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Impact of TCFA on Unanticipated Ischemic Events in Medically Treated Diabetes Mellitus

Insights From the PROSPECT Study

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ABSTRACT

OBJECTIVES This study sought to investigate the relationship between thin-cap fibroatheromas (TCFAs) on major adverse cardiac events (MACEs) arising from medically treated nonculprit lesions (NCLs) in patients with acute coronary syndromes (ACS) with and without diabetes mellitus (DM).

BACKGROUND MACEs occur frequently in patients with DM and ACS. The impact of plaque composition on subsequent MACEs in DM patients with ACS is unknown.

METHODS In the PROSPECT (Providing Regional Observations Study Predictors of Events in the Coronary Tree) study, using 3-vessel radiofrequency intravascular ultrasound, we analyzed the incidence of NCL-MACE in 2 propensity-matched groups according to the presence of DM and TCFA.

RESULTS Among 697 patients, 119 (17.7%) had DM. The 3-year total MACE rate (29.4% vs. 18.8%; $p = 0.01$) was significantly higher in patients with versus without DM, driven by a higher rate of NCL-MACE in DM (18.7% vs. 10.4%; $p = 0.02$). Propensity score matching generated 2 balanced groups with and without DM of 82 patients each. Among DM patients, the presence of ≥1 TCFA was associated with higher NCL-MACE at 3 years (27.8% vs. 8.9% in patients without a TCFA, hazard ratio: 3.56; 95% confidence interval: 0.98 to 12.96; $p = 0.04$). DM patients without a TCFA had a similar 3-year rate of NCL-MACE as patients without DM (8.9% vs. 8.9%; hazard ratio: 1.09; 95% confidence interval: 0.27 to 4.41; $p = 0.90$).

CONCLUSIONS ACS patients with DM and ≥1 TCFA have a high rate of NCL-MACE at 3 years. In contrast, the prognosis of ACS patients with DM but no TCFAs is favorable and similar to patients without DM. (J Am Coll Cardiol Img 2017;10:451–8) © 2017 by the American College of Cardiology Foundation.

Patients with diabetes mellitus (DM) and those presenting with acute coronary syndromes (ACS) are known to have a higher risk of adverse events after percutaneous coronary intervention (PCI) than patients without DM and without ACS (1–5). It is believed that these unfavorable outcomes are due not only to worse outcomes from the PCI-treated segments (culprit lesions), but also to symptomatic progression of disease elsewhere in the coronary tree (i.e., from nonculprit lesions [NCLs]), which are often not apparent on baseline angiography (6). Whether intravascular ultrasound (IVUS) assessment can identify morphologic characteristics of NCLs that predict future events was

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CABG = coronary artery bypass graft surgery

CI = confidence interval

DM = diabetes mellitus

HR = hazard ratio

IVUS = intravascular ultrasound

MACE = major adverse cardiac event(s)

MLA = minimal luminal area

NCL = nonculprit lesions

PB = plaque burden

PCI = percutaneous coronary intervention

TCFA = thin-cap fibroatheroma

examined in the PROSPECT (Providing Regional Observations Study Predictors of Events in the Coronary Tree) study (7). PROSPECT demonstrated that lesions that are otherwise angiographically mild but have features consistent with vulnerable plaques, including thin cap fibroatheroma (TCFA), plaque burden (PB) ≥70%, or a minimal lumen area (MLA) of ≤4 mm^2 are prone to rapid lesion progression and major adverse cardiac events (MACE). Furthermore, insulin-treated DM was found to be a positive predictor for future MACE arising from medically treated NCLs (NCL-MACE). Marso et al. (5), in a descriptive overview of the gray-scale and radiofrequency IVUS findings in DM patients from the PROSPECT trial, reported that patients with DM had higher rates of NCL-MACE at 3 years than those without DM or with metabolic syndrome, a finding confirmed by others (8). They also showed that patients with as opposed to without DM were more likely to have ≥1 NCL containing multiple high-risk plaque features shown to correlate with future unanticipated MACE.

