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Comparison of Neoatherosclerosis and Neovascularization Between Patients With and Without Diabetes

An Optical Coherence Tomography Study

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ABSTRACT

OBJECTIVES This study aimed to investigate the characteristics of neoatherosclerosis (NA) in patients with diabetes mellitus (DM) after drug-eluting stent (DES) implantation using optical coherence tomography.

BACKGROUND NA is an important substrate for stent failure. In vivo NA characteristics in DM patients have not been investigated.

METHODS A total of 397 patients with 452 DES who underwent follow-up optical coherence tomography examination after DES implantation were enrolled. Characteristics of NA were compared between DM and non-DM patients. Neovascularization was defined as signal-poor holes or tubular structures with a diameter of 50 to 300 μm.

RESULTS A total of 123 DES with NA lesions in 115 patients were identified. The incidence of NA was similar between DM and non-DM patients (29.6% vs. 28.6%; $p = 0.825$). Compared with the non-DM group, neovascularization was more frequently observed in the DM group (55.1% vs. 32.4%; $p = 0.012$). The multivariate logistic model demonstrated that DM (odds ratio: 3.00; 95% confidence interval: 1.31 to 6.81; $p = 0.009$) and follow-up duration (odds ratio: 1.03; 95% confidence interval: 1.02 to 1.05; $p < 0.001$) were the independent predictors for neovascularization in NA lesions. DM patients with glycated hemoglobin ≥7.0% had a higher prevalence of thin-cap fibroatheroma compared with those with glycated hemoglobin <7.0% (40.0% vs. 8.3%; $p = 0.01$).

CONCLUSIONS The incidence of NA was similar between patients with and without DM. Neovascularization in NA lesions was more frequent in those with DM. Poorly controlled DM patients had a higher incidence of thin-cap fibroatheroma, compared with those with well-controlled DM. (J Am Coll Cardiol Intv 2015;8:1044–52)

Emerging evidence suggests in-stent neoatherosclerosis (NA) is an important substrate for both in-stent restenosis and late stent thrombosis (1). Tian et al. (2) assessed the characteristics of neointimal hyperplasia after drug-eluting stent (DES) implantation in patients with diabetes mellitus (DM) by optical coherence tomography (OCT) and found that glycated hemoglobin (A_{1C}) levels in DM patients

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contributed to the development of neointimal hyperplasia and in-stent NA. However, the difference in NA characteristics after DES implantation in patients with and without DM has not been reported. OCT is an emerging intravascular imaging modality with a resolution of 10 to 20 μm. It can characterize microscopic morphological features of atherosclerotic plaques, such as fibrous cap thickness, thin-cap fibroatheroma (TCFA), macrophage accumulations, neovascularization, thrombus, and calcification (3). The present study aimed to investigate characteristics of NA in DM patients after DES implantation using OCT imaging.

ABBREVIATIONS AND ACRONYMS

A_{1C} = glycated hemoglobin
CKD = chronic kidney disease
DES = drug-eluting stent(s)
DM = diabetes mellitus
MGH = Massachusetts General Hospital
NA = neoatherosclerosis
OCT = optical coherence tomography
TCFA = thin-cap fibroatheroma

METHODS

STUDY POPULATION. The Massachusetts General Hospital (MGH) OCT registry is a multicenter registry of patients undergoing OCT of the coronary arteries and includes 20 sites across 6 countries. Any patient who underwent an OCT procedure was eligible for the registry. For the present study, we identified 486 patients with 554 previously implanted DES from the MGH OCT between August 2010 and November 2013. Among these patients, we excluded those with <6 months of follow-up OCT examination (n = 77). Stents with poor OCT image quality (n = 12) were also excluded. A total of 452 DES in 397 patients were included in the final analysis. The presence of lipid-laden neointima or calcification inside of the stents was defined as NA in the present study. Subjects were assigned to the DM group if they were receiving an oral hypoglycemic agent or insulin or if they had a known fasting blood glucose value ≥126 mg/dl or post-prandial 2-h blood glucose value ≥200 mg/dl. NA characteristics were compared between DM and non-DM subjects. Moreover, DM subjects were divided into 2 groups based on A_{1C} level <7.0% or ≥7.0%, and NA characteristics were compared. The study protocol was approved by the institutional review board at each site, and written informed consent was obtained from all patients. The MGH OCT Registry is registered on ClinicalTrials.gov (NCT01110538).

