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ORIGINAL RESEARCH

Superior Risk Stratification With Coronary Computed Tomography Angiography Using a Comprehensive Atherosclerotic Risk Score

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ABSTRACT

OBJECTIVES This study was designed to assess the prognostic value of a new comprehensive coronary computed tomography angiography (CTA) score compared with the stenosis severity component of the Coronary Artery Disease-Reporting and Data System (CAD-RADS).

BACKGROUND Current risk assessment with coronary CTA is mainly focused on maximal stenosis severity. Integration of plaque extent, location, and composition in a comprehensive model may improve risk stratification.

METHODS A total of 2,134 patients with suspected but without known CAD were included. The predictive value of the comprehensive CTA score (ranging from 0 to 42 and divided into 3 groups: 0 to 5, 6 to 20, and >20) was compared with the CAD-RADS combined into 3 groups (0% to 30%, 30% to 70% and ≥70% stenosis). Its predictive performance was internally and externally validated (using the 5-year follow-up dataset of the CONFIRM [Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry], n = 1,971).

RESULTS The mean age of patients was 55 ± 13 years, mean follow-up 3.6 ± 2.8 years, and 130 events (myocardial infarction or death) occurred. The new, comprehensive CTA score showed strong and independent predictive value using the Cox proportional hazard analysis. A model including clinical variables plus comprehensive CTA score showed better discrimination of events compared with a model consisting of clinical variables plus CAD-RADS (0.768 vs. 0.742, p = 0.001). Also, the comprehensive CTA score correctly reclassified a significant proportion of patients compared with the CAD-RADS (net reclassification improvement 12.4%, p < 0.001). Good predictive accuracy was reproduced in the external validation cohort.

CONCLUSIONS The new comprehensive CTA score provides better discrimination and reclassification of events compared with the CAD-RADS score based on stenosis severity only. The score retained similar prognostic accuracy when externally validated. Anatomic risk scores can be improved with the addition of extent, location, and compositional measures of atherosclerotic plaque. (Comprehensive CTA risk score calculator is available at: http://18.224.14.19/calcApp/) (J Am Coll Cardiol Img 2019;12:1987–97) © 2019 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CAD = coronary artery disease

CAD-RADS = Coronary Artery Disease–Reporting and Data System

CI = confidence interval

CTA = computed tomography angiography

HR = hazard ratio

NRI = net reclassification improvement

Coronary computed tomography angiography (CTA) provides direct noninvasive anatomical assessment of the coronary arteries and has a high diagnostic accuracy for detection and exclusion of obstructive coronary artery disease (CAD) (≥50% stenosis) compared with invasive coronary angiography (1). Coronary CTA also provides prognostic information for prediction of future cardiovascular events (2,3). Several studies have shown that obstructive CAD on coronary CTA is associated with worse outcomes compared to nonobstructive or no CAD (4-6). Current coronary CTA reading is guided by the Coronary Artery Disease - Reporting and Data system (CAD-RADS), which is mainly based on maximal stenosis severity. However, other coronary plaque characteristics including plaque extent, location, and composition carry prognostic value (2,7,8). The location of coronary plaque (proximal versus distal), the number of plaques, and plaque composition (noncalcified or mixed versus calcified lesions) have all been associated with clinical outcomes in cohort studies (7,9,10). The integration of this complex information into a risk score may further optimize risk stratification and enable maximum use of information derived from coronary CTA. The purpose of the current study was to determine whether a new comprehensive risk score may provide incremental prognostic value over the stenosis severity component of the CAD-RADS score.

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METHODS

STUDY POPULATION. Derivation cohort from Leiden, the Netherlands. The primary study cohort to derive the novel risk score included a consecutive series of 2,809 stable patients with suspected or known CAD who were clinically referred for coronary CTA at the Leiden University Medical Center (LUMC), the Netherlands, between 2005 and 2015. Exclusion criteria for coronary CTA were cardiac arrhythmias, known hypersensitivity to iodine contrast media, or pregnancy. Patients with an uninterpretable CTA examination (n = 125); previous percutaneous intervention, coronary artery bypass surgery, or myocardial infarction (MI) (n = 148); coronary CTA in the setting of suspected acute coronary syndrome (n = 144); missing plaque composition data (n = 65); or missing follow-up (n = 193) were excluded, leaving

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2,134 patients in the derivation cohort. Cardiovascular risk factors consisted of diabetes mellitus (defined as a fasting glucose ≥126 mg/dl or the use of insulin/oral hypoglycemic agents), hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or the use of antihypertensive medication), hypercholesterolemia (serum total cholesterol ≥230 mg/dl or serum triglycerides ≥200 mg/dl or treatment with lipid-lowering drugs), family history of CAD (presence of CAD in first-degree family members at <55 years of age in men and <65 years of age in women), and currently smoking. Chest pain typicality was categorized as nonanginal, atypical, and typical chest pain.

Demographic and clinical data were prospectively collected from the departmental electronic information system (EPD-Vision, LUMC). The LUMC Institutional Review Board approved this evaluation of clinically acquired data and waived the need for patient written informed consent.

