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JACC: CARDIOVASCULAR IMAGING VOL. 15, NO. 10, 2022

PUBLISHED BY ELSEVIER

ORIGINAL RESEARCH

Association Between Changes in Perivascular Adipose Tissue Density and Plaque Progression

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ABSTRACT

BACKGROUND The association between the change in vessel inflammation, as quantified by perivascular adipose tissue (PVAT) density, and the progression of coronary atherosclerosis remains to be determined.

OBJECTIVES The purpose of this study was to explore the association between the change in PVAT density and the progression of total and compositional plaque volume (PV).

METHODS Patients were selected from a prospective multinational registry. Patients who underwent serial coronary computed tomography angiography studies with ≥2-year intervals and were scanned with the same tube voltage at baseline and follow-up were included. Total and compositional PV and PVAT density at baseline and follow-up were quantitatively analyzed for every lesion. Multivariate linear regression models using cluster analyses were constructed.

RESULTS A total of 1,476 lesions were identified from 474 enrolled patients (mean age 61.2 ± 9.3 years; 65.0% men). The mean PVAT density was −74.1 ± 11.5 HU, and total PV was 48.1 ± 83.5 mm^3 (19.2 ± 44.8 mm^3 of calcified PV and 28.9 ± 51.0 mm^3 of noncalcified PV). On multivariate analysis (adjusted for clinical risk factors, medication use, change in lipid levels, total PV at baseline, luminal HU attenuation, location of lesions, and tube voltage), the increase in PVAT density was positively associated with the progression of total PV (estimate = 0.275 [95% CI: 0.004-0.545]; $P = 0.047$), driven by the association with fibrous PV (estimate = 0.245 [95% CI: 0.070-0.420]; $P = 0.006$). Calcified PV progression was not associated with the increase in PVAT density ($P > 0.050$).

CONCLUSIONS Increase in vessel inflammation represented by PVAT density is independently associated with the progression of the lipid component of coronary atherosclerotic plaques. (Progression of AtheRosclerotic PlAque Determined by Computed TomoGraphic Angiography Imaging [PARADIGM]; NCT02803411)
(J Am Coll Cardiol Img 2022;15:1760–1767) © 2022 by the American College of Cardiology Foundation.

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ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2022.04.016

Inflammation is one of the primary mechanisms responsible for the development and progression of coronary atherosclerosis.[1,2] Inflammation plays a vital role in initiating the development of a coronary plaque, and suppression of inflammation using medication attenuates the progression of coronary artery disease (CAD).[3,4] Accordingly, considerable effort has been put toward the development of imaging technologies that can directly visualize and quantify vessel inflammation that relates to the development and progression of coronary plaques, using both invasive and noninvasive coronary imaging modalities.[5-7]

Recently, increased computed tomography (CT) attenuation (HU) in perivascular adipose tissue (PVAT) density assessed by coronary computed tomography angiography (CTA) has been proposed as a reliable quantitative marker of vessel inflammation that drives the development and progression of CAD.[8-10] Increased PVAT density differentiates various stages of CAD,[11] and is associated with the presence of high-risk plaque (HRP) features that are correlated with future clinical events[12] and culprit lesions in patients with acute coronary syndromes.[13]

Few studies have investigated the association between the changes in PVAT and plaque progression, but are limited by small patient numbers and short follow-up periods.[14,15] Therefore, whether the change in PVAT density affects the progression of each coronary plaque has not been fully evaluated.

In this study, we explored the association between the changes in PVAT density and the progression of total and compositional plaque volume (PV) in patients with CAD from a large multicenter registry of serial coronary CTAs.

METHODS

STUDY DESIGN AND POPULATION. The PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging) study is a dynamic multinational observational registry that prospectively collected the clinical, procedural, and follow-up data on 2,252 consecutive patients who underwent clinically indicated serial coronary CTAs. The interscan interval was ≥2 years, and patient data were collected from 13 sites in 7 countries between 2003 and 2015.[16] The study protocol was approved by the institutional review boards of all participating centers.