QUANTITATIVE CORONARY ANGIOGRAPHY. Coronary angiograms were analyzed using off-line software (CAAS 5.10.1, Pie Medical Imaging BV, Maastricht, the Netherlands). Diameter stenosis, reference diameter, and minimum lumen diameter were measured. Angiographic restenosis was defined as a diameter stenosis >50% at follow-up angiography.

OCT IMAGE ACQUISITION. The time-domain OCT system (M2/M3 Cardiology Imaging System, LightLab Imaging, Inc., Westford, Massachusetts) or the frequency-domain OCT system (C7-XR OCT Intravascular Imaging System, St. Jude Medical, St. Paul, Minnesota) was used in this study. In the M2/M3 system, an occlusion balloon (Helios, LightLab Imaging) was inflated proximal to the stent at 0.4 to 0.6 atm during image acquisition. The optical probe was automatically pulled back from distal to proximal at a rate of 1.0 to 3.0 mm/s, and saline was continuously infused from the tip of the occlusion balloon. In the C7XR system, a 2.7-F OCT imaging catheter was carefully advanced distal to the stent. The automated pullback was performed at 20 mm/s, while blood was displaced by a short injection of contrast media or Dextran through the guiding catheter (4). All OCT images were stored digitally, deidentified, and submitted to the MGH laboratory for off-line analysis.

OCT IMAGE ANALYSIS. Cross-sectional OCT images were analyzed at 1-mm intervals. For quantitative analysis, stent and luminal cross-sectional areas (CSAs) were measured, and neointimal hyperplasia (NIH) CSA was calculated as: stent CSA − luminal CSA. Mean values were reported in this study. The thickness of neointimal hyperplasia was measured as the distance between the endoluminal surface of the neointima and the strut. An uncovered strut was defined when no material covering a strut was identified. The percentage of uncovered struts in each stented lesion was calculated as: ([number of uncovered struts/total number of struts in all cross sections of the lesion] × 100). For qualitative analysis, a lipid was defined as a diffusely bordered, signal-poor region with rapid signal attenuation. Lipid-laden neointima was defined as a neointima with lipid (5) (**Figure 1**). Calcification was defined as a clearly delineated, signal-poor region with low backscatter. TCFA was defined by lipid-rich neointima with cap thickness ≤65 μm and an angle of lipidic tissue ≥180° (6). Neovascularization was defined as a signal-poor hole or tubular structure with a diameter ≥50 and ≤300 μm that was present on at least 3 consecutive frames (7). Disrupted neointima was a break in the fibrous cap that connected the lumen with the underlying lipid pool (8). Thrombus was a mass protruding into the vessel lumen, discontinuous from the surface of the vessel wall and with a dimension ≥250 μm (9).

OCT images were analyzed at the MGH OCT core laboratory by 2 independent investigators blinded to patient information (L.G., T.S.). All cross-sectional

