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ORIGINAL RESEARCH

Impact of Pre-Diabetes on Coronary Plaque Composition and Clinical Outcome in Patients With Acute Coronary Syndromes

An Analysis From the PROSPECT Study

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ABSTRACT

OBJECTIVES The aim of this study was to investigate the impact of pre-diabetes (pre-DM) on coronary plaque characteristics and ischemic outcomes in patients with acute coronary syndromes (ACS).

BACKGROUND Pre-DM (i.e., the early stages of glucometabolic disturbance) is common among patients with ACS, but the extent to which pre-DM influences coronary plaque characteristics and the risk for adverse ischemic events is unclear.

METHODS In the PROSPECT (Providing Regional Observations to Study Predictors of Events in Coronary Tree) study, patients with ACS underwent quantitative coronary angiography, grayscale intravascular ultrasound, and radiofrequency intravascular ultrasound after successful percutaneous coronary intervention. Patients were divided into 3 groups according to their glucometabolic status, as defined by the American Diabetes Association: normal glucose metabolism (NGM), pre-DM, and diabetes mellitus (DM). These groups were compared with regard to coronary plaque characteristics and the risk for major adverse cardiac events (MACEs) (defined as cardiac death or arrest, myocardial infarction, or rehospitalization for unstable or progressive angina).

RESULTS Among 547 patients, 162 (29.6%) had NGM, 202 (36.9%) had pre-DM, and 183 (33.4%) had DM. There were no significant differences between the groups with regard to intravascular ultrasound findings indicative of vulnerable plaques. Patients with DM had a higher crude rate of MACEs than those with pre-DM or NGM (25.9% vs. 16.3% and 16.1%; $p = 0.03$ and $p = 0.02$, respectively). In an adjusted Cox regression model using NGM as the reference group, DM (hazard ratio: 2.20; 95% confidence interval: 1.25 to 3.86; $p = 0.006$) but not pre-DM (hazard ratio: 1.29; 95% confidence interval: 0.71 to 2.33; $p = 0.41$) was associated with increased risk for MACEs.

CONCLUSIONS Impaired glucose metabolism is common among patients presenting with ACS. DM but not pre-DM is associated with an increased risk for MACEs. Thus, preventing patients from progressing from pre-DM to DM is important. (PROSPECT: An Imaging Study in Patients With Unstable Atherosclerotic Lesions; NCT00180466)
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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

ADA = American Diabetes Association

CAD = coronary artery disease

CI = confidence interval

CSA = cross-sectional area

DM = diabetes mellitus

EEM = external elastic membrane

IVUS = intravascular ultrasound

MACE = major adverse cardiac event

MLA = minimum luminal area

NGM = normal glucose metabolism

OR = odds ratio

PCI = percutaneous coronary intervention

pre-DM = pre-diabetes

TCFA = thin-cap fibroatheroma

Diabetes mellitus (DM) is strongly associated with coronary artery disease (CAD) and is a major threat to global public health (1). Undiagnosed DM and pre-diabetes (pre-DM) are common among patients with CAD (2,3), including patients with acute coronary syndromes (ACS) (4). Several small studies have reported a correlation between pre-DM and indexes of coronary plaque vulnerability (5,6), but it is unclear if pre-DM affects plaque morphology and the risk for ischemic adverse events. The PROSPECT (Providing Regional Observations to Study Predictors of Events in Coronary Tree) study investigated the natural history of coronary atherosclerosis in a population of patients admitted for ACS and treated successfully with percutaneous coronary intervention (PCI) (7). The aim of the present study was to investigate the impact of early stages of glucometabolic disturbance on morphologic features of coronary atherosclerotic lesions and the risk for 3-year ischemic events.

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METHODS

STUDY POPULATION. PROSPECT was conducted at 37 centers in the United States and Europe. The study design and main results have been published elsewhere (7). In brief, 697 patients with ACS who were treated successfully with PCI for all lesions deemed responsible for the index event were enrolled. All included patients underwent angiography as well as grayscale and intravascular ultrasound virtual histology (IVUS-VH) (Volcano Corporation, San Diego, California) of the left main coronary artery as well as 6 to 8 cm of the proximal portion of each major epicardial coronary vessel.

