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Authors

Ceponiene, Indre
Nakanishi, Rine
Osawa, Kazuhiro
et al.

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Coronary Artery Calcium Progression Is Associated With Coronary Plaque Volume Progression

Results From a Quantitative Semiautomated Coronary Artery Plaque Analysis

Indre Ceponiene, MD, MSc,[a,b] Rine Nakanishi, MD, PhD,[a] Kazuhiro Osawa, MD, PhD,[a] Mitsuru Kanisawa, MD,[a] Negin Nezarat, MD,[a] Sina Rahmani, MD,[a] Kendall Kissel,[a] Michael Kim, BS,[a] Eranthi Jayawardena, BS,[a] Alexander Broersen, PhD,[c] Pieter Kitslaar, MSc,[c,d] Matthew J. Budoff, MD[a]

ABSTRACT

OBJECTIVES The aim of this study was to determine whether coronary artery calcium (CAC) progression was associated with coronary plaque progression on coronary computed tomographic angiography.

BACKGROUND CAC progression and coronary plaque characteristics are associated with incident coronary heart disease. However, natural history of coronary atherosclerosis has not been well described to date, and the understanding of the association between CAC progression and coronary plaque subtypes such as noncalcified plaque progression remains unclear.

METHODS Consecutive patients who were referred to our clinic for evaluation and had serial coronary computed tomography angiography scans performed were included in the study. Coronary artery plaque (total, fibrous, fibrous-fatty, low-attenuation, densely calcified) volumes were calculated using semiautomated plaque analysis software.

RESULTS A total of 211 patients (61.3 ± 12.7 years of age, 75.4% men) were included in the analysis. The mean interval between baseline and follow-up scans was 3.3 ± 1.7 years. CAC progression was associated with a significant linear increase in all types of coronary plaque and no plaque progression was observed in subjects without CAC progression. In multivariate analysis, annualized and normalized total plaque ($\beta = 0.38$; $p < 0.001$), noncalcified plaque ($\beta = 0.35$; $p = 0.001$), fibrous plaque ($\beta = 0.56$; $p < 0.001$), and calcified plaque ($\beta = 0.63$; $p = 0.001$) volume progression, but not fibrous-fatty ($\beta = 0.03$; $p = 0.28$) or low-attenuation plaque ($\beta = 0.11$; $p = 0.1$) progression, were independently associated with CAC progression. Plaque progression did not differ between the sexes. A significantly increased total and calcified plaque progression was observed in statin users.

CONCLUSIONS In a clinical practice setting, progression of CAC was significantly associated with an increase in both calcified and noncalcified plaque volume, except fibrous-fatty and low-attenuation plaque. Serial CAC measurements may be helpful in determining the need for intensification of preventive treatment. (J Am Coll Cardiol Img 2017;■:■–■)
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From the [a]Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center, Torrance, California; [b]Departments of Cardiology and Radiology, Academy of Medicine, Lithuanian University of Health Sciences, Kaunas, Lithuania; [c]Division of Image Processing, Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands; and the [d]Medis Medical Imaging Systems, Leiden, the Netherlands. This research was supported by R01 HL071739 (to Dr. Budoff). Dr. Kitslaar is an employee of Medis Medical Imaging Systems and has a research appointment at the Leiden University Medical Center. Dr. Budoff has served as a consultant for General Electric. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

CAC = coronary artery calcium

CAD = coronary artery disease

CT = computed tomography

CTA = computed tomography angiography

CVD = cardiovascular disease

IVUS = intravascular ultrasound

NCP = noncalcified plaque

PV = plaque volume

Atherosclerotic plaque progression is a complex process that is associated with multiple factors, such as wall shear stress, plaque structural stress, inflammation, endothelial dysfunction, neovascularization, and alterations in mineral metabolism (1-6). Coronary plaque progression might have an added value in risk stratification as risk stratification of plaques based on the morphological characteristics at a single region of the plaque, usually the minimal lumen diameter, may be misleading (7).

Several invasive modalities, such as intravascular ultrasound (IVUS) and optical coherence tomography, allow for the visualization, categorization, and quantification of coronary plaque and are used for the assessment of plaque progression. Until recently, visual assessment and visual quantification of coronary plaque was only possible during cardiac (coronary) computed tomography angiography (CTA). New methods for semiquantitative plaque assessment have emerged with good correlation to IVUS, allowing a more precise quantification of coronary plaque (8), suggesting that it potentially can be an alternative tool to identify coronary atherosclerosis and its progression.

