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EDITORIAL COMMENT

Second-Generation Drug-Eluting Stents and Bioresorbable Vascular Scaffolds in Patients With Diabetes*

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Diabetes mellitus (DM) is a global health issue; the worldwide prevalence of the adult diabetic population is projected to reach one-half billion people in 2030. Currently, one-fourth of the diabetic U.S. population is treated with insulin (ITDM) (1,2). Atherosclerosis and its phenotypic manifestations are accelerated in DM, as coronary artery disease (CAD) more often displays complex multivessel disease with a higher risk of in-stent restenosis and stent thrombosis (scaffold/stent thrombosis [ST]) after percutaneous coronary intervention (PCI). Progression of CAD and stent complications in DM are driven by the combined effects of hyperglycemia, insulin resistance, and free fatty acids, resulting in endothelial dysfunction with impaired vasodilation, increased monocyte migration, neointimal hyperplasia, and platelet reactivity (3,4).

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Compared with bare metal stents, first-generation drug-eluting stents (DESs) markedly decreased the rate of restenosis in patients with diabetes; however, safety concerns regarding late ST were documented in both diabetic and nondiabetic patients. Drug deliverability was improved in second-generation DESs, which have been evaluated in several studies involving patients with diabetes. Overall event rates after percutaneous coronary intervention (PCI) are still considerably higher than in patients without diabetes; however, those rates are primarily driven by ITDM (3). The FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial showed that patients with ITDM also had more cardiovascular events than patients with non-ITDM after both multivessel PCI and coronary artery bypass procedure (CABG). Furthermore, event rates after PCI (mostly with first-generation DESs) were uniformly higher than after CABG in both the ITDM and non-ITDM strata and the event curves only separated after 2 to 3 years (5), suggesting the particular long-term implications of DM in the diffuse nature of CAD and the limitations of DESs. Therefore, all new-generation DESs should be studied in patients with DM and long-term follow-up should be mandatory.

No head-to-head comparisons have been performed to date between everolimus-eluting stents (EES) and zotarolimus-eluting stents (ZES) or everolimus-eluting bioresorbable vascular scaffolds (BVS) in patients with DM. In this issue of *JACC: Cardiovascular Interventions*, 2 studies with such comparisons are reported (6,7).

Patients with DM may be prone to long-term vascular inflammation caused by the durable polymer or the permanent local metal endoprosthesis of second-generation DESs. However, technological advances have enabled the creation of new types of DESs with bioresorbable polymer and scaffold. In the comparison of EES with BVS, Muramatsu et al. (6) present promising results at 1 year. In patients with BVS, the incidence of target lesion failure (TLF), cardiac death, myocardial infarction (MI), and ischemia-driven target lesion revascularization (ID-TLR) was numerically lower in patients with diabetes (3.7%) compared with patients without (5.1%). Virtually every other study conducted in the era of stenting has shown higher event rates in patients with diabetes (8). Diabetic patients with a BVS had nonsignificantly lower rates of TLF and ST than matched patients with EES.

In the pooled analysis of diabetic patients from the SPIRIT FIRST (A Clinical Trial of the Abbott Vascular XIENCE V Everolimus Eluting Coronary Stent System), SPIRIT II (A Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System), SPIRIT III (Clinical Trial of the XIENCE V Everolimus Eluting Coronary Stent System [EECSS]), SPIRIT IV Clinical Trial (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System), ABSORB Cohort B, and ABSORB EXTEND trial, the SPIRIT IV trial was the largest contributor of patients with cobalt-chromium EES. Inclusion criteria in the SPIRIT IV trial were, however, more liberal and included patients with complex lesions, as opposed to the ABSORB trials. The authors have tried to overcome these baseline population differences by fitting a

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model for propensity scores with variables of angiographic lesion complexity, but 25% of patients from the SPIRIT trials had to be excluded as they had missing baseline characteristics necessary to compute the propensity score. The final matched comparison of BVS and EES consequently rested on few and highly selected patients. Due to the restrictive angiographic inclusion criteria in ABSORB, the severity of diabetes in the patients with an implanted BVS was presumably milder than in the diabetic background population, also indicated by the similar baseline characteristics between the diabetes and nondiabetes group with a BVS and by the comparatively low prevalence of insulin use, a known marker for complications (3,4) that was confirmed in this study.

