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Predictive Value of Age- and Sex-Specific Nomograms of Global Plaque Burden on Coronary Computed Tomography Angiography for Major Cardiac Events

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Background—Age-adjusted coronary artery disease (CAD) burden identified on coronary computed tomography angiography predicts major adverse cardiovascular event (MACE) risk; however, it seldom contributes to clinical decision making because of a lack of nomographic data. We aimed to develop clinically pragmatic age- and sex-specific nomograms of CAD burden using coronary computed tomography angiography and to validate their prognostic use.

Methods and Results—Patients prospectively enrolled in phase I of the CONFIRM registry (Coronary CT Angiography Evaluation for Clinical Outcomes) were included (derivation cohort: n=21,132; 46% female) to develop CAD nomograms based on age–sex percentiles of segment involvement score (SIS) at each year of life (40–79 years). The relationship between SIS age–sex percentiles (SIS%) and MACE (all-cause death, myocardial infarction, unstable angina, and late revascularization) was tested in a nonoverlapping validation cohort (phase II, CONFIRM registry; n=3030, 44% female) by stratifying patients into 3 SIS% groups (≤50th, 51–75th, and >75th) and comparing annualized MACE rates and time to MACE using multivariable Cox proportional hazards models adjusting for Framingham risk and chest pain typicality. Age–sex percentiles were well fitted to second-order polynomial curves (men: R^2=0.86±0.12; women: R^2=0.86±0.14). Using the nomograms, there were 1576, 965, and 489 patients, respectively, in the ≤50th, 51–75th, and >75th SIS% groups. Annualized event rates were higher among patients with greater CAD burden (2.1% [95% confidence interval: 1.7%–2.7%], 3.9% [95% confidence interval: 3.0%–5.1%], and 7.2% [95% confidence interval: 5.4%–9.6%] in ≤50th, 51–75th, and >75th SIS% groups, respectively; P<0.001). Adjusted MACE risk was significantly increased among patients in SIS% groups above the median compared with patients below the median (hazard ratio [95% confidence interval]: 1.9 [1.3–2.8] for 51–75th SIS% group and 3.4 [2.3–5.0] for >75th SIS% group; P<0.01 for both).

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Conclusions—We have developed clinically pragmatic age- and sex-specific nomograms of CAD prevalence using coronary computed tomography angiography findings. Global plaque burden measured using SIS% is predictive of cardiac events independent of traditional risk assessment.

Clinical Trial Registration—URL: https://www.clinicaltrials.gov. Unique identifier: NCT01443637.

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Key Words: computed tomography angiography ■ coronary artery disease ■ coronary angiography ■ epidemiology ■ nomograms

Coronary heart disease (CHD) remains to be a leading cause of morbidity and mortality in developed countries.[1] Its prevalence increases with age, which is a significant driver of absolute CHD event risk irrespective of coexisting conventional cardiac risk factors.[2] Although age is important for absolute risk stratification, measures of coronary atherosclerotic burden that are adjusted for age and sex such as that provided by quantified coronary artery calcium scoring (CACS) are predictive of increased relative risk of CHD-related events.[3,4]

See Editorial by Raggi and Alexopoulos
See Clinical Perspective

Coronary computed tomography angiography (CCTA) also has proven utility in the prediction of future CHD events beyond traditional risk factor assessment and across a range of age groups and patient populations.[5–8] Unlike CACS, the focus with CCTA has been on identifying obstructive coronary artery disease (CAD) not only as a marker of risk but also because of its association with myocardial ischemia, symptoms, and as an indicator for the potential need for invasive angiographic assessment. Quantifying the overall atherosclerotic disease burden may also be important; however, with a recent study showing that plaque extent quantified by CCTA provides additive risk prediction for cardiac events in a model integrating both clinical risk assessment and the presence and severity of CAD.[9] Moreover, there is growing evidence that the burden of nonobstructive CAD identified on CCTA[10] or conventional angiography[11] is also associated with increased risk of CHD events and mortality. A measure of global plaque burden from CCTA has been described: the segment involvement score (SIS) and has been shown to predict adverse outcomes.[6] Despite this, the assessment of the overall burden of CAD often has minimal impact on clinical decision making because of lack of a clinically pragmatic tool for integrating it into clinical practice. Nomographic data documenting the age- and sex-specific extent of CAD observed among patients presenting for CCTA present such a tool.

We accordingly performed a study with 3 aims; first, to develop age- and sex-specific nomograms of SIS percentiles (SIS%) using CCTA data in a derivation cohort; second, to assess the relationship between SIS% and major adverse cardiovascular events (MACE); and third, to test the relationship between SIS% from the derivation cohort and observed events in a validation cohort.

Methods

Patient Population

Two study populations were identified from nonoverlapping phase I (derivation) and phase II (validation) cohorts of the CONFIRM registry (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter). The rationale and methods of the CONFIRM registry have been previously described.[12] Study approval from the local ethics committee or institutional review board was obtained by the site principal investigator when required.

The present analysis involved 2 components: first, CCTA data from the derivation cohort were used to develop sex-specific nomograms based on SIS (defined below) by age percentiles and analyzed in relation to MACE risk at medium-term follow-up (≈2 years); second, the nomograms were validated by assessing observed MACE rates in the validation cohort based on SIS% assigned by cross-referencing individual patient age, sex, and SIS values to the corresponding percentile on the derived nomograms.

Derivation Cohort

Phase I of the CONFIRM trial prospectively enrolled 27 125 consecutive patients aged >18 years, and undergoing clinically indicated

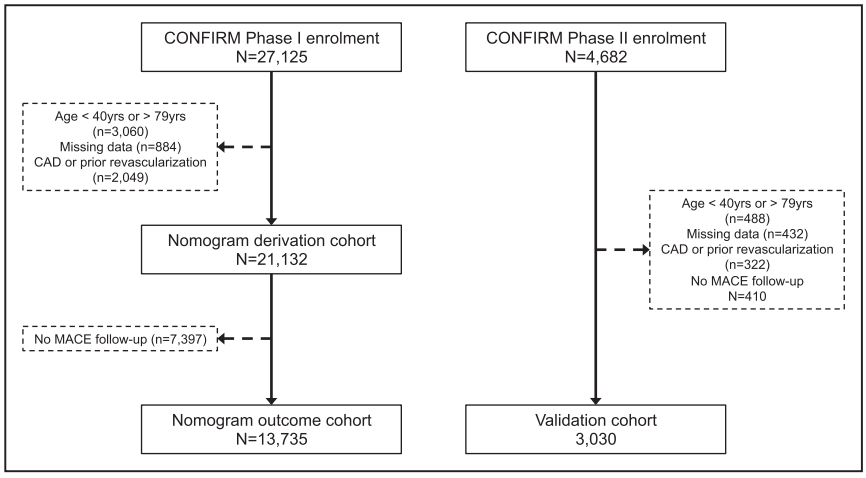

Figure 1. Study flow chart demonstrating populations comprising the derivation and validation cohorts. CAD indicates coronary artery disease; CONFIRM, Coronary CT Angiography Evaluation for Clinical Outcomes; and MACE, major adverse cardiovascular event.

