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CLINICAL RESEARCH

5-Year Results of a Randomized Comparison of XIENCE V Everolimus-Eluting and TAXUS Paclitaxel-Eluting Stents

Final Results From the SPIRIT III Trial (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions)

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Objectives This study sought to evaluate the long-term safety and efficacy of everolimus-eluting stents (EES) and paclitaxel-eluting stents (PES) in patients with obstructive coronary artery disease.

Background The use of EES compared to PES has been shown to result in improved clinical outcomes in patients undergoing PCI. However, there have been concerns regarding the durability of these benefits over longer-term follow-up.

Methods SPIRIT III was a prospective, multicenter trial in which 1,002 patients were randomized 2:1 to EES versus PES. Endpoints included ischemia-driven target vessel failure (TVF) (death, myocardial infarction (MI), or ischemia-driven target vessel revascularization [TVR]), the pre-specified primary endpoint), target lesion failure (TLF) (cardiac death, target-vessel MI, or ischemia-driven target lesion revascularization [TLR]), major adverse cardiac events (MACE) (cardiac death, MI, or ischemia-driven TLR), their individual components and stent thrombosis.

Results Five-year follow-up was available in 91.9% of patients. Treatment with EES versus PES resulted in lower 5-year Kaplan-Meier rates of TVF (19.3% vs. 24.5%, $p = 0.05$), TLF (12.7% vs. 19.0%, $p = 0.008$), and MACE (13.2% vs. 20.7%, $p = 0.007$). EES also resulted in reduced rates of all-cause death (5.9% vs. 10.1%, $p = 0.02$), with nonsignificantly different rates of MI, stent thrombosis, and TLR, and no evidence of late catch-up of TLR over time.

Conclusions At 5 years after treatment, EES compared to PES resulted in durable benefits in composite safety and efficacy measures as well as all-cause mortality. Additionally, the absolute difference in TLR between devices remained stable over time without deterioration of effect during late follow-up. (J Am Coll Cardiol Intv 2013;6:1263–6) © 2013 by the American College of Cardiology Foundation

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Drug-eluting stents (DESs) preserve the mechanical advantages of bare-metal stents, providing greater acute luminal gain compared with balloon angioplasty, although concerns have arisen regarding the long-term benefits of DESs due to observations of late stent thrombosis and increases in target lesion revascularization (TLR) over time. To properly evaluate the comparative risks and benefits of DESs, clinical outcomes must be examined over longer-term follow-up than is required for initial device approval. The SPIRIT III (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients with De Novo Native Coronary Artery Lesions) trial, the pivotal approval trial for the XIENCE V (Abbott Vascular, Santa Clara, California) DES in the United States, randomized patients with symptomatic, noncomplex coronary artery disease to TAXUS EXPRESS2 paclitaxel-eluting stents (PESs) (Boston Scientific, Natick, Massachusetts) or XIENCE V everolimus-eluting stents (EESs) (1). In the SPIRIT III, treatment with EESs was associated with a significant reduction in the amount of in-segment late loss at 8 months (the primary angiographic endpoint), as well as noninferiority with respect to the primary clinical endpoint of target vessel failure (TVF) at 9 months. Given the paucity of long-term data on the safety and efficacy of DESs, we performed a 5-year follow-up analysis of the SPIRIT III trial.

Abbreviations and Acronyms

DES = drug-eluting stent(s)
EES = everolimus-eluting stent(s)
MACE = major adverse cardiac event(s)
PES = paclitaxel-eluting stent(s)
TLF = target lesion failure
TLR = target lesion revascularization
TVF = target vessel failure

Methods

The SPIRIT III trial was a prospective, multicenter, randomized, single-blind, controlled clinical trial in which 1,002 patients with either 1 or 2 de novo native coronary artery lesions (maximum of 1 lesion per epicardial coronary artery) were randomized in a 2:1 ratio to receive the everolimus-eluting XIENCE V stent (Abbott Vascular) or the paclitaxel-eluting TAXUS EXPRESS2 stent (Boston Scientific). The trial's inclusion and exclusion criteria, protocol, primary and pre-specified clinical endpoints are as described in the primary publication (1). Statistical analysis for the 5-year follow-up were similar to that performed for the 2- and 3-year follow-up analyses of the SPIRIT III and performed using SAS version 9.1.3 (SAS Institute, Cary, North Carolina) (2,3).