In the present analysis, patients were divided according to their glucometabolic status into those with normal glucose metabolism (NGM), pre-DM, and DM on the basis of recommendations of the American Diabetes Association (ADA) (8). DM was defined as a history of DM or ongoing treatment with glucose-lowering medication or dietary control and/or fasting glucose ≥126 mg/dl and/or glycated hemoglobin ≥6.5%. Pre-DM was defined as fasting glucose ≥100 and <126 mg/dl and/or glycated hemoglobin ≥5.7% in patients who did not meet any of the criteria for DM. NGM was defined as fasting glucose <100 mg/dl and/or glycated hemoglobin <5.7% and the absence of all criteria for DM. All laboratory measurements were performed while fasting during the hospitalization for the index procedure (9).

GRAYSCALE IVUS AND IVUS-VH. Grayscale IVUS and IVUS-VH analyses were performed using QCU-CMS (Medis Medical Imaging Systems, Leiden, the Netherlands). pcVH 2.1 (Volcano Corporation) was used for contouring and data output, and proprietary software (qVH, Cardiovascular Research Foundation, New York, New York) was used for segmental quantitative and qualitative analyses (10,11). The external elastic membrane (EEM) and lumen borders were detected at approximately every 0.4-mm interval (depending on heart rate) and used to determine the EEM cross-sectional area (CSA), lumen CSA, and plaque plus media CSA and burden (defined as 100 × [plaque + media]/EEM CSA). A nonculprit lesion was defined as ≥3 consecutive frames with plaque burden ≥40%. IVUS-VH allows the characterization of 4 different plaque components (red corresponds to necrotic core, green to fibrous tissue, light green to fibrofatty, and white to dense calcium). On the basis of its compositional traits, each lesion was classified as thin-cap fibroatheroma (TCFA), thick-cap fibroatheroma, pathological intimal thickening, fibrotic plaque, or fibrocalcific plaque (11,12). All IVUS frames were coregistered to the angiographic roadmap using fiduciary side branches for alignment.

CLINICAL ENDPOINTS. The primary endpoint was the incidence of major adverse cardiac events (MACEs), defined as cardiac death or arrest, myocardial infarction, or rehospitalization for unstable or progressive angina. Endpoints were adjudicated by a

Cardiovascular Systems, Sanofi USA, Shanghai BraccoSine Pharmaceutical, and AstraZeneca; and holds equity in Claret Medical and Elixir Medical Corporation. Dr. Kirtane has received institutional research grants to Columbia University from Boston Scientific, Medtronic, Abbott Vascular, Abiomed, St. Jude Medical, Vascular Dynamics, and Eli Lilly. Dr. Serruys is a consultant for Abbott Laboratories, AstraZeneca Pharmaceuticals, Biotronik, Cardialysis, GLG Research, Medtronic, Sino Medical Sciences Technology, Tianjin China, Société Europa Digital & Publishing, Stentys France, Svelte Medical Systems, Volcano Europe, and Q3 Medical Devices. Dr. Mintz is a consultant for Boston Scientific and ACIST; has received fellowship and grant support from Volcano, Boston Scientific, and InfraReDx; and has received honoraria from Boston Scientific and ACIST. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Farhan and Redfors contributed equally to this work. David Moliterno, MD, served as the Guest Editor for this paper.

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TABLE 1 Baseline Characteristics Stratified According to Glucose Metabolism

