Catheterization and Cardiovascular Interventions 77:1012–1017 (2011)

Four-Year Clinical Follow-Up of the XIENCE V Everolimus-Eluting Coronary Stent System in the Treatment of Patients With *De Novo* Coronary Artery Lesions: The SPIRIT II Trial

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This report describes the 4-year clinical outcomes of the SPIRIT II study, which randomized 300 patients to treatment with the XIENCE V everolimus-eluting stent (EES), or the TAXUS paclitaxel-eluting stent. At 4-year clinical follow-up, which was available in 256 (85.3%) patients, treatment with EES lead to a trend for lower rates of ischemia-driven major adverse cardiovascular events, a composite of cardiac death, myocardial infarction, and ischemia-driven target lesion revascularization (EES 7.7% vs. paclitaxel-eluting stent 16.4%, $P = 0.056$). Treatment with EES also resulted in a trend toward lower rates of cardiac death and numerically lower rates of myocardial infarction, ischemia-driven target lesion revascularization, and stent thrombosis. Overall, this study reports numerically fewer clinical events in patients treated with EES at 4-year follow-up, which is consistent with results from earlier follow-up. © 2010 Wiley-Liss, Inc.

Key words: percutaneous coronary intervention (PCI); angiography coronary (ANGO); diagnostic cardiac catheterization (CATH)

INTRODUCTION

Second-generation drug-eluting stents (DES), such as the XIENCE V everolimus-eluting stent (EES; Abbott Vascular, Santa Clara, CA), were developed with the aim of improving the safety profile of DES, after reports of stent thrombosis (ST) with first-generation devices [1]. These newer-generation stents elute everolimus or zotarolimus, use more biocompatible polymers, and have cobalt chromium stent platforms. Current results from randomized studies evaluating the EES indicate favorable clinical outcomes, together with lower rates of ST when compared with first-generation DES; however, results are limited to only medium-term follow-up [2–5]. Ensuring that these benefits are sustained long-term is important, not only because drug elution ceases within 6 months of stent implantation, but also because of the permanence of the stent platform and polymer. Therefore, in this study, we report the 4-year clinical outcomes of patients randomized to treatment with either EES or the TAXUS paclitaxel-eluting stent (PES; Boston Scientific, Natick, MA) in the SPIRIT II study.

METHODS

Study Design

The study design and outcomes at 6-, 12-, 24-, and 36-months follow-up are reported elsewhere [2,6–8]. In brief, this multicenter, prospective, single-blind study randomized 300 patients with up to two *de novo* coronary artery lesions in a ratio of 3:1 to treatment with either EES ($n = 223$) or PES ($n = 77$). The primary endpoint was in-stent late loss at 180 days.

Endpoints

Clinical endpoints assessed at 4 years included ischemia-driven major adverse cardiac events (ID-MACE), a composite of cardiac death, myocardial infarction (MI), and ischemia-driven target lesion

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Conflict of interest: Karine Miquel-Hebert is an employee of Abbott Vascular. The other authors have no conflicts of interest to report.

Study sponsor: Abbott Vascular

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Received 9 June 2010; Revision accepted 6 August 2010

DOI 10.1002/ccd.22770
Published online 3 December 2010 in Wiley Online Library (wileyonlinelibrary.com)

revascularization (ID-TLR) by percutaneous coronary intervention or coronary artery bypass graft surgery, and its individual components. All events up to 4 years were adjudicated by an independent clinical event committee that was blinded to the treatment assignments.

Definitions

Complete definitions are provided elsewhere [2,6–8]. All deaths were considered cardiac unless an undisputed noncardiac cause was present. Q-wave MI was defined as the development of new pathological Q waves. A non-Q-wave MI was defined as a typical rise and fall of creatine kinase myoglobin band (CK-MB), with at least one of the following: ischemic symptoms; electrocardiographic changes indicative of ischemia (ST segment elevation or depression); or an associated coronary artery intervention. For a nonprocedural or spontaneous MI, the CK-MB was required to be $\geq$2 times the upper limit of normal (ULN). A CK-MB $\geq$3 times the ULN or $\geq$5 times the ULN was required for an MI to be defined postpercutaneous coronary intervention or postcoronary artery bypass graft, respectively. ID-TLR was defined as revascularization of the target lesion in association with any of the following: a positive test of ischemia, using either exercise testing, or fractional/coronary flow reserve; ischemic symptoms and an angiographic diameter stenosis $\geq$50% by on-line quantitative coronary angiography (QCA); or a diameter stenosis $\geq$70% by on-line QCA without ischemic symptoms or a positive functional study. ST was classified according to the Academic Research Consortium classification [9].