Coronary artery calcium (CAC) visualized on noncontrast computed tomography (CT) is a robust marker of atherosclerosis because CAC reflects overall coronary atherosclerosis burden including calcified and noncalcified plaques (9). Several studies demonstrated a strong association of CAC progression with the risk of cardiovascular disease (CVD) and cardiovascular mortality (10-12). However, the natural history of coronary atherosclerosis has not been well described to date, and the clinical and pathological understanding of the association between CAC progression and other coronary plaques such as noncalcified plaque progression remains unclear. However, reports of CAC progression associated with statin use has cast doubt on the underlying atherosclerotic process occurring as CAC progresses (stabilization versus progression).

We aimed to evaluate the association of CAC progression with change in atherosclerotic plaque volume and its subtypes using quantitative plaque analysis software.

METHODS

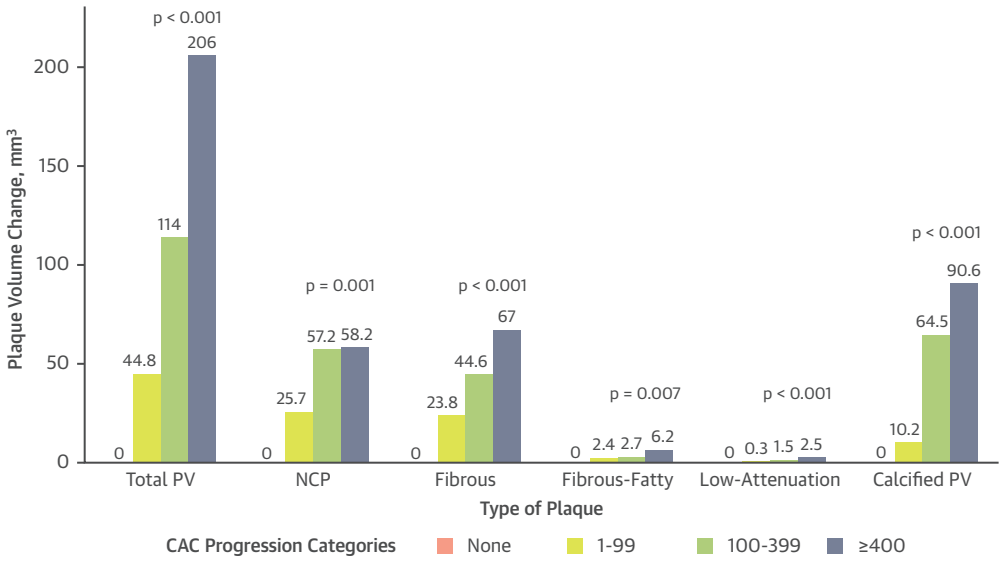
STUDY POPULATION. Two hundred eleven consecutive patients, who were referred to our clinic for evaluation and had serial cardiac CT (coronary CTA) scans performed, were included in the study. Patients with nondiagnostic baseline or follow-up scans, previous coronary artery bypass grafts, coronary revascularization between baseline and follow-up, or <1-year interval between baseline and follow-up scans were excluded from the study. Coronary artery disease (CAD) risk factors were defined as previously reported (13). This study was approved by the Institutional Review Board of our institution (Los Angeles BioMedical Institute at Harbor UCLA Medical Center, Torrance, California).

NONCONTRAST CT IMAGE ACQUISITION AND CORONARY CTA IMAGE ACQUISITION PROTOCOLS. All patients were scanned using a 64-slice CT scanner (Lightspeed VCT, General Electric Healthcare, Milwaukee, Wisconsin), and noncontrast CT was performed before coronary CTA scanning. CAC and coronary CTA acquisition were performed in accordance with the guidelines (14). CAC was measured on a dedicated workstation (AW Volume Share, GE Medical Systems, Milwaukee, Wisconsin), and quantified using the Agatston score (15).

Coronary CTAs were evaluated by experienced readers for the presence of coronary plaque, and plaque volumes were quantified using semi-automated plaque analysis software (QAngioCT Research Edition version 2.1.2, Medis Medical Imaging Systems, Leiden, the Netherlands). Coronary plaque was visually identified by any hyperdense or hypodense structure distinct from the lumen and >1 mm^2 in size. Detected plaques were allocated according to a modified 17-segment American Heart Association coronary tree model (14). Semiautomated plaque volume quantification was performed using methodology described previously (8,16,17). Vessel and plaque volumes at baseline and follow-up were measured in segments with sufficient image quality and ≥1.5 mm in lumen diameter. Segments with stents were excluded.