	NGM (n = 162)	Pre-DM (n = 202)	DM (n = 183)	p Value
Age, yrs	58.1 (50.4–66.7)	57.4 (50.2–65.8)	60.8 (54.0–69.1)	0.03
Male	80.9 (131/162)	77.7 (157/202)	72.1 (132/183)	0.15
Insulin-treated DM	–	–	9.8 (18/183)	
Waist circumference, cm	98.0 (89.9–104.1)	100.3 (92.9–110.2)	104.1 (95.0–114.3)	0.002
Body mass index, kg/m^2	27.1 (24.9–29.6)	28.1 (25.1–31.6)	29.6 (26.3–32.8)	<0.0001
Systolic blood pressure, mm Hg	129 (112–140)	130 (119–141)	130 (117–147)	0.36
Diastolic blood pressure, mm Hg	72 (64–83)	75 (67–83)	73 (67–84)	0.67
Prior myocardial infarction	10.5 (17/162)	8.5 (17/199)	11.5 (21/182)	0.62
Prior PCI	9.3 (15/162)	11.4 (23/202)	12.6 (23/183)	0.62
Family history of coronary artery disease	43.8 (64/146)	42.7 (76/178)	40.9 (65/159)	0.87
History of congestive heart failure	1.2 (2/162)	2.0 (4/201)	2.2 (4/182)	0.79
Hypertension	37.3 (60/161)	43.3 (87/201)	60.8 (110/181)*	<0.0001
Hyperlipidemia	40.1 (61/152)	39.1 (70/179)	53.5 (92/172)	0.01
Clinical presentation				
ST-segment elevation myocardial infarction >24 h	24.7 (40/162)	27.2 (55/202)	29.0 (53/183)	0.67
Non–ST-segment elevation myocardial infarction	70.4 (114/162)	68.3 (138/202)	67.8 (124/183)	0.86
Unstable angina	4.9 (8/162)	4.5 (9/202)	3.3 (6/183)	0.73
Current smoking	50.6 (82/162)	47.7 (94/197)	37.8 (68/180)	0.04
Serum creatinine, mg/dl	0.9 (0.8–1.0)	0.94 (0.8–1.11)	0.9 (0.8–1.1)	0.20
Estimated glomerular filtration rate <60 ml/min	8.3 (13/157)	9.7 (19/195)	14.0 (25/178)	0.99
Total cholesterol, mg/dl	167.5 (152.0–193.5)	171 (150–200)	166 (141–195)	0.41
High-density lipoprotein cholesterol, mg/dl	38.6 (33–43)	38.6 (35–46)	38.6 (32–48)	0.33
Low-density lipoprotein cholesterol, mg/dl	100.8 (85.4–127.4)	103.7 (80.1–130.9)	94.5 (74.4–124.8)	0.25
Triglycerides, mg/dl	123 (88.6–177.1)	122.5 (88.6–175.0)	135 (88.6–185.0)	0.33
Fasting glucose, mg/dl	90 (86–95)	104 (95–110)	132 (108–159)	<0.0001
HbA_{1c}, %	5.4 (5.0–5.6)	5.8 (5.5–6.0)	6.5 (5.9–7.2)	<0.0001
Medications				
Use of aspirin within 7 days before admission	31.1 (50/161)	33.3 (65/195)	40.2 (72/179)	0.17
Statin use at admission	45.7 (74/162)	40.1 (81/202)	42.6 (78/183)	0.56
Statin at discharge	87.0 (141/162)	83.1 (167/201)	85.2 (155/182)	0.58
Aspirin at discharge	96.9 (157/162)	98.0 (198/202)	97.3 (178/183)	0.79
Thienopyridine at discharge	98.1 (159/162)	99.0 (200/202)	97.3 (178/183)	0.44
Angiotensin-converting enzyme inhibitor at discharge	54.3 (88/162)†	65.3 (132/202)	67.0 (122/182)	0.03
Angiotensin receptor blocker at discharge	4.3 (7/161)†	7.0 (14/201)	11.5 (21/183)	0.04
Beta-blocker at discharge	91.4 (148/162)	91.6 (185/202)	91.3 (167/183)	0.99
Hypoglycemic medication at discharge	–	–	48.9 (89/182)	–

Values are median (interquartile range) or % (n/N). *p < 0.001 comparing DM with NGM and pre-DM. †p < 0.03 comparing NGM with pre-DM and DM.
DM = diabetes mellitus; HbA_{1c} = glycosylated hemoglobin; NGM = normal glucose metabolism; pre-DM = pre-diabetes; PCI = percutaneous coronary intervention.

committee using original source documents and without knowledge of other patient data. On the basis of follow-up angiography, recurrent MACEs were adjudicated as occurring at initially treated (culprit) or previously untreated (nonculprit) lesions. On the basis of principal results (7), a high-risk lesion was defined as having 2 or more of the following: plaque burden ≥70%, minimum luminal area (MLA) ≤4.0 mm^2, or TCFA.

