Is Diabetes the Achilles’ Heel of Limus-Eluting Stents?

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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.

Articles see p 886 and p 893

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
narrowing 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 DES. There are, however, several 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, 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, demonstrated
the lower late lumen loss with SES versus PES, it
might have increased the likelihood of performing reinterven-
tions for asymptomatic restenosis. The reduction of angiog-
ographic 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 pa-
tients, 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. Apparently, the reduction of restenosis with
everolimus-based DES in patients with diabetes is not of
sufficient magnitude to be translated in decreased reinterven-
tion rates in trials without protocol-mandated follow-up
angiography, such as those that numerically dominate the
pooled analysis of Stone et al.

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. 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

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
stent 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. SES led to a
marked reduction (73%) of the need for target-lesion revas-
cularization 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.

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. The lack of nondiabetic
patients in the later trial prevents us from identifying a
possible interaction between diabetes and differential com-
parative 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.

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, Biotroninc, 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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