Table 1. Clinical Characteristics of the Nomogram Derivation Cohort

Demographics	All Patients N=21 132*	10-Year Age Group 40–49 y N=4485	50–59 y N=6755	60–69 y N=6670	70–79 y N=3222	*P* Value†
Age, y	58.5±9.8	45.1±2.8	54.6±2.9	64.3±2.8	73.7±2.8	<0.001 (<0.001)
Female sex, no. (%)	9714 (46)	1779 (40)	3009 (45)	3209 (48)	1717 (53)	<0.001 (<0.001)
Body mass index, kg/m^2	27.3±5.2	27.9±5.5	27.6±5.4	27.2±5.0	26.7±4.5	<0.001 (<0.001)
Cardiac risk factors						
Diabetes mellitus	3230 (15)	459 (10)	951 (14)	1221 (18)	599 (19)	<0.001 (<0.001)
Hypertension	10 581 (51)	1742 (39)	3180 (48)	3642 (55)	2017 (63)	<0.001 (<0.001)
Dyslipidemia	11 873 (57)	2004 (45)	3810 (57)	4104 (62)	1955 (61)	<0.001 (<0.001)
Current smoker	3671 (17)	1135 (25)	1263 (19)	945 (14)	328 (10)	<0.001 (<0.001)
Chest pain typicality						
Typical angina	2755 (15)	585 (15)	832 (14)	837 (14)	501 (19)	<0.001 (<0.001)
Atypical angina	7272 (39)	1797 (45)	2440 (41)	2141 (37)	894 (33)	<0.001 (<0.001)
Noncardiac	2097 (11)	496 (12)	602 (10)	639 (11)	360 (13)	<0.001 (0.22)
Asymptomatic	6417 (35)	1157 (29)	2131 (35)	2177 (38)	952 (35)	<0.001 (<0.001)
					Overall	<0.001 (<0.001)
Framingham risk score						
Risk score, mean±SD	13.4±9.8	7.2±4.6	11.9±6.8	16.6±9.7	18.8±14.1	<0.001 (<0.001)
Risk category, no. (%)						
<10%	9672 (46)	3592 (81)	3255 (49)	1725 (26)	1100 (34)	<0.001 (<0.001)
10%–20%	7386 (35)	735 (17)	2638 (40)	3043 (46)	970 (30)	<0.001 (<0.001)
>20%	3849 (18)	114 (3)	783 (12)	1822 (28)	1130 (35)	<0.001 (<0.001)
					Overall	<0.001 (<0.001)
Coronary artery disease						
Normal	8396 (40)	2815 (63)	3005 (44)	1998 (30)	578 (18)	<0.001 (<0.001)
Nonobstructive	7596 (36)	1113 (25)	2353 (35)	2731 (41)	1399 (43)	<0.001 (<0.001)
Obstructive (≥50%)	5140 (24)	557 (12)	1397 (21)	1941 (29)	1245 (39)	<0.001 (<0.001)
					Overall	<0.001 (<0.001)

*Body mass index (n=16 721); diabetes mellitus (n=21 014); hypertension (n=20 932); dyslipidemia (n=20 987); current smoker (n=20 984); chest pain typicality (n=18 541); Framingham risk score (n=20 907); otherwise complete.

†*P* values for analysis of variance or χ^2 test (*P* value for χ^2 test for trend or Cuzick's test for trend in brackets).

CCTA between 2005 and 2009 in an observational registry performed across 12 cluster sites in 6 countries (United States, Canada, Germany, Switzerland, Italy, and South Korea) with the primary aim of identifying CCTA characteristics predictive of death and MACE at medium-term follow-up. Patients enrolled in CONFIRM phase I without a known history of CAD (defined as prior myocardial infarction and revascularization) and aged between 40 and 79 years were included for the development of the CAD nomograms (patients aged <40 and ≥80 years were excluded because of relatively small numbers of patients in these age categories). The relationship between SIS% and outcomes was assessed in the subgroup of patients from 8 of 12 sites that obtained MACE follow-up.

Validation Cohort

The Phase II CONFIRM registry cohort is a nonoverlapping population of 4682 patients prospectively enrolled between 2005 and 2010 with similar data collected to that in phase I, at 6 sites in 4 countries (United States, Canada, Austria, and South Korea). Patients in this cohort aged between 40 and 79 years with no history of prior CAD and with MACE follow-up were included.

Baseline Clinical Evaluation

In both phase I and II cohorts, patients underwent prospective clinical evaluation at the time of CCTA including identification of baseline demographic data, traditional cardiac risk factors, and assessment of chest symptom typicality for angina as previously defined.[12]

Coronary CT Angiography

CCTA was performed at all participating sites using a scan platform with a minimum detector width of 64 slices according to either local institutional policy or guidelines issued by the Society of Cardiovascular Computed Tomography.[13,14] Image interpretation was performed at all sites by experienced observers with level III (or equivalent) accreditation and board certification in CCTA. Segmental analysis was performed using a 16-segment model of the coronary arteries. Coronary atherosclerosis was considered present in a segment if there were any tissue structures >1 mm2 located either within or adjacent to the coronary artery lumen that could be differentiated from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself.[12] To provide a clinically pragmatic nomographic tool, the

Table 2. Age- and Sex-Related Differences in Coronary Artery Disease Prevalence and Characteristics

	Men N=11 418					Women N=9714				
	All	40–49 y	50–59 y	60–69 y	70–79 y	All	40–49 y	50–59 y	60–69 y	70–79 y
CAD Severity	N=11418	N=2706	N=3746	N=3461	N=1505	N=9714	N=1779	N=3009	N=3209	N=1717
Normal	3495 (31)	1491 (55)	1219 (33)	627 (18)	158 (10)*	4901 (50)†	1324 (74)	1786 (59)	1371 (43)	420 (24)*
Nonobstructive	4585 (40)	828 (31)	1557 (42)	1555 (45)	645 (43)*	3011 (31)†	285 (16)	796 (26)	1176 (37)	754 (44*
Obstructive (≥50%)	3338 (29)	387 (14)	970 (26)	1279 (37)	702 (47)*	1802 (19)†	170 (10)	427 (14)	662 (21)	543 (32)*
Segmental involvement										
Segment involvement score	2.6±2.8	1.2±2.0	2.3±2.7	3.4±2.9	4.2±3.0†	1.5±2.2†	0.6±1.3	1.1±1.8	1.8±2.3	2.7±2.6*
Absolute segment involvement, no. (%)										
0 segment	3495 (31)	1491 (55)	1219 (33)	627 (18)	158 (11)*	4901 (50)†	1324 (74)	1786 (59)	1371 (43)	420 (24)*
1 segment	1832 (16)	477 (18)	667 (18)	505 (15)	183 (12)*	1515 (16)	203 (11)	469 (16)	549 (17)	294 (17)*
2 segments	1381 (12)	255 (9)	486 (13)	484 (14)	156 (10)‡	1035 (11)†	113 (6)	287 (10)	391 (12)	244 (14)*
3 segments	1174 (10)	166 (6)	377 (10)	441 (13)	190 (13)*	721 (7)†	61 (3)	178 (6)	282 (9)	200 (12)*
4 segments	948 (8)	98 (4)	317 (9)	327 (9)	206 (14)*	475 (5)†	31 (2)	88 (3)	189 (6)	167 (10)*
≥5 segments	2588 (23)	219 (8)	680 (18)	1077 (31)	612 (41)*	1067 (11)†	47 (3)	201 (7)	427 (13)	392 (23)*
Plaque characteristics, segments per patient										
Calcified plaque	0.9±1.8	0.3±0.9	0.8±1.6	1.3±2.1	1.7±2.5*	0.6±1.3†	0.1±0.5	0.3±0.9	0.7±1.4	1.2±1.9*
Noncalcified plaque	0.3±0.9	0.3±0.8	0.3±0.9	0.4±0.9	0.4±1.0*	0.2±0.7†	0.2±0.6	0.2±0.7	0.3±0.8	0.3±0.8*
Mixed plaque	0.8±1.8	0.4±1.2	0.8±1.7	1.1±2.0	1.3±2.2*	0.4±1.2†	0.1±0.7	0.3±1.0	0.5±1.3	0.8±1.5*
Stenosis severity score	3.7±4.5	1.6±3.0	3.2±4.2	4.7±4.8	6.1±5.2*	2.0±3.3†	0.8±1.9	1.4±2.7	2.4±3.5	3.7±4.1*

Plus-minus values are mean±SD. CAD indicates coronary artery disease.

*P<0.001 for analysis of variance or χ^2 test for comparison between 10-year age groups (and P<0.001 for χ^2 test for trend or Cuzick's test for trend).

†P<0.001 for unpaired comparison (χ^2 test or Mann–Whitney test) between men and women.

