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# Natural History of Diabetic Coronary Atherosclerosis by Quantitative Measurement of Serial Coronary Computed Tomographic Angiography

## Results of the PARADIGM Study (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging)

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## ABSTRACT

**OBJECTIVES** This study aimed to determine the rate and extent of plaque progression (PP), changes in plaque features, and clinical predictors of PP in patients with diabetes mellitus (DM).

**BACKGROUND** The natural history of coronary PP in patients with DM is not well established.

**METHODS** A total of 1,602 patients (age 61.3 ± 9.0 years; 60.3% men; median scan interval 3.8 years) who underwent serial coronary computed tomography angiography over a period of at least 24 months were enrolled and analyzed from the PARADIGM (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging) trial. Study endpoints were changes in plaque features in diabetics with PP and risk factors for PP by serial coronary computed tomography angiography between patients with and without DM. PP was defined if plaque volume at follow-up minus plaque volume at baseline was >0.

**RESULTS** DM was an independent risk factor for PP (84.6%; 276 of 326 patients with PP) in multivariate analysis (odds ratio [OR]: 1.526; 95% confidence interval [CI]: 1.100 to 2.118; $p = 0.011$). Independent risk factors for PP in patients with DM were male sex (OR: 1.485; 95% CI: 1.003 to 2.199; $p = 0.048$) and mean plaque burden at baseline ≥75% (OR: 3.121; 95% CI: 1.701 to 5.725; $p \leq 0.001$). After propensity matching, percent changes in overall plaque volume (30.3 ± 36.9% in patients without DM and 36.0 ± 29.7% in those with DM; $p = 0.032$) and necrotic core volume (−7.0 ± 35.8% in patients without DM and 21.5 ± 90.5% in those with DM; $p = 0.007$) were significantly greater in those with DM. The frequency of spotty calcification, positive remodeling, and burden of low-attenuation plaque were significantly greater in patients with DM.

**CONCLUSIONS** People with DM experience greater PP, particularly significantly greater progression in adverse plaque, than those without DM. Male sex and mean plaque burden >75% at baseline were identified as independent risk factors for PP. (J Am Coll Cardiol Img 2018;■:■–■) © 2018 by the American College of Cardiology Foundation.


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**ABBREVIATIONS AND ACRONYMS**

**CAD** = coronary artery disease

**CTA** = computed tomography angiography

**DM** = diabetes mellitus

**$HbA_{1c}$** = glycosylated hemoglobin

**HRP** = high-risk plaque

**HU** = Hounsfield unit

**IVUS** = intravascular ultrasound

**LAP** = low-attenuation plaque

**LDL** = low-density lipoprotein

**MACE** = major adverse cardiac event(s)

**NCV** = necrotic core volume

**PP** = plaque progression

**PR** = positive remodeling

**PV** = plaque volume

**SC** = spotty calcification

Diabetes mellitus (DM) is associated with an increased risk of coronary artery disease (CAD) and related adverse cardiac events. In fact, patients with DM have been reported to have a 2- to 5-fold higher incidence of major adverse cardiovascular events (MACE) than those without DM (1,2). Recent registry data have also demonstrated that patients with DM assessed by coronary computed tomography angiography (CTA) have a higher prevalence, extent, and severity of CAD (3); however, there are only limited data evaluating the natural history of the diabetic atherosclerotic process

Intravascular ultrasound (IVUS) has helped to elucidate the natural history and pathophysiology of coronary atherosclerosis in patients with DM (4-6); however, these studies only enrolled a small number of patients, and IVUS is notably both invasive and costly, thereby limiting its use in a typically higher-risk population. Coronary CTA not only allows for noninvasive assessment of luminal stenosis but also enables evaluation of plaque characteristics and features (7,8). Therefore, this study aimed to evaluate the characteristics of plaque progression (PP) in patients with DM, as well as changes in coronary atherosclerotic plaque morphology and composition as measured by serial coronary CTA in patients with DM and to compare these with matched nondiabetic subjects. We also sought to determine clinical predictors of PP among patients with DM.

## METHODS

**STUDY DESIGN AND POPULATION.** The PARADIGM (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging) trial is an international, multicenter, retrospective, observational registry designed to identify serial changes in coronary atherosclerotic plaque features over time. The study design of the registry has been described in

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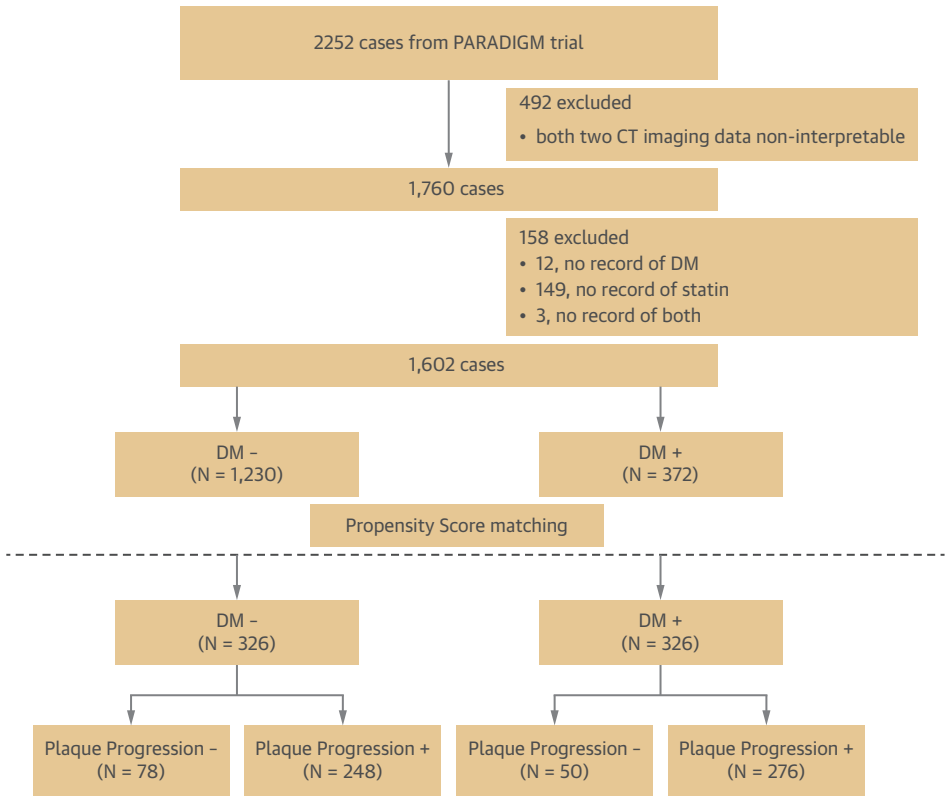
**FIGURE 1** Flow Chart of the Study Population




