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ORIGINAL RESEARCH

# Relationship Between Coronary Artery Calcium and Atherosclerosis Progression Among Patients With Suspected Coronary Artery Disease

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## ABSTRACT

**BACKGROUND** Among symptomatic patients, it remains unclear whether a coronary artery calcium (CAC) score alone is sufficient or misses a sizeable burden and progressive risk associated with obstructive and nonobstructive atherosclerotic plaque.

**OBJECTIVES** Among patients with low to high CAC scores, our aims were to quantify co-occurring obstructive and nonobstructive noncalcified plaque and serial progression of atherosclerotic plaque volume.

**METHODS** A total of 698 symptomatic patients with suspected coronary artery disease (CAD) underwent serial coronary computed tomographic angiography (CTA) performed 3.5 to 4.0 years apart. Atherosclerotic plaque was quantified, including by compositional subgroups. Obstructive CAD was defined as ≥50% stenosis. Multivariate linear regression models were used to measure atherosclerotic plaque progression by CAC scores. Cox proportional hazard models estimated CAD event risk (median of 10.7 years of follow-up).

**RESULTS** Across baseline CAC scores from 0 to ≥400, total plaque volume ranged from 30.4 to 522.4 $mm^3$ ($P < 0.001$) and the prevalence of obstructive CAD increased from 1.4% to 49.1% ($P < 0.001$). Of those with a 0 CAC score, 97.9% of total plaque was noncalcified. Among patients with baseline CAC <100, nonobstructive CAD was prevalent (40% and 89% in CAC scores of 0 and 1-99), with plaque largely being noncalcified. On the follow-up coronary CTA, volumetric plaque growth ($P < 0.001$) and the development of new or worsening stenosis ($P < 0.001$) occurred more among patients with baseline CAC ≥100. Progression varied compositionally by baseline CAC scores. Patients with no CAC had disproportionate growth in noncalcified plaque, and for every 1 $mm^3$ increase in calcified plaque, there was a 5.5 $mm^3$ increase in noncalcified plaque volume. By comparison, patients with CAC scores of ≥400 exhibited disproportionate growth in calcified plaque with a volumetric increase 15.7-fold that of noncalcified plaque. There was a graded increase in CAD event risk by the CAC with rates from 3.3% for no CAC to 21.9% for CAC ≥400 ($P < 0.001$).

**CONCLUSIONS** CAC imperfectly characterizes atherosclerotic disease burden, but its subgroups exhibit pathogenic patterns of early to advanced disease progression and stratify long-term prognostic risk.
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**ABBREVIATIONS AND ACRONYMS**

**ASCVD** = atherosclerotic cardiovascular disease

**CAC** = coronary artery calcium

**CAD** = coronary artery disease

**CTA** = computed tomographic angiography

**MI** = myocardial infarction

Among asymptomatic populations, there is a strong association between coronary artery calcium (CAC) scores and major coronary artery disease (CAD) events.[1] When compared with the diagnostic evaluation of symptomatic patients, a major goal of testing has been detection of significant obstructive CAD. Increasingly, there is an evolving interest in diagnostic testing beyond identifying obstructive stenosis to include assessment of the burden of atherosclerotic plaque. Evidence is unfolding supporting varying atherosclerotic plaque characteristics, such as lipid-rich or noncalcified plaque, as highly predictive of acute coronary events.[2] Among symptomatic patients, CAC testing is also performed to detect atherosclerosis, as well as provide an estimate of future risk.[3] Yet, the evidence has been conflicting as to whether a CAC score alone is sufficient, or if it misses obstructive and nonobstructive stenosis and a sizeable volume of atherosclerotic plaque, thus placing the symptomatic patient at risk for major CAD events.

The PARADIGM (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging) registry has largely focused on volumetric progression, including observational comparisons by treatment with statins as well as secondary analyses in key patient subgroups, such as patients with diabetes.[4] From this registry, an examination of the relationship between a baseline CAC score and alterations in the severity of obstructive stenosis and nonobstructive atherosclerotic plaque has yet to be undertaken. Thus, the primary aims of the current analysis were 2-fold: 1) to measure the volume of atherosclerotic plaque, including that which is noncalcified, on a baseline coronary computed tomographic angiography (CTA); and 2) to measure progression of atherosclerotic plaque, including noncalcified and calcified, as well as worsening severity or new obstructive stenosis among symptomatic patients based on their index CAC findings. Exploratory analysis also focused on the prognostic findings after the baseline coronary CTA in symptomatic patients.

## METHODS

### STUDY DESIGN AND PATIENT SELECTION CRITERIA.

The Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging was a prospective, multinational registry of patients who underwent serial coronary CTAs (time interval ≥2 years).[5] From 13 centers and 7 countries, 2,252 patients were enrolled. For this analysis, we excluded 492 patients with 1 coronary CTA, 306 patients with known CAD, 33 asymptomatic patients, 50 patients with intercurrent coronary revascularization, and 673 patients without baseline or follow-up CAC measurement (Figure 1). Thus, 698 symptomatic patients remained for the current analysis. This registry

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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.

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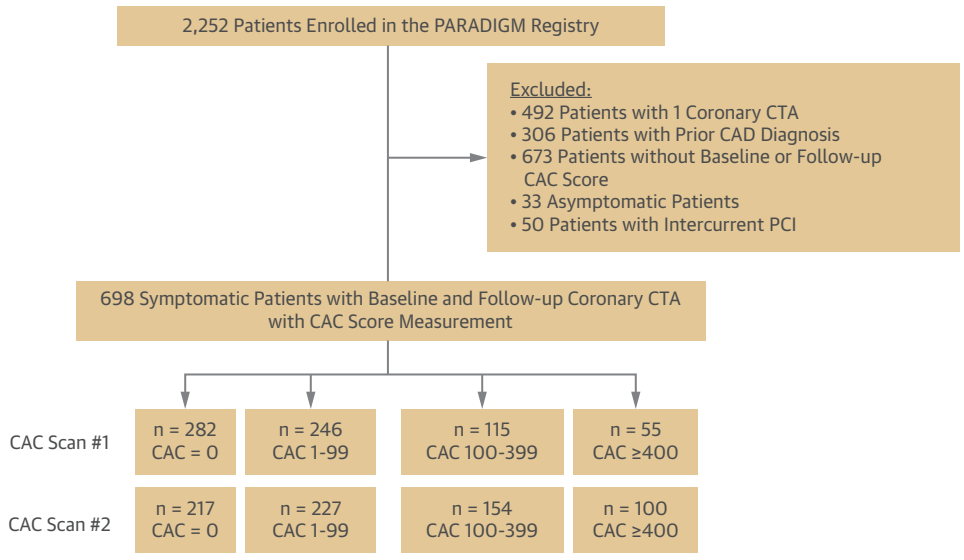
**FIGURE 1 CONSORT Diagram**