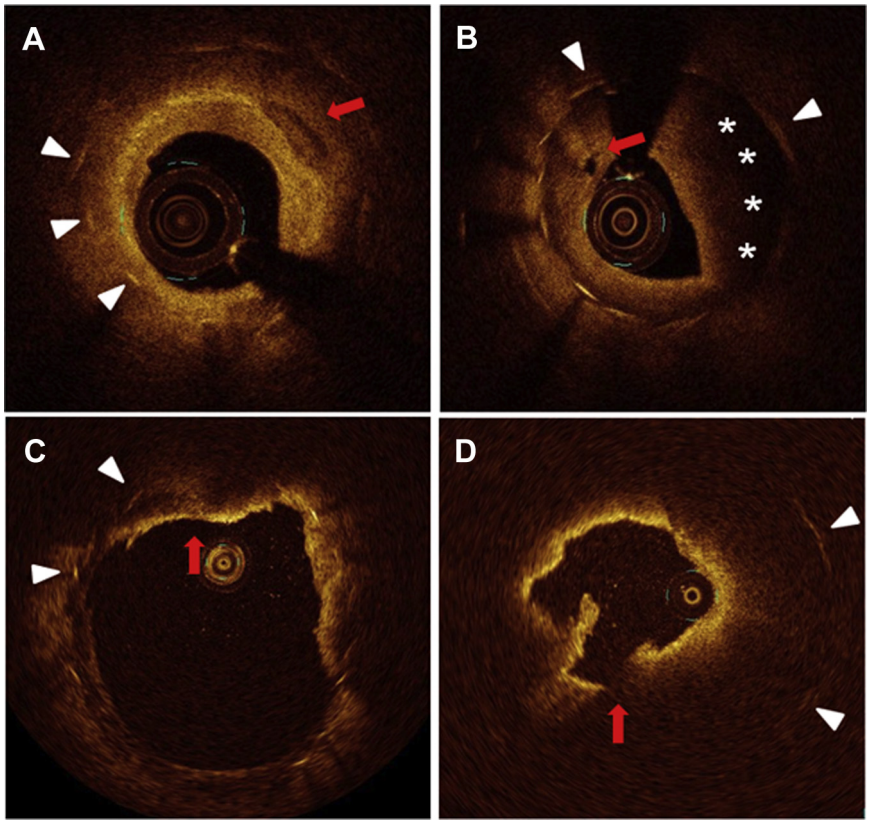
images were initially screened for quality assessment and were excluded from analysis if a side branch occupied >45° of the cross section; if any portion of the stent was out of the screen; or if the image had poor quality caused by artifact, residual blood, or reverberation. When there was discordance between the readers, a consensus reading was obtained from a third independent investigator (R.V.). Examples are shown in Figure 1.

STATISTICAL ANALYSIS. Categorical data were expressed as counts and percentages and compared using a chi-square or Fisher exact test, depending on the distribution of the data. Continuous measurements were expressed as mean ± SD and analyzed with the Student *t* test. Multiple logistic regression analyses were performed to assess the independent predictors for the presence of neovascularization. Multiple regression models included the parameters that showed statistical significance with $p < 0.1$ in the univariate analysis. The Generalized Estimating Equations approach was used to take into account the within-subject correlation due to multiple stents analyzed within a single patient. Interobserver and intraobserver reliabilities were estimated using the κ coefficient for the assessment of neointimal tissue morphology. All statistical analyses were performed with SPSS version 17.0 (SPSS Inc., Chicago, Illinois). A 2-tailed p value <0.05 was considered statistically significant.

RESULTS

CLINICAL CHARACTERISTICS. From a total of 397 patients, we identified 123 DES with NA lesions in 115 patients. There was no significant difference in the

FIGURE 1 Representative Images of Neoatherosclerosis



(A) Calcified neointima is defined as a signal-poor or heterogeneous region with a sharply delineated border **(red arrow)**. **(B)** Neovascularization showing small vesicular or tubular structures with 50- to 300-μm diameter **(red arrow)** differentiated from branch vessels. Lipid-laden neointima shows a diffusely bordered signal-poor region with overlying signal-rich homogeneous band **(white asterisks)**. **(C)** Lipid-laden neointima. **(D)** Intimal rupture **(red arrow)** surrounded by thin-cap fibroatheroma–containing neointima. All **white arrowheads** indicate stent struts.

incidence of NA (29.6% vs. 28.6%; p = 0.825) between DM and non-DM patients. Patient characteristics between the NA and non-NA groups are summarized in Table 1. There was no significant difference in age, sex, prevalence of hypertension, hyperlipidemia, smoking, and diabetes mellitus between the 2 groups. Creatinine level was significantly higher in NA patients than in non-NA patients (1.2 ± 1.5 mg/dl vs. 0.9 ± 0.6 mg/dl; p = 0.006). Chronic kidney disease (CKD) (stages 3 to 5) was significantly more frequent in NA patients compared with non-NA patients (7.8% vs. 2.5%; p = 0.014). Although fasting glucose level was lower in the NA group, A1c was not different between the groups with and without NA. The use of statins, aspirin, and clopidogrel was significantly less frequent in NA patients than in non-NA patients.

