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ORIGINAL RESEARCH

Prognostic Value of AI-Based Quantitative Coronary CTA vs Human Reader-Based Visual Assessment

Results From the CONFIRM2 Registry

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ABSTRACT

BACKGROUND The severity and extent of whole heart coronary plaque volume and stenosis can be reliably measured by artificial intelligence–guided quantitative coronary computed tomography angiography (AI-QCT). Limited data are available on the potential incremental prognostic value compared with currently recommended qualitative coronary computed tomography angiography (CTA) reads and the coronary artery calcium score (CACS).

OBJECTIVES The aim of this study was to evaluate the prognostic value of AI-QCT compared with human coronary CTA reads, including the CAD-RADS (Coronary Artery Disease–Reporting and Data System), CACS, and the modified Duke Index.

METHODS CONFIRM2 (Quantitative COroNary CT Angiography Evaluation For Evaluation of Clinical Outcomes: An InteRnational, Multicenter Registry) is a multicenter, international, observational cohort study of patients undergoing clinically indicated coronary CTA with follow-up for major adverse cardiac events (MACE). Asymptomatic patients and those with cardiac history were excluded. Coronary artery disease presence, extent, and composition were quantified by AI-QCT across the coronary tree, yielding 24 patient-, vessel-, and plaque-level variables. On the basis of prior analyses, noncalcified plaque burden and diameter stenosis were identified as the strongest predictors and combined for statistical modeling as "AI-QCT." Comparator computed tomography scores included CAD-RADS, CACS, and the modified Duke Index, whereas clinical predictors were summarized in the risk factor–weighted clinical likelihood score. Area under the curve (AUC) and continuous net reclassification index (NRI) were calculated to assess the incremental value. The primary endpoint was MACE (death, myocardial infarction [MI], stroke, heart failure, late revascularization, or hospital stay for unstable angina), and the secondary endpoint was death or MI.

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ABBREVIATIONS AND ACRONYMS

AI-QCT = artificial intelligence–guided quantitative coronary computed tomography angiography

AUC = area under the curve

CACS = coronary artery calcium score

CAD = coronary artery disease

CT = computed tomography

CTA = computed tomography angiography

LAP = low attenuation plaque

MACE = major adverse cardiac events

MI = myocardial infarction

NCPV = noncalcified plaque volume

NRI = net reclassification index

PAV = percent atheroma volume

RESULTS In 1,916 patients with all risk scores available, 87 (4.5%) MACE and 27 (1.4%) death/MI events occurred during 3 years of follow-up. There was a stepwise risk increase with higher coronary artery disease classifications with CAD-RADS and CACS. The addition of AI-QCT significantly improved risk stratification for MACE compared with CAD-RADS (AUC: 0.81 vs 0.79; $P < 0.001$ and NRI: 0.47; $P < 0.001$), CACS (AUC: 0.79 vs 0.70; $P < 0.001$ and NRI 0.61; $P < 0.001$), the modified Duke Index (AUC: 0.81 vs 0.76; $P < 0.001$ and NRI: 0.52; $P < 0.001$), and CAD-RADS + CACS model (AUC: 0.81 vs 0.79; $P = 0.004$ and NRI: 0.54; $P < 0.001$). AI-QCT also improved discrimination when results were adjusted for the risk factor–weighted clinical likelihood and for the prediction of death/MI. Excluding 195 patients with severe stenosis (≥70%), in a multivariable model of CAD-RADS and AI-QCT, only AI-QCT was significantly associated with MACE and death/MI, and AI-QCT significantly improved risk stratification compared with CAD-RADS for MACE (AUC: 0.77 vs 0.72; $P < 0.001$ and NRI: 0.54; $P < 0.001$) and death/MI (AUC: 0.81 vs 0.73; $P = 0.011$ and NRI: 0.69; $P = 0.001$).

CONCLUSIONS AI-QCT provided incremental prognostic information compared with CAD-RADS 2.0, CACS, and the modified Duke Index for the prediction of MACE as well as the secondary endpoint of death or nonfatal MI. (JACC Cardiovasc Imaging. 2025;■:■–■)

Coronary computed tomography angiography (CTA) has emerged as a noninvasive modality capable of characterizing the extent and composition of coronary atherosclerosis. The recent advent of artificial intelligence (AI)-based analytical platforms has enabled rapid, automated, and reproducible quantification of plaque burden and morphology,

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thus facilitating a comprehensive evaluation of coronary atherosclerosis in clinical practice. Artificial intelligence-guided quantitative coronary computed tomography angiography (AI-QCT) has shown high concordance with intravascular ultrasound and optical coherence tomography in assessing atherosclerotic burden and identifying high-risk plaque features.[1] A prior single-center study demonstrated that AI-derived total plaque burden conferred superior prognostic value compared with the CAD-RADS (Coronary Artery Disease-Reporting and Data System) 2.0 score in predicting major adverse cardiac events (MACE).[2] However, the CAD-RADS score in this study was derived using quantitative atherosclerosis evaluation, and it remains to be determined whether AI-QCT provides incremental prognostic value compared with conventional reader-dependent visual interpretation of coronary CTA, including established clinical and imaging-based risk assessment tools such as the coronary artery calcium score (CACS), CAD-RADS 2.0, and the modified Duke Index.[3,4]

Each of these conventional approaches addresses a specific aspect of the coronary atherosclerosis spectrum. The CACS, for example, has historically been used for risk stratification rather than diagnostic evaluation. It functions as a surrogate marker of total plaque burden but assesses only the calcified component.[5] As a result, it does not reveal noncalcified plaque and may therefore underestimate disease burden, particularly in patients younger than 50 years, who had most plaque as noncalcified.[6] In contrast, the CAD-RADS 2.0 and the modified Duke Index were developed primarily for the diagnostic assessment of coronary artery disease (CAD), with an emphasis on luminal stenosis severity and the extent of obstructive disease.

Although growing evidence supports the prognostic value of total plaque quantification, its routine use in clinical practice remains limited, primarily because of the time-intensive nature of manual analysis. AI-QCT has the advantage of assessing many aspects of atherosclerosis from the entire coronary tree, which cannot be fully captured by visual computed tomography (CT) interpretation. Accordingly, the present study aims to evaluate the prognostic utility of plaque quantification using AI-QCT in a large cohort of symptomatic patients with suspected CAD and to determine whether it provides incremental prognostic value compared with traditional clinical risk scores on the basis of human reader-based visual interpretation.

METHODS

STUDY DESIGN AND PATIENT POPULATION. CONFIRM2 (COroNary CT Angiography Evaluation For Evaluation of Clinical Outcomes: An InteRnational, Multicenter Registry) is an ongoing multicenter, international, observational cohort study. Detailed descriptions of the study design have been published previously.[7] The primary aim of the CONFIRM2 registry is to assess the prognostic value of AI-based quantitative measures of coronary atherosclerosis, including plaque burden, morphology, and composition, as well as the degree of luminal obstruction for predicting MACE in patients referred for coronary CTA. Participating sites prospectively and/or retrospectively included sequential patients with a clinically indicated coronary CTA of ≥64-detector rows. Exclusion criteria for enrollment were absence of coronary CTA data or follow-up information for clinical events, pregnancy, or a noncardiac illness with life-expectancy <2 years.