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Despite these findings, the importance of TCFAs in explaining the high-risk nature of DM has been incompletely characterized. We therefore performed a further analysis from PROSPECT to isolate the effect of TCFAs in combination with DM on future NCL-MACE.

METHODS

The design of the PROSPECT study has been previously described (7). PROSPECT enrolled 697 ACS patients after successful and uncomplicated PCI of all angiographically evident culprit coronary lesions. Following PCI, both gray-scale and radiofrequency IVUS of the left main coronary artery and the proximal 6 to 8 cm of each of the 3 major epicardial coronary arteries was performed. Angiographic core laboratory qualitative and quantitative measurements were obtained for each 1.5 mm of the coronary tree, including each epicardial vessel and side branch that was ≥1.5 mm in diameter. Analysis of all angiographic lesions with ≥30% visible diameter stenosis was also pre-specified. In the IVUS core laboratory, a lesion was defined as ≥3 consecutive frames with PB of ≥40%. Plaque components were identified by radiofrequency analysis as dense calcium, necrotic core, fibro-fatty tissue, or fibrous tissue, with the cross-sectional area and percentage of total plaque area reported for each component. Lesions were further classified as either TCFAs, thick-cap fibroatheromas, pathologic intimal thickening, fibrotic plaques, or fibrocalcific plaques (7). A fibroatheroma was defined as the presence of >10% confluent necrotic core. If ≥30° of necrotic core abutted the lumen in ≥3 consecutive frames, the fibroatheroma was classified as a TCFA; otherwise, it was categorized as a thick-cap fibroatheroma.

ENDPOINTS AND DEFINITIONS. DM was identified by patient history and was classified as treatment with exercise and/or diet, oral hypoglycemic agents, or insulin. The definitions of the endpoints assessed and the event adjudication process has been previously described (7). The primary endpoints were adjudicated by a clinical events committee, using original source documents. The pre-specified primary endpoint in PROSPECT was the incidence of MACE (a composite of death from cardiac causes, cardiac arrest, myocardial infarction, or rehospitalization from unstable or progressive angina). On the basis of follow-up angiography, MACE were further adjudicated as occurring at initially treated sites (culprit lesions) or at previously untreated coronary segments (NCLs). If follow-up angiography was not performed, the site associated with the event was classified as indeterminate.

STATISTICAL METHODS. NCL-MACEs were evaluated according to the presence of medically treated DM. To isolate the effects of DM, 2 equal-sized propensity-matched groups were created on the basis of the following variables: sex, hypertension, hyperlipidemia, family history of coronary disease, current smoking, presence of ≥1 lesion with PB ≥70%, presence of ≥1 lesion with MLA ≤4 mm^2, and presence of ≥1 TCFA. Matching was performed using the SAS macro %GREEDMTCH (SAS Institute, Cary, North Carolina) (8), which implements a Greedy 5 → 1 Digit Match algorithm that matches pairs using their propensity score that is iteratively rounded to 1 less decimal place if no perfect match is found. In the matched cohort used in this analysis, 61.0% of the pairs have propensity scores that are perfect matches to the fifth decimal place, and the largest difference in the propensity scores of matched pairs was 0.04914; the c-statistic for the propensity score model was 0.697. To evaluate the impact of DM and TCFA on future adverse events originating from NCLs, the NCL-MACE rate was evaluated according to presence of DM and TCFA in the matched populations.

Categorical outcomes were compared by the chi-square test. Continuous variables are presented as

mean ± SD and were compared by the Student *t* test. Cumulative event rates were estimated using time-to-event methods and compared by the log-rank test. A p value of <0.05 was considered statistically significant. All analyses were performed with SAS, version 9.2 (SAS Institute).

RESULTS

BASELINE CHARACTERISTICS. Of the 697 patients enrolled in PROSPECT, 119 (17.1%) had medically treated DM. Propensity matching generated 2 groups with and without DM, each with 82 patients. Among the 82 DM patients, 10 (12.2%) were treated with insulin. The baseline characteristics of the matched DM and non-DM groups are shown in **Table 1**, and the baseline characteristics of the unmatched groups appear in Online Table 1. Before matching, patients with compared to those without DM were older and had a higher incidence of hypertension and hypercholesterolemia, but a lower incidence of smoking. The baseline characteristics were well balanced after matching.

