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Sirolimus-Eluting Stents for Treatment of Infrapopliteal Arteries Reduce Clinical Event Rate Compared to Bare-Metal Stents

Long-Term Results From a Randomized Trial

Aljoscha Rastan, MD,* Klaus Brechtel, MD,† Hans Krankenberg, MD,‡ Rainer Zahorsky, MD,§ Gunnar Tepe, MD,‖ Elias Noory, MD,* Uwe Schwarzwälder, MD,* Roland Macharzina, MD,* Thomas Schwarz, MD,* Karlheinz Bürgelin, MD,* Sebastian Sixt, MD,‡ Thilo Tübler, MD,‡ Franz-Josef Neumann, MD,* Thomas Zeller, MD*

Bad Krozingen, Tübingen, and Hamburg, Germany

Objectives The study investigated the long-term clinical impact of sirolimus-eluting stents (SES) in comparison with bare-metal stents (BMS) in treatment of focal infrapopliteal lesions.

Background There is evidence that SES reduce the risk of restenosis after percutaneous infrapopliteal artery revascularization. No data from randomized trials are available concerning the clinical impact of this finding during long-term follow-up.

Methods The study extended the follow-up period of a prospective, randomized, multicenter, double-blind trial comparing polymer-free SES with placebo-coated BMS in the treatment of focal infrapopliteal de novo lesions. The main study endpoint was the event-free survival rate defined as freedom from target limb amputation, target vessel revascularization, myocardial infarction, and death. Secondary endpoints include amputation rates, target vessel revascularization, and changes in Rutherford-Becker class.

Results The trial included 161 patients. The mean target lesion length was 31 ± 9 mm. Thirty-five (23.3%) patients died during a mean follow-up period of 1,016 ± 132 days. The event-free survival rate was 65.8% in the SES group and 44.6% in the BMS group (log-rank $p = 0.02$). Amputation rates were 2.6% and 12.2% ($p = 0.03$), and target vessel revascularization rates were 9.2% and 20% ($p = 0.06$), respectively. The median (interquartile range) improvement in Rutherford-Becker class was –2 (–3 to –1) in the SES group and –1 (–2 to 0) in the BMS group, respectively ($p = 0.006$).

Conclusions Long-term event-free survival, amputation rates, and changes in Rutherford-Becker class after treatment of focal infrapopliteal lesions are significantly improved with SES in comparison with BMS. (YUKON-Drug-Eluting Stent Below the Knee - Randomised Double-Blind Study [YUKON-BTX]; NCT00664963) (J Am Coll Cardiol 2012;60: 587–91) © 2012 by the American College of Cardiology Foundation

Greater life expectancy and the increasing prevalence of diabetes mellitus in developed countries lead to a progressively rising number of patients with critical limb ischemia (CLI) and intermittent claudication (IC) due to infrapopliteal artery (IPA) disease (1).

Over the past years prospective nonrandomized and randomized trials revealed that sirolimus-eluting stents (SES) are significantly superior to percutaneous transluminal balloon angioplasty (PTA) and bare-metal stents (BMS) concerning patency rates, and in parts target lesion revas-

From *Angiologie, Herz-Zentrum Bad Krozingen, Bad Krozingen, Germany; †Radiologische Klinik, Diagnostische und Interventionelle Radiologie, Eberhard-Karls-Universität, Tübingen, Germany; ‡Universitäres Herz-und Gefäßzentrum Hamburg, Hamburg, Germany; §Herzzentrum Hamburg West, Hamburg, Germany; and ‖RoMed Klinikum Rosenheim, Institut für Radiologie, Hamburg, Germany. Dr. Zeller is a member of the advisory boards to Medtronic-Invatec, Medtronic-Ardian, W.L. Gore & Associates, Angioslide, and Covedian-ev3; has received consulting fees from Sanofi-Aventis, C.R. Bard, J&J Cordis, Covedian-ev3, Boston Scientific, Straub Medical, Invatec, Biotronik, Optimed, Pathway Medical, and W. L. Gore & Associates; and has received research grants from Cook, KrauthMedical, Pathway Medical, Abbott Vascular, J&J Cordis, Angioside, Ardian, Biotronik, Invatec, InnoRa, and W. L. Gore & Associates. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Abbreviations and Acronyms