‡P<0.001 for χ^2 test for comparison between 10-year age groups and P=0.01 for χ^2 test for trend.

SIS, defined as the number of coronary segments with any atherosclerotic plaque irrespective of stenosis severity, was used to quantify atherosclerotic burden (score between 0 and 16) for the purpose of developing the nomograms. In addition, the presence of obstructive disease was also assessed by visual assessment and is reported at baseline on a per-patient basis (≥50% luminal narrowing in any coronary segment), and incorporated into the stenosis severity score by summing the product of segmental involvement (0 or 1) by stenosis severity (0–3) for each of the 16 segments yielding a total score between 0 and 48.[8]

Outcomes

All patients in the CONFIRM registry were followed for all-cause death for ≥1 year. In US sites, death was determined from the national death index; and in non-US sites, death was determined by direct interview, telephone contact with the patient's family or primary care physician, or review of medical records. Additional events were ascertained at some sites including myocardial infarction, unstable angina, and late revascularization by direct patient interview, telephone contact, or review of medical record.

For the present analysis, the primary end point was MACE inclusive of all-cause death, myocardial infarction, unstable angina, or late revascularization (defined as revascularization occurring >90 days from enrollment).

Statistical Analysis

Continuous variables are presented as mean± SD and categorical variables as frequencies (%). Comparisons between 2 groups were performed using a χ^2 test or Mann–Whitney test, and between multiple groups using a χ^2 test and χ^2 test for trend or 1-way analysis of variance and Cuzick's test for trend, as appropriate.

Nomograms were developed from the derivation cohort by first plotting percentiles (10th, 20th, 30th, 40th, 50th, 60th, 70th, 80th, and 90th) of SIS values at each year of life for men and women. Polynomial curves (second order) were subsequently fitted to each percentile using GraphPad Prism (V6.0d; GraphPad Software, La Jolla, CA).

To assess the relationship between SIS% and MACE risk in the derivation cohort, patients were divided into 3 SIS% groups (≤50th, 51–75th, and >75th) based on the distribution of observed SIS values within 10-year age groups (40–49, 50–59, 60–69, and 70–79 years) for both sexes separately using data from the overall derivation cohort. MACE risk was then analyzed in relation to SIS% group in the subgroup from sites with MACE follow-up using univariable Cox proportional hazards models with reporting of the hazard ratio and 95% confidence interval.

The relationship between SIS% and MACE risk was then assessed using the nomograms. In the validation cohort, each patient was individually assigned an SIS% value by cross-referencing patient age (by year of life), sex, and SIS value to the corresponding SIS% on the nomograms. Patients were then similarly divided into 3 SIS% groups (≤50th, 51–75th, and >75th) using the individually assigned SIS%, and MACE risk was analyzed between SIS% groups using multivariable Cox proportional hazards models adjusting for Framingham risk score and chest pain typicality.

In both derivation and validation cohorts, time to MACE was analyzed according to SIS% group (≤50th, 51–75th, and >75th) using Kaplan–Meier survival curves with reporting of the log-rank test P value. Patients who underwent early revascularization (within 90 days of enrollment) were censored at the time

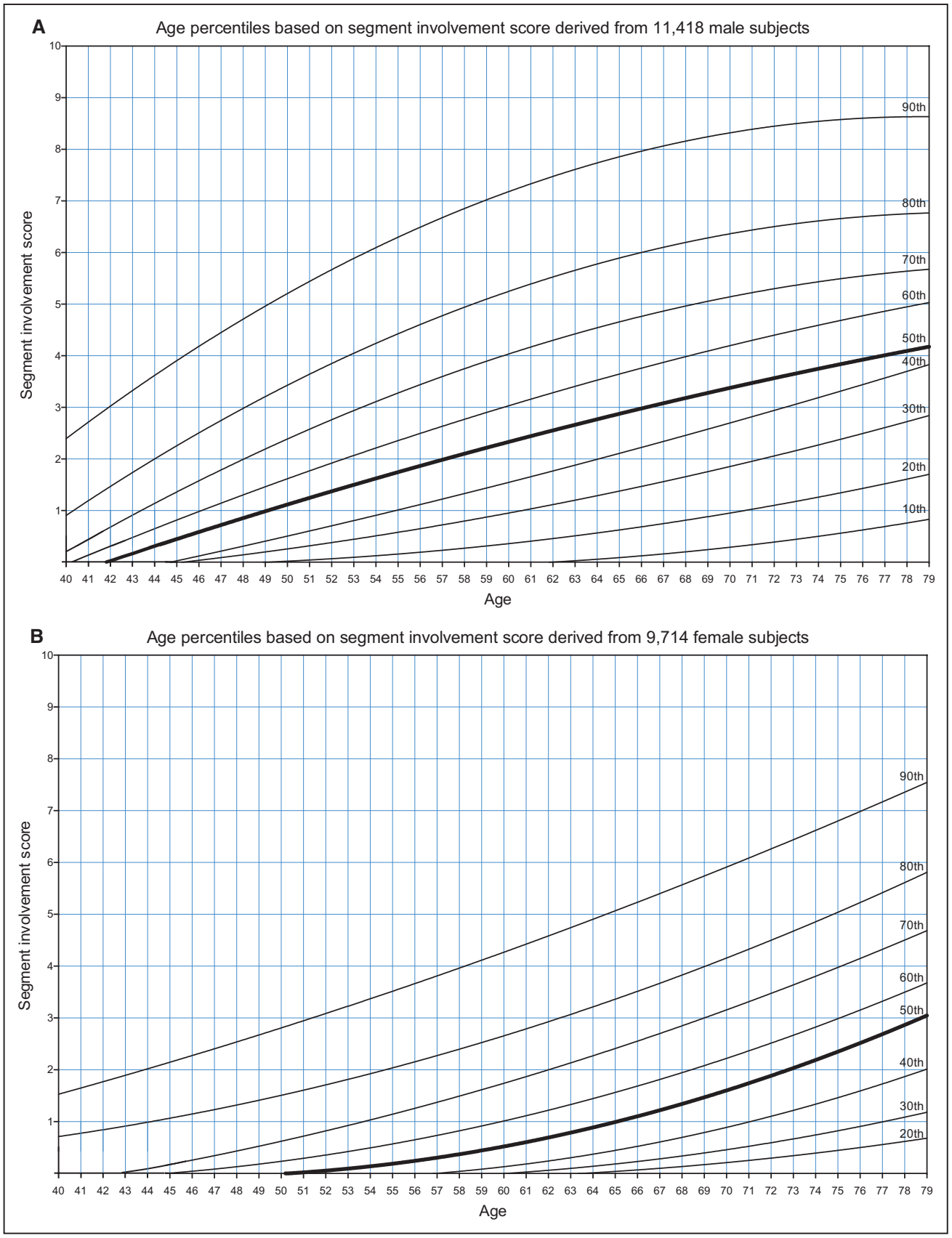

Figure 2. Coronary artery disease nomograms by age percentiles for males (**A**) and females (**B**).