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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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TABLE 1 Demographic and Baseline Characteristics

	All Patients (N = 1,916)	Patients Without MACE (n = 1,829, 95.0%)	Patients With MACE (n = 87, 5.0%)	*P* Value
Age, y	59.00 (51.00-67.00)	59.00 (51.00-67.00)	62.00 (56.00-70.00)	0.0009
Male	937 (48.9)	883 (48.3)	54 (62.1)	0.012
Race				0.222
Asian	82 (4.3)	77 (4.2)	5 (5.7)	
Black or African American	57 (3.0)	57 (3.1)	0 (0.0)	
Other	270 (14.1)	261 (14.3)	9 (10.3)	
White	1,507 (78.7)	1,434 (78.4)	73 (83.9)	
Cardiovascular risk factors				
Body mass index, kg/m^2	26.82 (24.05-30.66)	26.81 (23.96-30.65)	27.83 (24.82-30.93)	0.185
Smoker	229 (12.0)	212 (11.6)	17 (19.5)	0.020
Diabetes	289 (15.1)	266 (14.5)	23 (26.4)	0.003
Hypertension	994 (51.9)	939 (51.3)	55 (63.2)	0.044
Dyslipidemia	802 (41.9)	762 (41.7)	40 (46.0)	0.469
Family history positive for CAD	570 (29.7)	542 (29.6)	28 (32.2)	0.611
Atrial fibrillation	102 (5.3)	97 (5.3)	5 (5.7)	0.973
Heart failure	101 (5.3)	96 (5.2)	5 (5.7)	0.780
Peripheral artery disease	15 (0.8)	14 (0.8)	1 (1.1)	0.525
Cardiac symptoms				
Typical angina	296 (15.4)	274 (15.0)	22 (25.3)	0.009
Atypical angina	744 (38.8)	712 (38.9)	32 (36.8)	0.688
Noncardiac chest pain	170 (8.9)	162 (8.9)	8 (9.2)	0.914
Dyspnea	414 (21.6)	398 (21.8)	16 (18.4)	0.456
Palpitations	138 (7.2)	134 (7.3)	4 (4.6)	0.336
Syncope	27 (1.4)	24 (1.3)	3 (3.4)	0.121
Other symptoms	413 (21.6)	394 (21.5)	19 (21.8)	0.946
RF-CL				0.0005
Very low	696 (40.2)	680 (41.2)	16 (20.5)	
Low	678 (39.2)	642 (38.9)	36 (46.2)	
Moderate	356 (20.6)	330 (20.0)	26 (33.3)	
Unknown	186 (9.7)	177 (9.7)	9 (10.3)	

Values are median (Q1-Q3) or n (%), unless otherwise indicated.
CAD = coronary artery disease; MACE = major adverse cardiac events; RF-CL = risk factor–weighted clinical likelihood score.

For this analysis, we included patients with cardiac symptoms and without *prior CAD* (defined as a prior myocardial infarction [MI], prior percutaneous coronary intervention, coronary artery bypass grafting, or known ≥50% stenosis on invasive coronary angiography) who had at least 3 years of follow-up for clinical events. This study was conducted in accordance with the Declaration of Helsinki. Institutional review board approval was obtained at each participating center.

IMAGE ACQUISITION AND ANALYSIS. Coronary CTA scans were performed using various CT platforms, all of which met the requirement of using multislice CT scanners with ≥64 slices. The imaging protocol adhered to the guidelines set forth by the Society of Cardiovascular Computed Tomography.[8] Patient preparation, data acquisition, and image analysis were conducted according to the institutional policies of the participating sites. Quantitative coronary atherosclerosis evaluation was performed for every coronary artery and its branches by using an automated U.S. Food and Drug Administration–cleared AI-enabled software platform (Cleerly Labs, Cleerly Inc). The AI-enabled software uses validated convolutional neural networks for image quality assessment, coronary segmentation and labeling, lumen wall evaluation, vessel contour determination, and plaque characterization. Prior validation of the software has been documented in multicenter trials, comparing it to expert consensus, quantitative coronary angiography, fractional flow reserve, and intravascular ultrasound.[1,9] This analysis was performed on all coronary CTA scans, and only coronary segments with a diameter of ≥1.5 mm were included. Each segment was assessed for the presence of coronary atherosclerosis, defined as any tissue structure ≥1 mm^3 within the coronary artery wall that could be distinguished from surrounding

TABLE 2 AI-QCT Atherosclerotic Features for Patients With and Without Events

	All Patients (N = 1,916)	Patients Without MACE (n = 1,829, 95.0%)	Patients With MACE (n = 87, 5.0%)	*P* Value
Plaque volumes				
Total plaque volume, mm^3	55.80 (15.95-191.25)	52.80 (14.70-173.80)	315.80 (103.20-566.00)	<0.0001
Noncalcified plaque volume, mm^3	42.30 (13.05-125.55)	39.90 (12.40-114.10)	202.10 (84.50-312.30)	<0.0001
Calcified plaque volume, mm^3	5.45 (0.00-53.10)	4.80 (0.00-47.80)	64.20 (5.60-206.90)	<0.0001
Stenosis				
Quantitative diameter stenosis				<0.0001
0%	192 (10.0)	192 (10.5)	0 (0.0)	
1%-24%	999 (52.1)	981 (53.6)	18 (20.7)	
25%-49%	403 (21.0)	382 (20.9)	21 (24.1)	
50%-69%	174 (9.1)	155 (8.5)	19 (21.8)	
70%-99%	96 (5.0)	77 (4.2)	19 (21.8)	
100%	52 (2.7)	42 (2.3)	10 (11.5)	

Values are median (Q1-Q3) or n (%), unless otherwise indicated.

AI-QCT= artificial intelligence-guided quantitative computed tomography; other abbreviation as in Table 1.

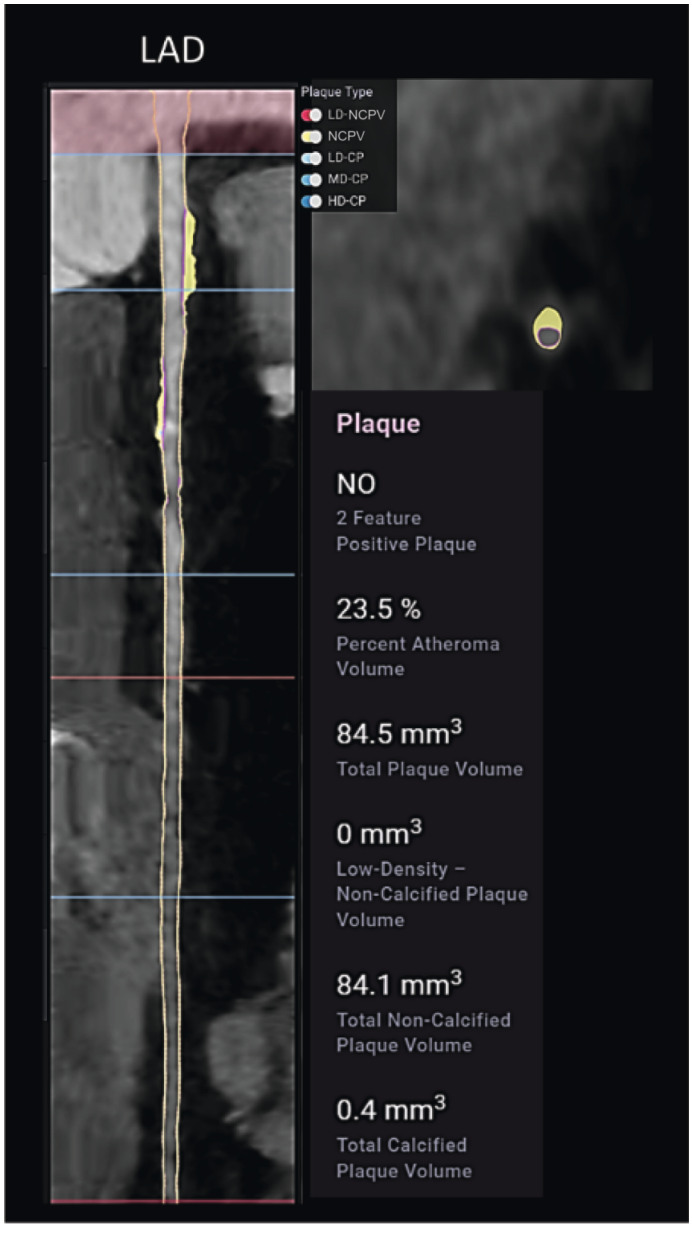
TABLE 3 Prevalence and Prognostic Value of CAD-RADS, CACS, and the Modified Duke Index