CT = computed tomography; DM = diabetes mellitus; PARADIGM = Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging.

detail previously (9). The study population includes 2,252 adults who underwent serial coronary CTA over a period of at least 24 months at 13 cardiovascular centers. Of the initial 2,252 patients, a total of 1,602 were included in the present study owing to exclusion of patients with coronary CTAs of inadequate image quality for quantitative plaque analysis (n = 492) or lack of available information on diabetic status or statin use (n = 158). Of the 2,252 baseline coronary CTA DICOM (Digital Imaging and Communications in Medicine) images, 492 scans were noninterpretable by 0.5-mm cross-sectional analysis because of poor image quality on the basis of Society of Cardiovascular Computed Tomography guidelines (10,11). Among these 492 patients, follow-up coronary CTA scans were also noninterpretable in 385 patients. A total of 372 subjects with DM were identified. Among the total cohort, 652 patients with 1,654 lesions were selected by a propensity score-matching technique to compare coronary plaques of those with DM to those without on a per-person and a per-lesion basis (**Figure 1**). DM was defined as treatment with oral hypoglycemic agents or insulin, or fasting glucose ≥126 mg/dl. Institutional review boards approved this study at each site.

**CORONARY CTA DATA MEASUREMENTS AND ANALYSIS.** Anonymized coronary CTA image datasets with clinical information of patients were transferred to the PARADIGM core laboratory (Severance Hospital, Seoul, South Korea), where a modified 17-segment American Heart Association model for coronary segment classification was used (10,11). Quantitative data at baseline and follow-up coronary CTAs were measured and analyzed by 9 independent level III-experienced readers masked to clinical results, using semiautomated plaque analysis software (QAngioCT Research Edition v2.1.9.1, Medis Medical Imaging Systems, Leiden, the Netherlands) (12). Previous studies demonstrated excellent intraobserver, interobserver, and interscan reproducibility in plaque

**TABLE 1 Baseline Characteristics**

| | Total Cohort (N = 1,602) | | | Matched Cohorts (N = 652) | | |
|---|---|---|---|---|---|---|
| | No DM (N = 1,230) | DM (N = 372) | p Value | No DM (N = 326) | DM (N = 326) | p Value |
| Age, yrs | 60 ± 9 | 62 ± 8 | 0.001 | 63 ± 9 | 62 ± 8 | 0.420 |
| Male | 736 (59.8) | 226 (60.8) | 0.752 | 183 (56.1) | 189 (58.0) | 0.635 |
| Body mass index, kg/m$^2$ | 25.3 ± 3.3 | 25.4 ± 3.4 | 0.615 | 24.8 ± 3.3 | 25.1 ± 3.1 | 0.257 |
| Hypertension | 620 (50.5) | 258 (69.4) | <0.001 | 213 (65.3) | 219 (67.2) | 0.619 |
| Hyperlipidemia | 499 (40.8) | 166 (44.6) | 0.194 | 137 (42.0) | 132 (40.5) | 0.691 |
| Current smoker | 198 (16.2) | 75 (20.2) | 0.07 | 67 (20.6) | 69 (21.2) | 0.847 |
| Ethnicity | | | <0.001 | | | <0.001 |
| African | 3 (0.2) | 3 (0.8) | | 0 | 0 | |
| Caucasian | 357 (29.0) | 43 (11.6) | | 60 (18.4) | 21 (6.4) | |
| Asian | 817 (66.4) | 315 (84.7) | | 265 (81.3) | 304 (93.3) | |
| Latin American | 53 (4.3) | 11 (3.0) | | 1 (0.3) | 1 (0.3) | |
| Clinical symptoms | | | | | | |
| Asymptomatic | 241 (19.7) | 57 (15.4) | 0.062 | 52 (16.0) | 32 (9.8) | 0.019 |
| Shortness of breath | 100 (8.2) | 28 (7.5) | 0.702 | 20 (6.1) | 28 (8.6) | 0.230 |
| Atypical chest pain | 801 (65.4) | 253 (68.2) | 0.317 | 231 (70.9) | 242 (74.2) | 0.334 |
| Noncardiac chest pain | 107 (8.7) | 35 (9.4) | 0.679 | 28 (8.6) | 33 (10.1) | 0.501 |
| Typical chest pain | 58 (4.7) | 26 (7.0) | 0.086 | 11 (3.4) | 19 (5.8) | 0.135 |
| Medications at baseline | | | | | | |
| Aspirin | 523 (43.1) | 220 (59.3) | <0.001 | 204 (62.6) | 196 (60.1) | 0.520 |
| Beta-blocker | 386 (31.9) | 140 (37.7) | 0.037 | 125 (38.3) | 124 (38.0) | 0.936 |
| ACE inhibitor/ARB | 337 (27.4) | 166 (44.6) | <0.001 | 127 (42.0) | 146 (44.8) | 0.477 |
| Statin | 540 (45.0) | 205 (56.3) | <0.001 | 177 (54.3) | 178 (54.6) | 0.937 |
| Laboratory findings at baseline coronary CTA | | | | | | |
| LDL cholesterol, mg/dl | 117.2 ± 34.7 | 101.1 ± 34.0 | <0.001 | 112.0 ± 36.7 | 100.8 ± 33.8 | <0.001 |
| $HbA_{1c}$, % | 5.7 ± 0.4 | 7.5 ± 1.3 | <0.001 | 5.7 ± 0.3 | 7.4 ± 1.3 | <0.001 |
| Laboratory findings at follow-up coronary CTA | | | | | | |
| LDL cholesterol, mg/dl | 102.2 ± 33.1 | 87.2 ± 28.8 | <0.001 | 96.8 ± 30.1 | 87.3 ± 29.2 | <0.001 |
| $HbA_{1c}$, % | 6.0 ± 1.9 | 7.2 ± 1.2 | <0.001 | 6.3 ± 3.5 | 7.2 ± 1.1 | 0.001 |

