More Deserved Focus on Diabetic Patients

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Worldwide diabetes mellitus has reached epidemic proportions, and its prevalence is rising. Estimates predict an increase in the prevalence of diabetes from 2.8% (171 million) in 2000 to 4.4% (366 million) in 2030. The prevalence of coronary heart disease is as high as 55% among adult patients with diabetes. Patients with diabetes have a 2- to 4-fold increase in the risk of coronary artery disease, which accounts for three-quarters of diabetes-related deaths and is by far the most common cause of mortality in these patients. Patients with diabetes have accelerated and more diffuse coronary artery disease with longer lesions often associated with negative coronary remodeling, smaller diameter vessels on angiography, and reduced collateral development. The diffuse and rapidly progressing atherosclerosis increases the need for revascularization therapy in diabetic patients. Thus, in the United States, one-quarter to one-third of all revascularization procedures are performed in diabetic patients. Of note, compared with nondiabetic patients, patients with diabetes have worse outcomes after surgical or catheter-based revascularization procedures.

Diabetes has been a “minefield” for percutaneous coronary interventions (PCI), presenting an exceptionally high risk of restenosis up to 71% after plain balloon angioplasty and up to 38% after bare-metal stents (BMS). In addition, diabetic patients carry a higher risk of total vessel occlusion after stenting, leading to myocardial infarction, reduced ventricular function, and congestive heart failure. These factors along with the accelerated progression of atherosclerosis reduce long-term survival of patients with diabetes. The limitations of balloon angioplasty and BMS have contributed to the superiority of coronary artery bypass graft surgery over PCI shown in previous trials comparing these 2 treatment strategies in diabetic patients.

With the development and clinical use of drug-eluting stents (DES), restenosis was markedly reduced among patients with and without diabetes. Despite further recent developments in stent technology, improved periprocedural care, and current antithrombotic drugs, revascularization therapy is still suboptimal in diabetic patients. Apart from restenosis, which still remains higher in diabetic patients, several other areas of uncertainty in the field of revascularization therapy for patients with diabetes still remain. First, the most complex diabetic patients, that is, those with multivessel or diffuse coronary artery disease, have been excluded from recruitment in the DES trials. Thus, the efficacy of DES in these patients most in need of revascularization procedures is largely unknown. Second, current knowledge of the efficacy of PCI in diabetic patients is largely derived from subgroup analyses, which are markedly underpowered to detect the outcomes of interest with statistical fidelity. Third, the possibility of increased risk of stent thrombosis in patients with diabetes has been a matter of particular concern, considering its potential for fatal outcome. Several studies have confirmed higher rates of stent thrombosis in diabetic patients. Fourth, it is generally thought that the length of follow-up is still too short in many DES trials including patients with diabetes. Similarly, the optimal duration of antithrombotic therapy after DES implantation in diabetic patients has not yet been established. Fifth, the criteria for repeat revascularization might be less reliable in diabetic patients. It must be recognized that diabetic patients have a defective anginal warning system and are prone to silent ischemia. In diabetic patients, the majority of ischemia episodes might be silent; myocardial infarction can be silent in 10% to 15% of cases, and there is an increased risk of sudden cardiac death in diabetic patients with exercise-induced silent ischemia. Because restenosis can remain silent in up to 36% of cases with diabetes, clinically driven guidance of repeat revascularization procedures may underestimate the real need for revascularization in diabetic patients. Sixth, with a variety of approved DES, there is a need to compare their efficacy in diabetic patients with coronary artery disease. This not only because of their excess risk of restenosis, which requires treatment with best possible DES, but also because diabetes may generate mechanisms that differently affect the efficacy of the drugs currently used in DES technology. Attenuation of the mammalian target of rapamycin signaling pathway has been described in patients with type 2 diabetes, with a potential negative impact on the efficacy of limus-based DES in these patients. Although data from randomized trials have not confirmed this assumed negative impact at least for sirolimus compared with paclitaxel, recent subset analyses have shown that in diabetic patients, everolimus-eluting stents lose their superiority over paclitaxel-eluting stents (PES) observed in nondiabetic patients. Finally, information on the efficacy of PCI in diabetic patients is largely derived mostly by subgroup analyses of small- to modest-sized randomized studies. It has been demonstrated that ruptured atherosclerotic plaques per se have a large necrotic core. Moreover, morphological studies have demonstrated that diabetes is associated with greater inflammatory infiltrate,
larger necrotic core size, and more diffuse atherosclerosis in the coronary arteries. Thus, ST-segment–elevation myocardial infarction in diabetic patients may be associated with excessive thrombotic material superimposed on ruptured plaques with a large necrotic core, which increases the risk for stent malapposition, stent thrombosis, and poorer outcomes in these patients.

