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Pericoronary Adipose Tissue Attenuation in Patients with Future Acute Coronary Syndromes: The ICONIC Study

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Purpose: Pericoronary adipose tissue attenuation (PCATa) measured at coronary CT angiography (CCTA) is an imaging biomarker of coronary inflammation associated with long-term adverse cardiac events. The authors hypothesized that PCATa may independently identify patients at risk for acute coronary syndromes (ACS).

Materials and Methods: The authors performed a retrospective substudy of the Incident Coronary Syndromes Identified by Computed Tomography (ICONIC) study, a propensity-matched case-control study of patients with CCTA followed by ACS. Two hundred analyzable case and control pairs were identified from the original 234 pairs. PCATa was measured using the adjusted attenuation of fat around proximal coronary vessels. The primary analysis applied conditional Cox models with cluster-robust standard errors to predict patient-level incident ACS, with adjustment for quantitative plaque volumes and clinical reporting-oriented findings of maximal stenosis and high-risk plaque features (HRPF).

Results: A total of 400 patients with 1174 matched measurable vessels were included. PCATa was not significantly different between patients with future ACS versus controls ($-72.99 \text{ HU} \pm 9.42$ vs $-73.96 \text{ HU} \pm 9.47$; $P = .08$). Conversely, PCATa was significantly associated with incident ACS events in Cox models (adjusted for noncalcified plaque hazard ratio [HR]: 1.015; 95% CI: 1.001, 1.028; $P = .03$; adjusted for total plaque HR: 1.015; 95% CI: 1.002, 1.029; $P = .03$; adjusted for stenosis and HRPF HR: 1.014; 95% CI: 1.000, 1.028; $P = .049$).

Conclusion: Limited quantitative difference in PCATa between patients and controls matched for risk factors and coronary artery disease suggests that PCATa may not be a useful single marker to identify future ACS. Nonetheless, significant differences seen in adjusted survival models identify a small biologic effect for increased risk of future ACS independent of traditional risk factors.

Clinical trials registration no. NCT02959099

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Acute coronary syndromes (ACS) occur in approximately 3% of all U.S. adults (1). Prediction of ACS events through standard risk stratification remains limited (2). Pericoronary tissue attenuation (PCATa) measured at coronary CT angiography (CCTA) is an established surrogate imaging biomarker of vascular inflammation and may be able to improve identification of patients with coronary disease at risk for ACS (3–5). PCATa identifies differences in attenuation, which are related to a bidirectional relationship between the pericoronary adipose tissue and the underlying coronary arteries. Paracrine effects of vascular inflammation result in cachexia-type perivascular adipocytes, resulting in smaller amounts of lipid and a relative increase in aqueous content in adipose tissue around the coronary arteries (6). This in turn results in higher Hounsfield unit values around coronary arteries at CCTA (7). We hypothesized that PCATa, as a biomarker of coronary inflammation, may help identify

patients at risk for ACS, independent of quantitative coronary plaque measurements and clinical risk factors. We investigated this hypothesis within the Incident Coronary Syndromes Identified by Computed Tomography (ICONIC) study (8).

Materials and Methods

Patient Population

Patients were drawn from the ICONIC study (NCT02959099) (8). Briefly, the ICONIC study is a nested case-control study within the Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter registry, a longitudinal cohort study of patients undergoing CCTA (9). The ICONIC study screened patients from 13 sites to identify patients without previously known coronary artery disease defined by prior myocardial infarction or revascularization, with site adjudica-

Abbreviations

ACS = acute coronary syndromes, BMI = body mass index, CCTA = coronary CT angiography, HR = hazard ratio, HRPf = high-risk plaque features, ICONIC = Incident Coronary Syndromes Identified by Computed Tomography, LCX = left circumflex coronary artery, LM = left main coronary artery, PCATa = pericoronary adipose tissue attenuation, RCA = right coronary artery

Summary

Pericoronary adipose tissue attenuation, a marker of coronary inflammation, shows minimal quantitative differences between patients with and without future incident acute coronary syndromes in a matched case-control multicenter cohort of patients who underwent coronary CT angiography but is independently associated with future incident acute coronary syndromes in adjusted survival analyses.

