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ORIGINAL RESEARCH

The Relationship Between Coronary Calcification and the Natural History of Coronary Artery Disease

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ABSTRACT

OBJECTIVES The aim of the current study was to explore the impact of plaque calcification in terms of absolute calcified plaque volume (CPV) and in the context of its percentage of the total plaque volume at a lesion and patient level on the progression of coronary artery disease.

BACKGROUND Coronary artery calcification is an established marker of risk of future cardiovascular events. Despite this, plaque calcification is also considered a marker of plaque stability, and it increases in response to medical therapy.

METHODS This analysis included 925 patients with 2,568 lesions from the PARADIGM (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging) registry, in which patients underwent clinically indicated serial coronary computed tomography angiography. Plaque calcification was examined by using CPV and percent CPV (PCPV), calculated as (CPV/plaque volume) $\times$ 100 at a per-plaque and per-patient level (summation of all individual plaques).

RESULTS CPV was strongly correlated with plaque volume (r = 0.780; p < 0.001) at baseline and with plaque progression (r = 0.297; p < 0.001); however, this association was reversed after accounting for plaque volume at baseline (r = –0.146; p < 0.001). In contrast, PCPV was an independent predictor of a reduction in plaque volume (r = –0.11; p < 0.001) in univariable and multivariable linear regression analyses. Patient-level analysis showed that high CPV was associated with incident major adverse cardiac events (hazard ratio: 3.01: 95% confidence interval: 1.58 to 5.72), whereas high PCPV was inversely associated with major adverse cardiac events (hazard ratio: 0.529; 95% confidence interval: 0.229 to 0.968) in multivariable analysis.

CONCLUSIONS Calcified plaque is a marker for risk of adverse events and disease progression due to its strong association with the total plaque burden. When considered as a percentage of the total plaque volume, increasing PCPV is a marker of plaque stability and reduced risk at both a lesion and patient level. (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging [PARADIGM]; NCT02803411)
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ABBREVIATIONS AND ACRONYMS

CAC = coronary artery calcification

CTA = computed tomography angiography

CPV = calcified plaque volume

HR = hazard ratio

HRP = high-risk plaque

HU = Hounsfield units

MACE = major adverse cardiac event(s)

PCPV = percent calcified plaque volume

PV = plaque volume

Coronary artery calcification (CAC) is indicative of the presence of coronary atherosclerosis and is a robust marker of coronary plaque burden (1,2). Multiple studies have consistently shown that CAC is a reliable, reproducible, and independent predictor of future cardiovascular events (3,4), providing incremental information beyond traditional cardiovascular risk factors (5,6). Current guidelines endorse CAC scoring to improve cardiovascular risk assessment in asymptomatic individuals at intermediate risk to guide use of preventive therapies (7,8).

Previous studies have shown that an interval increase in coronary artery calcium is a marker of increased cardiovascular risk (9,10); however, statins induce an increase in plaque calcification despite a well-documented role in the reduction of cardiovascular events (11-13). Thus, there is an apparent paradox in our current understanding of coronary calcium in which it connotes both risk and stability, with progression portending both an increased risk of events and a response to therapy.

The aim of the current study was to examine the relationship between coronary plaque calcification, plaque volume (PV) and progression, and downstream cardiovascular risk. The hypotheses tested were 2-fold. The first hypothesis was that at a patient level, calcified plaque would be a marker a marker for risk and progression due to its association with total plaque burden, both calcified and noncalcified. The second hypothesis was that at a plaque lesion level, heavily calcified plaque, defined according to percentage of PV composed of calcium, would be a marker of stability and thus a lack of progression.
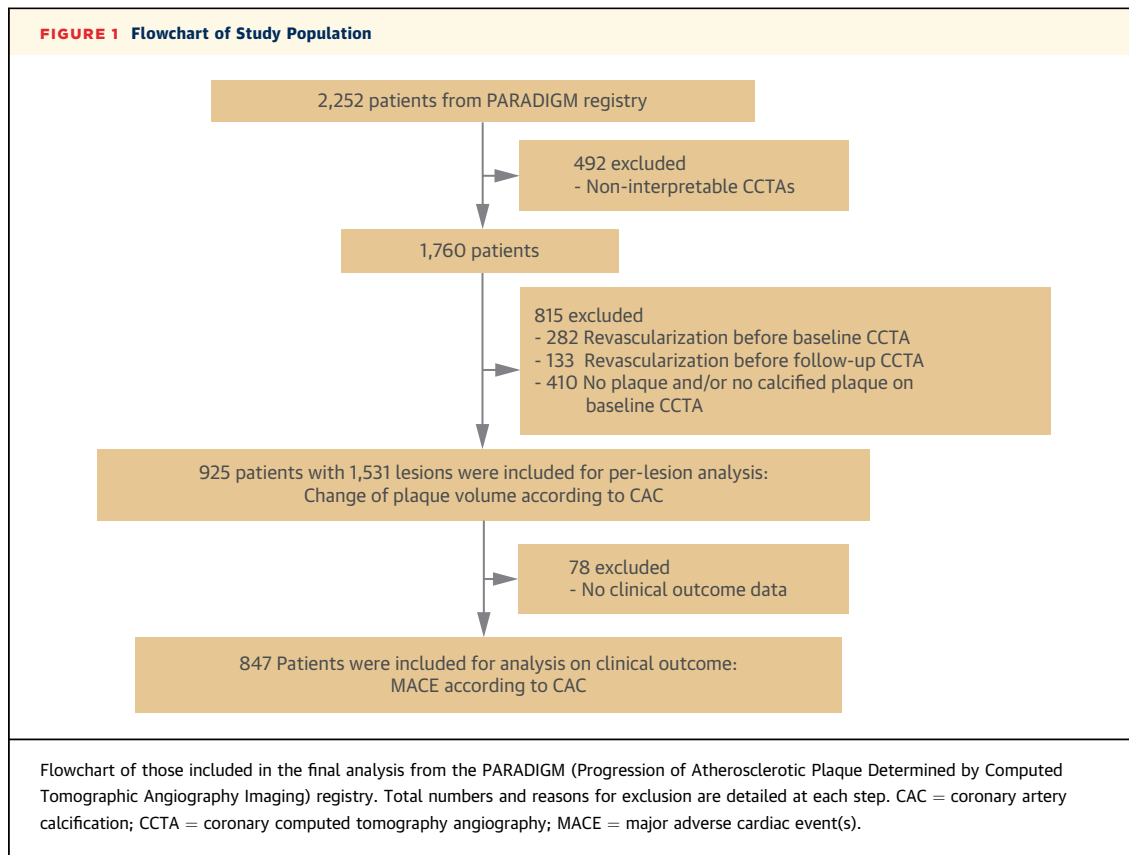
METHODS