Two trials published in this issue of *Circulation: Cardiovascular Interventions* are a commendable effort to address at least some of the abovementioned open questions in diabetic patients. The study by Witzenbichler et al.\(^\text{24}\) represents an analysis of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial that sought to assess the efficacy of PES versus BMS in patients with acute myocardial infarction stratified according to diabetic status (present in 478 patients). About two-thirds of the patients were still on dual antiplatelet therapy at 1 year. Expectedly, the primary end point (a composite of death, reinfarction, stroke, and ischemia-driven target vessel revascularization) was observed more often in diabetic (14.8%) than in nondiabetic patients (10.3%), mostly driven by differences in mortality (6.3% versus 3.0%) and stroke (2.0% versus 0.8%). As compared with BMS, PES were able to significantly reduce the risk of target lesion revascularization in the entire population, and the diabetes status did not show any significant interaction with treatment effect: The reduction was 37% among non-diabetics and 55% in diabetics (65% in insulin-requiring and 45% in noninsulin-requiring patients).\(^\text{24}\) The risk of stent thrombosis in this study was affected neither by diabetes status (3.3% in diabetic versus 3.2% in nondiabetic patients) nor by the stent type (3.2% in the PES group versus 3.3% in the BMS group) but was highest among insulin-requiring diabetic patients (8.3%). These latter patients also showed the greatest benefit from the use of DES in terms of reduction of major adverse cardiac events (MACE).

In “Novel Approaches for Preventing or Limiting Events in Diabetic Patients (Naples-Diabetes) Trial: A Randomized Comparison of 3 Drug-Eluting Stents in Diabetic Patients” Briguori et al.\(^\text{25}\) randomly assigned 226 diabetic patients with stable or unstable angina, with lesions in native coronary arteries and without prior revascularization, to receive 1 of the following DES: SES, PES, and zotarolimus-eluting stent (ZES). The duration of dual antiplatelet therapy was >6 months in >70% of the patients. The primary end point was a 3-year composite of MACE, including death of any cause, nonfatal myocardial infarction, or clinically driven target lesion or target vessel revascularization. The impact of microvascular complications and metabolic control on primary outcome was selected as the secondary end point. The 3-year cumulative MACE rate was 13.2% in the SES group, 17.5% in the PES group, and highest, with 35.6%, in the ZES group \((P=0.006)\). The differences in MACE rates were mostly driven by differences in the need for repeat revascularization and the incidence of stent thrombosis was low (only 4 patients; 1 patient in the SES group and 3 patients in the ZES group). The multivariable analysis identified ZES, multivessel disease, diabetic retinopathy, and poor metabolic control as independent correlates of MACE.\(^\text{25}\)

These 2 studies are complementary in some aspects. The study of Witzenbichler et al., based on the HORIZONS-AMI trial data, provides a new and stronger confirmation of the 1-year safety and efficacy of DES in an important high-risk subset of patients with acute myocardial infarction, those with diabetes mellitus.\(^\text{24}\) It lacks a specifically randomized design for diabetic patients, but the number of diabetic patients is impressive, and the assessment is based on careful clinical and angiographic analyses. The study also lacks data on the quality of metabolic control in diabetic patients, yet it suggests that diabetic patients may not represent a homogeneous group regarding the risk of adverse events and the extent of benefit from DES. The fact that insulin-requiring diabetic patients carried the highest risk is not unexpected to us. More unexpected, and, for this reason, even more interesting, is the finding that it was insulin-requiring diabetics who drew the major benefit from DES. A more complete report on the optimal treatment of diabetic patients with acute myocardial infarction would have included both data on antithrombotic therapy and its possible interaction with the type of stent and data from optical coherence tomography that was performed in a subset of patients enrolled in the HORIZONS-AMI trial.\(^\text{26}\) Readers are certainly looking forward to seeing this information in future publications from this group of authors.

As a complementary contribution, the authors of the Naples-Diabetes trial offered a specific study on diabetic patients without acute myocardial infarction with a randomized design, a follow-up extended to 3 years, a comparison among 3 different DES types, and detailed information on the quality of metabolic control. They showed several independent factors with impact on the outcomes after placement of DES in diabetic patients. With best results shown for a sirolimus-eluting stent and worst results for a ZES, the study suggests that simply being a member of the limus drug family is not sufficient to predict a good or poor response of coronary vessels in the diabetic patient. The most relevant lesson from this study is, however, that at least 2 independent determinants of treatment results in diabetic patients—the type of DES and metabolic control—are largely under the physician’s control, which gives hope for our ability to favorably affect on the outcomes of these patients.

Thus, these 2 studies confirm once again the complexity of the issue of PCI in diabetic patients with coronary artery disease. These patients do not represent a homogenous group with respect to outcomes. They also may be more sensitive to the type of DES used and the quality of metabolic control. More and more focused studies on diabetics are needed to adequately address this complexity. DES represent a significant advancement in the treatment of diabetic patients with coronary artery disease. Further improvement of interventional and drug treatment of these patients will strongly depend on the execution of studies specifically designed for diabetic patients, with sufficiently large sample size, long-term follow-up, and the use of modern intravascular imaging modalities.

**Disclosures**

Dr Kastrati received honoraria from Abbott, Biosensors, Biotronic, and Cordis and served on the European Steering Committee of the HORIZONS-AMI trial.
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