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Five-Year Long-Term 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 FIRST Trial

Marcus Wiemer,[1*] MD, Patrick W. Serruys,[2] MD, PhD, Karine Miquel-Hebert,[3] PhD, Franz-Josef Neumann,[4] MD, Jan J. Piek,[5] MD, PhD, Eberhard Grube,[6] MD, Jürgen Haase,[7] MD, PhD, Leif Thuesen,[8] MD, and Christian Hamm,[9] MD

Background: Drug-eluting stents have shown to be superior over bare metal stents in clinical and angiographic outcomes after percutaneous treatment of coronary artery stenosis. However, long-term follow-up data are scarce and only available for sirolimus- and paclitaxel-eluting stents. Aim: To assess the feasibility and performance of the XIENCE V everolimus-eluting stent (EES) versus an identical bare metal stent after a 5-year follow-up period. Methods: SPIRIT FIRST was a First in Man, multicentre, prospective, single-blind, clinical trial, randomizing 60 patients with a single *de novo* coronary artery lesion in a ratio of 1:1 to either an everolimus eluting or a bare metal control stent. Results: At 5-year clinical follow-up, data were available in 89% and 86% of patients in the everolimus and control arm, respectively. In the everolimus arm, no additional death, myocardial infarction, clinically driven target lesion revascularization (TLR), or clinically driven target vessel revascularization (TVR) events were observed between 1- and 5-year follow-up. The 5-year hierarchical major adverse cardiac events (MACE) and target vessel failure (TVF) rates for the everolimus arm were 16.7% (4/24) for both endpoints. In the control group, no additional cardiac death, myocardial infarction, or clinically driven TLR events were observed between 2- and 5-year follow-up. No additional clinically driven TVR events were observed between 3- and 5-year follow-up. The 5-year hierarchical MACE and TVF rates for the control arm were 28.0% (7/25) and 36.0% (9/25), respectively. No stent thromboses were observed in either the everolimus arm or the control arm up to 5 years. Conclusion: The favorable 5-year long term clinical outcome of the EES is consistent with the results from other studies of the EES with shorter follow-up.

Key words: coronary artery disease; percutaneous coronary intervention; drug-eluting stents

[1]Department of Cardiology, Heart and Diabetes Center North Rhine-Westphalia, Ruhr University Bochum, Bad Oeynhausen, Germany
[2]Interventional Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands
[3]Clinical Research, Abbott Vascular, Diegem, Belgium
[4]Department of Cardiology, Heart Center, Bad Krozingen, Germany
[5]Department of Cardiology, Academisch Medisch Centrum, Amsterdam, The Netherlands
[6]Department of Cardiology, Heart Center Siegburg, Siegburg, Germany
[7]Department of Cardiology, Red Cross Hospital, Frankfurt, Germany
[8]Department of Cardiology, Skejby Sygehus, Aarhus, Denmark
[9]Department of Cardiology, Kerckhoff Clinic, Bad Nauheim, Germany

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*Correspondence to: Marcus Wiemer, MD, Kardiologische Klinik, Herz- und Diabeteszentrum Nordrhein-Westfalen, Ruhr-Universität Bochum, Georgstr.11, 32545 Bad Oeynhausen, Germany.
E-mail: mwiemer@hdz-nrw.de

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INTRODUCTION

Large randomized studies have shown the superiority of drug-eluting stents (DES) over bare metal stents (BMS) in clinical and angiographic outcomes after percutaneous treatment of coronary artery stenosis [1–9]. Thus far, long-term follow-up data are limited and available only for sirolimus- and paclitaxel-eluting stents (SES and PES) [10–13]. There have been concerns that, when compared to BMS, the first generation of DES coated with sirolimus and paclitaxel are associated with an increased risk of very late stent thrombosis (>1 year) [14]. An everolimus-eluting stent (EES) has been developed with the goal of improving the safety of DES.