Key Points

- Pericoronary adipose tissue attenuation (PCATa) can be measured using standard coronary CT angiography and quantifies a bidirectional relation of inflammation between coronary arterial tissue and the surrounding adipose tissue.
- Mean PCATa between patients with future incident coronary syndrome events and a demographic and risk-factor matched control cohort was not significant on per-patient and per-vessel bases, suggesting limited immediate clinical utility in this multicenter cohort.
- In survival analyses, PCATa is associated with incident acute coronary syndrome events with and without adjustment for noncalcified plaque volume, total plaque volume, and maximal stenosis plus high-risk plaque features (unadjusted hazard ratio [HR]: 1.014; 95% CI: 1.001, 1.027 per HU; $P = .03$; adjusted for noncalcified plaque HR: 1.015; 95% CI: 1.001, 1.028; $P = .03$; adjusted for total plaque HR: 1.015; 95% CI: 1.002, 1.029; $P = .03$; adjusted for stenosis and high-risk plaque features HR: 1.014; 95% CI: 1.000, 1.028; $P = .049$), suggesting that despite limited immediate clinical utility, there may be detectable biologic processes by this marker that are independent of traditional assessments.

Keywords

CT-Angiography, Inflammation, Coronary Arteries, Acute Coronary Syndrome, Pericoronary Adipose Tissue Attenuation, Noncalcified Plaque, ICONIC Study, Cardiovascular Risk

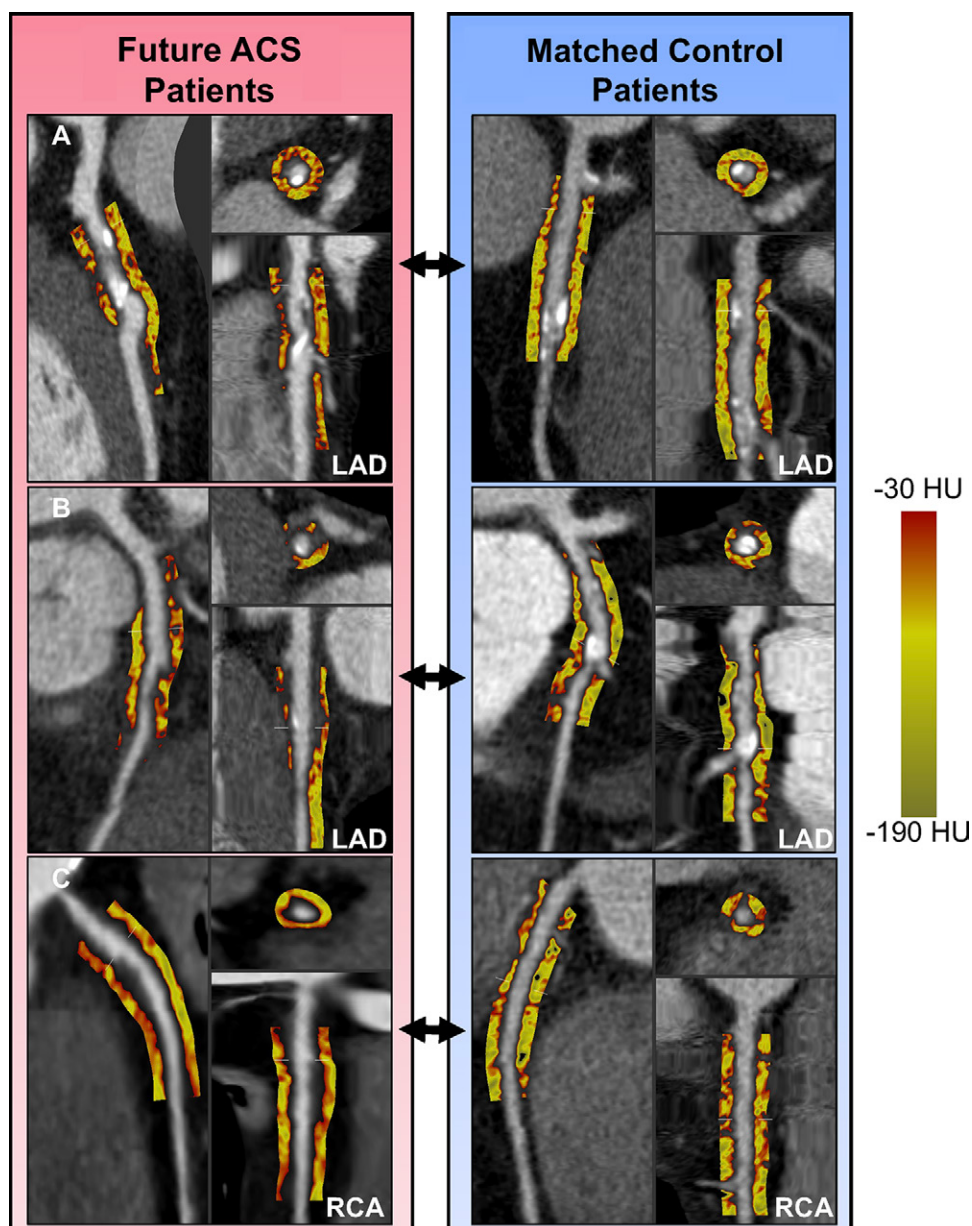
tion of ACS and death. Blinded to CCTA evaluation and using cardiac enzyme, electrocardiography, and invasive coronary angiography data, the Clinical and Data Coordinating Center at the Dalio Institute of Cardiovascular Imaging adjudicated the ACS as ST-elevation myocardial infarction, non-ST-segment elevation myocardial infarction, unstable angina, or unclassified myocardial infarction (in cases with an ambiguous adjudication electrocardiography which precluded definitive classification of ST-elevation myocardial infarction or non-ST-segment elevation myocardial infarction). The location of the culprit lesion was defined using invasive coronary angiography images and electrocardiograms at presentation for ACS. In ICONIC, a total of 234 patients with ACS were propensity matched 1:1 to controls by age, sex, clinical risk factors, and number of vessels with more than 50% diameter stenosis. The ICONIC cohort has been previously studied for the effects of plaque characteristics but has not previously been analyzed for PCATa (8,10–17). For this study, we included all matched pairs ($n = 200$) who were adjudicated as experiencing ST-segment elevation myocardial infarction, type I non-ST-segment elevation myocardial infarction, unstable angina, and unclassified myocardial infarction (eight pairs excluded) who had accessible Digital Imaging

