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CTA-Derived Plaque Characteristics and Risk of Acute Coronary Syndrome in Patients With Coronary Artery Calcium Score of Zero: Insights From the ICONIC Trial

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BACKGROUND. Coronary artery calcium (CAC) scoring is used to stratify acute coronary syndrome (ACS) risk. Nonetheless, patients with a CAC score of zero (CAC_0) remain at risk from noncalcified plaque components.

OBJECTIVE. The purpose of this study was to explore CTA-derived coronary artery plaque characteristics in symptomatic patients with CAC_0 who subsequently have ACS through comparisons with patients with a CAC score greater than 0 ($CAC_{>0}$) who subsequently have ACS as well as with patients with CAC_0 who do not subsequently have ACS.

METHODS. This study entailed a secondary retrospective analysis of prior prospective registry data. The international multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry collected longitudinal observational data on symptomatic patients who underwent clinically indicated coronary CTA from January 2004 to May 2010. ICONIC (Incident Coronary Syndromes Identified by CT) was a nested cohort study conducted within CONFIRM that identified patients without known coronary artery disease (CAD) at the time of CTA who did and did not subsequently have ACS (i.e., the ACS and control groups, respectively) and who were propensity matched in a 1:1 ratio on the basis of CAD risk factors and CAD severity on CTA. The present ICONIC substudy selected matched patients in the ACS and control groups who both had documented CAC scores. CTA examinations were analyzed using artificial intelligence software for automated quantitative plaque assessment. In the ACS group, invasive angiography findings were used to identify culprit lesions.

RESULTS. The present study included 216 patients (mean age, 55.6 years; 91 women and 125 men), with 108 patients in each of the ACS and control groups. In the ACS group, 23% ($n = 25$) of patients had CAC_0. In the ACS group, culprit lesions in the subsets of patients with CAC_0 and $CAC_{>0}$ showed no significant differences in fibrous, fibrofatty, or necrotic-core plaque volumes ($p > .05$). In the CAC_0 subset, patients with ACS, compared with control patients, had greater mean (± SD) fibrous plaque volume (29.4 ± 42.0 vs 5.5 ± 15.2 mm^3, $p < .001$), fibrofatty plaque volume (27.3 ± 52.2 vs 1.3 ± 3.7 mm^3, $p < .001$), and necrotic-core plaque volume (2.8 ± 6.4 vs 0.0 ± 0.1 mm^3, $p < .001$).

CONCLUSION. After propensity-score matching, 23% of patients with ACS had CAC_0. Patients with CAC_0 in the ACS and control groups showed significant differences in volumes of noncalcified plaque components.

CLINICAL IMPACT. Methods that identify and quantify noncalcified plaque forms may help characterize ACS risk in symptomatic patients with CAC_0.

The coronary artery calcium (CAC) score is routinely used to prognosticate an individual's risk for acute coronary syndrome (ACS), with a higher CAC score indicating higher ACS risk. Additionally, a CAC score of 0 (CAC_0) has been inferred to indicate a low risk of ACS in comparison with a CAC score greater than zero ($CAC_{>0}$). Indeed, CAC_0 has consistently been cited as justification for delaying statin therapy in patients with coronary artery disease (CAD), with such patients instead reassessed after an interval of up to 10 years [1].

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Confidence in CAC-based risk assessment is grounded in the results of both multicenter trials showing low annual population-based rates of ACS in patients with CAC_0 [2–4] and studies showing increases in mortality or major adverse cardiovascular events (MACE) in patients with increasing CAC scores [5–7]. Nonetheless, data from large cohort studies have shown that one in four cardiovascular events occurs in patients with CAC_0 [8]. Furthermore, results from the PARADIGM (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging) trial suggest that accelerated formation of calcified plaque and slowed progression of noncalcified plaque represent a stabilizing disease pattern that may account for the improved outcomes associated with statin use [9]. Similarly, the SCOT-HEART (Scottish Computed Tomography of the HEART) trial and the ICONIC (Incident Coronary Syndromes Identified by CT) study identified subsets of noncalcified plaque, such as low-attenuation, fibrofatty, and necrotic-core plaque, that may be characterized by coronary CTA and serve as strong independent risk factors for adverse outcomes [10–13]. Such findings suggest the presence of alternative pathologic plaque characteristics that are unaddressed by CAC-based assessment, given that method's inherent reflection of calcified plaque only. The role of CAC scores in indicating ACS risk, independent of confounding factors such as demographic characteristics or plaque burden, remains incompletely addressed, particularly in symptomatic patients.

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Highlights

Key Finding

- *Among propensity score–matched symptomatic patients who underwent coronary CTA and had CAC_0, ACS group patients had significantly greater mean fibrous, fibrofatty, and necrotic-core plaque volumes than control patients (29.4 ± 42.0 vs 5.5 ± 15.2 mm^3, 27.3 ± 52.2 vs 1.3 ± 3.7 mm^3, and (2.8 ± 6.4 vs 0.0 ± 0.1 mm^3, p < .001).*

Importance

- *Symptomatic patients without known CAD and with CAC_0 remain at risk for ACS and may warrant testing by alternative methods sensitive to noncalcified plaque components.*

The aim of this study was to explore CTA-derived coronary artery plaque characteristics in symptomatic patients with CAC_0 who subsequently have ACS through comparisons with patients with $CAC_{>0}$ who subsequently have ACS, as well as with patients with CAC_0 who do not subsequently have ACS.

Methods

This study entailed a secondary retrospective analysis of prospective international registry data. All participating sites obtained approval from the local institutional review board (IRB) before registry enrollment. HIPAA compliance was maintained for participating U.S. sites. The requirement for written informed consent for patient entry into the registry was waived. No further IRB approval was required for conduct of the present analysis.

Patient Selection

The dynamic CONFIRM registry collected longitudinal observational data for consecutive symptomatic patients who underwent clinically indicated coronary CTA, to determine the association of coronary CTA findings in predicting future ACS events. Thirteen sites from eight countries in North America, Europe, and Asia participated in the registry. The registry included 25,251 patients who underwent coronary CTA from January 2004 to May 2010 and who had available follow-up assessment (mean, 3.4 ± 2.1 [SD] years) for MACE [14].