CONSORT (Consolidated Standards of Reporting Trials) diagram for enrollment of symptomatic patients with suspected CAD who underwent serial coronary CTA including CAC score measurements. CAC = coronary artery calcium; CAD = coronary artery disease; CTA = computed tomography angiography; PARADIGM = Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging; PCI = percutaneous coronary intervention.

had institutional review board approval for data collection and follow-up, with active approval during the conduct of this secondary analyses.

**CAC SCORES AND CORONARY CTA PROTOCOL AND INTERPRETATION.** Coronary CTAs were performed using guidelines from the Society of Cardiovascular Computed Tomography[6] and analyzed by level-III certified physicians at a core laboratory for centralized image interpretation. Readers were blinded to the patient's clinical history. Coronary CTAs were interpreted using a semi-automated plaque analysis software (QAngioCT Research Edition v2.1.9.1, Medis Medical Imaging Systems).[7] Atherosclerotic plaque was defined as ≥1 $mm^2$ tissue within or adjacent to the lumen identified in >2 planes delineated from surrounding pericardial tissue, epicardial fat, or lumen. Arterial segments ≥2 mm were evaluated.

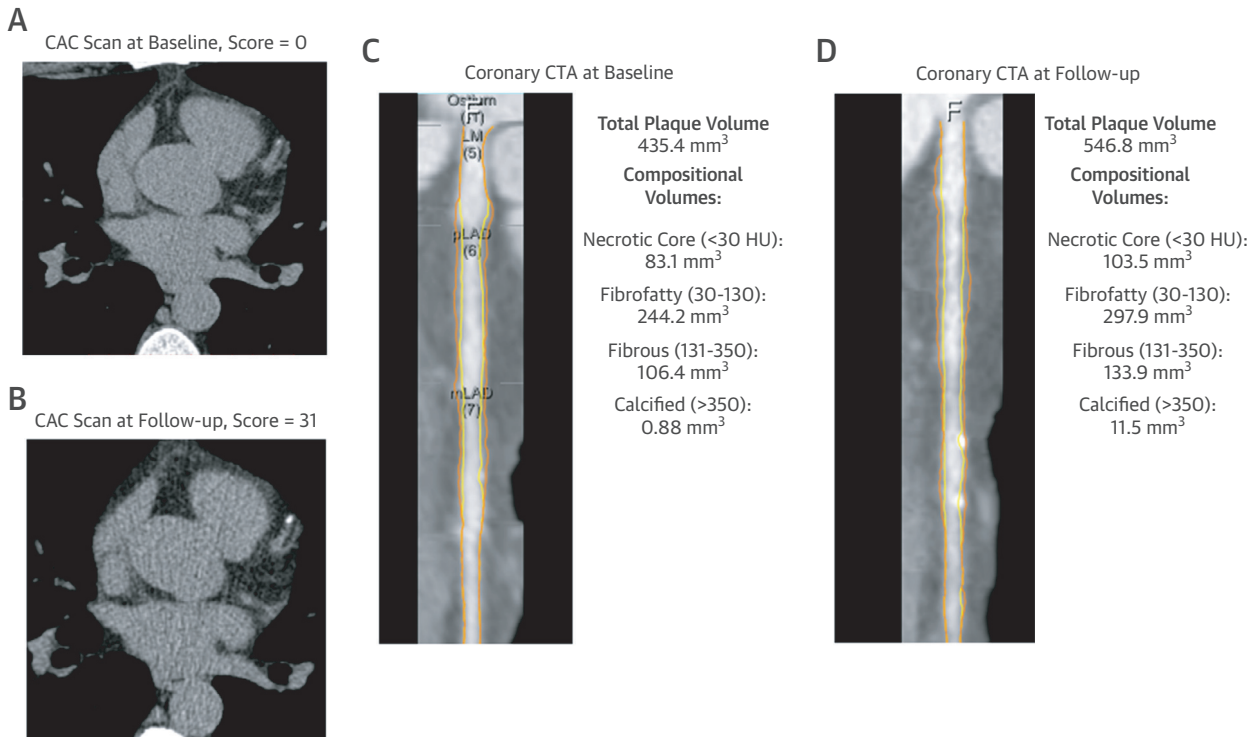
Each patient's coronary tree was quantitatively analyzed to calculate total plaque volume ($mm^3$). Plaque volumes were categorized using HU densities for necrotic core (−30 to 30 HU), fibro-fatty (31-130 HU), fibrous (131-350 HU), and calcified (>350). The volume of necrotic core was small (eg, median at baseline = 0.03 $mm^3$) and, thus, we combined necrotic core with fibrofatty plaque volumes (≤130 HU) to enhance clinical generalizability of our findings. An example of serial CAC and coronary CTA scan findings is detailed in Figure 2. The interobserver and intraobserver correlations for plaque volume ranged from 0.95 to 0.99.[8] Stenosis severity was categorized as 0%, 1% to 24%, 25% to 49%, and ≥50%. We defined positive remodeling with an index ≥1.1 and low attenuation plaque with HU densities from −30 to 30.

From the noncontrast images, we calculated the CAC score using a dedicated workstation (Vitrea v7.6, Vital Images, Inc). CAC scores were categorized as 0, 1 to 99, 100 to 399, and ≥400.

**CLINICAL ENDPOINT ASCERTAINMENT.** The median duration of follow-up was 10.7 (95% CI: 10.5-10.9) years. All clinical endpoints were confirmed using national or regional medical records.[9] Major adverse events were defined as death, nonfatal myocardial infarction (MI), or late (>90 days) coronary revascularization. Acute MI was defined using the universal definition. All coronary revascularization procedures were clinically indicated; patients having early procedures (<90 days after the baseline coronary CTA) were not included in the composite endpoint.