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CTA = computed tomography angiography; DM = diabetes mellitus; $HbA_{1c}$ = hemoglobin $A_{1c}$; LDL = low-density lipoprotein.

analysis of coronary CTA using a semiautomated plaque analysis software.

**PLAQUE ASSESSMENT.** Quantitative parameters related to coronary artery plaque morphology and composition and high-risk plaque (HRP) features at baseline and follow-up coronary CTA were measured for assessment and comparison of patients with (DM+) and without (DM−) DM. Parameters included lesion length, vessel volume, lumen volume, plaque volume (PV), mean plaque burden, fibrous volume, fibro-fatty volume, necrotic core volume (NCV), and dense calcium volume in per-person and per-lesion analyses. Lesion length was calculated semi-automatically as the distance between the proximal and distal ends of the coronary lesion. Mean plaque burden was defined as mean value for all plaque burden measurements over the entire length of the segment and reported as a percentage. Fixed Hounsfield unit (HU) cutoff values were used, including −30 to 75 HU for NCV, 76 to 130 HU for fibro-fatty volume, 131 to 350 HU for fibrous volume, and >351 for dense calcium volume (13). HRP parameters included low-attenuation plaque (LAP), spotty calcification (SC), and positive remodeling (PR) between those with and without DM. LAP was defined if a pixel with HU ≤30 existed in the lesion (14). SC was defined as a small (3 mm), dense (>130 HU) plaque component surrounded by noncalcified plaque tissue (15). A remodeling index was defined as maximal lesion vessel area divided by proximal reference vessel area. A remodeling index threshold of ≥1.1 was suggested as PR (15).

**LONGITUDINAL ANALYSIS OF PLAQUE FEATURES.** Differences and percent changes in parameters measured from baseline and follow-up coronary CTA were used for longitudinal analysis of coronary artery plaque morphology and composition (16). The difference in parameters between baseline and

**TABLE 2 Demographics of Patients With DM According to PP**

| | Total DM Patients (N = 326) | | |
|---|---|---|---|
| | No PP (N = 50) | PP (N = 276) | p Value |
| Age, yrs | 60.4 ± 8.0 | 62.9 ± 8.5 | 0.051 |
| Male | 18 (36.0) | 171 (62.0) | 0.001 |
| Body mass index, kg/m$^2$ | 25.2 ± 3.1 | 25.1 ± 3.1 | 0.864 |
| Hypertension | 31 (62.0) | 188 (68.1) | 0.397 |
| Hyperlipidemia | 16 (32.0) | 116 (42.0) | 0.184 |
| Current smoker | 5 (10.0) | 64 (23.2) | 0.036 |
| Medications | | | |
| Aspirin | 29 (58.0) | 167 (60.5) | 0.739 |
| Beta-blocker | 18 (36.0) | 106 (38.4) | 0.747 |
| ACE inhibitor/ARB | 18 (36.0) | 128 (46.4) | 0.175 |
| Statin | 23 (46.0) | 155 (56.2) | 0.184 |
| Laboratory findings at baseline CT | | | |
| LDL cholesterol, mg/dl | 107.1 ± 35.7 | 99.6 ± 33.4 | 0.151 |
| $HbA_{1c}$, % | 7.3 ± 1.4 | 7.4 ± 1.2 | 0.678 |
| Laboratory findings at follow-up CT | | | |
| LDL cholesterol, mg/dl | 91.1 ± 27.4 | 86.6 ± 29.5 | 0.322 |
| $HbA_{1c}$, % | 6.9 ± 0.7 | 7.3 ± 1.2 | 0.042 |

Values are mean ± SD or n (%).

CT = computed tomography; HDL = high-density lipoprotein; PP = plaque progression; other abbreviations as in Table 1.

follow-up coronary CTA was defined and calculated as follows:

Value of parameter at follow-up coronary CTA − value of parameter at baseline coronary CTA

The percent change in parameters was defined and calculated as follows:

$$= \frac{\text{Value of Parameter at FU coronary CTA} - \text{Value of Parameter at Baseline coronary CTA}}{\text{Value of parameter at Baseline coronary CTA}} \times 100$$

PP was defined as follows: (PV at follow-up coronary CTA − PV at baseline coronary CTA) > 0.

**STUDY ENDPOINTS.** Study endpoints examined the frequency, extent, and patterns of PP among those with DM: 1) changes of plaque features and independent risk factors for PP between nonmatched cohorts with and without DM; 2) relative change of coronary artery PV and composition between matched patients with and without DM during follow-up; and 3) changes in atherosclerosis plaque features between diabetic patients with and without PP (also examined to determine predictors of PP in those with DM).

Secondary endpoints were composites of MACE such as revascularization by percutaneous coronary intervention and coronary artery bypass graft, myocardial infarction, and all-cause mortality (Online Table 2).