STUDY DESIGN AND SELECTION OF PARTICIPANTS. The PARADIGM (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging) study is an international, multicenter, observational registry prospectively collecting clinical, procedural, and follow-up data. Enrolled patients underwent clinically indicated serial coronary computed tomography angiography (CTA) with ≥64 detector rows for evaluation of coronary artery disease at a ≥2-year interscan interval across 13 sites in 7 countries. The design of the study has been previously described in detail (14). The PARADIGM study was approved by each of the institutional review boards at the participating sites, and all participants provided written informed consent.

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FIGURE 1 Flowchart of Study Population

Flowchart of those included in the final analysis from the PARADIGM (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging) registry. Total numbers and reasons for exclusion are detailed at each step. CAC = coronary artery calcification; CCTA = coronary computed tomography angiography; MACE = major adverse cardiac event(s).

Of the 2,252 patients in the PARADIGM registry, 492 were excluded due to inadequate image quality for plaque analysis. To examine the role of calcification on the natural time course of plaque, patients who underwent revascularization before baseline (n = 282) or their follow-up (n = 133) coronary CTA were excluded from the analysis, as were those without calcification on baseline coronary CTA (n = 410). For the outcome analysis, an additional 51 patients were excluded due to missing data on clinical outcomes, leaving 874 patients in this analysis (Figure 1).

DATA ACQUISITION AND IMAGE ANALYSIS. All coronary CTA investigations were performed on ≥64-detector CT scanners. Patient preparation, acquisition, and interpretation of CTA data were performed in accordance with Society of Cardiovascular Computed Tomography guidelines (15). All datasets including clinical information were transferred to a single core laboratory for blinded image analysis. Plaque analysis was performed by using QAngioCT Research Edition version 2.1.9.1 (Medis Medical Imaging Systems, Leiden, the Netherlands) (16).

Quantitative analysis was performed for each segment with a diameter ≥2 mm (15). These measurements included vessel length, volume, mean plaque burden, and PV at baseline and follow-up coronary CTA. Plaque composition was analyzed for all atherosclerotic plaques by using predefined Hounsfield unit (HU) thresholds: necrotic core (−30 to 30 HU), fibro-fatty (30 to 130 HU), fibrous (131 to 350 HU), and calcified (≥350 HU) plaque.

Coronary calcification was quantified in 2 ways: 1) calcified PV (CPV), which is the total volume of calcium in atherosclerotic plaque; and 2) percent CPV (PCPV), which is the degree to which the plaque is calcified and was calculated as: PCPV = (CPV/PV) × 100.

Longitudinal analysis of changes in PV was calculated as annualized rates to account for the variability in time between baseline and follow-up coronary CTA. For longitudinal volumetric comparisons of plaque according to degree of plaque calcification, participants were split into quartiles of PCPV.

In each coronary segment with plaque, we performed further qualitative evaluation for the presence of stenosis and high-risk plaque (HRP) (17-19).