**STATISTICAL ANALYSIS.** Categorical variables are presented as absolute values and percentages and

**FIGURE 2 Patient Case**




An example of a patient with a baseline CAC score of 0 and coronary CTA measures of atherosclerotic plaque volume. **(A)** CAC scan at baseline, score = 0. **(B)** CAC scan at follow-up, score = 31. **(C)** Coronary CTA at baseline. **(D)** Coronary CTA at follow-up. LM = left main coronary artery; mLAD = mid left anterior descending artery; pLAD = proximal left anterior descending artery; other abbreviations as in Figure 1.

compared using a chi-square test. Continuous variables are presented as mean ± SD and compared using the Wilcoxon Rank test or correlation tests to obtain a *P* value for trend. Multivariate linear regression models were calculated to compare changes in CAC score groups with plaque volume. Other analytic approaches, including generalized linear models, with bootstrap analysis (1,000 samples) and linear mixed models were also performed. Thresholds of change were assigned a priori as Δ total plaque volume ≥100 $mm^3$ and noncalcified plaque volume ≥10 $mm^3$, representing ≥80th percentile of change.[2,10] As secondary analyses, multivariable logistic regression models were calculated to estimate plaque and stenosis progression. From the models, we calculated OR and 95% CI. Variable collinearity was considered when selecting variables entering the models. Model overfitting was considered by limiting only 1 variable per 10 outcomes. For all models, covariate adjustment included factors influencing atherosclerosis progression including statin use, time to second coronary CTA, and the atherosclerotic cardiovascular disease (ASCVD) risk score. Other candidate variables considered but not retained as covariates were body habitus measures (eg, body mass index).

A Kaplan-Meier survival curve plotted CAC subgroups with comparisons using the log-rank statistic. Multivariable Cox proportional hazard models were used to compare the association between CAC scores with adverse events with covariate adjustment using baseline statin use and the ASCVD risk score. HRs and 95% CIs were calculated from the Cox model. The proportional hazards assumption was evaluated by viewing the constancy of the parallel plotted lines in the log-log graph and tested using the Schoenfeld residuals. Analyses were performed using SAS (version 9.4) or R (R Development Core Team). A $P < 0.05$ was considered statistically significant.

## RESULTS

**BASELINE CLINICAL CHARACTERISTICS OF THE STUDY PATIENTS.** Of the 698 symptomatic patients,

**TABLE 1 Baseline Clinical Characteristics of 698 Symptomatic Patients Across CAC Score Subgroups**

| | CAC Score = 0 (n = 282) | CAC Score 1-99 (n = 246) | CAC Score 100-399 (n = 115) | CAC Score ≥400 (n = 55) | Overall (N = 698) |
|---|---|---|---|---|---|
| Baseline CAC score, AU | 0 ± 0 | 33.3 ± 27.7 | 200.9 ± 78.4 | 973.1 ± 772.4 | 121.5 ± 338.4 |
| Age, y | 57.9 ± 9.8 | 61.0 ± 8.8 | 64.8 ± 7.8 | 69.9 ± 8.8 | 61.1 ± 9.7 |
| Female | 131 (46) | 108 (44) | 53 (46) | 20 (36) | 312 (45) |
| ASCVD risk score, % | 9 ± 9 | 13 ± 12 | 17 ± 12 | 23 ± 14 | 13 ± 12 |
| <7.5% | 160 (57) | 85 (35) | 26 (23) | 6 (11) | 277 (40) |
| CAD risk factors | | | | | |
| Hypertension | 123 (44) | 154 (63) | 85 (75) | 41 (75) | 403 (58) |
| Dyslipidemia | 57 (20) | 66 (27) | 36 (32) | 26 (47) | 185 (27) |
| Diabetes | 43 (15) | 75 (31) | 38 (33) | 14 (25) | 170 (24) |
| Current smoker | 48 (17) | 39 (16) | 23 (20) | 16 (29) | 126 (18) |
| Medication use | | | | | |
| Statins | 80 (28) | 104 (43) | 65 (58) | 39 (74) | 288 (42) |
| Beta-blockers | 79 (28) | 58 (24) | 36 (31) | 20 (36) | 193 (28) |
| Calcium-channel blockers | 64 (23) | 80 (33) | 40 (35) | 18 (33) | 202 (29) |
| RAAS inhibitors | 67 (24) | 78 (32) | 46 (40) | 28 (51) | 219 (31) |
| Aspirin | 94 (33) | 107 (43) | 69 (60) | 28 (51) | 298 (43) |
| Presenting symptoms[a] | | | | | |
| Dyspnea | 21 (7) | 15 (6) | 9 (8) | 7 (13) | 52 (7) |
| Atypical chest pain | 226 (80) | 201 (82) | 96 (83) | 50 (91) | 573 (82) |
| Noncardiac chest pain | 46 (16) | 31 (13) | 15 (13) | 5 (9) | 97 (14) |
| Typical angina | 9 (3) | 11 (4) | 4 (3) | 0 (0) | 24 (3) |

Values are mean ± SD or n (%). All % are rounded to the nearest whole %, except for values <1% [a]Symptom descriptors were coded as mutually exclusive.

AU = Agatston units; ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; CAD = coronary artery disease; RAAS = renin-angiotensin-aldosterone system.

the mean age was 61.1 ± 9.7 years and 45% were women. CAC score subgroups were as follows: 0 (n = 282), 1 to 99 (n = 246), 100 to 399 (n = 115), and ≥400 (n = 55). Patients with CAC scores <100 were younger, with fewer risk factors, and lower ASCVD risk scores (Table 1).

## BASELINE CORONARY CTA FINDINGS.

**Baseline obstructive and nonobstructive CAD stenosis.** For patients with no CAC, only 1.4% (n = 4) had a ≥50% stenosis, whereas 40% had nonobstructive stenosis of 1% to 49%. Across the baseline CAC subgroups, there was a graded increase in the rate of obstructive CAD stenosis ≥50% (Figure 3) ($P < 0.001$), with obstructive CAD reported in nearly half of patients with a CAC score ≥400. All patients with a CAC score ≥100 had nonobstructive or obstructive CAD.