Despite the caveats and risk of residual bias, this study provides an early and, to date, the only indication of a favorable profile of BVS, as suggested by the reduced event rate, albeit nonsignificantly, compared with EES in diabetic patients with noncomplex lesions. However, these results may very well be due to a type II error. It will be interesting to see the long-term follow-up data at 2 years and beyond because some of the beneficial effects of BVS (e.g., absence of permanent vessel caging, which facilitates restoration of vasomotor function; adaptive shear stress; cyclic strain; and late luminal enlargement [9]) cannot be expected at 1 year. Restoration of vasomotor function might be of particular interest in diabetes as decreased nitric oxide production by endothelial dysfunction decreases vasodilation.

Conversely, EES have been studied in diabetes before. In a pooled analysis from the SPIRIT II through IV 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) trials, EES significantly reduced mortality, MI, and ST, compared with first-generation paclitaxel-eluting stents (PES) in patients without diabetes (8). However, a highly significant interaction was identified between DM and stent type for 2-year clinical outcome. In diabetic patients, EES failed to improve safety and efficacy over PES (8). Additionally, in non-ITDM, ID-TLR was reduced with EES, whereas in ITDM, a trend toward increased ID-TLR was seen compared with PES (8). In the following randomized SPIRIT V diabetic study (10), lumen loss and 1-year cardiac death or MI was significantly reduced with EES. However, the ID-TLR rate was, again, considerably higher with EES and more than 2-fold increased compared with PES. In contrast, the ESSENCE-DIABETES (Everolimus-Eluting Stent Versus Sirolimus-Eluting Stent Implantation for de Novo Coronary Artery Disease in Patients with Diabetes Mellitus) study found an extremely low ID-TLR rate with EES, which could have been due to a much smaller proportion of ITDM in the ESSENCE-DIABETES study among patients with EES compared with the SPIRIT V diabetic study.

These hypothesis-generating data may be explained by the different mechanisms through which paclitaxel (PES) and rapamycin (EES and ZES) analogs reduce in-stent restenosis. Paclitaxel interferes with pathways of in-stent restenosis by disrupting microtubular function that affects smooth muscle cell proliferation and migration, extracellular matrix production, and intercell signaling. The effects of paclitaxel are hence diverse and may therefore be relatively independent of the diabetic state. Conversely, rapamycin only interferes with mitosis that is tightly regulated by glycosylation-dependent enzymes, which in turn may be affected by hyperglycemia. Stone et al. (8) showed an increasing gradient of event rates among patients treated with EES, with event rates lowest in nondiabetic patients, intermediate in non-ITDM patients, and highest in ITDM patients. No such relationship was apparent in patients treated with PES. Whether the explanation lies in differences between insulin-deficient and -resistant states or in a direct effect of insulin on vascular response to second-generation limus eluting stents is unknown (8).

Park et al. (7) compared the XIENCE EES and Resolute ZES (R-ZES) in 1,855 all-comer diabetic patients. After unrestricted use, despite a higher risk profile in R-ZES patients, both the EES and R-ZES showed comparable and low incidences of TLF (3.5%) and ST (0.3%) at 1 year, suggesting excellent safety of both stent types. Patient-related outcomes were, however, 3-fold higher than stent-related outcomes, stressing the importance of integrated secondary prevention and medical management of comorbidities in diabetes.

The efficacy of the EES and R-ZES was more difficult to evaluate. Rates for any MI, including target vessel, nontarget vessel, and ST (0.8% for the EES and 0.6% for the ZES), were much lower than in previous studies, as systematic collection of cardiac enzymes after PCI is not routine practice in South Korea, and several centers have same-day discharge standards. Both stent- and patient-related outcomes included MI and were hence most likely underreported and not generalizable. Conversely, an optional angiography was performed at 9 months, which might have inflated the patient-related outcome, which included any revascularization. However, this was a systemic bias and, therefore, we do learn from this study that the EES and R-ZES most likely perform equally in DM.

Second-generation stent scaffolds with rapamycin-eluting durable polymers certainly have improved safety profiles with very low ST risk also in diabetic patients. It is still unknown whether this advantage will translate in parallel into efficacy or is hampered by the possible effects of hyperglycemia on limus eluting stents or inflammation-mediated restenotic responses of the diabetic milieu to new durable stent polymers. In this context, the results of everolimus-eluting BVS are promising and may constitute an attractive treatment alternative. Currently, however, the perspective for patients

with diabetes and complex multivessel disease remains; CABG may still be the way to go, even with the improved second-generation DESs. The ongoing EXCEL (Evaluation of XIENCE Everolimus Eluting Stent Systems Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial among patients with DM will provide answers.

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Key Words: bioresorbable scaffold ■ coronary artery disease ■ diabetes mellitus ■ drug-eluting stent.