The SPIRIT V Diabetic Study: A randomized clinical evaluation of the XIENCE V everolimus-eluting stent vs the TAXUS Liberté paclitaxel-eluting stent in diabetic patients with de novo coronary artery lesions

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Background Diabetic patients respond less favorably to revascularization and have poorer long-term outcomes. Our main aim was to evaluate the angiographic efficacy of XIENCE V (everolimus-eluting stent, or EES) in diabetic patients compared with TAXUS Liberté (paclitaxel-eluting stent, or PES).

Methods The SPIRIT V Diabetic Study was a prospective, single-blind, randomized study that enrolled 324 diabetic (insulin and non–insulin dependent) patients at 28 sites in Europe and Asia Pacific. Randomization was 2:1 between EES (n = 218) and PES (n = 106). The primary end point was sequential noninferiority and superiority of EES for in-stent late loss at 9 months. Secondary clinical end points included stent thrombosis, death, myocardial infarction, and revascularization rates up to 1 year.

Results Everolimus-eluting stent was superior to PES for in-stent late loss at 9 months (0.19 mm vs 0.39 mm, respectively; $P_{superiority}$ = .0001). The composite rate of death, myocardial infarction, and target vessel revascularization was the same in the 2 groups at 1 year (16.3% vs 16.4%). No stent thromboses (Academic Research Consortium definite and probable) were seen through 1 year with EES compared with 2 of 104 (2%) with PES (P = .11).

Conclusion In this prospective, randomized trial in a high-risk group of diabetic patients, implantation of EES compared with PES resulted in significantly better inhibition of intimal hyperplasia with a comparable safety outcome. (Am Heart J 2012;163:867-875.e1.)

Cardiovascular disease is the leading cause of death in diabetic patients.[1] These patients not only have an increased risk for developing cardiovascular disease but have a more diffuse and advanced pattern of the disease. Those undergoing percutaneous coronary intervention (PCI) have smaller vessels and longer lesions, requiring treatment with multiple stents, which might explain their less favorable response to treatment and poorer long-term outcomes.[2-4]

First-generation drug-eluting stents (DESs) reduced the need for repeat revascularization with a similar safety profile when compared with bare-metal stents.[5,6] Deployment of DES is considered the preferred treatment strategy for diabetic patients who are at a substantially higher risk for restenosis after bare-metal stenting.[5,7,8] Furthermore, PCI, using the second-generation everolimus-eluting stent (EES), has been shown to result in better long-term outcomes than when first-generation DES are used in all-comer populations,[9,10] However, a post hoc pooled analysis of 4 randomized trials showed a marked attenuation of this beneficial effect in subsets of diabetic patients.[11] This may be due to suppression of the antiproliferative effect of everolimus, a phenomenon reflected in attenuation, in a small subset of patients with diabetes, of the marked reduction in late loss (LL)

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observed with EES in nondiabetic patients in an angiographic subset of the SPIRIT III study.[10] However, although SPIRIT III enrolled 300 diabetic patients, only 96 lesions in the EES arm and 31 lesions in the paclitaxel-eluting stent (PES) arm were available for assessment of 8-month angiographic LL, with the resulting lack of power limiting the robustness of the subgroup observation. Furthermore, post hoc linear regression analysis revealed no significant interaction between treatment assignment and angiographic outcome in the diabetic subset. The angiographic analysis of SPIRIT II was even more limited with respect to sample size and rate of follow-up.[11] An angiographic comparison powered to address the mechanistic questions that may impact on clinical outcomes is, thus, needed.

The SPIRIT V Diabetic Study was a prospective, single-blind, multicenter, randomized trial designed to compare outcomes after stenting with the XIENCE V EES compared with the Taxus Liberte PES, specifically in diabetic patients undergoing nonemergent PCI. The primary aim was to compare 9-month angiographic outcomes. Secondary aims included comparisons between the groups of clinical events and stent thrombosis at 1 year, although the study was not powered for these events.