The IVUS characteristics of patients with and without DM for the matched and unmatched cohorts are shown in **Table 2** and Online Table 2, respectively. In the unmatched analysis, patients with versus those without DM showed a trend toward a higher incidence of NCLs with PB ≥70% and/or MLA ≤4 mm^2, and had a significantly higher incidence of lesions with all 3 high-risk characteristics (TCFA, PB ≥70%, and MLA ≤4 mm^2). After matching, these high-risk lesion types were similarly distributed. The angiographic and IVUS characteristics of the individual lesions were not significantly different in both the matched and unmatched groups (**Table 3** and Online Table 3, respectively). Of note, the average diameter stenosis of the NCLs in patients with and without DM in the matched groups by quantitative coronary angiography was mild (36.2% vs. 37.9% for angiographically evident lesions and 13.2% vs. 12.6% for IVUS detected lesions, respectively). The baseline, demographic, and IVUS findings of DM as well as non-DM patients according to presence versus absence of TCFA are presented in Online Tables 5 and 6, respectively.

TABLE 1 Baseline Clinical Characteristics and Medication Compliance in the Propensity-Matched Groups With and Without Diabetes

	Diabetes (n = 82)	No Diabetes (n = 82)	p Value
Age, yrs	61.9 ± 11.3	60.9 ± 11.0	0.63
Male	76.8 (63)	78.0 (64)	0.85
Prior MI	8.5 (7)	9.9 (8)	0.77
History of known CAD (stenosis ≥50%)	13.4 (11)	13.8 (11)	0.95
Family history of CAD	34.1 (28)	32.9 (27)	0.87
Hypertension	57.3 (47)	54.9 (45)	0.75
Hypercholesterolemia	57.3 (47)	57.3 (47)	1.0
Smoking	42.7 (35)	39.0 (32)	0.63
Clinical syndrome at presentation			
ST-segment elevation MI >24 h	31.7 (26)	25.6 (21)	0.39
Non–ST-segment elevation MI	67.1 (55)	72.0 (59)	0.5
Unstable angina	1.2 (1)	2.4 (2)	1.0
Creatinine clearance, ml/min	97.1 (71.1–127.8)	88.9 (71.5–114.8)	0.1
HbA1c	6.70 (6.20–7.70)	5.60 (5.10–5.85)	<0.01
Cardiac medications			
Any lipid-lowering medication			
At discharge	89.0 (73)	90.2 (74)	0.80
At 3 yrs	92.3 (60)	90.7 (68/75)	0.73
Statins			
At discharge	84.1 (69)	89.0 (73)	0.36
At 3 yrs	86.2 (56)	89.3 (67/75)	0.57
Lipid-lowering medication (nonstatin)			
At discharge	11.0 (9)	3.7 (3)	0.07
At 3 yrs	12.3 (8)	6.7 (5/75)	0.25
Aspirin			
At discharge	97.6 (80)	96.3 (79)	1.0
At 3 yrs	92.3 (60)	84.0 (63/75)	0.13
Thienopyridines			
At discharge	98.8 (81)	97.6 (80/82)	1.0
At 3 yrs	47.7 (31)	33.3 (25/75)	0.08
ACE inhibitors			
At discharge	69.1 (56)	69.5 (57)	0.96
At 3 yrs	63.1 (41)	61.3 (46/75)	0.83
Angiotensin-receptor blocker			
At discharge	15.9 (13)	5.0 (4/80)	0.02
At 3 yrs	23.1 (15)	12.2 (9/74)	0.09
Beta blockers			
At discharge	91.5 (75)	91.5 (75)	1.0
At 3 yrs	80.0 (52)	88.0 (66/75)	0.19
Calcium channel blockers			
At discharge	20.0 (16)	8.6 (7/81)	0.04
At 3 yrs	20.6 (13)	14.7 (11/75)	0.36

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

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; CAD = coronary artery disease; MI = myocardial infarction; PCI = percutaneous coronary intervention.