	n (%)	MACE Event Rate, n (%)	HR (95% CI) for MACE	*P* Value	Death/MI Event Rate, n (%)	HR (95% CI) for Death/MI	*P* Value
CAD-RADS 0	653 (34.1)	9 (1.4)	Ref.		3 (0.46)	Ref.	
CAD-RADS 1	392 (20.5)	4 (1.0)	0.74 (0.23-2.41)	0.621	3 (0.77)	1.67 (0.34-8.30)	0.528
CAD-RADS 2	377 (19.7)	12 (3.2)	2.34 (0.98-5.54)	0.054	3 (0.80)	1.74 (0.35-8.62)	0.497
CAD-RADS 3	299 (15.6)	25 (8.4)	6.28 (2.93-13.45)	<0.0001	13 (4.3)	9.59 (2.73-33.67)	0.0004
CAD-RADS 4A	145 (7.6)	29 (20.0)	16.04 (7.59-33.89)	<0.0001	3 (2.1)	4.52 (0.91-22.39)	0.065
CAD-RADS 4B	31 (1.6)	6 (19.4)	15.08 (5.37-42.37)	<0.0001	1 (3.2)	6.99 (0.73-67.24)	0.092
CAD-RADS 5	19 (1.0)	2 (10.5)	7.92 (1.71-36.67)	0.008	1 (5.3)	11.78 (1.23-113.27)	0.033
AUC			0.79 (0.74-0.84)	<0.0001[a]		0.74 (0.64-0.83)	0.002[a]
CACS 0	826 (42.6)	15 (1.8)	Ref.		4 (0.48)	Ref.	
CACS 1-99	541 (28.2)	20 (3.7%)	2.07 (1.06-4.04)	0.034	8 (1.5)	3.08 (0.93-10.23)	0.066
CACS 100-299	270 (14.1)	20 (7.4)	4.21 (2.15-8.21)	<0.0001	5 (1.9)	3.86 (1.04-14.37)	0.044
CACS 300-999	210 (11.0)	21 (10.0)	5.77 (2.97-11.19)	<0.0001	5 (2.4)	4.98 (1.34-18.56)	0.017
CACS >1,000	69 (3.6)	11 (15.9)	9.36 (4.30-20.37)	<0.0001	5 (7.2)	15.42 (4.14-57.44)	<0.0001
AUC			0.70 (0.65-0.76)	<0.0001[a]		0.70 (0.60-0.80)	0.002[a]
CACS, per 50-unit increase			1.03 (1.02-1.04)	<0.0001		1.03 (1.01-1.05)	0.001
AUC			0.71 (0.65-0.76)	<0.0001		0.71 (0.61-0.81)	0.002
Modified Duke Index							
Stenosis <50%	1,423 (74.3)	26 (1.8)	Ref.		9 (0.63)	Ref.	
1 vessel ≥50%	183 (9.6)	10 (5.5)	3.05 (1.47-6.32)	0.003	6 (3.3)	5.22 (1.86-14.68)	0.002
2 vessels ≥50%	65 (3.4)	12 (18.5)	11.27 (5.69-22.34)	<0.0001	6 (9.2)	15.37 (5.47-43.18)	<0.0001
1 vessel ≥50% (including proximal LAD)	108 (5.6)	15 (13.9)	8.01 (4.24-15.13)	<0.0001	2 (1.9)	2.91 (0.63-13.49)	0.171
3 vessels ≥50%/2 vessels ≥50% (including proximal LAD)	78 (4.1)	15 (19.2)	11.32 (5.99-21.37)	<0.0001	3 (3.8)	6.09 (1.65-22.50)	0.007
3 vessels ≥50% (including proximal LAD)	35 (1.8)	5 (14.3)	8.30 (3.19-21.61)	<0.0001	0 (0.0)	No events	
Left main stenosis ≥50%	22 (1.1)	4 (18.2)	10.50 (3.67-30.10)	<0.0001	1 (4.5)	7.18 (0.91-56.70)	0.061
Left main stenosis ≥70%	2 (0.1)	0 (0.0)	No events		0 (0.0)	No events	
AUC			0.76 (0.70-0.81)	<0.0001[a]		0.74 (0.65-0.84)	0.0001[a]

[a]The *P* value is from the type 3 analysis of effects tests, irrespective of whether the variable as a whole (ie, considering all categorical levels of the variable) has a statistically significant effect on the outcome after adjusting for other variables in the model.

AUC = area under the curve; CACS = coronary artery calcium score; CAD-RADS = Coronary Artery Disease-Reporting and Data System; LAD = left anterior descending artery; MI = myocardial infarction; Ref. = Reference; other abbreviation as in Table 1.

FIGURE 1 Case of a Patient With a CACS of 0 Who Experienced a Myocardial Infarction 1.8 Years After Index Coronary CTA



A 77-year-old woman underwent clinically indicated coronary CTA for chest pain. CACS demonstrated an Agatston score of 0, indicating no detectable calcifications. However, coronary CTA revealed noncalcified plaque in the LAD with a volume of 84.1 mm^3, along with a small calcified component (0.4 mm^3) identified using AI-based plaque analysis. The minimal calcified burden was below the detection threshold of the Agatston method, yielding a CACS of 0. The patient was initiated on statin therapy, but nevertheless experienced a myocardial infarction 1.8 years after index coronary CTA. Images provided by Cleerly, Inc, demonstrate the AI-based plaque quantification tool. AI = artificial intelligence; CACS = coronary artery calcium score; CTA = computed tomography angiography; HD-CP = high-density calcified plaque; LAD = left anterior descending artery; LD-CP = low-density calcified plaque; LD-NCPV = low-density noncalcified plaque volume; MD-CP = mid-density calcified plaque; NCPV = noncalcified plaque volume.

epicardial tissue, epicardial fat, or the vessel lumen. Plaque volumes (in cubic millimeters) were calculated for each coronary lesion and summed to determine the total plaque volume at the patient level. Plaque types are categorized on the basis of HU ranges: low attenuation plaque (LAP) as <30 HU, noncalcified plaque as HU between 30 and 350, and calcified plaque as >350 HU. The vessel volume includes all coronary segments with a diameter of ≥1.5 mm, regardless of plaque presence, differing from other quantitative CT software, which may include only segments containing plaque. In cases where image quality was degraded by motion, insufficient opacification, beam hardening, or other artifacts, only the portions of the coronary artery with compromised quality were omitted from the analysis. Finally, a credentialed and trained radiologic technologist provides a quality assurance overview of the AI-based analysis.

STANDARD CT EVALUATION. From the clinical reports derived from the individual sites, we derived CAD-RADS, CACS, and the modified Duke Index. Patients were categorized into CAD-RADS categories according to its standardized reporting system,[3] and if the specific category was not reported in the document, it was based on circumstantial information provided within the report. In cases where quantitative stenosis percentages were not explicitly reported, CAD-RADS scores were inferred using the descriptive terminology provided in the clinical reports. Terms such as "mild," "moderate," or "severe" were systematically mapped to CAD-RADS categories by analyzing the reporting patterns within the institution. In addition, high-risk plaque was reported in only a very small number of cases, and the overall burden of atherosclerosis was not reported systematically. As such, these modifiers were not included. The CACS was derived from the report, and the modified Duke Index was calculated on the basis of its individual components.[4]

ENDPOINTS. The primary endpoint was the incidence rate of MACE over a minimum follow-up of 3 years. MACE was defined as a composite of all-cause mortality, MI, stroke, congestive heart failure, late revascularizations (occurring >90 days after index coronary CTA), and hospital stay for unstable angina. Event definitions have been previously published.[7] Death status was confirmed through signed verification forms submitted by the local principal investigators. The secondary endpoint was a composite of all-cause mortality and MI. MACE was recorded and adjudicated by a clinical events committee.