Results

Between June 2005 and March 2006, a total of 1,002 patients were randomized at 65 U.S. sites to receive the EES (n = 669) or the PES (n = 332). Baseline characteristics for the 2 well-matched groups were as reported previously (1–3). Antiplatelet agent use at 5-year follow-up was not significantly different with regard to use of aspirin (89.6% in the EES group vs. 93.2% in the PES group, p = 0.10) or a thienopyridine (44.2% in the EES group vs. 44.0% in the PES group, p = 0.99). Follow-up through 5 years was completed in 91.9% (921 of 1,002) of patients, including 92.8% (621 of 669) of patients receiving EESs and 90.9% (300 of 333) of patients receiving PESs. Rates of major clinical endpoints at 5 years are represented in Figure 1 and Online Table 1. EESs resulted in a lower incidence of the primary composite endpoint of TVF (19.3% vs. 24.5% in the PES group, p = 0.05). Compared with 1 year, at which time the EES was associated with an absolute 2.5% lower rate of TVF compared with the PES, at 5 years the absolute difference between stent types had increased to 5.2%. Additionally, the EES resulted in significantly lower 5-year rates of target-lesion failure (TLF) (12.7% vs. 19.0%, p = 0.008) and major adverse cardiovascular events (MACE) (13.7% vs. 20.2%, p = 0.007). There was a trend present toward a lower 5-year rate of ischemia-driven TLR with the EES compared with the PES (8.6% vs. 12.1%, p = 0.08). The difference between EES and PES in the rate of ischemia-driven TLR between year 1 and year 5 was stable or slightly increasing (absolute difference of 2.1% favoring the EES at year 1; absolute difference of 3.5% favoring the EES at year 5). All-cause mortality at 5 years was significantly lower with the EES compared with the PES (5.9% vs. 10.1%, p = 0.02), representing a 43% relative reduction in the risk of death. After 1 year, very late Advanced Research Consortium definite/probable stent thrombosis occurred in 0.5% of EES-treated patients compared with 1.0% of PES-treated patients (p = 0.36) (Online Table 2).

The interactions between treatment assignment and important subgroups with regard to the primary endpoint of TVF were evaluated in pre-specified subgroups with borderline significant interactions present with respect to age (p = 0.05) and sex (p = 0.03). The interaction between randomized treatment group and diabetic status was not significant (p = 0.20), although diabetic patients had similar 5-year rates of TVF with each type of stent (22.9% with the EES vs. 23.0% with the PES).

Discussion

The principal findings of the 5-year analysis from the multicenter, randomized SPIRIT III trial are the following: 1) compared with the PES, treatment with the EES resulted in lower 5-year rates of the composite safety and efficacy endpoints of TVF, TLF, and MACE; 2) all-cause mortality was also reduced at 5 years in patients treated with the EES compared with the PES; 3) the 5-year rates of myocardial infarction, stent thrombosis, and