and Communications in Medicine files for PCATa analysis (26 pairs excluded). For any excluded study, the corresponding matched case or control was also excluded (Fig S1). Each institution received local institutional review board or ethics board approval, submitting deidentified data to the Clinical and Data Coordinating Center.

CCTA Image Analysis

PCATa was measured by trained advanced cardiac imaging readers with level III experience (A.C.K., E.T., E.K.) using a previously described standardized technique (18). PCATa analysis was performed on CCTA datasets by semiautomated software (Autoplaque version 2.5; Cedars Sinai Medical Center). Briefly, Digital Imaging and Communications in Medicine images were provided to the readers, blinded to case and control status. Image quality and clarity of the proximal portions of coronary vessels was assessed. Segments of the proximal portions of each coronary vessel (right coronary artery [RCA], left main coronary artery [LM], left anterior descending coronary artery, and left circumflex coronary artery [LCX]) were selected because these regions typically have large-caliber vessels with minimal branching, and previous research has demonstrated high reproducibility with this approach (18). The LM portion included a 10-mm segment starting from the ostium; the left anterior descending coronary artery and LCX portions included 40-mm segments starting from the respective vessel ostia; and the RCA segment was 40 mm, starting 10 mm from the RCA. If the LM segment was less than 8 mm or the measurable segment of the left anterior descending coronary artery, LCX, or RCA was less than 35 mm in length due to termination of the vessel or obscuring artifact, the segment was excluded from analysis. The software automatically measures the Hounsfield units of adipose tissue surrounding the coronary artery (defined as within -30 to -190 HU) in concentric volumetric shells. Values for the PCATa were taken as the mean Hounsfield units in the radial 3-mm shell around the coronary artery (Figure). We adjusted for differences in acquisition voltage between CT scanners by dividing by a kilovoltage peak–based correction factor for those not performed at 120 kVp, as previously validated (correction for kilovoltage peak = 100: 1.11485; correction for kilovoltage peak = 135: 0.89095) (5,19). Unmatched vessels within matching patient pairs (eg, if only one of the pair had an interpretable RCA) were excluded to ensure equal vessel representation in case and control cohorts ($n = 426$ segments were excluded; LM, $n = 230$; left anterior descending coronary artery, $n = 8$; LCX, $n = 110$; RCA, $n = 78$; primarily due to short LM or small non-dominant LCX or RCA).