STATISTICAL ANALYSIS. Baseline clinical and imaging data were stratified on the basis of glucometabolic status. Categorical variables are expressed as percentages and were compared using the chi-square test or the Fisher exact test. Continuous variables are reported as median (interquartile range) and were compared using the Kruskal-Wallis test. Outcomes are reported as Kaplan-Meier percentages and numbers of events and were compared using log-rank tests. Logistic regression analysis adjusted for age and sex was used to estimate the relationship between pre-DM and DM with risk for having IVUS features of high-risk plaque (MLA ≤4 mm^2, TCFA, and plaque burden ≥70%). A multivariate Cox proportional hazards regression model was used to assess the adjusted risk for 3-year MACEs associated with glucometabolic status. Both DM and pre-DM were entered into this multivariate model, with NGM as the

TABLE 2 Patient-Level Intravascular Ultrasound Features of Nonculprit Lesions Stratified According to Glucose Metabolism

	NGM (n = 162)	Pre-DM (n = 202)	DM (n = 183)	p Value
Grayscale intravascular ultrasound				
Number of lesions	5.0 (4.0-6.0)	5.0 (4.0-6.0)	5.0 (3.0-6.0)	0.46
≥1 echolucent plaque	20.1 (34/169)	13.5 (26/192)	16.7 (26/156)	0.25
≥1 plaque rupture	16.6 (28/169)	14.6 (28/192)	13.5 (21/156)	0.73
Total lesion length, mm	70.9 (46.3-104.9)	72.2 (42.1-103.5)	73.2 (45.1-104.6)	0.78
Plaque volume, %	49.6 (47.0-52.5)	49.4 (46.7-52.2)	49.0 (46.6-51.7)	0.46
Average EEM CSA, mm^3/mm	16.5 (14.2-18.7)	16.0 (13.9-18.9)	16.3 (14.1-18.5)	0.80
Average luminal CSA, mm^3/mm	8.0 (6.9-9.5)	8.1 (7.0-9.6)	8.4 (6.9-9.6)	0.96
IVUS-VH				
Average necrotic core CSA, mm^3/mm	0.5 (0.3-0.8)	0.5 (0.3-0.8)	0.5 (0.3-0.8)	0.85
Average dense calcium CSA, mm^3/mm	0.2 (0.1-0.4)	0.21 (0.1-0.4)	0.2 (0.1-0.4)	0.83
Average fibrous tissue CSA, mm^3/mm	2.8 (2.1-3.5)	2.5 (1.9-3.2)	2.5 (1.9-3.2)	0.08
Average fibrofatty CSA, mm^3/mm	0.9 (0.6-1.4)	0.8 (0.5-1.1)	0.8 (0.4-1.3)	0.16
Total number of VH-TCFA lesions per patient	1.0 (0.0-1.0)	1.0 (0.0-2.0)	1.0 (0.0-2.0)	0.48
Total number of FA lesions per patient	3.0 (2.0-4.0)	3.0 (1.0-4.0)	3.00 (1.0-4.0)	0.88
High-risk plaque characteristics				
≥1 lesion with minimum luminal area ≤4 mm^2	58.0 (98/169)	53.1 (102/192)	55.1 (86/156)	0.65
≥1 lesion with plaque burden ≥70%	35.5 (60/169)	31.3 (60/192)	32.1 (50/156)	0.67
≥1 VH-TCFA	53.5 (85/159)	59.2 (103/174)	55.2 (79/143)	0.56

Values are median (interquartile range) or as % (n/N).

CSA = cross-sectional area; EEM = external elastic membrane; FA = fibroatheroma; IVUS-VH = intravascular ultrasound virtual histology; TCFA = thin-cap fibroatheroma; VH = virtual histology; other abbreviations as in Table 1.

reference category. Other variables included in the model were ≥1 TCFA, patients with ≥1 lesion with MLA ≤4 mm^2, age, sex, use of aspirin in the preceding 7 days, and previous PCI. A p value <0.05 was considered to indicate statistical significance. All statistical tests were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS. Among 697 patients enrolled in the PROSPECT study, data on glucometabolic status were available in 547 patients. Application of the ADA criteria for diagnosis of pre-DM and DM resulted in 29.6% of patients (n = 162) with NGM, 36.9% (n = 202) with pre-DM, and 33.4% (n = 183) with DM. Among patients with DM, 56.3% (n = 103) had diagnoses of DM at admission. Patients with DM were older and were more likely to have hypertension and/or hyperlipidemia requiring medication than those with NGM and pre-DM. Waist circumference and body mass index were higher in patients with pre-DM and DM compared with those with NGM. In contrast, NGM patients were significantly more likely to be current smokers compared with those with DM. There were no significant differences in clinical presentation across the 3 groups, and serum creatinine, estimated glomerular filtration rate, and serum lipid profile were similar among the groups. Patients with DM were significantly more likely to receive angiotensin-converting enzyme inhibitors or angiotensin receptor blockers at discharge than patients with pre-DM or NGM (Table 1).