The characteristics of 115 patients with NA by DM status are summarized in Table 2. A total of 45 (39.1%) patients had DM and 70 (60.9%) did not have DM. No significant differences were observed in the baseline characteristics between the 2 groups, except for a higher prevalence of CKD in the DM group (15.6% vs. 2.9%; p = 0.013). Medications at follow-up were similar between the 2 groups, except for a lower use of β-blockers in the DM group (40.0% vs. 65.7%; p = 0.007). The DM group consisted of 23 subjects with A_{1C} ≥7.0% and 22 subjects with A_{1C} <7.0%. In the A_{1C} ≥7.0% group, 14 subjects (60.9%) were receiving insulin therapy, 6 subjects (26.1%) were taking oral agents, and 3 subjects (13.0%) were not taking any medicine. In the A_{1C} <7.0% group, 15 subjects (68.2%) were receiving insulin therapy, 5 subjects (22.7%) were taking oral agents, and 2 subjects (9.0%) were not taking any medicine.

PROCEDURAL INFORMATION AND FOLLOW-UP ANGIOGRAPHIC FINDINGS. Stent information and the results of angiographic analysis between the DM and non-DM groups are shown in Table 3. The target vessel was the left anterior descending artery in 50.4% of cases, the left circumflex in 17.1%, and the right coronary artery in 31.7%. This distribution was not different between the 2 groups. First-generation DES was used in >75% of cases. Subtypes of DES, stent diameter, and stent length were not different between the 2 groups. As shown in Table 3, in-stent percent diameter stenosis, minimum lumen diameter, and incidence of in-stent restenosis were not different between the DM and non-DM groups.

OCT FINDINGS BETWEEN THE DM AND NON-DM GROUPS. The mean follow-up duration between DES implantation and follow-up OCT study was 30.3 ± 28.9 months in the DM group and 29.4 ± 26.1 months in the non-DM group (p = 0.856). All OCT images at follow-up were acquired successfully without any complications. Comparisons of quantitative OCT findings between the DM and non-DM groups are shown in Table 4. Mean luminal area, stent area, and neointimal area were similar between the 2 groups. The incidence of uncovered stent struts was similar between the 2 groups. The prevalences of OCT qualitative characteristics of NA are also shown in Table 4. The prevalence of lipid-laden intima was similar between the 2 groups, as was the prevalence of calcification, OCT-defined TCFA, neointima disruption, and thrombus. However, neovascularization was observed more frequently in the DM group (55.1% vs. 32.4%; p = 0.012). Interobserver and intraobserver agreements were κ = 0.92 and 0.94 for lipid-laden intima and κ = 0.93 and 0.92 for neovascularization, respectively.

TABLE 1 Baseline Patient Characteristics

	NA (n = 115)	Non-NA (n = 282)	p Value
Age, yrs	61.3 ± 12.6	61.1 ± 9.8	0.829
Male	88 (76.5)	210 (74.5)	0.668
Hypertension	73 (63.5)	189 (67.0)	0.499
Hyperlipidemia	86 (74.8)	209 (74.1)	0.890
DM	45 (39.1)	107 (37.9)	0.825
Smoking	53 (46.1)	152 (53.9)	0.158
CAD family history	8 (7.0)	28 (9.9)	0.349
CKD	9 (7.8)	7 (2.5)	0.014
Creatinine, mg/dl	1.2 ± 1.5	0.9 ± 0.6	0.006
Total cholesterol, mg/dl	165.3 ± 42.7	165.0 ± 44.4	0.964
LDL cholesterol, mg/dl	93.8 ± 32.2	90.1 ± 34.7	0.315
Triglycerides, mg/dl	155.1 ± 93.5	154.7 ± 110.2	0.978
Fasting serum glucose, mg/dl	108.8 ± 32.1	118.0 ± 41.7	0.035
A_{1C}, %	6.2 ± 1.3	6.3 ± 1.3	0.554
Prior myocardial infarction	23 (20.0)	79 (28.0)	0.097
Prior CABG	0 (0)	5 (1.8)	0.151
LVEF, %	61.5 ± 8.5	62.6 ± 8.3	0.237
Clinical presentation at stenting			
ACS	39 (33.9)	116 (41.1)	0.181
SAP	76 (66.1)	166 (58.9)	0.181
Medications at follow-up			
Statins	94 (81.7)	266 (94.3)	<0.001
Aspirin	108 (93.9)	276 (97.9)	0.044
Clopidogrel	83 (72.2)	263 (93.3)	<0.001
ACEI/ARB	56 (48.7)	118 (41.8)	0.212
β-blockers	62 (53.9)	144 (51.1)	0.606

Values are mean ± SD or n (%).