Coronary plaque assessment was previously performed as part of the ICONIC study (8). In brief, all coronary segments in the 18-segment Society of Cardiovascular CT model (20) with a diameter greater than or equal to 2 mm were analyzed by blinded independent level III–experienced readers in a core laboratory setting at Severance Hospital of Yonsei University. Quantitative analysis was performed using semiautomated software (QAngioCT Research Edition version 2.1.9.1; Medis Medical Imaging Systems) to measure maximal diameter stenosis and generate plaque volumes and plaque composition by predefined Hounsfield units thresholds (necrotic: -30 to 30 HU, fibrofatty:



CT images of pericoronary adipose tissue attenuation measurements of matched vessel pairs of (left column) patients with future acute coronary syndrome (ACS) and (right column) controls. **(A)** CT images of left anterior descending coronary artery (LAD); the patient with future ACS experienced an ACS event 233 days after imaging. **(B)** CT images of LAD; the patient with ACS experienced an ACS event 28 days later. **(C)** CT images of right coronary artery (RCA); the patient with future ACS experienced an ACS event 406 days later.

31 to 130 HU, fibrous: 131 to 350 HU, and calcified: >350 HU (21). Qualitative assessment by expert readers included identification of high-risk plaque features (HRPF) including positive remodeling with remodeling index greater than 1.1, low attenuation plaque with attenuation less than 30 HU, spotty calcification with a nodule of 3 mm or less, and presence or absence of a central hypoattenuation and peripheral hyperattenuation pattern consistent with a napkin-ring sign (8,21).

Statistical Analysis

Descriptive analysis variables were reported as means $\pm$ SDs, medians and IQRs, or frequencies and percentages as appropriate. Normality testing was performed by Shapiro-Wilk testing for all continuous variables. Comparisons were performed be-

tween groups including ACS versus matched non-ACS cases for PCATa and quantitative plaque characteristics using t test, Wilcoxon test, analysis of variance, or χ^2 testing as appropriate. Associations between per-vessel PCATa and traditional risk factors were estimated within the ACS cases using mixed-effects linear regression models accounting for within-patient measurements.

The primary analysis consisted of a conditional Cox regression model with cluster-robust standard errors to account for matched pairs and inpatient clustering, with the primary outcome as time to a patient-level ACS event, the primary covariate as PCATa (per unit Hounsfield unit increase) in each vessel, with and without adjustment for noncalcified plaque volume or total plaque volume as an established measures of quantitative plaque risk, and adjustment for factors considered within the Coronary

Table 1: Demographic and Acquisition Features between Patients with ACS and Controls