STATISTICAL ANALYSIS. Kruskal-Wallis test was used for comparisons between several groups of nonparametric continuous variables (**Figure 1**). The Mann-Whitney *U* test was used for the comparison between nonparametric data (**Figure 2**). Chi-square test was used for comparison between categorical variables (**Table 1**). Each plaque volume (PV) was derived from [vessel volume - lumen volumes (mm^3)] at baseline and follow-up. Normalized PV was calculated as [(PV / total length of measured coronary arteries) multiplied by mean total length for all studies divided by number of subjects] (16). Change in PV was estimated as the difference of volumes between baseline and follow-up. Wilcoxon test was used for paired comparisons (**Table 2**). CAC progression was

FIGURE 1 Association of Coronary Plaque Subtypes and CAC Progression



Kruskal-Wallis analysis was performed comparing progression of different plaque subtypes (total, noncalcified, fibrous, fibrous-fatty, low attenuation, calcified) in categories of no coronary artery calcium (CAC) progression or CAC progression of 0 to 99, 100 to 399, and ≥400 Agatston units. Increase in CAC was significantly associated with an increase in all types of plaque. All data are presented as medians. NCP = noncalcified plaque; PV = plaque volume.

log-transformed as log(CAC+1) and annualized. Cases with CAC regression were treated as no CAC progression. Noncalcified plaque (NCP) volume was calculated as total PV minus calcified PV. Median normalized PV changes in each plaque subtype were compared among CAC progression categories of 0, 1 to 99, 100 to 399, and ≥400 Agatston units. Multivariate linear regression was used to determine the association between CAC progression and each plaque subtype progression. All multivariate models were adjusted for age, sex, race, presence of diabetes, hyperlipidemia, statin use, hypertension, antihypertensive medications, and current smoking. Correlation between plaque progression and CAC progression was assessed with Spearman correlation test and presented in Figure 3. Normally distributed data were presented as mean ± SD, and nonparametric variables as median (25% to 75% interquartile range); p values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 20 (IBM Corporation, Armonk, New York).

RESULTS

Baseline patient characteristics are described in Table 1. Of 211 patients, 18.5% (n = 39) had a history of CAD and 18.0% (n = 38) indicated recent chest pain. Duration of follow-up was 3.3 ± 1.7 years. The mean number of segments on coronary CTA included in the analysis was 12.7 ± 2.3. Baseline coronary plaque characteristics are shown in Table 2.

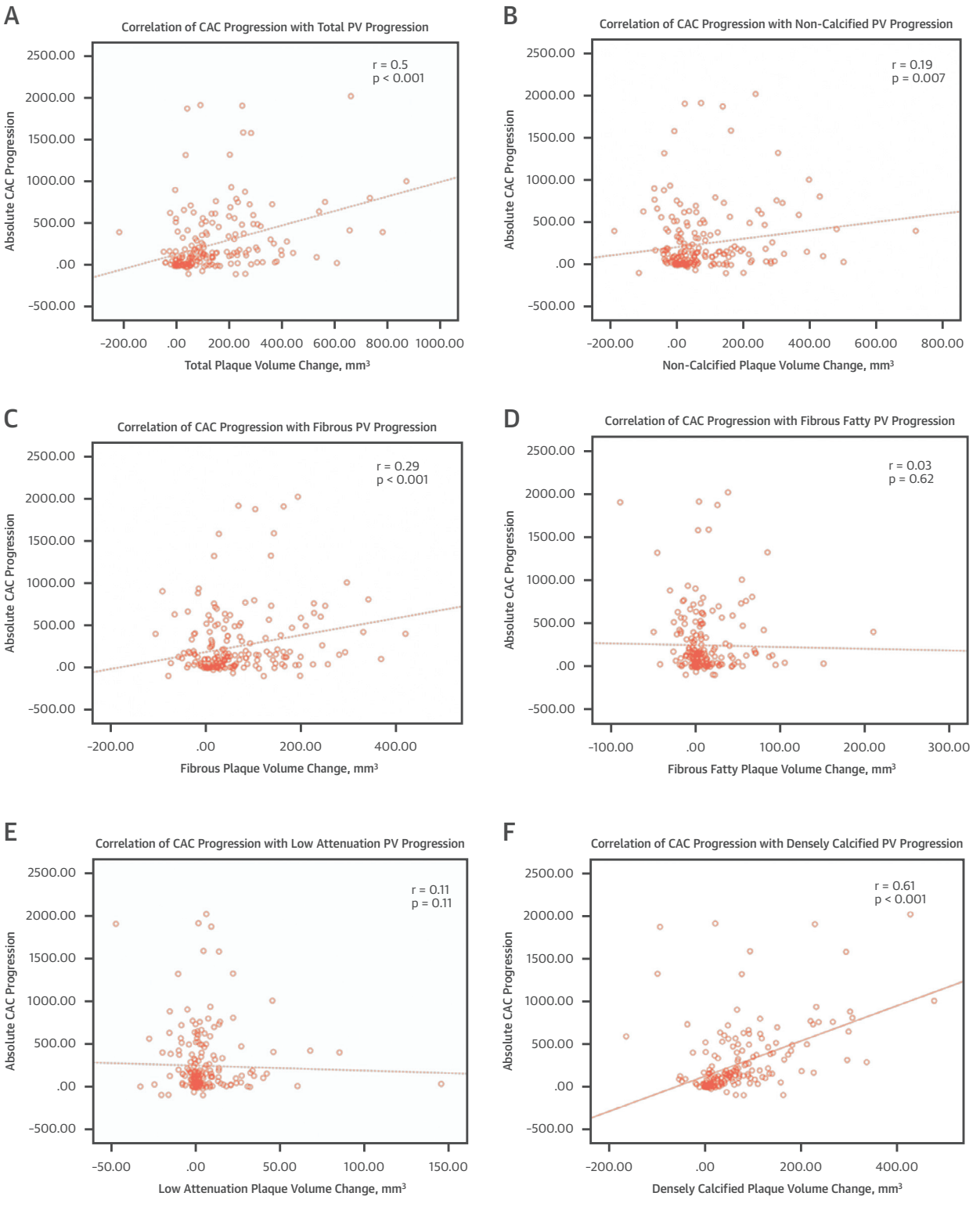
Median annualized CAC progression was 32.73 (interquartile range: 3.70 to 96.60). No CAC progression and CAC progression by 1 to 99, 100 to 399, and ≥400 Agatston units was observed in 17.5%, 31.3%, 28.9%, and 22.3% of patients, respectively. CAC progression was associated with a significant linear increase in all types of coronary plaque (Figure 1).