Statistical Methods

All analyses were conducted according to the intention-to-treat principle. Binary variables are presented as percentages (counts), and compared using the Fisher's exact test. Cumulative events curves were generated using the Kaplan–Meier method, and the two groups were compared using the log-rank test. Hazard ratios with 95% confidence intervals were calculated using the Cox proportional hazards model.

RESULTS

Clinical follow-up was available in 256 (85.3%) patients (EES 192 [86.1%] and PES 64 [83.1%]) with a similar proportion of patients (EES 15 [6.7%] and PES 4 [5.2%]) lost because of failure to complete a new consent form, which was required after a change to the initial protocol to allow extended follow-up to 5 years. Other reasons for incomplete follow-up included death (EES 10 and PES 7), loss to follow-up (EES 2), and withdrawal (EES 4 and PES 2).

Baseline Demographic Data

Baseline demographic, clinical, and angiographic characteristics, which were comparable between both treatment groups are described in full elsewhere [6] and summarized in Table I.

Clinical Outcomes

Clinical outcomes in terms of cardiac death, MI, ID-TLR, all TLR, and ID-MACE at 4-year follow-up are shown in Table II. At 4 years, there was a trend for lower rates of cardiac mortality, all TLR, and ID-MACE in patients treated with EES. Rates of MI and ID-TLR were numerically lower with EES, although these differences were not statistically significant. Kaplan–Meier cumulative curves are shown in Fig. 1A–D.

The rate of definite or probable ST out to 4-year follow-up was 0.9% and 2.8% in patients treated with EES and PES, respectively ($P = 0.27$, Fig. 1E, Table III). Of note, no ST events were observed in the EES arm after 24 months of follow-up, whereas only one ST event was observed in the PES arm around month 30. The proportion of patients returning for 4-year follow-up, who were still taking dual antiplatelet therapy were 17.7% (34 of 192) and 21.9% (14 of 64) for patients treated with EES and PES, respectively. All patients experiencing an ST event were taking aspirin at the time of the event, with only one patient also taking clopidogrel (Table III).

DISCUSSION

This study represents the longest available follow-up of EES in a randomized patient population and, thereby, provides important data on the long-term efficacy and the safety of EES. The assessment of long-term outcomes is particularly important for DES because the elution of antiproliferative agents is largely exhausted within 6 months of stent deployment. Therefore long-term efficacy is not a consequence of drug elution, but more dependent on the stent platform and polymer. Newer-generation DES, such as EES and the Endeavor (Medtronic, Santa Rosa, CA) zotarolimus-eluting stent (ZES), use a cobalt chromium stent platform that enables struts to be thinner, which ultimately can reduce vascular injury, leading to a lower risk of restenosis and ST. In addition, the improvement in the biocompatibility of the stent polymer is designed to improve the stent's safety profile, potentially reducing the risk of ST further [10].

TABLE I. Baseline Patient Data

	Everolimus stent ($n = 223$)	Paclitaxel stent ($n = 77$)	All patients ($n = 300$)
Age (years)	62 ± 10	62 ± 9	62 ± 10
Male gender (%)	71	79	73
Current smoker (%)	32	30	31
Diabetes (%)	23	24	23
Hypertension requiring medication (%)	67	65	67
Hyperlipidemia requiring medication (%)	69	75	70
Prior target vessel intervention (%)	4	4	4
Prior MI (%)	35	25	32
Stable angina (%)	62	62	62
Unstable angina (%)	27	32	28
Target vessel (%)	No. of lesions = 260	No. of lesions = 91	No. of lesions = 351
Left anterior descending	41	47	42
Left circumflex	29	19	26
Right coronary artery	30	34	31
AHA/ACC lesion class (%)			
A	1	0	1
B1	21	20	21
B2	65	67	66
C	13	13	13
Reference vessel diameter (±SD) (mm)	2.70 ± 0.52	2.82 ± 0.58	2.73 ± 0.54
Lesion length (±SD) (mm)	13.0 ± 5.7	13.2 ± 6.4	13.0 ± 5.9

There was no significant difference between the everolimus and paclitaxel treatment arms.
MI, myocardial infarction; AHA/ACC, American Heart Association/American College of Cardiology.

Besides this study, the only other randomized data to support the potential benefits of second- versus first-generation DES at long-term (>3 years) follow-up are the ENDEAVOR III study, which randomized patients to either the Cypher (Cordis, Warren, NJ) sirolimus-eluting stent (SES), or ZES [11]. Although the 6-months results from the ENDEAVOR III study failed to demonstrate noninferiority of ZES with respect of the primary endpoint of in-segment late loss (ZES 0.34 ± 0.44 mm vs. SES 0.13 ± 0.32 mm; $P < 0.001$), long-term results suggest a more durable performance of ZES [12]. In particular, respective rates of death, TLR, target vessel failure, and ST between 1- and 5-year follow-up rose by 4.6%, 1.6%, 5.9%, and 0.7% for ZES, compared with rises of 13.0%, 3.0%, 7.0%, and 0.9% for SES, such that the early superiority of SES was not sustained at final follow-up.