Characteristic	Patients with ACS (n = 200)	Controls (n = 200)	Total (n = 400)	P Value
Age (y)	62.4 ± 11.5	62.6 ± 10.3	62.5 ± 10.9	.96
Male	131 (65.5)	126 (63.0)	257 (64.2)	.60
Risk factors				
Hypertension	128 (64.6)	124 (62.0)	252 (63.3)	.58
Dyslipidemia	111 (56.1)	105 (52.5)	216 (54.3)	.48
Diabetes	39 (19.5)	63 (31.5)	102 (25.5)	.01
Smoking	94 (57.3)	72 (48.0)	166 (52.9)	.10
Premature family history of CAD	84 (43.3)	77 (38.7)	161 (41.0)	.35
Body mass index*	27.3 ± 4.6	27.1 ± 4.4	27.2 ± 4.5	.92
Chest pain	138 (81.2)	105 (64.0)	243 (72.8)	<.001
Medications				
Statin	84 (60.0)	73 (52.1)	157 (56.1)	.19
ASA/clopidogrel	77 (66.4)	74 (64.3)	151 (65.4)	.75
ACE-I/ARB	56 (42.4)	53 (37.9)	109 (40.1)	.44
Beta blocker	54 (36.5)	54 (36.5)	108 (36.5)	>.99
Lipid profile (mg/dL)				
Total	193.4 ± 49.1	185.9 ± 51.2	190.4 ± 50.0	.22
LDL	116.3 ± 41.8	113.7 ± 36.5	115.4 ± 39.9	.70
HDL	48.4 ± 13.9	46.2 ± 15.5	47.6 ± 14.5	.46
Coronary artery calcium score				.35
0	23 (18.1)	23 (21.1)	46 (19.5)	
1–100	33 (26.0)	37 (33.9)	70 (29.7)	
101–400	33 (26.0)	20 (18.3)	53 (22.5)	
>400	38 (29.9)	29 (26.6)	67 (28.4)	
Follow-up duration (y)	1.06 ± 1.68	3.72 ± 2.28	2.39 ± 2.40	<.001
CCTA scanner type				.19
64 section	83 (45.1)	74 (38.1)	157 (41.5)	
Dual source	71 (38.6)	77 (39.7)	148 (39.2)	
Other	30 (16.3)	43 (22.2)	73 (19.3)	
Contrast material dose (mL)	89.2 ± 15.9	86.0 ± 14.4	87.4 ± 15.2	.53
Prospective gating	28 (30.4)	5 (7.0)	33 (20.2)	<.001
Kilovolts				.08
100	49 (24.5)	52 (26.0)	101 (25.2)	
120	138 (69.0)	144 (72.0)	282 (70.5)	
135	13 (6.5)	4 (2.0)	17 (4.2)	

Note.—Data are means ± SDs or frequencies with percentages in parentheses. ACE-I = angiotensin converting enzyme inhibitor, ACS = acute coronary syndrome, ARB = angiotensin II receptor blocker, ASA = aspirin, CAD = coronary artery disease, CCTA = coronary CT angiography, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

* Body mass index was calculated by dividing the patient's weight in kilograms by the patient's height in meters squared.

Artery Disease Reporting and Data System 2.0 scoring system of maximal diameter stenosis and presence of two or more HRPf on a per-patient basis. Given the propensity-matched design of the parent dataset, which remained balanced in our subcohort, we did not perform further matching on patient demographics or clinical risk factors because these were accounted for within the matching. Proportionality assumption was assessed using Schoenfeld residuals.

Secondary analyses included similar conditional Cox models comparing PCATa of defined culprit vessels in patients with ACS to PCATa in the vessel with the highest degree of stenosis in controls to assess the ability to identify vessel-level signal, and comparing RCA PCATa alone in cases and controls given that the RCA has had extensive previous validation and standardization (5,7,22). Additionally, mixed effects linear regression was

used to assess the relation of traditional risk factors with PCATa in patients with ACS with random effects term accounting for within-patient measurements. Statistics were performed using R version 4.0.0 (R Foundation for Statistical Computing); a *P* value less than .05 was considered significant.

Results

Of the original 234 patients with ACS and control pairs, 200 of each were included in our final study population, with 587 matched vessels analyzed for PCATa in each cohort, and 135 identified culprit vessels. Comparison between the included and excluded groups revealed no significant clinical differences (Table S1). The included population mean age was 62.5 years ± 10.9, and 64.2% of patients were male (Table 1). Between patients and controls, significant differences were present in

Table 2: Univariable and Multivariable Conditional Cox Models with Cluster-Robust SEs for Relation of Pericoronary Adipose Tissue Attenuation and Time to ACS or Culprit Vessel Event