In multivariate regression analysis, annual CAC progression was significantly associated with total plaque volume, NCP, fibrous PV, and densely calcified PV progression (Table 3). CAC progression was not associated with low-attenuation plaque or fibrous-fatty plaque progression.

For within subject analysis, absolute CAC progression significantly and moderately correlated with total and calcified plaque progression (Spearman's r = 0.5 and 0.61, respectively; p < 0.001), and weakly correlated with noncalcified and fibrous plaque progression (Figure 2). There was no correlation between CAC and low-attenuation or fibrous-fatty plaque subtypes.

Figure 3 illustrates the association between each plaque progression and clinical risk factors. No statistically significant differences in plaque progression

FIGURE 2 Correlation Between Change of CAC and Plaque Progression



Scatterplots and Spearman correlation coefficients between absolute CAC progression and different plaque subtypes, that is, **(A)** total, **(B)** noncalcified, **(C)** fibrous, **(D)** fibrous-fatty, **(E)** low attenuation, and **(F)** calcified, are presented. Abbreviations as in Figure 1.

TABLE 1 Baseline Patient Characteristics

Age, yrs	61.3 ± 12.7
Male	159 (75.4)
Race/ethnicity	
White	110 (52.1)
Asian	24 (11.4)
African American	28 (13.3)
Hispanic	39 (18.5)
Other	9 (4.3)
History of CAD	39 (18.5)
Systolic BP, mm Hg	128.4 ± 18.4
Diastolic BP, mm Hg	77.6 ± 11.5
BMI, kg/m^2	28.7 ± 6.1
Past smoking	77 (36.5)
Current cigarette smoker	33 (15.6)
Diabetes mellitus	78 (37.0)
Family history of CVD	116 (55.0)
Hypertension and/or antihypertensive medications	119 (56.4)
Hyperlipidemia and/or lipid-lowering medication	112 (53.1)
Statin use	72 (34.1)

Values are mean ± SD or n (%).
BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CVD = cardiovascular disease.

TABLE 2 CAC and Coronary Plaque Characteristics at Baseline and Follow-Up

	Baseline	Follow-Up	p Value
Coronary artery calcium score			
Total CAC Agatston score	275.00 (21.00-981.00)	469.00 (51.00-1,327.00)	<0.001
CAC category			<0.001
0	30 (14.4)	23 (10.9)	
1-99	47 (22.3)	35 (16.6)	
100-399	41 (19.4)	39 (18.5)	
≥400	93 (44.1)	114 (54.0)	
Plaque measurements on coronary CTA			
Total segment length, mm	464.6 ± 121.3	466.1 ± 119.4	0.62
Vessel volume, mm^3	3285.9 ± 1218.8	3372.5 ± 1324.8	0.003
Lumen volume, mm^3	2858.2 ± 1107.1	2814.6 ± 1196.2	0.009
Absolute PV			
Total PV, mm^3	261.42 (63.90-655.60)	370.20 (142.50-853.70)	<0.001
Noncalcified PV, mm^3	148.40 (41.00-380.30)	210.67 (68.40-476.70)	<0.001
Fibrous PV, mm^3	126.80 (34.60-322.20)	173.30 (62.60-389.62)	<0.001
Fibrous-fatty PV, mm^3	17.40 (3.20-52.00)	22.60 (5.50-70.10)	<0.001
Low-attenuation PV, mm^3	3.00 (0.20-14.60)	5.00 (0.70-20.70)	<0.001
Dense calcium PV, mm^3	82.00 (7.70-268.30)	133.00 (21.00-373.00)	<0.001
Normalized PV			
Total PV, mm^3	1.20 (0.30-3.10)	1.80 (0.70-4.10)	<0.001
Noncalcified PV, mm^3	0.70 (0.19-1.80)	1.00 (0.30-2.30)	<0.001
Fibrous PV, mm^3	0.60 (0.20-1.50)	0.82 (0.30-1.85)	<0.001
Fibrous-fatty PV, mm^3	0.08 (0.01-0.30)	0.11 (0.03-0.33)	<0.001
Low-attenuation PV, mm^3	0.010 (0.000-0.070)	0.010 (0.001-0.070)	<0.001
Dense calcium PV, mm^3	0.40 (0.04-1.30)	0.63 (0.10-1.77)	<0.001