External validation cohort, CONFIRM Registry. The comprehensive CTA score was tested in an external validation cohort (details described below) using the CONFIRM (Coronary CT angiography Evaluation for Clinical Outcomes: An International Multicenter) registry; a dynamic, international, multicenter, observational cohort study that prospectively collected clinical and follow-up data of patients undergoing ≥64-slice coronary CTA; the rationale and design of CONFIRM have been previously described (11). In brief, this cohort comprised 12,086 patients with 5-year follow-up data among 17 centers in 9 countries between 2002 and 2009 (12). Patients with missing coronary system dominance or plaque composition data (n = 5,553); missing follow-up data regarding MI (n = 3,763); and previous percutaneous intervention, coronary artery bypass surgery, or MI (n = 799) were excluded. In total, 1,971 patients were included in the CONFIRM external validation cohort. Institutional review board approval was received for each study site and each patient provided written informed consent.

CTA ACQUISITION AND IMAGE ANALYSIS. For the derivation cohort (Leiden, the Netherlands), patients were scanned using a 64-slice CT scanner (Aquillion64, Toshiba Medical Systems, Ōtawara, Tochigi, Japan) or a 320-slice CT scanner (Toshiba Multi-slice Aquilion ONE System, Toshiba Medical Systems). Before the examination, the patient's heart rate and blood pressure were monitored. In the absence of contraindications, patients with a heart rate exceeding 60 beats/min were administered beta-blocking medication (50 to 150 mg oral metoprolol, with an additional intravenous dose up to 15 mg if needed). Furthermore, sublingual nitroglycerine (0.4 mg) was administered before scanning. All scan parameters have been previously published (13). Post-processing of the coronary CTA examinations was performed with dedicated software (Vitrea2 and VitreaFx, Vital Images, Minnetonka, Minnesota). Coronary anatomy was assessed using a 17-segment model according to a modified American Heart Association classification (14). Stenosis severity was visually assessed for each coronary plaque and categorized as: normal, <30%, 30% to 50%, 50% to 70%, 70% to 99%, and occluded (7). In addition, plaque composition was determined in all diseased segments and graded as noncalcified plaque (plaques having lower density compared with the contrast-enhanced lumen), calcified plaque (plaques with high density), and mixed plaque (containing elements of both noncalcified and calcified plaque). The CTA examinations were interpreted by 2 physicians highly experienced in CTA reading as previously described (13). Image analysis from the external validation cohort was uniformly performed at each site in accordance with the computed tomography (CT) guidelines, as previously described (11).

CAD-RADS. The CAD-RADS categories are based on the highest grade coronary stenosis per patient and are defined as follows: CAD-RADS 0 = no coronary plaque, CAD-RADS 1 = 1% to 24% stenosis or present coronary plaque without stenosis, CAD-RADS 2 = 25% to 49% stenosis, CAD-RADS 3 = 50% to 69% stenosis, CAD-RADS 4a = 70% to 99% stenosis in 1 or 2 coronary arteries, CAD-RADS 4b = 70% to 99% stenosis in 3 coronary arteries or ≥50% stenosis in the left main, CAD-RADS 5 = occlusion. According to these definitions, patients in the present analysis were categorized in their appropriate CAD-RADS group, where a stenosis <30% was considered equal to 1% to 24% and 30% to 49% was considered equal to 25% to 49%. The CAD-RADS classification also includes the presence of vulnerable high-risk plaque, however, this information was not included in the present study because the high-risk plaque features were not systematically assessed. To allow for comparisons with the comprehensive CTA score, the several CAD-RADS categories were merged into 3 groups: group 1 = CAD-RADS 0 or 1 (no to minimal CAD), group 2 = CAD-RADS 2 or 3 (moderate CAD), and group 3 = CAD-RADS 4 or 5 (severe CAD).

COMPREHENSIVE CTA SCORE. A comprehensive CTA score incorporating the presence, extent, severity,

location, and composition of CAD was constructed based on the following:

1. A 17-segment model of the coronary artery tree based on American Heart Association criteria (14).
2. Previous literature describing the individual predictive value of plaque extent, severity, and composition variables as observed on coronary CTA (2,3,7,9).
3. The Leaman score which provides weight factors for plaque location (15).

Regarding the presence and extent of CAD on coronary CTA, several studies have shown that the number of segments with CAD is associated with increased risk for events (2,3,5,6). When stratifying the diseased segments according to plaque composition, van Werkhoven et al. (7) observed a hazard ratio (HR) of 1.1 for segments with calcified plaque, 1.2 for segments with noncalcified plaque, and 1.3 for segments with mixed plaques. Based on these findings, the weight factor for the presence, extent, and composition of plaque in the score are 1.1, 1.2, or 1.3, respectively, for calcified, noncalcified, or mixed plaque. In addition to plaque presence, extent, and composition, stenosis severity is also an important predictor for future events. In the comprehensive CTA score the weight factor for stenosis severity was based on the previously observed HR of 1.4 (95% CI: 1.2 to 1.6) for the number of segments with obstructive stenosis (7). Finally, lesions in more proximal coronary artery segments are known to convey a higher risk for cardiovascular events, possibly due to the larger volume of affected myocardium in case of a coronary occlusion (5). As a result, plaque location was integrated into the comprehensive CTA score using the Leaman score, which places weights on each segment's relative contribution to the total left ventricular blood flow (15).

