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ORIGINAL RESEARCH

PERIPHERAL

Randomized Trial Comparing a Stent-Avoiding With a Stent-Preferred Strategy in Complex Femoropopliteal Lesions

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ABSTRACT

BACKGROUND Limited comparative data exist on different interventional strategies for endovascular revascularization of complex femoropopliteal interventions.

OBJECTIVES In this study, the authors aimed to compare a stent-avoiding (SA) vs a stent-preferred (SP) strategy, promoting optimal lesion preparation and the use of drug-eluting technologies in both arms.

METHODS Within a prospective, multicenter, pilot study, 120 patients with symptomatic complex femoropopliteal lesions (Rutherford classification 2-4, mean lesion length 187.7 ± 78.3 mm, 79.2% total occlusions) were randomly assigned in a 1:1 fashion to endovascular treatment with either paclitaxel-coated balloons or polymer-coated, paclitaxel-eluting stents. Lesion preparation including the use of devices for plaque modification and/or removal was at the operators' discretion in both treatment arms.

RESULTS In the SA group, lesion preparation was more frequently performed (71.7% SA [43/60] vs 51.7% [31/60] SP; $P = 0.038$) with a high provisional stenting rate (48.3% [29/60]). At the 12-month follow-up, primary patency was 78.2% (43/55) in the SA group and 78.6% (44/56) in the SP group ($P = 1.0$; relative risk: 0.995; 95% CI: 0.818-1.210). Freedom from major adverse events was determined in 93.1% (54/58) in the SA group and in 94.9% (56/59) in the SP group ($P = 0.717$; relative risk: 0.981; 95% CI: 0.895-1.075), with all adverse events attributable to clinically driven target lesion revascularization.

CONCLUSIONS Both endovascular strategies promoting lesion preparation before the use of drug-eluting devices suggest promising efficacy and safety results in complex femoropopliteal procedures with a high proportion of total occlusions through 12 months. Ongoing follow-up will show whether different results emerge over time. (Best Endovascular Strategy for Complex Lesions of the Superficial Femoral Artery [BEST-SFA]; NCT03776799)
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Peripheral arterial disease (PAD) of the lower extremities represents a major health problem issue affecting an estimated 40 million adults in Europe and North America and over 100 million people worldwide.[1] Advances in endovascular therapy have led to the widespread use of interventional techniques to restore blood flow in symptomatic patients requiring revascularization.[2] New treatment modalities have been developed to improve patency rates because standard balloon angioplasty for femoropopliteal disease has been limited by high acute technical failure and restenosis rates, especially in complex lesions.[3,4] In addition to modern stent technologies, the evolution of drug-coated devices including paclitaxel-coated balloons (PCBs) and paclitaxel-eluting stents (PESs) has been a major advance, inhibiting neointimal hyperplasia by exposing the vessel to an antiproliferative agent.[5-11] In addition, in line with the concept of vessel preparation, several devices for lesion modification and debulking were introduced, including specialty balloons and various atherectomy systems. Despite frequent use in routine clinical practice, the reported benefits consisted primarily of improved acute outcomes, such as reduced flow-limiting dissections and bailout stenting, but no clear signal of improved patency rates over time was observed.[12,13]

Importantly, most recent randomized controlled trials (RCTs) on drug-eluting technologies have examined patency rates for a specific single device in mostly short- and intermediate-length femoropopliteal lesions,[7,9,10,14] whereas in clinical routine, long, complex lesions with advanced calcification and a high proportion of chronic total occlusions represent the main challenge. Endovascular strategies with extensive lesion preparation are often postulated for the treatment of complex femoropopliteal lesions, but so far only limited research has addressed these concepts within clinical trials with core lab-adjudicated prospective patency assessment.[15]

The BEST-SFA (Best Endovascular Strategy for Complex Lesions of the Superficial Femoral Artery) study aimed to evaluate patency rates in complex, femoropopliteal lesions that were so far underrepresented in clinical trials comparing the efficacy and safety of a stent-avoiding (SA) vs a stent-preferred (SP) strategy, promoting optimal lesion preparation and the use of drug-eluting devices in both arms.

METHODS

STUDY DESIGN AND PATIENT POPULATION. The BEST-SFA study was designed as an investigator-initiated, prospective, multicenter, randomized, controlled pilot trial aiming to include patients with moderate to severe intermittent claudication or ischemic rest pain (Rutherford category 2-4) undergoing endovascular intervention in 4 participating vascular centers located in Germany (Supplemental Appendix). The key inclusion criteria comprised de novo or restenotic femoropopliteal lesions with ≥70% stenosis documented angiographically and no prior stent in the target lesion. Lesions were eligible if classified as Trans-Atlantic Inter-Society Consensus (TASC) II type B to D not involving the infrageniculate popliteal artery, a minimum length >10 cm for stenotic and >5 cm for occluded lesions without restricting maximum length, and patency of at least 1 infrapopliteal artery to the ankle (<50% diameter stenosis) in continuity with the native femoropopliteal artery. Both treatment options (SA vs SP strategy) should be feasible at the discretion of the operator. The key exclusion criteria comprised angiographic evidence of severe calcification making an SA approach not feasible based on operator judgment or intraluminal evidence of fresh thrombus. Detailed inclusion and exclusion criteria are provided in Supplemental Table 1.

