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A Prospective Randomized Multicenter Comparison of Balloon Angioplasty and Infrapopliteal Stenting With the Sirolimus-Eluting Stent in Patients With Ischemic Peripheral Arterial Disease

1-Year Results From the ACHILLES Trial

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Objectives The study investigated the efficacy and safety of a balloon expandable, sirolimus-eluting stent (SES) in patients with symptomatic infrapopliteal arterial disease.

Background Results of infrapopliteal interventions using balloon angioplasty and/or bare stents are limited by a relatively high restenosis rate, which could be potentially improved by stabilizing the lesion with a SES.

Methods Two hundred patients (total lesion length 27 ± 21 mm) were randomized to infrapopliteal SES stenting or percutaneous transluminal balloon angioplasty (PTA). The primary endpoint was 1-year in-segment binary restenosis by quantitative angiography.

Results Ninety-nine and 101 patients (mean age 73.4 years; 64% diabetics) were randomized to SES and PTA, respectively (8 crossover bailout cases to SES). At 1 year, there were lower angiographic restenosis rates (22.4% vs. 41.9%, p = 0.019), greater vessel patency (75.0% vs. 57.1%, p =0.025), and similar death, repeat revascularization, index-limb amputation rates, and proportions of patients with improved Rutherford class for SES versus PTA.

Conclusions SES implantation may offer a promising therapeutic alternative to PTA for treatment of infrapopliteal peripheral arterial disease. (J Am Coll Cardiol 2012;60:2290–5) © 2012 by the American College of Cardiology Foundation

Patients with critical limb ischemia may have multiple comorbidities rendering them unsuitable for open bypass surgery. Up to one-third, mainly those with diabetes mellitus or compromised renal function, have isolated infrapopliteal disease (1,2). Today, percutaneous transluminal balloon angioplasty (PTA) is the predominant therapeutic nonsurgical approach. The similarity in diameter to coronary arteries, the better scaffolding, and superior efficacy led

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to the use of drug-eluting stents for the below-the-knee territory. Four small prospective single-center studies (3–6) showed that the CYPHER SELECT sirolimus-eluting stent (SES) (Cordis, Johnson & Johnson, Bridgewater, New Jersey) reduced the incidence of restenosis and repeat intervention in below-the-knee lesions for up to 1 year (3–7). Later studies confirmed and expanded these findings (8–11).

The ACHILLES prospective multicenter randomized trial was designed to compare the performance of SES and PTA in de novo and restenotic infrapopliteal lesions using angiographic 1-year in-segment binary restenosis rate as primary endpoint.

Abbreviations and Acronyms

PAD = peripheral arterial disease

PTA = percutaneous transluminal balloon angioplasty

SES = sirolimus-eluting stent(s)

TLR = target lesion revascularization

Methods

The ACHILLES trial was conducted in 16 centers in 9 European countries. It was conducted according to the Declaration of Helsinki and Good Clinical Practice with oversight by a Data Safety Monitoring Board, protocol approval by the Ethical Committee of each clinical institution, and written informed consent from each patient. A Clinical Events Committee adjudicated adverse events, an independent core laboratory (BioImaging, Leiden, the Netherlands) analyzed arteriographic and radiographic images, and the investigational centers analyzed the duplex ultrasound studies. Data management was conducted by a contract research organization (Clinquest Europe, Leiden, the Netherlands) independent from the sponsor (Cordis, Johnson & Johnson, Bridgewater, New Jersey).

Study design and endpoints. The ACHILLES trial compared the clinical utility of SES with PTA in patients with symptomatic peripheral arterial disease (PAD; Rutherford class 3 to 5) manifested in the infrapopliteal arterial territory.

The primary endpoint was 12-month in-segment binary restenosis (in and/or 5 mm proximal/distal to treated length) determined by quantitative angiography. Primary patency was defined as absence of clinically driven target lesion revascularization (TLR) and binary restenosis assessed by angiography or duplex ultrasonography (DUS) if angiography was unavailable. Pre-specified secondary endpoints included death, repeat revascularization, index-limb amputation, various angiographic parameters, stent fractures (plain x-ray film assessment) at 12 months, and index-limb wound status at screening, 6 weeks, and 6 and 12 months (the latter assessment will be published separately). The primary endpoint for the diabetic population, and the cumulative event rate for the composite of death, TLR, bypass, and Rutherford class ≥4 were analyzed post-hoc.