ICONIC was a nested cohort study conducted within the CONFIRM registry [11]. ICONIC identified patients in the registry who did and did not experience ACS (as adjudicated by site investigators) after coronary CTA, who were then propensity matched in a 1:1 within-site ratio [11, 14]. The matching was based on CAD risk factors as well as CAD severity on coronary CTA, as described later in the Methods [11]. Patients in the registry were only eligible for selection for the ICONIC study through the matching process if they had no known CAD (defined as no prior coronary revascularization or myocardial infarction) at the time of baseline coronary CTA. The propensity-matching process yielded 234 patients with ACS and 234 control patients without ACS, comprising the ICONIC study's nested cohort. The earlier ICONIC study publication provided further information on the process of ACS adjudication [11].

For the present substudy of the ICONIC study, 126 patients in the ACS group without a documented CAC score from baseline coronary CTA were excluded, leaving 108 patients in the ACS group with a documented CAC score. Subsequently, 108 propensity-matched patients with a documented CAC score from the control group were selected. For the present investigation, this process resulted in a final cohort of 108 patients in the ACS group

TABLE 1: Characteristics of Patients in ACS and Control Groups, Stratified by CAC Scores

	Control Group				ACS Group						
Parameter	All (*n* = 108)	CAC_0 (*n* = 23)	$CAC_{1–99}$ (*n* = 35)	$CAC_{\geq 100}$ (*n* = 50)	All (*n* = 108)	CAC_0 (*n* = 25)	$CAC_{1–99}$ (*n* = 23)	$CAC_{\geq 100}$ (*n* = 60)	p^a	p^b	p^c
Age (y), mean ± SD	62.9 ± 9.7	55.6 ± 11.5	61.5 ± 7.9	66.0 ± 9.2	61.8 ± 10.9	55.6 ± 11.0	57.7 ± 1.2	66.0 ± 8.9	.60	.002	< .001
Sex									.70	.12	.47
Male	57 (61)	39 (9)	60 (21)	62 (31)	59 (64)	52 (13)	61 (14)	62 (37)			
Female	44 (47)	61 (14)	40 (14)	38 (19)	41 (44)	48 (12)	39 (9)	38 (23)			
BMI, mean ± SD	27.1 ± 4.7	26.2 ± 5.2	26.9 ± 5.2	27.7 ± 4.2	27.5 ± 5.0	27.0 ± 3.5	27.6 ± 5.1	27.6 ± 5.4	.79	.10	.86
BSA (m^2), mean ± SD	1.9 ± 0.3	1.9 ± 0.3	1.9 ± 0.2	1.9 ± 0.3	1.9 ± 0.3	1.9 ± 0.2	1.9 ± 0.3	1.9 ± 0.3	.64	.22	.74
Risk factor											
Hypertension	64 (69)	35 (8)	66 (23)	76 (38)	65 (70)	52 (13)	70 (16)	68 (41)	.82	.002	.27
Hyperlipidemia	58 (63)	39 (9)	60 (21)	66 (33)	60 (65)	52 (13)	55 (12)	67 (40)	.66	.05	.13
Diabetes	28 (30)	17 (4)	34 (12)	28 (14)	17 (18)	20 (5)	17 (4)	15 (9)	.05	.58	.57
Smoker	26 (28)	9 (2)	37 (13)	26 (13)	37 (40)	44 (11)	43 (10)	32 (19)	.21	.38	.21
Family history of CAD	45 (49)	52 (12)	37 (13)	48 (24)	45 (49)	56 (14)	39 (9)	43 (26)	.85	.94	.49

Note—Unless otherwise indicated, data are percentage with count in parentheses. ACS = acute coronary syndrome, CAC = coronary artery calcium, CAC_0 = CAC score of 0, $CAC_{1–99}$ = CAC score of 1–99, $CAC_{\geq 100}$ = CAC score of 100 or greater, BSA = body surface area, CAD = coronary artery disease.

[a]Comparison of all patients in the ACS and control groups.

[b]Comparison of three patient subsets based on CAC scores within the control group.

[c]Comparison of three patient subsets based on CAC scores within the ACS group.

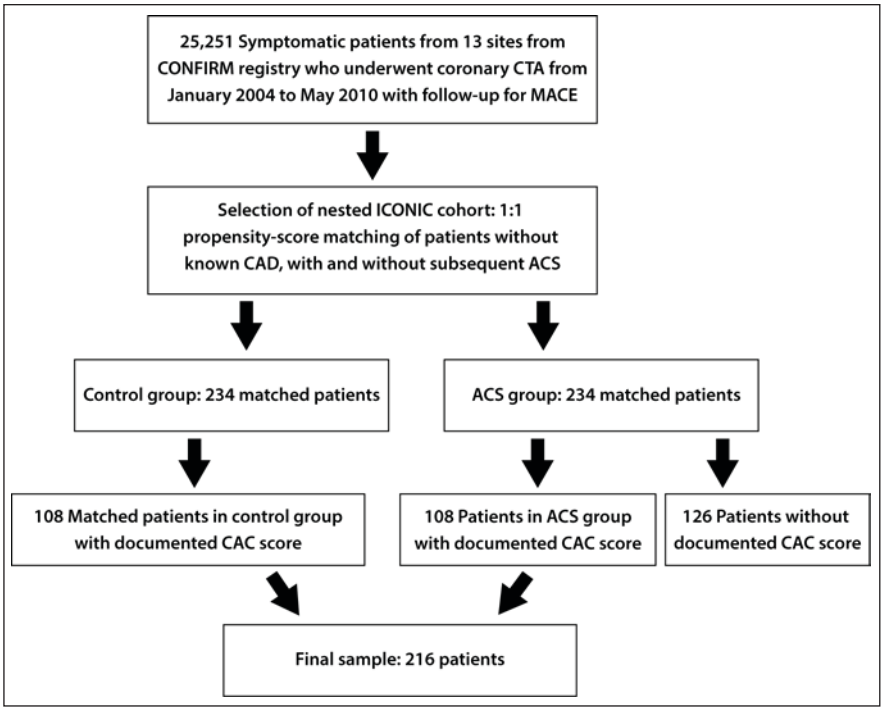

Fig. 1—Flowchart shows patient selection process. CONFIRM = Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter, MACE = major adverse coronary events, ICONIC = Incident Coronary Syndromes Identified by CT, CAD = coronary artery disease, ACS = acute coronary syndrome, CAC = coronary artery calcium.

