JACC: CARDIOVASCULAR IMAGING
VOL. ■, NO. ■, 2016

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2015.12.023

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

Insights From the PROSPECT Study

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ABSTRACT

OBJECTIVES We 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 2016;■:■-■) © 2016 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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Manuscript received September 28, 2015; revised manuscript received November 30, 2015, accepted December 1, 2015.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndromes

CABG = coronary artery bypass graft surgery

CI = confidence interval

DM = diabetes mellitus

HR = hazard ratio

IVUS = intravascular ultrasound

MACE = major adverse cardiac events

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.

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.