Similarly, this report demonstrates the long-term safety and sustained efficacy of EES, which is consistent with other results observed from the evaluation EES at shorter follow-up [2–5]. It is noteworthy that the long-term efficacy of everolimus was previously called into question after the delayed late-loss observed in the EES angiographic subset of this study at 2 years [8]. Importantly, this delayed late-loss had little effect on reported clinical outcomes at 3-year follow-up, and, reassuringly, this is consistent with the present results, which show absolute differences between EES and PES for cardiac death, MI, ID-TLR, and ID-MACE, which are all at least as good at 4-years follow-up as they were at 1- and 2-year follow-up. Clearly, in the absence of further QCA analyses, it is not possible to definitively state whether these durable clinical results entirely dismiss the significance of the previously observed delayed late-loss. In contrast, in the SIRTAX-LATE study, the delayed late-loss observed with SES (Δ 0.18 mm between 1 and 5 years) was associated with the absolute difference in TLR between SES and PES falling from 3.5% at 1 year to 3.0% at 5 years [13]. With both EES and SES, drug elution is complete within 6 months, reiterating that other factors such as the type of stent platform and polymer biocompatibility are important factors in influencing the long-term efficacy of DES.

TABLE II. Clinical Outcomes at 4-Year Follow-up

0–1,460 Days, % (n)	EES ($n = 195$)	PES ($n = 67$)	P-value[a]
MACE	7.7 (15)	16.4 (11)	0.056
Cardiac death	0.5 (1)	4.5 (3)	0.053
Myocardial infarction	3.6 (7)	7.5 (5)	0.19
Ischemia-driven TLR	5.1 (10)	10.4 (7)	0.15
All TLR	5.9 (12)	12.7 (9)	0.073

MACE hierarchical, and all others nonhierarchical.
[a]From Fisher's exact test.MACE, major adverse cardiovascular events (a composite of cardiac death, myocardial infarction, and ischemia-driven target lesion revascularization); TLR, target lesion revascularization.