Altogether, the comprehensive CTA score is calculated using the following approach. First, the presence of CAD is determined in each segment. When plaque is absent the score is 0. When plaque is present a score of 1.1, 1.2, or 1.3 is given according to plaque composition (calcified, noncalcified, and mixed plaque, respectively). Subsequently, this score is multiplied by a weight factor for the location of the segment in the coronary artery tree (0.5 through 6 according to vessel, proximal location, and system dominance), and multiplied by a weight factor for stenosis severity (1.4 for ≥50% stenosis and 1.0 for stenosis <50%). The final score (range 0 to 42) is calculated by addition of the individual segment scores (**Figure 1**). An online calculator is available (16).

FOLLOW-UP AND STUDY ENDPOINTS. For the derivation cohort (Leiden, the Netherlands), mortality data were retrieved from the municipal civil registry of the Netherlands; and MI was assessed by clinical visit report review or standardized telephone interviews with confirmation from medical file data. The average follow-up time was 3.6 ± 2.8 years. For the external validation cohort (the CONFIRM registry), death was ascertained by a query of the national death index for U.S. sites and by direct interview or telephone contact with the patient's family, primary physician, or review of the medical charts for non-U.S. sites; and MI was ascertained by direct interview, telephone contact (and confirmed from the medical files), or medical record review. The primary endpoint was all-cause mortality or nonfatal MI (defined according to the standard definitions) (17,18). Patients were followed for a mean of 5.2 ± 1.7 years.

STATISTICAL ANALYSIS. Continuous variables were presented as mean ± SD or median (25% to 75% interquartile range), according to the distribution. Categorical variables were presented as a number and percent. Event-free survival was estimated using the Kaplan-Meier method and the log-rank test was used to compare the event-free survival distributions of the groups within each score. The 2 scores were available for all patients; <1.5% of data was missing regarding cardiovascular risk factors or medication use. The univariable and multivariable HRs with 95% confidence intervals (CIs) were generated by Cox proportional hazard regression analysis. In each case, the proportional hazards assumption was met. Model overfitting was avoided by limiting multivariable models to 1 variable for every 10 clinical outcomes. Two multivariable models were created including clinical characteristics (age, sex, hypertension, hypercholesterolemia, diabetes mellitus, smoking, and family history of CAD) together with the CAD-RADS (model 1) or the comprehensive CTA score (model 2). The discriminatory ability of several models was assessed using receiver operating characteristics curve analysis and compared with the DeLong method (19). The incremental value of the comprehensive CTA score compared with the CAD-RADS was assessed using the net reclassification improvement (NRI) statistic based on the methods developed by Pencina et al. (20). The 5-year predicted risk categories were defined as 0% to 3%, 3% to 10%, and >10%. These specific risk thresholds were previously described by Polonsky et al. (21). The use of different cutoff values had minimal effect on the NRI (<0.5% change). The 3 comprehensive CTA score groups were defined using scores of: 0 to 5, 6 to 20, and >20, as

these values revealed the best discriminatory value. For modeling of the comprehensive CTA score, internal validation was performed with bootstrapping analysis using 1,000 replicates and using a 70:30 random split of the derivation cohort for the training and validation cohorts, respectively. Then, this model was externally validated using data from the independent CONFIRM registry. All statistical analyses were 2-sided and $p < 0.05$ was considered statistically significant. The analyses were performed using SAS version 9.4 (SAS, Cary, North Carolina) and SPSS version 24 (IBM, Armonk, New York).

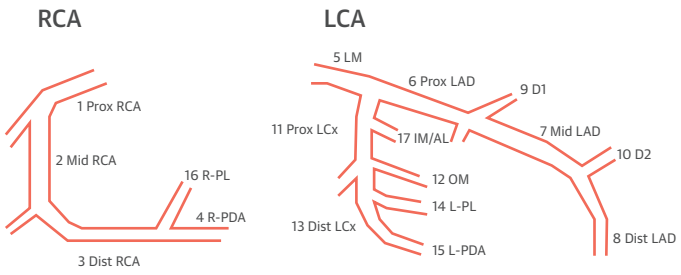
RESULTS

CONVENTIONAL AND NEW COMPREHENSIVE CTA SCORE. In total, 1,150 (53.9%) patients had CAD-RADS 0 to 1, 867 (40.6%) patients had CAD-RADS 2 to 3, and 117 patients (5.5%) had CAD-RADS 4 to 5 in the derivation cohort. Only 18 (2%) patients in the CAD-RADS 0 to 1 group had >2 segments with plaque. According to the comprehensive CTA score, 1,274 (59.7%) patients had the lowest score (0 to 5), 725 (34.0%) patients had a score of 6 to 20, and 135 (6.3%) had the highest risk score category (>20). A mean score of 6.37 ± 3.85 was observed, ranging from 0 to 42. The primary endpoint occurred in 130 patients of the derivation cohort. Events occurred in 22 patients with CAD-RADS 0 to 1 (2.5%), in 93 patients with CAD-RADS 2 to 3 (8.1%), and in 15 patients with CAD-RADS 4 to 5 (12.8%). Events occurred in 33 patients with score 0 to 5 (2.6%), in 67 with score 6 to 20 (9.2%) and in 30 with score >20 (22.2%).