Values are median (interquartile range), n (%), or mean ± SD. Wilcoxon test was used for paired comparisons.
CAC = coronary artery calcium; CTA = computed tomography angiography; PV = plaque volume.

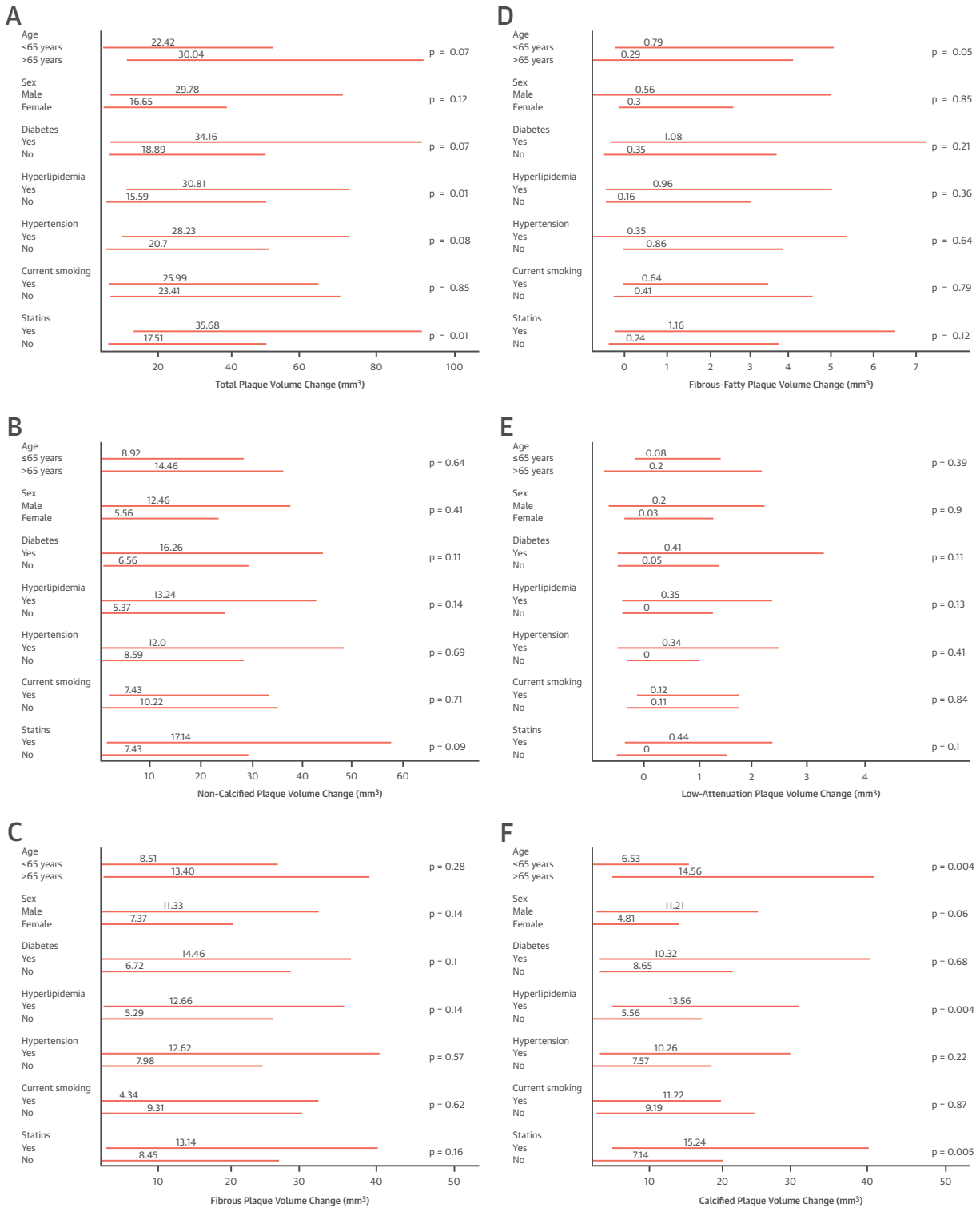
were found between the sexes, despite an observed trend toward a higher total, fibrous, and calcified PV progression in men. Compared with the older age subgroup, the ≤65 years of age subgroup included more men (82.4% vs. 66.3%; p = 0.007) and current smokers (21.1% vs. 10.1%; p = 0.036). More subjects in the older age subgroup had diabetes (51.1% vs. 27.1%; p < 0.001), hypertension (71.9% vs. 46.6%; p < 0.001), and hyperlipidemia (64.4% vs. 45.8%; p = 0.007). Annualized densely calcified plaque progression was higher among subjects older than 65 years of age (p = 0.004), compared with patients 65 years of age or younger. Annualized fibrous-fatty plaque progression was higher in the younger subgroup (p = 0.05). No differences in other plaque types were found between age subgroups. Hyperlipidemia was statistically significantly associated with total and calcified PV progression. Statin use was significantly inversely associated with total and calcified PV progression (**Figure 3**). An example of plaque progression in mid LAD is provided in **Figure 4**.