Methods

Trial design

The study was funded by Abbott Vascular (Santa Clara, CA). The protocol was approved by the research ethics committee of each participating institution. All patients provided written informed consent. Patients were randomized 2:1 to EES vs PES through an interactive voice response system (ICON Clinical Research, Eastleigh, UK). Randomization was stratified by insulin-dependence status and number of lesions treated (single vs multiple). Dedicated study monitors performed 100% source document verification of all data points.

Study population

Diabetic patients, as documented by history, who were 18 years or older with evidence of myocardial ischemia (eg, stable or unstable angina, silent ischemia, positive functional study, or a reversible change in ECG consistent with ischemia) were eligible for the study. They had to be acceptable for coronary artery bypass graft surgery and had to agree to undergo all protocol-required follow-up examinations. Coronary anatomy had to be suitable for optimal planned treatment with a maximum of 4 EES in de novo target lesions with a target vessel reference diameter between 2.25 and 4.0 mm, a lesion length of ≤28 mm, a stenosis of ≥50%, and a thrombolysis in myocardial infarction (MI) flow of ≥1, all by visual estimate. A maximum of 1 de novo target lesion per native major epicardial vessel or side branch was allowed. Enrolled patients also had to be suitable to receive treatment with the PES according to its instructions for use.

Patients were excluded from the study in the presence of the following: an acute MI within 3 days preceding the baseline procedure; current unstable arrhythmias; left ventricular ejection fraction <30%; renal insufficiency; suspected or documented liver disease; history of bleeding diathesis or coagulopathy; any major bleeding event within the past 6 months; awaiting an organ transplant; contraindication to aspirin, clopidogrel, heparin, or any study-related drugs; participation in another device or drug study; or completion of the follow-up phase of another study within 30 days before study entry. Patients were also excluded if target lesions were aorto-ostial, previously stented or treated with brachytherapy, in-stent restenotic or totally occluded (thrombolysis in myocardial infarction flow 0), located in the left main or within 2 mm of the origin of the left anterior descending or left circumflex, or when excessive tortuosity, heavy calcification, or visible thrombus was present in the target vessel.

Device details

Details of the XIENCE V stent have been previously published.[12] The commercially available TAXUS Liberté stent (Boston Scientific, Natick, MA) served as the comparator device.

Study procedure

Angiographic inclusion and exclusion criteria were confirmed before the procedure. Unfractionated heparin or bivalirudin was allowed for procedural anticoagulation. Platelet glycoprotein IIb/IIIa inhibitor use was left to the discretion of the investigator. All patients were to receive a loading dose of at least 300 mg clopidogrel before the procedure. Planned use of up to 4 stents was allowed. Predilatation was mandatory, and postdilatation was allowed if indicated. All patients were to receive clopidogrel (75 mg/d) for at least 6 months and aspirin (≥ 75 mg/d) indefinitely after the procedure. Angiographic follow-up was performed at 9 months, and clinical follow-up was performed at 1 year after randomization. Originally, clinical follow-up was to continue yearly for 5 years; however, because of reallocation of priorities of the sponsor, follow-up was terminated after 1 year.

Quantitative coronary angiography

Baseline, post-PCI and 9-month follow-up angiograms were assessed by an independent core laboratory (BioClinica, Leiden, NL). The stented segment and the peristent segments (defined by a length of 5 mm proximal and distal to the stent edge) were analyzed in each patient. Minimal lumen diameter (MLD), reference vessel diameter (RVD), and percent diameter stenosis were computed. *Binary restenosis* was defined in every segment as a diameter stenosis of ≥50% at follow-up.

Study end points

An independent clinical event committee adjudicated all study end points according to the Academic Research Consortium definitions.[13] All adverse events were reported bimonthly to an independent data and safety monitoring board, which reviewed data to identify any safety issues related to the conduct of the study.

The primary end point was *in-stent LL at 9 months* defined as the difference between MLD postprocedure and MLD at follow-up. Secondary angiographic end points included in-segment LL, in-stent and in-segment angiographic binary restenosis rates, in-stent and in-segment percent diameter stenosis, and acute