BASELINE CHARACTERISTICS ACCORDING TO RISK SCORE CATEGORIES. Table 1 presents the baseline characteristics of the derivation cohort compared with the external validation cohort across the 3 comprehensive CTA score categories (0 to 5, 6 to 20, and >20). The mean patient's age was consistently lower in the derivation cohort compared with the external validation cohort. Moreover, in the derivation cohort fewer patients were men, and the prevalence of hypertension, hypercholesterolemia, or smoking was lower; conversely, diabetes mellitus was more prevalent in the derivation cohort.

PROGNOSTIC PERFORMANCE OF THE NOVEL COMPREHENSIVE CTA SCORE. Table 2 shows the univariable and multivariable clinical and CTA Cox regression models. For the CAD-RADS, univariable HR for CAD-RADS 2 to 3 was 3.19 (95% CI: 2.00 to 5.07, $p < 0.001$) and for CAD-RADS 4 to 5 the HR was 6.28 (95% CI: 3.26 to 12.11, $p < 0.001$), with CAD-RADS 0 to 1 as reference group. A strong association with events was also observed using the comprehensive CTA score categories: the HR of a score of 6 to 20 was 3.71 (95% CI: 2.44 to 5.62, $p < 0.001$) and the HR of a score >20 was 8.00 (95% CI: 4.88 to 13.13, $p < 0.001$) with a score of 0 to 5 as the reference group. A similar pattern was observed after adjusting for clinical characteristics (Table 2). The event-free survival curves are presented in Figure 2. In both approaches, a dose-dependent relationship is observed between the degree of CAD and worse event-free survival. For the CAD-RADS, event-free survival rates ranged from

FIGURE 1 Comprehensive CTA Score Calculation



Location Weight Factor

Segment	Right Dominant	Left Dominant
LM	5	6
Prox LAD	3.5	3.5
Mid LAD	2.5	2.5
Dist LAD	1	1
D1	1	1
D2	0.5	0.5
Prox LCx	1.5	2.5
Dist LCx	1	1.5
AL/IM	1	1
OM	1	1
L-PL	0.5	0.5
L-PDA	0	1
Prox RCA	1	0
Mid RCA	1	0
Dist RCA	1	0
R-PL	0.5	0
R-PDA	1	0

Plaque Weight Factor

No Plaque	0
Calcified	1.1
Non-Calcified	1.2
Mixed	1.3

Stenosis Weight Factor

<50%	1
≥50%	1.4

Segment (n) score =
Plaque Weight Factor
x
Stenosis Weight Factor
x
Location Weight Factor

Comprehensive / Leiden CTA risk score = Σ Segment (1-17) score

The new, comprehensive CTA score is calculated by addition of the individual segment scores, which are obtained by multiplication of the plaque weight factor, the stenosis weight factor, and the location weight factor. For example, a patient with a right dominant system with a noncalcified plaque with >50% stenosis in the middle RCA, and a mixed plaque with <50% stenosis in the proximal LAD has the following score: Segment 2 score ($1.2 \times 1.4 \times 1 = 1.68$) + Segment 6 score ($1.3 \times 1 \times 3.5 = 4.55$) + other segments score (0) = 6.23. Comprehensive CTA risk score calculator is available at: http://18.224.14.19/calcApp/. AL = anterolateral segment; CTA = computed tomography angiography; D1 = diagonal 1; D2 = diagonal 2; IM = intermediate segment; LAD = left anterior descending coronary artery; LCA = left coronary artery; LCx = left circumflex coronary artery; LM = left main segment; L-PDA = left posterior descending artery; L-PL = left posterolateral segment; OM = obtuse marginal segment; RCA = right coronary artery; R-PDA = right posterior descending artery; R-PL = right posterolateral segment.