CLINICAL OUTCOMES. Three-year clinical outcomes in patients with and without DM in the matched and unmatched groups are presented in **Table 4** and in Online Table 4, respectively. In the unmatched analysis, the total 3-year MACE rate was significantly higher in patients with versus without DM (29.4% vs. 18.8%; hazard ratio [HR]: 1.66; 95% confidence interval [CI]: 1.11 to 2.49; p = 0.01). The same was also true for NCL-MACE (18.7% vs. 10.4%; HR: 1.84; 95% CI: 1.09 to 3.10; p = 0.02). After propensity matching, DM was associated with higher total MACE (32.5% vs. 15.2%; HR: 2.35; 95% CI: 1.17 to 4.72; p = 0.01), and a trend toward higher NCL-MACE (18.7% vs. 8.9%; HR: 2.22; 95% CI: 0.88 to 5.56; p = 0.08). The greater NCL-MACE rate in patients with DM was driven mainly by rehospitalization for

TABLE 2 Patient-Level NCL Baseline IVUS Findings in the Propensity-Matched Groups With and Without Diabetes

	Diabetes (n = 82)	No Diabetes (n = 82)	p Value
Number of IVUS NCLs	5 (4–6)	5 (4–7)	0.10
IVUS NCLs: volumetric data			
Total lesion length, mm	67.85 (47.53–97.98)	82.38 (46.11–107.18)	0.25
Plaque volume, %	49.3 (46.7–51.9)	49.3 (46.6–52.6)	0.94
Prevalence of patients with ≥1 high-risk NCL characteristic			
MLA ≤4 mm^2	57.3 (47)	57.3 (47)	1.0
PB ≥70%	39.0 (32)	40.2 (33)	0.87
TCFA	52.4 (43)	51.2 (42)	0.88
MLA ≤4 mm^2 and PB ≥70%	29.3 (24)	31.7 (26)	0.73
MLA ≤4 mm^2 and TCFA	34.1 (28)	31.7 (26)	0.74
PB ≥70% and TCFA	25.6 (21)	24.4 (20)	0.86
All 3 high-risk characteristics	20.7 (17)	20.7 (17)	1.0

Values are median (interquartile range) and % (n).
IVUS = intravascular ultrasound; MLA = minimum lumen area; NCL = nonculprit lesion; PB = plaque burden; TCFA = thin cap fibroatheroma.

unstable or progressive angina, and almost all hospitalized patients required revascularization. Comparing patients with and without DM, the greater MACE rate in patients with DM was driven by NCL-related events; there were no significant differences in MACE arising from culprit lesions in both the unmatched and matched comparisons (**Figure 1**, **Table 4**, Online Table 4).

TABLE 3 Quantitative Coronary Angiography of the Nonculprit Lesions in the Propensity-Matched Groups With and Without Diabetes

	Diabetes	No Diabetes	p Value
Angiographic-defined lesions	n = 193	n = 208	
Reference vessel diameter, mm	2.36 (1.86–2.93)	2.19 (1.88–2.72)	0.09
Minimal lumen diameter, mm	1.53 (1.14–1.97)	1.35 (1.11–1.73)	0.02
Diameter stenosis, %	36.2 (31.1–44.2)	37.9 (33.1–46.8)	0.09
Lesions with QCA DS ≥50%	17.6 (32/182)	18.8 (37/197)	0.76
Lesions with QCA DS ≥70%	4.4 (8/182)	4.1 (8/197)	0.87
Thrombus	0.5 (1/193)	0.5 (1)	1.0
Eccentricity	6.2 (12/193)	3.4 (7)	0.18
Coronary artery lesion location			
Left main	1.6 (3)	0.0 (0)	0.11
Left anterior descending (or branches)	37.5 (72)	38.6 (80)	0.81
Left circumflex (or branches)	31.3 (60)	29.0 (60)	0.62
Right (or branches)	29.7 (57)	32.4 (67)	0.56
IVUS-defined lesions	n = 397	n = 429	
Reference vessel diameter, mm	2.94 (2.55–3.44)	2.99 (2.53–3.44)	0.71
Minimal lumen diameter, mm	2.47 (2.03–2.97)	2.49 (2.07–3.10)	0.61
Diameter stenosis, %	13.2 (6.9–23.0)	12.6 (6.5-–2.5)	0.55
Lesions with QCA DS ≥50%	2.0 (8)	1.9 (8)	0.88
Lesions with QCA DS ≥70%	0.3 (1)	0.0 (0)	0.48
Thrombus	0.3 (1)	0.2 (1)	1.0
Eccentricity	1.0 (4)	1.9 (8)	0.3
Coronary artery lesion location			
Left main	5.0 (20)	4.2 (18)	0.56
Left anterior descending (or branches)	31.0 (123)	32.6 (140)	0.61
Left circumflex (or branches)	25.4 (101)	25.2 (108)	0.93
Right (or branches)	38.5 (153)	38.0 (163)	0.87