TABLE 4 Models of AI-QCT Without and With CAD-RADS

	MACE	*P* Value	Death/MI	*P* Value
Model: AI-QCT				
Lumen diameter stenosis, per 10%	1.32 (1.23-1.43)	<0.0001	1.26 (1.09-1.44)	0.001
Noncalcified plaque volume, per 50 mm^3	1.05 (1.01-1.10)	0.026	1.08 (1.01-1.16)	0.036
AUC	0.79 (0.75-0.84)		0.79 (0.71-0.87)	
Model: CAD-RADS + AI-QCT				
CAD-RADS category				
0	Ref.		Ref.	
1	0.63 (0.19-2.04)	0.436	1.27 (0.25-6.37)	0.770
2	1.56 (0.64-3.82)	0.326	0.92 (0.18-4.84)	0.924
3	3.03 (1.27-7.22)	0.013	2.90 (0.65-12.95)	0.163
4A	5.08 (1.90-13.57)	0.001	0.74 (0.10-5.39)	0.768
4B	5.10 (1.57-16.62)	0.007	1.32 (0.11-15.89)	0.829
5	1.26 (0.21-7.68)	0.803	0.72 (0.04-11.67)	0.814
Lumen diameter stenosis, per 10%	1.16 (1.04-1.29)	0.008	1.26 (1.05-1.51)	0.015
Noncalcified plaque volume, per 50 mm^3	1.06 (1.01-1.12)	0.029	1.08 (1.01-1.15)	0.032
AUC	0.81 (0.76-0.86)		0.80 (0.72-0.88)	

Values are HR (95% CI), unless otherwise indicated.
Abbreviations as in Tables 2 and 3.

STATISTICAL ANALYSIS. Continuous variables were assessed for normality using the Kolmogorov-Smirnov test. All the continuous variables were non-normally distributed and thus they are presented as median (Q1-Q3); the Wilcoxon rank sum test was used to test a group difference. Categorical variables are expressed as absolute numbers and percentages, and the chi-square test was conducted to assess a group difference.

AI-QCT statistical model. Prior multivariable evaluation of the CONFIRM2 data identified quantitative diameter stenosis and noncalcified plaque volume (NCPV) as the 2 independent determinants for MACE.[10] Briefly, 24 candidate CT metrics based on clinical utility and prior studies were evaluated for their prognostic value: percent diameter stenosis, percent area stenosis, number of moderate stenoses (50%-69%), number of severe stenoses (≥70%), total plaque volume, calcified plaque volume, NCPV, LAP volume, percent atheroma volume (PAV), PAV calcified plaque, PAV noncalcified plaque, PAV LAP, number of high-risk plaques, plaque diffuseness (total plaque volume/vessel length), total vessel length, left main with moderate stenosis, left main with severe stenosis, proximal left anterior descending artery with moderate stenosis, proximal left anterior descending artery with severe stenosis, number of chronic total occlusions (100% stenosis), lumen volume, vessel volume, lumen volume/vessel length, and minimal luminal diameter. A logistic regression model was used to exclude collinear variables (variance inflation factor >5). Using backward selection ($P < 0.05$), a parsimonious multivariable model was created to identify independent predictors of MACE among candidate AI-QCT variables, which eventually consisted of only 2 variables: diameter stenosis and NCPV.

Univariable and multivariable Cox regression analyses were performed to identify the prognostic value of the specific risk scores. Furthermore, the incremental prognostic value of AI-QCT compared with the standard CT risk scores was evaluated by assessing the increase in the area under the curve (AUC). A continuous net reclassification index (NRI) was used to assess the incremental value of AI-QCT in predicting outcomes compared with CACS, modified Duke Index, and CAD-RADS scores. These analyses were adjusted for the European Society of Cardiology's risk factor-weighted clinical likelihood score, including age, sex, symptoms, and traditional risk factors. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc). A value of $P < 0.05$ was considered statistically significant.

RESULTS

PATIENTS AND AI-QCT FINDINGS. A total of 1,916 patients (median age: 59 years [Q1-Q3: 51-67 years]; 48.9% male) had all risk scores (CAD-RADS, CACS, and the modified Duke Index) available. During the 3-year follow-up period, 87 primary events (14 deaths [16%], 11 MI [13%], 40 revascularizations [46%], 2 congestive heart failure [2%], 9 cerebrovascular accidents [10%], and 11 unstable angina [13%]) and 27

TABLE 5 AUC and NRI Analysis of AI-ACT in Addition to the CACS, Modified Duke Index, and CAD-RADS Scores for the Prediction of MACE and Death/MI

	MACE	Death/MI
CAD-RADS	0.79 (0.74-0.84)	0.74 (0.64-0.83)
vs	vs	vs
CAD-RADS + AI-QCT[a]	0.81 (0.76-0.86)	0.80 (0.72-0.88)
AUC	$P = 0.0003$	$P = 0.004$
NRI	0.47 (0.26-0.68)	0.55 (0.18-0.93)
	$P < 0.0001$	$P = 0.004$
CACS categories	0.70 (0.65-0.76)	0.70 (0.60-0.80)
vs	vs	vs
CACS categories + AI-QCT[a]	0.79 (0.74-0.84)	0.79 (0.70-0.87)
AUC	$P < 0.0001$	$P = 0.018$
NRI	0.61 (0.40-0.82)	0.57 (0.19-0.94)
	$P < 0.0001$	$P = 0.004$
Modified Duke Index	0.76 (0.70-0.81)	0.74 (0.65-0.84)
vs	vs	vs
Modified Duke Index + AI-QCT[a]	0.81 (0.77-0.86)	0.81 (0.72-0.89)
AUC	$P < 0.0001$	$P = 0.006$
NRI	0.52 (0.31-0.74)	0.53 (0.15-0.90)
	$P < 0.0001$	$P = 0.007$
Controlled for RF-CL		
CAD-RADS	0.80 (0.75-0.86)	0.79 (0.70-0.88)
vs	vs	vs
CAD-RADS + AI-QCT[a]	0.83 (0.78-0.88)	0.85 (0.76-0.94)
AUC	$P = 0.002$	$P = 0.006$
NRI	0.52 (0.30-0.74)	0.83 (0.45-1.20)
	$P < 0.0001$	$P = 0.0001$
CACS categories	0.72 (0.66-0.78)	0.70 (0.59-0.82)
vs	vs	vs
CACS categories + AI-QCT[a]	0.80 (0.75-0.85)	0.81 (0.73-0.89)
AUC	$P < 0.0001$	$P = 0.028$
NRI	0.63 (0.40-0.85)	0.82 (0.43-1.21)
	$P < 0.0001$	$P = 0.0001$
Modified Duke Index	0.77 (0.70-0.83)	0.80 (0.72-0.88)
vs	vs	vs
Modified Duke Index + AI-QCT[a]	0.82 (0.76-0.87)	0.84 (0.75-0.93)
AUC	$P = 0.0004$	$P = 0.048$
NRI	0.53 (0.31-0.75)	0.61 (0.20-1.03)
	$P < 0.0001$	$P = 0.004$

Values are AUC or NRI values with 95% CI. [a]AI-QCT: consisting of the variables quantitative noncalcified plaque volume and diameter stenosis.

NRI = net reclassification index; other abbreviations as in Tables 1 to 3.