TABLE 2: Comparison of ACS and Control Groups in Terms of CAC Scores and Lesions

Variable	Control Group (*n* = 108)	ACS Group (*n* = 108)	*p*
CAC score			
Mean ± SD	334.2 ± 689.8	366.4 ± 551.1	.44
Category			.39
0	21 (23)	23 (25)	
1–99	32 (35)	21 (23)	
≥ 100	46 (50)	56 (60)	
No. of lesions			
Mean ± SD	3.4 ± 2.7	3.5 ± 2.5	.38
> 1	81 (88)	90 (97)	.08
Total by CAC score	370	382	
CAC_0	11	32	
$CAC_{1–99}$	97	77	
$CAC_{\geq 100}$	262	273	
Total plaque volume, mean ± SD			
All	247.1 ± 292.1	252.4 ± 255.1	.41
By CAC score			
CAC_0	12.6 ± 36.8	65.7 ± 98.6	.002
$CAC_{1–99}$	126.2 ± 121.4	162.3 ± 195.8	.82
$CAC_{\geq 100}$	439.6 ± 318.6	364.7 ± 262.8	.28

Note—Unless otherwise indicated, data are expressed either as count or as percentage with count in parentheses. ACS = acute coronary syndrome, CAC = coronary artery calcium, CAC_0 = CAC score of 0, $CAC_{1–99}$ = CAC score of 1–99, $CAC_{\geq 100}$ = CAC score of 100 or greater.

and 108 propensity-matched patients in the control group (i.e., no ACS). A diagram outlining the current study's selection process is provided in Figure 1. Variables recorded for all patients included age, sex, BMI, and body surface area (BSA).

Coronary CTA Analysis and Plaque Characterization

Baseline coronary CTA examinations were performed using CT scanners with at least 64 detector rows and with protocols in accordance with Society of Cardiovascular CT (SCCT) guidelines [15, 16]. The examinations were processed in a central study core laboratory at Severance Hospital of Yonsei University (Seoul, Korea). For the purposes of the present investigation, the examinations were analyzed by commercially available, artificial intelligence (AI)-enabled cloud-based software (Cleerly, Cleerly) approved by the FDA for automated quantitative plaque assessment on coronary CTA. This program uses a series of validated convolutional neural network models (including the Visual Geometry Group [VGG]-19 network, 3D U-Net, and VGG Network Variant) for image quality assessment, coronary artery segmentation and labeling, lumen wall evaluation, vessel contour determination, and plaque characterization based on attenuation value (expressed as Hounsfield units) cutoffs. One of approximately 70 quality control technicians with training in cardiac CT performed an additional review of the AI output and performed manual adjustment when the automated segmentations appeared inaccurate [17].

The AI software identified coronary artery lesions (i.e., plaques) and classified plaque components using predefined attenuation value ranges: low-attenuation plaque was defined as plaque with attenuation of less than 30 HU, necrotic-core plaque as plaque with attenuation of −30 to 30 HU; fibrofatty plaque as plaque with attenuation of 31–130 HU; fibrous plaque as plaque with attenuation of 131–349 HU; and calcified plaque as plaque with attenuation of at least 350 HU [15, 18]. The software classified each plaque in terms of the presence or absence of a low-attenuation component and calculated the volumes of the remaining components (necrotic-core, fibrofatty, and fibrous components) as well as the total volume of noncalcified components (aside from the low-attenuation component). The software also determined each plaque's associated percent diameter stenosis (DS), which was further classified in a binary manner (< 50% [nonobstructive] vs ≥ 50% [obstructive]). In addition, for each plaque, the software computed the arterial remodeling ratio by dividing the vessel diameter (inclusive of any lesion) by the vessel's normal reference diameter; a plaque was considered to show positive remodeling if its arterial remodeling ratio was greater than 1.10. The software also determined for each plaque the lesion length, vessel volume, lumen volume, and per-

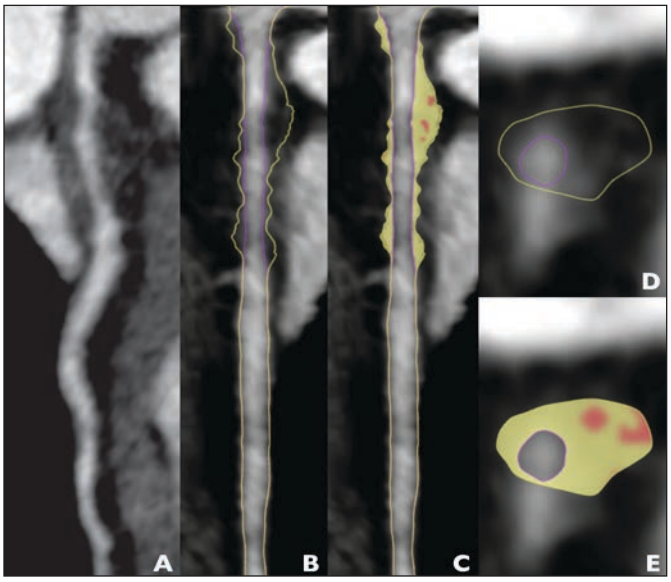

Fig. 2—40-year-old patient who presented with myocardial infarction without ST elevation and underwent coronary CTA. Patient had coronary artery calcium score of 0. Patient had acute coronary syndrome develop 8 days after coronary CTA was performed. Invasive coronary angiography identified culprit lesion in proximal left anterior descending (LAD) artery.
A, Curved multiplanar reconstructed image shows proximal LAD artery.
B, Straightened multiplanar image, generated by artificial intelligence quantitative plaque analysis software (Cleerly, Cleerly), shows outlines of lumen boundary (*purple*) and outer boundary of vessel wall boundary (*yellow*).
C, Straightened reconstructed image with color overlay shows long lesion composed of noncalcified plaque (*yellow*) with low-attenuation elements (*red*).
D, Short-axis cross-section image of lesion without color overlay shows outline of outer boundary of vessel wall (*yellow*).
E, Short-axis cross-section image with color overlay shows noncalcified plaque (*yellow*) with low-attenuation regions (*red*). Lesion has diameter stenosis of 46%, length of 36 mm, and total volume of noncalcified plaque components of 290 mm^3.