TABLE 1 Baseline Characteristics of the Study Population (N = 925)

Age, yrs	61.9 ± 8.95
Male	553 (59.8)
Follow-up interval of coronary CTA, yrs	2.9 (2.1-3.8)
BMI, kg/m^2	25.0 (23.3-27.1)
Current smoker	176 (19.0)
Diabetes mellitus	209 (22.6)
Hypertension	518 (56.0)
Dyslipidemia	384 (41.5)
Familial history of CAD	268 (29.0)
HbA$_{1c}$, %	6.0 (5.7-6.9)
Total cholesterol, mg/dl	189.9 ± 38.7
LDL cholesterol, mg/dl	114.5 ± 34.1
Serum creatinine, mg/dl	1.0 (0.8-1.1)
Medications	
Aspirin	373 (40.3)
Beta-blockers	243 (26.3)
Calcium-channel blocker	213 (23.0)
ACE inhibitor/ARB	278 (30.1)
Statins	404 (43.7)

Values are mean ± SD, median (interquartile range), or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; BMI = body mass index; CAD = coronary artery disease; CTA = computed tomography angiography; HbA$_{1c}$ = glycosylated hemoglobin; LDL = low-density lipoprotein.

STUDY ENDPOINTS. The primary endpoint of the current study was to compare the annualized per-lesion change in PV according to PCPV quartile. Secondary endpoints included the association between annualized change in PV and baseline constituent plaque elements, as well as the effect of stenosis severity on the change in PV according to quartile of PCPV. The secondary clinical endpoint was the time

to major adverse cardiac events (MACE), the definition of which included myocardial infarction, cerebrovascular accident, coronary revascularization, and cardiac death.

STATISTICAL ANALYSIS. Continuous data are presented as mean ± SD. Differences in continuous variables between the quartile groups of PCPV were determined by 1-way analysis of variance for normal distribution and the Kruskal-Wallis test for non-normal distribution. Post hoc pairwise comparison with the Scheffé test was performed for variables for which there was a significant difference between groups. Categorical variables were expressed as frequencies and percentages, which were compared by using the Pearson chi-square test between the 4 PCPV quartiles. The correlation of CPV with PV was analyzed by using Spearman's correlation test, and partial correlation analysis was used to analyze the association of CPV and annualized change in PV, accounting for baseline PV. Univariable and multivariable linear regression models were used to identify variables associated with the annualized change in PV at a per-lesion level without cluster adjustment. Plaque volumes were log transformed for linear regression due to non-normal distribution of the residuals. The association of calcified plaque with clinical outcomes was investigated with the Cox proportional hazards model using univariable and stepwise multivariable analyses. The stepwise multivariable analyses included all clinical risk factors, variables of CTA, and statin use. For this analysis, we used values of CPV and PCPV in the patient-level data, which

TABLE 2 Coronary Plaque Characteristics on Baseline Coronary CTA According to Quartile of PCPV

	PCPV, Quartile					
	1 (n = 642)	2 (n = 643)	3 (n = 641)	4 (n = 643)	p Value*	Total Lesions (N = 2,568)
PCPV range, %	0.01-17.1	17.2-40.0	40.1-63.5	63.6-99.6	<0.001	41.2 ± 27.4
Lesion length, mm	23.2 ± 13.8	23.6 ± 15.8	22.8 ± 15.6	21.2 ± 14.9	0.027	22.7 ± 14.8
Total PV, mm^3	54.2 ± 77.9	52.4 ± 83.8	47.0 ± 75.0	40.5 ± 70.9	0.007	48.5 ± 77.2
Fibrous PV, mm^3	30.6 ± 41.0	29.0 ± 45.3	19.9 ± 31.0	8.9 ± 15.8	<0.001	22.1 ± 36.2
Fibro-fatty PV, mm^3	17.8 ± 30.1	8.0 ± 16.0	2.7 ± 6.9	0.6 ± 2.4	<0.001	7.3 ± 18.7
Calcified PV, mm^3	3.7 ± 7.5	14.8 ± 25.1	24.3 ± 38.7	31.1 ± 54.8	<0.001	18.5 ± 37.4
Necrotic core volume, mm^3	2.1 ± 6.0	0.6 ± 2.0	0.2 ± 0.9	0.04 ± 0.3	<0.001	0.75 ± 3.3
Plaque burden, mm^3	39.5 ± 17.4	39.3 ± 16.6	40.7 ± 17.6	42.9 ± 16.6	<0.001	40.6 ± 17.1
Area stenosis, %	29.8 ± 18.8	31.7 ± 19.2	32.5 ± 19.4	34.6 ± 19.9	<0.001	32.2 ± 19.4
Low-attenuation plaque	135 (21.0)	36 (8.4)	10 (3.1)	2 (0.3)	<0.001	211 (8.2)
Spotty calcium	139 (21.7)	111 (17.3)	48 (7.5)	18 (2.8)	<0.001	316 (12.3)
Positive remodeling	487 (75.9)	435 (67.7)	449 (70.0)	449 (69.9)	0.01	1,820 (70.9)
Napkin-ring sign	3 (0.5)	4 (0.6)	0 (0.0)	0 (0.0)	0.06	7 (0.3)
High-risk plaque	250 (9.7)	82 (12.0)	33 (1.3)	4 (0.2)	<0.001	369 (14.4)

Values are range, or mean ± SD, or n (%). *The p value is for the overall comparison among the groups by analysis of variance or Pearson chi-square test.