Values are median (interquartile range), % (n/N), and % (n).
DS = diameter stenosis; IVUS = intravascular ultrasound; QCA = quantitative coronary angiography.

As shown in **Figure 2**, among matched group patients with DM, the presence of ≥1 TCFA was strongly associated with a higher rate of NCL-MACE at 3 years compared with patients without a TCFA (27.8% vs. 8.9%; HR: 3.56, 95% CI: 0.98 to 12.96; p = 0.04). A similar trend was also observed in patients without DM, but the difference was not significant (**Figure 2**). DM patients without a TCFA had a similar 3-year rate of NCL-MACE as all patients without DM (8.9% vs. 8.9%; HR: 1.09; 95% CI: 0.27 to 4.41; p = 0.90). There was also no significant difference in the 3-year NCL-MACE rate in DM and non-DM patients without a TCFA (8.9% vs. 5.2%, respectively; HR: 1.69; 95% CI: 0.28 to 10.10; p = 0.57). Conversely, in patients with a TCFA, the 3-year NCL-MACE rate was higher in DM compared with non-DM patients (27.8% vs. 12.3%, respectively; HR: 2.54; 95% CI: 0.87 to 7.45; p = 0.08). Finally, 7 patients with DM who developed NCL-MACE during follow-up had 1 or more TCFAs identified in their coronary tree at baseline by intravascular imaging. Of these, 3 plaques responsible for the NCL-MACE were originally TCFAs, 2 were thick-cap fibroatheromas, and 2 were pathologic intimal thickening. A TCFA was present in 3 of 4 coronary arteries in which the NCL-MACE arose from a non-TCFA. Among 5 non-DM patients with at least 1 baseline TCFA and subsequent NC-MACE, 4 events arose from a TCFA.

DISCUSSION

In the present analysis from the PROSPECT study, the increased risk of long-term MACE in patients with DM compared with those without DM was due to a greater rate of unanticipated events arising from medically treated NCLs. Moreover, this risk was predominately isolated to DM patients with a TCFA. A synergistic relationship was present between diabetic status and lesion phenotype such that patients with DM and a TCFA had a greater risk of 3-year NCL-MACE than patients without DM and a TCFA. Conversely, patients with DM but without a TCFA had a similar prognosis as patients without DM (with or without a TCFA).

Our study extends the prior analysis of Marso et al. (5) by focusing on the role of the TCFA in patients with and without DM. TCFAs are more prevalent in patients with DM and may reflect the greater level of inflammation and macrophage infiltration predisposing to future ACS in these patients (9–11). In the present study in which propensity matching was used

TABLE 4 Clinical Outcomes at 3 Years in the Propensity-Matched Groups With and Without Diabetes