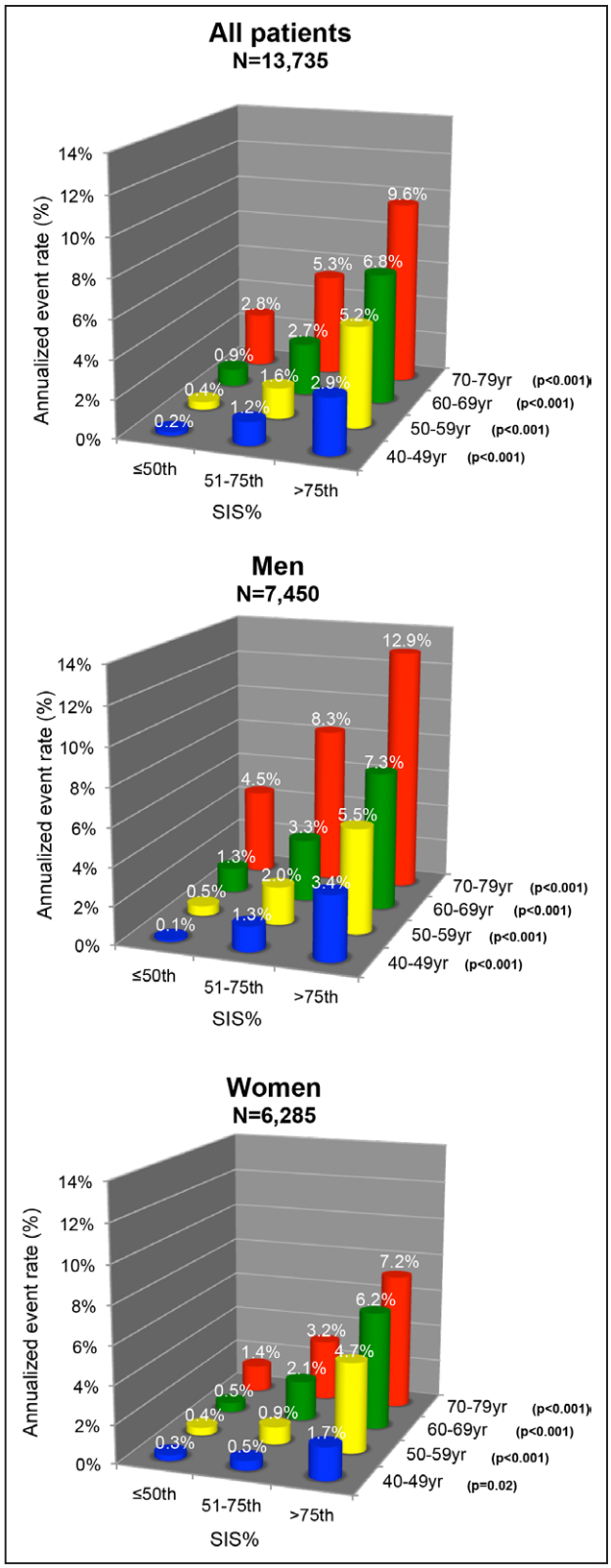

Figure 3. Annualized event rates in the derivation cohort stratified by segment involvement score (SIS%) groups, 10-year age group and sex.

of revascularization (included as no event during follow-up to the time of their early revascularization) for the MACE survival analyses to avoid inclusion of potentially nonclinically driven revascularization that occurred immediately after obtaining CT coronary angiography results.

Statistical analyses were performed using STATA statistical software, version 13 (StataCorp, College Station, TX) and a 2-tailed *P* value <0.05 was considered statistically significant.

Results

Among the 27 125 patients enrolled in phase I of the CONFIRM registry, 21 132 patients met the above inclusion criteria and comprised the nomogram derivation cohort. Of these, MACE follow-up was available in 13 735 patients, who comprised the nomogram outcome cohort. Among the 4682 patients in phase II, 3030 patients met inclusion criteria for the validation cohort (Figure 1).

Nomogram Derivation Cohort

Baseline clinical characteristics of the nomogram derivation cohort are presented in Table 1 stratified by 10-year age groups. The prevalence of cardiovascular risk factors increased with age apart from smoking, which decreased. Age- and sex-related differences in CAD prevalence and plaque characteristics are reported in Table 2. As expected, global plaque burden quantified by SIS was higher overall in men compared with women (2.6±2.8 versus 1.5±2.2; *P*<0.001) and increased with age in both sexes.

There were 11 141 male and 9730 female subjects in the derivation cohorts for the CAD nomograms presented in Figure 2 with adequate numbers of patients represented at each year of life between 40 and 79 years (289±97 and 243±80 patients per year of life for men and women, respectively, Figure I in the Data Supplement).Coefficient and R^2 values for the second-order polynomial curves fitted to each age percentile (10th–90th) are presented in Table I in the Data Supplement and demonstrated in Figure II in the Data Supplement. The age cutoffs at which the median (50th) SIS% corresponded to the presence of CAD (SIS score ≥1) were 49 years for men and 65 years for women. SIS% values

Table 3. MACE Risk According to SIS% Value in the Derivation Cohort

	HR (95% CI)	*P* Value
All (n=13 735)		
≤50th percentile SIS%	Reference	…
51–75th percentile SIS%	2.6 (2.1–3.3)	<0.001
>75th percentile SIS%	6.9 (5.7–8.4)	<0.001
Males (n=7450)		
≤50th percentile SIS%	Reference	…
51–75th percentile SIS%	2.3 (1.8–3.0)	<0.001
>75th percentile SIS%	5.6 (4.4–7.2)	<0.001
Females (n=6285)		
≤50th percentile SIS%	Reference	…
51–75th percentile SIS%	2.9 (1.9–4.3)	<0.001
>75th percentile SIS%	9.2 (6.6–12.8)	<0.001

CI indicates confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event; and SIS, segment involvement score.

increased more rapidly with ageing in women compared with men (Figure 2).

Relationship Between SIS% and MACE in the Derivation Cohort

Differences in baseline characteristics between patients from sites with MACE follow-up versus patients from sites without MACE follow-up are presented in Table II in the Data Supplement. Cardiovascular risk factors and typical angina were less prevalent in patients with MACE follow-up.

Among the 13 375 patients in the nomogram outcome cohort, there were a total of 541 events (187 female; 354 male) at a mean follow-up of 2.4±1.2 years (138/541 all-cause death; 173/541 myocardial infarction/unstable angina, and 230/541 late revascularization). The annualized event rate was 1.8% (95% confidence interval [CI]: 1.6%–1.9%) and increased with age (40–49 years: 0.7% [95% CI: 0.6%–1.0%]; 50–59 years: 1.3%; 60–69 years: 2.0% [95% CI: 1.8%–2.3%]; 70–79 years: 4.6% [3.9%–5.3%]; $P<0.001$). Annualized MACE rates were increased in the higher SIS% groups (51st–75th and >75th) compared with patients in the ≤50th SIS% group within each 10-year age group; however, the highest event rates were observed in older patients (Figure 3).

Both men and women in the higher SIS% groups also had an increased relative MACE risk (Table 3; Figure 4). However, in younger women (<60 years), the presence of CAD burden above the median was not associated with an increase in relative MACE risk unless the degree of CAD burden was elevated >75th percentile (Table 4). Conversely, among younger men, the presence of any CAD burden above the median was associated with a markedly elevated relative MACE risk that appeared to diminish with older age, although remain significant.

Patients in higher SIS% groups also had an increased relative risk of all-cause death when this was analyzed separately in the entire derivation cohort (Table III in the Data Supplement).

Validation Cohort

After assigning SIS% to all patients in the validation cohort by cross-referencing with the derivation nomograms, there were 1576, 965, and 489 patients, respectively, in the ≤50th, 51–75th, and >75th SIS% groups. Clinical and cardiac CT characteristics of the validation cohort are presented in Table IV in the Data Supplement. Overall, patients in the validation cohort had relatively higher overall cardiovascular risk with 716 of 3030 (25%) of patients having a Framingham Risk Score >20%. Apart from diabetes mellitus, cardiovascular risk factors were more prevalent among patients in SIS% groups above the 50th percentile; however, the Framingham Risk Score did not correlate with SIS% group.