DISCUSSION

In the current study, by using semiautomated plaque quantification software we demonstrated that CAC progression was associated not only with calcified plaque progression, as expected, but also with NCP, namely fibrous plaque, progression. To our knowledge, our study is the first to evaluate the association between progression of CAC and different coronary plaque subtypes, although several studies addressed the association of CAC progression with cardiovascular outcomes (18-20).

Our current findings regarding the association of progression between CAC scores and noncalcified plaque volumes provide support to the concept that CAC progression is associated with more CVD events (18-20). Calcified plaque has been considered to be a result of plaque stabilization or healing, whereas calcified plaque burden reflects overall coronary atherosclerosis burden including noncalcified plaque. An autopsy study in 67 sudden death victims demonstrated that microcalcification and punctate calcification was more common in early and late fibroatheromas compared with the less advanced types of plaque, such as pathological intima thickening (5). In this study, calcification was observed in all cases of early and late fibroatheromas, and the latter demonstrated more confluent areas of calcification. Importantly, in the transition of early plaque to late plaque the presence of macrophages and buildup of apoptotic bodies increased, while simultaneously there was increasing presence of calcification (5). As suggested by recent research, the natural

FIGURE 3 Association of Annualized PV Progression With Cardiovascular Risk Factors



Association of progression of different types of PV, that is, **(A)** total, **(B)** noncalcified, **(C)** fibrous, **(D)** fibrous-fatty, **(E)** low attenuation, and **(F)** calcified, with age, sex, diabetes status, hyperlipidemia, hypertension, current smoking, and statin use. Mann-Whitney *U* test was performed for comparison between the groups. PV was divided by years of follow-up. Data are presented as median ± 25 to 75% interquartile range. Abbreviations as in Figure 1.

process of atherosclerosis is highly dynamic rather than linear and depends on the local pathobiological stimuli for plaque progression, such as local remodeling response (7,21,22), and progression in calcified and noncalcified plaques may coexist during the process. In this regard, individuals with CAC progression may also experience progression in total plaque burden including both calcified and noncalcified plaques that is observed in the current study, resulting in a higher incidence of CVD events. Overall, this may be more suitable to evaluate CVD risk at a per-patient basis.

In the current study, despite a significant association between CAC progression and all types of plaque in univariate analysis, this association was no longer statistically significant for low-attenuation and fibrous-fatty plaque subtypes in multivariate analysis and did not correlate with absolute CAC progression. These findings were of interest as multiple observational studies demonstrated that lipid-rich or vulnerable plaques as well as CAC progression are associated with increased risk of cardiovascular events. However, the relationship of risk in acute coronary syndrome between per-lesion and per-patient bases is complex and still an ongoing debate (23). Progression in CAC and lipid-rich plaques may not always parallel, as there are many potential risk markers of CAD such as plaque burden, vulnerable plaque features, plaque activity, stenosis degree, and ischemia, all of which are associated with increased risk for CVD events but not always coexist (24). In this regard, despite showing a similar positive trend, overall CAC progression may not always correlate well with progression in lipid-rich plaque associated with acute coronary syndrome that is described in the current study. Also, factors such as noncalcified plaque burden or traditional clinical risk factors other than CAC progression are associated with lipid-rich plaque progression. In a study of 142 matched subjects with and without diabetes, overall noncalcified plaque burden, but not baseline CAC score, was associated with fibrous-fatty and low-attenuation plaque progression (17). A serial IVUS and near-infrared spectroscopy study in 66 patients revealed that lipid-rich plaque burden was significantly associated with plaque burden, diabetes, and prior myocardial infarction, with plaque burden as the best predictor of the extent of lipid-rich plaques (25). These plaque subtypes are more likely to convert from more pathogenetically unstable noncalcified plaque, rather than more pathogenetically stable plaque, such as fibrous or calcified plaque (26). Therefore, noncalcified plaque burden may be more closely associated with fibrous-fatty and low-attenuation plaque progression.