The SPIRIT FIRST clinical trial represents the first clinical evaluation of the XIENCE V everolimus eluting coronary stent system in which its safety and efficacy were studied and compared to identical BMS. The 6 months angiographic and intravascular ultrasound (IVUS) follow-up showed significantly less neointimal hyperplasia with the EES [15]. At 1 year, these angiographic and IVUS results were maintained. Furthermore, the clinically driven percutaneous revascularization rate at target vessel was reduced by more than 50% for patients treated with an EES [16]. Between 1- and 2-year follow-up, no additional death, myocardial infarction, clinically driven target lesion revascularization (TLR), or clinically driven target vessel revascularization (TVR) events were observed in the everolimus arm [17].

The assessment of the EES continued with the SPIRIT II and the larger SPIRIT III studies. Both involved the randomized comparison of EES to a TAXUS (Boston Scientific, Natick, MA) PES in patients with a maximum of two *de novo* coronary artery lesions. In both studies, there was a reduction in major adverse cardiac events (MACE) with EES compared to PES at 12-month follow-up [18,19]. Most recently, 1 year results from SPIRIT IV were presented [20], and confirmed the superiority of XIENCE V compared to TAXUS Express2 in target lesion failure.

This article presents the 5-year long-term clinical outcome of patients enrolled in the SPIRIT FIRST study treated with either EES or an identical BMS. This represents the longest available clinical follow-up for the EES stent albeit in a small size population.

METHODS

Patient Population

The patient population has been described previously [15–17]. In brief, SPIRIT FIRST was a multicentre, prospective, single-blind, clinical trial, enrolling 60 patients with a single *de novo* coronary artery lesion. They were randomized in a ratio of 1:1 to receive either an EES, XIENCE V (Abbott Vascular, Santa Clara, CA) ($n = 28$) or a bare metal control stent (MULTI-LINK VISION, Abbott Vascular, Santa Clara, CA) ($n = 32$). A detailed description of everolimus and the EES stent is provided elsewhere [15,21]. The ethics committee of each participating institution approved the study protocol, and all patients gave written informed consent.

Patients enrolled in the study had a single *de novo* coronary artery lesion required to be, as assessed by on-line quantitative coronary angiography (QCA), in a vessel with a reference vessel diameter of 3.0 mm; less than or equal to 12 mm in length; and have a percentage diameter stenosis (DS) between 50 and 99%, with a thrombolysis in myocardial infarction flow grade $\geq$1. Major exclusion criteria included an evolving myocardial infarction, a stenosis of an unprotected left main coronary artery, an aorto-ostial location, a location within 2 mm of a bifurcation, a lesion with moderate to heavy calcification, an angiographically visible thrombus within the target vessel, a left ventricular ejection fraction of less than or equal to 30%; patients awaiting a heart transplant, or patients suffering a contraindication to aspirin, heparin, clopidogrel or ticlopidine, cobalt, chromium, nickel, tungsten, everolimus, acrylic, and fluoropolymers or contrast sensitivity.

Study Procedure

Patients were randomized in a 1:1 ratio in a single-blinded manner to either a XIENCE V EES or a MULTI-LINK VISION Stent (control). Target lesions were treated according to standard interventional techniques with mandatory pre-dilatation. Post-dilatation was left to the discretion of the operator. However, if performed, balloons were required to be shorter than and fit within the boundaries of the stent. In the event of a bailout procedure and the need for an additional stent, this was required to be a single additional 8 or 18 mm MULTI-LINK VISION Stent, a limitation based on pre-clinical information available at that time. Peri-procedural pharmaceutical treatment was administrated according to standard hospital practice. All patients enrolled into the study received $\geq$80 mg of aspirin daily for a minimum of 1 year, and clopidogrel 75 mg for a minimum of 3 months following the index procedure.

Follow-Up

Patient review was planned at 30, 180, and 270 days, with annual evaluation up to 5 years following the procedure. At outpatient visits, patients were

specifically questioned about the development of angina or the occurrence of any adverse events. The angiographic and IVUS follow-up for all patients were planned at 180 days and at 1 year.

Study Endpoints and Definitions

The primary endpoint was in-stent late loss at 180 days. The major secondary endpoint was percent in-stent volume obstruction (%VO) at 180 days based on IVUS analysis.

The clinical endpoints of this 5-year follow-up focus on the following: (a) MACE comprised of cardiac death, Q-wave or non-Q-wave myocardial infarction, or clinically driven surgical or percutaneous TLR; (b) target vessel failure (TVF) comprised of MACE and clinically driven TVR, and (c) stent thromboses.