Population	Vessel Pairs	Univariable			Adjusted for Noncalcified Plaque Volume			Adjusted for Total Plaque Volume			Adjusted for Maximal Stenosis and High-Risk Features		
		HR (95% CI)	SE	P Value	HR (95% CI)	SE	P Value	HR (95% CI)	SE	P Value	HR (95% CI)	SE	P Value
All vessels (ACS) vs all vessels (control)	587	1.014 (1.001, 1.027)	0.007	.03	1.015 (1.001, 1.028)	0.007	.03	1.015 (1.002, 1.029)	0.007	.03	1.014 (1.000, 1.028)	0.007	.049
Culprit (ACS) vs most stenotic (control)	135	1.040 (1.014, 1.066)	0.013	.002	1.042 (1.011, 1.073)	0.015	.007	1.046 (1.019, 1.074)	0.014	.0008	1.047 (1.020, 1.074)	0.013	.0005
RCA (ACS) vs RCA (control)	151	1.013 (0.995, 1.031)	0.009	.2	1.010 (0.991, 1.030)	0.010	.3	1.011 (0.993, 1.031)	0.010	.2	1.011 (0.992, 1.031)	0.010	.2

Note.—ACS = acute coronary syndrome, HR = hazard ratio, RCA = right coronary artery, SE = standard error.

the frequency of diabetes (patients with ACS: 19.5% vs controls: 31.5%), presenting symptoms of chest pain (patients with ACS: 81.2% vs controls: 64.0%), and follow-up duration (patients with ACS: 1.06 years $\pm$ 1.68 vs controls: 3.72 years $\pm$ 2.28), although these proportions and differences were also present in the original propensity-matched ICONIC study (8). In analyses of the event type, location, and timing within the patients with ACS, most patients experienced non-ST-segment elevation myocardial infarction, and over half occurred within 1 year of the CCTA. In 135 cases in which the culprit lesion was verified, left anterior descending coronary artery culprit lesions were the most common, followed by RCA, LCX, and LM, respectively (Table S2). Comparing between patients with ACS and controls, there were significantly increased fibrofatty (23.5 mm³ vs 15.0 mm³; P = .01) and necrotic core (1.1 mm³ vs 0.4 mm³; P = .03) plaque volumes, nonsignificant differences between fibrous (82.8 mm³ vs 64.7 mm³; P = .06) and total plaque volume (187.5 mm³ vs 158.1 mm³; P = .16), and significantly increased total noncalcified plaque (122.2 mm³ vs 92.2 mm³; P = .02). Additionally, measures of maximal stenosis showed higher degrees of stenosis in patients with ACS (diameter stenosis: 40.1% vs 33.2%; P < .01), and prevalence of at least two HRPf was not significantly different between groups (28.5% vs 25.5%; P = .5). Overall, at a per-patient level, there were no differences in PCATa between patients with ACS and controls by maximum vessel value within patients, mean of all vessels, or RCA values (Table S3).

In the primary analysis of the 200 matched patient pairs with 587 matched vessel pairs, mean PCATa was not significantly different between groups of patients with future ACS versus controls (-72.99 HU $\pm$ 9.42 vs -73.96 HU $\pm$ 9.47; P = .08). Nonetheless, in Cox analyses, PCATa was significantly associated with time to ACS events in univariable analysis (hazard ratio [HR]: 1.014; 95% CI: 1.001, 1.027 per Hounsfield unit; P = .03). Adjustment for noncalcified plaque volume resulted in minimal change to the PCATa results (adjusted HR: 1.015; 95% CI: 1.001, 1.028; P = .03), similarly for total plaque volume (adjusted HR: 1.015; 95%

CI: 1.002, 1.029; P = .03) and adjustment for maximal stenosis and at least two HRPf (adjusted HR: 1.014; 95% CI: 1.000, 1.028; P = .049) (Table 2).