MACE occurred in 162 of 3030 patients (19/162 all-cause death; 69/162 myocardial infarction/unstable angina, and 74/162 late revascularization) at a mean follow-up of 2.0±1.2 years yielding an annualized event rate of 3.3% (95% CI: 2.8%–3.9%). There was a significant correlation between SIS% group and the observed annualized event rates in the validation cohort (2.1% [95% CI: 1.7%–2.7%], 3.9% [95% CI: 3.0%–5.1%], and 7.2% [95% CI: 5.4%–9.6%] in ≤50th, 51–75th, and >75th SIS% groups, respectively; $P<0.001$). Differences in annualized

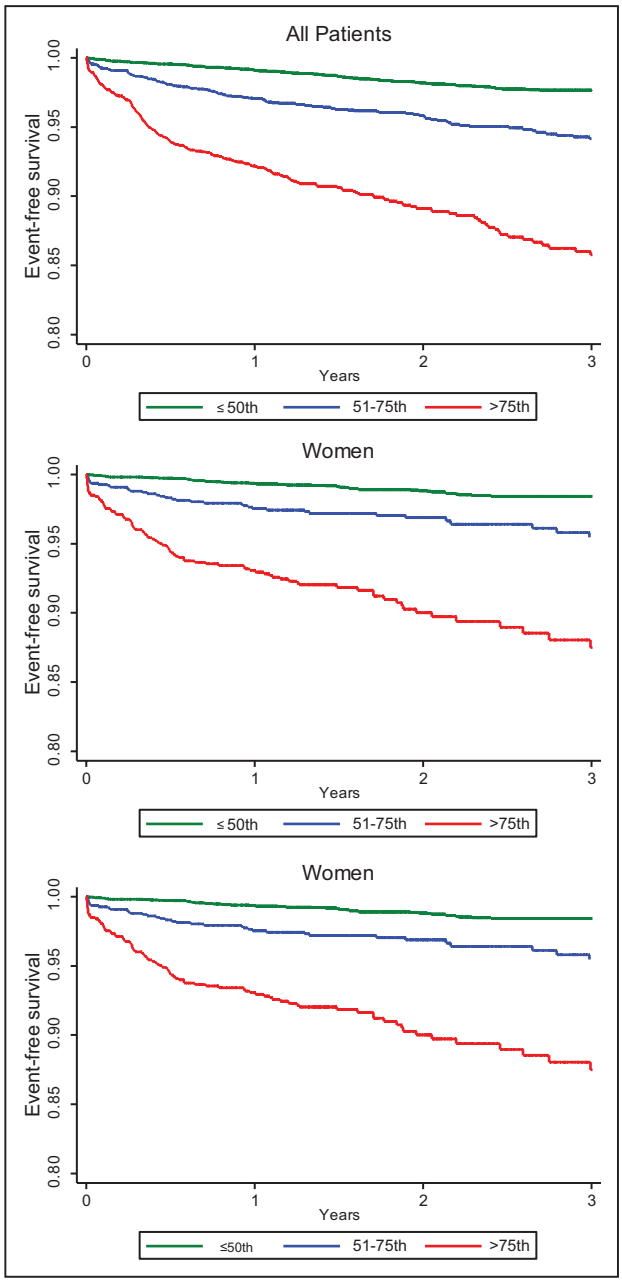

Figure 4. Kaplan–Meier curves demonstrating major adverse cardiovascular event-free survival in the derivation cohort stratified by segment involvement score (SIS%) groups. *P* value for log-rank test for comparison with ≤50th SIS% group.

event rates between SIS% groups (≤50th, 51–75th, and >75th) remained significant for myocardial infarction/unstable angina, and late revascularization but not death (Table 5). SIS% was predictive of annualized event rates in the validation cohort for each 10-year age group (Figure 5). For both sexes, SIS% groups above the median had an elevated risk of MACE compared with patients below the median (Figure 6). After adjusting for Framingham risk and chest pain typicality, MACE remained significantly increased in patients with an SIS% above the median (Table 6).

Discussion

We have developed age- and sex-specific nomograms of CAD extent using CCTA findings from a large multicenter registry.

Table 4. MACE Risk According to SIS% Within 10-Year Age Groups and Stratified by Sex in the Derivation Cohort

	40–49 y		50–59 y		60–69 y		70–79 y	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Males								
≤50th percentile SIS%	Reference	…	Reference	…	Reference	…	Reference	…
51–75th percentile SIS%	11.0 (3.2–37.9)	<0.001	4.1 (2.2–7.4)	<0.001	2.5 (1.5–4.0)	<0.001	1.8 (1.1–3.0)	0.03
>75th percentile SIS%	26.2 (7.7–89.2)	<0.001	10.7 (6.0–19.2)	<0.001	5.0 (3.4–7.4)	<0.001	2.7 (1.7–4.2)	<0.001
Females								
≤50th percentile SIS%	Reference	…	Reference	…	Reference	…	Reference	…
51–75th percentile SIS%	1.5 (0.2–12.1)	0.73	2.2 (1.0–5.0)	0.053	3.9 (2.0–7.5)	<0.001	2.3 (1.1–4.9)	0.04
>75th percentile SIS%	5.1 (1.4–18.1)	0.01	10.3 (5.2–20.2)	<0.001	10.9 (6.3–18.9)	<0.001	5.0 (2.7–9.2)	<0.001

CI indicates confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event; and SIS, segment involvement score.

In doing so, we provide a clinically pragmatic approach for quantifying global plaque burden using CCTA on an individual patient level and relative to the disease burden observed in patients of the same age and sex referred for CCTA. Importantly, SIS% derived from the nomograms was shown to predict both annualized event rates and adjusted relative MACE risk in a nonoverlapping validation cohort. These findings emphasize the important prognostic use of estimating global plaque burden by age percentiles independent of traditional Framingham risk and without the need to incorporate information regarding stenosis severity, CAD location, or plaque features.

Despite a prevailing clinical perception that CAD is ubiquitous in older age and more common in men than women, the extent of CAD burden by year of life and differences in segmental involvement between men and women have been poorly documented. With the growing clinical adoption of coronary CTA for the evaluation of low-to-intermediate risk patients, nomographic data are becoming increasingly pertinent. Such data facilitate an understanding of CCTA findings on an individual patient level in the context of expected disease burden among patients of the same age and sex analogous to the interpretation of CACS.[15] As prior studies have described age- and sex-related trends in the prevalence of obstructive CAD, cardiovascular events, and the extent of coronary artery calcification,[1,8,15] there are no studies reporting segmental disease burden stratified by age percentiles. Importantly, there are no such studies using CCTA, which is able to identify noncalcified plaque that is not captured by calcium scoring and is more sensitive for identifying nonobstructive plaque than both invasive angiography and coronary flow reserve testing.

An important component of our study was the ability to demonstrate a relationship between global plaque burden quantified by SIS% using the nomograms and cardiac events in a validation cohort and independent of traditional Framingham risk. The incremental prognostic use of coronary CCTA beyond traditional risk assessment is now well established across a range of patient populations including patients without any cardiac risk factors.[16] These studies have focused largely on defining the value of CCTA through the identification of obstructive CAD, particularly proximal and multivessel disease, while looking at nonobstructive disease in a binary fashion. Moreover, recent CCTA studies have evaluated the ability of CCTA to predict events based on the presence of high-risk plaque features. In our study, we intentionally used age-based segmental involvement to preserve the simplicity of the nomograms and found it was also predictive of events. Many studies have now established a clear relationship between CAD burden and outcomes irrespective of stenosis assessment.[6] The prognostic use of CACS, a quantitative measure of overall calcific atherosclerotic burden, has been demonstrated in numerous studies although these have primarily evaluated asymptomatic patients (17–18). Similarly, CCTA studies have demonstrated prognostic utility using scores that quantify CAD burden with and without stenosis weighting (stenosis severity score and SIS, respectively).[5] More recently, plaque extent using CCTA was shown to have incremental risk prediction for CHD events in a model that included clinical risk assessment and the presence and

Table 5. Annualized Event Rates Stratified by SIS% Group in the Validation Cohort

	Annualized Event Rate (95% CI)			
	≤50th SIS%	51–75th SIS%	>75th SIS%	*P* Value
MACE (combined end point)	2.1% (1.7%–2.7%)	3.9% (3.0%–5.1%)	7.2% (5.4%–9.6%)	<0.001
Death	0.3% (0.1%–0.6%),	0.4% (0.2%–0.9%)	0.5% (0.2%–1.2%)	0.50
Myocardial infarction/UA	0.8% (0.6%–1.3%),	0.9% (0.6%–1.5%)	2.6% (1.8%–3.9%),	<0.001
Late revascularization	1.1% (0.8%–1.5%),	2.3% (1.6%–3.2%)	3.7% (2.5%–5.6%	<0.001

CI indicates confidence interval; MACE, major adverse cardiovascular event; SIS, segment involvement score; and UA, unstable angina.