An independent blinded clinical events committee (CEC) evaluated all clinical endpoints, and a Data and Safety Monitoring Board, not affiliated with the study, ensured the safe conduct of the trial.

All deaths that could not be clearly attributed to another cause were considered cardiac deaths. The onset of the trial was prior to the publication of the Academic Research Consortium's (ARC) consensus definitions for DES study endpoints. Therefore, the only cardiac enzymes available in all patients to adjudicate events were creatinine kinase (CK) and creatinine kinase myoglobin fraction (CK-MB). A non-Q-wave myocardial infarction was defined as an increase in the CK-MB level to greater than or equal to (1) twice the upper limit of the normal range (nonprocedural), (2) three times the upper limit of the normal range (post-PCI), or (3) five times the upper limit of the normal range (post-CABG).

Clinically driven TLR was defined as revascularization of the target lesion in association with any of the following: a positive test of ischaemia or ischemic symptoms and an angiographic DS $\geq$ 50% determined by QCA; or DS $\geq$ 70% by QCA without either angina or a positive functional study.

Clinically driven TVR was defined as revascularization of the target vessel in association with a positive test of ischaemia or ischemic symptoms.

Stent thrombosis was defined as a total coronary artery occlusion by angiography at the stent site with abrupt onset of symptoms, elevated biochemical markers, and ECG changes consistent with an MI. Stent thrombosis was categorized as acute (<1 day), subacute (1–30 days) and late (>30 days).

In addition, retrospectively, events were re-adjudicated by the CEC according to the ARC definitions [22].

Statistical Analysis

The primary endpoint and all other trial endpoints were analyzed on the per-treatment evaluable population. The per-treatment evaluable population consisted of patients who had no bailout and no major protocol deviations. The data of all patients were reviewed in a blinded manner to determine whether the patient should be included in this analysis population. Patients were included in the treatment arm corresponding to the study stent actually received.

The rationale for sample size calculations for this study has previously been reported [15]. The trial was not powered to detect any specific differences between the control and the everolimus group for the secondary endpoints.

In this article, *P*-values were calculated with Fisher's exact test for binary variables and with the Wilcoxon's Rank Sum test for continuous variables.

Survival curves were constructed for time-to-event variables using Kaplan-Meier estimates, and compared by the log-rank test. Statistical analyses were performed using the SAS statistical package (version 9.1.3 SAS Institute, Cary, NC).

RESULTS

Patient Population and Lesion Characteristics

Between December 2003 and April 2004, a total of 60 study patients (32 control arm; 28 everolimus arm) were randomized and consecutively enrolled at nine European investigational sites. Of these patients, four were excluded from the per-treatment population (one due to bailout procedure in the everolimus arm, two due to bailout procedures in the control arm, and one due to a major protocol deviation (waiting list for a heart-transplant) in the control arm). Hence, the per-treatment population includes 56 patients (27 everolimus arm and 29 control arm).

As previously reported [15] and summarized in Table I, both arms had similar demographic, angiographic, and procedural characteristics with the exception of a significantly higher number of patients with hypertension requiring treatment in the everolimus arm (70% vs. 41%).

Figure 1 shows the clinical follow-up of patients from enrolment to 5 years, on a per-treatment basis. Overall, clinical assessment was available in 49 patients (88%) made up of 24 of the original 27 EES patients, (89%) and 25 of the original 29 control patients (86%). The reasons for incomplete follow-up are shown in Fig. 1.

The angiographic and IVUS outcomes at 6 months and 1 year, and the clinical outcomes at 6 months, 1 year, and 2 years, have all been presented elsewhere

TABLE I. Baseline Characteristics of the Patient Population (Per-Treatment Population)