CTA = coronary computed tomography angiography; PCPV = percent calcified plaque volume; PV = plaque volume.
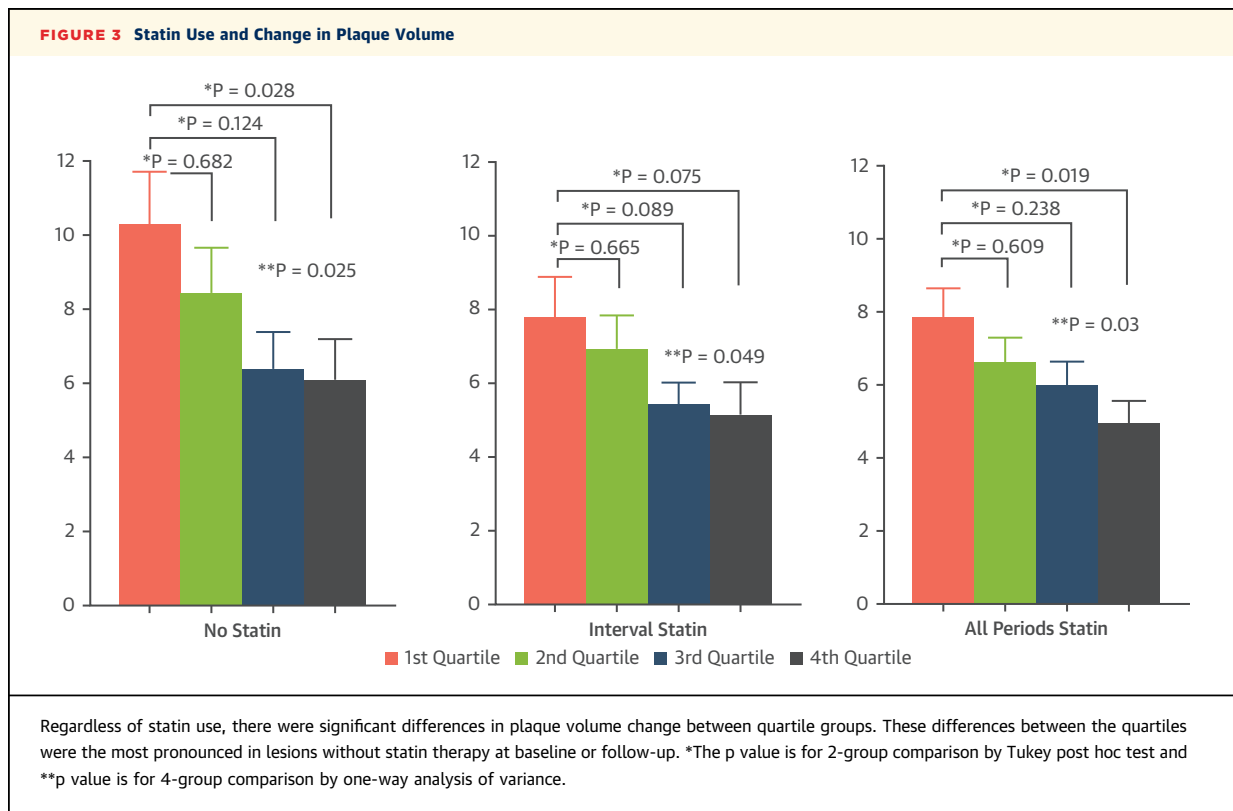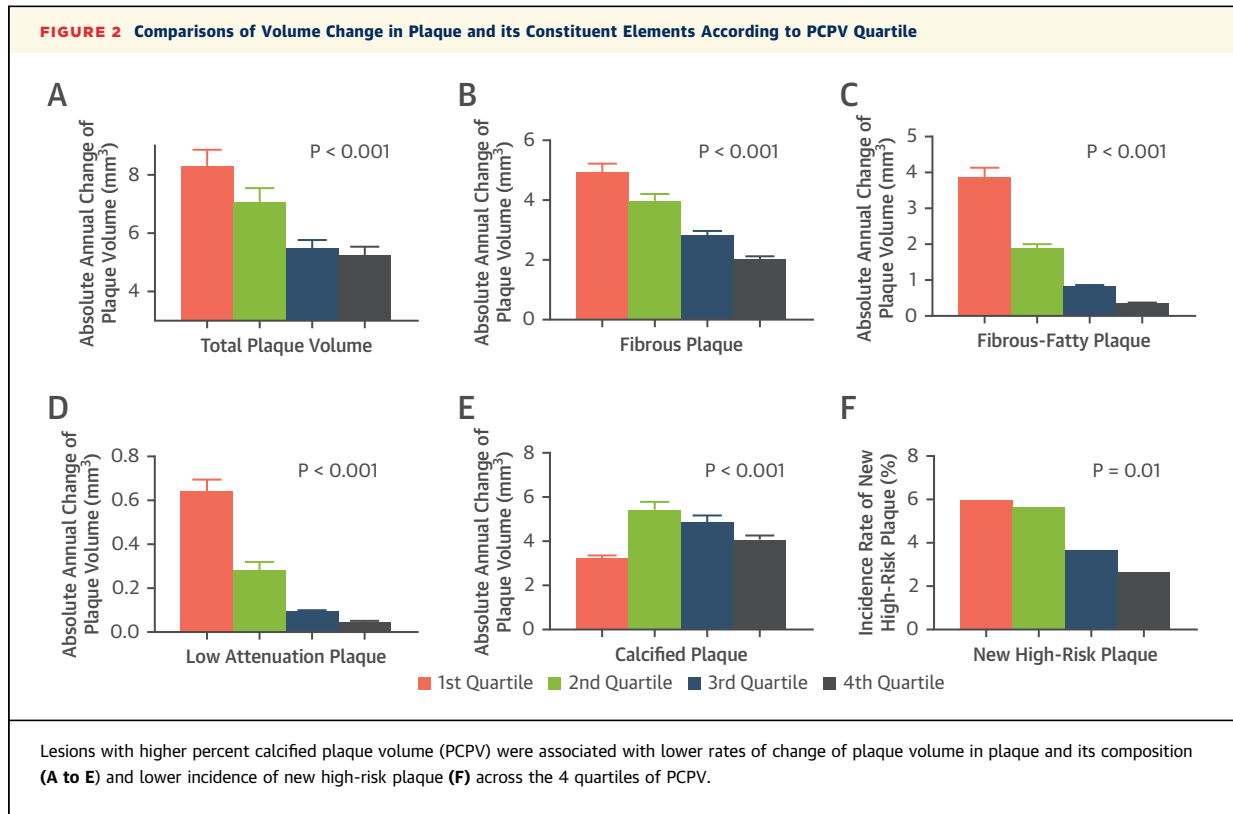
FIGURE 2 Comparisons of Volume Change in Plaque and its Constituent Elements According to PCPV Quartile

