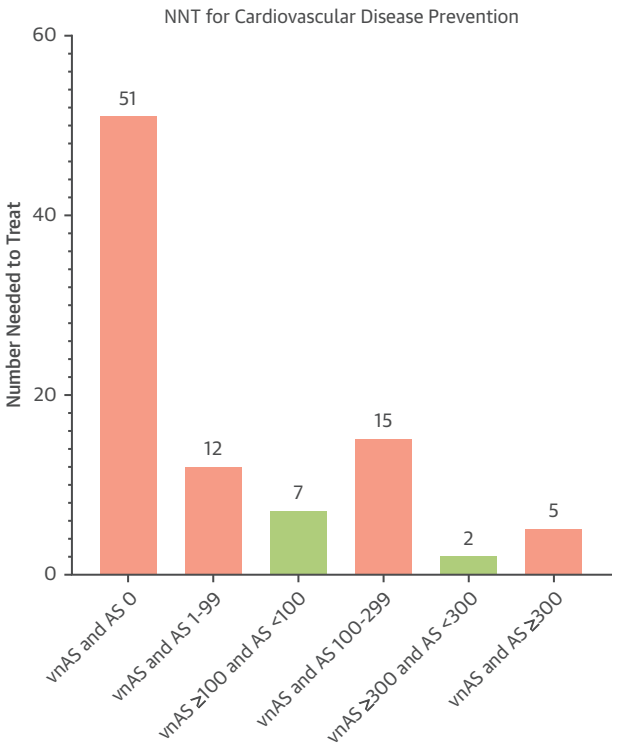
Currently used American Heart Association (AHA)/American College of Cardiology (ACC) and European Society of Cardiology (ESC) guidelines, in addition to other risk factors, apply an AS threshold of 100 for consideration of pharmacological treatment.[9-11] Therefore, to assess whether the vnAS outperforms AS for risk classifications, we also applied this presently used AS threshold of 100. With this threshold, 85 (11%) MESA participants were reclassified from the low to the high calcium group. Of these reclassified individuals, 15.3% and 23.5% experienced a CHD or ASCVD event, respectively. This was equal to the difference of 8.3% and 5.3% between the low calcium group and reclassified individuals, respectively, to which they were originally assigned based on the vendor-specific AS. The significantly improved prediction of events was only found to apply to CHD, but not to ASCVD events. The HR of CHD was higher for

TABLE 7 HR (95% CI) Examining the Likelihood of Coronary Heart Disease

	HR (95% CI)	*P* Value
Race		
White	Ref.	
Black	1.08 (0.81-1.46)	0.586
Hispanic	1.34 (0.94-1.92)	0.110
Sex		
Female	Ref.	
Male	1.29 (0.98-1.70)	0.077
Age	1.03 (1.02.-1.05)	<0.001
Antihypertensive medication		
Yes	1.16 (0.89-1.52)	0.249
Systolic blood pressure	1.01 (1.01-1.02)	<0.001
HDL	0.99 (0.98-0.99)	0.014
Total cholesterol	1.00 (0.99-1.04)	0.954
Lipid-lowering therapy		
Yes	0.87 (0.64-1.20)	0.385
Cigarette smoking		
Yes	1.59 (1.12-2.20)	0.008
Family history		
Yes	1.36 (1.06-1.74)	0.014
Diabetes		
Yes	1.34 (0.97-1.84)	0.074
Coronary calcium group		
0 calcium	Ref.	
Low calcium	1.64 (1.10-2.44)	0.014
Reclassified individuals	3.39 (1.82-6.35)	<0.001
High calcium	4.25 (2.97-6.07)	<0.001

The proportional multivariable Cox regression was adjusted for all variables.
HDL = high-density lipoprotein; Ref. = Reference.

FIGURE 5 Benefit of Statins in Primary Prevention



The estimated benefit of statins in primary prevention by AS and vnAS in intermediate risk group individuals from MESA (Multi-Ethnic Study on Atherosclerosis). The ASCVD risk was calculated based on a 10-year risk calculator. The 16-year number needed to treat (NNT) shows that in reclassified groups, the NNT was lower as compared with baseline groups. Blue bars indicate NNT in nonreclassified subjects. Red bars indicate NNT in reclassified individuals. Abbreviations as in Figure 1.

reclassified individuals in comparison with individuals from the low calcium group. For ASCVD events, this was less pronounced. The stronger association of vnAS with CHD in comparison with ASCVD might be explained by the fact that coronary calcium directly reflects atherosclerotic processes within coronary arteries. Therefore, the association of vnAS with CHD in a relatively small sample will be more pronounced. This stronger association of CAC with CHD than with ASCVD was previously shown by Folsom et al.[24] Importantly, as the mean age of reclassified individuals was 67, this difference may have long-term consequences.

Independent studies found that CAC quantification improved risk classification of asymptomatic individuals at risk by 14% to 30%.[14] Therefore, the AHA recommends CAC measurement in asymptomatic individuals at intermediate ASCVD risk to plan lipid-lowering therapy.[11] To investigate the influence of vnAS on statin therapy, we used a subcohort of MESA participants who met the criteria of intermediate ASCVD risk group patients.[9,11] As indicated by current AHA/ACC and ESC guidelines, initiation of statin therapy is recommended in individuals with AS >100. In addition, the National Lipid Association recommends an intensive statin therapy for those with AS >300.[9-11] In our sample, 30 (11%) participants were reclassified from the nonstatin therapy group into the statin therapy group, and 34 (28%) participants were reclassified from the statin therapy group to the intensive statin therapy group. The NNT for both reclassified groups was lower when compared with the groups to which they were classified based on MDCT-AS. This further indicates that for reclassified individuals, (intensive) statin therapy would be more efficient. Therefore, vnAS might be a valuable tool allowing for more appropriate treatment decision making for patients at intermediate ASCVD risk.