	Everolimus stent ($n = 27$)	Control ($n = 29$)	All patients ($n = 56$)
Age (years)	64 ± 10	61 ± 9	63 ± 9
Male gender (%)	70	76	73
Current smoker (%)	28	31	30
Diabetes (%)	11	10	11
Hypertension requiring medication (%)	70	41	55
Hyperlipidaemia requiring medication (%)	70	76	73
Prior intervention (%)	19	7	13
Prior MI (%)	24	14	19
Stable angina (%)	78	79	79
Unstable angina (%)	19	14	16
Target vessel (%)			
Left anterior descending	48	45	46
Left circumflex	22	21	21
Right coronary artery	30	34	32
AHA/ACC lesion class (%)			
A	0	10	5
B1	41	28	34
B2	59	62	61
C	0	0	0
Reference vessel diameter (mm ± SD)	2.61 ± 0.40	2.71 ± 0.28	2.66 ± 0.34
Lesion length (mm ± SD)	10.1 ± 2.6	10.9 ± 3.3	10.5 ± 3.0

AHA/ACC, American Heart Association/American College of Cardiology.

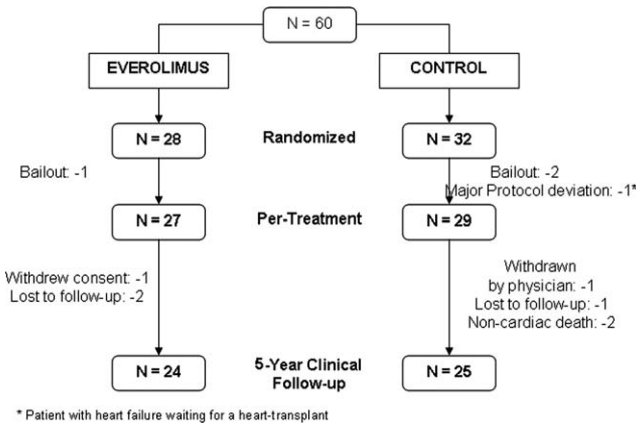

Fig. 1. Number of patients randomized from the enrolment through 5-year follow-up.

TABLE II. Hierarchical Patients Counts of Adverse Events Through 5 Years (Per-Treatment Population)

	EES		Control	
Event, 0 to 1,853 days	$n = 24$	%	$n = 25$	%
Cardiac death	0	0	0	0
Myocardial infarction	2	8.3	0	0
Q-wave	1	4.2	0	0
Non-Q-wave	1	4.2	0	0
Clinically driven TLR	2	8.3	7	28.0
Clinically driven TLR-CABG	0	0	1	4.0
Clinically driven TLR-PCI	2	8.3	6	24.0
Clinically driven TVR[a]	0	0	2	8.0
Clinically driven TVR-CABG[a]	0	0	1	4.0
Clinically driven TVR-PCI[a]	0	0	1	4.0
Target vessel failure	4	16.7	9	36.0
Major adverse cardiac events	4	16.7	7	28.0

[a]Excludes target lesion revascularizations.

[15–17]. In brief, at 6 months, EES demonstrated significantly reduced in-stent late loss and volume obstruction (VO) when compared to the control (0.10 mm vs. 0.87 mm, $P < 0.001$ for late loss and 8.0% vs. 28.1%, $P < 0.001$ for VO). Clinical outcomes in terms of MACE, TVF and clinically driven TLR were all better with EES at 6 months, 1 year, and 2 years when compared to the control. Three of the four overall MACE events in the everolimus arm were non-study device-related events. One Q-wave MI was in a non-target vessel, one TLR was due to dissection during the procedure, and one non-Q-wave MI occurred during follow-up IVUS procedure. Both the angiographic and IVUS measurements showed that the patency of the target vessel treated with EES was maintained at 1 year. The EES demonstrated reduced in-stent late loss and %VO when compared to the control (0.24 mm vs. 0.84 mm, $P < 0.001$ for late loss and 10% vs. 28%, $P < 0.001$ for VO).

Clinical Outcomes at Five-Year Follow-Up

The hierarchical and non-hierarchical events at 5-year clinical follow-up are shown in Tables II and III, respectively. Figures 2–4 show the Kaplan Meier survival curves for MACE, TVF, and clinically-driven TLR, respectively.