IVUS ANALYSIS OF NONCULPRIT LESIONS. IVUS parameters stratified by glucometabolic status are presented in Table 2. Grayscale IVUS revealed no differences in average EEM and luminal CSA and percentage plaque volume among patients with DM, pre-DM, and NGM. There was no difference in number of MLA ≤4 mm^2, plaque burden >70%, and TCFA among the 3 investigated groups. Similarly, no significant differences were observed between NGM, pre-DM, and DM with regard to plaque composition.

FEATURES OF HIGH-RISK PLAQUE. In a logistic linear regression analyses adjusted for age and sex, neither DM nor pre-DM was predictive of having plaques with the high-risk features: ≥1 TCFA (pre-DM vs. NGM: odds ratio [OR]: 1.17; 95% confidence interval [CI]: 0.75 to 1.84; p = 0.36; and DM vs. NGM: OR: 0.97; 95% CI: 0.61 to 1.53; p = 0.56), MLA ≤4 mm^2 (pre-DM vs. NGM: OR: 0.91; 95% CI: 0.59 to 1.39; p = 0.48; and DM vs. NGM: OR: 1.06; 95% CI: 0.68 to 1.66; p = 0.56), and plaque burden ≥70% (pre-DM vs. NGM: OR: 0.97; 95% CI: 0.62 to 1.54; p = 0.63; and DM vs. NGM: OR: 1.14; 95% CI: 0.72 to 1.82; p = 0.47).

3-YEAR OUTCOMES. The occurrence of MACEs and their components is presented in Table 3. Patients

TABLE 3 Cumulative Rates of Major Adverse Cardiac Events Stratified by Glucose Metabolism

	NGM (n = 162)	Pre-DM (n = 202)	DM (n = 183)	p Value
Overall				
Major adverse cardiac events*	16.1 (24)	16.3 (31)	25.9 (43)	0.03
Cardiac death	2.7 (4)	0.6 (1)	1.8 (3)	0.30
Myocardial infarction	1.3 (2)	1.0 (2)	4.4 (7)	0.09
Cardiac death, arrest, or myocardial infarction	3.4 (5)	1.6 (3)	6.2 (10)	0.08
Rehospitalization due to unstable or increasing angina	14.7 (22)	15.2 (29)	22.2 (37)	0.10
Revascularization (PCI or CABG)	12.1 (18)	13.6 (26)	21.9 (36)	0.03
Stent thrombosis†	2.7 (4)	1.7 (3)	3.0 (5)	0.66
Culprit lesion				
Major adverse cardiac events*	9.6 (14)	11.5 (22)	15.7 (26)	0.19
Cardiac death	0.0 (0)	0.0 (0)	0.6 (1)	0.36
Myocardial infarction	0.6 (1)	0.5 (1)	2.4 (4)	0.20
Cardiac death, arrest, or myocardial infarction	0.6 (1)	0.5 (1)	3.0 (5)	0.09
Rehospitalization due to unstable or increasing angina	9.6 (14)	11.5 (22)	13.3 (22)	0.49
Revascularization (PCI or CABG)	7.5 (11)	9.9 (19)	13.4 (22)	0.20
Stent thrombosis†	0.6 (1)	1.1 (2)	2.4 (4)	0.37
Nonculprit lesion				
Major adverse cardiac events*	9.5 (14)	8.5 (16)	15.9 (26)	0.06
Cardiac death	0.0 (0)	0.0 (0)	0.0 (0)	–
Myocardial infarction	0.0 (0)	0.5 (1)	1.4 (2)	0.37
Cardiac death, arrest, or myocardial infarction	0.0 (0)	0.5 (1)	1.4 (2)	0.37
Rehospitalization due to unstable or increasing angina	9.5 (14)	7.9 (15)	15.2 (25)	0.06
Revascularization (PCI or CABG)	8.9 (13)	7.4 (14)	14.1 (23)	0.09
Indeterminate lesion‡				
Major adverse cardiac events*	3.4 (5)	1.1 (2)	3.7 (6)	0.26
Cardiac death	2.7 (4)	0.6 (1)	1.3 (2)	0.26
Myocardial infarction	0.7 (1)	0.0 (0)	0.6 (1)	0.55
Cardiac death, arrest, or myocardial infarction	2.7 (4)	0.6 (1)	1.9 (3)	0.30
Rehospitalization due to unstable or increasing angina	0.7 (1)	0.5 (1)	1.9 (3)	0.43
Revascularization (PCI or CABG)	0.0 (0)	0.0 (0)	0.0 (0)	–

Values are % (n). *Cardiac death or arrest, myocardial infarction, rehospitalization for unstable or increasing angina. †Definite or probable stent thrombosis according to the Academic Research Consortium definition. ‡A lesion was classified as indeterminate if angiography was not performed at the time of the event, which was the case in 13 subjects.