Ethics approval was obtained from the University of Leipzig Ethics Committee (approval no. 330/18-ek) and subsequently at each participating site's ethics board. Patients provided written informed consent before enrollment.

PROCEDURE. Preprocedural data collection included assessment of the patient's medical history as related to PAD, documentation of Rutherford category, and completion of the Walking Impairment Questionnaire (WIQ).

After successful wire crossing and positive assessment of angiographic eligibility criteria, patients were randomly assigned in a 1:1 fashion (permuted block randomization, block size of 6) to an SA vs an SP strategy. The study protocol did not restrict the use of adjunctive devices for vessel preparation but rather encouraged their use for plaque modification and removal in both treatment arms at the operators' discretion. Adjunct vessel preparation in both groups was performed using scoring balloons (AngioSculpt [Philips] and UltraScore [Becton Dickinson]), a peripheral cutting balloon (Boston Scientific), and high-pressure balloons (Conquest [Becton Dickinson] and Athletis [Boston Scientific]). In addition, various atherectomy devices were used (directional

ABBREVIATIONS AND ACRONYMS

CD-TLR = clinically driven target lesion revascularization

IVUS = intravascular ultrasound

KM = Kaplan-Meier

PAD = peripheral arterial disease

PCB = paclitaxel-coated balloon

PES = paclitaxel-eluting stent(s)

RCT = randomized controlled trial

SA = stent avoiding

SP = stent preferred

TASC = Trans-Atlantic Inter-Society Consensus

WIQ = Walking Impairment Questionnaire

atherectomy with HawkOne [Medtronic], rotational atherectomy with Jetstream [Boston Scientific], and orbital atherectomy with the Diamondback 360 Peripheral Orbital Atherectomy System [Abbott]) as well as mechanical thrombectomy (Rotarex [Straub Medical]).

In the SA therapy arm, clinically proven, conformité européenne-certified PCBs from different manufacturers could be used. Considering all study centers, PCBs from 5 different manufacturers were used (IN.PACT Admiral and IN.PACT Pacific [Medtronic], Luminor [iVascular], Ranger [Boston Scientific], Stellarex [Philips], and Passeo-18 Lux [Biotronik]). In lesions longer than the longest available PCB, additional PCBs could be deployed with an overlap of at least 1 cm. Postdilatation was at the discretion of the investigator but mandated by the protocol in the case of flow-limiting dissections or residual stenosis ≥30%. Focal postdilatation with short percutaneous transluminal angioplasty balloons of minimal length sufficient to cover the remaining stenotic segment was recommended exclusively within the previously dilated area. If bailout stenting was deemed necessary by the operator because of flow-limiting dissection or relevant recoil (persistent 50% or higher residual stenosis [visual estimate] or >10 mm Hg translesional gradient) despite prolonged postdilation, spot stenting with self-expandable bare metal nitinol stents was performed. In the SP arm, Eluvia (Boston Scientific) PESs were implanted for full lesion coverage. Postdilation was at the investigator's discretion to achieve a residual stenosis <30%.

In both treatment arms, the Supera self-expanding stent (Abbott) could be used for focal areas of severe calcification in which the superior radial strength of the interwoven stent was preferred by the operator. Calcification was assessed by the core laboratory according to the peripheral arterial calcification scoring system (grade 0: none; grade 1: unilateral, <5 cm; grade 2: unilateral, ≥5 cm; grade 3: bilateral, <5 cm; and grade 4: bilateral, ≥5 cm).[16]