BMS = bare-metal stent(s)
CI = confidence interval
CLI = critical limb ischemia
HR = hazard ratio
IC = intermittent claudication
IPA = infrapopliteal arteries
PTA = percutaneous transluminal balloon angioplasty
SES = sirolimus-eluting stent(s)
TVR = target vessel revascularization

cularization (TVR) rates and improvement in Rutherford-Becker class (2–5). However, none of these studies confirm an advantage of SES regarding amputation rate, limb salvage, and mortality. Moreover, due to the fact of higher costs and inconclusive evidence from nonrandomized, single-center studies advocating a clinical impact of SES in a long-term follow-up, PTA and BMS potentially remain the gold standard in treatment of focal IPA lesions (6,7).

To gain more evidence regarding the clinical impact of SES placement in treatment of IPA lesions, the follow-up period of a prospective, double-blind, randomized, multicenter trial comparing polymer-free SES with BMS was extended. This trial confirms significantly higher patency rates and greater improvement in Rutherford-Becker class in patients treated with SES in comparison with BMS. No significant difference could be observed concerning limb salvage rate, target lesion revascularization, and event-free survival 1 year after index procedure (5).

Methods

Patient selection and study design. Between April 2006 and April 2008 CLI and IC patients were enrolled in this prospective, randomized, double-blind trial. Patients were eligible for the study if they were at least 21 years old, were not pregnant, and suffered from peripheral artery disease Rutherford-Becker class of 3 to 5. Angiographic eligibility criteria were the presence of a single de novo lesion in an IPA that did not exceed 45 mm in length. We allocated patients to the 2 treatment groups (polymer-free SES and BMS) using a computer-generated random sequence. All patients received aspirin (100 mg daily) and clopidogrel (loading dose of 600 mg before the procedure followed by 75 mg daily for 6 months). Study design, study procedures, and 1-year results of this trial were published (5).

After completion of the 1-year results the extension of the follow-up period was approved by the ethics committee on August 12, 2011. All patients gave written informed consent.

Follow-up. Clinical follow-up was obtained through outpatient visits, direct phone call assessments, and correspondence with the primary physician with attention directed to a questionnaire regarding the clinical course of each patient including target limb major and minor amputation, TVR, myocardial infarction, and causes of death. In addition, in patients who were willing and capable a determination of the Rutherford-Becker class was performed.

Study endpoints. The main study endpoint was the event-free survival rate defined as freedom from TVR, major and minor target limb amputation, myocardial infarction, and death. Secondary endpoints included amputation rate, TVR, and change in Rutherford-Becker class. All events were determined cumulatively for the 1,100 days after stent placement.

Statistical analysis. Data for all endpoints were evaluated in the intention-to-treat analysis. Continuous data are expressed as mean ± SD. Categorical variables were compared with the use of the 2-sided chi-square test and continuous variables were compared with the use of the 2-sided Student *t* test. Changes in Rutherford-Becker class were expressed as median with interquartile range, and group comparisons were performed using the Mann-Whitney *U* test. Event-free survival was compared by Kaplan-Meier analysis with the use of the Mantel-Cox log-rank. A 2-sided p value <0.05 was considered to indicate statistical significance. To summarize differences in the primary endpoint between the study groups, we derived hazard ratios (HR) with associated 95% confidence intervals (CI) from the Cox proportional hazards model. To assess the interaction of stent type with stage of disease (CLI or IC) and to adjust for remaining imbalance, we performed Cox regression analyses. In addition to the interaction term, the multivariable models included demographic, clinical, and interventional variables (Table 1) with a difference between the 2 study groups at a value of $p \leq 0.1$. All statistical analyses were performed with the SPSS software, version 18.0 (SPSS Inc., Chicago, Illinois).