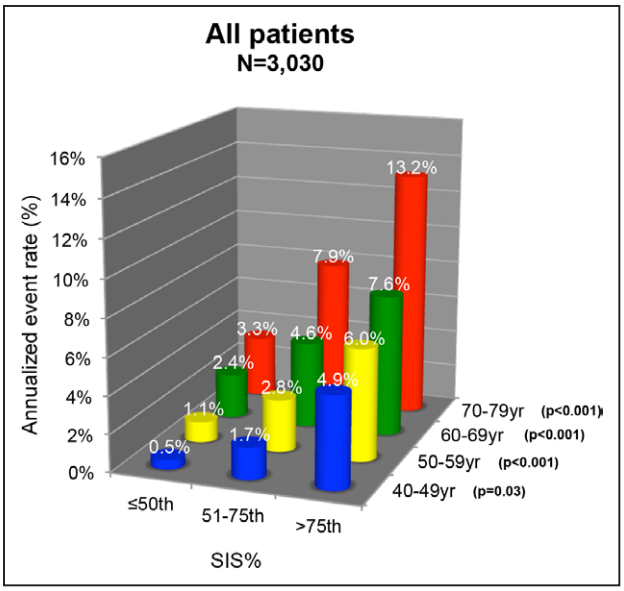

Figure 5. Annualized event rates in the validation cohort based on segment involvement score (SIS%) groups assigned using the derived nomograms and stratified by 10-year age groups.

severity of CAD.[9] Although there is no doubt that the extent and severity of obstructive disease and plaque features confer prognostic information, it seems that simple quantification of CAD segmental involvement alone also provides prognostically useful information independent of traditional clinical risk assessment. This may be because of an association between higher disease burden and an increased likelihood of coexisting luminal stenosis as was evident in our study (Table IV in the Data Supplement). Alternatively, the higher rates of CHD events may be related to an increased likelihood of developing vulnerable plaques that are capable of causing a cardiac event in patents with more atherosclerosis. Until now, however, there have been no clinically useful tools for understanding age- and sex-specific disease burden using CCTA on the individual patient level.

Apart from establishing nomographic data and establishing its prognostic use, our data also emphasize the importance of age as a clinical risk factor for CHD events. Although SIS% was predictive of increased relative MACE risk at all age groups, the annualized event rates were more significantly increased in older patients (Figure 3), particularly among women. Age has been a long-established driver of absolute risk for CHD events. Indeed, age is significantly weighted in absolute risk models based on the presence and severity of conventional cardiac risk factors, such as the Framingham risk score.[2,17] Patients in older age groups often have an increased risk independent of cardiovascular risk factors; and conversely, patients in younger age groups often do not reach treatment thresholds despite significant risk factors especially young women.[18] This may be simply explained by the higher disease burden seen in older age[19] (as shown in the nomograms). Future applications of the nomogram as a risk tool for guiding clinical decision making in addition to risk factor assessment need to assess its performance relative to that of absolute SIS for disease burden quantification, analogous to the studies that have shown improved prediction of cardiac events using absolute CACS compared with age- and sex-race/ethnicity percentiles.[20]

Limitations

First, our derivation cohort consisted of predominantly symptomatic patients and our nomographic data therefore do not reflect normative CAD burden for the general population. However, CCTA is not routinely performed in the general population and normative data for patients in whom CCTA is clinically indicated remain important. In the present study, we did adjust for symptom typicality in the outcomes analysis in the validation cohort and importantly found that SIS percentiles were still predictive of MACE. Nevertheless, future

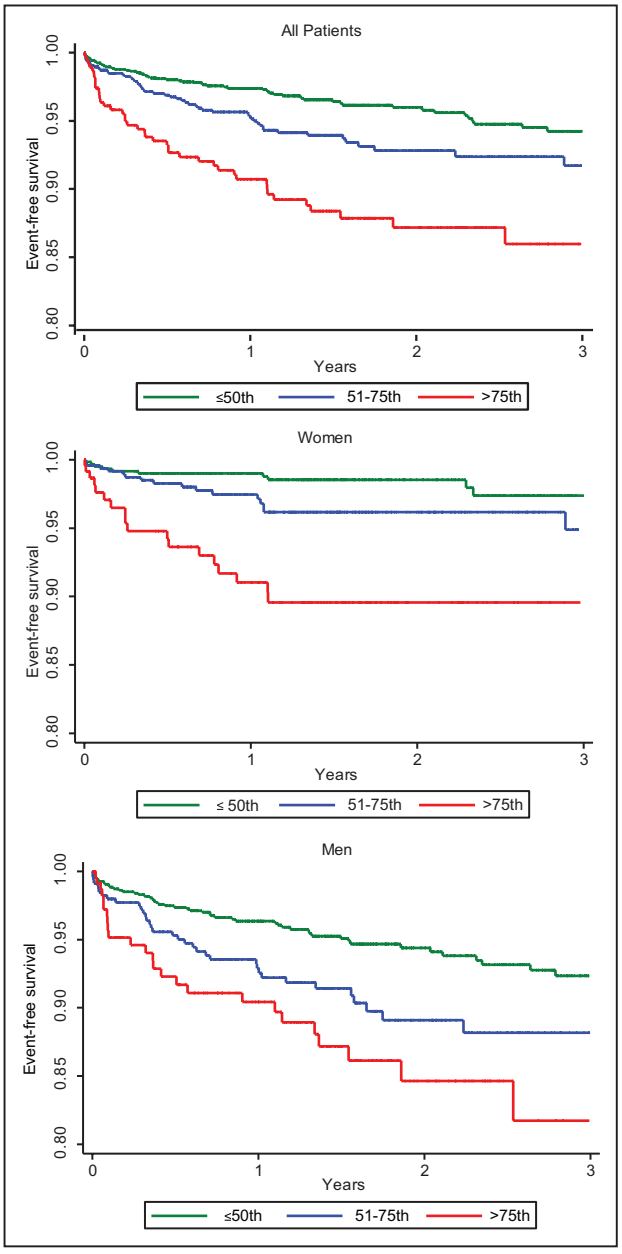

Figure 6. Kaplan–Meier curves demonstrating major adverse cardiovascular (MACE)-free survival in the validation cohort stratified by segment involvement score (SIS%) groups assigned using the derived nomograms. *P* value for log-rank test for comparison with ≤50th SIS% group.

Table 6. Adjusted MACE Risk* According to SIS% Value in Validation Cohort

	All Patients	
	HR (95% CI)	*P* Value
All (n=3030)		
≤50th percentile SIS%	Reference	…
51–75th percentile SIS%	1.9 (1.3–2.8)	0.001
>75th percentile SIS%	3.4 (2.3–5.0)	<0.001
Males (n=1572)		
≤50th percentile SIS%	Reference	…
51–75th percentile SIS%	1.9 (1.3–3.1)	0.002
>75th percentile SIS%	2.8 (1.7–4.6)	<0.001
Females (n=1240)		
≤50th percentile SIS%	Reference	
51–75th percentile SIS%	2.5 (1.1–5.3)	0.02
>75th percentile SIS%	5.8 (2.8–13.4)	<0.001

CI indicates confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event; and SIS, segment involvement score.