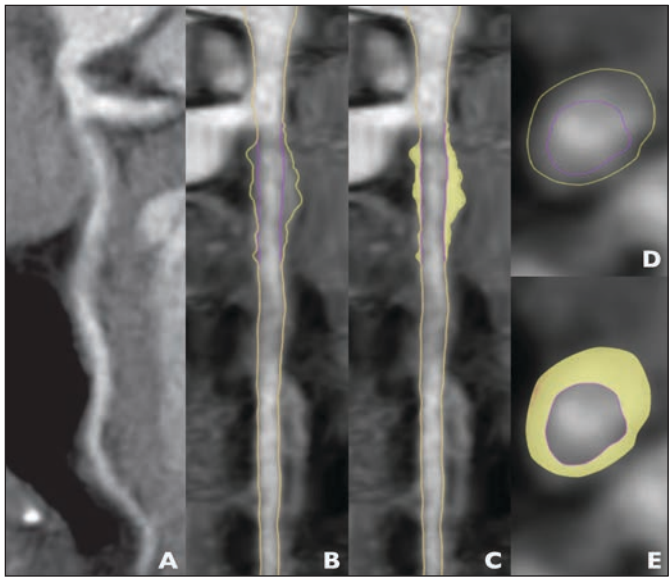

Fig. 3—70-year-old patient who presented with unstable angina and underwent coronary CTA. Patient had coronary artery calcium score of 0. Patient had acute coronary syndrome develop 77 days after coronary CTA was performed. Coronary CTA identified lesion in proximal left anterior descending (LAD) artery, which was nonculprit lesion based on invasive coronary angiography.
A, Curved multiplanar reconstructed image shows proximal LAD artery.
B, Straightened multiplanar image, generated by artificial intelligence quantitative plaque analysis software (Cleerly, Cleerly), shows outlines of lumen boundary (*purple*) and outer boundary of vessel wall (*yellow*).
C, Straightened reconstructed image with color overlay shows long lesion composed of noncalcified plaque (*yellow*). Lesion has no low-attenuation regions.
D, Short-axis cross-section image of lesion without color overlay shows outlines of lumen boundary (*purple*) and outer boundary of vessel wall (*yellow*).
E, Short-axis cross-section image with color overlay shows noncalcified plaque (*yellow*). Lesion has diameter stenosis of 32%, length of 17 mm, and total volume of noncalcified plaque components of 184 mm^3.

TABLE 3: Patient- and Lesion-Level Comparisons Between CAC_0 and $CAC_{>0}$ Subsets of ACS Group

Parameter	Patient-Level Assessment (n = 108)			Lesion-Level Assessment (n = 382)		
	CAC_0 (n = 25)	$CAC_{>0}$ (n = 83)	p	CAC_0 (n = 32)	$CAC_{>0}$ (n = 350)	p
DS (%)[a]	31.4 ± 16.4	41.0 ± 16.4	.03	23.8 ± 16.0	27.0 ± 15.6	.54
DS ≥ 50%	12 (3)	47 (39)	.002	6 (2)	8 (29)	.76
Positive remodeling	64 (16)	93 (77)	.001	66 (21)	79 (278)	.003
Spotty calcification	4 (1)	31 (26)	.006	3 (1)	12 (41)	.13
Low-attenuation plaque	20 (5)	47 (39)	.02	22 (7)	17 (61)	.97
Napkin ring sign	0 (0)	4 (3)	> .99	0 (0)	1 (3)	.08
Lesion length (mm^2)[a]	26.0 ± 28.2	108.5 ± 65.4	< .001	16.2 ± 12.0	25.5 ± 17.7	< .001
Vessel volume (mm^3)[a]	2115.0 ± 919.7	2330.4 ± 1105.5	.52	151.4 ± 153.3	241.5 ± 259.2	.002
Lumen volume (mm^3)[a]	2049.3 ± 923.1	2021.8 ± 1043.7	.68	110.5 ± 102.7	169.2 ± 169.5	.003
PAV (%)[a]	3.7 ± 5.9	14.2 ± 11.3	< .001	17.3 ± 15.6	25.0 ± 13.8	.03
Fibrous plaque volume (mm^3)[a]	29.4 ± 42.0	137.4 ± 113.4	< .001	18.3 ± 29.1	32.2 ± 45.5	.007
Fibrofatty plaque volume (mm^3)[a]	27.3 ± 52.2	47.1 ± 61.5	.006	15.0 ± 32.0	11.1 ± 22.0	.40
Necrotic-core plaque volume (mm^3)[a]	2.8 ± 6.4	4.6 ± 11.4	.04	3.8 ± 17.6	1.06 ± 5.3	.34
Calcified plaque volume[a]	6.2 ± 28.0	119.7 ± 137.1	< .001	3.9 ± 16.6	28.0 ± 52.5	< .001
Noncalcified plaque volume (necrotic core, fibrous, fibrofatty)[a]	59.5 ± 89.0	189.2 ± 162.9	< .001	37.1 ± 65.9	44.3 ± 63.8	.57

Note—Unless otherwise indicated, data are percentage with count in parentheses. CAC_0 = coronary artery calcium [CAC] score of 0, $CAC_{>0}$ = CAC score greater than 0, ACS = acute coronary syndrome, DS = diameter stenosis, PAV = percent atheroma volume.
[a]Data are mean ± SD.

cent atheroma volume, (PAV). Similar methods were used to obtain the plaque characteristics at the level of individual coronary segments having a diameter of at least 2 mm, on the basis of the modified 18-segment SCCT model [15]. The segment-based values were used to obtain patient-based values on the basis of previously described methods and were not otherwise used in the present analysis [11]. These features were previously described in further detail in the ICONIC study, which had derived the features using different software [11].