TABLE 1 Patient Characteristics

	Comprehensive CTA Score 0-5			Comprehensive CTA Score 5-20			Comprehensive CTA Score >20		
	Derivation Cohort (n = 1,274)	External Cohort (n = 1,096)	p Value	Derivation Cohort (n = 725)	External Cohort (n = 746)	p Value	Derivation Cohort (n = 135)	External Cohort (n = 129)	p Value
Age, yrs	50.9 ± 12.4	58.2 ± 12.2	<0.001	59.9 ± 10.5	64.6 ± 10.0	<0.001	63.0 ± 9.8	67.0 ± 8.0	<0.001
BMI, kg/m^2	26.6 ± 5.0	26.8 ± 4.4	0.287	26.9 ± 4.4	27.0 ± 4.1	0.836	27.2 ± 4.9	27.2 ± 3.7	0.950
Male	559 (44)	603 (55)	<0.001	392 (54)	548 (74)	<0.001	95 (70)	102 (79)	0.104
Chest pain symptoms			<0.001			<0.001			0.071
Asymptomatic	504 (40)	466 (44)		304 (42)	319 (44)		61 (45)	41 (32)	
Noncardiac	214 (17)	177 (17)		92 (13)	96 (13)		13 (10)	16 (13)	
Atypical angina	466 (37)	306 (29)		248 (34)	178 (25)		38 (28)	35 (27)	
Typical angina	89 (7)	119 (11)		81 (11)	133 (18)		23 (17)	36 (28)	
Cardiovascular risk factors									
Diabetes mellitus	270 (21)	88 (8)	<0.001	235 (32)	112 (15)	<0.001	64 (47)	43 (33)	0.020
Hypertension	441 (35)	572 (52)	<0.001	398 (55)	504 (68)	<0.001	90 (67)	96 (75)	0.138
Hypercholesterolemia	296 (23)	507 (46)	<0.001	261 (36)	477 (64)	<0.001	66 (49)	92 (72)	<0.001
Family history of CAD	508 (40)	343 (32)	<0.001	292 (40)	263 (35)	0.049	53 (39)	44 (34)	0.412
Currently smoking	206 (16)	241 (22)	<0.001	120 (17)	223 (30)	<0.001	42 (31)	47 (37)	0.337
Cardiovascular medication									
Beta-blocker	359 (29)	181 (17)	<0.001	282 (39)	179 (24)	<0.001	46 (35)	28 (22)	0.028
ACE-I	181 (15)	155 (14)	0.868	190 (27)	163 (22)	0.053	49 (37)	34 (27)	0.074
Statin	313 (25)	260 (24)	0.486	305 (43)	329 (45)	0.432	71 (53)	76 (60)	0.294
Calcium antagonist	104 (8)	63 (7)	0.110	90 (13)	68 (11)	0.413	25 (19)	15 (14)	0.339
Aspirin	237 (19)	198 (18)	0.626	191 (27)	237 (32)	0.022	50 (38)	40 (32)	0.302

Values are mean ± SD or n (%).

ACE-I = angiotensin converting enzyme-inhibitor; BMI = body mass index; CAD = coronary artery disease; CTA = computed tomography angiography.

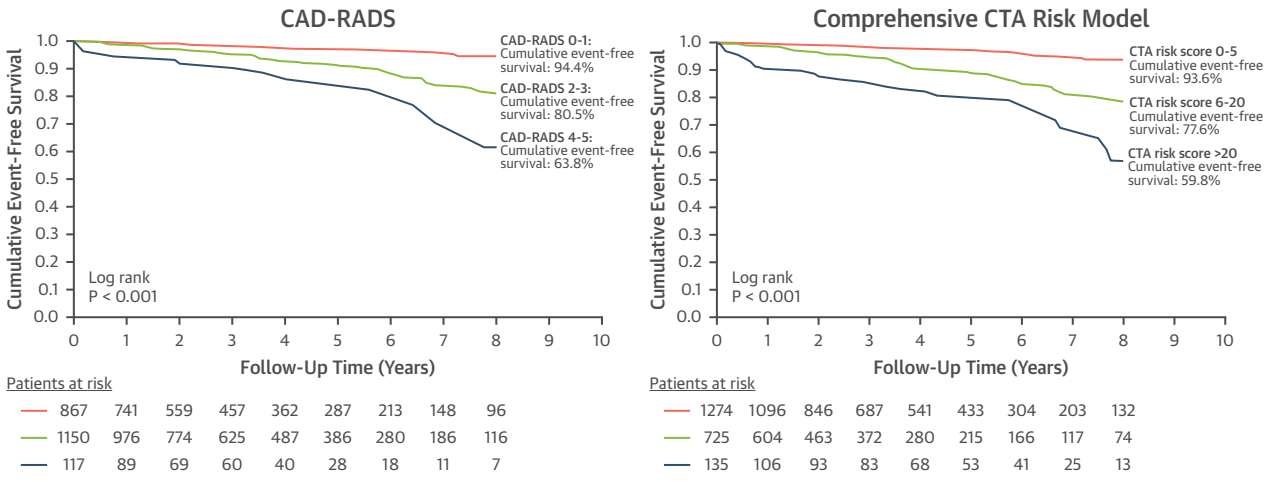
TABLE 2 Univariable and Multivariable Cox Regression on the Derivation Cohort