A_{1C} = glycated hemoglobin; ACEI = angiotensin-converting enzyme inhibitor; ACS = acute coronary syndrome; ARB = angiotensin II receptor blocker; CABG = coronary artery bypass graft; CAD = coronary artery disease; CKD = chronic kidney disease; DM = diabetes mellitus; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; NA = neoatherosclerosis; SAP = stable angina pectoris.

TABLE 2 Baseline Patient Characteristics With NA

	DM (n = 45)	Non-DM (n = 70)	p Value
Age, yrs	60.5 ± 12.3	61.9 ± 12.9	0.562
Male	31 (68.9)	57 (81.4)	0.122
Hypertension	33 (73.3)	40 (57.1)	0.078
Hyperlipidemia	33 (73.3)	53 (75.7)	0.774
Smoking	18 (40.0)	35 (50.0)	0.294
CAD family history	1 (2.2)	7 (10.0)	0.110
CKD	7 (15.6)	2 (2.9)	0.013
Creatinine, mg/dl	1.5 ± 1.7	1.1 ± 1.3	0.147
Total cholesterol, mg/dl	167.3 ± 47.3	164.0 ± 39.9	0.684
LDL cholesterol, mg/dl	93.8 ± 32.2	93.9 ± 32.4	0.985
Triglycerides, mg/dl	165.0 ± 112.3	148.7 ± 79.3	0.365
Fasting serum glucose, mg/dl	129.5 ± 39.6	95.5 ± 15.7	<0.001
A_{1C}, %	7.1 ± 1.4	5.6 ± 0.7	<0.001
Prior myocardial infarction	8 (17.8)	15 (21.4)	0.633
Prior CABG	0 (0)	0 (0)	NS
LVEF, %	63.3 ± 7.0	60.3 ± 9.1	0.060
Clinical presentation at stenting			
ACS	13 (28.9)	26 (37.1)	0.362
SAP	32 (71.1)	44 (62.9)	0.362
Medications at follow-up			
Statins	37 (82.2)	57 (81.4)	0.914
Aspirin	43 (95.6)	65 (92.9)	0.555
Clopidogrel	33 (73.3)	50 (71.4)	0.824
ACEI/ARB	24 (53.3)	32 (45.7)	0.425
β-blockers	18 (40.0)	44 (65.7)	0.007

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

TABLE 3 Angiographic Characteristics

	DM (n = 49)	Non-DM (n = 74)	p Value
Location of stent			
LAD	21 (42.9)	41 (55.4)	0.173
LCX	9 (18.4)	13 (17.6)	0.910
RCA	19 (38.8)	20 (27.0)	0.170
Stent diameter, mm	2.8 ± 0.3	2.8 ± 0.3	0.652
Stent length, mm	23.1 ± 6.7	22.3 ± 6.6	0.532
Stent type			
SES	32 (65.3)	44 (59.5)	0.514
PES	6 (12.2)	12 (16.2)	0.542
ZES	4 (8.2)	4 (5.4)	0.544
EES	7 (14.3)	14 (18.9)	0.504
QCA at follow-up			
Diameter stenosis, %	53.1 ± 20.2	49.6 ± 18.7	0.330
Minimum lumen diameter, mm	1.5 ± 0.8	1.6 ± 0.8	0.342
Reference diameter, mm	3.0 ± 0.6	3.1 ± 0.7	0.530
In-stent restenosis	28 (57.1)	43 (58.1)	0.916

Values are n (%) or mean ± SD.
DM = diabetes mellitus; EES = everolimus-eluting stent(s); LAD = left anterior descending artery; LCX = left circumflex artery; PES = paclitaxel-eluting stent(s); QCA = quantitative coronary angiography; RCA = right coronary artery; SES = sirolimus-eluting stent(s); ZES = zotarolimus-eluting stent(s).

MULTIPLE REGRESSION ANALYSES FOR NEOVASCULARIZATION FORMATION IN NA LESIONS. As shown in Table 5, univariate and multivariate logistic regression analysis were performed to assess the determinants of neovascularization formation in NA lesions. In the univariate model, DM, CKD, follow-up duration, and statin use were all associated with neovascularization formation in NA lesions. The multiple logistic regression model demonstrated that only DM and follow-up duration were independent risk factors for neovascularization formation in NA lesions after adjustment for other factors.