Additionally, for the purposes of the ICONIC study, one of five cardiologists or 10 technologists with level III training had previously evaluated each examination at the core laboratory using software (QAngioCT Research Edition, version 2.1.9.1 [Medis Medical Imaging Systems]), blinded to clinical outcomes [11], to quantitatively characterize the morphology of plaques. Specifically, these readers assessed each plaque for the presence versus absence of spotty calcification (visible calcification measuring 3 mm or less in all dimensions) and napkin-ring sign (configuration of noncalcified plaque resembling a ring, with circumferential hyperattenuating plaque surrounding hypoattenuating plaque), representing additional markers of high-risk plaque. The readers' plaque-level morphologic assessments from the ICONIC study were matched to the plaques identified and characterized as part of the present analysis. These features were also converted to patient-based assessments.

For each examination, the CAC score was determined by local site investigators in accordance with SCCT guidelines [19] and was stratified as CAC_0 versus $CAC_{>0}$. Cases of $CAC_{>0}$ were further stratified as a CAC score of 1–99 ($CAC_{1–99}$) or a CAC score of 100 or greater ($CAC_{\geq 100}$).

All of these assessments were performed as part of the ICONIC study or other studies within the CONFIRM registry. The coronary CTA images did not undergo additional dedicated analysis for purposes of the current study.

Propensity-Score Matching

Matching was conducted by the ICONIC study investigators for the purposes of the initial ICONIC study and included factors such as age, sex, hypertension, hyperlipidemia, diabetes, smoking history, family history of CAD, and CAD severity assessed by coronary CTA (classified at the threshold of ≥ 50% DS as nonobstructive, one-vessel obstructive, two-vessel obstructive, or either three-vessel or left-main obstructive). These factors were determined a priori and were incorporated into a logistic regression model to calculate a propensity score. A greedy nearest-neighbor approach was subsequently performed at each site to generate a 1:1 match between patients with ACS and control patients. Relaxed models for missing variables were used to allow all cases to be matched regardless of missing data [20]. Additional information on propensity-scoring methods is outlined in the ICONIC study [11].

Culprit Lesions

For patients in the ACS group who underwent invasive coronary angiography (ICA), a single culprit lesion was identified on the basis of ICA findings. The culprit lesions identified at ICA were then coregistered to the coronary CTA examinations, to link the culprit identified by ICA with a lesion on coronary CTA. In patients with an identified culprit lesion, all lesions on coronary CTA other than the coregistered culprit lesion were considered nonculprit lesions.

This identification of culprit and nonculprit lesions was performed as part of the ICONIC study and has been previously described [11].

Statistical Analysis

Continuous variables were expressed as means (± SD), and categorical variables were expressed as counts and percentages. Differences between categorical variables were analyzed using the McNemar test or chi-square test, and differences between continuous variables were assessed using a paired Wilcoxon rank-sum test. Multivariable marginal Cox models adjusting for conventional clinical risk factors were used to compare groups in terms of plaque characteristics, accounting for propensity matching between patients with ACS and control patients. Additionally, the models used the robust variance estimator to account for clustering within matched pairs. For analysis at the per-lesion level, marginal Cox regression analysis was used to account for patient effects. The multivariable regression analysis did not use components of the propensity score. A two-sided *p* less than .05 was considered statistically significant. All analyses were performed using SAS software (version 9.4, SAS Institute) and R (version 3.3.0).

Results

Patients, CAC Scores, and Lesions

The 216 total patients between the ACS and control groups had a mean age of 62.4 ± 10.3 years; 91 were women and 125 were men. Table 1 summarizes patient characteristics. The 108 patients with ACS had a mean age of 61.8 ± 10.9 years; 64 were men and 44 were women. The 108 control patients had a mean age of 62.9 ± 9.7 years; 61 were men and 47 were women. In the 108 patients with ACS, the time from coronary CTA to ACS ranged from 2 to 26 weeks. Patients in the two groups showed no significant difference in age, sex, BMI, BSA, or frequencies of hypertension, hyperlipidemia, diabetes, status as a smoker, or family history of CAD (all $p \geq .05$).

Table 2 summarizes the CAC scores and distributions of numbers of lesions (i.e., plaques) in the two groups. The mean CAC score was 366.4 ± 551.1 in the ACS group versus 334.2 ± 689.8 in the control group ($p = .44$). The distribution of patients with CAC_0, $CAC_{1\text{-}99}$, and $CAC_{\geq 100}$ was 23%, 21%, and 55%, respectively, in the ACS group, versus 21%, 32%, and 46%, respectively, in the control group ($p = .39$). The AI software identified a total of 382 lesions in the ACS group and 370 lesions in the control group. The mean number of lesions was 3.5 ± 2.5 in the ACS group versus 3.4 ± 2.7 in the control group ($p = .38$). The fraction of patients with at least one lesion was 90% in the ACS group versus 81% in the control group ($p = .08$). The mean plaque volume was 252.4 ± 255.1 cm^3 in the ACS group versus 247.1 ± 292.1 cm^3 in the control group ($p = .41$).