TABLE 3 Association of Plaque and Annualized CAC Progression in Linear Multivariate Regression Analysis

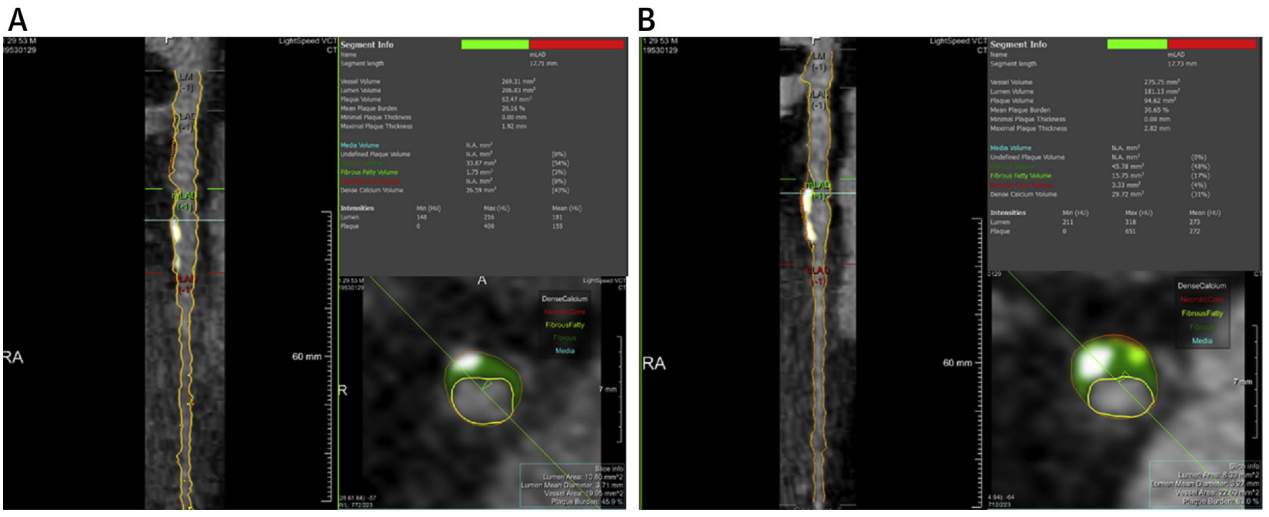
Plaque Type	β	SE	95% CI	p Value
Annualized plaque progression				
Total PV, mm^3	0.002	<0.001	0.001 to 0.003	<0.001
NCP, mm^3	0.002	<0.001	0.001 to 0.003	0.001
Fibrous PV, mm^3	0.003	0.001	0.001 to 0.004	<0.001
Fibrous-fatty PV, mm^3	0.003	0.002	-0.002 to 0.007	0.27
Low-attenuation PV, mm^3	0.007	0.004	-0.001 to 0.014	0.096
Calcified PV, mm^3	0.36	0.09	0.18 to 0.53	<0.001
Annualized normalized plaque progression				
Total PV, mm^3	0.38	0.09	0.21 to 0.55	<0.001
NCP, mm^3	0.35	0.11	0.14 to 0.55	0.001
Fibrous PV, mm^3	0.56	0.15	0.27 to 0.85	<0.001
Fibrous-fatty PV, mm^3	0.53	0.48	-0.43 to 1.48	0.28
Low-attenuation PV, mm^3	1.37	0.84	-0.27 to 3.00	0.10
Calcified PV, mm^3	0.63	0.19	0.26 to 1.01	0.001

Log-transformed and annualized CAC score. Adjusted for age, race, sex, diabetes, hyperlipidemia, statin use, hypertension, and current smoking.

CI = confidence interval; NCP = noncalcified plaque; other abbreviations as in Table 2.