CABG = coronary artery bypass grafting; other abbreviations as in Table 1.

with DM had significantly higher rates of MACEs than those with pre-DM and NGM (25.9% vs. 16.3% vs. 16.1%, respectively; p = 0.03), which was attributed mainly to a higher rate of revascularization in patients with DM (21.9% vs. 13.6% vs. 12.1%; p = 0.03) (**Table 3, Figure 1A**). When events were broken down into those occurring in culprit versus nonculprit vessels, patients with DM had numerically higher rates of both culprit- and non-culprit-related MACEs than patients with pre-DM and NGM, but these differences were not statistically significant (**Table 3, Figures 1B and 1C**). In 13 patients (2.4%), no coronary angiography at the time of the event was performed. Those events were classified as indeterminate (**Table 3**). In an adjusted Cox regression analysis using NGM as the reference group, DM but not pre-DM was predictive of overall as well as culprit lesion MACEs (**Figure 2,** Supplemental Table 1). There was no statistically significant interaction between DM status and any of the high-risk plaque characteristics with regard to MACEs ($p_{interaction} > 0.10$ for all).

DISCUSSION

The main findings of the present analysis of the PROSPECT study are that: 1) the prevalence of DM and pre-DM is high among patients admitted for ACS when ADA criteria are applied; and 2) DM but not pre-DM was an independent predictor of MACEs, although patients with neither DM nor pre-DM had more severe CAD than patients with NGM, as detected by indexes of plaque morphology.

Recent treatment advancements for patients with CAD have been less effective in patients with versus without DM (13). This is concerning, because the prevalence of DM continues to increase and currently constitutes a growing threat to public health (13). The high prevalence of impaired glucose metabolism in

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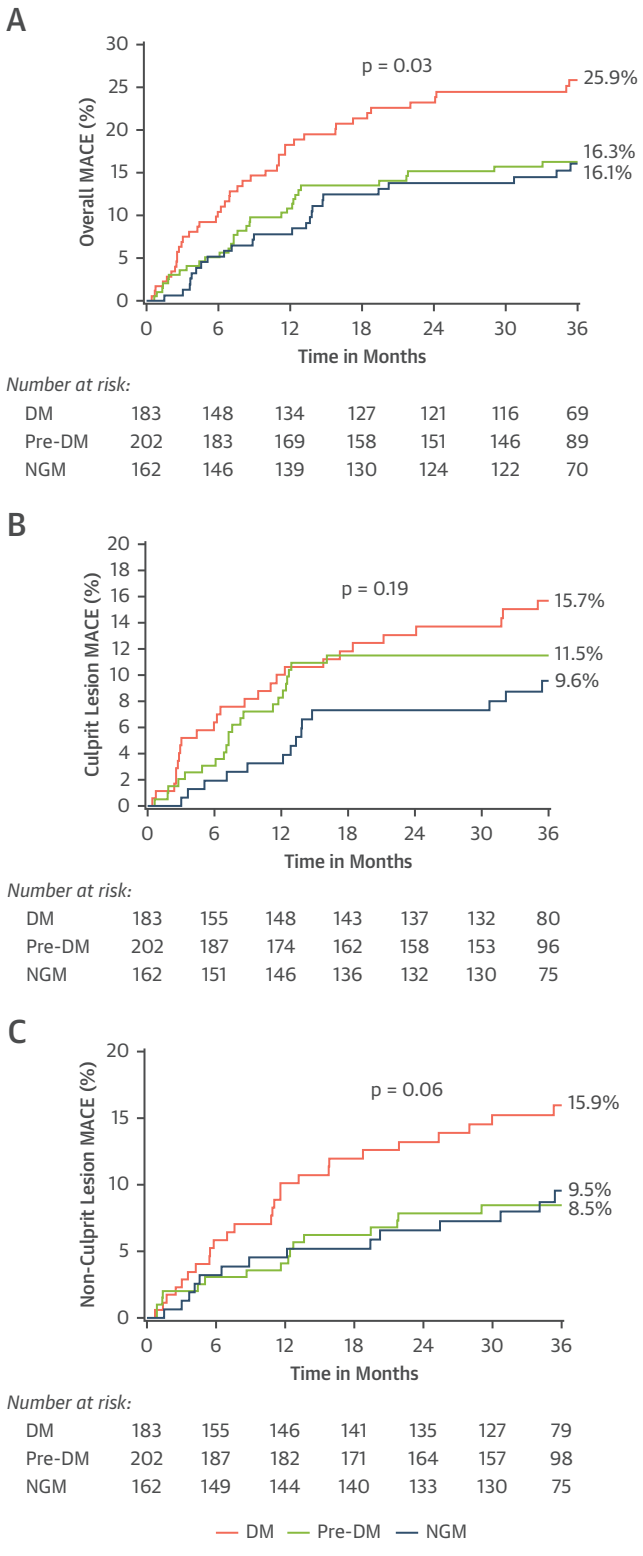
FIGURE 1 Kaplan-Maier Curves