	Univariable		Multivariable Model 1		Multivariable Model 2	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Age, yrs	1.07 (1.05-1.08)	<0.001	1.06 (1.04-1.08)	<0.001	1.05 (1.03-1.07)	<0.001
BMI, kg/m^2	1.01 (0.97-1.05)	0.734				
Male	1.17 (0.83-1.65)	0.369	1.09 (0.76-1.57)	0.622	0.98 (0.68-1.40)	0.902
Chest pain symptoms*		0.134				
Noncardiac	0.48 (0.56-0.90)				–	
Atypical	0.89 (0.60-1.31)				–	
Typical	1.04 (0.60-1.79)				–	
Cardiovascular risk factors						
Diabetes mellitus	1.44 (1.01-2.06)	0.046	1.39 (0.85-2.03)	0.086	1.27 (0.88-1.88)	0.193
Hypertension	1.46 (1.03-2.06)	0.033	0.98 (0.68-1.42)	0.928	0.94 (0.65-1.35)	0.722
Hypercholesterolemia	0.80 (0.55-1.18)	0.263	0.62 (0.41-0.92)	0.019	0.59 (0.39-0.89)	0.011
Family history of CAD	0.55 (0.38-0.81)	0.002	0.78 (0.46-1.01)	0.054	0.66 (0.45-0.98)	0.038
Currently smoking	1.70 (1.15-2.50)	0.008	2.01 (1.39-3.13)	<0.001	1.90 (1.26-2.86)	0.002
CAD-RADS†						
CAD-RADS 2-3	3.19 (2.00-5.07)	<0.001	1.95 (1.19-3.20)	0.008	–	
CAD-RADS 4-5	6.28 (3.26-12.11)	<0.001	2.68 (1.30-5.53)	0.007	–	
Comprehensive CTA score‡						
6-20	3.71 (2.44-5.62)	<0.001	–		2.69 (1.72-4.22)	<0.001
>20	8.00 (4.88-13.13)	<0.001	–		4.64 (2.63-8.16)	<0.001

*Asymptomatic is the reference. †CAD-RADS 0-1 is the reference. ‡Comprehensive CTA score 0-5 is the reference.

CAD-RADS = Coronary Artery Disease - Reporting and Data System; CI = confidence interval; HR = hazard ratio; other abbreviation as in Table 1.

FIGURE 2 Event-Free Survival for the CAD-RADS and the Comprehensive CTA Score



Both classifications were associated with increased risk for events (death and myocardial infarction) over time. CAD = coronary artery disease; RADS = reporting and data system; other abbreviation as in Figure 1.

94.4% for CAD-RADS 0 to 1, 80.5% for CAD-RADS 2 to 3, and 63.8% for CAD-RADS 4 to 5 ($p < 0.001$). By comparison, the event-free survival rate for a comprehensive CTA score of 0 to 5 was 93.6%, 77.6% for a score of 6 to 20, and 59.8% for a score >20 ($p < 0.001$).

The concordance index (c-index) of a model containing clinical variables (age, sex, hypertension, hypercholesterolemia, diabetes mellitus, smoking, and family history of CAD) was 0.727. Adding the CAD-RADS increased the c-index to 0.742. A model consisting of clinical variables plus the comprehensive CTA score performed significantly better (c-index 0.768 [95% CI: 0.725 to 0.811], $p = 0.001$) compared with a model including clinical variables plus CAD-RADS, as shown in Supplemental Figure 1. Moreover, the model with the comprehensive CTA score significantly correctly reclassified patients, using risk thresholds of <3%, 3% to 10%, and >10%, as shown by an NRI of 12.4% (95% CI: 5.7% to 19.1%, $p < 0.001$). Reclassification data for patients with and without events are included in Supplemental Tables 1a and 1b.