Lesions with higher percent calcified plaque volume (PCPV) were associated with lower rates of change of plaque volume in plaque and its composition **(A to E)** and lower incidence of new high-risk plaque **(F)** across the 4 quartiles of PCPV.

FIGURE 3 Statin Use and Change in Plaque Volume

Regardless of statin use, there were significant differences in plaque volume change between quartile groups. These differences between the quartiles were the most pronounced in lesions without statin therapy at baseline or follow-up. *The p value is for 2-group comparison by Tukey post hoc test and **p value is for 4-group comparison by one-way analysis of variance.

TABLE 3   Variables Associated With the Change of PV in Linear Regression Model

	Univariable		Multivariable	
	Correlation Coefficient	p Value	Unstandardized Coefficient (95% CI)	p Value
PCPV*	−0.08	<0.001	−0.82 (−1.10 to −0.55)	<0.001
Calcified PV*	0.37	<0.001	0.81 (0.55 to 1.07)	<0.001
Total PV*	0.42	<0.001	−†	
Necrotic core volume*	0.23	<0.001	0.02 (−0.05 to 0.08)	0.64
Mean plaque burden*	0.42	<0.001	0.53 (0.22 to 0.85)	0.001
Lesion length	0.52	<0.001	0.024 (−0.13 to 0.61)	0.20
Area stenosis	0.14	<0.001	0.01 (−0.10 to 0.13)	0.82
Any HRP	0.19	<0.001	0.04 (−0.17 to 0.24)	0.73
Spotty calcification	0.18	<0.001		
Low attenuation plaque	0.19	<0.001		
Positive remodeling	0.13	<0.001		
Napkin-ring sign	0.05	0.008		

*Log-transformed for analysis. †Total PV was excluded in the multivariable model due to strong correlation with calcified plaque volume.

CI = confidence interval; HRP = high-risk plaque; other abbreviations as in **Table 2**.

were classified into 2 groups by the median value of each of these.

The Cox model was used to estimate the risk of a given variable as expressed by a hazard ratio (HR) with corresponding 95% confidence interval (CI). Survival curves were generated by using the Kaplan-Meier method, and the difference between curves was assessed by using the log-rank test. A p value ≤ 0.05 was considered statistically significant. All statistical analysis was performed by using SPSS version 22 (IBM SPSS Statistics, IBM Corporation, Armonk, New York) and SAS 9.2 (SAS Institute, Inc., Cary, North Carolina) software.

RESULTS

STUDY POPULATION. Of the 2,252 patients, 925 (mean age 61.9 ± 8.95 years; 59.8% male) with 2,568 lesions were included in the final analysis. Clinical and laboratory characteristics of this cohort are shown in **Table 1**.