Patient selection. The trial enrolled patients with infrapopliteal PAD. Reasons for exclusion were significant stenoses (>50%) distal to the target lesion that might require revascularization or impede runoff; angiographically evident thrombus or history of thrombolysis within 72 h; untreated lesions (>75% stenosis) in the common or external iliac; common or superficial femoral and popliteal artery; infrapopliteal trifurcation lesions requiring 2- or 3-branch treatment; stent placement across or within 1 cm of the knee joint or in an artery subject to external compression; prior stenting within the target vessel(s) or aneurysm in the SFA or popliteal artery; history of thrombophlebitis, deep venous thrombosis, or impaired renal function (Cr >2.5 mg/dl); life expectancy <12 months; or known intolerance to antiplatelet medication. The Online Appendix includes a full list of inclusion/exclusion criteria and secondary endpoints.

Randomization. Eligible patients were randomized on a 1:1 basis using a numbered envelope system to either PTA or SES implantation. To minimize crossover from PTA to stenting, further balloon post dilation(s) was encouraged in case of unsatisfying immediate PTA results before bailout stent placement.

Interventional procedure and pharmacological regimen. Following standard interventional technique, patients in the SES group received up to 4 CYPHER SELECT stents (lengths 8 to 33 mm; diameters 2.5, 3.0, and 3.5 mm) within 1 vessel, or up to 2 stents per lesion in 2 different vessels, up to a total lesion length of 120 mm in a 1.1:1 stent-to-artery diameter ratio. Although performed rarely, treatment of distal lesions was allowed during the index procedure. Pre-dilation, albeit left to the operator's discretion, was mandatory for severely calcified lesions and chronic total occlusions. The selection of the angioplasty balloon was left to the operator's discretion. Fluoroscopic documentation of balloon inflation was mandatory to allow for treatment segment identification. Aspirin and a loading dose of 300 mg of clopidogrel (or 2 × 250 mg ticlopidine) were given pre-procedure. Intraprocedural heparin was used to maintain activated clotting time levels ≥250 s, and low-dose aspirin and—in the SES arm only—75 mg clopidogrel (or 2 × 250 mg ticlopidine) were maintained for 6 months.

Clinical and angiographic follow-up. In follow-up visits, planned at 6 weeks, 6 months, and 12 months post–index procedure, Rutherford classification (treadmill test–based clinical assessment), ankle-brachial index, duplex ultrasound, and index-limb wound status were assessed. Quantitative angiography and plain x-ray film imaging of the index limb were performed at baseline and at 12 months.

Statistical analysis. Analyses were performed on the intent-to-treat and as-treated population, although only intent-to-treat results are presented here. Mean value, standard deviation, median, and range were used for continuous variables, and count and percentages for categorical variables. Continuous variable normality was checked with