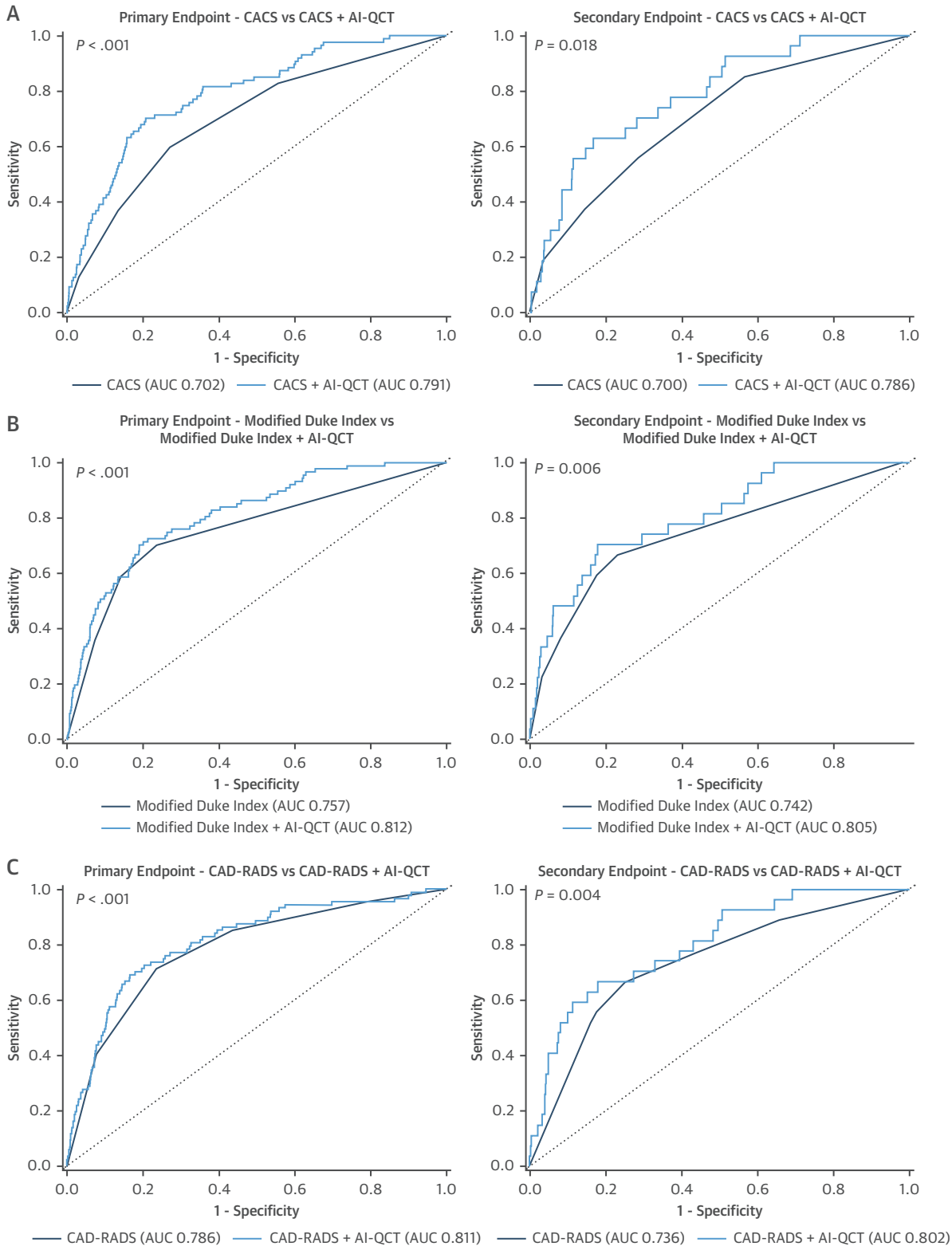
secondary events (16 deaths [59%] and 11 MI [41%]) occurred. Patients mainly presented with atypical angina (38.8%) (n = 744) or dyspnea (21.6%) (n = 414) (Table 1). Patients with MACE were significantly older, more often male, and had higher prevalences of current smoking, diabetes, and hypertension. Total plaque volume and its subcomponents—NCPV and calcified plaque volume—were higher in those with MACE, as was the maximum quantitative diameter stenosis by AI-QCT (Table 2). Supplemental Table 1 lists the median values of total plaque volume, NCPV, and calcified plaque volume for each of the CAD-RADS, CACS, and the modified Duke Index categories.

PROGNOSTIC VALUE OF STANDARD CT QUALITATIVE EVALUATION. The CAD-RADS, CACS, and modified Duke Index categories are provided in Table 3. Most patients were within the lowest-risk groups: 42.6% (n = 826) had a CACS of 0, 74.3% (n = 1,423) had stenosis <50% according to the modified Duke Index, and 34.1% (n = 653) had a CAD-RADS of 0. There was a stepwise increase in risk with higher CAD classifications by CAD-RADS and CACS (Table 3). Figure 1 illustrates a case of a patient with a CACS of 0 who experienced an MI 1.8 years after index coronary CTA. For CAD-RADS, no significant association with events was observed for categories 1 and 2, while risk increased significantly for categories ≥3. All CACS categories >0 and modified Duke Index categories with ≥1 artery with ≥50% diameter stenosis were associated with events (Table 3). The AUCs for MACE and death/MI, respectively, were 0.79 (95% CI: 0.74-0.84) and 0.74 (95% CI: 0.64-0.83) for CAD-RADS categories, 0.70 (95% CI: 0.65-0.76) and 0.70 (95% CI: 0.60-0.80) for CACS categories, and 0.76 (95% CI: 0.70-0.81) and 0.74 (95% CI: 0.65-0.84) for modified Duke Index categories (Table 3).

PROGNOSTIC VALUE OF AI-QCT. The AI-QCT model, consisting of quantitative diameter stenosis and NCPV, predicted MACE and death/MI, with AUCs of 0.79 (95% CI: 0.75-0.84) and 0.79 (95% CI: 0.71-0.87), respectively (Table 4). In a combined model of CAD-RADS and AI-QCT, CAD-RADS categories 3, 4A, and 4B and quantitative diameter stenosis and NCPV measured by AI-QCT were significantly associated with MACE. For the endpoint death/MI, only AI-QCT was a significant predictor (Table 4). Supplemental Tables 2 and 3 present the combined models of CAD-RADS, CACS, and AI-QCT, where NCPV is reported in quartiles, showing associations of the upper quartile of NCPV with MACE (HR: 4.2; 95% CI: 1.3-13.9) and death/MI (HR: 3.0; 95% CI: 0.9-10.6).

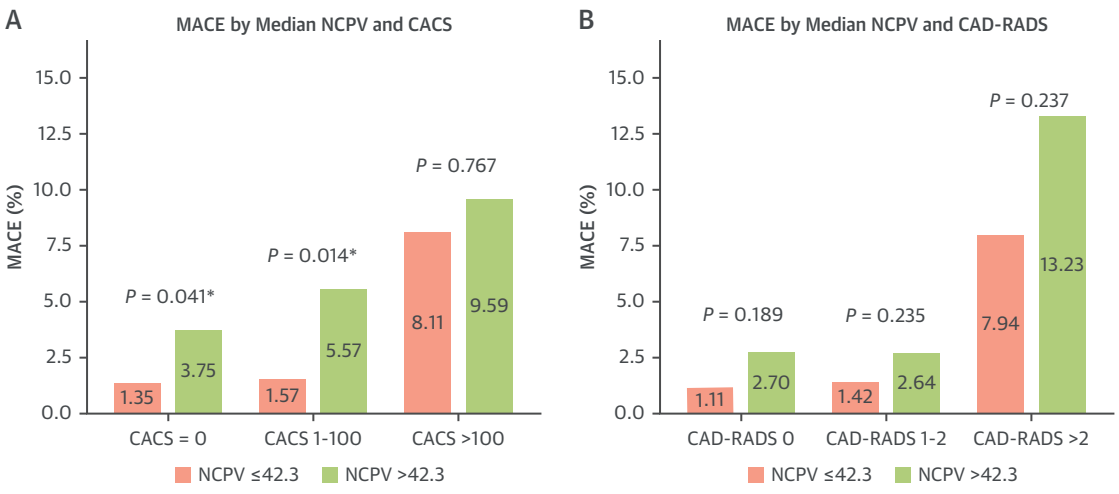
INCREMENTAL PROGNOSTIC VALUE OF AI-QCT COMPARED WITH CAD-RADS, CACS, AND THE MODIFIED DUKE INDEX. The addition of AI-QCT significantly improved discrimination for MACE compared with a model of clinical predictors (risk factor-weighted clinical likelihood score) combined with either CACS (AUC: 0.80 [95% CI: 0.75-0.85] vs 0.72 [95% CI: 0.66-0.78]; $P < 0.001$), modified Duke Index (AUC: 0.82 [95% CI: 0.76-0.87] vs 0.77 [95% CI: 0.70-0.83]; $P = 0.0004$), or CAD-RADS (0.83 [95% CI: 0.78-0.88]) vs 0.80 [95% CI: 0.75-0.86]; $P = 0.002$)