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CT = computed tomography

CTA = computed tomography angiography

HRP = high-risk plaque

PV = plaque volume

PVAT = perivascular adipose tissue

For the current analysis, patients were excluded for the following reasons: patients scanned with a different tube voltage at baseline and follow-up coronary CTAs (n = 1,150)[17]; patients with coronary CTA results that were uninterpretable for either quantitative assessment (n = 492) or PVAT density analysis (n = 125); and those who experienced clinical events that resulted in coronary revascularization between the coronary CTAs (n = 11). Overall, 1,476 lesions from the remaining 474 patients were included in the final analysis (**Figure 1**).

Patients were considered to be statin-naive when they were not treated with statins at both baseline and follow-up coronary CTAs, and statin-taking if they were treated with statins at the follow-up coronary CTA.

CORONARY CTA ANALYSIS PROTOCOL. Acquisition and analysis of the coronary CTAs were performed following the guidelines provided by the Society of Cardiovascular Computed Tomography.[18,19] Coronary CTA data sets were analyzed at a core laboratory by Level III experienced readers using semiautomated plaque analysis software (QAngioCT Research Edition version 2.1.9.1, Medis Medical Imaging) with manual correction as described previously.[20,21]

Briefly, all coronary lesions with diameters ≥2 mm were evaluated for every coronary artery and its

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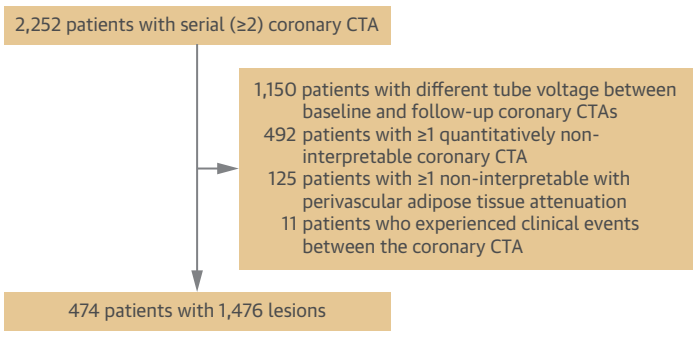
Todd Villines, MD, served as Guest Editor for this paper.

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.

Manuscript received August 19, 2021; revised manuscript received April 11, 2022, accepted April 19, 2022.

FIGURE 1 The CONSORT Diagram



CTA = computed tomography angiography.

branches using a modified 17-segment American Heart Association model.[19,22] The presence of an atherosclerotic plaque was defined as any tissue ≥1 mm^3 within, or adjacent to, the lumen that could be discriminated from the surrounding pericardial tissue, epicardial fat, or lumen, and identified in ≥2 planes.[19,22] For serial comparisons of coronary CTAs, coronary lesions were coregistered between the coronary CTA-1 and -2 evaluations using fiduciary landmarks, including the distance from the ostium and the branch vessels.

Stenosis severity on the percent diameter stenosis (DS) (%) and total plaque volume (PV) (mm^3) were determined for each lesion. Total PV was further subclassified as follows into compositional PVs using predefined HU cutoff values[23]: 1) noncalcified (−30 to 350 HU) PV encompassing necrotic core (−30 to 30 HU), fibro-fatty (30-130 HU), and fibrous (131-350 HU) PV; and 2) calcified PV (≥351 HU).[24,25] The progression of PV was defined as the change in PV divided by the coronary CTA intervals. The presence of HRP features, defined as coronary lesions with evidence of ≥2 of the following criteria: positive arterial remodeling, low-attenuation plaque, or spotty calcification, were also determined based on the qualitative assessment.[22,26]