	Diabetes (n = 82)	No Diabetes (n = 82)	HR (95% CI)	p Value
Any MACE	32.5 (23)	15.2 (12)	2.35 (1.17–4.72)	0.01
Clinical outcomes arising from culprit lesions				
Cardiac death	0.0 (0)	0.0 (0)	–	–
Cardiac arrest	1.4 (1)	0.0 (0)	–	0.29
MI	2.7 (2)	1.3 (1)	2.25 (0.20–24.82)	0.50
Cardiac death, arrest, or MI	2.7 (2)	1.3 (1)	2.25 (0.20–24.82)	0.50
Rehospitalization for unstable or progressive angina	12.9 (9)	10.1 (8)	1.25 (0.48–3.24)	0.65
Culprit lesion MACE (composite of above)	14.3 (10)	11.4 (9)	1.25 (0.51–3.07)	0.63
Revascularization (PCI or CABG)	14.3 (10)	10.2 (8)	1.42 (0.56–3.60)	0.46
Clinical outcomes arising from NCLs				
Cardiac death	0.0 (0)	0.0 (0)	–	–
Cardiac arrest	0.0 (0)	0.0 (0)	–	–
MI	1.8 (1)	1.3 (1)	1.19 (0.07–19.01)	0.90
Cardiac death, arrest, or MI	1.8 (1)	1.3 (1)	1.19 (0.07–19.01)	0.90
Rehospitalization for unstable or progressive angina	17.0 (12)	8.9 (7)	2.03 (0.80–5.17)	0.13
NCL-MACE (composite of above)	18.7 (13)	8.9 (7)	2.22 (0.88–5.56)	0.08
Revascularization (PCI or CABG)	17.3 (12)	8.9 (7)	2.02 (0.80–5.14)	0.13
Clinical outcomes arising from an indeterminate location				
Cardiac death	2.8 (2)	1.3 (1)	2.22 (0.20–24.45)	0.50
Cardiac arrest	0.0 (0)	0.0 (0)	–	–
MI	1.4 (1)	0.0 (0)	–	0.29
Cardiac death, arrest, or MI	4.2 (3)	1.3 (1)	3.36 (0.35–32.35)	0.26
Rehospitalization for unstable or progressive angina	1.6 (1)	0.0 (0)	–	0.27
Indeterminate MACE (composite of above)	5.7 (4)	1.3 (1)	4.56 (0.51–40.80)	0.14
Revascularization (PCI or CABG)	0.0 (0)	0.0 (0)	–	–

Values are % (n). Rates are Kaplan-Meier estimates.

CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac event(s); other abbreviations as in Tables 1 and 2.

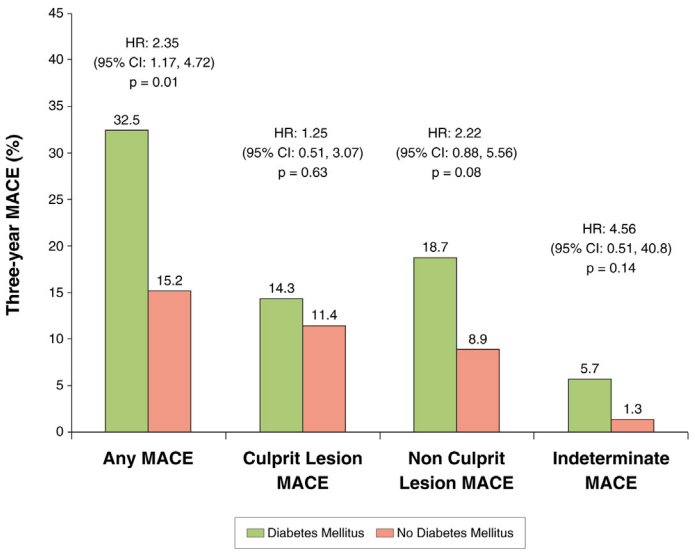
to eliminate the effects of measured confounders, DM patients had a 32.5% 3-year MACE rate, with more than one-half of events arising from angiographically mild NCLs. Furthermore, the presence of at least 1 TCFA in patients with DM was associated with a >3-fold higher MACE rate compared with DM patients without a TCFA, and >5-fold higher MACE compared with patients without DM or TCFA, thus representing a very high-risk group for future adverse events.

In the overall PROSPECT population, DM patients had a significantly higher rate of NCL-MACE than non-DM patients. A similar trend was present in the propensity-matched analysis, which did not reach statistical significance, likely because of reduced power. In conjunction with the findings of Marso et al. (5), the current analysis demonstrates that the worse outcomes in patients with versus without DM can be ascribed not only to a higher prevalence of high-risk lesions at baseline, but also to more rapid progression of atherosclerosis at NCL sites, particularly TCFAs.