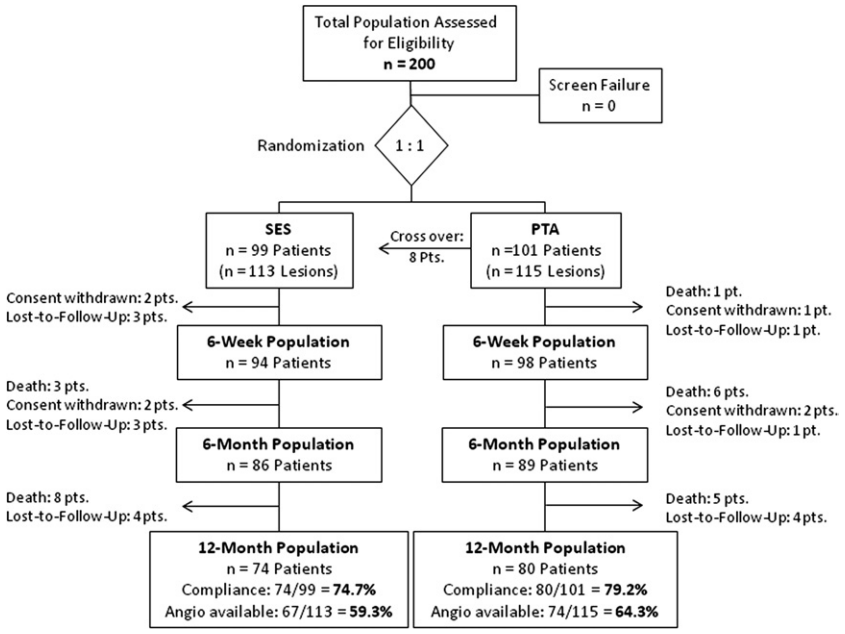

Figure 1 Patient Flow Through the Study: Intent-to-Treat Population

PTA = percutaneous transluminal balloon angioplasty; SES = sirolimus-eluting stent(s).

the Shapiro-Wilk test, if given a 2-sample *t* test, otherwise a nonparametric Wilcoxon–Mann-Whitney test was used to assess group differences. Event-specific adjusted denominators were employed for cumulative rates and included all patients experiencing an event within 360 days, and those not experiencing an event within 360 days and with at least 330 days of follow-up after index procedure. Kaplan-Meier estimates and log-rank test survival methods were used to assess death, TLR, amputation, and Rutherford class ≥4. All statistical analyses were performed with SAS (version 9.1 or higher, SAS Institute, Cary, North Carolina).

Sample size estimation. Assuming a binary restenosis rate of 45% and 20% for the PTA and SES groups (56% relative reduction), 61 evaluable lesions (or 56 patients, assuming an average lesion/patient ratio of 1.1 and between-lesion independence) per group will have approximately 80% power (2-sided 5% significance level; lesion-based analysis; 2-group continuity corrected c^2 test). The total sample size per group was increased to 94 lesions (n= 86) to account for a potential dropout of ~35%, and finally to 100 patients to accommodate potential crossovers.

Results

Patient population and lesion complexity. Two hundred patients were enrolled between March 2008 and January 2010 and randomized to receive SES (n = 99 patients, 113 lesions) or PTA (n = 101, 115 lesions) (patient flow in Fig. 1). The 12-month clinical follow-up was available for 154 of 200 patients (77%): 23 of 200 (11.5%) patients died, 7 of 200 (3.5%) withdrew consent, and 16 of 200 (8%) were lost to follow-up. Evaluable angiograms were available for 67 of 113 (59.3%) and 74 of 115 (64.3%) lesions in the SES and PTA arms, respectively. For determination of patency, DUS data were used when angiography was unavailable.

Patients in both arms were well matched according to baseline characteristics and clinical risk factors (Table 1). Mean age was 73.4 years, 64.5% were diabetic, 65.0% had a history of PAD, 72.9% had a history of hyperlipidemia, and 90.5% had arterial hypertension.

Lesions treated had a high degree of complexity (Table 2): the average reference-vessel diameter was 2.6 mm, the mean total lesion length was 26.9 mm, and 81.3% of stented patients had at least 1 total occlusion. Highly calcified lesions were present in 15% of patients.

Table 1 Patient Demographics

	All Patients (n = 200)	SES (n = 99)	PTA (n = 101)	p Value (SES vs. PTA)
Age, yrs	73.4 ± 8.8	72.4 ± 9.4	74.3 ± 8.2	0.117
Male, %	71.5	67.7	75.2	0.274
Diabetes, %	64.5	64.6	64.4	1.000
History of PAD, %	65.0	66.7	63.4	0.658
History of CAD, %	45.0	45.5	44.6	1.000
Hypertension, %	90.5	89.9	91.1	0.813
Hyperlipidemia, %	72.9	77.6	68.3	0.154
Smoker, %	32.3	38.4	26.3	0.094

Values are mean ± SD or %.

CAD = coronary artery disease; PAD = peripheral arterial disease; PTA = percutaneous transluminal balloon angioplasty; SES = sirolimus-eluting stent(s).