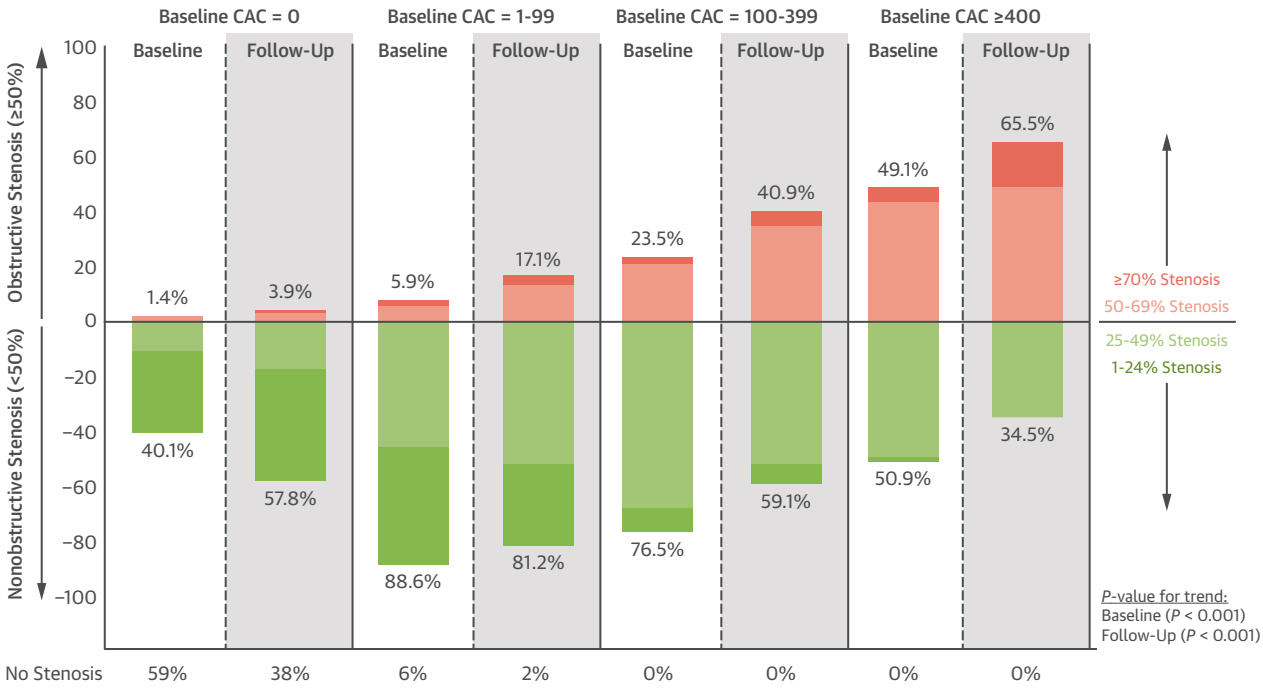
**Baseline quantitative atherosclerotic measurement.** At baseline, the average plaque volume ranged from 30.4 $mm^3$ for patients with no CAC and increased to 522.4 $mm^3$ for those with CAC scores ≥400 ($P < 0.001$). Thus, there was a graded relationship between higher CAC scores and increasing total plaque volume (Figure 4) ($P < 0.001$). The proportion of the total plaque volume categorized as noncalcified was inversely related to CAC scores; with the total plaque of patients with lower CAC scores largely being noncalcified. Among patients with a 0 CAC score, 98% of total plaque was categorized as noncalcified.

**Baseline high-risk plaque features.** The patterns of high-risk plaque features varied for patients with 0 CAC scores as compared with those with scores >0. The rate of low attenuation plaque ($P < 0.001$) and positive remodeling ($P < 0.001$) was higher for those with detectable CAC (Table 2). However, 18% and 36% of patients with a 0 CAC score had low attenuation plaque and positive remodeling. For those with a 0 CAC score, the presence of any low attenuation plaque was greater among those who smoke ($P = 0.001$) and patients with diabetes ($P < 0.001$). Among patients with a 0 CAC score, 10% of patients had a low attenuation plaque volume >10 $mm^3$, with this subset also having luminal stenosis (72%; $P < 0.001$) and a larger total plaque volume ($P < 0.001$).

## CORONARY CTA ATHEROSCLEROSIS PROGRESSION.

**CAC score progression.** The follow-up coronary CTA was performed 3.8 ± 1.4 years following the baseline scan; with similar times across CAC subgroups (Figure 1) ($P = 0.084$). CAC scores increased at follow-up across the subgroups, with the largest absolute change occurring among patients with a baseline CAC ≥400 (Table 3). From baseline to follow-up, only 0.2% of those with a baseline 0 CAC score increased