Results

Patient characteristics. At baseline 161 patients were included in this trial. Eighty-two patients were randomly assigned to receive the polymer-free SES, and 79 were

Table 1 Baseline Characteristics of the Overall Patient Population and of Each Treatment Group*

	All Patients (N = 161)	SES (n = 82)	BMS (n = 79)
Age, yrs	72.9 ± 9	73.4 ± 8	72.3 ± 9
Male, %	66.5	67.9	64.9
Body mass index, kg/m^2	27 ± 4	28 ± 5	27 ± 4
Diabetes mellitus, %	53.8	56.8	50.6
Dyslipidemia, %	76.6	76.5	76.6
Hypertension, %	89.9	91.4	88.3
Current smoker, %	28.5	28.4	28.6
Renal insufficiency, % (creatinine ≥1.5 mg/dl)	35.4	35.8	35.1
Critical limb ischemia,† %	46.6	51.2	41.8
Target lesion, %			
Anterior tibial artery	27	22	31
Tibioperoneal trunk	37	42	33
Peroneal artery	21	19	23
Posterior tibial artery	15	17	13

Values are mean ± SD or %. *There were no significant differences between the treatment groups except for body mass index (p = 0.004). †Critical limb ischemia was defined according to the Rutherford-Becker classification.
BMS = bare-metal stent(s); SES = sirolimus-eluting stent(s).

assigned to receive the BMS. With exception of a significantly higher body mass index in the SES group, the 2 groups were similar with respect to all baseline variables. A total of 155 patients (96.3%) had 0 or just 1 patent IPA to the ankle joint (SES group, 95.1%; BMS group, 96.2%; p = 0.9) at baseline (Table 1).

Long-term clinical follow-up. The mean follow-up time was 1,005 ± 139 days in the SES group and 1,027 ± 123 days in the BMS group (p = 0.38). Concerning the primary endpoint, event-free survival rate compared by Kaplan-Meier analysis was 65.8% in the SES group and 44.6% in the BMS group (p = 0.02) (Fig. 1). Thus, in comparison with SES, BMS placement was associated with a HR for adverse events of 1.8 (95% CI: 1.1 to 2.9; p = 0.02). The higher risk of adverse event occurrence associated with BMS prevailed after adjustment for renal insufficiency, CLI, and body mass index. The corresponding adjusted HR was 1.7 (95% CI: 1.1 to 2.8; p = 0.03). No significant interaction (p = 0.29) could be observed between stent type (SES or BMS) and stage of disease (CLI and IC) regarding the primary endpoint when added to the Cox regression model. The impact of the SES on the incidence of adverse events in various subgroups of patients is presented in Figure 2.

Seventeen patients (22.6%) in the SES group and 18 patients (24%) in the BMS group (p = 0.84) died during follow-up. Thirteen patients (8.6%) died because of major cardiac events (myocardial infarction, heart failure). Seven patients (4.6%) died in consequence of gastrointestinal and pulmonary infections or cancer. In 15 patients (10%) the cause of death remained uncertain. Ten (6.2%) patients (6 in the SES group and 4 in the BMS group; p = 0.75) were lost to follow-up.