FIGURE 2 Comparisons of AUC When AI-QCT (Consisting of the Variables Quantitative Noncalcified Plaque Volume and Diameter Stenosis) Are Added to the Indicated Scores



Incremental prognostic value of AI-QCT added to CACS (A), the modified Duke Index (B), and the CAD-RADS score (C). AI-QCT = artificial intelligence–guided quantitative computed tomography; AUC = area under the curve; CAD-RADS = Coronary Artery Disease–Reporting and Data System; other abbrevations as in Figure 1.

FIGURE 3 MACE Rates Across Subgroups of CACS and CAD-RADS Stratified by Median Noncalcified Plaque Volume



MACE rates across subgroups defined by CACS (A) and CAD-RADS score (B), with additional risk stratification by noncalcified plaque volume. MACE = major adverse cardiac events; other abbreviations as in Figures 1 and 2.

(Table 5). Similarly, for the endpoint death/MI and for models uncorrected for the risk factor-weighted clinical likelihood, the addition of AI-QCT significantly improved risk prediction (Table 5, Figure 2). AI-QCT resulted in a statistically significant NRI when added to CAD-RADS, CACS, and the modified Duke Index (Table 5). The addition of NCPV quartiles significantly improved the NRI compared with CAD-RADS alone (Supplemental Table 2).

Figure 3 depicts MACE rates stratified by CACS and CAD-RADS categories, further subdivided on the basis of whether NCPV is above or below the median value of 42.3 mm^3 (Q1-Q3: 13.05-125.5 mm^3) (Central Illustration).

INCREMENTAL PROGNOSTIC VALUE OF AI-QCT COMPARED WITH CAD-RADS COMBINED WITH CACS. In a multivariable model combining CAD-RADS, CACS, and AI-QCT, only CAD-RADS categories 3, 4A, and 4B and the AI-QCT variables diameter stenosis and noncalcified plaque were associated with MACE while only AI-QCT was predictive for death/MI (Table 6). Risk stratification improved significantly with the addition of AI-QCT to CAD-RADS + CACS for MACE (AUC: 0.81 vs 0.79; $P = 0.004$ and NRI: 0.54; $P < 0.0001$) and for death/MI (AUC: 0.81 vs 0.76; $P = 0.083$ and NRI: 0.67; $P = 0.0006$) (Table 7).

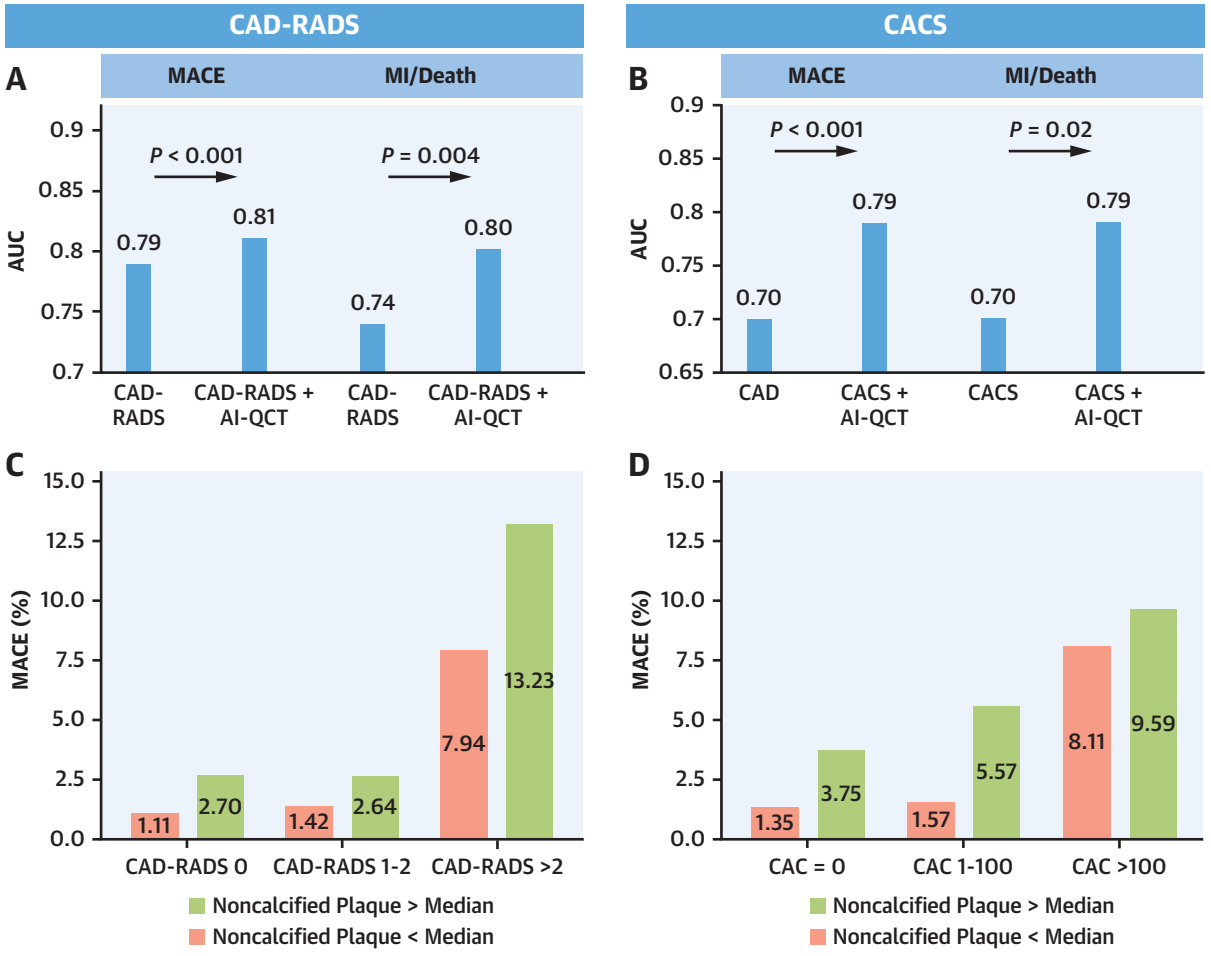
PROGNOSTIC VALUE OF STANDARD CT EVALUATION AND AI-QCT IN PATIENTS WITHOUT SEVERE STENOSIS. After excluding 195 (10%) patients with >70% stenosis (or CAD-RADS category >4), 1,721 (90%) patients remained in the study cohort. In a statistical model of both AI-QCT and CAD-RADS, only diameter stenosis and NCPV were associated with MACE and/or death/MI. The AUC for the prediction of MACE was 0.72 (95% CI: 0.65-0.79) for CAD-RADS, which increased significantly to 0.77 (95% CI: 0.69-0.84) ($P < 0.0001$) with the addition of AI-QCT (Table 8). Moreover, adding AI-QCT to CAD-RADS increased the AUC for the endpoint death/MI: 0.81 (95% CI: 0.72-0.90) vs 0.73 (95%: CI 0.62-0.85) (Table 8, Figure 4). The addition of AI-QCT to CAD-RADS significantly improved the NRI for both endpoints (Table 8).