Characteristics are further compared among patients with CAC_0, $CAC_{1\text{–}99}$, or $CAC_{\geq 100}$ within the ACS and control groups in Table 1. In

TABLE 4: Comparison of Lesion Characteristics Among Lesions Stratified by CAC Score and Culprit Status, Among Patients in the ACS Group

Parameter	CAC_0		p[a]	$CAC_{>0}$, Culprit Lesion ($n = 65$)	p[b]
	Culprit Lesion ($n = 12$)	Nonculprit Lesion ($n = 28$)			
DS (%)[c]	31.3 ± 19.1	19.2 ± 12.3	.03	34.2 ± 15.3	.61
DS ≥ 50%	17 (2)	0 (0)	NA	14 (9)	.04
Positive remodeling	75 (9)	43 (12)	.09	72 (47)	.85
Spotty calcification	0 (0)	4 (1)	NA	11 (7)	NA
Low-attenuation plaque	33 (4)	11 (3)	.05	23 (15)	.45
Napkin-ring sign	0 (0)	0 (0)	NA	3 (2)	NA
Lesion length (mm^2)[c]	24.0 ± 10.7	12.9 ± 11.0	.001	34.6 ± 23.3	.01
Vessel volume (mm^3)[c]	80.6 ± 103.5	111.6 ± 122.8	.006	373.6 ± 339.8	.047
Lumen volume (mm^3)[c]	155.4 ± 91.9	91.5 ± 102.6	.01	248.2 ± 218.6	.01
PAV (%)[c]	29.2 ± 16.2	12.2 ± 12.4	< .001	29.3 ± 15.2	.97
Fibrous plaque volume (mm^3)[c]	34.9 ± 45.0	11.2 ± 14.8	.05	55.0 ± 65.9	.18
Fibrofatty plaque volume (mm^3)[c]	34.3 ± 50.8	6.7 ± 13.8	.047	20.5 ± 31.3	.34
Necrotic-core plaque volume (mm^3)[c]	11.4 ± 2.4	0.5 ± 1.6	.21	2.6 ± 11.3	.32
Calcified plaque volume[c]	8.6 ± 29.4	1.9 ± 5.5	.31	47.5 ± 71.1	.001
Noncalcified plaque volume (necrotic core, fibrous, fibrofatty)[c]	80.6 ± 103.5	18.4 ± 26.5	.03	78.1 ± 93.0	.93

Note—Unless otherwise indicated, data are percentage with count in parentheses. CAC = coronary artery calcium, ACS = acute coronary syndrome, CAC_0 = CAC score of 0, $CAC_{>0}$ = CAC score greater than 0, DS = diameter stenosis, NA = not applicable (no *p* value obtained given frequency of zero in one of the comparison groups), PAV = percent atheroma volume.

[a]Comparison of CAC_0 culprit lesion versus CAC_0 nonculprit lesion.

[b]Comparison of CAC_0 culprit lesion versus $CAC_{>0}$ culprit lesion.

[c]Data are mean ± SD.

TABLE 5: Comparison of Patient- and Lesion-Level Assessments Between the ACS and Control Groups, Among Patients With CAC_0

Parameter	Patient-Level Assessment (n = 48)			Lesion-Level Assessment (n = 70)		
	Control Group (n = 23)	ACS Group (n = 25)	p	Control Group (n = 30)	ACS Group (n = 40)	p
DS (%)[a]	24.7 ± 20.9	31.4 ± 16.4	.32	25.1 ± 13.8	23.8 ± 16.0	.39
DS ≥ 50%	4 (1)	12 (3)	.61	3 (1)	5 (2)	.44
Positive remodeling	17 (4)	64 (16)	.001	20 (6)	53 (21)	.008
Spotty calcification	0 (0)	4 (1)	> .99	0 (0)	3 (1)	NA
Low-attenuation plaque	0 (0)	20 (5)	.05	0 (0)	18 (7)	NA
Napkin-ring sign	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Lesion length (mm^2)[a]	8.0 ± 25.8	26.0 ± 28.2	< .001	6.2 ± 9.0	16.2 ± 12.0	.001
Vessel volume (mm^3)[a]	2045.2 ± 1033.0	2115.0 ± 919.7	.62	42.7 ± 64.3	151.4 ± 153.3	.001
Lumen volume (mm^3)[a]	2032.6 ± 1035.1	2049.3 ± 923.1	.85	33.1 ± 47.7	110.5 ± 102.7	.001
PAV (%)[a]	0.7 ± 1.9	3.7 ± 5.9	< .001	7.4 ± 11.9	17.3 ± 15.6	< .001
Fibrous plaque volume (mm^3)[a]	5.5 ± 15.2	29.4 ± 42.0	< .001	4.2 ± 7.7	18.3 ± 29.1	.003
Fibrofatty plaque volume (mm^3)[a]	1.3 ± 3.7	27.3 ± 52.2	< .001	1.0 ± 1.9	15.0 ± 32.0	.006
Necrotic-core plaque volume (mm^3)[a]	0.0 ± 0.1	2.8 ± 6.4	< .001	0.0 ± 0.1	3.8 ± 17.6	.18
Calcified plaque volume[a]	5.7 ± 19.4	6.2 ± 28.0	.06	4.4 ± 13.6	3.9 ± 16.6	> .99
Noncalcified plaque (necrotic core, fibrous, fibrofatty) volume[a]	6.8 ± 18.8	59.5 ± 89.0	< .001	5.2 ± 9.0	37.1 ± 65.9	.003

Note—Unless otherwise indicated, data are percentage with count in parentheses. ACS = acute coronary syndrome, CAC_0 = coronary artery calcium [CAC] score of 0, DS = diameter stenosis, NA = not applicable (no p value obtained given frequency of zero in one of the comparison groups), PAV = percent atheroma volume.
[a]Data are mean ± SD.

the ACS group, these three subsets based on CAC volume showed significant differences in mean age (55.6 ± 11.0, 57.7 ± 1.2, and 66.0 ± 8.9 years, respectively; p < .001). In the control group, these three subsets showed significant differences in mean age (55.6 ± 11.5, 61.5 ± 7.9, and 66.0 ± 9.2 years, respectively; p = .002) and frequency of hypertension (35%, 66%, and 76%, respectively; p = .002).

