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Impact of Coronary Lesion Complexity on Drug-Eluting Stent Outcomes in Patients With and Without Diabetes Mellitus

Analysis From 18 Pooled Randomized Trials

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Objectives The aim of this study was to investigate whether baseline lesion complexity affects drug-eluting stent (DES) outcomes according to diabetic status.

Background Previous studies have reported conflicting results regarding DES safety and efficacy in patients with and without diabetes mellitus (DM).

Methods Patient-level data from 18 prospective randomized trials were pooled. DES treatment outcomes in patients with versus without DM were analyzed in 2 propensity score–matched groups further stratified according to lesion complexity (American College of Cardiology and American Heart Association class A/B1 vs. B2/C). Remaining baseline differences were adjusted for by multivariate analysis.

Results DM was present in 3,467 of 18,441 patients (18.8%). DM was a predictor of 1-year repeat revascularization (target lesion revascularization: hazard ratio: 1.34; 95% confidence interval: 1.05 to 1.70; target vessel revascularization: hazard ratio: 1.40; 95% confidence interval: 1.15 to 1.72) and cardiac death or myocardial infarction (hazard ratio: 1.40; 95% confidence interval: 1.09 to 1.81). Rates of target lesion and target vessel revascularization were significantly higher in patients with versus those without DM with type B2/C lesions (8.0% vs. 4.5% and 10.6% vs. 5.9%, respectively, $p < 0.0001$ for both), but not in patients with only type A/B1 lesions (4.6% vs. 4.8%, $p = 0.87$, and 7.4% vs. 6.8%, $p = 0.47$, respectively), with a significant interaction between DM and lesion type observed for both endpoints ($p = 0.01$ and $p = 0.02$, respectively). No interaction was observed for death or myocardial infarction ($p = 0.28$).

Conclusions In the DES era, patients with DM remain at increased risk for cardiac death or myocardial infarction. However, DM is a risk factor for repeat revascularization only in those patients with complex lesions; patients with DM and noncomplex lesions have similar rates of 1-year freedom from repeat revascularization as do patients without DM. (J Am Coll Cardiol 2014;63:2111–8) © 2014 by the American College of Cardiology Foundation

Diabetes mellitus (DM) is a well-established predictor of angiographic restenosis and ischemia-driven target lesion revascularization (TLR) and target vessel revascularization (TVR) after percutaneous coronary intervention (PCI) with bare-metal stents (BMS) (1,2). Drug-eluting stents (DES) significantly reduce restenosis rates in patients with and those without DM, compared with BMS (3–6). Some

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Abbreviations and Acronyms

ACC = American College of Cardiology
AHA = American Heart Association
BMS = bare-metal stent(s)
CABG = coronary artery bypass grafting
CI = confidence interval
DES = drug-eluting stent(s)
DM = diabetes mellitus
HR = hazard ratio
MACE = major adverse cardiac event(s)
MI = myocardial infarction
PCI = percutaneous coronary intervention
TLR = target lesion revascularization
TVR = target vessel revascularization

studies comparing outcomes after PCI with DES suggest than DM is no longer a correlate of restenosis (7,8), whereas others still identify DM as a predictor of TLR and TVR (9). Whether the efficacy of DES in eliminating diabetes as a risk factor for restenosis depends on lesion complexity is unknown. In this regard, lesions in patients with DM are known to be longer and present in smaller vessels than in patients without DM (10). It is thus conceivable that DM is a risk factor for restenosis given the propensity for more complex lesions in this condition and that DM might not predict adverse outcomes after controlling for lesion complexity. We therefore analyzed the efficacy and safety of DES from a large patient-level pooled database of 18,471 patients from 18 prospective randomized trials and examined the impact of DM on patient outcomes as a function of baseline lesion complexity.

Methods

To perform a comprehensive, patient-level pooled analysis, we combined 18 databases maintained at the Cardiovascular Research Foundation from prospective, randomized trials in which 1-year follow-up of patients treated with DES was available. The designs of these specific trials have been previously described and are summarized in Table 1 (3–5,11–25). One-year follow-up was completed in all trials, comprising the follow-up period for this study. The TAXUS, SIRIUS (Sirolimus-Eluting Stent in De Novo Native Coronary Lesions), and ENDEAVOR series of trials evaluated the use of first-generation paclitaxel-eluting, sirolimus-eluting, and zotarolimus-eluting stents, respectively, compared with BMS or other DES, whereas the SPIRIT (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions) series of trials and COMPARE (Comparison of the Everolimus Eluting XIENCE-V Stent With the Paclitaxel Eluting TAXUS LIBERTÉ Stent in All-Comers: A Randomized Open Label Trial) compared a second-generation everolimus-eluting stent with the first-generation paclitaxel-eluting stent. The ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial compared 3 different pharmacological treatments in patients with moderate-risk and high-risk acute coronary syndromes who underwent invasive treatment. Stent choice (BMS or first-generation DES) was at the discretion of the operator. In the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial, patients presenting with ST-segment elevation were randomized to PCI with the first-generation paclitaxel-eluting stent versus an otherwise identical BMS stent.

Endpoints and statistical methods. Because the purpose of this study was to analyze DES outcomes in patients with versus without DM, only DES-treated patients were included in this analysis. Efficacy endpoints were rates of TLR and TVR. We also examined the rates of TVR-non-TLR (i.e., TVR remote from the target lesion). Safety endpoints were all-cause death, cardiac death, myocardial infarction (MI), definite and probable stent thrombosis (as defined by the Academic Research Consortium) (26), and composite cardiac death or MI. Major adverse cardiac events (MACE) were defined as the composite of all-cause death, MI, or TVR. TLR was defined as any repeat revascularization procedure (percutaneous or surgical) of the original target lesion site, including the stent and 5-mm proximal and distal margins. TVR was defined as any revascularization procedure occurring within the major epicardial vessel in which the stent was implanted or its branches. TVR-non-TLR was defined as any TVR occurring outside the TLR segment, as described earlier. Events as adjudicated in each trial were used for the pooled analysis. All analyses are by intention to treat.

Outcomes of all patients treated with DES were evaluated according to the presence of medically treated DM. To evaluate the impact of baseline lesion severity on efficacy and safety endpoints, patients with American College of Cardiology (ACC) and American Heart Association (AHA) classification A/B1 lesions versus those with any B2/C lesions were compared in the DM and non-DM cohorts (27). Patients with multiple PCI lesions were included in the B2/C group if at least 1 lesion was B2 or C in complexity; otherwise, they were included in the A/B1 group. To minimize differences in baseline characteristics of patients with and those without DM, 2 equal-sized propensity score–matched groups were created on the basis of the following variables: sex, hypertension, hyperlipidemia, previous MI, previous PCI, clinical syndrome at presentation, and stent type. The C-statistic for this model was 0.64. Stepwise Cox proportional-hazards multivariate analysis was performed to further correct for baseline differences that remained despite the propensity matching, adjusting for baseline Thrombolysis in Myocardial Infarction flow and baseline reference vessel diameter. Interactions between DM and ACC/AHA lesion type on 1-year major safety and efficacy outcomes were examined.

Categorical outcomes were compared using chi-square tests. Continuous variables are presented as mean ± SD and were compared using Student *t* tests. Cumulative event rates were estimated using time-to-event methods and were compared using the log-rank test. A p value <0.05 was considered statistically significant. All analyses were performed in SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).