The secondary analyses included comparisons limited to identified culprit ACS vessels versus the vessel with the highest degree of stenosis in the matched control (n = 135 vessel pairs) and comparison of RCA PCATa only in patients with ACS versus controls (n = 151 vessel pairs). In the comparison of culprit ACS vessels versus highest degree of stenosis in the controls, PCATa remained significant (univariable HR: 1.040; 95% CI: 1.014, 1.066; P = .002; adjusted for noncalcified plaque HR: 1.042; 95% CI: 1.011, 1.073; P = .007; adjusted for total plaque HR: 1.046; 95% CI: 1.019, 1.074; P = .0008; adjusted for maximal stenosis and at least two HRPf HR: 1.047; 95% CI: 1.020, 1.074; P = .0005). Findings were nonsignificant in RCA-only analyses (univariable HR: 1.013; 95% CI: 0.995, 1.031; P = .2; adjusted for noncalcified plaque HR: 1.010; 95% CI: 0.991, 1.030; P = .3; adjusted for total plaque HR: 1.011; 95% CI: 0.993, 1.031; P = .2; adjusted for maximal stenosis and at least two HRPf HR: 1.011; 95% CI: 0.992, 1.031; P = .2) (Table 2). In associations between PCATa and traditional risk factors by mixed effects linear regression, PCATa was inversely associated with hyperlipidemia (β = -2.42 ; P = .04) and body mass index (BMI; β = -0.34 ; P < .01) in univariable analyses, and BMI alone in multivariable analyses (β = -0.38 ; P = .003) (Table 3), which was not significantly different between patients with ACS and controls (Table 1).

Discussion

Our study examined the relation of PCATa to incident ACS events at both a patient- and a culprit vessel-level. The primary findings were threefold. First, there was no significant difference between mean PCATa values between patients with future ACS and controls. Second, within adjusted time-to-event models, on a vessel basis, PCATa had a small but significant association with ACS events, as well as in the subgroup of culprit vessels versus matched highest-stenosis vessels in controls. Finally, these associations were not seen in analyses comparing only the proximal RCA (independent of culprit vessel status). These results appear

Table 3: Univariable and Multivariable Linear Regression Analysis Assessing the Relation of Pericoronary Adipose Tissue Attenuation to Traditional Risk Factors

Characteristic	Univariable			Multivariable		
	β	SE	P Value	β	SE	P Value
Sex	-0.66	1.20	.59	-0.28	1.17	.8
Age	-0.03	0.05	.55	-0.10	0.05	.05
Hypertension	-1.01	1.20	.40	—	—	—
Hyperlipidemia	-2.42	1.15	.04	-1.65	1.14	.1
Diabetes	-0.50	1.45	.73	—	—	—
Smoking	-0.19	1.21	.87	—	—	—
Family history	-1.15	1.16	.32	—	—	—
Body mass index	-0.34	0.12	<.01	-0.38	0.13	.003
Statin use	2.05	1.32	.12	—	—	—
Low density lipoprotein	-0.01	0.02	.47	—	—	—
Log(CAC+1)	-0.11	0.30	.72	—	—	—

Note.—Multivariable analysis including sex, age, and significant univariable factors. CAC = coronary artery calcium score, SE = standard error.

to be due to a small, but likely true, effect size, because ACS PCATa measurements were consistently greater (less negative) than in controls. Power calculation with an α of .05 and a power of 80% suggests that as opposed to our 587 matched pairs, 695 matched pairs would be necessary to show a difference in the group means. However, even if a significant difference were seen, the overall effect size would be unlikely to support the use of PCATa as a single marker for the identification of patients at risk for ACS.

Compared with prior research, our mean effect size of approximately 1 HU is much more narrow than previously published works, which typically display differences of 4–6 HU (3,23–25). We acknowledge that this measurement was previously performed in distinct contexts with the exception of one recent study that assessed PCATa around subsequent lesions versus proximal segments (23); most have either examined longer-term outcomes or only measured PCATa immediately after ACS events (3,5,24,25). Thus, although our findings of higher (less negative) PCATa values in patients with ACS are consistent with previous studies, our study design may result in a lower effect size because we provide a unique patient- and vessel-matched one-to-one case-control design across a multisite study to assess these findings, which results in high proportions of patients with ACS and a control population with relatively high rates of cardiovascular comorbidities and disease. Additionally, the international multicenter cohort used a broad array of CCTA scanners, with the majority being older generation 64-section models. This diversity may have increased variability in PCATa, which may not be seen with single-center more modern CCTA scanners, including new photon-counting or ultra-high-resolution approaches (26).

