EDITORIAL COMMENT

Diabetes and Drug-Eluting Stents

What You Get and What You Don’t*

Steven P. Marso, MD

Kansas City, Missouri

The clinical introduction of drug-eluting stents (DES) in 2003 was a major milestone in the field of interventional cardiology. There was an early and rapid adoption of DES into clinical practice, which has undoubtedly impacted our interventional practices. In particular, DES use has prompted operators to intervene in many more patients with advanced disease, often with accompanying comorbidities. In the past, these patients were likely referred for coronary artery bypass grafting (CABG) or treated conservatively. Perhaps no comorbidity has received more attention in the percutaneous coronary intervention (PCI) population than diabetes mellitus. Patients with diabetes have long been recognized as a complex PCI cohort. These observations date back to even the initial National Heart, Lung, and Blood Institute percutaneous transluminal coronary angioplasty registry publications (1). Today, diabetes continues to be associated with an increased risk of major adverse cardiovascular events, including death and myocardial infarction (MI). Along with lesion length and reference vessel diameter, diabetes is also consistently associated with restenosis and need for repeat revascularization after PCI.

Thus, the findings from Mulukutla et al. (2) in this issue of JACC: Cardiovascular Interventions are of interest to practicing interventionalists. These investigators report 1-year outcomes for a cohort of diabetic patients enrolled in the National Heart, Lung, and Blood Institute Dynamic PCI Registry. In over 2,500 patients with diabetes, DES therapy decreased the need for repeat revascularization compared with bare-metal stents (BMS). Although the insulin-treated population was somewhat underpowered, the magnitude of benefit in DES-treated diabetic patients was similar between patients receiving and not receiving insulin treatment. There was no apparent procedural-related cost of death or nonfatal MI.

This work raises numerous points for discussion. Although multicenter national PCI registries provide important insights into PCI treatment strategies and outcomes, changes in patient demographics and interventional techniques must be considered when interpreting these findings. As the investigators note, registry enrollment spanned nearly a decade. In observational registries of extended duration, important bias is often present in selecting treatment strategies that cannot be fully accounted for with statistical methods. Over the past 10 years, much has changed with respect to the PCI population. Today, PCI patients are older and have a greater number of comorbidities, including decreased ejection fraction, chronic renal insufficiency, and a greater number of diseased vessels (3) when compared with the PCI population 10 years ago. The prevalence of diabetes in the PCI population has increased dramatically. At our institution, the prevalence of diabetes in the setting of PCI increased from 8% to more than 30% over a 20-year time span. Changing demographics result in very different short- and long-term risks for disease progression and subsequent atherosclerotic complications, including death and MI. Evaluating therapies solely based on these observational datasets often lead to erroneous conclusions regarding the benefit or risk of evaluable therapies.

This was especially evident during the evaluation phase of DES. The introduction of DES has likely influenced operator decisions regarding revascularization strategy. For example, data (4) over a 5-year period from the American College of Cardiology National Cardiovascular Data Registry (ACC/NCDR) catheter/PCI registry show a rapid diffusion of DES. Before 2003, approximately 1 of 4 patients with a class I indication for CABG underwent PCI. By the end of 2004, DES were used in over 80% of all PCI cases. In the DES era, this ratio increased to 1 of 3. Furthermore, for every 10% increase in DES use, there was a corresponding 4% increase in PCI attempts in patients with a class I indication for CABG. These findings suggest a willingness on the part of operators to attempt PCI more often in complex cases. Data from Sweden (5) further support the contention that the DES cohort is more complex. The DES-treated patients were more likely to have diabetes, multistem procedures, prior PCI, and prior CABG compared with the BMS cohort. It is likely that changing demographics between DES and BMS cohorts partially explain the studies presented in late 2006 showing an increased hazard for death/MI. For example, early studies suggested an increase in the risk of mortality for DES-treated patients (6,7). In a large meta-analysis of 17 randomized trials comparing sirolimus-eluting or paclitaxel-

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From Saint Luke’s Health System, Mid America Heart Institute, Kansas City, Missouri. Dr. Marso is a consultant for Amylin, Sanofi-Aventis, and Volcano Corporation and has received research grants from Boston Scientific, The Medicines Company, and Volcano Corporation.
eluting stents to BMS, Nordmann et al. (6) found a graded increase in all-cause mortality associated with DES with increasing length of follow-up. However, several recent publications have improved clarity (and reversed thought) about the safety of DES (8–12). For example, in a meta-analysis of 38 randomized trials, Stettler et al. (9) reported significantly lower target lesion revascularization rates in patients randomized to sirolimus-eluting or paclitaxel-eluting stents compared with BMS but no differences in death or MI between either DES platform or BMS.

Likewise, there has also been increasing confusion with respect to the risk or benefit of DES in diabetic patients based on early published data. For this reason alone, Mulukutla et al. (2) provide an important contribution to the literature by helping to clarify the risk/benefit of DES in the diabetic population. Early sirolimus data (13,14) showed an impressive reduction in late loss and target vessel revascularization (TVR), yet the benefit seemed to be attenuated in the insulin-treated diabetic subgroup. However, as the studies accumulated and pooled analysis became available, Boyden et al. (15) showed an acceptable mean late loss of 0.12 mm in diabetic patients randomized to sirolimus-eluting stents. Paclitaxel-eluting stents seem to have less variability in the late loss in diabetic patients, albeit numerically greater (0.34 mm) (15) when compared with sirolimus-eluting stents. Other data have raised concerns about the safety of sirolimus-eluting stents in the diabetic cohort. Spaulding et al. (8) compared 4 sirolimus trials that showed a significant increase in risk of death for sirolimus-treated diabetic patients when compared with BMS (overall survival 87.8% vs 95.6%; sirolimus-eluting stents vs. BMS, p = 0.004). However, this finding requires cautious interpretation because of the very low number of events in the diabetic subgroup. This analysis from the Dynamic Registry of DES in diabetic patients extends findings of an early meta-analysis (15), which clearly showed a significant reduction in the vessel patency for diabetic patients randomized to DES.

Although there is much yet to learn, there is an accumulating body of literature supporting the benefit of DES in diabetic patients. These data allow for some generalizations. What you get: 1) Improved vessel patency. DES improves vessel patency as measured by either late loss or need for target vessel revascularization. 2) An acceptable safety profile. The latest studies more firmly establish DES as not only efficacious, but also safe. There does not seem to be an increased hazard for either death or MI among diabetic patients related to DES treatment. What you do not get: 1) Neutralization of restenosis risk. Although the data are less than complete, it seems that diabetes will still be consistently associated with the need for greater repeat revascularization rates (compared with nondiabetic subjects) of the target lesion in the DES era. 2) An optimal DES platform ideally suited for diabetic patients. There have been a series of comparative studies between sirolimus and paclitaxel in diabetic subjects. The details are beyond the scope of this editorial. In brief, these studies are consistently discordant. Neither is definitively superior. The ideal stent has yet to be developed for this high-risk group of patients. Perhaps the third-generation DES will provide superior efficacy for patients with diabetes mellitus.

Reprint requests and correspondence: Dr. Steven P. Marso, Saint Luke’s Health System, Mid America Heart Institute, 4401 Wornall Road, Kansas City, Missouri 64111. E-mail: smarso@st-lukes.org.

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