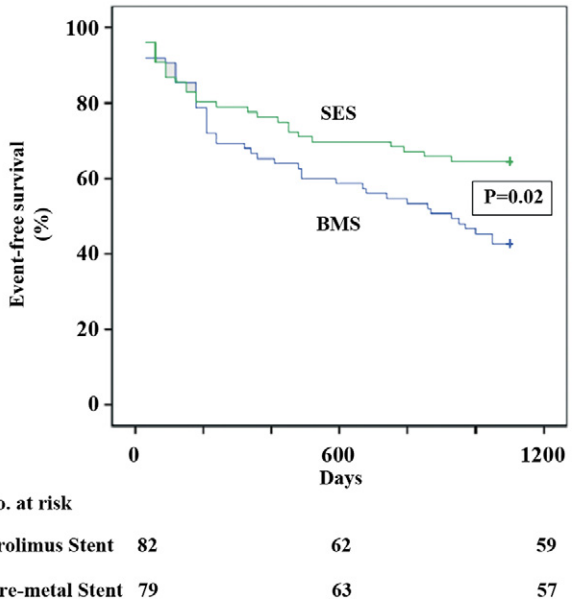

Figure 1 Event-Free Survival in the SES and BMS Groups

Survival free from target vessel revascularization, major and minor amputation, myocardial infarction, and death was compared by Kaplan-Meier analysis with the use of the Mantel-Cox log-rank test. BMS = bare-metal stent(s); SES = sirolimus-eluting stent(s).

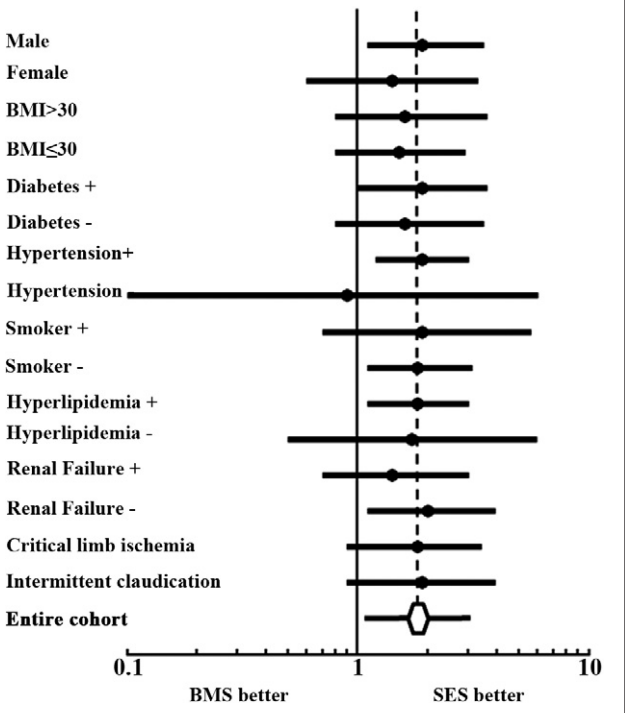

Figure 2 Impact of SES on Adverse Events in Various Subgroups of Patients

Comparison of the treatment groups concerning the incidence of adverse events including target vessel revascularization, major and minor amputation, myocardial infarction, and death by the use of the Cox regression model. BMI = body mass index; other abbreviations as in Figure 1.

Freedom from any target limb amputation was documented in 97.4% in the SES group and 87.8% in the BMS group (p = 0.03). Limb salvage rates were 98.7% and 94.6% (p = 0.17), respectively.

Clinically driven (recurrent symptoms of IC and/or worsening skin lesion) TVR was performed in 7 patients (9.2%) in the SES group and in 15 patients (20%) in the BMS group (p = 0.06). The median (interquartile range) improvement in Rutherford-Becker class was −2 (−3 to −1) and −1 (−2 to 0; p = 0.006), respectively (Table 2).

Long-term clinical follow-up in patients with CLI and IC. Concerning patients with CLI event-free survival was 57.9% in the SES group and 32.3% (p = 0.07) in the BMS group (Fig. 3). Amputation was needed in 2 patients treated with SES (1 major and 1 minor, 5.3%) and in 7 patients treated with BMS (4 major and 3 minor, 22.6%; p = 0.04) (Table 3).