No prior study has specifically examined the impact of TCFA and DM in ACS patients. However, Nasu et al. (12) reported that the atherosclerotic lesions of DM patients have an increased amount of dense calcium and necrotic core as well as a greater frequency of TCFA and fibrocalcific lesions. Nicholls et al. (13) reported that DM is associated with more extensive atherosclerosis, inadequate compensatory remodeling, and accelerated plaque progression. The present study extends the findings from these 2 prior analyses.

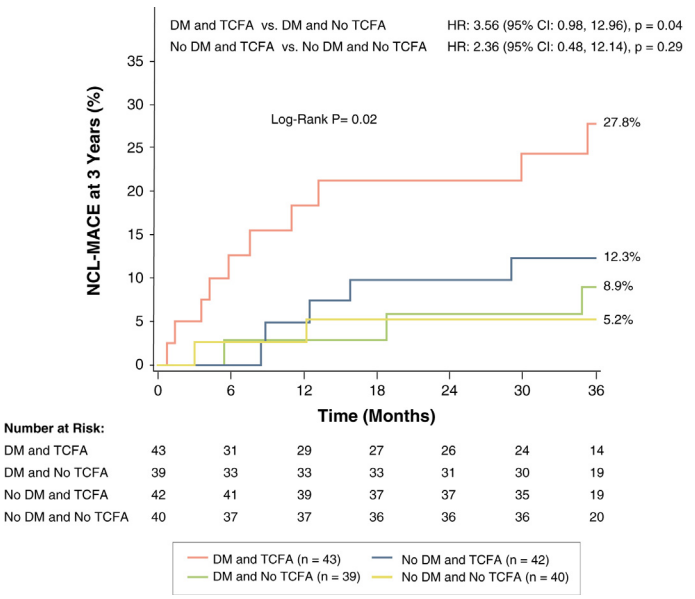
Our results also suggest a mechanistic explanation for the greater rates of MACE after PCI in patients with DM (3,14) and explain why coronary artery bypass graft surgery (CABG) may be superior to PCI in diabetic patients with extensive coronary artery disease (15,16). As shown in our analysis, the main driver of 3-year MACE in DM patients was not events originating from the treated culprit lesions (e.g., from restenosis or stent thrombosis), but rather from new lesions arising from medically treated NCLs. Fewer than 2% of these NCLs had an angiographic diameter stenosis of >50%, and thus would not be treated by PCI. Indeed, such lesions are not even registered in anatomic risk instruments such as the Syntax score. Anatomic risk scores may thus be of less utility in patients with DM than those without DM. Furthermore, because almost all NCLs were angiographically

FIGURE 1 MACE Rates at 3 Years in DM and Non-DM Patients



Time-to-event estimates of Culprit Lesion Related MACE, Non-Culprit Lesion Related MACE, indeterminate MACE, and any MACE according to the presence of diabetes at 3 years in the propensity-matched groups of patients with and without diabetes. CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac event(s).

FIGURE 2 MACE Outcomes According to Presence of DM and TCFA



Time-to-Event Estimates of non-culprit Lesion-Related MACE, according to the presence of diabetes and/or a TCFA at 3 years in the propensity-matched groups of patients with and without diabetes. DM = diabetes mellitus; NCL = nonculprit lesion; TCFA = thin-cap fibroatheroma; other abbreviations as in Figure 1.

mild at baseline, and few had a MLA <2.5 mm^2 (7), it is unlikely that many of these lesions would be ischemic at baseline (17,18). Thus, targeting only ischemic lesions (e.g., using the recently proposed functional Syntax score approach) (19) would be unlikely to meaningfully improve PCI outcomes in DM patients. Moreover, the high event rates observed in DM patients in our study occurred despite tight monitoring and high adherence with guideline directed medical therapies, far beyond that typically achieved in current daily practice (20).