DM SUBGROUP ANALYSIS. DM patients were divided into 2 subgroups depending on glycemic control: high A_{1C} group (A_{1C} ≥7.0%, n = 25) and the low A_{1C} group (A_{1C} <7.0%, n = 24) (Figure 2). The frequency of OCT-defined TCFA-containing neointima was significantly higher in the high A_{1C} group than in the low A_{1C} group (40.0% vs. 8.3%; p = 0.010). The prevalence of lipid-laden intima (100.0% vs. 100.0%), calcification (12.0% vs. 4.2%; p = 0.371), neovascularization (48.0% vs. 62.5%; p = 0.308), neointima disruption (24.0% vs. 12.5%; p = 0.299), and thrombus (12.0% vs. 8.3%; p = 0.672) were not different between the 2 groups.

DISCUSSION

To the best of our knowledge, this is the first study utilizing OCT to compare NA characteristics between patients with and without DM. The present study demonstrated no significant difference in the incidence of NA between DM and non-DM patents after 2.5 years. Neovascularization was more frequent in the DM group than in the non-DM group. When DM patients were further divided into 2 groups based on A_{1C} level, the NA lesions in patients with A_{1C} ≥7.0% had a higher prevalence of OCT-defined TCFA compared with those with A_{1C} <7.0%.

DM AND NA. The precise mechanisms of NA development in DES remain unknown to date. Our previous study demonstrated that traditional clinical risk factors for atherosclerosis in native coronary arteries including DM were not associated with NA formation (10). This is consistent with the present observations, which showed no significant difference in the prevalence of NA between DM and non-DM groups. This may suggest a different mechanism in the development of atherosclerosis inside the stents from those in the native coronary arteries. Tian et al. (2) reported that the prevalence of NA was 18.3% in DM patients and 5.5% in non-DM patients. The prevalence of NA was higher in our study compared with the report by

Tian et al. (2). The most likely explanation for this discrepancy is that mean follow-up time was almost 30 months in our study, whereas the study by Tian et al. (2) included patients with OCT follow-up only 12 months after DES implantation. Previous OCT studies demonstrated more frequent lipid-laden neointima in late restenosis of bare-metal stents compared with early restenosis (11,12). Also in DES, Kang et al. (13) demonstrated that the incidence of TCFA increases over time and that the best cutoff of follow-up time to predict TCFA was 20 months. Irrespective of stent type, stent age is obviously 1 of the strongest promoting factors for NA (10).

NA CHARACTERISTICS IN DM AND NON-DM PATIENTS. Diabetes is an independent factor for mortality in coronary artery disease, especially in acute coronary syndrome, which may be due to metabolic abnormalities and atherosclerotic plaque characteristics in DM patients. A post-mortem study showed that, compared with non-DM patients, DM patients had plaques with larger necrotic cores and increased macrophage infiltration (14). A recent in vivo study demonstrated that nonculprit plaques in patients with DM had a wider lipid arc, a longer lipid length, a larger lipid index, and a higher prevalence of calcification and thrombus (15). However, few studies have explored the NA morphology in diabetic patients. The present study demonstrated that NA characteristics, including the presence of lipid-laden intima, calcification, TCFA-containing neointima, neointima disruption, and thrombus detected by OCT, were not different between DM and non-DM patients; however, neovascularization formation was more frequently observed in the DM group. Recently, Suzuki et al. (16) reported a similar observation that microvessels were observed frequently in in-stent restenotic tissue in patients with DM.

Neovascularization has been recognized as an important process for the progression of atherosclerotic plaques and has also been recently identified as 1 of the features of plaque vulnerability (17,18). The molecular mechanisms underlying plaque neovascularization are not fully understood. DM is associated with pro-oxidative and inflammatory states leading to systemic elevation of endothelial adhesion molecules and cytokines, which leads to increased leucocyte emigration, monocyte/macrophage influx, and subintimal proliferation favoring neovessel formation. Recent studies have documented increased inflammation, neovascularization, and intraplaque hemorrhage in human diabetic atherosclerosis (19,20). Previous investigations using OCT showed that neovascularization might play a key role in identifying lesions more prone to plaque destabilization and rupture (21). Inhibition of neovascularization is an effective approach to treat and prevent de novo atherosclerosis (22). Following stent implantation, the expression of lipid-laden intima is closely associated with neointimal neovascularization (11). Tian et al. (23) also observed that the incidence of NA was higher in the sections with a higher degree of neovascularization. These results indicate that expanded neointima neovascularization may also play a key role in NA progression and tissue instability. According to our results, neovascularization was more frequently observed in NA areas in patients with DM. Thus, it is conceivable that inhibition of neovascularization may