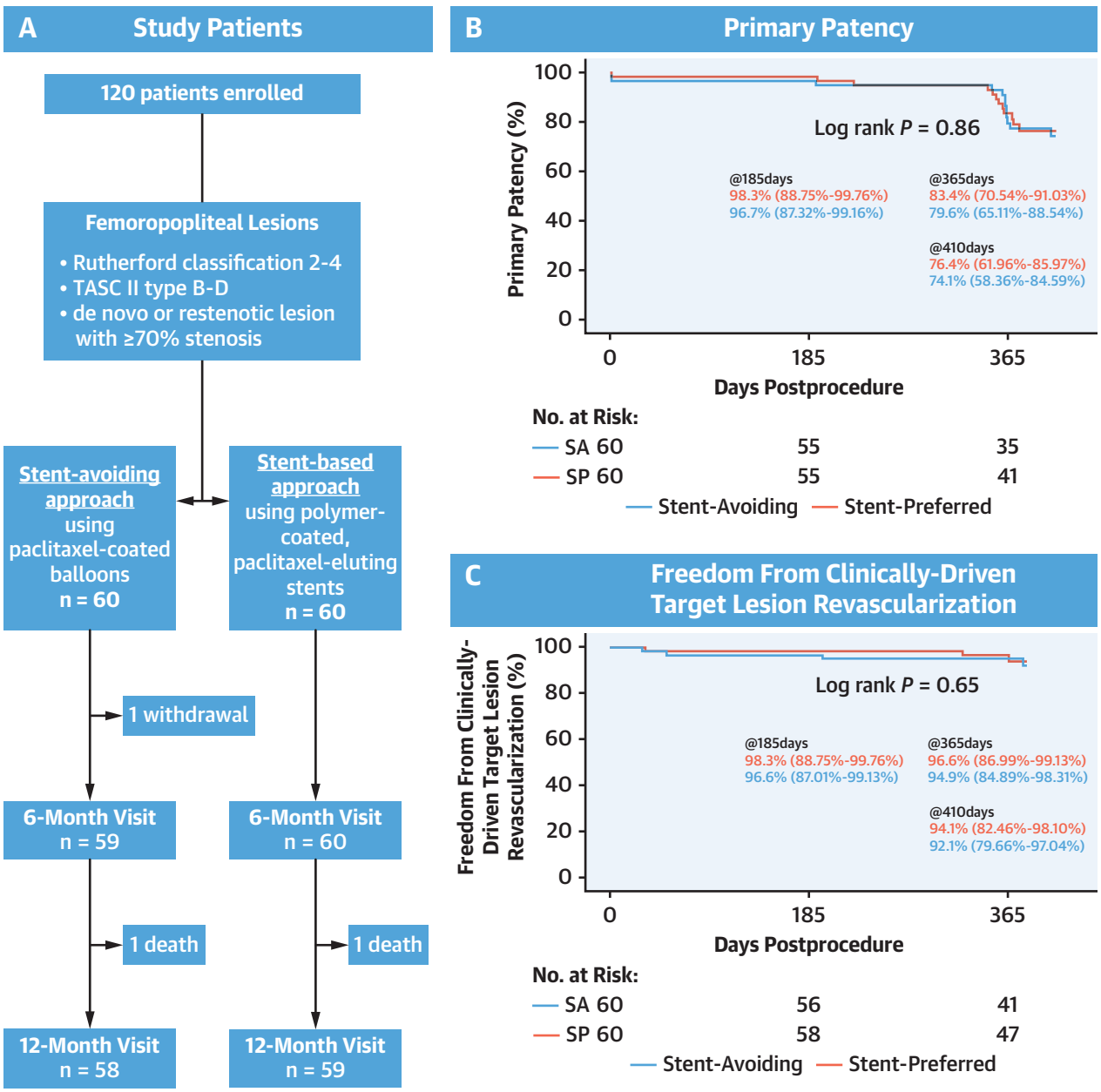
Investigators could prescribe concomitant anticoagulant and antiplatelet medications consistent with current local clinical practice. To minimize potential bias, the same antiplatelet therapy was recommended in both study arms. Before the study procedure, subjects should receive an antiplatelet medication (aspirin or clopidogrel) for at least 3 days preprocedure or a loading dose on the day of intervention. Dual antiplatelet therapy should be continued for at least 4 weeks consisting of aspirin 100 mg and clopidogrel 75 mg after the procedure; thereafter, single antiplatelet therapy was recommended throughout the study period and lifelong.

PATIENT FOLLOW-UP. Clinical assessment, hemodynamic measurements, and duplex ultrasound of the treated vessel segment were performed before discharge. Patients were phoned 1 month after the procedure for the evaluation of clinical status, medication compliance, and adverse events. In-house follow-up visits were scheduled at 6, 12, and 24 months with the assessment of medical conditions, Rutherford category, WIQ, medication, and patency evaluated by duplex ultrasound. To detect the hypoechogenic halo ultrasound phenomenon reported in previous PES studies,[17-20] a systematic B-mode duplex ultrasound examination was performed in the transverse plane during the 6-month and 1-year follow-up. The ultrasound core lab identified the hypoechogenic halo as an echolucent layer with regular, well-defined borders seen adjacent to/around the stented arterial segment in a transverse view without detectable flow. In patients who missed in-house study visits, contact attempts were made at least twice by phone and once by mail as well as contacting the subject's primary physician. In case patients could be reached but declined to return for follow-up visits, information on safety events was obtained by phone. Patients were considered lost to follow-up if 2 consecutive study visits were missed and all contact efforts were unsuccessful. Additional follow-up for safety events (death, amputation, and target lesion revascularization) will be performed via an annual telephone call through 5 years.

OUTCOMES. The primary efficacy endpoint was primary patency at 12 months defined as the absence of clinically driven target lesion revascularization (CD-TLR) or binary restenosis determined as a peak systolic velocity ratio >2.4 assessed by duplex ultrasound core laboratory analysis. CD-TLR was defined as a reintervention performed for ≥50% diameter stenosis (confirmed by angiography) within ±5 mm proximal and/or distal to the target lesion after documentation of recurrent clinical symptoms of PAD (increase of 1 Rutherford class or more) and/or a drop in the ankle-brachial index (≥20% or >0.15 compared to the maximum early postprocedural level).