**STATISTICAL ANALYSIS.** Previous studies demonstrated excellent intraobserver and interobserver reproducibility in coronary CTA imaging analysis protocol and methodology of the core laboratory, validated against IVUS as a gold standard (17,18). Continuous variables were expressed as mean ± SD. Variables were compared with chi-square test for categorical variables and independent sample Student's *t*-test for continuous variables. If dependent variables were not normally distributed, the Mann-Whitney *U* test was used to compare differences between 2 independent groups. Paired Student's *t*-test was performed for paired continuous variables, and the McNemar test was performed for paired categorical variables. Multivariate logistic regression analysis was performed to detect independent risk factors for PP in all patients before matching and in patients with DM. Variables for univariate analysis in nonmatched cohorts were age; DM; hypertension; current smoking; pre-study use of aspirin, beta blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, or statin treatment; and low-density lipoprotein (LDL), glycosylated hemoglobin ($HbA_{1c}$), PV, and mean plaque burden at baseline. Variables for univariate analysis in patients with DM were age, male gender, current smoker, LDL level, $HbA_{1c}$, PV, and mean plaque burden at baseline computed tomography. To reduce the impact of differences in baseline characteristics between the 2 patient groups on the study endpoints, we adjusted for confounding factors using propensity score matching. Estimated propensity scores were used to match patients between DM and non-DM. In this study, propensity scores were calculated for each of the patients using a logistic regression model that included age, sex, hypertension, body mass index, current smoking, hyperlipidemia, and medications used. The calibration ability and discrimination of the propensity score model were assessed by means of the Hosmer-Lemeshow goodness-of-fit test and Harrell's C-index. All statistical analysis was performed by SPSS version 22.0 (SPSS, Inc., Chicago, Illinois) and R version 2.8.0 (R Development Core Team, Vienna, Austria).

## RESULTS

**BASELINE CHARACTERISTICS.** Baseline characteristics of the entire cohort are shown in Table 1. Patients

**TABLE 3 Plaque Characteristics in Patients With DM According to PP**

| | No PP (N = 50) | PP (N = 276) | p Value |
|---|---|---|---|
| Plaque volume, $mm^3$ | | | |
| Baseline coronary CTA | 84.3 ± 155.4 | 145.9 ± 192.7 | <0.001 |
| Follow-up coronary CTA | 78.0 ± 147.9 | 237.9 ± 260.2 | <0.001 |
| Differences | −6.2 ± 13.7 | 91.9 ± 101.5 | <0.001 |
| % Change | −5.9 ± 12.2 | 43.6 ± 25.2 | <0.001 |
| Fibrous volume, $mm^3$ | | | |
| Baseline coronary CTA | 37.9 ± 71.1 | 62.7 ± 79.2 | 0.040 |
| Follow-up coronary CTA | 28.1 ± 52.5 | 93.6 ± 100.4 | <0.001 |
| Differences | −9.7 ± 24.6 | 30.9 ± 51.4 | <0.001 |
| % Change | −2.9 ± 53.0 | 32.1 ± 160.7 | 0.001 |
| Fibrous fatty volume, $mm^3$ | | | |
| Baseline coronary CTA | 18.6 ± 35.8 | 25.4 ± 37.5 | 0.235 |
| Follow-up coronary CTA | 9.5 ± 17.2 | 31.3 ± 48.9 | <0.001 |
| Differences | −9.1 ± 23.1 | 5.8 ± 32.8 | 0.002 |
| % Change | −19.5 ± 37.7 | 41.0 ± 190.0 | <0.001 |
| Necrotic core volume, $mm^3$ | | | |
| Baseline coronary CTA | 3.3 ± 7.1 | 2.9 ± 7.6 | 0.042 |
| Follow-up coronary CTA | 2.2 ± 7.8 | 3.7 ± 9.3 | <0.001 |
| Differences | −1.0 ± 6.4 | 0.7 ± 6.5 | 0.012 |
| % Change | −44.4 ± 29.5 | 24.6 ± 97.3 | 0.026 |
| Dense calcium volume, $mm^3$ | | | |
| Baseline coronary CTA | 24.3 ± 58.2 | 54.8 ± 110.8 | 0.059 |
| Follow-up coronary CTA | 37.9 ± 91.8 | 109.3 ± 161.3 | <0.001 |
| Differences | 13.6 ± 36.9 | 54.5 ± 73.7 | <0.001 |
| % Change | 154.8 ± 761.2 | 132.1 ± 1,057.1 | 0.437 |

Values are mean ± SD.
Abbreviations as in Tables 1 and 2.

**TABLE 4 Independent Risk Factors for Plaque Progression in the Nonmatched Cohort (N = 1,602) and in Patients With DM (N = 326) on Multivariate Logistic Regression Analysis**

| | OR | 95% CI | p Value |
|---|---|---|---|
| Nonmatched cohort | | | |
| Age ≥55 yrs | 1.418 | 1.080–1.862 | 0.012 |
| DM | 1.526 | 1.100–2.118 | 0.011 |
| Hypertension | 1.302 | 1.011–1.677 | 0.041 |
| Statin treatment at baseline | 0.716 | 0.555–0.923 | 0.010 |
| Mean plaque burden ≥75% at baseline | 3.151 | 1.988–4.995 | <0.001 |
| DM patients | | | |
| Male | 1.485 | 1.003–2.199 | 0.048 |
| Mean plaque burden ≥75% at baseline | 3.121 | 1.701–5.725 | <0.001 |