As underlined in ACC/AHA and ESC guidelines, CAC is a useful tool when the decision about statin therapy is uncertain.[11,25,26] Hence, the vnAS should be applied only in patients who are already referred

for a CAC scoring scan. Therefore, our calibration tool does not change the management of patients who have already been on statin therapy, experienced ASCVD event in the past, or suffer from diabetes mellitus. Moreover, for the AS of 0 the vnAS remains 0, and therefore it does not affect this group of patients.

CAC evaluation is not only important for initial risk stratification, but also in follow-up analysis, as indicated by Lehmann and colleagues,[12] who showed that CAC progression was more pronounced in patients with CHD events than in those without events. Patients with baseline and follow-up AS below 400 had 9.1% risk of ASCVD events within 10 years, while for those with baseline AS below 400 but follow-up AS exceeding 400, the ASCVD risk was 19.1%. These results prompted the National Lipid Association to recommend repeated CAC measurements depending on ASCVD risk.[9] However, in the previously mentioned study by Lehmann et al,[12] both scans were performed on the same EBT system. In clinical practice, it is almost impossible to scan a patient every time on the same CT scanner. Knowing that the AS might differ up to 48% between different vendors, the importance of being able to calculate a vnAS for a follow-up scoring is self-evident.

Importantly, to derive an approximate unified AS between different CT scanners, including electron beam computed tomography (EBCT) scanners, which were used in half of the centers participating in MESA, results published by MESA were phantom-calibrated.[2] However, in everyday clinical practice, calibrated ASs are not obtained. Therefore, to best reflect current clinical practice, we applied uncalibrated CAC scores to validate the proposed vnAS. What needs to be underlined is the high temporal resolution of EBCT, which is only approximated by the latest-generation dual-source CT scanners, which constitute just a small minority of currently used MDCT systems. Approximately 90% of medical centers worldwide depend on CT scanners, which have a much lower temporal resolution compared with EBCT.[27] Furthermore, these older scanners are likely to be situated in middle to lower income countries which are disproportionately affected by a much higher cardiovascular disease burden. Therefore, our proposed calibration factor is a low cost and easy to implement refinement toward achieving a unified AS, where it is needed most.

We would like to underscore that our goal was not to develop a new calcium scoring method, but to provide a method that enables clinicians to calculate a vnAS that closely reflects the EBCT calcium score, based on which current guidelines and risk calculators have been created. This approach can be implemented easily in existing workflows and leverages the strengths of the well-validated AS, while simultaneously helping to further improve patients' risk classification.

STUDY LIMITATIONS. First, our vnAS is based on static anthropomorphic phantom scans only. Although the linear attenuation coefficients of the phantoms were in line with human materials, a phantom does not completely simulate an actual human, with all internal organs, patient-specific variations, or coronary artery motion. Further, large-scale, in vivo validation of the vnAS is recommended in advance of widespread clinical acceptance. Second, for the vnAS validation we used older MDCT systems, as these were used to scan participants of the MESA. Other cohort studies that both used state-of-the-art MDCT and had long-term follow-up are not available yet. This is, of course, also true for state-of-the-art CT techniques such as photon-counting CT, which exhibits a phenomenal increase in spatial resolution that might greatly influence CAC assessment.[28] However, the MESA cohort used in our study did use 2 MDCT systems from different manufacturers. Third, as a consequence of 50% of participants exhibiting a 0 calcium score, the absolute number of 85 reclassified MESA participants was relatively small and constituted 2.7% of all subjects in the first cohort. On the other hand, these patients constituted 11% of the low-risk individuals group. In addition to the large and rising number of CT CAC assessments, this reclassification percentage is clinically relevant. Fourth, applying cutoff values for validation of vnAS, which is a continuous variable, might be questionable. Nevertheless, although different guidelines differ on the exact clinical approach, professional societies such as AHA, ACC, ESC, and Society of Cardiovascular Computed Tomography base their treatment advice on clearly defined CAC cutoff values.

CONCLUSIONS

We developed a calibration tool that enables calculation of a vnAS that was validated in the MESA cohort. Based on the vnAS, reclassified individuals experienced more CHD events in comparison with the baseline group. Moreover, the NNT for statin therapy was reduced by using vnAS for MESA participants at intermediate cardiovascular risk. Therefore, our calibration tool for modern CT systems, if applied in daily clinical practice, may improve patient management and outcome. We believe that vnAS, which reflects EBT-derived AS,

might be easily applied in daily clinical practice when reporting calcium scores.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The vnAS reduces calcium scoring variability and improves patient risk stratification.

TRANSLATIONAL OUTLOOK: Despite promising results for the vnAS, older MDCT systems were used to scan participants of the MESA. Therefore, other cohort studies that use state-of-the-art MDCT and have long-term follow-up data should verify our results.

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KEY WORDS Agatston score, atherosclerotic cardiovascular disease, coronary artery calcification, coronary heart disease, phantoms, statins

APPENDIX For an expanded Methods section as well as supplemental figures and tables, please see the online version of this paper.