The primary safety endpoint was a composite of freedom from device- and procedure-related death through 30 days, freedom from major target limb amputation, and CD-TLR within 12 months post-index procedure. Protocol prespecified secondary endpoints included all-cause mortality, CD-TLR, all target lesion revascularization, target vessel

CENTRAL ILLUSTRATION **BEST-SFA: Efficacy and Safety of SA and SP Strategy in Symptomatic Complex Femoropopliteal Lesions (N = 120)**



- At 12 months, primary patency (the primary efficacy endpoint) did not significantly differ for the stent-avoiding and stent-preferred strategies
- At 12 months, freedom from major adverse events (the primary safety endpoint) did not significantly differ for the stent-avoiding and -preferred strategies, and all adverse events were attributable to clinically-driven target lesion revascularization

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(A) Patient flow diagram. (B) Primary patency analysis. Kaplan-Meier (KM) estimates of primary patency for the stent-avoiding (SA) group (blue) and the stent-preferred (SP) group (red). (C) Clinically driven target lesion revascularization analysis. KM estimates of freedom from clinically driven target lesions revascularization for the SA group (blue) and the SP group (red). TASC = Trans-Atlantic Inter-Society Consensus.

TABLE 1 Baseline Patient Characteristics

	Stent-Avoiding Group (n = 60)	Stent-Preferred Group (n = 60)	*P* Value
Demographic			
Age, y	66.2 ± 9.4	66.5 ± 8.00	0.228
Female	15 (25.0)	11 (18.3)	0.253
BMI, kg/m^2	28.0 ± 4.73	27.2 ± 5.80	0.538
BMI ≥30 kg/m^2	35 (21)	26.7 (16)	0.429
Clinical presentation			
Rutherford class			0.910
2	21.7 (13)	25.0 (15)	
3	75.0 (45)	71.7 (43)	
4	3.3 (2)	3.3 (2)	
Target limb ABI[a]	0.58 ± 0.24	0.60 ± 0.24	0.537
Medical history			
Hypertension	96.7 (58)	93.3 (56)	0.679
Hyperlipidemia	86.7 (52)	85.0 (51)	1.000
Diabetes mellitus	45.0 (27)	36.7 (22)	0.458
Insulin	40.7 (11)	63.6 (14)	0.262
Smoking			0.409
Current	50.0 (30)	60.0 (36)	
Former	35.0 (21)	31.7 (19)	
Never	15.0 (9)	8.3 (5)	
Coronary artery disease	30.0 (18)	43.3 (26)	0.185
Cerebrovascular disease	10.0 (6)	15.0 (9)	0.582
Respiratory disease	31.7 (19)	13.3 (8)	0.028
Renal insufficiency[b]	25.0 (15)	18.3 (11)	0.507
Medication at baseline			
Any antiplatelet drug	80.0 (48)	90.0 (54)	0.200
Aspirin	73.3 (44)	85.0 (51)	0.177
Clopidogrel	20.0 (12)	18.3 (11)	1.000
DAPT	13.3 (8)	15.0 (9)	1.000
Other antiplatelet drug	0	1.7 (1)	1.000
Direct factor Xa inhibitors	16.7 (10)	8.3 (5)	0.269
Other anticoagulants	1.7 (1)	5.0 (3)	0.619
Any lipid-lowering agent	85.0 (51)	81.7 (49)	0.907
Statins	85.0 (51)	80.0 (48)	0.632
Other lipid-lowering agent	7 (11.7)	4 (6.7)	0.529
ACE inhibitor or ARB	83.3 (50)	76.7 (46)	0.494
Beta blocker	51.7 (31)	65.0 (39)	0.195
Other antihypertensive drug	61.7 (37)	55.0 (33)	0.579
Medication at discharge			
Any antiplatelet drug	100.0 (60)	100.0 (60)	
Aspirin	86.7 (52)	98.3 (59)	0.032
Clopidogrel	100 (60)	91.7 (55)	0.057
DAPT	86.7 (52)	95.0 (57)	0.204
Other antiplatelet drug	0	5.0 (3)	0.244
Direct factor Xa inhibitors	13.3 (8)	3.3 (2)	0.095
Other anticoagulants	1.7 (1)	1.7 (1)	1.000
Any lipid-lowering agent	98.3 (59)	96.7 (58)	1.000
Statins	98.3 (59)	95.0 (57)	0.619
Other lipid-lowering agent	11.7 (7)	6.7 (4)	0.529
ACE inhibitor or ARB	90.0 (54)	78.3 (47)	0.132
Beta blocker	50.0 (30)	70.0 (42)	0.040
Other antihypertensive drug	61.7 (37)	56.7 (34)	0.711

Values are mean ± SD or n (%). [a]Excluding 5 patients with noncompressible arteries and 4 patients with missing values. [b]Defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2.