**FIGURE 3 Prevalence of Obstructive and Nonobstructive Stenosis at Baseline and Follow-Up by CAC Score Subgroups**



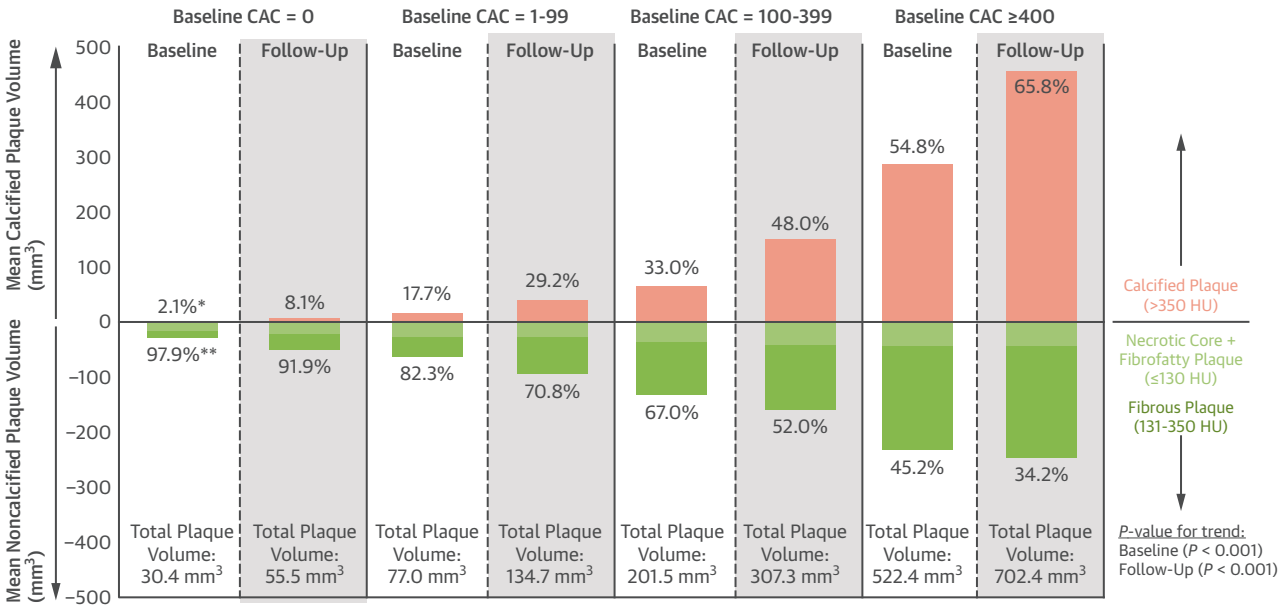

The rate at which patients developed new stenosis, across severity groups. Nonobstructive stenosis (**dark green**, 1%-24% stenosis; and **light green**, 25%-49% stenosis) is the lower portion of the figure, and obstructive stenosis (50%-69% in **light red** and ≥70% in **dark red**) is the upper portion of the figure. The frequency of no luminal stenosis is at the base of the figure. Abbreviation as in **Figure 1**.

their score by ≥100 as compared with 82% of those with a baseline CAC score of ≥400 ($P < 0.001$). In a multivariable model, a 0 CAC score had a 98% lower odds of CAC progression ≥100 ($P = 0.001$) when compared with a CAC score of 1 to 99. By comparison, the adjusted odds for CAC progression ≥100 was elevated 13.6-fold for those with a CAC score ≥400 ($P < 0.001$) (Supplemental Table 1). Multivariate generalized linear models were also analyzed, with similar findings reported in **Figure 5**. Based on a multivariate linear regression, the adjusted progression in the CAC score is plotted by the baseline CAC score in Supplemental Figure 1.

**Progression of obstructive and nonobstructive CAD.** From **Figure 3**, the prevalence of obstructive stenosis increased across all CAC subgroups from baseline to follow-up coronary CTA ($P < 0.001$). Across the CAC subgroups of 0, 1 to 99, 100 to 399, and ≥400, the rate of new stenosis ≥50% was 2%, 11%, 17%, and 16%, respectively ($P < 0.001$). **Figure 3** also illustrates how the baseline severity of nonobstructive CAD shifted over time. Patients with a 0 CAC score largely developed more nonobstructive CAD over time. Within subgroups, 17% and 16% of patients with a CAC score of 100 to 399 and ≥400 had a lower rate of nonobstructive CAD on the follow-up coronary CTA; this co-occurred with increasing rates of obstructive CAD, thus reflecting stenosis worsening over time.

**Quantitative atherosclerosis progression.** Progression of total plaque volume ranged, on average, from 25.1 $mm^3$ for patients with no CAC to 180.0 $mm^3$ for those with CAC scores ≥400 (**Figure 4**) ($P < 0.001$). These changes in total plaque volume remained significant in generalized linear models including the ASCVD risk score, baseline statin use, and the time interval between scans (**Figure 5**). Based on a multivariate linear regression, plots of the adjusted plaque progression (ie, total, calcified, and noncalcified) by baseline CAC score are detailed in Supplemental Figure 1. Total plaque progression ≥100 $mm^3$ occurred in 7.8% of patients with a 0 CAC score and in 64.8% of patients with a CAC score ≥400 ($P < 0.0001$). Among patients with a 0 CAC score, total plaque progression occurred more often among patients with any luminal stenosis on their baseline coronary CTA ($P < 0.001$). In a multivariable

**FIGURE 4 Mean Plaque Volumes at Baseline and Follow-Up by CAC Score Subgroups**




Plaque subtypes were defined by HU subgroups as lower density, necrotic core, and fibrofatty plaque (≤130 HU, **light green**) and fibrous (131-350 HU, **dark green**), seen beneath the axis and calcified (>350 HU, **red**), seen above the axis. Total plaque volume is at the base of the figure. *Mean proportion (%) calcified plaque of total plaque volume. **Mean proportion (%) noncalcified plaque of total plaque volume. Abbreviation as in Figure 1.

logistic model, the adjusted odds of total plaque progression ≥100 mm³ was elevated 1.9- to 5.7-fold for patients with a baseline CAC score of 100 to 399 ($P = 0.017$) and ≥400 ($P < 0.001$) (Supplemental Table 1).

We also examined compositional changes in atherosclerotic plaque across CAC scores and revealed that predominant growth among patients with lower CAC scores was noncalcified plaque, whereas among those with higher-risk CAC scores, plaque growth was more often calcified ($P < 0.001$) (Figure 4). For example, patients with a 0 CAC score had disproportionate growth in noncalcified plaque, and for every 1 mm³ increase in calcified plaque, there was a 5.5 mm³ increase in noncalcified plaque volume. By comparison, patients with high CAC scores ≥400 had disproportionate growth in calcified plaque and for every 1 mm³ increase in noncalcified plaque, there was a 15.7 mm³ increase in calcified plaque volume. In a multivariable model estimating progression of combined noncalcified plaque volume ≥10 mm³, the baseline CAC score was not statistically significant

**TABLE 2 Prevalence of Low Attenuation Plaque, Defined as HU Density <30, and Positive Remodeling, Defined as ≥1.1 in the 698 Symptomatic Patients Across CAC Score Subgroups**

| | CAC Score = 0 (n = 282) | CAC Score 1-99 (n = 246) | CAC Score 100-399 (n = 115) | CAC Score ≥400 (n = 55) | Overall (N = 698) | *P* Value |
|---|---|---|---|---|---|---|
| Low attenuation plaque (−30 to 30 HU) | | | | | | |
| Baseline | 18 | 29 | 35 | 24 | 25 | <0.001 |
| Follow-up | 18 | 32 | 35 | 33 | 27 | <0.001 |
| Positive remodeling ≥1.1 | | | | | | |
| Baseline | 36 | 86 | 96 | 100 | 69 | <0.001 |
| Follow-up | 53 | 91 | 99 | 100 | 78 | <0.001 |

Values are %.
Abbreviation as in Table 1.