ANALYSIS OF PVAT DENSITY. PVAT density was assessed in all quantitatively analyzed coronary lesions.[8,9,14] For each lesion, volumes located within the radial distance from the vessel wall equal in thickness to the average diameter of the lesion were set by the readers and traced automatically with software (QAngioCT Research Edition version 3.2.0.5, Medis Medical Imaging) using the vessel wall contour previously confirmed for the quantitative analysis of coronary CTAs.[9,14,27] In this region, PVAT density was then calculated as the average attenuation of all voxels in the range of −190 to −30 HU (for identifying fat tissues).[8,9,13,14,27] The mean luminal attenuation (HU) was also identified for each lesion. PVAT density was considered high when >70.1 HU.[9,27]

STATISTICAL ANALYSIS. Categorical variables are presented as absolute counts and percentages, and continuous variables are expressed as mean ± SD or median (IQR), as appropriate. Differences between categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate, while differences between continuous variables were assessed using the Student's *t*-test.

To explore the association between PVAT density and PVs at baseline and follow-up at the lesional level, we constructed multivariable linear mixed effect models with random effects to account for clustering of observations within the same individual. Models were adjusted for age; male sex; body mass index; systolic blood pressure; smoking history; hypertension; diabetes mellitus; family history of CAD; level of low-density lipoprotein; medication use including statins, antiplatelets, and beta-blockers; and luminal attenuation. For the association between the change in PVAT density and the change in PVs, models were repeated with additional adjustments using changes in low-density lipoprotein levels, baseline PVs, luminal attenuation at baseline and follow-up, location of lesions within the major 3 vessels, and tube voltage. The statistical significance of the estimate of PVAT in each model was assessed using the likelihood ratio test, according to recent recommendations.

A 2-tailed value of $P < 0.05$ was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute Inc) and R 3.3.0 (R Development Core Team, 2016).

RESULTS

STUDY POPULATION AND BASELINE CHARACTERISTICS. In total, 474 patients (age 61.2 ± 9.3 years; 65% men) were included (Table 1). Hypertension was present in 60.3% of the study population, and the prevalence of diabetes mellitus and hyperlipidemia was 23.6% and 48.1%, respectively. Statins were used in 60.8% of the study population. The interscan interval between coronary CTAs was 3.3 ± 1.2 years. Coronary CTA scans were performed using 100 kV in 47.9% of patients and 120 kV in 51.5%.

LESION BASED CORONARY CTA FINDINGS. In total, 1,474 lesions were identified from the 474 enrolled patients (Table 2). Most of the lesions were nonobstructive; the mean diameter stenosis was 18.8% ±

TABLE 1 Clinical Characteristics of the Study Population at Baseline (n = 474)

Age, y	61.2 ± 9.3
Male	308 (65.0)
Coronary CTA interval, y	3.3 ± 1.2
Body mass index, kg/m^2	26.2 ± 3.4
Hypertension	286 (60.3)
Diabetes mellitus	112 (23.6)
Hyperlipidemia	228 (48.1)
Family history of CAD	130 (27.4)
Smoking	222 (46.8)
Total cholesterol, mg/dL	186.8 ± 40.2
Low-density lipoprotein, mg/dL	113.5 ± 36.9
High-density lipoprotein, mg/dL	48.3 ± 11.8
Triglycerides, mg/dL	149.9 ± 92.6
Statin	288 (60.8)
Antiplatelets	245 (51.7)
Beta-blockers	172 (36.3)
Coronary CTA acquisition parameters	
Tube voltage	
80 kV	3 (0.6)
100 kV	227 (47.9)
120 kV	244 (51.5)
Tube current, mA	582.2 ± 245.3
Radiation dose, DLP	706.1 ± 455.7
Heart rate, beats/min	60.9 ± 9.9
Coronary CTA acquisition parameters at follow-up	
Tube current, mA	439.9 ± 231.1
Radiation dose, DLP	580.2 ± 456.3
Heart rate, beats/min	60.9 ± 9.5

Values are mean ± SD or n (%).
CAD = coronary artery disease; CTA = computed tomography angiography; DLP = dose length product.

