Patients with diabetes have a 2- to 4-fold increase in the risk of coronary artery disease. They have accelerated and more diffuse coronary artery disease with increased need for revascularization therapy. In addition, patients with diabetes have worse outcomes after surgical or catheter-based revascularization procedures. Diabetes promotes endothelial dysfunction and platelet deposition, which enhance the propensity to thrombosis. Hyperglycemia is associated with overexpression of several growth factors, and advanced glycosylation promotes inflammatory cell recruitment and smooth muscle cell proliferation. Indeed, an excess risk of coronary thrombosis and restenosis has characterized the outcomes of diabetic patients treated with balloon angioplasty or bare-metal stents (BMS). Although drug-eluting stents (DES) provide better chances than BMS for diabetic patients who need coronary revascularization, diabetes remains an important risk factor for coronary events even in the DES era. Moreover, findings about an attenuation of the mammalian target of rapamycin (mTOR) signaling pathway in patients with type 2 diabetes have generated concerns about a possible specific limitation of limus-eluting stents in diabetic patients that has not been fully dispelled by existing clinical evidence.

Diabetic patients are in bad need of the best available DES, and 2 studies published in the current issue of Circulation considerably serve our efforts in defining optimal DES strategy in these patients. In the study of Stone et al., the investigators pooled together the individual patient data from 4 randomized trials—the Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions (SPIRIT) II, SPIRIT III, SPIRIT IV trials, and the Second-Generation Everolimus-Eluting and Paclitaxel-Eluting Stents in Real-Life Practice (COMPARE) trial—that compared everolimus-eluting stents (EES) with paclitaxel-eluting stents (PES) in patients with coronary disease and focused on the interaction between the presence of diabetes and the treatment effect of EES over 2 years of follow-up. Previously, each of these 4 trials had shown the clear superiority of EES over PES in their entire cohorts, composed of all-comer patients in the COMPARE trial and relatively selected patients in the series of SPIRIT trials. The strengths of the present data set are the availability of individual patient data, the large number of diabetic patients (1869 patients), and the fact that randomization was stratified by the presence of diabetes in 3 of the 4 included trials. Yet, this cannot be considered a full substitute for randomized trials specifically designed for diabetic patients. In addition, a 2-year follow-up cannot be considered long enough to catch all possible advantages of an interventional treatment strategy, especially in diabetic patients. Last, although this analysis is well endowed to assess clinically relevant differences in restenosis, it might not be able to evaluate the entire restenotic response to DES, particularly in diabetic patients, in whom restenosis remains silent in more than one-third of the cases.

The current pooled analysis confirmed the excess risk carried by diabetic patients undergoing a coronary intervention procedure. Indeed, the incidences of death, myocardial infarction, and target-lesion revascularization were all higher in diabetic than in nondiabetic patients. These findings are not new to the medical community. The most interesting results emerged when the treatment effect of DES type was analyzed according to the presence or absence of diabetes. Diabetes status did not affect the treatment effect of EES versus PES regarding cardiac death, but a significant interaction was found when looking at stent thrombosis, myocardial infarction, and target-lesion revascularization. Whereas there was a significant reduction of these 3 events for EES compared with PES, with adjusted odds ratios ranging from 0.15 to 0.50 in nondiabetic patients, the corresponding odds ratios ranged from 0.80 to 0.90, and lost statistical significance, in diabetic patients. The erosion of the clinical advantage of EES compared with PES was more pronounced in insulin-treated diabetic patients. The message of this study is clear: EES is markedly superior to PES in nondiabetic patients, but its advantages are largely attenuated in diabetic patients. At the same time, the presented data should not be interpreted as indicating that patients with diabetes and coronary artery disease represent a special niche for the use of PES.

In the Randomized Comparison of Everolimus-Eluting Stent versus Sirolimus-Eluting Stent Implantation for De Novo Coronary Artery Disease in Patients with Diabetes Mellitus (ESSENCE-DIABETES) trial of Kim et al., the investigators randomly assigned 300 patients with diabetes to receive either EES or sirolimus-eluting stents (SES) for treatment of coronary lesions. The study hypothesis was that EES is noninferior to SES—the most important first-generation DES—with respect to in-segment late lumen loss in diabetic patients. The investigators were able to clearly show the noninferiority of EES compared with SES. Although no superiority testing was foreseen once noninferiority was demonstrated, some, but not all, angiographic measures of restenosis at follow-up favored EES. However,
in-stent late lumen loss, a very sensitive index of lumen renarrowing after DES implantation, was not significantly different between EES and SES. Moreover, the incidence of clinical events was also similar in both groups, although, of course, the low number of enrolled patients limits the strength of the clinical outcome data. In brief, the ESSENCE-DIABETES trial suggests that diabetic patients do not draw a relevant benefit when their coronary artery disease is treated with EES instead of SES. Is failed superiority of the second-generation EES in the ESSENCE-DIABETES trial related to the decreased efficacy of EES in diabetic patients shown in the pooled analysis of Stone et al?9 If the hypothesis generated by the decreased efficacy of EES in diabetic patients shown in the generation EES in the ESSENCE-DIABETES trial related to their coronary artery disease is treated with EES instead of SES. Is failed superiority of the second-generation EES in the ESSENCE-DIABETES trial related to the decreased efficacy of EES in diabetic patients shown in the pooled analysis of Stone et al.?9 If the hypothesis generated by the pooled analysis of SPIRIT I, II, III, and COMPARE trials only implies EES and not other limus drugs, we should expect a clear superiority of EES over SES in nondiabetic patients. Conversely, if the results of Stone et al.?9 are extrapolatable to other limus drugs, then the Korean colleagues might have compared 2 limus-based DES that are poorly effective in diabetes, with the obvious result of equivalence between them.