DISCUSSION

CONFIRM2 is a multicenter global registry using AI-guided coronary CTA assessment, and the present study demonstrated that quantification of stenosis and the totality of noncalcified plaque from the coronary tree improved risk stratification compared with qualitative coronary CTA reporting methods, including the modified Duke Index, CAD-RADS 2.0, and CACS (Central Illustration).

The CACS represents a simple, highly reproducible metric that can be obtained without the need for contrast administration and serves as a robust surrogate for the presence and extent of coronary atherosclerosis. It correlates closely with total plaque burden and provides proportionate predictive value for future adverse cardiovascular events.[5] In addition, CACS offers incremental prognostic information

CENTRAL ILLUSTRATION **Incremental Prognostic Value of AI-QCT Compared With CAD-RADS and CACS**



van Rosendael A, et al. JACC Cardiovasc Imaging. 2025;■(■):■-■.

A and B show the significant increase in AUC when AI-QCT (consisting of the variables quantitative noncalcified plaque volume and diameter stenosis) is added to CAD-RADS (A) and CACS (B) for the MACE endpoint and Death/MI. C and D show the MACE rates among subgroups of CAD-RADS and CACS and when patients are stratified according the median of the noncalcified plaque volume. AI-QCT = artificial intelligence-guided quantitative computed tomography; AUC = area under the curve; CACS = coronary artery calcium score; CAD-RADS = Coronary Artery Disease-Reporting and Data System; MACE = major adverse cardiac events; MI = myocardial infarction.

beyond traditional risk factors and has been integrated into decision-making frameworks for initiating preventive pharmacologic therapies and as a gatekeeper for further testing in patients with chronic coronary syndromes. However, CACS does not capture the burden of noncalcified plaque, which is regarded as an early manifestation of atherosclerosis and is more prone to rupture. In contrast, CACS increases with the densification of calcium, which actually relates to a reduction in future coronary event risk. In a pooled cohort of 37,808 asymptomatic subjects with a CACS of 0, noncalcified plaques were present in 10% of cases and 1.1% demonstrated obstructive CAD due to noncalcified lesions.[11] Although these rates are substantially higher in symptomatic patients, a study from the CONFIRM-1 trial involving 10,037 symptomatic individuals found that 3.5% of those without calcifications were found to have obstructive CAD.[12] In the present study, CACS provided significant risk estimation, with a 10-fold and 15-fold increase in risk for MACE and death/MI, respectively, in patients with CACS >1,000. Nevertheless, overall risk discrimination by AUC was moderate (0.70; 95% CI: 0.65-0.76). This finding is

TABLE 6 Models of CAD-RADS + CACS Without and With AI-QCT

	MACE	*P* Value	Death/MI	*P* Value
Model: CAD-RADS + CACS				
CAD-RADS				
0	Ref.		Ref.	
1	0.82 (0.22-3.10)	0.772	0.92 (0.09-9.67)	0.941
2	2.52 (0.80-7.96)	0.116	0.84 (0.07-10.22)	0.889
3	6.50 (2.15-19.65)	0.001	4.06 (0.39-42.72)	0.243
4A	16.12 (5.37-48.37)	<0.0001	1.75 (0.13-22.59)	0.670
4B	14.43 (3.79-54.92)	<0.0001	2.37 (0.11-51.08)	0.582
5	7.68 (1.35-43.70)	0.022	3.77 (0.18-79.69)	0.394
CACS				
0	Ref.		Ref.	
1-99	0.85 (0.34-2.12)	0.720	2.19 (0.27-17.40)	0.460
100-299	0.98 (0.39-2.50)	0.971	1.94 (0.22-17.48)	0.553
300-999	0.99 (0.39-2.52)	0.977	2.16 (0.24-19.74)	0.496
>1,000	1.26 (0.45-3.54)	0.664	6.01 (0.64-56.36)	0.116
AUC	0.79 (0.74-0.84)		0.76 (0.67-0.85)	
Model: CAD-RADS + CACS + optimal AI-QCT				
CAD-RADS				
0	Ref.		Ref.	
1	0.86 (0.23-3.19)	0.823	0.92 (0.09-9.26)	0.943
2	2.44 (0.77-7.68)	0.128	0.72 (0.06-8.67)	0.799
3	4.92 (1.58-15.35)	0.006	2.32 (0.21-25.57)	0.492
4A	8.00 (2.41-26.53)	0.001	0.61 (0.04-8.94)	0.716
4B	8.71 (2.16-35.09)	0.002	1.12 (0.05-26.04)	0.943
5	1.82 (0.27-12.41)	0.542	0.59 (0.02-16.20)	0.755
CACS				
0	Ref.		Ref.	
1-99	0.62 (0.24-1.57)	0.315	1.64 (0.21-12.93)	0.640
100-299	0.57 (0.22-1.51)	0.260	1.07 (0.12-9.83)	0.951
300-999	0.50 (0.18-1.36)	0.172	1.00 (0.11-9.48)	0.999
>1,000	0.44 (0.14-1.42)	0.169	1.43 (0.12-16.69)	0.774
Lumen diameter stenosis, per 10%	1.17 (1.05-1.30)	0.004	1.26 (1.05-1.52)	0.015
Noncalcified plaque volume, per 50 mm^3	1.08 (1.02-1.14)	0.013	1.08 (0.99-1.17)	0.078
AUC	0.81 (0.76-0.86)		0.80 (0.72-0.89)	

Values are HRs and AUC values with 95% CIs, unless otherwise indicated.
Abbreviations as in Tables 2 and 3.

TABLE 7 AUC and NRI Analysis of AI-QCT in Addition to the CAD-RADS and CACS for the Prediction of MACE and Death/MI

	MACE	Death/MI
CAD-RADS + CACS	0.79 (0.74-0.84)	0.76 (0.67-0.85)
vs	vs	vs
CAD-RADS + CACS + AI-QCT	0.81 (0.76-0.86)	0.81 (0.72-0.89)
AUC	$P = 0.004$	$P = 0.083$
NRI	0.54 (0.33-0.75)	0.67 (0.31-1.03)
	$P < 0.0001$	$P = 0.0006$
CAD-RADS + CACS + RF-CL	0.81 (0.76-0.86)	0.80 (0.70-0.89)
vs	vs	vs
CAD-RADS + CACS + RF-CL + AI-QCT	0.83 (0.79-0.88)	0.85 (0.76-0.94)
AUC	$P = 0.002$	$P = 0.018$
NRI	0.26 (0.03-0.48)	0.83 (0.45-1.20)
	$P = 0.026$	$P = 0.0001$

Values are HRs or AUCs with 95% CIs.
Abbreviations as in Tables 1 to 3 and 5.

comparable to a recent study of 2,404 patients followed for all-cause death and MI over 7 years.[13] This study similarly showed that the addition of overall plaque burden (noncalcified and calcified) improved event discrimination compared to CACS. Presumably, the reduced prognostic accuracy could be explained by the fact that calcium is not the primary driver of events, given that noncalcified plaque burden has a stronger association with outcomes.[10,13] Moreover, the calcification of atherosclerosis may represent a more "stabilizing" sign, as indicated by serial coronary CTA studies involving statins.[14-16] In addition, trials with icosapent ethyl and colchicine have shown efficacy in reducing low-density volume or NCPV on serial coronary CTA, without affecting calcium levels.[14-18]

CAD-RADS 2.0 was developed to standardize the assessment and improve the reporting of coronary