(A) Overall major adverse cardiac events (MACEs), **(B)** culprit lesion MACEs, and **(C)** nonculprit lesion MACEs stratified by glucometabolic status. DM = diabetes mellitus; NGM = normal glucose metabolism; pre-DM = pre-diabetes.

our study is consistent with previous work showing that pre-DM and DM are prevalent among patients with CAD, particularly among those with ACS (2,3).

In the present study the risk for MACEs was approximately double for patients with versus without DM, a finding that is consistent with previous studies showing that the risk for adverse events after PCI is approximately double for patients with DM versus without DM (14). In contrast, the risk for patients with pre-DM was similar to that of patients with NGM. This may seem surprising, but it is consistent with a report from the Euro Heart Survey on DM and the heart (15) that showed that patients with pre-DM have better coronary prognosis compared with those with DM. In fact, recent studies have demonstrated the importance of DM duration (16,17) and cumulative hyperglycemic insults (18,19) among patients with long-standing DM on the risk for adverse ischemic events. Hence, pre-DM may represent a stage at which few of the end-organ effects of hyperglycemia, including effects on the coronary arterial tree, have occurred. Our findings support this hypothesis.

That being said, whether early stages of glucometabolic impairment affect coronary plaque morphology is still a matter of debate. Hyperglycemia and insulin resistance promote the release of proinflammatory cytokines (e.g., tumor necrosis factor-α, interleukin-6, plasminogen activator inhibitor, and angiotensin). This leads to a proinflammatory state with accelerated atherosclerosis, vascular inflammation, and endothelial dysfunction (20–22). Furthermore, hyperinsulinemia and daily glucose fluctuations have been associated with coronary plaque vulnerability (22,23). Amano et al. (5) investigated coronary culprit lesions of patients with CAD and found higher plaque volume and lipid content in patients with DM as well as in those with early stages of glucose abnormalities. Similarly, Kurihara et al. (6) showed a higher degree of yellow vulnerable plaque in patients with pre-DM and DM using coronary angioscopy. It may therefore seem surprising that we found no differences in the prevalence of high-risk plaque characteristics between any of the study groups. The reason for the discrepant findings between our investigation and previous studies could be explained by the difference in study design and the investigated population. Only a minority of the patients in PROSPECT had insulin-treated DM, and patients with insulin-treated DM have been shown to have considerably more extensive CAD than patients with non-insulin-treated DM (24). Thus, compared with patients with DM in other studies, patients with DM in PROSEPCT likely had less severe and less long-standing hyperglycemia at the time of coronary assessment (9). We prospectively

studied nonculprit lesions after successful PCI, whereas the other studies focused on culprit lesions. It is possible that the association between DM and high-risk plaque characteristics that has been described for culprit lesions is less pronounced in nonculprit lesions (25,26). Notably, only the proximal 6 to 8 cm of each major epicardial coronary artery was evaluated in the PROSPECT study (7). Necropsy studies have shown that DM affects predominantly distal portions of coronary arteries (27), which could explain the apparent lack of differences in high-risk plaque features. Microvascular dysfunction, which is prevalent among patients with DM, may have contributed to the increased risk for MACE among patients with DM (28). Last, the diagnostic criteria used to detect pre-DM and latent DM were different in our study than in the other studies (29). It is possible that stratification of patients into NGM, pre-DM, and DM groups, as per the ADA guidelines, is not the most efficient means of predicting the presence of high-risk plaque characteristics. In fact, a previous publication from PROSPECT that focused on established DM and metabolic syndrome rather than pre-DM showed that patients with neither DM nor metabolic syndrome had the most favorable plaque characteristics, although these differences were small in magnitude (30). The differences between the present analysis and that of Marso et al. (30) appear amplified because Marso et al. conducted their analysis using lesion-level data.