The Cox model analyses revealed small but significant associations, with the lower range of the 95% CI near unity for our all vessels and culprit versus most stenotic analyses, with and without adjustment. PCATa has been previously associated with noncalcified plaque, which has been associated with adverse cardiac events (4,27–30), and a previous study has shown persistent association after adjustment for plaque volumes (24). There are reported

associations with PCATa and hemodynamically significant stenosis (31), though conflicting reports either in significance or directionality of the attenuation change have also been published (28,32), and significant associations with high-risk plaque have also been reported (25,33). We recognize that the HRs were small and thus similar to our comments regarding the population means such that PCATa would be unlikely to be clinically useful as a single predictor of future risk; however, by adjusting for the features we chose, we aimed to demonstrate persistent additive relevance to current clinical reading settings using maximal stenosis and HRPf similar to Coronary Artery Disease Reporting and Data System 2.0 and quantitative plaque measures, which are becoming more commonly offered.

Within the secondary analyses, the relation of BMI with PCATa was inverse, meaning lower PCATa values with higher BMIs, which was the opposite of what was expected both from a metabolic health (eg, less healthy would likely have higher PCATa) and attenuation (eg, more attenuation would have a higher PCATa) standpoint. Thus, this may represent latent confounders such as overall changes to the body fat depots, or an inability to distinguish between metabolically healthy and unhealthy changes in BMI, though given the similar distributions of BMI between our patients and controls, this is unlikely to affect our conclusions. We also noted that per-patient comparisons of RCA PCATa were not significant. Previously, proximal RCA measurements have been commonly used as the best representative of per-patient inflammatory risk (7), given the lack of branch vessels and typical high amount of pericoronary fat. Our significant findings in culprit vessel analysis may reflect more significant local increases in PCATa, which help further differentiation between patients with ACS and controls, whereas nonspecific comparison of RCA vessels had insufficient signal to differentiate matched patients and controls. Combining the prior and the current findings suggests that there may be both global coronary (as reflected in the primary analysis) and local culprit inflammation (as reflected in the culprit vessel analysis) occurring, with the local culprit inflammation being more significant than the global

changes. This should be investigated in future analyses. Potential explanations for lack of signal in the RCA analysis may include patient selection in ICONIC, whereby matching results in more similar patients than prior studies, or a higher risk of motion artifact in the RCA territory versus other coronary territories, given that our study included older CT scanner generations that may have had more difficulty with motion artifact.

Our study had some limitations. Image analyses could not be performed in all patients and all vessels within the cohort, resulting in exclusion of a portion of the population. To preserve matching, we excluded unmatched patients and vessels. We used conditional Cox models and cluster-robust standard errors to account for cohort matching and within-patient measurements. Given that patients retained relatively similar demographic distributions and there were no significant differences between the excluded and included populations, we believe that the populations remained well balanced. The benefit of this population is the unique ability to include larger numbers of patients with ACS than previous studies. Additionally, as a multicenter cohort, we recognize that there were potentially higher degrees of heterogeneity within our study population in terms of image acquisition, with differences in scanner type, gating methodology, and acquisition energy than in most single-center studies. We expect this heterogeneity to be primarily nondifferential and therefore bias toward the null. This is a limitation of the design that may reflect other latent confounders but may also potentially provide a more realistic assessment of real-world performance accounting for heterogeneity. Finally, it is also possible given the significant numbers of patients who had short-term events, some of these patients may have been undergoing ACS events as their original referral to CCTA because referrals for chest pain were more frequent in the ACS population.

In conclusion, PCATa appears to have a weak association with outcomes, which limits its individual clinical use, but is overall significantly associated with future ACS in time-to-event models in a case-control analysis matched for risk factors and coronary artery disease. The associations appear stronger in per-vessel and culprit vessel analyses as opposed to per-patient analyses and are independent of noncalcified plaque volume, total plaque volume, and traditional clinical measurements of maximal stenosis and HRPf.

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