In patients with IC event-free survival compared by Kaplan-Meier analysis was 71.1% in the SES group and 50% (p = 0.07) in the BMS group, TVR rates were 7.9% and 25% (p = 0.04), and changes in Rutherford-Becker

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Table 2 Rutherford-Becker Class at Baseline and at Follow-Up of the Overall Patient Population and of Each Treatment Group

	All Patients	SES	BMS	p Value
	Rutherford-Becker Class at Baseline			
	(N = 161)	(n = 82)	(n = 79)	
2	10 (6.2)	4 (4.9)	6 (7.6)	
3	76 (41.8)	36 (43.9)	40 (50.6)	
4	9 (5.6)	7 (8.5)	2 (2.5)	
5	66 (41)	35 (42.7)	31 (39.3)	
Median (IQR)	3 (3 to 5)	4 (3 to 5)	3 (3 to 5)	0.40
	Rutherford-Becker Class at Follow-Up			
	(N = 86)	(n = 44)	(n = 42)	
Median (IQR)	2 (1 to 3)	2 (1 to 3)	2 (2 to 3)	0.02
Improvement by ≥1 class	62 (72.1)	37 (84.1)	25 (59.5%)	
No change	22 (25.6)	7 (15.9)	15 (35.7%)	
Worse by ≥1 class	2 (2.3)	0 (0)	2 (4.8%)	
Median change	−1 (−3 to 0)	−2 (−3 to −1)	−1 (−2 to 0)	0.006

Values are n (%) or median (interquartile range [IQR]).

class were −2 (−2 to −1) and −1 (−1 to 0; p = 0.03) (Table 3), respectively.

Discussion

To our knowledge, this is the first prospective, randomized, multicenter study showing favorable clinical outcomes for SES compared with BMS in IPA application during long-term follow-up. While PTA and BMS placement provide promising acute procedural results in treatment of IPA the technical durability is hampered by restenosis rates of more than 50% after 1 year (2,8,9). There is evidence from nonrandomized and randomized trials that SES is superior to PTA and BMS concerning patency rates, TVR, and improvement in Rutherford-Becker class (2,5,10). However, no data from randomized studies are available concerning the clinical impact of this finding demonstrating fewer amputations and higher limb salvage rates after SES placement in comparison with PTA and BMS.

The present trial reveals that the SES has significant advantages regarding event-free survival and amputation rates over BMS. Moreover, significantly greater improvement in Rutherford-Becker class and a clearly lower TVR rate compared with BMS was noticeable in the long-term follow-up. No significant interaction was found between stent type and stage of disease (CLI or IC) concerning the primary endpoint.

Clinical results in patients with CLI. To date, there are only few data released from nonrandomized trials regarding long-term results after treatment of IPA lesions. Moreover, most of these trials exclusively address CLI patients. Therefore an accurate comparison with the present trial investigating patients with CLI and IC is restricted. Although the number of patients included in the present trial limits the validity of a subgroup analysis limb salvage and mortality rates of CLI patients treated with BMS are comparable with the results of CLI patients treated with PTA in former studies (8,11).

A nonrandomized, single-center study including 106 patients illustrates a limb salvage rate of 94 ± 2% in patients treated with SES in a 27 ± 19 months follow-up period. Target limb reintervention was performed in 15% and the mortality rate was 29% (6). In a prospective registry investigating the performance of SES versus BMS for CLI at 3

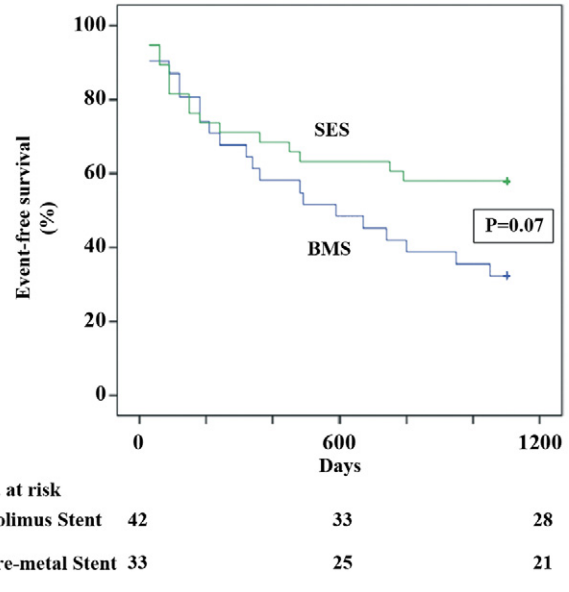

Figure 3 Event-Free Survivals in Patients With Critical Limb Ischemia in the SES and BMS Groups

Survival free from target vessel revascularization, major and minor amputation, myocardial infarction, and death was compared by Kaplan-Meier analysis with the use of the Mantel-Cox log-rank test. Abbreviations as in Figure 1.