TABLE 4 OCT Findings in DM and Non-DM

	DM (n = 49)	Non-DM (n = 74)	p Value
Quantitative			
Mean luminal area, mm^2	5.8 ± 1.6	6.1 ± 1.5	0.192
Mean stent area, mm^2	7.2 ± 2.6	7.5 ± 2.1	0.572
Mean neointimal area, mm^2	1.4 ± 0.6	1.5 ± 0.8	0.424
Minimal luminal area, mm^2	1.8 ± 1.2	2.1 ± 1.9	0.371
Neointimal thickness, μm	157 ± 69	165 ± 91	0.254
Uncovered stent strut, %	4.5 ± 7.1	3.1 ± 5.5	0.353
Qualitative			
Lipid-laden intima	47 (95.9)	71 (94.7)	0.751
Calcification	4 (8.2)	6 (8.1)	0.991
Incidence of TCFA	12 (24.5)	25 (33.8)	0.271
Neovascularization	27 (55.1)	24 (32.4)	0.012
Disruption	9 (18.4)	16 (21.6)	0.661
Thrombus	5 (10.2)	17 (23.0)	0.070

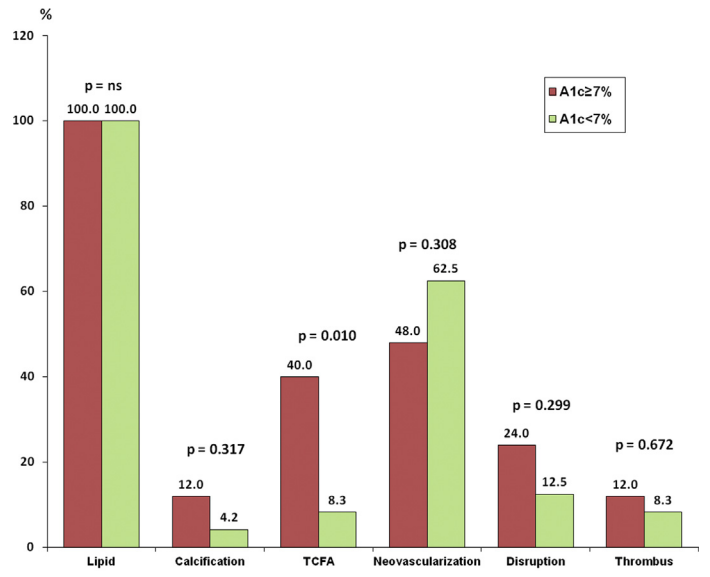
Values are mean ± SD or n (%).
DM = diabetes mellitus; TCFA = thin-cap fibroatheroma.

TABLE 5 Multiple Logistic Regression Model for Neovascularization

	Univariate Models			Multivariate Models		
	Odds Ratio	95% CI	p Value	Odds Ratio	95% CI	p Value
Age, per yr	1.02	0.99–1.05	0.237			
Male	0.82	0.36–1.86	0.629			
First-generation DES	1.32	0.58–3.03	0.507			
ACS	1.43	0.69–2.96	0.337			
DM	2.56	1.21–5.38	0.013	2.57	1.09–6.07	0.031
Hypertension	1.34	0.72–2.11	0.352			
Hyperlipidemia	0.74	0.33–1.67	0.471			
CKD	4.28	1.08–17.02	0.039	2.87	0.63–13.02	0.171
Follow-up duration, months	1.03	1.02–1.05	<0.001	1.03	1.02–1.05	<0.001
Stent diameter, per mm	0.66	0.15–2.84	0.576			
Stent length, per mm	1.02	0.96–1.07	0.572			
ACEI/ARB use	1.74	0.85–3.60	0.133			
Statin use	0.42	0.16–1.07	0.069	0.65	0.22–1.92	0.435

CI = confidence interval; DES = drug-eluting stent(s); other abbreviations as in Table 1.

FIGURE 2 Comparison of Neoatherosclerosis Characteristics Between High A_{1C} Group and Low A_{1C} Group



A_{1C} = glycated hemoglobin; TCFA = thin-cap fibroatheroma.

be an effective approach for preventing NA in DM patients.