CHANGE OF ATHEROSCLEROTIC PV AND CORONARY ARTERY CALCIFICATION. A lesion-level analysis was performed for a total of 2,586 lesions. For volumetric comparisons of plaque, participants were classified into 4 groups according to quartile of PCPV value in baseline coronary CTA (**Table 2**). Lesions with the highest PCPV (fourth quartile) were shorter lesions, with a lower volume of plaque, greater severity of stenosis, higher plaque burden, and less frequent HRP compared with lower PCPV (all; p < 0.05). Annualized change in PV was greatest in lesions with the lowest PCPV (first quartile) and decreased monotonically across the 4 quartiles of PCPV, which

was statistically significant in an intergroup comparison (all; p < 0.001) (**Figure 2A**). The same trend was observed in the volume of each of the plaque components, which were statistically significant in an intergroup comparison (all; p < 0.001) (**Figures 2B to 2D**). The rate of newly detected HRP on follow-up CT imaging, similarly, was highest in the lowest PCPV quartile and decreased across the 4 quartiles with increasing PCPV (**Figure 2F**). Change in CPV was smallest in the first quartile, but change was greatest in the second quartile and decreased across the third and fourth quartiles (**Figure 2E**).

These observations were robust when analyzed according to the severity of stenosis, as well as baseline or interval statin prescription. Regardless of stenosis severity, there were significant differences in annualized change in PV between PCPV quartile groups (**Figure 3**, Supplemental Figure 1). Statin therapy either at baseline or interval prescription between the coronary CTAs was associated with a greater increase in the PCPV than those never treated with a statin (never statin 3.5 ± 7.7% per year; baseline/interval statin 4.3 ± 6.9% per year; p = 0.017).

CORRELATION BETWEEN CORONARY CALCIFICATION, PV, AND ITS CHANGE. The CPV was strongly correlated with PV at the baseline CT scan (r = 0.780; p < 0.001). On univariable linear regression analysis, factors significantly and positively associated with change in PV were baseline CPV, lesion length, necrotic core volume, mean plaque burden, area stenosis, and HRP (all; p < 0.001). In contradistinction, PCPV was significantly and inversely associated with change in PV (r = −0.08; p < 0.001) (3). A partial correlation model was also used to account for baseline PV due to a strong association between CPV and PV, which showed that CPV was significantly and inversely correlated with change in PV after adjustment for PV at baseline coronary CTA (r = −0.146; p < 0.001). After adjustment, PCPV was independently and inversely associated with change in total PV on the multivariable linear regression analysis (B: −0.82; 95% CI: −1.10 to −0.55; p < 0.001), whereas CPV remained positively associated with change in PV (B: 0.81; 95% CI: 0.55 to 1.07; p < 0.001) (**Table 3**).

CORONARY CALCIFICATION AND CLINICAL OUTCOMES. A total of 874 patients (mean age 62.1 ± 9.1 years; 58.2% male) were included in the analyses of clinical outcomes (Supplemental Table 1). Over a median follow-up of 4.3 years (interquartile range 2.6 to 6 years), 110 patients (12.6%) experienced MACE, which was mostly driven by revascularization (n = 106 [12.1%]). Patients with high PCPV had a significantly