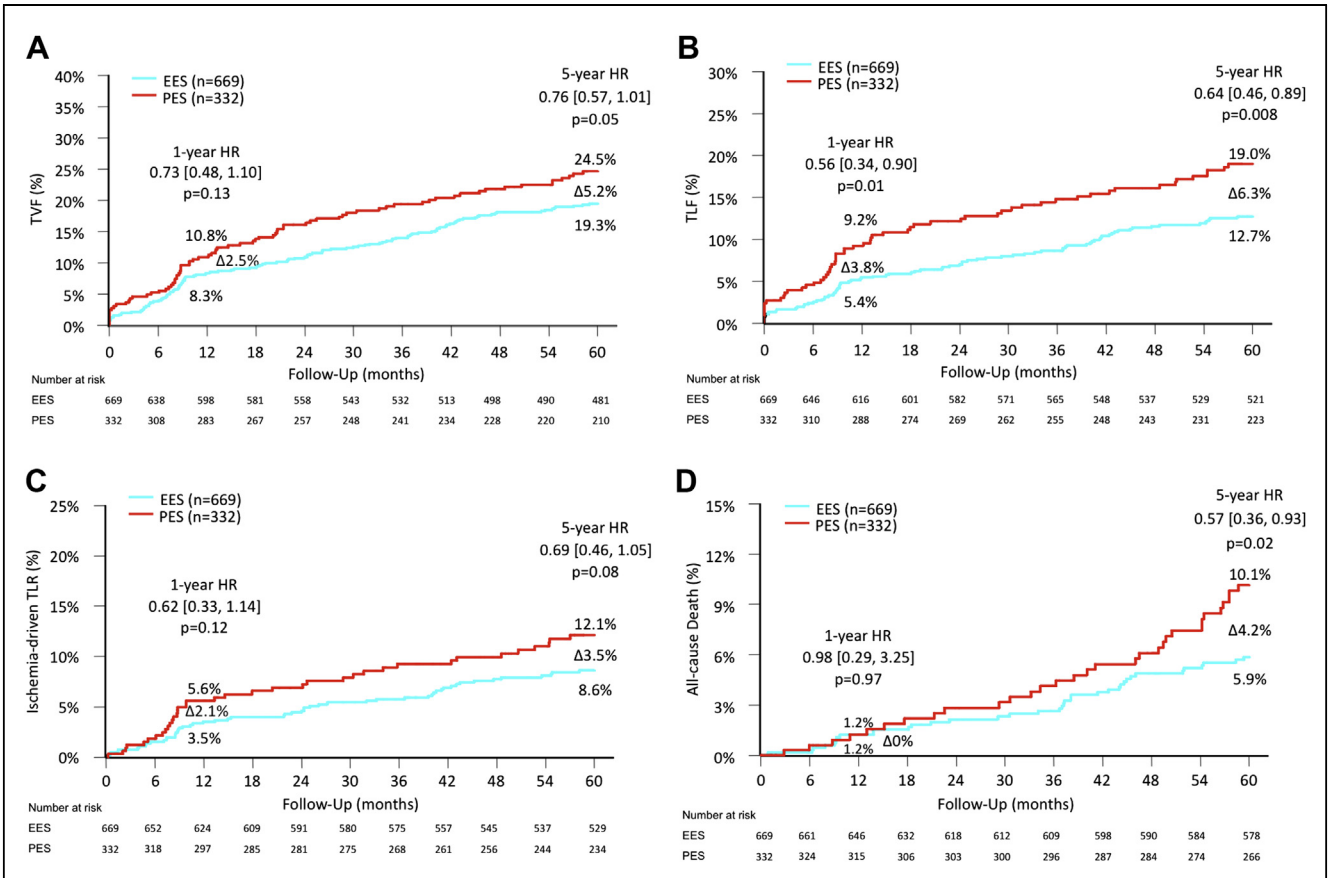

Figure 1. Time-to-Event Curves Through 5 Years

Time-to-event curves of TVF **(A)**, TLF **(B)**, ischemia-driven TLR **(C)**, and all-cause death **(D)**. EES = everolimus-eluting stent(s); HR = hazard ratio; PES = paclitaxel-eluting stent(s); TLF = target lesion failure; TLR = target lesion revascularization; TVF = target vessel failure.

ischemia-driven TLR were not significantly different between the EES and the PES in the present trial; and 4) there was no apparent erosion in the relative magnitude of TLR with the EES compared with the PES during the 5-year follow-up period.

Study limitations. The SPIRIT III was powered for non-inferiority between the EES and the PES for the endpoint of TVF at 9-month follow-up. The results of the present study should thus be considered hypothesis generating, especially concerning differences in low-frequency clinical endpoints and subgroups.

Conclusions

The present 5-year analysis represents the longest assessment of outcomes with the EES and the PES to date. Larger clinical studies comparing the EES with the PES were subsequently performed, albeit with shorter durations of follow-up. In the SPIRIT IV trial (N = 3,687), the primary endpoint of TLF at 1-year was significantly lower with the EES compared with the PES (4.2% vs. 6.9%, $p < 0.001$) (4). The COMPARE (Second-Generation Everolimus-Eluting and Paclitaxel-Eluting Stents in Real-Life Practice) trial also demonstrated significantly lower rates of MACE (defined as all-cause mortality, myocardial infarction, or clinically driven TVR) at 1-year with the EES compared with the PES (6.2% vs. 9.1%, $p = 0.02$) (5). Follow-up to 2 years has been completed in these trials and confirmed the benefits of the EES over the PES at this time point. The present analysis, extending these findings to 5 years, confirms the durability of the safety and effectiveness of the EES compared with the PES with regard to the primary clinical outcome of TVF.

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Key Words: coronary artery disease ■ drug-eluting stent(s) ■ in-stent restenosis ■ stent thrombosis ■ target vessel failure.

APPENDIX

For supplemental tables, please see the online version of this article.