In a subanalysis for assessing the relationship between clinical risk factors and plaque progression, calcified plaque progression was greater in patients >65 years of age, compared with patients ≤65 years of age who had higher fibrous-fatty plaque progression. These results are in line with the natural history of atherosclerosis, starting with lipid pool accumulation in the vessel wall, infiltration of macrophages, subsequent necrotic core formation in the fibroatheroma, and calcification at a later stage of plaque development (5,27). Our results suggest that factors determining the composition of atherosclerotic plaque may differ with age. By contrast, coronary plaque progression did not significantly differ between the sexes. The finding is consistent with a prior IVUS study showing no significant difference regarding the rates of plaque progression or regression between the sexes, whereas women had more risk factors but less underlying coronary atherosclerosis (28). We observed a significantly increased total and calcified plaque progression in statin users. This finding might have 2 explanations. First, in clinical practice statins are prescribed in individuals with intermediate or high baseline cardiovascular risk, hence relatively more coronary plaque progression could be anticipated. Second, the results might have been influenced by the effect of statins on the composition of coronary plaque, described by other studies (29–31). Our data support both the concept that statins inhibit noncalcified plaque progression and the recommendation

FIGURE 4 An Example of Plaque Progression in the Mid-LAD



(A) Mid-left anterior descending artery (LAD) model and plaque burden at baseline; **(B)** mid-LAD and plaque burden at follow-up.

of intensive statin therapy for primary and secondary prevention by the current guidelines (32,33).

Of importance, we observed that patients with a CAC of 0 or no CAC progression experienced only minimal progression in total and noncalcified plaques during a mean follow-up of 3.3 years. This finding partially supports the concept that a CAC of 0 or no progression is associated with very low risk of CVD events (10,11,18,19). Min et al. have demonstrated that patients with a CAC of 0 experienced no CAC progression 4 to 5 years after the scan, suggesting that a warranty period of a CAC of 0 is at least 5 years (34), even in high-risk patients such as those with diabetes (35). Indeed, in our previously described study, we similarly observed that patients with a CAC of 0 experienced much less plaque progression over time compared with those with higher CAC (17). Despite limited ability of noncontrast CT to visualize noncalcified plaque, patients with a baseline CAC of 0 or no progression over time are at low risk of noncalcified plaque progression, indicating low possibility of future CVD events, even in diabetes patients, and may not require intensive treatment (36–38). Our findings suggest that patients in whom the presence and progression of coronary atherosclerosis is not evident are considered to have low CVD risk, at least for a short period, regardless of any risk factors present.

STUDY LIMITATIONS. The strength of our study was a real-life clinical practice setting. However, there were some limitations. Our study population was heterogeneous, including both symptomatic and asymptomatic individuals, as well as patients with a history of CAD.

For the present study, only patients who had 2 or more coronary CTA scans were enrolled. However, under current guidelines, most patients diagnosed as having severe CAD according to their baseline coronary CTA would likely have been referred to invasive coronary angiography and might subsequently have undergone revascularization. Conversely, in any case of patients with normal coronary anatomy at baseline coronary CTA, follow-up coronary CTA is typically not recommended. As a result, patients with either severe disease or normal coronaries at baseline would have been largely omitted from the current registry, introducing a potential selection bias in the enrollment. However, as addressed previously, we found the only minimum progression in patients with normal CTA, which strongly supports the consensus for coronary CTA-based decision making by the current guideline for reassuring normal coronary CTA (39).

CAC progression and plaque volume progression are also associated with moderate to advanced chronic kidney disease (4). We did not have data in patients with renal failure, as only patients with normal or close to normal renal function underwent coronary CTA.

Although our study has clearly described the clinical impact on the association between CAC

and other plaque characteristics progression, we assessed plaque progression on a per-patient basis, not a per-lesion basis that has been described in multiple IVUS studies. In this regard, we did not have the information of progression between the site of CAC and plaque on coronary CTA. The aforementioned study (26) has demonstrated the association among plaque stability, histological composition, and its area, but they did not provide the association with the volume changes of plaque characteristics, which may give more important insights to understand the pathophysiological role of plaque compositions and the relation with the stability or future risk in acute coronary syndrome overtime per global plaque basis. That should be studied in the near future.

CONCLUSIONS

CAC progression was significantly associated with both calcified and noncalcified plaque progression. Serial CAC measurements may be helpful in determining the need for intensive preventive treatment.

ADDRESS FOR CORRESPONDENCE: Dr. Rine Nakanishi, Los Angeles Biomedical Research Institute at Harbor UCLA, 1124 West Carson Street, Torrance, California 90502. E-mail: rnakanishi@labiomed.org.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: CAC progression during 3.3 years of follow-up is associated with an increase in both calcified and noncalcified plaque volume, except fibrous-fatty and low attenuation plaque.

TRANSLATIONAL OUTLOOK: There is an ongoing discussion whether serial CAC testing adds to patient management. We demonstrated that CAC progression is associated with both noncalcified and calcified plaque volume progression. These results suggest that serial CAC measurements may be helpful in determining patients at risk in need of preventive treatment intensification. More research is needed to understand the natural process of atherosclerosis and factors determining progression of vulnerable plaque.

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