Thus, because they ignore vulnerable plaque, the current risk models are suboptimal to accurately predict future adverse events in high-risk populations, such as those with DM. Further studies are required to determine whether a combination of intravascular imaging plus functional assessment of coronary lesions might provide better risk stratification in diabetic patients, and as described in the following section, improve choice of therapy. Furthermore, newer intravascular imaging modalities including near infrared spectroscopy and optical coherence tomography may provide advantages over IVUS for the detection of vulnerable plaques (21,22). Natural history studies such as PROSPECT are required to validate the utility of these imaging tools.

The present study also has potential implications for the therapeutic approach to patients with DM. In the setting of complex multivessel disease, CABG is an excellent option because it bypasses many untreated vulnerable NCLs in the same territories as the ischemic culprit lesions. CABG is not an optimal solution, however, for vessels with only nonischemic but otherwise high-risk NCLs, because of the high risk of graft occlusion from competitive flow (23). In the PRAMI (Preventive Angioplasty in Myocardial Infarction) trial (24), PCI of all angiographically detected NCLs with diameter stenosis >50% in patients presenting with ST-segment elevation MI and multivessel disease resulted in better outcomes than treatment of the infarct lesion only, suggesting that a combination of ischemia relief and "preventive" plaque passivation might be beneficial in high-risk ACS patients. However, the underlying severity (and ischemic potential) of these lesions has not been described, and composition of these plaques is unknown. Finally, proprotein convertase subtilisin/kexin type 9 inhibitors have shown great promise in markedly reducing low-density lipoprotein levels beyond that achieved by high-dose statins (25,26), and also warrant study in high-risk DM patients with ACS and vulnerable plaque.

STUDY LIMITATIONS. The current report is on the basis of a post hoc patient-level analysis and should

therefore be considered hypothesis generating. The sizes of the matched groups were modest, although the results were consistent with those from the entire study population. Nonetheless, propensity matching cannot control for unmeasured confounders. Although the rate of guideline directed medication use was high throughout the study duration, we cannot be certain that risk factor control was similar in both groups. Moreover, the medication adherence in this study is superior to that achieved in daily clinical practice and therefore the present outcomes should be considered as the best achievable with medical therapy. Follow-up angiography was not available in all patients with events; therefore, the origin of these events was classified as indeterminate. This may have led to an underestimation of either the culprit lesion or NCL event rates. We have thus presented the total MACE rates as well as the NCL-MACE rates in patients with and without DM to place these results in perspective. The present study cannot be used to establish causality given the limited numbers of events, the occurrence of some events at lesion sites without baseline intravascular imaging, and the absence of serial follow-up imaging and angiography in all patients. Finally, because of the limited resolution of IVUS, it is possible that not all fibroatheromas defined as TCFAs had a cap thickness of <65 μm, the usual pathologic criterion. Furthermore, because fractional flow reserve was not routinely performed in PROSPECT, we cannot exclude that some NCLs may result in ischemia, although the proportion is likely to be small given the mild diameter stenosis of these lesions (27).

CONCLUSIONS

These limitations notwithstanding, the present study demonstrates that in high-risk patients presenting with ACS and DM, the presence of an untreated TCFA is associated with a very high rate of MACE at 3 years, explaining to a large extent the poor prognosis of the high-risk diabetic cohort. Conversely, the prognosis of DM patients without TCFA was similar to that of the patient without DM. Considering the increasing global prevalence of DM, further studies are warranted to determine whether identification of vulnerable plaques by either intravascular or noninvasive imaging in high-risk DM patients might inform more accurate prognosis and improved decision-making regarding potent medical therapies and strategies for revascularization.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In medically treated, high-risk patients with diabetes mellitus presenting with an acute coronary syndrome, the presence of an untreated TCFA is associated with a high rate of major adverse cardiac events at 3 years. In contrast, the prognosis of diabetic patients without an untreated TCFA is similar to that of lower risk acute coronary syndrome patients without diabetes.

TRANSLATIONAL OUTLOOK: Considering the growing worldwide prevalence of diabetes, further studies are warranted to determine whether information derived from imaging modalities capable of identifying high-risk plaques (e.g., TCFA) may lead to more accurate prognosis and improve clinical decision-making regarding use of more potent medical therapies and revascularization strategies.

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KEY WORDS diabetes mellitus, major adverse cardiac event(s), thin-cap fibroatheroma

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