ABI = ankle-brachial index; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; DAPT = dual antiplatelet therapy.

revascularization, target limb major amputation, clinical outcomes, and changes in WIQ scores.

The trial included independent oversight by a Data and Safety Monitoring Board and Clinical Events Committee (Supplemental Appendix) that reviewed and adjudicated all major adverse events. Angiographic and duplex ultrasound images were independently analyzed by a core laboratory (CoreLab Black Forrest).

STATISTICAL ANALYSIS. Because BEST SFA was designed as a pilot study for the preliminary evaluation of 2 different treatment strategies for complex femoropopliteal lesions, no formal sample size calculation or hypothesis testing was performed. Outcomes were analyzed using the intention-to-treat principle. For descriptive statistics, data were presented as the number (percentage) for categoric data and mean ± SD for continuous data. Differences between groups at baseline were performed using the unpaired Student *t*-test for continuous variables or the Fisher exact test for categoric variables as appropriate. Results from the WIQ assessment at 6 and 12 months were compared by the paired Student's *t*-test within the groups vs baseline and by the unpaired Student's *t*-test between the groups at each time point.

Primary patency and CD-TLR were assessed using Kaplan-Meier (KM) time-to-event analyses through 410 days (12-month follow-up plus 45-day visit window). Patients without an event at 410 days of follow-up or later were censored at 410 days. Differences in survival curves between groups were tested with the log-rank statistics. All analyses were performed using SPSS version 29.0 (IBM Corp), and a *P* value <0.05 was considered statistically significant (NCT03776799).

Role of the funding source. BEST SFA is an investigator-initiated study, and the study sponsor is the University of Leipzig with industry-independent funding through the medical faculty of the University of Leipzig and the Helmholtz Institute for Metabolism, Obesity and Vascular Research. The funding source was not involved in collecting, monitoring, or analyzing study data. Investigators (T.W. and S.S.) prepared all data presentation and manuscript drafts, which were then critically reviewed and edited by the other authors. The funding source had no access to data or manuscript review.

RESULTS

PATIENT AND PROCEDURAL CHARACTERISTICS. Between January 2019 and August 2022, 120 patients

were enrolled at 4 sites in Germany (Central Illustration). The treatment groups were well-balanced with respect to baseline demographics and lesion characteristics (Tables 1 and 2). Only with regard to the TASC classification of the target lesions was there a statistically significant difference (P = 0.047); in the SA group, more TASC II B lesions (SA group: 46.7% [28/60] vs SP group: 25.0% [15/60]) but less TASC II C and D lesions (SA group: 53.3% [32/60] vs SP group: 75.0% [45/60]) were treated. More than one-third of the patients were diabetics, and the mean lesion length was 187.7 ± 78.3 mm with around two-thirds of the lesions longer than 150 mm. More than two-thirds of the interventions were performed in lesions with moderately severe or severe calcification according to the peripheral arterial calcification scoring system classification, highlighting the complexity of the included lesions. At discharge, disease-modifying medical therapy was prescribed in a very large proportion of patients (Table 1) and remained high at the 6- and 12-month follow-ups (Supplemental Table 2).

Procedural data are provided in Table 2. Lesion preparation was more frequently performed in the SA group (SA group: 71.7% [43/60] vs SP group: 51.7% [31/60]; P = 0.038), and the most commonly used devices were directional atherectomy and scoring balloons. In the SA group, bailout stenting was required in almost half of the patients (48.3% [29/60]) despite lesion preparation.

Relevant intraprocedural complications included 4 ipsilateral embolic events (1 in the SA group and 3 in the SP group) necessitating manual embolectomy and 2 target vessel perforations in the SP group requiring implantation of self-expandable stent grafts (Viabahn, Gore). With respect to drug-eluting technologies (PCBs and PESs), no device malfunction was reported in either group.

Residual stenosis ≥30% was observed in 45.0% (27/60) in the SA group and 23.3% (14/60) in the SP group. Procedural success, defined as residual stenosis <50% and the absence of procedural complications (death, major target limb amputation, thrombosis of the target lesion, or CD-TLR) before discharge, was achieved in the SA group in 91.7% (55/60) of the cases and in the SP group in 98.3% (59/60).