The results derived from the present study have clinical implications. First, given the high incidence of pre-DM and DM observed in this study, patients who present with ACS should be carefully screened for DM. Second, the lack of a clear association between pre-DM and MACEs should encourage patients and clinicians to devote the necessary efforts to prevent these patients from progressing to DM. Furthermore, the lack of a clear association between pre-DM, as well as DM, and high-risk plaque characteristics is encouraging. Given the fact that most patients in the DM group had non-insulin-dependent DM, our findings are consistent with previous observations that primary preventive measures appear to be more effective in patients with non-insulin-dependent versus insulin-dependent DM (31). Thus, even among patients who have progressed to non-insulin-treated DM, appropriate glucometabolic control and other therapeutic measures may prevent progression of CAD (32,33). This hypothesis should be tested in clinical trials specifically designed for patients with pre-DM or newly diagnosed non-insulin-dependent DM.

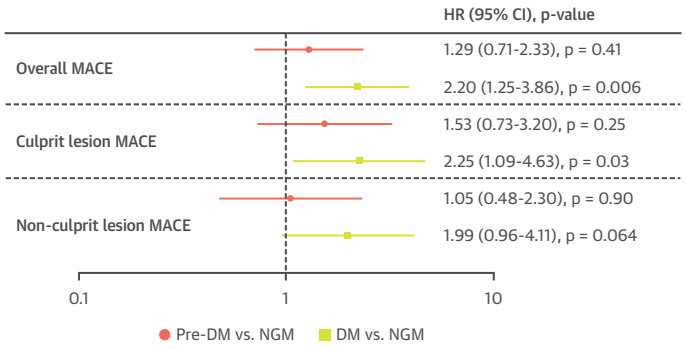
STUDY LIMITATIONS. This study had several limitations. First, this was a post hoc analysis of a prospective study, and our results should be considered hypothesis generating rather than confirmatory.

Second, plasma glucose concentrations may be increased in ACS, which increases the risk of inadvertently classifying patients with NGM as having pre-DM or DM (34); however, the GAMI (Glucose Tolerance in Acute Myocardial Infarction) study, which enrolled patients with acute myocardial infarction, showed that results were similar when glucose tolerance was estimated during the index hospitalization or 3 months later (35).

Third, we did not have detailed information related to the duration of DM.

Finally, in the present investigation, only nonculprit lesions were evaluated by imaging. Focusing more on the culprit lesion might have led to different results; however, PROSPECT is unique in that it focused on the nonculprit lesion.

FIGURE 2 Forest Plot



Adjusted risk for overall major adverse cardiac events (MACEs), culprit lesion MACE, and nonculprit lesion MACEs in patients with pre-diabetes (pre-DM) and diabetes mellitus (DM). Adjusted for age, sex, presence of thin-cap fibroatheroma, presence of minimal luminal area <4 mm^2, and prior percutaneous coronary intervention (overall MACEs) or age and sex (culprit and nonculprit MACEs). CI = confidence interval; HR = hazard ratio.

CONCLUSIONS

Impaired glucose metabolism is common among patients presenting with ACS. DM but not pre-DM is associated with an increased risk for MACEs. Thus, preventing patients from progressing from pre-DM to DM is important. Further studies are warranted to elucidate the impact of pre-DM on atherosclerosis development and clinical outcomes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This study shows that the prevalence of pre-DM and DM is high among patients with ACS. DM but not pre-DM was associated with increased risk for MACEs despite the absence of significant differences in IVUS indexes of coronary morphology.

TRANSLATIONAL OUTLOOK 1: Patients with ACS should be systematically screened for pre-DM and DM.

TRANSLATIONAL OUTLOOK 2: Clinicians should devote preventive measures to avoid the progression of pre-DM to manifest DM in patients with ACS.

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KEY WORDS coronary artery plaque, diabetes mellitus, intravascular ultrasound, pre-diabetes

APPENDIX For a supplemental table, please see the online version of this paper.