Variables for univariate analysis in nonmatched cohorts were age, DM, hypertension, current smoking, medication use (aspirin, beta-blocker, ACE inhibitor/ARB, statin) at baseline, LDL at baseline, $HbA_{1c}$ at baseline, plaque volume at baseline, and mean plaque burden at baseline. Variables for univariate analysis in patients with DM were age, male, current smoker, LDL level, $HbA_{1c}$, plaque volume at baseline coronary CTA, and mean plaque burden at baseline coronary CTA.
CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

with DM were older (62.2 ± 8.7 years vs. 60.4 ± 9.4 years; p = 0.001) and had a higher frequency of hypertension (69.4% vs. 50.5%; p ≤ 0.001), a higher rate of medication use at baseline, and a higher level of $HbA_{1c}$ (7.5 ± 1.3% vs. 5.7 ± 0.4%; p ≤ 0.001) than those without DM. The majority of patients in both groups were Asian (66.4% in DM− and 84.7% in DM+; p ≤ 0.001). There were no differences observed in mean coronary CTA scan interval between baseline and follow-up coronary CTA between the 2 groups (3.9 ± 1.6 years in DM− and 3.7 ± 1.4 years in DM+; p = 0.102). After risk adjustment by propensity score matching, baseline characteristics of age, sex, CAD risk factors, and medication use between those with and without DM became similar (Table 1). There was a difference in prevalence of asymptomatic individuals (16% in DM− and 9.8% in DM+; p = 0.019). Laboratory findings showed that LDL levels were lower in those with DM at the time of baseline coronary CTA (112.0 ± 36.7 mg/dl in DM- and 100.8 ± 33.8 mg/dl in DM+; p ≤ 0.001) and follow-up coronary CTA (96.8 ± 30.1 mg/dl in DM- and 87.3 ± 29.2 mg/dl in DM+; p ≤ 0.001). Baseline coronary CTA results showed that there were no differences in frequencies of nonobstructive stenosis (77.2% in DM− and 75.5% in DM+; p = 0.495) and obstructive stenosis (22.2% in DM− and 23.4% in DM+; p = 0.495) between the 2 groups.

**RELATIONSHIP BETWEEN DM AND PATTERNS AND EXTENT OF PP WITHIN THE ENTIRE COHORT.** PP was significantly more common in diabetics than nondiabetics (84.6% in DM+ and 76.1% in DM−; p = 0.006; mean 67.8 $mm^3$; 95% confidence interval [CI]: 60.5 to 76.9 $mm^3$). Demographic data among those with DM according to presence (PP+) and absence (PP−) of PP are presented in Table 2. There were significant differences in male sex (36.0% in PP− and 62.0% in PP+; p = 0.001), current smoking (10.0% in PP− and 23.2% in PP+; p = 0.036), and $HbA_{1c}$ (6.9 ± 0.7% in PP− and 7.3 ± 1.2% in PP+; p = 0.042) at follow-up coronary CTA. Table 3 displays plaque characteristics in patients with PP during follow-up. The percent changes in PV (−5.9 ± 12.2% in PP− and 43.6 ± 25.2% in PP+; p < 0.001), fibrous volume (−2.9 ± 53.0% in PP− and 32.1 ± 160.7% in PP+; p = 0.001), fibro-fatty volume (−19.5 ± 37.7% in PP− and 41.0 ± 190.0% in PP+; p < 0.001), NCV (−44.4 ± 29.5% in PP− and 24.6 ± 97.3% in PP+; p = 0.026) were greater in DM+ patients with PP than in those without PP. In multivariate analysis, independent risk factors for PP in the total cohort were age ≥55 years (OR: 1.418, 95% CI: 1.080 to 1.862; p = 0.012), DM (OR: 1.526; 95% CI: 1.100 to 2.118; p = 0.011), hypertension (OR: 1.302; 95% CI: 1.011 to 1.677; p = 0.041), statin treatment at baseline (OR: 0.716; 95% CI: 0.555 to 0.923; p = 0.010), and mean plaque burden at baseline ≥75% (OR: 3.151; 95% CI: 1.988 to 4.995; p < 0.001) (Table 4).

Independent risk factors for PP in patients with DM were male sex (OR: 1.485; 95% CI: 1.003 to 2.199; p = 0.048) and mean baseline plaque burden ≥75% (OR: 3.121; 95% CI: 1.701 to 5.725; p < 0.001) (Table 4).

**DIFFERENCES IN CHANGES IN MORPHOLOGY, COMPOSITION, AND PROGRESSION BETWEEN MATCHED PATIENTS WITH VERSUS WITHOUT DM.** Changes in plaque morphology and composition on a per-person analysis in patients with and without DM are shown in Table 5. Those with DM displayed greater percent changes in PV than those without DM (30.3 ± 36.9% in DM- and 36.0 ± 29.7% in DM+; p = 0.032). Among compositional changes, only percent changes in NCV in patients with DM were greater than in those without DM (−7.0 ± 35.8% in DM- and 21.5 ± 90.5% in DM+; p = 0.007) during follow-up (Online Table 1).

**HRP FEATURES IN MATCHED PATIENTS WITH VERSUS WITHOUT DM.** At baseline, there was no significant difference in the proportion of patients with and without DM who had LAP (Figure 2A), whereas at follow-up coronary CTA, the percentage of patients with LAP was significantly greater in those with DM than in the patients without DM (8.7% in DM- and 11.9% in DM+; p = 0.029). In patients without DM, the percentage of LAP was decreased at follow-up, but this was not significant (9.3% at baseline coronary CTA and 8.7% at follow-up coronary CTA; p = 0.575). In patients with DM, the percentage of LAP was increased at follow-up but was also nonsignificant (11.6% at baseline coronary CTA and 11.9% at follow-up coronary CTA; p = 0.784). In analysis of the frequency of SC, there were significant differences between the 2 groups at baseline coronary CTA (15.2% in DM- and 9.1% in DM+; p < 0.001). However, at follow-up, there were no differences between the 2 groups (14.5% in DM- and 12.3% in DM+; p = 0.191). At follow-up, the percentage of patients with DM who had SC was significantly increased (9.1% at baseline coronary CTA and 12.3% at follow-up coronary CTA; p = 0.020), but no change was observed in patients without DM (15.2% at baseline coronary CTA and 14.5% at follow-up coronary CTA; p = 0.511) (Figure 2B). Regarding analysis of the frequency of PR, there were no differences between the 2 groups at baseline and follow-up coronary CTA; however, at follow-up, the percentage of patients with PR was increased both in patients with DM (72.7% at baseline coronary CTA and 79.2% at follow-up coronary CTA; p < 0.001) and in those without DM (73.3% at baseline coronary CTA and 79.0% at follow-up coronary CTA; p = 0.001) (Figure 2C).