12.6%, and 14.4% of plaques exhibited HRP features. Total PV at baseline was 48.1 ± 83.5 mm^3, comprising 19.2 ± 44.8 mm^3 of calcified PV and 28.9 ± 51.0 mm^3 of noncalcified PV. At follow-up, total PV increased to 65.7 ± 102.2 mm^3 as a result of the summation of 29.6 ± 57.5 mm^3 of calcified PV and 36.1 ± 6.32 mm^3 of noncalcified PV.

Overall, the PVAT density was −74.1 ± 11.5 HU at baseline and −73.1 ± 11.7 HU at follow-up. When the lesions were divided according to the change in PVAT density, PVAT density was increased in 788 lesions and decreased in 688 lesions (Supplemental Table 1). At follow-up, the lesions with increased PVAT density possessed a greater total PV and noncalcified PV than those with decreased PVAT density (71.8 ± 112.5 mm^3 vs 58.7 ± 88.5 mm^3 and 41.8 ± 73.7 mm^3 vs 29.5 ± 47.7 mm^3, respectively, all $P < 0.05$).

ASSOCIATION BETWEEN PVAT DENSITY WITH TOTAL AND COMPOSITIONAL PVs. The cross-sectional analysis observed a negative association between the total and calcified PV and PVAT density at baseline (estimate = −0.5880 [95% CI: −1.1256 to −0.0505] and estimate = −0.2768 [95% CI: −0.5322 to −0.0214], respectively, all $P < 0.05$). However, no association was observed between all PVs and PVAT density at follow-up (Table 3).

When the lesions were divided according to the statin use, a negative association of PVAT density with total and calcified PV at baseline only existed in the lesions of statin-taking patients (Supplemental Table 2). In the lesions of statin-naive patients, no association was observed between the PVAT density and the total and compositional PVs (all $P > 0.05$).

The multivariable analysis model of the association of the change in PVAT density on the progression of plaque volumes is shown in Table 4. Increase in PVAT density demonstrated a positive association with the progression of total PV (estimate = 0.275 [95% CI: 0.004-0.545]; $P = 0.047$). The change in PVAT density was also positively associated with the progression of fibrous PV (estimate = 0.245 [95% CI: 0.0695-0.420]; $P = 0.006$), but not with the progression of calcified PV ($P > 0.05$) (Central Illustration).

DISCUSSION

In the analysis of the PARADIGM registry primarily involving non-obstructive CAD patients, the increase in PVAT density was significantly associated with the progression of coronary atherosclerosis as represented by total PV. Importantly, when total PV was subclassified into its constituents, only the increase of fibrous PV, a component of non-calcified PV, was positively associated with the increase in PVAT density, but the progression of calcified PV was not.

Inflammation plays a pivotal role in both the initiation of a coronary plaque and its progression. Previous cross-sectional studies have highlighted PVAT density as a potential imaging marker for vessel inflammation that could assist in better identification of high-risk patients by demonstrating a direct association between the increased PVAT density and more advanced stages of CAD, as well as the presence of HRP and downstream myocardial hypoperfusion.[11-13,27] Our findings are in line with these observations, as we reported that the increases in PVAT density (representing an increase in vessel inflammation) were significantly correlated with the increase in total PV, chiefly explained by the positive association with a component of noncalcified PV.