NA CHARACTERISTICS IN THE POORLY CONTROLLED DM GROUP (A_{1C} ≥7.0%). Our previous study suggested that patients with poorly controlled DM had more vulnerable plaques in the native nonculprit coronary lesions (15). However, the association of A_{1C} level with the characteristics of NA has not been investigated. The present study showed that the frequency of OCT-defined TCFA-containing neointima was significantly higher in the high A_{1C} group than in the low A_{1C} group (40.0% vs. 8.3%; p = 0.010). It coincides with the typical pathological features of vulnerable plaque in native coronary arteries (24). In the contemporary DES era, prospective studies have shown that A_{1C} level is 1 of the most important risk factors for adverse clinical events in DM patients (25,26). A recent study reported that the adjusted risk of major adverse cardiovascular events in diabetic patients with poor glycemic control (A_{1C} ≥7.0%) was more than double the risk in nondiabetics. This same study also showed that well-controlled diabetic patients had rates of adverse clinical events comparable to those of nondiabetic patients (27). Previous studies demonstrated that TCFA-containing neointima might lead to neointimal rupture and stent thrombosis (28). Furthermore, Thrombolysis In Myocardial Infarction flow at presentation was reduced in lesions showing neointimal rupture or TCFA-containing neointima (13), and pre-procedural OCT findings of TCFA-containing neointima were significantly correlated with the peak level of post-percutaneous coronary intervention creatine kinase-myocardial band (29). The current findings suggest that 1 possible explanation for higher rates of major adverse cardiac events may be the presence of more vulnerable morphology features in diabetic patients with worse glycemic control.

Signal attenuation due to lipid-laden neointima and calcification and limited penetration depth of OCT images may not allow accurate evaluation of neovascularization in deep layers. In the present study, we found that although neovascularization was more commonly observed in patients with DM, there was similar incidence of neovascularization in subjects with HbA1c <7.0% compared with those with HbA1c ≥7.0%. One possible explanation is that the higher incidence of TCFA and calcification in the HbA1c ≥7.0% group (**Figure 2**) may have caused underestimation of the incidence of neovascularization in the group.

STUDY LIMITATIONS. First, this is a retrospective study using a registry database. Therefore, potential selection bias is unavoidable. Given the international multisite nature of the registry, we explored potential between-country differences in the prevalence of DM and neoatherosclerosis in our study population and found no statistically significant differences (data not shown). Second, this is not a natural history study of stented lesions in which the same stents are serially studied at different time points after implantation. Third, 4 types of DES, including sirolimus-, paclitaxel-, zotarolimus-, and everolimus-eluting stents, were included in the present study. Because of the relatively small number of each DES subtype, we could not evaluate the difference in the nature of NA among the subtypes of DES. Finally, lipid-laden intima, calcification, OCT-defined TCFA-containing neointima, neovascularization, neointimal disruption, and thrombus were not quantified or rigorously validated. Nakano et al. (30) reported that foamy macrophages accumulate on the luminal surface of neointimal in the stented coronary artery, which are identified in OCT as a typical appearance of a thin bright line with trailing shadows. This feature might have led to an overestimation of the presence of TCFA-containing neointima (30).

CONCLUSIONS

The present study provides several unique and potentially important insights into NA characteristics

after coronary DES implantation in DM patients versus non-DM patients. Although the incidence of NA was similar between DM and non-DM patients, NA lesions in DM patients had a higher prevalence of neovascularization. Moreover, patients with poorly controlled DM had lesions containing more vulnerable features. Further studies are warranted to aid in understanding the clinical implication of the present findings and whether vulnerable features of NA are associated with higher event rates in poorly controlled diabetic patients.

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PERSPECTIVES

WHAT IS KNOWN? Previous studies have reported that in-stent NA is an important mechanism for both in-stent restenosis and late stent thrombosis. However, the difference in NA characteristics after DES implantation in patients with and without DM has not been explored.

WHAT IS NEW? The present study demonstrated that NA lesions in DM patients had a higher prevalence of neovascularization. Moreover, patients with poorly controlled DM had lesions with more vulnerable features.

WHAT IS NEXT? Prospective studies are needed to test if better control of DM will prevent late stent complications related to NA.

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