Table 2 Baseline Lesion Characteristics and Procedural Parameters

	SES (n = 113 Lesions)	PTA (n = 115 Lesions)	p Value
Total lesion length, mm	26.9 ± 20.9	26.8 ± 21.3	0.913
Reference vessel diameter, mm	2.6 ± 0.5	2.6 ± 0.6	0.894
CTO, %	81.3	75.4	0.334
Total length of CTO,* mm	6.7 ± 19.3	11.0 ± 22.4	0.114
Restenotic lesions, %	5.3	1.8	0.171
Calcification (moderate/severe), %	15.1	15.2	1.000
Pre-procedure stenosis, %	68.8 ± 19.3	74.0 ± 19.0	0.039
Post-procedure stenosis, %	13.3 ± 14.3	25.9 ± 15.2	<0.001
Device success,† %	95.5	58.2	<0.001
Lesion success,‡ %	100	96.9	0.103
Procedure success,§ %	94.8	92.9	0.758

Values are mean ± SD or %. *Investigator reported. †Achievement of a final residual diameter stenosis of <30%, using the assigned device only. ‡Achievement of <50% residual in-stent or in-balloon diameter stenosis using any percutaneous method. §Successful recanalization with a final diameter stenosis of <50% using any percutaneous method, without the occurrence of a serious adverse event up to the catheter sheath introducer removal or the subject leaves the cath lab, whichever earlier.

CTO = chronic total occlusion; other abbreviations as in Table 1.

The technical success rate was 95.5% in the stent arm. There was an average of 1.8 stents/patient and mean stent length per patient was 27.6 mm. Eight patients crossed over from PTA to bailout stenting.

Angiographic and clinical endpoints. The primary endpoint, 1-year in-segment binary restenosis by quantitative angiography, was reached by 22.4% and 41.9% of patients in the SES and PTA groups (p = 0.019), respectively (Fig. 2). This difference was even more significant in the diabetic subgroup of 98 patients (17.6% vs. 53.2%, p < 0.001). Patient- and lesion-based analyses, patients with single or multiple lesions, or intent-to-treat and as-treated analyses yielded similar comparative results.

Table 3 summarizes the angiographic results. Vessel patency (absence of ≥50% diameter stenosis by angiography or duplex if angiogram missing and freedom from clinically driven TLR) was higher in SES versus PTA (75% vs. 57.1%, p = 0.025). Regarding clinical endpoints (Table 4), rates of death (10.1 vs. 11.9%, p = 0.822), clinically driven TLR (10.0 vs. 16.5%, p = 0.257), and index-limb amputation (13.8 vs. 20.0%, p = 0.307) were all numerically lower in the SES arm. Only 1 minor type II stent fracture was identified by plain x-ray film imaging.

Freedom from death, TLR, bypass/amputation, and Rutherford class ≥4 (Fig. 3) was higher in SES versus PTA (p = 0.0284).

Mean baseline Rutherford class was 4.1 ± 0.9 and 4.0 ± 0.9 in the stent and PTA arms, respectively. Ischemic symptoms of PAD improved gradually in both groups, numerically more in the SES arm. The proportion of patients in SES versus PTA arms with Rutherford class improvement was 61.54% (56 of 91) versus 61.54% (56 of 91) at 6 weeks (p = 1.00), 71.43% (55 of 77) versus 62.03% (49 of 79) at 6 months (p = 0.2141), and 76.06% (54 of 71) versus 67.11% (51 of 76) at 1 year (p = 0.2315), respectively.