Lipid-lowering medications, including statins and proprotein convertase subtilisin/kexin type 9 inhibitors, attenuate the atherosclerotic plaque progression as demonstrated in both invasive and

TABLE 2 Coronary CTA Characteristics of Lesions at Baseline and Follow-Up (n = 1,476)

	Baseline	Follow-Up	*P* Value
PVAT attenuation, HU	−74.1 ± 11.5	−73.1 ± 11.7	<0.001
Diameter stenosis, %	18.8 ± 12.6	21.5 ± 12.8	<0.001
High-risk plaque[a]	212 (14.4)	249 (16.9)	<0.001
Total PV, mm^3	48.1 ± 83.5	65.7 ± 102.2	<0.001
Calcified PV, mm^3	19.2 ± 44.8	29.6 ± 57.5	<0.001
Noncalcified PV, mm^3[b]	28.9 ± 51.0	36.1 ± 63.2	<0.001
Fibrous PV, mm^3	20.8 ± 35.9	26.8 ± 43.5	<0.001
Fibro-fatty PV, mm^3	7.2 ± 16.9	8.4 ± 21.7	0.001
Necrotic-core PV, mm^3	0.88 ± 3.68	0.98 ± 3.85	0.376

Values are mean ± SD or n (%). [a]PVAT density was considered high when >70.1 HU.[9,27] [b]High-risk plaque is defined as a lesion with ≥2 features indicative of positive arterial remodeling, low-attenuation plaque, or spotty calcification.

PV = plaque volume; PVAT = perivascular adipose tissue; other abbreviation as in Table 1.

noninvasive imaging studies,[28-30] not only by lowering the plasma level of low-density lipoprotein level, but also by their anti-inflammatory effects on the coronary vasculature.[3,31] Furthermore, statins were associated with the faster progression of calcified PV and slower progression of noncalcified PV, the component that determines plaque instability and is more directly associated with vessel inflammation and future clinical events.[20,30] Statin usage was also associated with decrease in PVAT density in noncalcified and mixed coronary plaques in a recent study.[15] This association between the plaque lipid components and inflammation is also supported by our findings that only fibrous PV, and not calcified PV, was associated with the increase in PVAT density.

Taken together, including the monitoring of PVAT density, may be considered for the assessment of CAD and monitoring the effects of medications, independent of the plaque itself. As per the current clinical guidelines, risk stratification and the determination of treatment strategies for CAD are predominantly determined by the degree of coronary stenosis.[32,33] However, recent studies have repeatedly demonstrated the importance of nonobstructive coronary lesions for the development of acute coronary syndromes.[34,35] The totality of coronary atherosclerosis, as represented by the overall plaque burden and its components, is maybe more important for risk stratification than the presence of an obstructive lesion.[34-38] Therefore, studies assessing the value of a more comprehensive evaluation of coronary atherosclerosis that includes data from the perivascular tissues other than plaques may be warranted to improve risk stratification.

Notably, the cross-sectional analysis in this study revealed a negative association between PVAT density and total PV at baseline. However, this negative association has only existed in lesions from statin-taking patients. CAD is a dynamic disease with plaques at various stages that can coexist in a single patient, such that one plaque may be developing while another is stabilizing, which could also contribute to this finding.[39] PARADIGM is an observational study with patients at various stages of CAD, including some patients who were already on statin treatment and others who were not. Furthermore, previous studies have shown the effect of statins on plaque compositions and characteristics, which resulted in plaque calcification and eventual stabilization.[20,30,40] Therefore, it is plausible to assume that most of lesions in statin-taking patients were already in stabilized status, thereby weakening the impact of elevated PVAT density with PVs at baseline. Still, the impact of change in PVAT density on the progression of PV, especially the noncalcified PV, remained significant even under the effect of statins.

TABLE 3 Impact of Perivascular Adipose Tissue Attenuation Density on Total and Compositional Plaque Volume at Baseline and Follow-Up