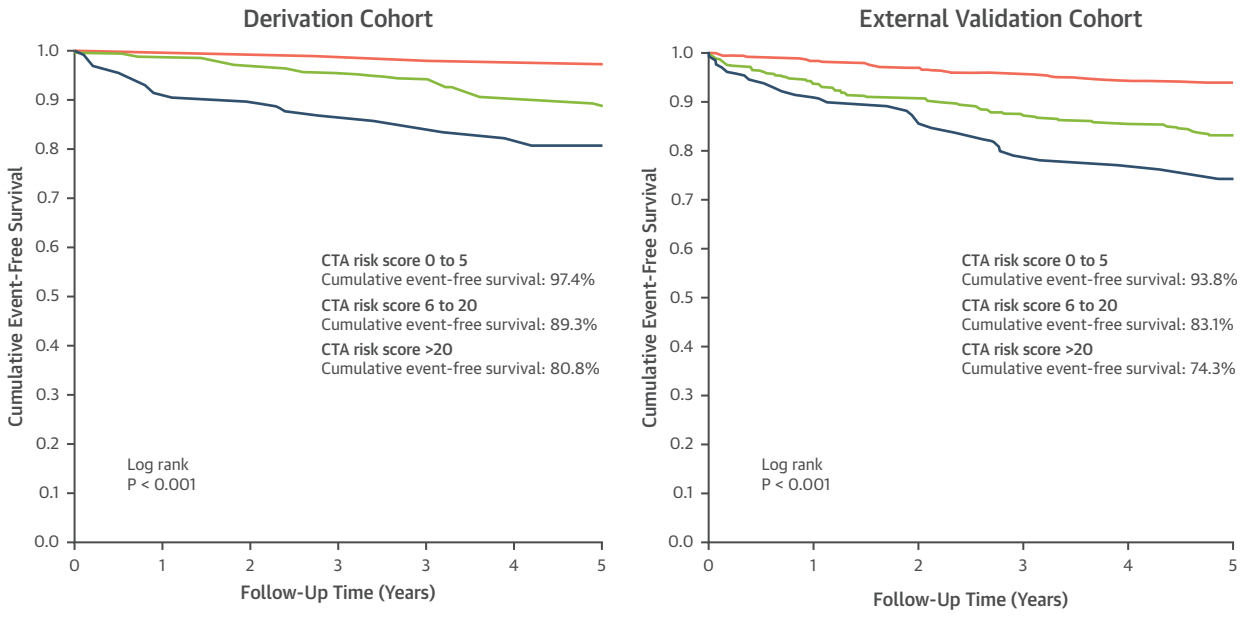
INTERNAL AND EXTERNAL VALIDATION OF THE COMPREHENSIVE CTA SCORE. In the external validation cohort, 1,096 (55.6%) patients had a score of 0 to 5, whereas 746 (37.8%) patients had a score of 6 to 20, and 129 (6.6%) patients had a score >20. The primary endpoint occurred in 254 patients. Supplemental Figure 2 shows the receiver operating characteristics curves for the internal validation (training sample: 70% of the patients, and validation sample: 30% of the patients) of the derivation cohort (Leiden, The Netherlands) and the external validation of the comprehensive CTA score within the external validation cohort (CONFIRM registry). The c-index of the training sample (derivation cohort), using a model containing clinical characteristics and the comprehensive CTA score was 0.749; the c-index of the validation sample was 0.789. In the external validation cohort, the c-index of this model was 0.718 (95% CI: 0.682 to 0.744), significantly higher than the clinical model (0.689, $p < 0.001$).

Figure 3 depicts the 5-year event-free survival curves of the derivation cohort and the external validation cohort showing a similar discriminatory ability of the comprehensive CTA score in both cohorts. The 5-year event-free survival for patients with the comprehensive CTA score of 0 to 5 was 97.4%; 89.3% for a score 6 to 20, and 80.8% for the highest score category (>20) in the derivation cohort. In the external validation cohort, event-free survival was 93.8% for a score 0 to 5, 83.1% for a score 6 to 20, and 74.3% for a score >20.

DISCUSSION

The current study has shown the improved prognostic significance of a comprehensive CTA score incorporating multiple aspects of plaque detected by coronary CTA (plaque extent, severity, location, and composition) to predict major clinical outcomes.

FIGURE 3 External Prognostic Validation (CONFIRM Registry) of the Comprehensive CTA Score



Comparison of 5-years cumulative event-free survival among the derivation and external validation cohort of the comprehensive CTA score showing similar discriminatory ability of the score. Abbreviations as in Figures 1 and 2.

Compared with the CAD-RADS, our new comprehensive score provided improved prediction of outcomes and reclassification of risk for future events. We further evaluated the significance of this comprehensive CTA score by establishing its ability to accurately stratify risk in an external validation cohort. Often risk scores perform suboptimal when externally validated. However, the current validation findings support the added prognostication with varying plaque characteristics to improve classification of major clinical outcomes.

PROGNOSTIC VALUE OF PLAQUE EXTENT, LOCATION, AND COMPOSITION. The CAD-RADS provides the current recommendations for coronary CTA reading (22). The majority of studies assessing the prognostic value of coronary CTA have used a stenosis severity-focused approach, which is the major component of the CAD-RADS. Patients without CAD have the lowest rate of major cardiovascular events with increasing clinical risk-adjusted HRs for nonobstructive CAD (ranging from 1.2 to 1.6) and obstructive CAD (ranging from 2.3 to 2.6) (23,24). The importance of nonobstructive CAD on coronary CTA has been addressed recently because the majority of patients who will experience have <50% stenosis (25). Although this approach permits risk stratification, it does not take full advantage of all information on coronary atherosclerosis that can be derived from coronary CTA. As a result, this method may considerably overestimate or underestimate the risk of events in both patients with obstructive and nonobstructive CAD, indicating the need for a more detailed, patient-tailored approach (fitting the new concept of precision medicine). Prognostic value of several plaque measures has been reported in individual studies (2,4,5,7,9), including number of segments with obstructive CAD (7,12), plaque composition (7), and the location of plaque in the coronary tree (5). Because all parameters have prognostic value, the current study aimed to bring all these CTA parameters together and integrate them into a comprehensive risk score.