Comparison of Plaque Characteristics Between the CAC_0 and $CAC_{>0}$ Subsets of the ACS Group

Table 3 compares plaque characteristics between CAC_0 and $CAC_{>0}$ subsets in the ACS group. At the patient level, the $CAC_{>0}$ subset (n = 83), in comparison with the CAC_0 subset (n = 25), showed significantly greater mean DS (41.0% ± 16.4% vs 31.4% ± 16.4%, p = .03), DS of at least 50% (47% vs 12%, p = .002), positive remodeling (93% vs 64%, p = .001), spotty calcification (31% vs 4%, p = .006), low-attenuation plaque (47% vs 20%, p = .02), mean lesion length (108.5 ± 65.4 vs 26.0 ± 28.2 mm^2, p < .001), mean PAV (14.2% ± 11.3% vs 3.7% ± 5.9%, p < .001), mean fibrous plaque volume (137.4 ± 113.4 vs 29.4 ± 42.0 mm^3, p < .001), mean fibrofatty plaque volume (47.1 ± 61.5 vs 27.3 ± 52.2 mm^3, p = .006), mean necrotic-core plaque volume (4.6 ± 11.4 vs 2.8 ± 6.4 cm^3, p = .04), mean calcified plaque volume (119.7 ± 137.1 vs 6.2 ± 28.0 mm^3, p < .001), and mean noncalcified plaque volume (189.2 ± 162.9 vs 59.5 ± 89.0 mm^3, p < .001). At the lesion level, the $CAC_{>0}$ subset (n = 350), in comparison with the CAC_0 subset (n = 32), showed significantly greater positive remodeling (79% vs 66%, p = .003), mean lesion length (25.5 ± 17.7 vs 16.2 ± 12.0 mm^2, p < .001), mean vessel volume (241.5 ± 259.2 vs 151.4 ± 153.3 mm^3, p = .002), mean lumen volume (169.2 ± 169.5 vs 110.5 ± 102.7 mm^3, p = .003), mean PAV (25.0% ± 13.8% vs 17.3% ± 15.6%, p = .03), mean fibrous plaque volume (32.2 ± 45.5 vs 18.3 ± 29.1 mm^3, p = .007), and mean calcified plaque volume (28.0 ± 52.5 vs 3.9 ± 16.6 mm^3, p < .001). Other plaque characteristics were not significantly different between the two subsets in either patient-based or lesion-based assessment (all p > .05).

Plaque Characteristics of Culprit Lesions in Patients With CAC_0 in the ACS Group

A total of 77 patients in the ACS group underwent ICA and had a culprit lesion identified. A total of 16% (12) of these patients had CAC_0, and 84% (65) had $CAC_{>0}$. In the 12 patients with CAC_0 and an identified culprit lesion, a total of 28 additional nonculprit lesions were identified on coronary CTA. Table 4 compares the plaque characteristics of culprit lesions in the CAC_0 subset with those of nonculprit lesions in the CAC_0 subset as well as with culprit lesions in the $CAC_{>0}$, all within the ACS group. In the CAC_0 subset, culprit lesions, in comparison with nonculprit lesions, showed significantly greater mean DS (31.3% ± 19.1% vs 19.2% ± 12.3%, p = .03), mean lesion length (24.0 ± 10.7 vs 12.9 ± 11.0 mm^2, p = .001), mean lumen volume (155.4 ± 91.9 vs 91.5 ± 102.6 mm^3, p = .01), mean PAV (29.2% ± 16.2% vs 12.2% ± 12.4%, p < .001), mean fibrofatty plaque volume (34.3 ± 50.8 vs 6.7 ± 13.8 mm^3, p = .047), and mean noncalcified plaque volume (80.6 ± 103.5 vs 18.4 ± 26.5 mm^3, p = .03); culprit lesions, in comparison with nonculprit lesions, showed significantly greater mean vessel volume (80.6 ± 103.5 vs 111.6 ± 122.8 mm^3, p = .006).

Culprit lesions in the $CAC_{>0}$ subset, in comparison with culprit lesions in the CAC_0 subset, showed significantly greater mean lesion length (34.6 ± 23.3 vs 24.0 ± 10.7 mm^3, $p = .01$), mean vessel volume (373.6 ± 339.8 vs 80.6 ± 103.5 mm^3, $p = .047$), mean lumen volume (248.2 ± 218.6 vs 155.4 ± 91.9 mm^3, $p = .01$), and mean calcified plaque volume (47.5 ± 71.1 vs 8.6 ± 29.4 mm^3, $p = .001$). Other comparisons of plaque characteristics were not significantly different between subsets (all $p > .05$). Figures 2, 3, S1, and S2 show representative lesions in the CAC_0 subset in the ACS group.

Comparisons of Plaque Characteristics Between the ACS and Control Groups Among Patients With CAC_0

Table 5 provides patient- and lesion-level comparisons of plaque characteristics between the ACS and control groups among patients with CAC_0. In the CAC_0 subset, patients with ACS ($n = 25$), in comparison with control patients ($n = 23$), had significantly greater positive remodeling (64% vs 17%, $p = .001$), mean lesion length (26.0 ± 28.2 vs 8.0 ± 25.8 mm^2, $p < .001$), mean PAV (3.7% ± 5.9% vs 0.7% ± 1.9%, $p < .001$), mean fibrous plaque volume (29.4 ± 42.0 vs 5.5 ± 15.2 mm^3, $p < .001$), mean fibrofatty plaque volume (27.3 ± 52.2 vs 1.3 ± 3.7 mm^3, $p < .001$), mean necrotic-core plaque volume (2.8 ± 6.4 vs 0.0 ± 0.1 mm^3, $p < .001$), and mean noncalcified plaque volume (59.5 ± 89.0 vs 6.8 ± 18.8 mm^3, $p < .001$). In the CAC_0 subset, lesions in the ACS group ($n = 40$), in comparison with lesions in the control group ($n = 30$), showed significantly greater positive remodeling (53% vs 20%, $p = .008$), mean lesion length (16.2 ± 12.0 vs 6.2 ± 9.0 mm^2, $p < .001$), mean vessel volume (151.4 ± 153.3 vs 42.7 ± 64.3 mm^3, $p < .001$), mean lumen volume (110.5 ± 102.7 vs 33.1 ± 47.7 mm^3, $p < .001$), mean PAV (17.3% ± 15.6% vs 7.4% ± 11.9%, $p < .001$), mean fibrous plaque volume (18.3 ± 29.1 vs 4.2 ± 7.7 mm^3, $p = .003$), mean fibrofatty plaque volume (15.0 ± 32.0 vs 1.0 ± 1.9 mm^3, $p = .006$), and mean total noncalcified plaque volume (37.1 ± 65.9 vs 5.2 ± 9.0 mm^3, $p = .003$). Other plaque characteristics were not significantly different between the two groups in either patient-based or lesion-based assessment (all $p > .05$).