The 5-years hierarchical MACE and TVF rates for the everolimus arm were 16.7% (4/24) for both

TABLE III. Non-Hierarchical Patients Counts of Adverse Events through 5 Years (Per-Treatment Population)

	EES		Control	
Event, 0 to 1,853 days	$n = 24$	%	$n = 25$	%
Cardiac death	0	0	0	0
Myocardial infarction	2	8.3	0	0
Q-wave	1	4.2	0	0
Non-Q-wave	1	4.2	0	0
Clinically driven TLR	2	8.3	7	28.0
Clinically driven TLR-CABG	0	0	1	4.0
Clinically driven TLR-PCI	2	8.3	6	24.0
Clinically driven TVR[a]	0	0	3	12.0
Clinically driven TVR-CABG[a]	0	0	1	4.0
Clinically driven TVR-PCI[a]	0	0	2	8.0
Stent Thrombosis				
Per protocol	0	0	0	0
ARC definite	0	0	0	0
ARC definite or probable	0	0	0	0
Any ARC criterion	0	0	0	0

[a]Excludes target lesion revascularizations.

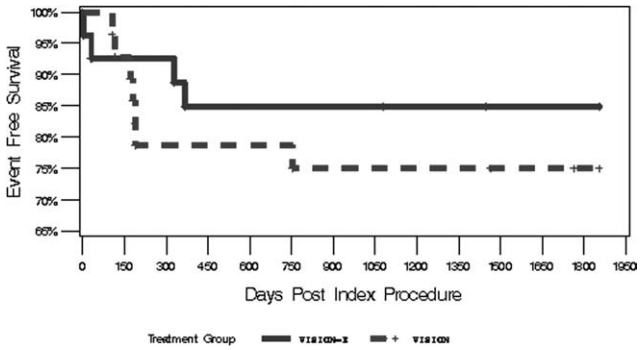

Fig. 2. Kaplan-Meier Survival Curve: MACE (Cardiac Death, MI or Clinically-Driven TLR) Survival to 5-year follow-up (Per-Treatment population).

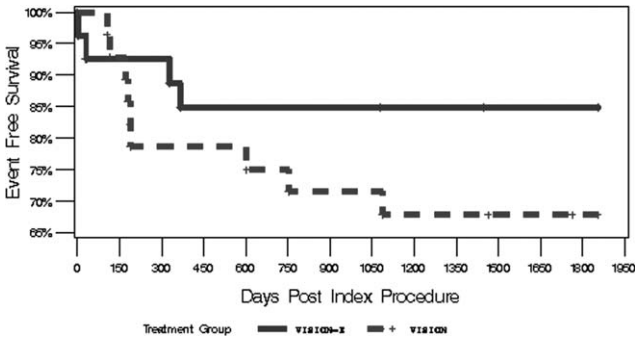

Fig. 3. Kaplan-Meier Survival Curve: TVF (Cardiac Death, MI or Clinically-Driven TVR) Survival to 5-year follow-up (Per-Treatment population).

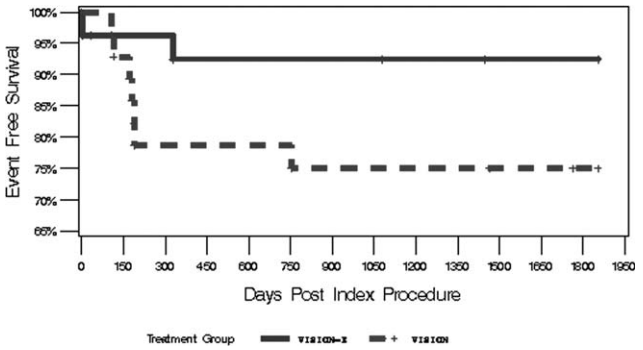

Fig. 4. Kaplan-Meier Survival Curve: Clinically-Driven TLR Survival to 5-year follow-up (Per-Treatment population).

endpoints (Table II). In the everolimus arm, no additional death, myocardial infarction, clinically driven TLR, or clinically driven TVR events were observed between 1 and 5 years follow-up.

The 5-years hierarchical MACE and TVF rates for the control arm were 28.0% (7/25) and 36.0% (9/25), respectively (Table II). In the control group, no additional cardiac death, myocardial infarction, or clinically driven TLR events were observed between 2 and 5 years follow-up.

The total non-hierarchical clinically driven TLR (PCI and CABG) rate at 5 years was 8.3% in the everolimus arm and 28.0% in the control arm (Table III). No stent thromboses were observed in either the everolimus arm or the control arm up to 5 years (Table III).