Table 3 Major Adverse Events and Limb Salvage at Follow-Up in Patients With Critical Limb Ischemia and Intermittent Claudication

Critical Limb Ischemia	SES (n = 38)	BMS (n = 31)	p Value
Death	10 (26.3)	10 (32.3)	0.60
Major/minor amputation	1/1 (5.3)	4/3 (22.6)	0.04
TVR	4 (10.5)	4 (12.9)	0.70
Myocardial infarction	0 (0)	2 (6.4)	0.20
Limb salvage	37 (97.4)	27 (87.1)	0.10
Intermittent Claudication	**SES (n = 38)**	**BMS (n = 44)**	
Death	7 (18.4)	8 (18.2)	1.0
Major/minor amputation	0/0 (0)	0/2 (4.7)	0.19
TVR	3 (7.9)	11 (25)	0.04
Myocardial infarction	1 (2.6)	2 (4.5)	0.50
Limb salvage	38 (100)	44 (100)	1.0
Rutherford-Becker class			
Median change (IQR)	−2 (−2 to −1)	−1 (−1 to 0)	0.03

Values are n (%) or median (interquartile range [IQR]).
TVR = target vessel revascularization.

years a significantly better primary patency (HR: 4.81; 95% CI: 2.91 to 7.94; $p < 0.001$), and a better intervention-free survival (HR: 2.56; 95% CI: 1.30 to 5.00; $p = 0.006$) in patients treated with SES could be observed (7). The present study reveals comparable results in particular concerning CLI patients treated with SES regarding amputation rate, TVR rate, and mortality. Moreover, in comparison with the BMS group significantly fewer amputations occur, and a considerably higher limb salvage rate could be documented in the SES group.

Clinical results in patients with IC. Although it has become an established treatment for CLI (1,12) endovascular therapy of IPA in patients with IC is not yet accepted as a therapy option, despite published data underlining the beneficial clinical effect (13–15). In this context, results of the present study support findings that the degree of IC is positively affected by successful and long-lasting interventions of IPA lesions (4,5,16). In addition, compared with BMS, SES placement in this patient cohort was associated with a significantly reduced TVR rate and significantly greater improvement in Rutherford-Becker class.

Study limitations. Changes in quality of life with standardized questionnaires and possible cost savings by using drug-eluting stents in IPA lesions needs to be clarified in upcoming studies.

It must be highlighted that this trial only addresses focal lesions. Particularly in patients with diabetes and renal failure the vast majority of IPA lesions appear as diffuse, long lesions. However, due to the absence of long devices and restricted applicability in juxta-articular regions (rigid scaffold of metallic stents) the use of stents (SES) in long IPA lesions is limited. Moreover, the polymer-free SES used in the present trial is not available in the United States. Whether comparable results can be achieved with next-generation stent devices (with thinner struts, rapamycin analogs) and drug-eluting balloons requires further investigation.

Conclusions

In a long-term follow-up, this prospective, randomized, multicenter study demonstrates significantly higher event-free survival rates and reduced amputation rates after treatment of focal IPA lesions with SES as compared with treatment with BMS. Both patients with CLI and IC profit from treatment with SES.

Reprint requests and correspondence: Dr. Aljoscha Rastan, Abteilung Angiologie, Herz-Zentrum Bad Krozingen, Südring 15, D-79189 Bad Krozingen, Germany. E-mail: aljoscha.rastan@herzzentrum.de.

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Key Words: angioplasty ■ infrapopliteal arteries ■ limb salvage ■ peripheral artery disease ■ sirolimus-eluting stent.