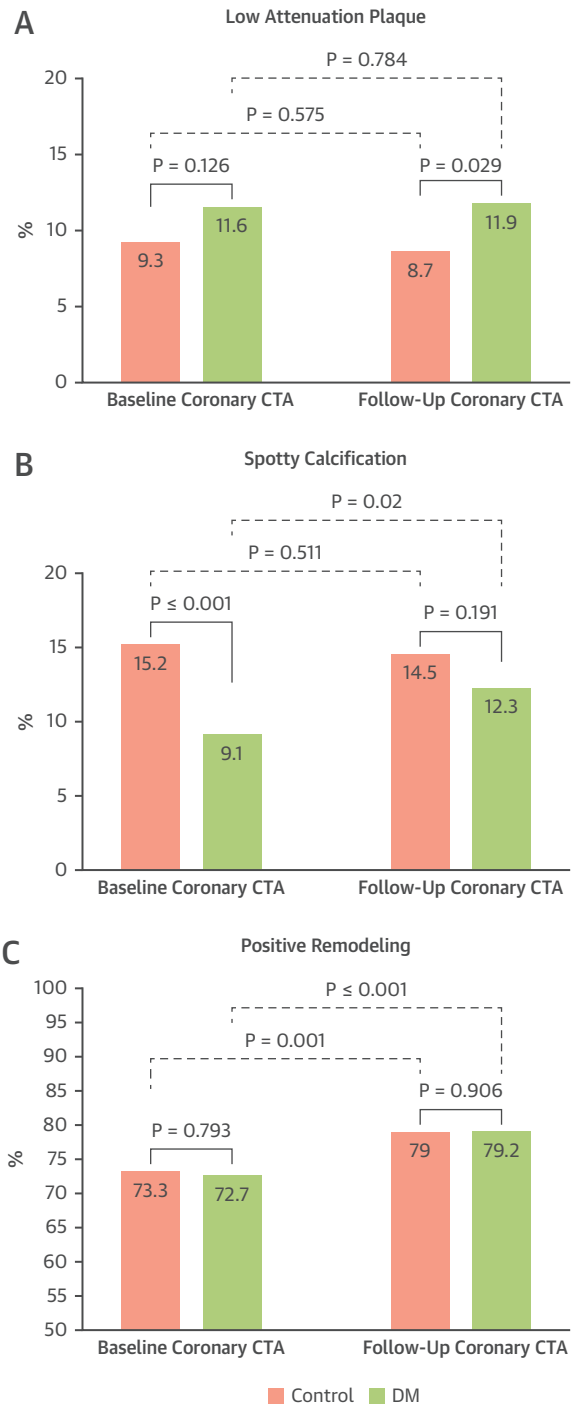
**TABLE 5 Changes of Plaque Morphology and Composition on Per-Person Analysis in Matched Patients With and Without DM**

| | Without DM (N = 326) | With DM (N = 326) | p Value |
|---|---|---|---|
| Morphological changes | | | |
| Lesion length, mm | | | |
| Baseline coronary CTA | 353.6 ± 143.7 | 347.3 ± 139.7 | 0.571 |
| Follow-up coronary CTA | 362.5 ± 141.5 | 353.5 ± 136.6 | 0.410 |
| Differences | 8.9 ± 33.4 | 6.2 ± 30.1 | 0.279 |
| % Change | 4.4 ± 20.8 | 4.3 ± 32.0 | 0.969 |
| Vessel volume, $mm^3$ | 2,024.7 ± 1,031.7 | 1,965.2 ± 1,038.1 | 0.463 |
| Baseline coronary CTA | | | |
| Follow-up coronary CTA | 2,080.4 ± 1,025.4 | 2,036.8 ± 1,057.6 | 0.594 |
| Differences | 55.6 ± 309.0 | 71.6 ± 324.8 | 0.519 |
| % Change | 4.7 ± 21.0 | 7.2 ± 39.9 | 0.328 |
| Lumen volume, $mm^3$ | 1,900.9 ± 1,001.0 | 1,828.6 ± 994.6 | 0.355 |
| Baseline coronary CTA | | | |
| Follow-up coronary CTA | 1,898.0 ± 974.6 | 1,823.4 ± 986.9 | 0.332 |
| Differences | -2.9 ± 303.7 | -5.1 ± 301.6 | 0.923 |
| % Change | -1.7 ± 21.2 | -2.2 ± 35.4 | 0.817 |
| Plaque volume, $mm^3$ | 123.7 ± 199.0 | 136.5 ± 188.5 | 0.401 |
| Baseline coronary CTA | | | |
| Follow-up coronary CTA | 182.5 ± 276.8 | 213.3 ± 252.8 | 0.138 |
| Differences | 58.7 ± 104.6 | 76.8 ± 100.0 | 0.024 |
| % Change | 30.3 ± 36.9 | 36.0 ± 29.7 | 0.032 |
| Compositional changes | | | |
| Fibrous volume, $mm^3$ | 53.5 ± 81.4 | 58.9 ± 78.4 | 0.386 |
| Baseline coronary CTA | | | |
| Follow-up coronary CTA | 69.5 ± 107.1 | 83.6 ± 97.5 | 0.081 |
| Differences | 16.0 ± 52.6 | 24.6 ± 50.4 | 0.034 |
| % Change | 21.1 ± 77.7 | 27.1 ± 148.3 | 0.522 |
| Fibrous fatty volume, $mm^3$ | 18.9 ± 37.5 | 24.4 ± 37.2 | 0.078 |
| Baseline coronary CTA | | | |
| Follow-up coronary CTA | 19.4 ± 34.5 | 27.9 ± 46.2 | 0.006 |
| Differences | 0.5 ± 24.3 | 3.5 ± 31.9 | 0.066 |
| % Change | 25.7 ± 152.0 | 34.4 ± 175.5 | 0.500 |
| Necrotic core volume, $mm^3$ | 2.2 ± 6.3 | 3.0 ± 7.5 | 0.178 |
| Baseline coronary CTA | | | |
| Follow-up coronary CTA | 2.0 ± 5.8 | 3.4 ± 9.1 | 0.017 |
| Differences | -0.2 ± 5.1 | 0.4 ± 6.5 | 0.129 |
| % Change | -7.0 ± 35.8 | 21.5 ± 90.5 | 0.007 |
| Dense calcium volume, $mm^3$ | 48.6 ± 114.3 | 50.1 ± 105.0 | 0.857 |
| Baseline coronary CTA | | | |
| Follow-up coronary CTA | 92.0 ± 177.4 | 98.4 ± 154.7 | 0.626 |
| Differences | 43.4 ± 81.1 | 48.2 ± 70.8 | 0.421 |
| % Change | 74.2 ± 450.5 | 114.2 ± 973.7 | 0.501 |