TABLE 2 Core Lab–Adjudicated Lesion Characteristics and Procedural Data

	Stent-Avoiding Group (n = 60)	Stent-Preferred Group (n = 60)	*P* Value
Lesions			
Arterial segment involved[a]			
Proximal SFA	48.3 (29)	65.0 (39)	0.097
Mid SFA	85.0 (51)	81.7 (49)	0.807
Distal SFA	90.0 (54)	95.0 (57)	0.491
Proximal popliteal artery	8.3 (5)	11.7 (7)	0.762
Lesion type			1.000
De novo	88.3 (53)	90.0 (54)	
Restenotic	11.7 (7)	10.0 (6)	
TASC II			0.047
B	46.7 (28)	25.0 (15)	
C	33.3 (20)	46.7 (28)	
D	20.0 (12)	28.3 (17)	
Lesion length, mm	183.70 ± 78.55	191.70 ± 78.50	0.578
Median	173.65	200.0	
Minimum	46.09	40.56	
Maximum	369.21	400.00	
Lesion length >150 mm	60.0 (36)	70.0 (42)	0.339
Treated length	213.99 ± 78.86	213.87 ± 76.23	0.993
Median	201.96	223.0	
Minimum	80.0	66.10	
Maximum	399.86	397.86	
Total occlusions	80.0 (48)	78.3 (47)	1.000
Length of total occlusions, mm	134.92 ± 91.09	147.78 ± 81.76	0.471
Reference vessel diameter, mm	5.02 ± 0.62	5.27 ± 0.67	0.034
Minimal diameter stenosis preprocedure	0.17 ± 0.40	0.21 ± 0.45	0.668
Grade of stenosis, %	96.68 ± 7.87	96.25 ± 8.50	0.777
Calcification[b]			0.733
Grade 0	5.1 (3)	5.0 (3)	
Grade 1	23.7 (14)	23.3 (14)	
Grade 2	0	3.3 (2)	
Grade 3	33.9 (20)	33.3 (20)	
Grade 4	37.3 (22)	35.0 (21)	
Patent runoff vessels[c]			0.914
0	5.5 (3)	5.2 (3)	
1	27.3 (15)	32.8 (19)	
2	29.1 (16)	29.3 (17)	
3	38.2 (21)	32.8 (19)	
Procedure			
Procedure time	97.42 ± 47.80	97.2 ± 54.83	0.982
Fluoroscopy time	19:25 ± 12:10	21:56 ± 12:54	0.275
Retrograde access	1.7 (1)	3.3 (2)	1.000
Distal superficial femoral artery	–	3.3 (2)	
Proximal anterior tibial artery	1.7 (1)	–	
Reentry device	20.9 (9)	19.4 (6)	1.000
Predilatation performed	85.0 (51)	91.7 (55)	0.394

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EFFECTIVENESS, SAFETY, AND CLINICAL BENEFIT THROUGH 12 MONTHS. The primary efficacy endpoint primary patency within 12 months occurred in 78.2% (n = 43/55) in the SA group and in 78.6% (n = 44/56) in the SP group (P = 1.000; relative risk: 0.995; 95% CI: 0.818-1.210) through 12 months. KM curves for primary patency were almost overlapping through 12 months (Central Illustration). Analyzing patency according to lesion length, more restenotic events were observed in the long lesion subgroups >150 mm, but no relevant differences between the groups were identified (P = 0.17) (Supplemental Figure 1). The composite primary safety endpoint freedom from device- and procedure-related death and target limb

TABLE 2 Continued

	Stent-Avoiding Group (n = 60)	Stent-Preferred Group (n = 60)	*P* Value
Predilatation balloon diameter, mm	4.53 ± 0.81	5.20 ± 7.56	<.001
Additional vessel preparation performed[d]	71.7 (43)	51.7 (31)	0.038
Scoring balloon	37.2 (16)	35.5 (11)	1.000
Cutting balloon	4.7 (2)	0	0.506
High-pressure balloon	2.3 (1)	12.9 (4)	0.154
Atherectomy	46.5 (20)	41.9 (13)	0.814
Directional atherectomy	80.0 (16)	69.2 (9)	0.780
Rotational atherectomy	15.0 (3)	23.1 (2)	0.780
Orbital atherectomy	5.0 (1)	7.7 (1)	0.780
Mechanical thrombectomy	27.9 (12)	16.1 (5)	0.274
Distal EPD	25.6 (11)	6.5 (2)	0.060
Number of study devices	2.28 ± 0.90	2.43 ± 0.81	0.340
Maximum study device diameter, mm	5.5 ± 0.62	6.47 ± 0.50	<.001
Cumulative length of study devices, mm	243.5 ± 102.54	247.17 ± 92.08	0.837
Bailout stenting	48.3 (29)	[e]	
Type of stent			
BMS	89.7 (26)	0	
PES	3.4 (1)	98.3 (59)	
Supera	6.9 (2)	1.6 (1)	
Vessel perforation	1.7 (1)	3.3 (2)	1.000
Perforation requiring covered stent implantation	0	100 (2)	
Postdilatation performed	63.3 (38)	96.7 (58)	<.001
Diameter stenosis postprocedure, %	30.13 ± 10.22	23.52 ± 9.53	<.001
Dissections post-study device			<.001
None	11.7 (7)	78.3 (47)	
B/C	26.7 (16)	13.3 (8)	
D/E	61.7 (37)	8.3 (5)	
Dissections in the final angiogram			<.001
None	31.7 (19)	80.0 (48)	
B/C	23.3 (14)	13.3 (8)	
D/E	45.0 (27)	6.7 (4)	
Residual stenosis ≥30%	45.0 (27)	23.3 (14)	0.020
Residual stenosis ≥50%	6.7 (4)	0	0.119
Procedural success[f]	91.7 (55)	98.3 (59)	0.207