	Baseline			Follow-Up		
	Estimate	95% CI	*P* Value	Estimate	95% CI	*P* Value
High-risk plaque[a]	0.0002	−0.0023 to 0.0027	0.877	0.0005	−0.002 to 0.003	0.6856
Total PV	−0.5880	−1.1256 to −0.0505	0.0321	−0.0053	−0.569 to 0.5585	0.9855
Calcified PV	−0.2768	−0.5322 to −0.0214	0.0337	−0.0524	−0.3533 to 0.2486	0.7327
Noncalcified PV[b]	−0.3127	−0.6732 to 0.0479	0.089	0.0004	−0.3952 to 0.3958	0.9988
Fibrous PV	−0.1503	−0.3977 to 0.0972	0.2335	0.0954	−0.1726 to 0.3634	0.4849
Fibro-fatty PV	−0.1364	−0.2616 to −0.0113	0.0327	−0.078	−0.2212 to 0.0654	0.2859
Necrotic-core PV	−0.0471	−0.0771 to −0.0171	0.0022	−0.0343	−0.061 to −0.0075	0.0122

Adjusted for age; male; body mass index; systolic blood pressure; smoking history; hypertension; diabetes mellitus; family history of CAD; level of low-density lipoprotein; medication use including statins, antiplatelets, and beta-blockers; luminal attenuation; location of lesions; and tube voltage. [a]High-risk plaque is defined as a lesion with ≥2 features indicative of positive arterial remodeling, low-attenuation plaque, or spotty calcification. [b]Noncalcified PV is the summation of fibrous, fibro-fatty, and necrotic core PV.

Abbreviations as in Tables 1 and 2.

TABLE 4 Impact of the Change in Perivascular Adipose Tissue Density on the Progression of Plaque Volumes

	Estimate	95% CI	*P* Value
Total PV	0.275	0.004 to 0.545	0.047
Calcified PV	0.023	−0.086 to 0.130	0.691
Noncalcified PV[a]	0.254	−0.003 to 0.512	0.053
Fibrous PV	0.245	0.0695 to 0.420	0.006
Fibro-fatty PV	0.049	−0.062 to 0.159	0.380
Necrotic-core PV	−0.022	−0.048 to 0.007	0.137

Adjusted for age; male; body mass index; systolic blood pressure; smoking history; hypertension; diabetes mellitus; family history of CAD; changes in low-density lipoprotein levels; medication use including statins, antiplatelets, and beta-blockers; plaque volume at baseline; luminal attenuation at baseline and follow-up; location of lesions; and tube voltage. [a]Noncalcified PV is the summation of fibrous, fibro-fatty, and necrotic core PV.

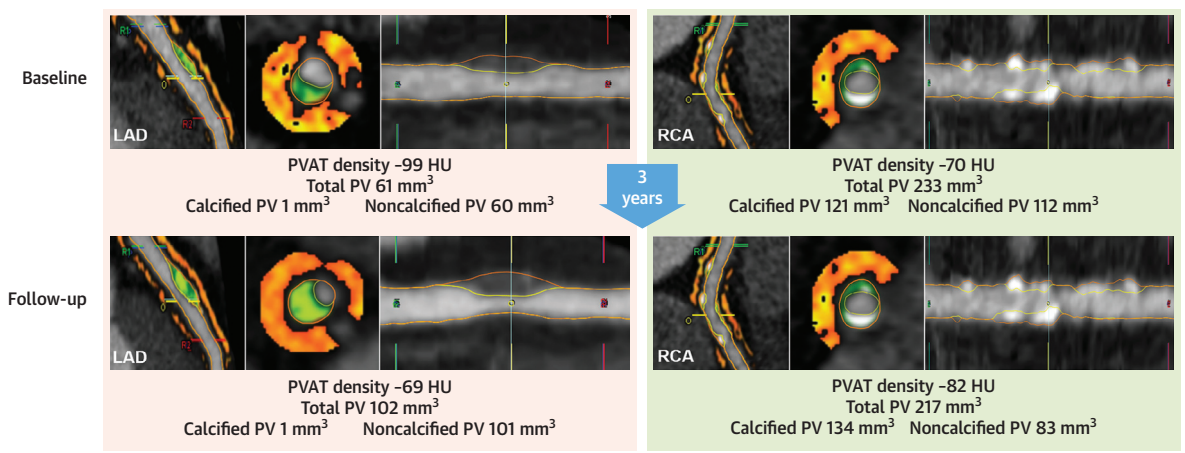
Abbreviations as in Tables 1 and 2.