**TABLE 3 Follow-Up Change (Δ) in CAC Scores by Baseline CAC Subgroups in 698 Symptomatic Patients With Suspected CAD**

| | CAC Score = 0 (n = 282) | CAC Score 1-99 (n = 246) | CAC Score 100-399 (n = 115) | CAC Score ≥400 (n = 55) | Overall (N = 698) | *P* Value |
|---|---|---|---|---|---|---|
| Follow-up CACS, in AU | 4 ± 13 | 89 ± 86 | 388 ± 213 | 1,449 ± 1,070 | 211 ± 498 | <0.001 |
| Δ CAC | 4 ± 13 | 55 ± 69 | 187 ± 183 | 476 ± 471 | 89 ± 203 | <0.001 |
| % Δ CAC | –[a] | 350 | 101 | 56 | 242 | <0.001 |
| % with Δ CAC ≥100 | 0.2 | 15 | 66 | 82 | 23 | <0.001 |

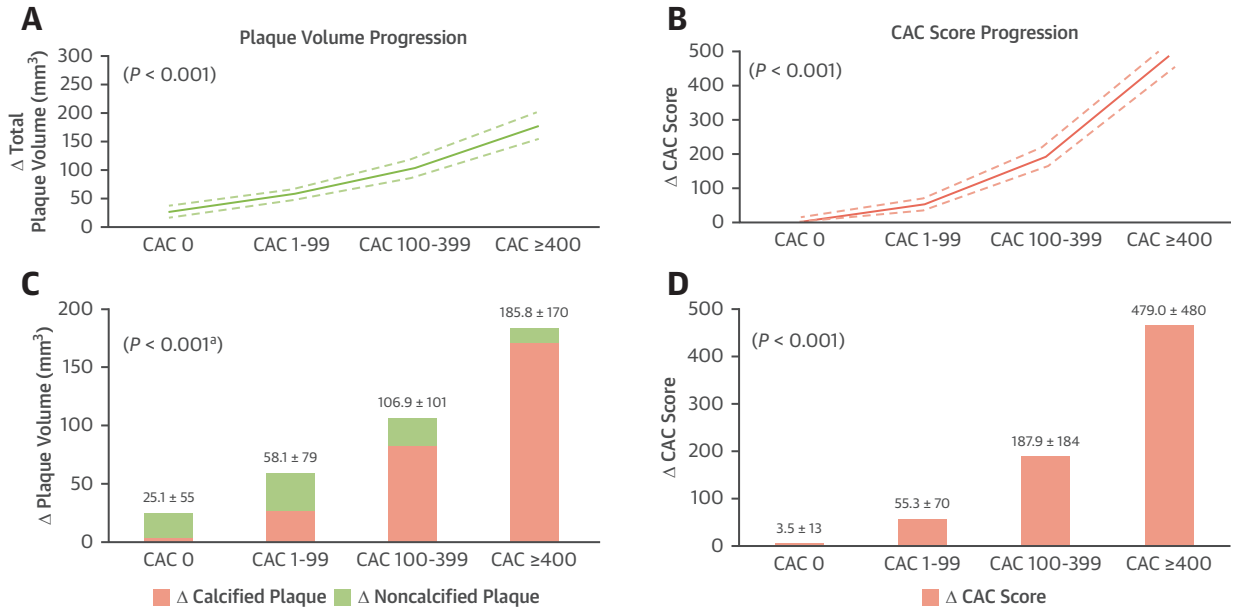
Values are mean ± SD unless otherwise indicated. All % are rounded to the nearest whole %, with exception for values <1%. [a]Δ CAC scores from 0 cannot be calculated. Abbreviations as in Table 1.

(Supplemental Table 1) ($P$ = 0.46). The **Central Illustration** plots the ratio of volumetric growth in noncalcified versus calcified plaque across CAC score subgroups. For both progression of noncalcified and calcified plaque volume, the presented results remained significant in generalized linear models including the ASCVD risk score, baseline statin use, and the time interval between scans.

**Follow-up high-risk plaque features.** The prevalence of positive remodeling increased whereby nearly half of patients with a 0 CAC score and nearly all patients with CAC score of ≥100 had a remodeling index ≥1.1 (Table 2; $P$ < 0.001). Among patients with no CAC, total plaque progression ($P$ < 0.001) and worsening stenosis severity ($P$ = 0.012) was greater among those with baseline burden of low attenuation plaque ≥10 mm$^3$.

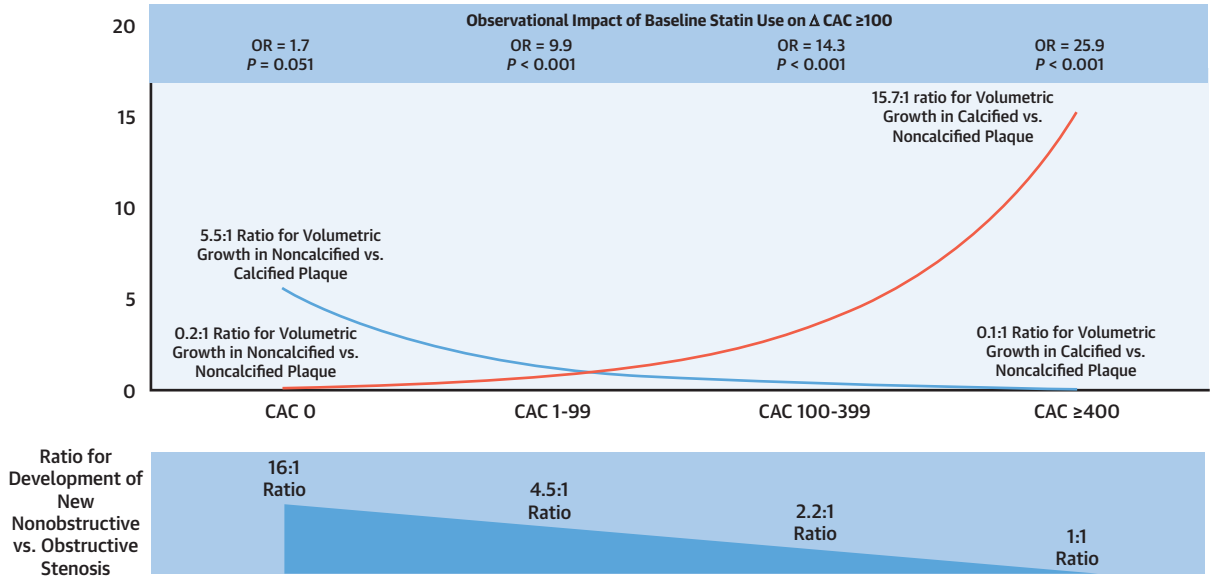
**EXPLORATORY PROGNOSTIC ANALYSIS BY CAC SUBGROUPS.** Clinical endpoints included 8 deaths or nonfatal MIs and 57 patients had late revascularization after the index coronary CTA. Beyond 90 days