CENTRAL ILLUSTRATION Plaque Progression and Major Adverse Cardiac Events According to Percent Calcified Plaque Volume and Calcified Plaque Volume
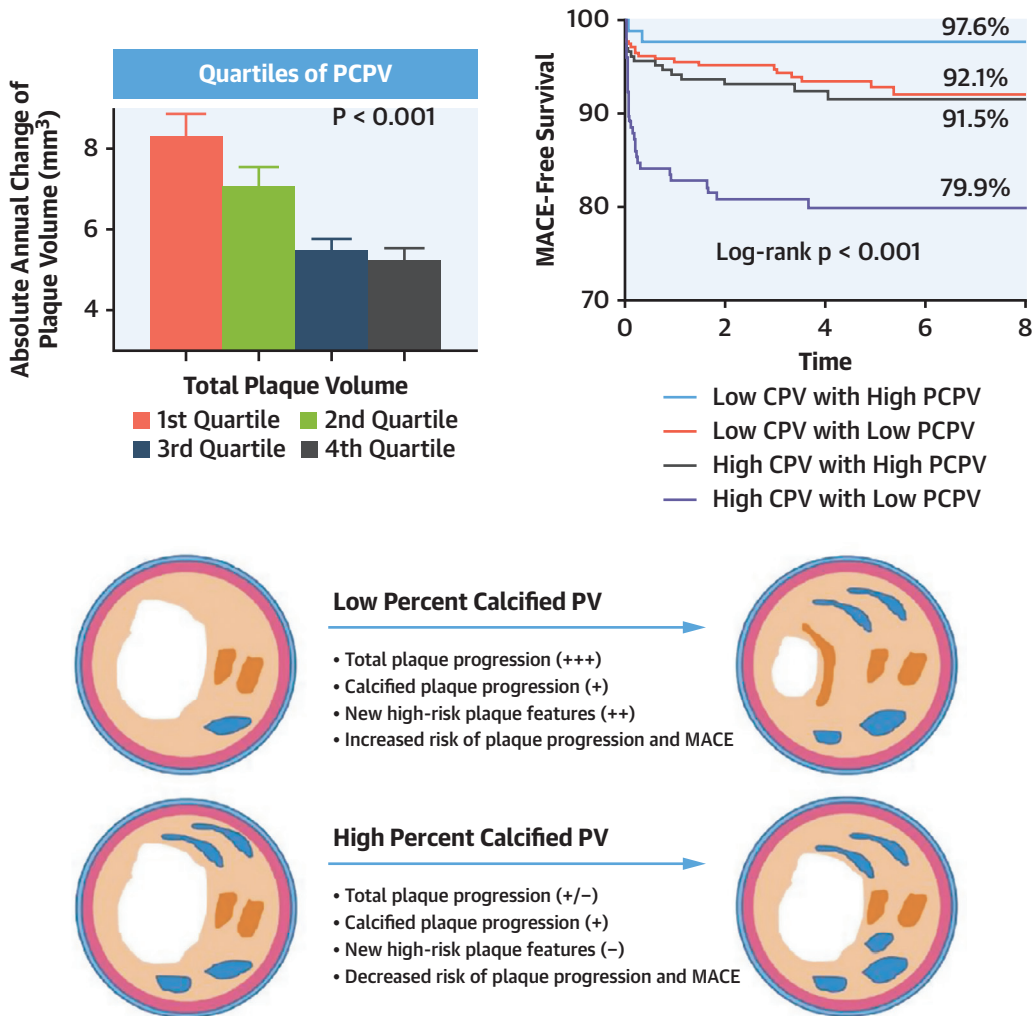
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Those with higher percent calcified plaque volume (PCPV) had greater rates of plaque progression **(top left)** and higher rates of major adverse cardiac event(s) (MACE) **(top right)**. The graphic summarizes the key characteristics of plaques with low and high PCPV.

lower incidence of MACE (14.6% vs. 9.4%; p = 0.022) and revascularization (14.3% vs 8.8%; p = 0.016) than those with low PCPV (Supplemental Table 2). When categorizing patients using PCPV and CPV, Kaplan-Meier analysis showed that the survival rate free from MACE was highest in patients with a high PCPV and low CPV (log rank test; p < 0.001) (Central Illustration).

On multivariable Cox proportional analysis, high PCPV was significantly and inversely associated with MACE (HR: 0.53; 95% CI: 0.29 to 0.97; p = 0.04), whereas high CPV was associated with increased risk

of MACE (HR: 3.01; 95% CI: 1.58 to 5.72; p = 0.001) (Table 4).

DISCUSSION

In the current study from a large prospective multi-national registry of patients undergoing serial coronary CTA, we found that calcified plaque is a marker of risk and disease progression due to its strong association with the total plaque burden. When considered as a percentage of the total PV, increasing calcification is a marker of plaque stability and

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TABLE 4 Predicting Factors for the Composite of Major Cardiovascular Events

| | Univariable Analysis | | | |
| | Unadjusted | | Adjusted* | |
	HR (95% CI)	p Value	HR (95% CI)	p Value
High percent calcified PV	0.57 (0.35-0.95)	0.029	0.56 (0.33-0.94)	0.029
High calcified PV	2.60 (1.61-4.20)	<0.001	2.65 (1.60-4.39)	<0.001
High total PV	2.14 (1.34-3.40)	0.001	2.09 (1.29-3.40)	0.003
High mean plaque burden	2.74 (1.69-4.46)	<0.001	2.72 (1.64-4.52)	<0.001
High necrotic core volume	3.03 (1.84-4.99)	<0.001	3.19 (1.89-5.39)	<0.001

| | Multivariable Analysis† | |
	HR (95% CI)	p Value
High percent calcified PV	0.53 (0.29-0.97)	0.039
High calcified PV	3.01 (1.58-5.72)	0.001
High total PV	2.04 (0.96-4.30)	0.06
High mean plaque burden	1.63 (0.79-3.39)	0.19
High necrotic core volume	2.13 (1.12-4.07)	0.022
Age >70 yrs	1.15 (0.69-1.90)	0.56
Male	1.08 (0.65-1.78)	0.34
Smoking	1.09 (0.67-1.78)	0.74
Diabetes mellitus	1.27 (0.79-2.06)	0.39
Hypertension	1.31 (0.79-2.19)	0.13
Dyslipidemia	0.82 (0.49-1.34)	0.89
Familial history of CAD	0.99 (0.59-1.70)	0.99
Statin use	0.53 (0.30-0.93)	0.028

High volume of plaque and its constituent elements were defined as above median value of each variable in turn. *Models were adjusted for the following covariates: age, sex, smoking, diabetes, hypertension familial history of CAD, and dyslipidemia. †All clinical risk factors, variables of coronary CTA, and statin use were applied together in a multivariate Cox proportional hazards regression.