STUDY LIMITATIONS. First, selection bias was inevitable because of the observational study design, as only patients with more than 2 coronary CTA scans were enrolled. High-risk patients subjected to invasive studies or revascularizations, or patients with normal coronaries would have been omitted from the registry. These issues resulted in a study population of CAD patients who were generally at low risk and had a low incidence of hard clinical events. Second, the study was not powered to estimate the coronary event risk of individual plaques as reflected by the low % diameter stenosis of the lesions. Thus, the relevance of the current results for high-risk populations and obstructive lesions is unknown. Moreover, the direct association between the changes in PVAT density to clinical outcomes could not be assessed.

Third, differences in vendors and scan parameters between the patients might have influenced the results. However, to minimize the effect of different scan acquisition parameters generated from the observational study design, we only included patients who were scanned with the same tube voltage at baseline and follow-up. We also adjusted for luminal HU attenuation, which was reported to be associated with quantitative coronary CT analysis in recent work from our network.[17]

To our knowledge, this is the first study to describe the value of the change in PVAT density in the clinical outcomes and the association of the changes in PVAT density with the progression of total and compositional PV in a large multinational registry. To overcome the limitations of this study, large population-based prospective studies with serial coronary CTAs should be conducted. However, as there are currently no recommendations on the use of serial coronary CTAs for the evaluating CAD in a low-risk population,[41] an observation registry such as the PARADIGM provides a unique opportunity to further understand the association between vessel inflammation represented by PVAT density with and the progression of coronary atherosclerosis.

CENTRAL ILLUSTRATION Association Between the Change in PVAT Density and Total and Compositional Plaque Progression



Lee S-E, et al. J Am Coll Cardiol Img. 2022;15(10):1760–1767.

Noncalcified PV is the summation of fibrous, fibro-fatty, and necrotic core PV. LAD = left anterior descending; PV = plaque volume; PVAT = perivascular adipose tissue; RCA = right coronary artery.

CONCLUSIONS

The increase in PVAT density was significantly associated with an increase in total PV, driven by the positive association with the progression of fibrous PV but not with the progression of calcified PV.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by the Korea Medical Device Development Fund grant funded by the Korea government (the Ministry of Science and ICT; the Ministry of Trade, Industry and Energy; the Ministry of Health and Welfare, Republic of Korea, the Ministry of Food and Drug Safety) (Project Number: 202016B02). The study was also funded in part by a grant from the Dalio Foundation. Dr Leipsic has served as a consultant for and holds stock options in HeartFlow and Circle CVI. Drs Kitslaar and Reiber are employees of Medis Medical Imaging. Dr Samady has served on the scientific advisory board of Philips; has equity interest in Covanos Inc; and has received a research grant from Medtronic. Dr Lin has received grant support from GE Healthcare. Dr Min has received funding from GE Healthcare; has served on the scientific advisory board of Arineta and GE Healthcare; and has an equity interest in and is an employee of Cleerly, Inc. Dr Chang has received funding from the Leading Foreign Research Institute Recruitment Program through the National Research Foundation (NRF) of Korea funded by the Ministry of Science and ICT (MSIT) (Grant No. 2012027176). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The change in vascular inflammation as represented by the pericoronary adipose tissue attenuation density is associated with the progression of coronary atherosclerosis driven by the association with the noncalcified plaque components.

TRANSLATIONAL OUTLOOK: Prospective studies should be employed to investigate whether a more comprehensive evaluation of coronary atherosclerosis that includes pericoronary tissues would improve the risk stratification of patients with CAD.

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KEY WORDS coronary artery atherosclerosis, coronary artery disease, coronary computed tomography angiography, perivascular adipose tissue, vessel inflammation

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