**FIGURE 5 Adjusted Comparison of Progression of Total (Noncalcified and Calcified) Plaque Progression and Serial Changes in CAC Scores by the Baseline CAC Score**




Using a multivariate generalized linear model[a] (including covariates of time between scans, baseline statin use, and the ASCVD risk score) with bootstrap analysis (n = 1,000 samples). **A** reveals the findings from the bootstrap analysis with mean adjusted changes in total plaque volume **(solid line)** and 95% CIs **(dotted lines)**, and **C** includes adjusted progression in calcified and noncalcified plaque (in mm$^3$) across the CAC subgroups. The mean ± SD Δ in total plaque volume (mm$^3$) is reported at the top of the CAC subgroup column. Similar analysis is depicted in **B and D** for CAC score progression. ASCVD = atherosclerotic cardiovascular disease; other abbreviation as in Figure 1. [a]$P$ < 0.001 for total, calcified, and noncalcified plaque volume. Additionally, linear mixed models were significant $P$ < 0.001 for total, noncalcified, calcified plaque, and CAC score progression.

**CENTRAL ILLUSTRATION Comparisons of Alterations in Stenosis Severity and Volumetric Progression by Composition**

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The ratio of volumetric growth in noncalcified vs calcified plaque **(blue line)** and the ratio of volumetric growth in calcified vs noncalcified plaque **(red line)** are plotted. These data reveal that the rate of volumetric growth is largely noncalcified for lower CAC scores. By comparison, as CAC scores increase, volumetric growth is largely calcified. All plots include an exponential fitted curve. In the bottom figure, the ratio for development of new nonobstructive vs obstructive stenosis reveals an inverse relationship with more nonobstructive stenosis developed in patients with lower CAC scores. For patients with CAC scores ≥400, there is a 1:1 ratio for development of nonobstructive vs obstructive stenosis. CAC = coronary artery calcium.

after the index coronary CTA, the rate of symptom-driven revascularization ranged from 4% to 31% for those with CAC scores from 0 to ≥400 ($P < 0.001$). Using this composite endpoint, the Kaplan-Meier event rate was 9.3%. Cox proportional hazard analysis revealed that the relative hazard for events increased with higher-risk CAC scores ($P < 0.001$) (Supplemental Figure 2). When comparing the CAC subgroup with scores from 1 to 99, the adjusted HRs were significantly lower for those with a 0 CAC score (HR: 0.22; 95% CI: 0.09-0.51; $P < 0.001$), and higher for those with CAC scores from 100 to 399 (HR: 1.67; 95% CI: 0.91-3.08; $P = 0.099$) and ≥400 (HR: 2.76; 95% CI: 1.33-5.74; $P = 0.006$), with adjustment by statin use and the ASCVD risk score.

In separate analyses, subgroups with total plaque volume from 0.1 to 75 $mm^3$ were not associated with an increase in CAD events ($P = 0.18$) when compared with patients with no atherosclerotic plaque. By comparison, for total plaque volumes from 75.0 to 99.9 to ≥300 $mm^3$, HRs ranged from 3.6 ($P = 0.033$) to 8.1 ($P < 0.001$) (Supplemental Table 2), even when including statin use and the ASCVD risk score as covariates. Moreover, the volume of necrotic core and fibrofatty plaque had HRs ranging from 3.0 to 7.6 for volumes from 0.1 to 19.9 to ≥100 $mm^3$ (Supplemental Table 2), even when adjusting for statin use and the ASCVD risk score.

## DISCUSSION

Nearly 3 decades ago, CAC scoring was introduced as a screening tool with the rationale that detection of calcified plaque was easy to measure and serves as a marker of the overall burden of atherosclerotic plaque. These reports did not examine the role of CAC scanning in symptomatic patients where the goal of diagnostic testing is to identify significant obstructive CAD that may warrant optimized medical therapy and/or coronary revascularization. The critical hurdle for acceptance of CAC scanning as a diagnostic test in symptomatic patients is whether the observed calcified plaque findings sufficiently encapsulate the burden of CAD and accurately categorize future risk of disease progression or events. Findings from our cohort are striking in several respects. First, patients

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with no to minimal CAC were accurately stratified at low CAD event risk, despite the unexpected burden of nonobstructive CAD that was largely noncalcified plaque. Moreover, lower-risk CAC contains largely smaller plaque volumes and represents an early stage of atherosclerosis that progressively worsened over time, with growth patterns of largely noncalcified plaque and development of new but mild luminal stenosis. Second, high CAC scores were synonymous with more advanced atherosclerosis, including a heavy burden of obstructive CAD that only worsened in severity and became more calcified over time. Beyond its well-known prognostic value validated herein, low- to high-risk CAC scores characterize distinct pathogenic patterns of atherosclerosis with varied volumetric and compositional changes over time.

**WHAT IS UNDERLYING A 0 CAC SCORE?** The "power of 0" is a message espousing the excellent negative predictive value and a low, long-term risk of major CAD events among asymptomatic individuals with a 0 CAC score.[11] For symptomatic patients, this message relates to a low prevalence of significant obstructive CAD (1.4% with 0 CAC). However, there has been concern that a 0 CAC score does not reveal the burden of noncalcified plaque (especially in the setting of a nonobstructive stenosis) commonly associated with vulnerability to an acute coronary event. What is unique from our analysis is that, among patients with a 0 CAC score, the overall prevalence of mild stenosis was sizeable (~40%) and increased during follow-up. Among those with a 0 CAC score, nearly all plaque was noncalcified and may provide a link for potential risk in this patient subgroup. On presentation for an acute coronary syndrome, prior angiographic evidence reports that more than 65% of patients had previously documented nonobstructive CAD.[12] More recent evidence also supports that prognosis worsens among those with nonobstructive CAD.[13] Thus, the potential of mild stenosis acting as a precursor for future acute events is concerning among this subgroup with a 0 CAC score.