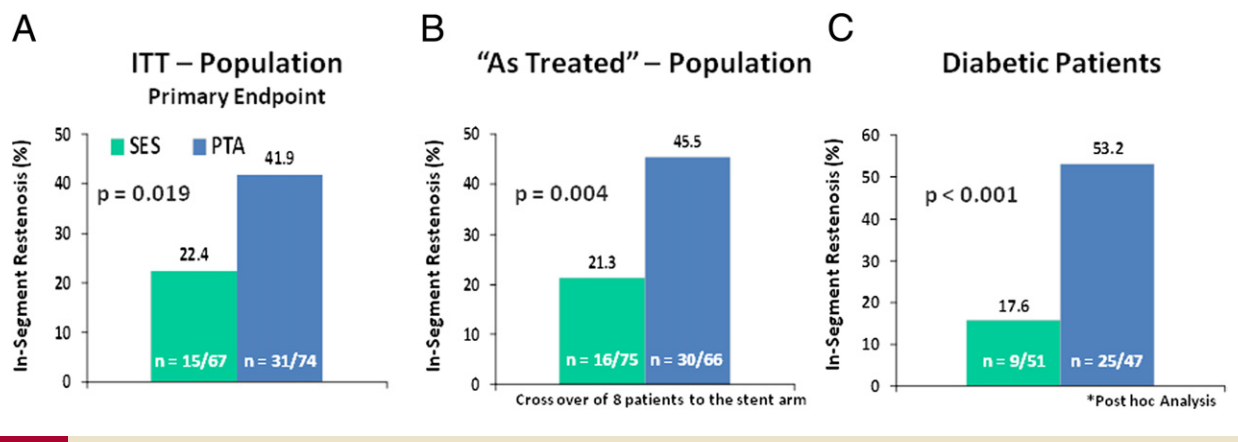

Figure 2 Angiographic Results at 12-Month Follow-Up

Primary endpoints for the intention-to-treat (ITT) population **(A)**, the as-treated population **(B)**, and the diabetic subpopulation **(C)**. Abbreviations as in Figure 1.

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Table 3 Angiographic Endpoints at 12-Month Follow-Up

	SES (n = 99)	PTA (n = 101)	p Value
In-segment measurements*			
Binary restenosis (primary endpoint)	15/67 (22.4)	31/74 (41.9)	0.019
Percent diameter stenosis, %	35.2 ± 21.7	48.3 ± 25.4	0.001
Minimal lumen diameter, mm	1.7 ± 0.7	1.4 ± 0.8	0.044
Late lumen loss, mm	0.5 ± 1.1	0.4 ± 1.0	0.979
In-lesion measurements†			
Percent diameter stenosis, %	34.3 ± 24.5	47.1 ± 25.7	0.002
Minimal lumen diameter, mm	1.7 ± 0.7	1.4 ± 0.8	0.016
Late lumen loss, mm	0.7 ± 0.8	0.6 ± 0.7	0.833

Values are n (%) or mean ± SD. *Within the stent or balloon area + adjacent 5 mm in both directions. †Within the stent or balloon area.
Abbreviations as in Table 1.

Discussion

Interventional treatment of infrapopliteal arteries has become an alternative to surgical revascularization. The ACHILLES trial sought to investigate SES for this indication and to compare its safety and performance with that of balloon angioplasty. The study is positive for the angiographic primary endpoint with a lower 1-year restenosis rate for SES over PTA (22.4% vs. 41.9%, p = 0.019) for patients with total lesion lengths below 120 mm, a difference that is even larger for diabetics (SES: 17.6% vs. PTA: 53.2%, p < 0.001) who constitute the majority of patients with peripheral infrapopliteal disease, overall and in this study (65%). The ACHILLES trial also confirms the technical feasibility of stenting in the infrapopliteal territory with higher device-, lesion-, and procedure-based success rates for the stent arm. Although the study protocol discouraged crossover for bailout, 8 patients in the PTA arm needed stents, which is probably still under-reflecting the incidence of bailout stent placement in routine practice.

Although the study was not powered for such comparisons and advanced disease stages with multiple comorbidities confound the analysis of clinical parameters, the safety outcomes generally favored the SES arm numerically including most importantly clinically driven TLR.

Previous related studies showed better 1-year primary patency and symptomatic improvement for a non-polymer SES versus bare-metal stent in a 161-patient randomized study (10), and higher 12-month index-vessel patency and numerically lower restenosis for the everolimus-eluting stent versus bare-metal stent in a 140-patient randomized study of critical limb ischemia patients (11). Other studies showed 3-year limb salvage and survival rates exceeding those of historical controls for drug-eluting stents (83% SES, 17% paclitaxel-eluting stent; 106-patient study) (12), and a 1-year 77.4% in-stent binary restenosis rate and 30% primary patency rate despite an initial 100% technical success rate for paclitaxel-eluting stent (29-patient series) (13).