HR = hazard ratio; other abbreviations as in Tables 1 and 3.

reduced risk at both a lesion and patient level. The current findings highlight that a more nuanced approach is required to use calcified plaque change in serial imaging studies as a risk marker. PCPV, which captures the interplay between calcified plaque and total PV, may be considered a marker of increasing plaque stability and should be additionally considered when assessing patient risk and treatment response.

INSIGHTS INTO THE ASSOCIATION BETWEEN CORONARY CALCIFICATION AND THE NATURAL HISTORY OF CORONARY ARTERY DISEASE. Extensive investigation has shown that CAC is an independent predictor of adverse events, with a significant incremental prognostic value over traditional risk stratification (3-6,20). To date, the majority of cardiac CT studies examining the role of coronary calcium in predicting coronary artery disease have used simple quantification and scoring of calcification without considering noncalcified plaque burden. Previous studies with intravascular ultrasound and coronary CTA have shown that calcified plaques are more resistant to change and progression of PV (21,22), although these studies used a qualitative or semi-quantitative method to evaluate the coronary calcification and were limited to short coronary segment assessment.

In the current study, we analyzed serial coronary CTA from a large prospective registry with a quantitative methodology, incorporating both the standard volume measurement of plaque calcification but also the novel metric of PCPV to contextualize CPV in terms of the plaque burden in its entirety (Central Illustration). The present data provide novel observations that PCPV was inversely related to change in PV and cardiovascular events, whereas CPV was positively associated with clinical outcomes and was more predictive when adjusted for PCPV. These findings are consistent with previous studies that coronary calcification is an independent risk factor for future adverse events, reflecting coronary atherosclerotic burden (3,4), with this plaque burden in turn positively associated with progression (22,23). Heavily calcified plaque was found to be associated with a lower interval change in PV and improved MACE-free survival in agreement with a study by Rosendael et al. (24) (i.e., that hyperdense plaque [>1,000 HU] is associated with a lower risk of subsequent acute coronary syndromes).

Several studies have shown that the calcium density on coronary artery calcium scoring studies is inversely related to future events (25,26). It may be that calcium density is a marker of the percentage of calcified plaque, as these observations on plaque density are congruent with our observations on PCPV. However, the calcium score uses only the single pixel with the highest attenuation to define plaque density, which may not distinguish a nodule of dense calcification sitting in a very large necrotic plaque from a dense isolated nodule of calcification. Further examination of coronary artery plaque calcification, density, PCPV, and risk is required to better understand how these factors relate.

CORONARY ARTERY CALCIFICATION AND MEDICAL THERAPY. Studies investigating the effect of statins on plaque composition show that statins promote coronary calcification, with progression in the CAC score (11-13). This finding, however, seems contradictory as CAC progression has been associated with poorer clinical outcome (9,10,27). Because statins affect both the volume of calcified and noncalcified plaque (11,12), measuring coronary calcification in isolation is limited in its assessment of the effects of statins. In this regard, PCPV may better reflect the beneficial effect of preventative therapies on coronary plaque. High-intensity statins increase the

calcium volume but not total PV, which results in a pronounced increase in PCPV. The fact that higher PCPV is in turn predictive of lower rates of plaque progression and cardiovascular events aligns with the expected clinical outcomes of this preventative therapy. These findings suggest that PCPV should be a factor when considering risk stratification by coronary calcium quantification.

STUDY LIMITATIONS. Calcium scoring was not routinely performed as part of the PARADIGM study, and thus as a result, the extent to which the current findings affect the translation of coronary artery calcium scoring cannot be examined. The current study analyzed those with clinically indicated serial coronary CTA, and thus the results need to be re-examined in a primary prevention cohort to determine if they are translatable into this cohort. We also excluded patients who underwent revascularization between their baseline and follow-up CT scan as this could physically and hemodynamically affect the natural course of lesions. Therefore, there is a possibility that the most severe and vulnerable lesions were excluded in the analysis.

CONCLUSIONS

Calcified plaque is a marker of risk and disease progression due to its strong association with the total plaque burden. When considered as a percentage of the total PV, increasing calcification is a marker of plaque stability and reduced risk at both a lesion and patient level. These findings suggest that PCPV should be considered when proposing risk stratification by coronary calcium quantification

AUTHOR DISCLOSURES

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Coronary artery calcification is a marker of cardiovascular risk. This is due to its strong association with total plaque burden. However, patients may have a low calcium burden with a high plaque burden or a high calcium burden with a low noncalcified plaque burden. When considered as a percentage of total plaque, a high percentage of calcified plaque is associated with lower risk of plaque progression and lower risk of MACE.

TRANSLATIONAL OUTLOOK: Preventative treatments such as statins increase calcified plaque burden. Given the findings of the current study, the percent CPV needs to be assessed in prospective interventional trials to determine if it better captures treatment response and reduction of risk.

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KEY WORDS atherosclerosis, coronary artery calcium, coronary artery disease, coronary computed tomography angiography, statins

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