COMPREHENSIVE CTA SCORE. The comprehensive CTA score categories of 0 to 5, 6 to 20, and >20 provided better discrimination and correct reclassification compared with risk groups based on stenosis severity only; event rates in the lowest category of both scores were similarly low. However, the 3 groups of both scores include different CAD extent. For instance, a patient with 2 obstructive calcified lesions in the first diagonal and mid-right coronary artery would have been classified in the

intermediate-/highest-risk group using the CAD-RADS but lowest according to the new comprehensive score. These findings support the hypothesis that a comprehensive approach to grade the severity of coronary atherosclerosis, instead of the classification based on the highest-grade stenosis, may improve risk stratification. This corresponds to previous observations that stenosis severity only plays a minor role in predicting plaque rupture and a significant proportion of acute MIs occur at sites with mild stenosis (25,26). Using coronary CTA, previous studies have shown that integration of several plaque measures increase risk prediction. The CONFIRM score incorporated clinical risk parameters and the presence of nonobstructive proximal-mixed or calcified plaques and proximal obstructive stenosis which increased predictive value over clinical scores (27). Mushtaq et al. (8) showed that the CT-Leaman score, integrating stenosis severity with the number and location of stenoses, was more strongly predictive of the segment involvement score (the total number of segments with plaque) or the segment stenosis score (obtained by grading the stenosis severity of each segment with plaque). The current study adds further to the existing literature by separating 3 risk groups which showed similar good discrimination of events in an external validation cohort, indicating its robustness. To be used in clinical practice, a risk score must be easy to use, include a limited number of variables, and be accurate. The current score fits this definition, and is based on location, composition, and stenosis severity in the classical 17-segment model. Previously, prognostic angiographic risk scores have been developed in patients who underwent invasive coronary angiography, such as the Leaman score (15). The CAD prognostic index was described by Mark et al. (28), which integrates information on lesion location, severity, and number of coronary arteries involved. These scores were obtained in patients undergoing clinically indicated invasive coronary angiography, are derived from higher-risk cohorts, and may not be optimal for the lower-risk patients undergoing coronary CTA.

CLINICAL IMPLICATIONS. It is currently not clear which extent of coronary atherosclerosis warrants the initiation or intensification of lipid-lowering therapy and the need for using aspirin. No randomized controlled trials have been performed to evaluate the benefit of treatment of coronary atherosclerosis based on coronary CTA findings. But previous observations have shown that the detection of atherosclerosis increased the prescription of medical therapy. In a study by Cheezum et al. (29), statin therapy was started or intensified in 46% of patients after the detection of nonobstructive or obstructive CAD, which was associated with significant reductions in plasma cholesterol levels. Furthermore, blood pressure therapy was intensified in patients with nonobstructive and obstructive CAD in 21% and 24% of patients, respectively; likewise, aspirin was started in 29% and 40% of patients, respectively. The CAD-RADS significantly improves risk prediction over clinical variables and permits risk assessment. However, this scoring system does not perfectly "phenotype" the individual patient with respect to the total coronary atherosclerotic burden in terms of plaque extent, location, and composition. The new score may be used to tailor medical treatment to the individual patient by maximizing therapy for patients in the highest risk group: targeting of very low cholesterol levels and optimizing blood pressure, and possibly reduce therapy for patients in the lowest risk group to minimize side effects of medication. Future studies should investigate whether clinical outcomes can be improved by the clinical application of this approach of personalizing risk stratification.

STUDY LIMITATIONS. The observational design of the study is a limitation; lifestyle changes, medical therapy, and revascularization after coronary CTA might have influenced outcome in the current cohort, but this limitation relates to all large registries. A direct comparison between the performances of the new comprehensive CTA risk score and the original CAD-RADS (including high-risk plaque features) could not be performed (because high risk plaque features were not systematically assessed) and remains to be evaluated. Patients in the derivation and validation cohort did not have similar cardiovascular risk profiles: patients in the external validation cohort were older and had more risk factors. This may clarify the higher event rates across the 3 risk categories for the validation cohort. Generalizability of the current study may be reduced by the lack of an independent core laboratory analysis or clinical event committee. Also, calculation of the new comprehensive score is more complex than the CAD-RADS; however, automated score calculation is feasible. The new comprehensive CTA score does not incorporate functional stenosis information, which can be derived with fractional flow reserve-CT. Future research should investigate the potential added value of this technique. Finally, a large number of patients in the external validation cohort were excluded which may have introduced selection bias.

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CONCLUSIONS

The CTA risk score incorporating coronary plaque extent, location, severity, and composition improved prediction of events compared with the CAD-RADS based on stenosis severity. Moreover, the model retained good prognostic accuracy in an external validation cohort. The proposed model allows precise prediction of future events and may help further guide risk stratification.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: A novel comprehensive CTA score based on the extent, severity, location, and composition of CAD incorporates all aspects of coronary atherosclerosis into 1 per patient score and provides superior risk stratification then a score based on stenosis severity only.

TRANSLATIONAL OUTLOOK: A holistic approach to classify CAD improves the estimation of a patient's risk for future cardiovascular events which may translate into more accurate post-CTA medical care and improved cardiovascular outcome.

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KEY WORDS coronary computed tomography angiography, risk stratification, stable coronary artery disease

APPENDIX For supplemental tables and figures, please see the online version of this paper.