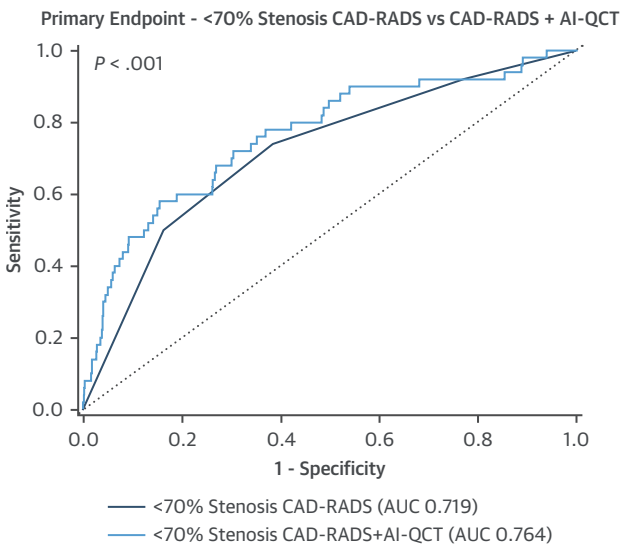
TABLE 8 AI-QCT and CAD-RADS Models in Patients With <70% Stenosis (N = 1,721)

	MACE	*P* Value	Death/MI	*P* Value
Model: CAD-RADS				
CAD-RADS				
0	Ref.		Ref.	
1	0.74 (0.23-2.41)	0.621	1.67 (0.34-8.29)	0.528
2	2.34 (0.99-5.55)	0.054	1.74 (0.35-8.62)	0.498
3	6.24 (2.91-13.38)	<0.0001	9.58 (2.73-33.61)	0.0004
AUC	0.72 (0.65-0.79)		0.73 (0.62-0.85)	
Model: AI-QCT				
Lumen diameter stenosis, per 10%	1.32 (1.18-1.47)	<0.0001	1.36 (1.16-1.60)	0.0001
Noncalcified plaque volume, per 50 mm^3	1.11 (1.05-1.17)	0.0002	1.11 (1.04-1.18)	0.001
AUC	0.77 (0.71-0.83)		0.81 (0.72-0.90)	
Model: CAD-RADS + AI-QCT				
CAD-RADS				
0	Ref.		Ref.	
1	0.57 (0.17-1.87)	0.355	1.25 (0.25-6.27)	0.789
2	1.27 (0.51-3.19)	0.608	0.88 (0.17-4.67)	0.881
3	2.04 (0.78-5.38)	0.147	2.62 (0.55-12.35)	0.224
Lumen diameter stenosis, per 10%	1.22 (1.06-1.40)	0.005	1.25 (1.02-1.54)	0.029
Noncalcified plaque volume, per 50 mm^3	1.10 (1.04-1.16)	0.001	1.10 (1.03-1.17)	0.005
AUC	0.77 (0.69-0.84)	<0.0001 (vs CAD-RADS)	0.81 (0.72-0.90)	0.011 (vs CAD-RADS)
NRI (CAD-RADS vs CAD-RADS + AI-QCT)	0.54 (0.27-0.82)	0.0002	0.69 (0.28-1.09)	0.001

Values are HRs, AUC, or NRI values with 95% CIs, unless otherwise indicated.
Abbreviations as in Tables 2 and 3.

CTA and facilitate research by providing a globally consistent system for evaluating CAD using coronary CTA.[3] This standardization enables comparison across studies and clinical practices. The CAD-RADS system primarily focuses on diagnosing CAD in symptomatic patients, inherently emphasizing the degree of luminal stenosis. Several studies, including the CONFIRM-1 trial, have demonstrated that obstructive CAD is a critical prognostic parameter, with a proportional increase in adverse events as the extent and severity of obstructive CAD increases.[19,20] A recent meta-analysis of 37,596 coronary CTA scans demonstrated that CAD-RADS 2.0 is a strong predictor of adverse events.[21] Notably, the AUC reported in this meta-analysis (0.82) closely mirrors the AUC observed in the present study. The present findings demonstrate that CAD-RADS primarily enhances risk stratification in patients with obstructive stenosis. However, they also highlight the limitations of relying on visual estimates of diameter stenosis in patients with nonobstructive CAD, as individuals categorized as CAD-RADS 1 and 2 did not exhibit a higher risk than did those with CAD-RADS 0. In these patients, the degree of stenosis alone may not be adequate for precise risk stratification. This is particularly relevant given the growing interest in the early detection of risk associated with nonobstructive plaque, supported by observations that extensive nonobstructive CAD may confer a risk comparable to obstructive stenosis.[22] These findings are further supported by the meta-analysis performed by Kato et al,[21] which demonstrated that the predictive value

FIGURE 4 Incremental Prognostic Value of AI-QCT Added to the CAD-RADS Score in Patients With <70% Diameter Stenosis



Abbreviations as in Figure 2.

of CAD-RADS 2.0 is particularly pronounced in higher CAD-RADS categories, specifically those beyond 4B. Stenosis assessment may also be affected by interpretive bias among readers who primarily focus on obstructive CAD, potentially resulting in reduced accuracy or attention in evaluating nonobstructive stenosis. This tendency is arguably driven in part by the demands of busy clinical practice, where the primary focus is on identifying obstructive appearing stenosis, as it typically leads to changes in management. Notably, in the SCOT-HEART (Scottish COmputed Tomography of the HEART) trial, although all subgroups showed benefit, the largest relative risk reduction with a coronary CTA-first strategy was observed in patients with nonanginal chest pain (HR: 0.45; 95% CI: 0.19-1.03) and those who received a diagnosis without angina due to CAD.[23] A study by Honigberg et al[24] further highlighted a significant gap in the management of patients who received a diagnosis of nonobstructive CAD after coronary CTA in the emergency department. Despite the known benefits of statin therapy, only 56% of these patients were prescribed statins after coronary CTA. Notably, 30% of patients with nonobstructive CAD and a 10-year atherosclerotic cardiovascular disease risk of ≥20% were not initiated on statin therapy by the end of the follow-up period.[24] This highlights the potential to improve risk-based treatment strategies and the substantial clinical benefit of managing subclinical CAD.

CAD-RADS 2.0 emphasizes that in addition to the most severe stenosis, a measure of plaque burden (such as CACS or segment involvement score) should be incorporated for risk stratification and medical management. The multivariable model in the present study, including CAD-RADS, CACS, and AI-QCT, shows that although CACS categories were not prognostic, NCPV was—findings that further reinforce the importance of focusing on this compositional plaque type.

STUDY LIMITATIONS. CONFIRM2 is an observational registry of patients with a clinical indication for coronary CTA, which is associated with inherent selection bias. Given the recommendation of CAD-RADS for clinical CT reporting, the referring physicians likely performed clinical management on the basis of this score, which may have had effects on MACE risk. AI-QCT evaluation was performed "retrospectively" and was not available to the physician at that time. Clinical reporting was site-determined and therefore potentially associated with a higher interobserver variability compared with core-laboratory adjudication. The low number of events limited robust and detailed analysis of the added value of AI-QCT within subgroups of the different CT scores. Furthermore, the relatively small sample size may limit the strength of the conclusions regarding adverse events and increase the risk of a type II error. In addition, the use of congestive heart failure might have introduced bias in the endpoint used; however, similar results were obtained pertaining the secondary endpoint of death/MI. CAD-RADS 2.0 also mentions high-risk plaque assessment, but this was reported in insufficient cases to be included in the present analysis.

CONCLUSIONS

This first multicenter global registry using AI-QCT, including plaque features such as NCPV and stenosis severity, provides evidence of improved risk stratification for MACE compared with conventional qualitative risk stratification tools, including CACS, the modified Duke Index, and CAD-RADS 2.0. The adoption of standardized, rapid, and quantitative assessment of CAD may facilitate the broader clinical integration of multidimensional plaque evaluation as a cornerstone component of risk stratification and management.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Quantification of noncalcified coronary plaque and stenosis provides incremental prognostic information to current standards or coronary CTA reporting, such as CAD-RADS and CACS. The findings strengthen the importance of noncalcified plaque assessment for prognosis, which can be facilitated with automated quantitative CT software.

TRANSLATIONAL OUTLOOK: Future trials should evaluate the efficacy of tailoring anti-atherosclerotic therapies or revascularization strategies on the basis of the quantification of CT-defined atherosclerosis.

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