**CAC AND NONOBSTRUCTIVE AND OBSTRUCTIVE CAD.** Our findings also revealed an expected graded relationship between CAC scores and obstructive CAD, consistent with prior findings.[14] However, we now report on the burden of nonobstructive CAD and revealed a surprisingly high rate among those with CAC scores <100 at baseline. These findings highlight the importance of identifying nonobstructive stenosis severity and likely explain the different results reported from the Scottish Computed Tomography of the HEART trial where obstructive CAD stenosis ≥70% was not ($P = 0.44$) predictive of coronary heart disease death or MI, whereas CAC was ($P = 0.011$).[3] Thus, if the goal for a given patient is detection of obstructive CAD, then CAC alone is likely insufficient.

**ATHEROSCLEROSIS PROGRESSION IN PATIENTS WITH HIGH-RISK CAC.** Our results are thematically consistent with evidence that the extent of coronary calcification corresponds to the overall plaque burden.[15] Thus, what is visualized on a CAC scan mirrors the volume of calcified plaque and indicates the total plaque burden and severity of obstructive CAD. All patients with a CAC score ≥100 had at least minimal coronary stenosis. Moreover, the dimensionality of any statement on CAC with total plaque burden should also focus on the severity of obstructive CAD that worsens over time.

We observed that a larger CAC burden at baseline resulted in greater volumetric progression of total plaque and CAC. Such that, CAC progression was greatest among patients with scores ≥400, with 82% increasing their CAC score by ≥100 and 65% increased total plaque volume ≥100 $mm^3$. Moreover, with increasing CAC scores, the composition of plaque categorized as noncalcified decreased, supporting a shift toward calcification as a stabilizing force within the heavy plaque burden. These findings, often termed a plaque paradox, were similarly reported with serial intravascular ultrasound noting atheroma alterations co-occurring with increases in coronary calcification.[16] Until recently, the process of calcification was considered passive, but these and related intravascular ultrasound data support that progressive increases in calcification are active and pathogenic.[1]

**EXPLORATORY PROGNOSTIC ANALYSIS WITH CAC SCORES.** Our exploratory prognostic findings emulate prior findings from asymptomatic cohorts.[1,17] We revealed stratification of long-term risk that was graded with increasing CAD event rates across low to high CAC scores. Importantly, there remained a low risk of events among patients with no CAC, despite the prevalent noncalcified plaque with nonobstructive stenosis. We propose that the volume of atherosclerotic plaque among patients with no CAC may be too small to elevate prognostic risk. Our data reveal an elevated hazard for events when the total plaque volume exceeded 75 $mm^3$. This supports the uniform findings of excellent risk stratification based on CAC findings and reveals further insight into the necessary burden required to influence prognosis. In

a recent review of 5 reports, the threshold for volumetric measurement of plaque associated with elevated event risk was ~117 $mm^3$.[2] The determination of prognostic volumetric thresholds requires further validation.

**STUDY LIMITATIONS.** Our registry was a prospective series of consecutively tested patients with enrollees from varied countries and institutional practice patterns. For those with a 0 CAC score, the lower spatial resolution of the noncontrast scans may have missed smaller calcifications not reaching the threshold HU density for categorization as calcified.[18] Registries with yearly scanning may provide more insight into varied rates of progression. Moreover, serial data on CAD risk factors were not available. In addition, the threshold HU density of >130 may not encompass all calcified plaque; recent evidence suggests that this threshold may need to be adjusted by scanner type and patient size.[19]

## CONCLUSIONS

Our findings reveal that symptomatic patients presenting with suspected CAD have varied patterns of early to advanced atherosclerosis across the range of CAC scores. Patients with no to minimal CAC are characteristic of those with early atherosclerosis and exhibit pathogenic changes over time that include new or worsening nonobstructive CAD and growth of largely noncalcified plaque. By comparison, a sizeable proportion of patients with higher CAC scores at baseline had obstructive CAD that became progressively more calcified and stenotic over time. These progressive increases in the burden of total and calcified atherosclerotic plaque reflect an advanced stage of atherosclerosis. CAC characterizes atherosclerotic disease burden, but its subgroups exhibit pathogenic patterns from early to advanced disease progression and stratify long-term prognostic risk.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Measurement of CAC is quick and low cost and has been proposed as a potential diagnostic test for symptomatic patients. A critical test of the value of CAC is the extent to which CAC misses noncalcified plaque and fails to detect patients at risk of progressive alterations in atherosclerotic plaque, including obstructive CAD. We report in a cohort of 698 symptomatic patients with CAC scores that underwent serial coronary CTA. Our findings are striking in several respects. First, patients with no to minimal CAC had an unexpected burden of nonobstructive CAD that was largely noncalcified plaque, albeit small in volume that resulted in a low risk of major CAD events. Moreover, this lower-risk CAC represents an early stage of atherosclerosis that progressively worsened over time, with growth patterns that largely included progressive noncalcified plaque volume and the development of new but mild luminal stenosis. Second, high CAC scores were synonymous with more advanced atherosclerosis with a heavy burden of obstructive CAD that only worsened in severity and became more calcified over time. Beyond its well-known prognostic value, low- to high-risk CAC scores characterize distinct pathogenic patterns of atherosclerosis with varied volumetric and compositional changes over time.

**TRANSLATIONAL OUTLOOK:** There is a fundamental knowledge gap regarding the rate of volumetric and compositional atherosclerotic plaque progression across varied subgroups of symptomatic patients. Future research should target serial assessment of atherosclerotic plaque and define key patient subgroups at risk for developing severe, obstructive CAD and more advanced coronary atherosclerosis.

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**KEY WORDS** atherosclerotic plaque, coronary artery calcium, coronary computed tomographic angiography, plaque progression

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