In summary, based on better angiographic and similar safety outcomes to PTA the ACHILLES trial supports the use of the SES in below-the-knee arteries as a therapeutic option for patients with infrapopliteal disease and critical limb ischemia. Randomized studies with other available drug-eluting stents and longer follow-up observations are required to further substantiate outcome differences, durability, and cost-effectiveness of this strategy.

Study limitations. The study encompassed mainly focal lesions with an average total length of 27 ± 21 mm (allowed maximum was 120 mm). Therefore, its findings may not equally apply to longer lesions. DUS studies were closely monitored but not analyzed by core laboratory and not correlated with arteriography if available. While they were not part of the primary endpoint analysis, limitations of their accuracy could have impact on vessel patency. There was a high rate of patients lost to follow-up mainly to death and withdrawal of consent. Although not unexpected, not exceeding the assumptions for sample size estimation, and comparable between arms, this may have introduced bias. The population included in the study poses significant challenges in terms of follow-up and outcome interpretation and relevance; nevertheless, the results of this study are consistent and compare favorably with those of previous ones using similar or different therapeutic approaches; they

Table 4 Clinical Endpoints at 12-Month Follow-Up

	SES (n = 99)	PTA (n = 101)	p Value
Death*	10/99 (10.1)	12/101 (11.9)	0.822
TLR (clinically driven)	8/80 (10.0)	14/85 (16.5)	0.257
TVR – non-TLR, count	5/78 (6.4)	2/84 (2.4)	0.263
Vessel patency†	54/72 (75.0)	44/77 (57.1)	0.025
Index limb amputation	11/80 (13.8)	17/85 (20.0)	0.307
Stent fractures	1/113 (0.9)	0/0 (0)	—

Values are n (%). Patient-based analyses, except for the stent fracture rate (lesion-based). *Up to 360 days. †Absence of hemodynamically relevant restenosis and of clinically driven TLR. Restenosis is assessed angiographically, and by Duplex ultrasound for patients without available angiographic follow-up.
TLR = target lesion revascularization; TVR = target vessel revascularization.

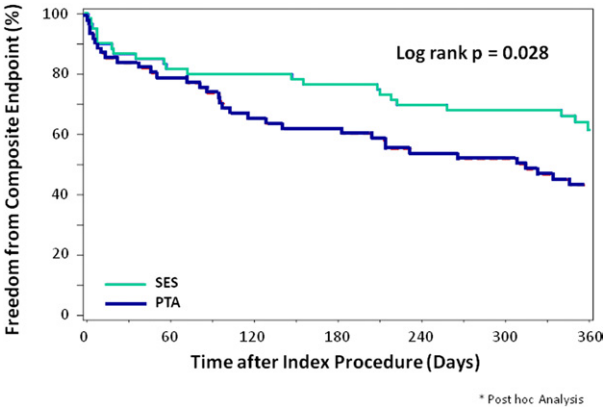

Figure 3 Freedom From Death, Target Lesion Revascularization, Bypass, Amputation, and Rutherford Class ≥4

The SES group had significantly greater freedom from the composite endpoint relative to the balloon angioplasty group. Abbreviations as in Figure 1.

are clinically relevant because the patient population studied is usually not amenable to surgical intervention, there is a clinical need to improve on outcomes from medical therapy alone, and the less invasive nature of endovascular therapy makes it theoretically a more attractive alternative for patients with critical limb ischemia and multiple comorbidities associated with higher mortality. Only 1 of the available SES was tested in this study; nevertheless, study results may apply similarly to other SES, which remains to be investigated.

Conclusions

The SES yields 1-year clinical and angiographic outcomes that are superior in efficacy and similar in safety for infrapopliteal arterial disease compared with PTA. Its use may constitute an attractive alternative for patients with claudication and critical limb ischemia. Treatment of the latter condition, particularly achievement of limb salvage, remains challenging regardless of approach given the multiple factors that affect disease pathogenesis and progression; endovascular intervention only addresses some of them and should be considered as part of a multispecialty intervention.

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Key Words: angioplasty ■ below the knee artery ■ critical limb disease ■ drug-eluting stent ■ peripheral arterial disease.

APPENDIX

For a list of investigators in the ACHILLES trial and an expanded Methods section, please see the online version of this article.