Values are % (n) or mean ± SD. [a]More than 1 segment per patient was allowed. [b]Calcification assessment according to the peripheral artery calcification scoring system. [c]Number of lesions, which could be adjudicated by the core lab for this variable. [d]Multiple answers possible. [e]2 patients received a covered stent because of perforation. [f]Procedural success defined as residual stenosis <50% and the absence of procedural complications (death, major target limb amputation, thrombosis of the target lesion, or clinically driven target lesion revascularization) before discharge.

BMS = bare-metal stent(s); EPD = embolic protection device; PES = paclitaxel-eluting stent(s); SFA = superficial femoral artery; TASC = Trans-Atlantic Inter-Society Consensus.

major amputation as well as CD-TLR within 12 months occurred in 54 of 58 (93.1%) patients in the SA group and in 56 of 59 (94.9%) patients in the SP group ($P = 0.717$; RR: 0.981; 95% CI: 0.895-1.075) through 12 months. No deaths were determined to be device- or procedure-related, and no major target limb amputation was reported during the first year after the index procedure. Thus, the primary safety endpoint was driven exclusively by CD-TLR. Freedom from CD-TLR per KM estimates through 12 months are presented in the **Central Illustration**. All-cause mortality was low, with only 1 late death in each group. One patient in the SA group with metastatic lung cancer died because of liver failure 299 days after the index intervention. One patient in the SP group died because of septic shock in the context of a wound infection with underlying acne inversa 265 days after the index intervention. All safety outcomes at 12 months are summarized in **Table 3**.

Most patients presented with no or mild clinical symptoms (Rutherford category 0 or 1) at 12 months (**Figure 1**). WIQ scores improved significantly at 6 and 12 months compared to baseline. The distance scores improved significantly more in the SP group ($P = 0.045$), and there was also a trend toward improved walking impairment in the SP group at the 12-month follow-up ($P = 0.066$) (Supplemental Table 3).

A hypoechogenic halo phenomenon was detected by duplex ultrasound in 43.5% (20/46) of the cases in the SP group, whereas in the SA group a halo-like signal was seen only in the context of bailout stenting in 22.2% (4/18) of the cases. No aneurysmatic changes and no association with clinical sequelae including primary patency failure or CD-TLR were detected.

DISCUSSION

The BEST-SFA study was designed to investigate the outcomes that can be achieved by promoting lesion preparation in addition to the use of drug-eluting technologies for the treatment of long, complex, femoropopliteal lesions in a real-world cohort. Approximately two-thirds of the treated lesions were longer than 15 cm, and 80% were chronic total occlusions with moderately severe and severe calcification in the majority of lesions, which is substantially more complex than most other studies focusing on drug-eluting technologies in long lesions.[21-23] Because the included patient population was considered at high risk of restenosis because of the advanced complexity of the lesions, paclitaxel-coated devices were preferred based on their extensive clinical efficacy data. In this pilot study, we compared 2 treatment strategies that are repeatedly chosen in clinical routine, in an RCT with core lab adjudication of angiograms and duplex ultrasound imaging, rather than focusing on the effectiveness of single devices.

Overall, lesion preparation was more common in the SA group because in over two-thirds of patients some form of additional devices was used, most commonly atherectomy in almost every second patient and scoring balloons in more than one-third. In the SP group, operators chose a lesion preparation device in every second case, mostly atherectomy.

TABLE 3 Safety Outcomes at 12 Months

	SA Group (n = 60)	SP Group (n = 60)	*P* Value	Relative Risk Estimate (95% CI)	
Primary patency	78.2 (43/55)	78.6 (44/56)	1.000	0.995	(0.818-1.210)
Primary safety composite[a]	93.1 (54/58)	94.9 (56/59)	0.717	0.981	(0.895-1.075)
All-cause mortality	1.7 (1/58)	1.7 (1/60)	1.000	1.034	(0.066-16.153)
Device- or procedure related death	0 (0/58)	0 (0/60)			
Major amputation	0 (0/58)	0 (0/60)			
Clinically driven TLR	6.9 (4/58)	5.1 (3/59)	0.717	1.356	(0.317-5.796)
All TLR[b]	8.6 (5/58)	5.1 (3/59)	0.490	1.695	(0.425-6.771)
Binary restenosis[c]	18.4 (9/49)	17.0 (9/53)	1.000	1.082	(0.468-2.501)