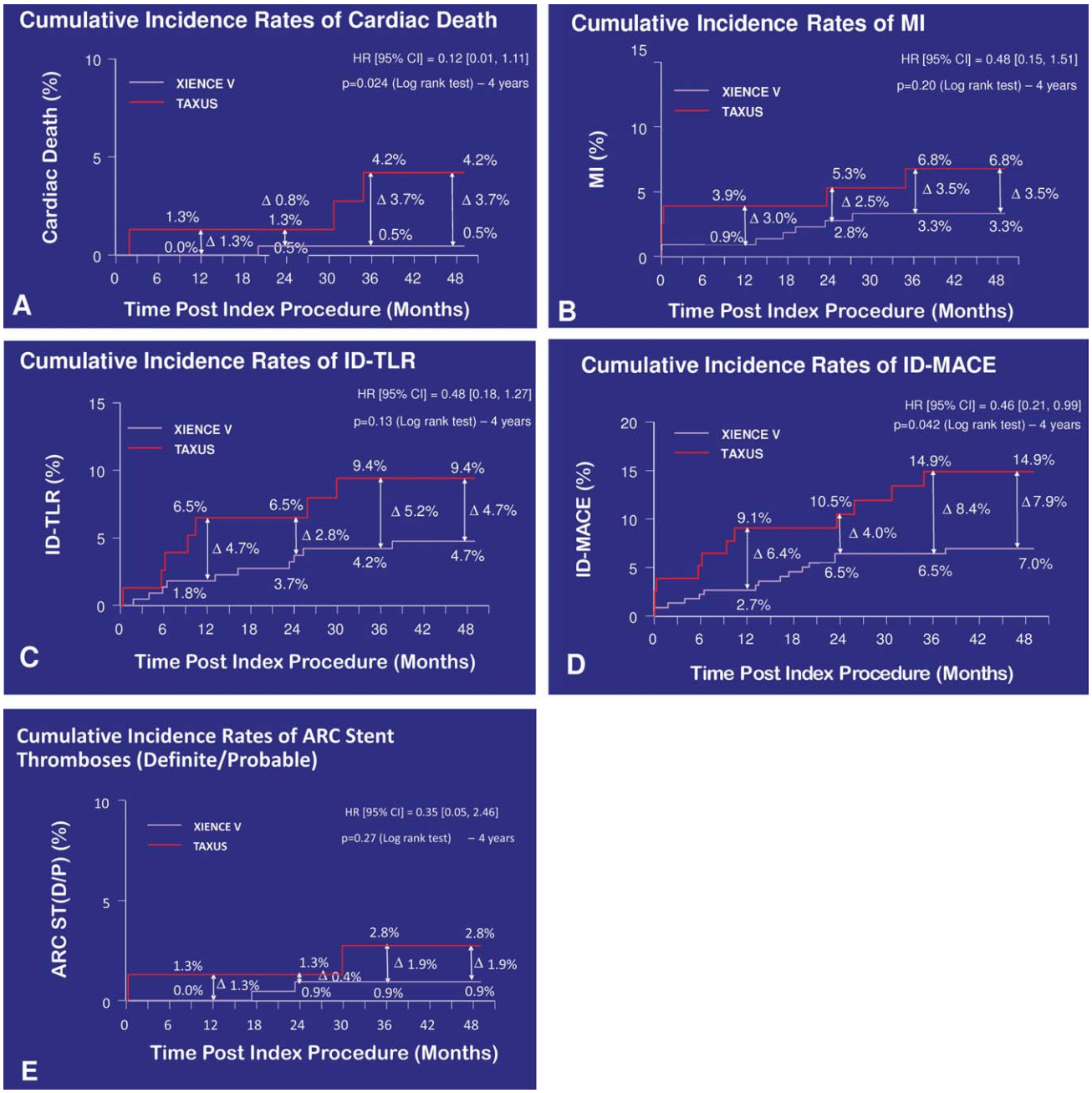

Fig. 1. Cumulative Kaplan–Meier estimates of the rates of key study endpoints. Cumulative risk of events at 1,460 days for (A) cardiac death; (B) myocardial infarction (MI); (C) ischemia-driven target lesion revascularization (ID-TLR); (D) ischemia-driven major adverse cardiac events (ID-MACE), a composite of cardiac death, nonfatal myocardial infarction (MI), and ischemia-driven target lesion revascularization (ID-TLR); and (E) definite/probable stent thrombosis. HR, hazard ratio.

Ultimately, the concerns over ST were one of the main driving forces behind the development of second-generation DES. EES has an acrylic fluorinated polymer, which is considered to be more biocompatible than that found on SES and PES; however, at present, no published study has been adequately powered to make any definitive conclusions regarding rates of ST between DESs. In this study, despite a lower proportion of patients taking dual antiplatelet therapy with EES at the time of follow-up, rates of ST remain numerically lower with EES, with no ST observed over the last 2 years of follow-up. The small sample size of this study must be taken into account; however, the absence of very late ST events during prolonged

TABLE III. Definite and Probable Stent Thrombosis Events Out to 4-Year Follow-up

Days to ST	Stent	Stented vessel	Antiplatelet therapy use throughout the study period	Events at time of ST	Worst hierarchical outcome
Definite ST					
9[a]	PES	Mid LAD	Aspirin throughout the study period; clopidogrel throughout the study period	Day 8: non-Q-wave MI; day 9: ID-TLR	Day 56: cardiac death
521	EES	Mid RCA	Aspirin throughout the study period; clopidogrel for 1 year, restarted on day 521 and stopped on day 956	Day 521: Non Q-wave MI	Day 521: non-Q-wave MI
897	PES	Distal RCA	Aspirin until day 1,026; clopidogrel for 6 months, restarted on day 1,009 and continued throughout the study period	Day 896: ID-TLR PCI	Day 1: non-Q-wave MI
Probable ST					
54[a]	PES	Mid LAD	Aspirin throughout the study period; clopidogrel throughout the study period	Day 54: non-Q-wave MI	Day 56: cardiac death
721	EES	Distal RCA	Aspirin throughout the study period; clopidogrel for 190 days	Day 700: non-Q-wave MI; day 721: ID-TLR	Day 700: non-Q-wave MI

[a]Same patient.

ST, stent thrombosis; PES, paclitaxel-eluting stent; EES, everolimus-eluting stent; LAD, left anterior descending artery; RCA, right coronary artery; MI, myocardial infarction; ID-TLR, ischemia-driven target lesion revascularization.

follow-up is important nevertheless. It will be of great interest to observe whether similar findings are seen during long-term follow-up of the more complex patient groups enrolled in the SPIRIT III and IV studies.

Limitations

The loss of patients during clinical follow-up, which was largely because of the failure of some patients to complete a new consent form that was required after a protocol amendment increasing follow-up of the study from 2 to 5 years, impacts on the power of the study to detect differences in clinical events. Moreover, interpretation of the current clinical results must take into account that the study was powered for in-stent late loss at 6-month follow-up and, therefore, not specifically designed to detect differences in clinical outcomes or ST.

CONCLUSIONS

This study reports numerically fewer clinical events at 4-year follow-up in patients treated with EES compared with the PES, which is consistent with other randomized studies of EES albeit at shorter follow-up. Overall, ST rates were low, with the absence of recent ST events remaining an important observation requiring careful surveillance.

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