*Adjusted for Framingham risk score and chest pain typicality.

studies validating the use of the nomograms in an asymptomatic population are needed to confirm the potential role of CCTA for cardiac risk stratification in a more general population, which have generally undergone such assessment using CACS. Second, the follow-up period was limited to the medium term (≈2 years). Although we would expect CAD burden to be more predictive of MACE in the long term, further studies are needed to confirm this. Third, only sites that obtained MACE follow-up were included, which resulted in a substantial proportion of patients in the derivation cohort not being included in the outcomes analysis. Selection bias may have therefore affected the outcomes analysis in the derivation cohort; however, all-cause mortality, which was collected at all sites, was shown to still be predicted by SIS% in a secondary analysis (Table III in the Data Supplement). Moreover, in the second component of our study, SIS% was shown to be prognostically important in an unrelated validation cohort confirming their prognostic use. Fourth, although the nomograms were predictive in the validation cohort, these patients were at higher risk and future studies should address the predictive value of our nomograms in different risk groups. Finally, we do not have data regarding downstream medical therapy, which was left to the discretion of the treating physician who was not blinded to the CCTA result. This treatment effect may have impacted subsequent events and future studies should address the impact of treatment modification based on global CAD burden on patient outcomes.

Conclusions

We have developed clinically pragmatic age- and sex-specific nomograms of CAD prevalence using CCTA findings for the first time that can be conveniently used to assess global CAD burden in an individual patient as it relates to all patients referred for CCTA. These findings provide for CCTA a measurement analogous to the coronary calcium score used in noncontrast gated cardiac CT. Segmental plaque involvement by age–sex percentiles is predictive of MACE in a nonoverlapping validation cohort, independent of traditional risk factor assessment, highlighting the prognostic importance of global plaque burden.

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Disclosures

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CLINICAL PERSPECTIVE

Coronary computed tomography angiography has established itself as a robust test for the diagnosis and exclusion of anatomic coronary artery disease with high sensitivity and overall accuracy as compared with invasive coronary angiography. Moreover, computed tomography coronary angiography provides important prognostic information including excellent prognosis in the absence of coronary artery disease and an elevated relative risk of major adverse cardiac events in the presence of nonobstructive disease and with increasing obstructive coronary artery disease severity and extent. Although atherosclerotic disease burden is a known predictor of major adverse cardiac event, it seldom affects clinical decision making because of a lack of nomographic data. In the present study, we develop age- and sex-specific nomograms based on data from 21 132 patients referred for clinically indicated coronary computed tomography angiography across the globe. These clinically pragmatic charts allow the clinician to now have a better understanding of how the individual patient's atherosclerotic disease burden relates to other patients of similar age and sex referred for coronary computed tomography angiography. Importantly, our nomographic curves were shown to be predictive of major adverse cardiac event in a separate validation cohort. These data allow the clinician to have a deeper understanding therefore of not only their patients' disease burden but also their risk, potentially facilitating more informed discussions around downstream risk modification.

Circulation
Cardiovascular Imaging

Predictive Value of Age- and Sex-Specific Nomograms of Global Plaque Burden on Coronary Computed Tomography Angiography for Major Cardiac Events

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SUPPLEMENTAL MATERIAL

Supplementary Table 1: Coefficients for second-order polynomial fitted curves* used in age-SIS percentile charts

	Coefficients			
	a	**b**	**c**	**R^2**
Males				
10th	0.0014	-0.1523	3.9630	0.60
20th	0.0013	-0.1052	2.1140	0.73
30th	0.0010	-0.0437	-0.1301	0.84
40th	0.0006	0.0436	-3.0490	0.90
50th	***-0.0008***	***0.2136***	***-7.4670***	***0.96***
60th	-0.0012	0.2788	-9.2010	0.91
70th	-0.0027	0.4620	-13.9600	0.95
80th	-0.0035	0.5684	-16.2100	0.94
90th	-0.0042	0.6570	-17.2000	0.92
			Mean ± SD	**0.86±0.12**
Females				
10th†	–	–	–	–
20th	0.0013	-0.1411	3.7290	0.53
30th	0.0018	-0.1885	4.8140	0.79
40th	0.0026	-0.2597	6.4210	0.88
50th	***0.0028***	***-0.2513***	***5.6480***	***0.93***
60th	0.0021	-0.1584	2.7850	0.93
70th	0.0015	-0.0517	-0.5120	0.94
80th	0.0018	-0.0794	1.0630	0.95
90th	0.0009	0.0462	-1.7710	0.93
			Mean ± SD	**0.86±0.14**

* Polynomial fitted curves for: $SIS = a \times (age)^2 + b \times (age) + c$.

†Curve not fitted due to SIS value of 0 at percentile 10 for all females between 40 and 79yrs.

Supplementary Table 2: Differences in baseline characteristics of patients from sites with MACE follow-up vs. patients from sites without MACE follow-up in the derivation cohort

Derivation Cohort	Patients from sites with no MACE follow-up N=7,397	Patients from sites with MACE follow-up N=13,735	P-value
Age – years	59.2±10.5	58.2±9.5	<0.001
BMI – kg/m^2	27.5±5.3*	27.3±5.1	0.01
Female Gender	3,429 (46)	6,285 (46)%	0.41
HTN	3,912 (53)	6,669 (49)%	<0.001
Dyslipidemia	4,120 (56)	7,753 (57)%	0.06
DM	1,359 (18)	1,871 (14)%	<0.001
Smoking	1,490 (20)	2,181 (16)%	<0.001
Chest pain typicality[†]			<0.001
Typical	1,421 (25)	1,334 (10)	<0.001
Atypical	1,749 (31)	5,523 (43)	<0.001
Non-Cardiac	1,011 (18)	1,086 (8)	<0.001
Asymptomatic	1,438 (26)	4,979 (39)	<0.001

* BMI available in 3,365/7,397 and 13,356/13,735 patients.

[†]Chest pain typicality available in 5,619/7,397 and 12,922/13/735 patients.

Supplementary Table 3: All cause death according to SIS% value in the derivation cohort

	HR (95% CI)	p-value
All (n=21,018)		
≤50th percentile SIS%	Reference	–
51-75th percentile SIS%	1.7 (1.3-2.3)	<0.001
>75th percentile SIS%	2.6 (2.0-3.5)	<0.001
Males (n=11,361)		
≤50th percentile SIS%	Reference	–
51-75th percentile SIS%	1.4 (1.0-2.0)	0.07
>75th percentile SIS%	2.0 (1.4-2.9)	<0.001
Females (n=9,657)		
≤50th percentile SIS%	Reference	–
51-75th percentile SIS%	2.3 (1.5-3.7)	<0.001
>75th percentile SIS%	3.8 (2.5-5.8)	<0.001

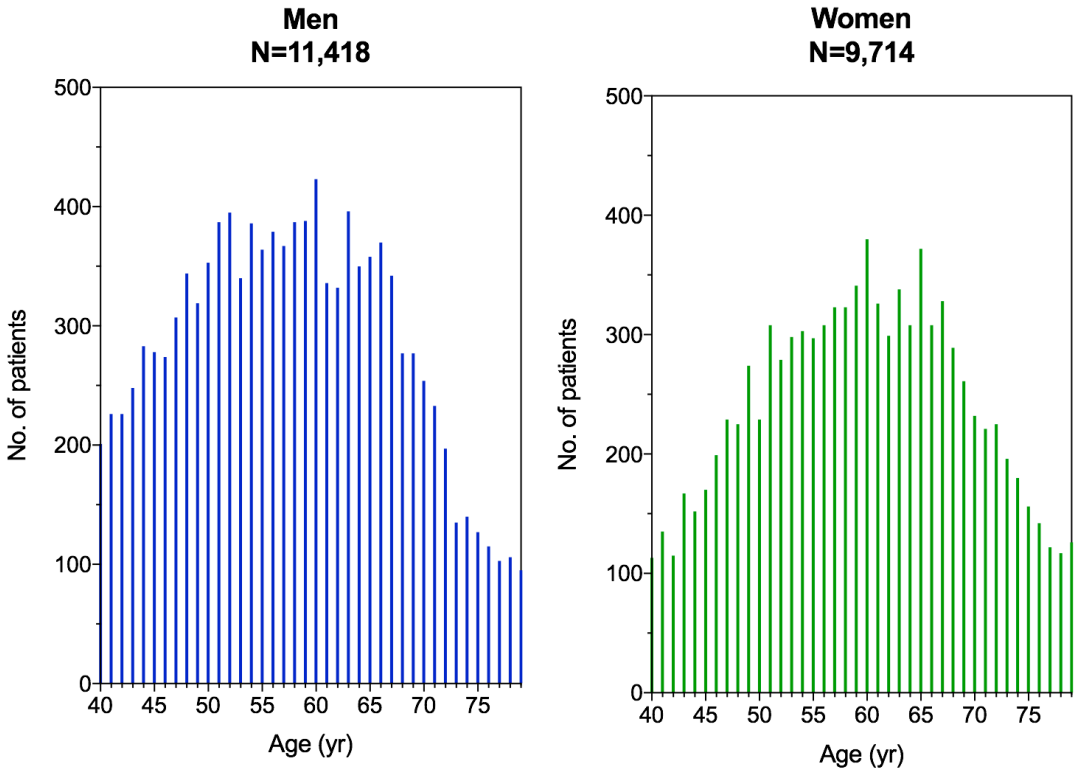
Supplementary Table 4: Baseline characteristics of the validation cohort stratified by SIS% groups