The Kaplan Meier curves (Figs. 2–4) show that the survival rates of MACE, TVF, and clinically-driven TLR were higher with EES at 5-year follow-up compared to the control arm (84.9% vs. 75.0%, $P_{\text{logrank}} =$ 0.392 for MACE, 84.9% vs. 67.9%, $P_{\text{logrank}} = 0.175$ for TVF and 92.4% vs. 75.0%, $P_{\text{logrank}} = 0.093$ for clinically-driven TLR).

DISCUSSION

Five-year clinical follow-up from the randomized SPIRIT FIRST trial demonstrates that the safety and efficacy of the XIENCE V stent observed at 1-year follow-up is maintained with no additional TVF events between 1 year and 5 years follow-up in the everolimus arm and no stent thromboses during the entire study period in either arm. This favorable 5-year long term clinical outcome of the EES is consistent with the results from other studies of the EES with shorter follow-up. Although a "late loss catch-up" with EES was suggested by the 2-year outcome data from SPIRIT II there was no significant difference in angiographic and clinical outcomes between the EES and PES stents, with a numerically lower observed MACE rate in the XIENCE V arm. These late loss results raised concerns about the clinical implications of "late loss catch-up" [23]. The concerns were proven unfounded when the 3 year data confirmed that this increase in neo-intimal

hyperplasia did not translate into higher clinical events [24]. In fact, the EES showed a reduction in cardiac events, clinical restenosis, overall MACE, and stent thrombosis rates at 3 year follow-up compared to PES. Likewise, the 2-year [25] and the 3-year [26] follow-up data from SPIRIT III have shown promising results with improvements in event free survival, and lower rates of stent thrombosis with the use of an EES.

The RAVEL study has been the longest ongoing clinical trial presenting recently 5-year follow-up data after sirolimus-eluting stent (SES) implantation [11]. Compared to a bare metal stent, SES resulted in a remaining significant reduction of MACE (25.8% vs. 35.2%) and TLR (10.3% vs. 26.0%). The present SPIRIT FIRST trial with 60 patients compared to 238 of the RAVEL trial is smaller but also randomized in a 1:1 ratio against a bare metal control stent. SPIRIT FIRST showed a lower rate of major adverse clinical events (16.7%) in the EES group compared to the rate for SES presented in RAVEL.

No cardiac death or stent thrombosis was seen in the SPIRIT FIRST patients compared to a rate of 4.7% or 3.3%, respectively, in the SES arm of the RAVEL study. However, these results have to be interpreted with caution since none of the studies were designed or powered for clinical events.

The 5-year results of the TAXUS II trial comparing the PES with slow release (SR, commercialized stent, $n = 131$ patients), moderate release (MR, three-fold higher dose, investigational only, $n = 135$) and an identical but uncoated bare-metal stent ($n = 270$) has been published very recently [27]. This trial showed rather comparable data as the SES with a rate of cardiac death of 2.4% (SR) and 1.6% (MR), myocardial infarction of 4.7 and 5.3% and stent thrombosis of 2.7 and 1.7%. The TLR rate was 10.3 (SR) and 4.5% (MR) compared to 8.3% in the SPIRIT FIRST trial. The 5-year results of the TAXUS VI trial are not comparable due to the treatment design of long and complex lesions with the three-fold higher dose in the TAXUS moderate release stent which is investigation-only and does not have any immediate commercial implications [28].

Although the sample size was small, the 5-year clinical results of the SPIRIT FIRST trial are within the range of, or even better than the first generation DES, but without any acute, late or very late stent thrombosis.

Limitations of the Study

The clinical results with the small sample size of the SPIRIT FIRST trial provide only limited long-term safety and efficacy data, and caution is required when interpreting the differences in events. The trial is limited by numerous coronary artery lesion related-exclusion criteria frequently encountered in routine clinical practice.

CONCLUSION

This report confirms and extends the safety and efficacy results of the XIENCE V everolimus eluting coronary stent system with a persistence of anti-restenotic effects throughout the 5-year period and the absence of any stent thrombosis compared with an otherwise identical bare metal stent.

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