Values are mean ± SD.
Abbreviations as in Table 1.

**RELATIONSHIP BETWEEN $HbA_{1c}$ AND PP WITHIN THE MATCHED POPULATION WITH VERSUS WITHOUT DM.** At baseline coronary CTA, there were no differences in $HbA_{1c}$ between the 2 groups (7.3 ± 1.4% in PP− and 7.4 ± 1.2% in PP+; p = 0.678). However, $HbA_{1c}$ levels at follow-up coronary CTA were higher in the PP group (6.9 ± 0.7% vs. 7.3 ± 1.2%; p = 0.042) (Figure 3).

**FIGURE 2** Change in High-Risk Plaque Features by Per-Lesion Analysis




Changes in low-attenuation plaque **(A)**, spotty calcification **(B)**, and positive remodeling **(C)**. CTA = computed tomography angiography; other abbreviations as in Figure 1.

**MACE WITHIN MATCHED POPULATION OF DM VERSUS NO DM AND BETWEEN PATIENTS WITH ADVERSE PLAQUE CHANGES (PP AND NEW HIGH-RISK FEATURES) AND THOSE WITHOUT BEFORE AND AFTER PROPENSITY SCORE MATCHING.** The incidence of composites of MACE was not different between the 2 groups (19.9% in DM- and 21.7% in DM+; p = 0.121) (Table 6). No relationship between MACE and adverse plaque changes or PP was found in patients with or without DM or after propensity score matching (p = NS for all) (Online Table 2).

## DISCUSSION

In the current study, through the analysis of a large cohort of diabetic subjects undergoing serial coronary CTA, we demonstrated that patients with DM are highly likely to experience PP, with baseline percentile of PV and male sex being predictors of progression. In addition, through propensity matching with nondiabetic subjects, we found that those with DM have more quantitative PP and significantly greater increases in LAP and SC. Notably, these findings have all been shown to be associated with an increased risk of incident MACE and therefore could provide potential links to the observed increased MACE rate in people with DM (3). Moreover, good glycemic control, as reflected by a reduction of serum $HbA_{1c}$ level over time, was predictive of DM without PP during follow-up coronary CTA and thus highlights the need for good DM control in combating diabetic CAD.

**CHARACTERISTICS AND MECHANISM OF PP IN DM.** From previous cross-sectional population studies and large computed tomography registries such as CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes), it is well established that people with DM have a higher prevalence, extent, and severity of CAD, as well as a higher risk of mortality than those without DM (3). However, these studies were not longitudinal in nature and thus are limited in their ability to shed light on the drivers of risk beyond baseline plaque characteristics and stenosis severity. In the current study, overall PV and NCV were significantly increased by quantitative measurements of serial coronary CTA in those with versus without DM. Our findings are concordant with other imaging and histopathological studies that have demonstrated that coronary atherosclerosis plaque of patients with DM is associated with a greater macrophage infiltration and large necrotic core (1,19–21). IVUS studies also have shown that abnormal glucose

regulation is associated with increased lipid-rich plaque and increased necrotic core of culprit lesion in DM patients compared with nondiabetic subjects (5,22). There are a number of potential mechanisms for this progression of atherosclerosis in patients with DM: 1) hyperglycemia and its glycation end-products are known to result in endothelial dysfunction and endothelial injury (6,23); 2) the milieu of chronic hyperglycemia can be related to elevated systemic inflammation and oxidative stress, and this will have an impact on accelerated atherosclerosis; and 3) hyperglycemia is known to potentiate foam cell generation by enhancing macrophage entry into the vascular wall and inhibiting cholesterol efflux (24).

**HRP FEATURES IN DM.** HRP features such as SC, LAP, and PR measured by coronary CTA have been shown to be independent risk factors of adverse cardiac events (8,25,26). Our analysis showed a greater rate of development of LAP and SC in patients with DM than in matched DM− subjects. Importantly, our study population consisted of low- to intermediate-risk subjects with low LDL levels and commonly nonobstructive CAD at baseline coronary CTA. The acceleration of PV with necrotic core and increased HRP features in DM+ patients within our population might provide a background and pathophysiological link as to why those with DM have worse prognosis than those without DM over time, which has been shown in several studies, such as the CONFIRM registry.

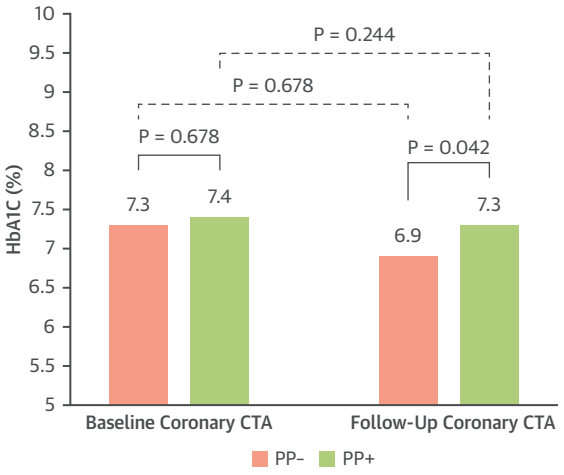
One study reported that among asymptomatic patients with type 1 or type 2 DM, use of coronary CTA to screen for CAD did not reduce the composite rate of MACE, including all-cause mortality, and insisted that coronary CTA screening was not supported for this population (27). However, this study did not perform detailed plaque analysis and did not suggest what kind of adverse plaque would progress in the future or why patients with DM will have more adverse outcomes in the future, although our study also showed no clinical differences in MACE.