Discussion

This study evaluated plaque characteristics on baseline coronary CTA in symptomatic patients without known CAD from the ICONIC study, in patients who had ACS after coronary CTA, and in matched patients who did not subsequently have ACS. CAC scores were not significantly different between patients in the two groups, and 23% of the patients in the ACS group had CAC_0. In the ACS group, $CAC_{>0}$ lesions, compared with CAC_0 lesions, had significantly greater volumes of fibrous plaque, but they had no significant differences in volumes of fibrofatty plaque or necrotic-core plaque or in the frequency of low-attenuation plaque. Additionally, in the ACS group, culprit lesions in the CAC_0 subset, compared with nonculprit lesions in the CAC_0 subset, showed significantly greater fibrofatty plaque volume, but they had no significant differences in the volumes of fibrous or necrotic-core plaque or in the frequency of low-attenuation plaque. Moreover, in the ACS group, culprit lesions in the CAC_0 and $CAC_{>0}$ subsets showed no significant differences in the volumes of fibrous plaque, fibrofatty plaque, or necrotic-core plaque or in the frequency of low-attenuation plaque. Furthermore, in the CAC_0 subset, patients in the ACS group showed greater volumes of noncalcified plaque components compared with the control group. These data provide novel insights regarding plaque characteristics in patients with CAC_0 on coronary CTA as well as associations with subsequent ACS.

This substudy cohort was derived from a nested cohort of patients from within the international CONFIRM registry. Patients with ACS were matched to control patients without ACS on the basis of propensity scores by use of a range of variables, including CAD risk factors and CAD severity on CTA but not including plaque composition. This process yielded a unique cohort that was controlled for common confounding demographic and physiologic factors.

A traditional CAC-based risk score would deem patients with CAC_0 to be at low risk. However, prior research has shown that symptomatic patients with CAC_0 remain at risk for ACS [8], indicating a role of noncalcified forms of plaque. For example, in the landmark SCOT-HEART trial, low-attenuation noncalcified plaque volume was the strongest predictor of ACS [11, 12]. Other trials, like ICONIC and PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain), included patients with varying CAC scores and likewise identified risk factors for ACS aside from CAC scores. In particular, the ICONIC trial observed that ACS precursors were associated with higher PAV composed of all plaque forms, including calcified and noncalcified components of plaque. Similarly, a subanalysis of the PROMISE trial identified high-risk plaque (i.e., plaques showing combinations of low attenuation, spotty calcifications, and positive remodeling) to be closely associated with future MACE, such that high-risk plaque was suggested to be a useful addition to standard atherosclerotic cardiovascular disease scoring in predicting future ACS [11, 21]. In the current study, among patients with CAC_0, those in the ACS group showed significantly greater positive remodeling as well as significantly greater fibrous, fibrofatty, and necrotic-core plaque volumes in comparison with the control group, indicative of identifiable high-risk factors in the CAC_0 subset.

Large trials like the PROMISE and ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) trials showed that CAC scores provide incremental benefit for predicting ACS risk beyond the traditional Framingham risk factors [21, 22]. Nonetheless, the current study adds to growing evidence of inherent limitations in the use of CAC scores for ACS risk assessment in symptomatic individuals, highlighting that symptomatic patients with CAC_0 have a risk for ACS that is not completely captured by a standalone calcium-based risk model. This view aligns with a study by Puchner et al. [23]; in that study, despite an association between total CAC and ACS in symptomatic individuals, local CAC was associated with plaque stability. Reflecting this evolving understanding, in the 2023 Multimodality Appropriate Use Criteria for detection and risk assessment of coronary disease, the use of CAC for risk assessment is largely considered appropriate for asymptomatic individuals but overall receives a classification of "may be appropriate" or "rarely appropriate" in symptomatic cohorts [24].

CAC scores are recognized to be useful for risk assessment in asymptomatic patients. The present findings help to inform the role of

CAC scores in screening for CAD in symptomatic patients. In such patients, CAC scores may be relatively more helpful to recategorize risk in older individuals, who are likely to have advanced calcified plaque burden. In contrast, younger symptomatic patients, who are more likely to have CAC_0, may benefit from more sensitive screening tests like coronary CTA, which are capable of identifying more dangerous plaque forms [25]. Although additional studies are required, the ICONIC study and this ICONIC substudy suggest that coronary CTA for plaque assessment may have clinical utility in helping to identify and quantify noncalcified plaque forms.

This study had limitations. First, the study was retrospective. Second, although the propensity matching used well-accepted risk factors for CAD and ACS, other possible confounding factors may have not been taken into consideration. Third, the CONFIRM registry included only symptomatic patients referred for clinically indicated coronary CTA, and the ICONIC study included only patients within the registry who did not have known CAD. The results may not be generalizable to asymptomatic patients or to patients who have previously received medical intervention for CAD. Additionally, only 77 of the 108 patients in the ACS group had a culprit lesion identified during execution of the ICONIC study. Fourth, results may be different using more recently introduced technologies, such as photon-counting detector CT [26]. Finally, the results do not show that screening for and identification of the described noncalcified plaque components reduce the incidence of ACS or improve mortality.

Conclusion

In this study of symptomatic patients without known CAD who were undergoing coronary CTA, patients with CAC_0 in the ACS and control groups showed significant differences in fibrous, fibrofatty, and necrotic-core plaque volumes after propensity-score matching was done for a range of prognostic factors. Screening methods that can identify and quantify noncalcified plaque forms may be useful in such patients.

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