A careful assessment of the accumulated evidence from randomized trials on DES may shed some light on this conundrum. The complexity of patients with diabetes and coronary artery disease, the peculiar nature of atherosclerosis progression, and the propensity for restenosis in these patients are a solid rationale for prospective, specifically designed studies for this pathology. We lack randomized trials that compare EES with BMS. The value of this second-generation EES has been established by comparisons with first-generation DES. There are, however, several randomized trials that compared SES with BMS in diabetic patients. The results of a meta-analysis that combined the individual patient data of 4 previous randomized trials of SES versus BMS in 583 diabetic patients were recently published.12 SES led to a marked reduction (73%) of the need for target-lesion revascularization over 5 years without any signal of increased hazards of stent thrombosis. Notwithstanding the inflating effect of protocol-mandated follow-up angiography in the observed odds ratio for target-lesion revascularization, these results confirm the high efficacy of a limus-family member drug, sirolimus, in the prevention of coronary restenosis in diabetic patients.

We have witnessed an increasing number of randomized trials aiming at head-to-head comparisons of various DES in cohorts of patients ever more resembling those of every day practice. Randomized DES comparisons in specific subsets of patients such as those with diabetes have attracted less attention, and the ESSENCE-DIABETES trial represents the only trial on EES in diabetic patients.10 The experience with first-generation DES comparisons in diabetes is richer. Again, pooled individual patient data from 6 randomized trials that compared SES with PES in 1183 diabetic patients have been analyzed in a recent meta-analysis based on clinical outcomes up to 5 years.13 SES reduced the incidence of target-lesion revascularization by 35% without having an impact on stent thrombosis (Figure 1). Although follow-up angiography, which was protocol-mandated in most of the trials included in the meta-analysis of Kufner et al,13 demonstrated the lower late lumen loss with SES versus PES, it might have increased the likelihood of performing reinterventions for asymptomatic restenosis. The reduction of angiographic and clinical restenosis by SES versus PES in these dedicated trials in patients with diabetes is comparable to that observed in mixed cohorts of diabetic and nondiabetic patients,14,15 refuting a significant negative influence of diabetes on the antirestenotic effect of sirolimus. Indeed, in-stent late lumen loss was also lower with EES compared with PES in the subgroups of diabetic patients in the SPIRIT II and III trials.16,17 Apparently, the reduction of restenosis with everolimus-based DES in patients with diabetes is not of sufficient magnitude to be translated in decreased reintervention rates in trials without protocol-mandated follow-up angiography, such as those that numerically dominate the pooled analysis of Stone et al.9

The second-generation EES has been quickly embraced by the interventional cardiology community as a user-friendly device with potent antirestenotic efficacy. In the diabetic cohort of the ESSENCE-DIABETES trial, it resulted in slightly improved angiographic outcomes compared with first-generation SES without, however, having a significant impact on clinical outcomes.11 The lack of nondiabetic patients in the later trial prevents us from identifying a possible interaction between diabetes and differential comparative antirestenotic efficacy of everolimus and sirolimus.
Several other randomized trials have compared EES with SES in mixed cohort of diabetic and nondiabetic patients with coronary artery disease. A formal meta-analysis of 5 randomized trials including 7370 patients showed no difference regarding stent thrombosis and statistically comparable need for reintervention between EES and SES (Figure 2).\(^{18}\) All together, these trials confirm the high efficacy of EES in both diabetic and nondiabetic patients with coronary artery disease. On the other hand, they also show the difficult-to-surpass efficacy of the pioneer first-generation SES. Surely this device deserved improvement of its metal stent platform instead of total abandonment from its manufacturer.

Figure 2. Comparison of everolimus-eluting stents (EES) with sirolimus-eluting stents (SES) regarding stent thrombosis (A) and target-lesion revascularization (B). The meta-analysis combined the results of 5 randomized trials in patients with coronary artery disease. Adapted from de Waha et al.\(^{18}\)

Diabetes remains the Achilles’ heel for all revascularization therapies including DES in patients with coronary artery disease. Newer coronary local drug-eluting technologies are being developed and entering the market, including DES with biodegradable polymers or no polymer at all, drug-eluting balloons, and biodegradable scaffolds, all with the potential of improving outcomes of patients with and without diabetes. Ongoing research is focused on the synthesis of more effective drugs. Until we have proof of an enhanced efficacy with these novel agents, the limus family members remain the drugs of choice for local delivery in the diseased coronary arteries of both diabetic and nondiabetic patients. It remains to be investigated whether diabetic patients require specific dose tuning of antiproliferative drugs or specific drug combinations that more fully address the diabetes-induced complex pathway of mechanisms that promote coronary restenosis and thrombosis. One size fits all might be the wrong solution, especially in diabetic patients.

Disclosures
Dr Kastrati has received honoraria from Abbott, Biosensors, Biotronic, Cordis, and Medtronic. He also holds patents or has patent applications related to components of drug-eluting stent technology such as microporous stent surface, biodegradable polymer/resin coating, and dual-drug delivery. Drs Massberg and Ndrepepa report no conflicts of interest.

References


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