	All N=3,030*	≤50th percentile N=1576	51-75th percentile N=965	>75th percentile N=489	p-value†
Demographics					
Age range – yrs	61±9	62±9	59±10	59±10	<0.001
Female sex – no. (%)	1,338 (44)	608 (39)	495 (51)	235 (48)	<0.001
Body-mass index	27.3±5.1	27.1±5.0	27.3±5.3	27.6±4.9	NS
Cardiovascular risk factors					
Diabetes	1,079 (36)	595 (38)	303 (32)	181 (37)	0.17
Hypertension	1,859 (62)	947 (60)	561 (59)	351 (73)	<0.001
Dyslipidaemia	1,367 (46)	644 (41)	459 (48)	264 (54)	<0.001
Current smoker	552 (20)	221 (15)	198 (22)	133 (29)	<0.001
Chest pain typicality					
Typical angina	734 (25)	343 (22)	257 (27)	134 (28)	0.001
Atypical angina	746 (25)	428 (28)	222 (24)	96 (20)	<0.001
Non-cardiac	503 (17)	238 (15)	171 (18)	94 (20)	0.01
Asymptomatic	985 (33)	540 (35)	293 (31)	152 (32)	NS
				Overall	0.10
Framingham risk score					
Risk score – mean ± SD	15.4±10.2	16.0±10.3	14.2±9.9	16.2±10.0	0.26
Risk category – no. (%)					
<10%	1,005 (36)	479 (33)	374 (41)	152 (33)	0.33
10-20%	1,091 (39)	567 (40)	344 (38)	180 (39)	NS
>20%	716 (25)	387 (27)	195 (21)	134 (29)	0.69
				Overall	0.43
Coronary artery disease					
Normal	1,076 (36)	913 (58)	163 (17)	0 (0)	<0.001
Non-obstructive	836 (28)	337 (21)	368 (38)	131 (27)	<0.001
Obstructive (≥50%)	1,118 (37)	326 (21)	434 (45)	358 (73)	<0.001
				Overall	<0.001

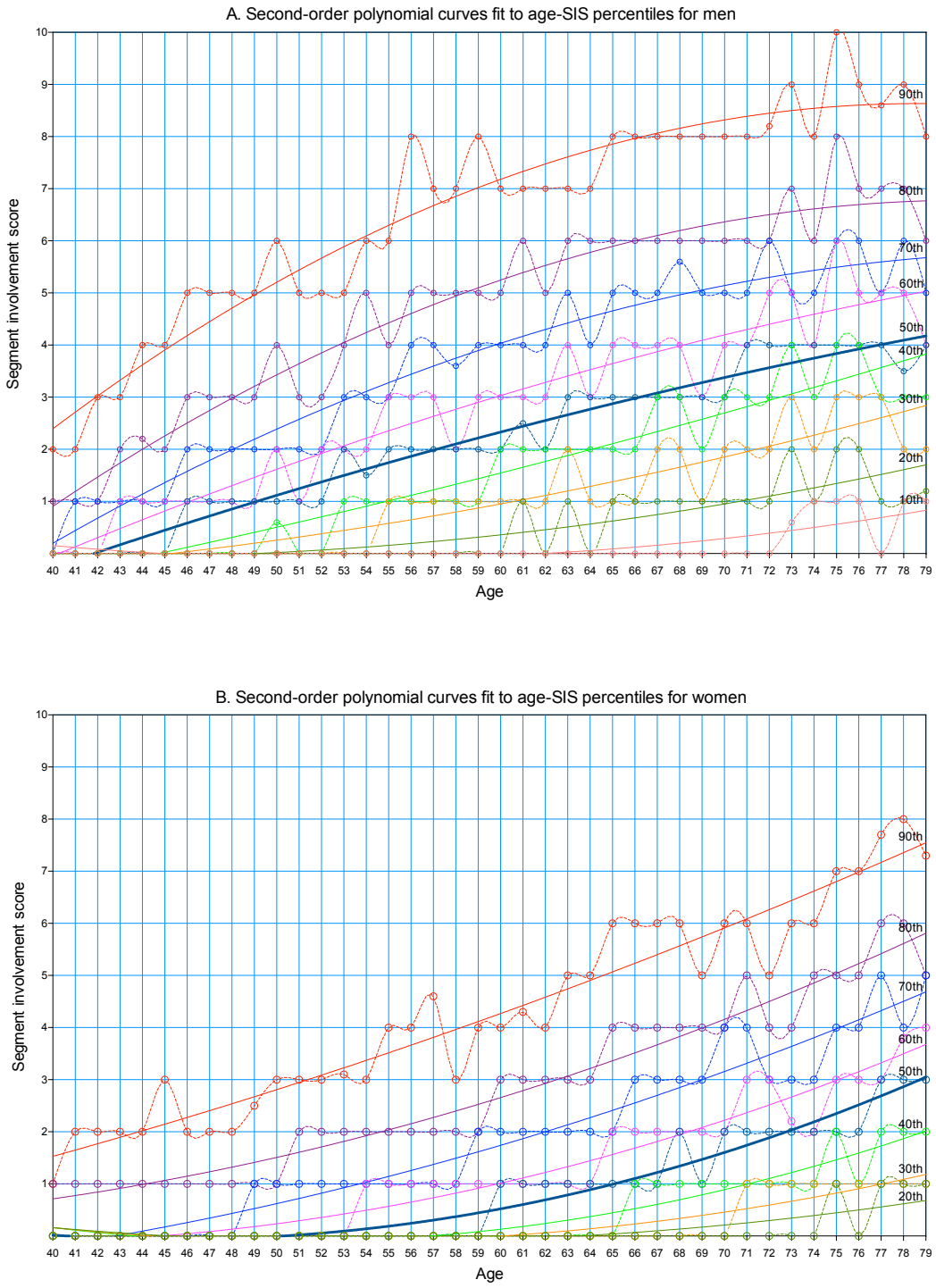
*BMI (n=2,450); FRS (n=2,812); diabetes (n=3,011); hypertension (n=3,008); dyslipidemia (n=3,005); smoking (n=2,813); chest pain typicality (n=2,968); otherwise complete.

†p-value for chi-square test for trend or Cuzik's test for trend. NS, not significant ANOVA or chi square test.

Supplementary Figures



Supplementary Figure 1: Number of patients at each year of life (40-79yrs) in the nomogram derivation cohort.



Supplementary Figure 2: Fitting of second-order polynomial curves (solid lines) to raw SIS percentiles at each year of life (joined by splines for demonstration, dotted lines) is shown for men (A) and women (B). For the final nomographic representation presented in the manuscript, the components of the curve that spill back to the left in the lower percentiles have been removed.