**POTENTIAL INSIGHT INTO TREATMENT STRATEGIES TO REDUCE PP IN DM.** The change in LDL was predictive of the degree and extent of atherosclerosis PP in those with DM but not in those without DM. In our analysis, mean LDL levels in patients with DM decreased from 100.8 mg/dl at baseline coronary CTA to 87.3 mg/dl at follow-up coronary CTA, but this reduction in LDL levels appears insufficient to reduce PP and stop the development of HRP with necrotic core and HRP features, because these adverse plaque features progressed nonetheless. Current American College of Cardiology/American Heart Association guidelines recommend LDL levels below 70 mg/dl for patients with DM and CAD because they are considered a high-risk group (28). Our data support these recommendations, which suggests that strategies to decrease LDL levels below 70 mg/dl as a treatment target could be necessary to help reduce PP.

As well, our study showed that tight glycemic control with lower $HbA_{1c}$ levels in DM+ patients was associated with a greater likelihood of plaque stabilization. Although further studies are needed to confirm our findings, these data are potentially quite informative not only to guide treatment strategy but also perhaps as a tool to assist with patient adherence to lifestyle modification.

**STUDY LIMITATIONS.** There are limitations of our study. First, the PARADIGM trial was designed in a

**FIGURE 3** Changes in $HbA_{1c}$ (%) in Patients With Versus Without PP




At baseline coronary CTA, there were no differences between patients without (PP−) and those with (PP+) plaque progression (PP) ($p = 0.678$). However, a significant difference in $HbA_{1c}$ levels between groups was noted at follow-up ($p = 0.042$). CTA = computed tomography angiography; $HbA_{1c}$ = hemoglobin $A_{1c}$.

**TABLE 6** Major Adverse Cardiac Events Between Groups From Baseline to Follow-Up Coronary CTA

| | No DM (N = 326) | DM (N = 326) | p Value |
|---|---|---|---|
| Follow-up duration after second coronary CTA, yrs | 3.5 ± 2.4 | 3.8 ± 2.3 | 0.112 |
| Major adverse cardiac events | | | 0.121 |
| Percutaneous coronary intervention | 50 (17.6) | 65 (21.0) | |
| Coronary artery bypass graft | 6 (2.1) | 2 (0.6) | |
| Myocardial infarction | 1 (0.4) | 2 (0.6) | |
| All-cause mortality | 8 (2.8) | 2 (0.6) | |
| Composites of major adverse cardiac events | 65 (19.9) | 71 (21.7) | 0.121 |

Values are mean ± SD or n (%).
Abbreviations as in Table 1.

retrospective fashion. We performed propensity score matching to overcome this; although not perfect, this could identify some characteristics of coronary atherosclerotic plaques in patients with DM. Although we performed propensity score matching to adjust for confounding factors, there could be unmeasured confounders such as changes in preventive therapy and lifestyle changes after initial coronary CTA (29). Although LDL and $HbA_{1c}$ at follow-up were analyzed, we would acknowledge that a detailed accounting of medication and lifestyle changes after the initial coronary CTA was not performed (including blood pressure control in follow-up). Thus, the impact of medication changes and lifestyle therapies on serial plaque measures requires further study. Second, mainly low-risk patients with mild and moderate CAD and low baseline LDL levels were enrolled. This, in addition to the relatively small cohort size and short-term follow-up, possibly explains why we did not observe differences in the frequency of MACE between the 2 groups, owing to a lack of power. Third, our cohort largely comprised subjects of East Asian ethnicity, and therefore, for example, body mass index was very low ($\approx$25 kg/m$^2$); as such, the generalizability of these findings is not certain. Fourth, there are known limitations in coronary CTA, including the following: 1) coronary CTA voxel size was greater than plaque pathologies being measured, which led to some uncertainty in measurements; 2) semiautomated border detection historically relies on varying HU cutoffs across the literature by fixed and adaptive threshold strategies; 3) PV measurements vary across computed tomography vendors, particularly in an era of low radiation dosing (30); 4) there is limited agreement for various plaque features, including low kappa for SC; and 5) coronary CTA has limitations for quantitative plaque analysis; however, although IVUS and optical coherence tomography are more accurate for plaque quantification, their invasive approach limits their use for serial observation of plaque, and prior meta-analysis has shown good correlation between coronary CTA and IVUS for PV (31). Fifth, we did not have detailed information on the clinical indications for the second coronary CTA scan, which could be related to potential for selection bias.

## CONCLUSIONS

Patients with DM more commonly had PP and had a significantly greater frequency of adverse plaque characteristics than those without DM. Among subjects with DM, male sex and mean plaque burden >75% at baseline were identified as independent risk factors for PP, whereas tighter glycemic control and lower LDL levels were associated with greater plaque stabilization.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Patients with DM exhibit a higher rate of plaque progression and a greater proportion of adverse plaque progression than those without DM. Interestingly, tighter glycemic control and lower LDL levels are associated with greater plaque stabilization.

**TRANSLATIONAL OUTLOOK:** Our analysis highlights apparent differences in the rate, extent, and pattern of plaque progression in patients with DM versus those without DM. These findings could help explain the increased risk of MACE among people with DM, with these measures potentially serving as endpoints in future trials to test various therapeutic strategies to help mitigate this risk.

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**KEY WORDS** computed tomography, coronary artery disease, diabetes mellitus, plaque, progression

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