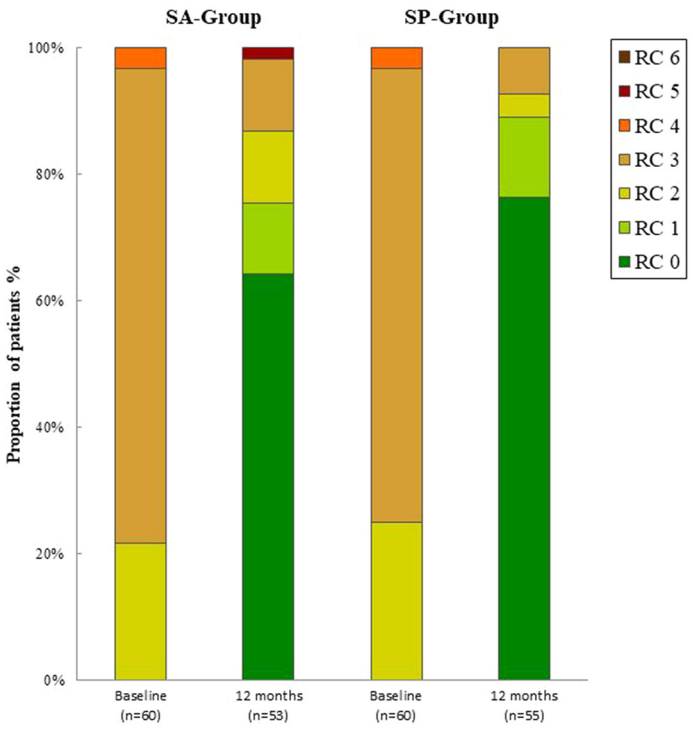
Values are % (n/N) unless otherwise indicated. [a]Freedom from device- and procedure-related death and target limb major amputation and clinically driven TLR within 12 months. [b]Includes clinically driven TLR and duplex-driven/incidental TLR. [c]Defined as a peak systolic velocity ratio >2.4 assessed by duplex ultrasound core laboratory analysis.

SA = stent avoiding; SP = stent preferred; TLR = target lesion revascularization.

Despite the availability of multiple device options and frequent use in clinical routine, there is currently little scientific evidence for lesion preparation and the use of debulking devices in the endovascular treatment of long, complex, femoropopliteal lesions. Previous studies have demonstrated that directional atherectomy is safe for the treatment of PAD with low reintervention rates, acceptable complication rates, and a lower need for bailout stenting (<10%) in less complex lesions than in our study population.[15,24,25] A prior systematic Cochrane review also highlighted that the use of atherectomy for PAD compared to other established treatments is associated with a decreased rate of dissections and need of bailout stents, but no significant differences were found for patency, mortality, and cardiovascular event rates.[12]

Despite extensive lesion preparation, especially in the SA group, bailout stenting was performed in almost every second case. This high rate of provisional stenting is probably caused by the complexity of the lesions included, which clearly show that in these cases, even with the use of adjunctive devices, there is relevant recoil and dissections requiring additional mechanical stent support. Core lab-adjudicated relevant residual stenosis ≥30%, which has been related to subsequent loss of patency even after PCB use in prior research,[26] was seen in almost half of the procedures (45%) in the SA group. Interestingly, almost 1 in 4 patients in the SP group also had a residual stenosis of at least 30% or more, which also may be related to an increased risk of restenosis and stent thrombosis. These observations emphasize the need for adequate lesion preparation even if stenting is intended in order to achieve an optimal acute outcome with minimal residual stenosis. From this point of view, lesion preparation was under- or inadequately performed in a relevant proportion of the procedures in our study. After 1 year of follow-up, no difference in primary patency was observed, with promising rates approaching 80% in both treatment groups. Interestingly, low reintervention rates with excellent freedom from CD-TLR of almost 95% at 1 year were reported, which were at least comparable or even better than other long lesion trials but with a different study design.[15,21-23] For PESs, the IMPERIAL (ELUVIA Drug-Eluting Stent Versus Zilver PTX Stent) long lesion cohort reported 91.0% primary patency and 93.3% reinterventions but included shorter lesions with a low proportion of chronic total occlusions.[23] In the single-arm REALITY (DiRectional AthErectomy + Drug CoAted BaLloon to Treat Long, CalcifIed FemoropopliTeal ArterY Lesions) study, all lesions were treated with directional atherectomy before PCB angioplasty. A 12-month primary patency rate of 76.7% and freedom from CD-TLR of 92.6% were seen, which are comparable to our results.[15] Other PCB registries including long lesions reported primary patency of approximately 85% and freedom from CD-TLR of around 90% at 1 year.[21,22] Similar to our results showing no difference between a primary stenting vs an angioplasty strategy with drug-eluting devices at 1 year in complex femoropopliteal lesions, previous RCTs found comparable outcomes for PESs and PCBs without adjunct lesion preparation at 1 year in terms of patency and reinterventions.[27,28] However, the 3-year results of the REAL-PTX (Randomized Evaluation of the Zilver PTX Stent vs. Paclitaxel-Eluting Balloons for Treatment of Symptomatic Peripheral Artery Disease of the Femoropopliteal Artery) trial suggested a potential benefit of PES implantation,[28] and it will be interesting to see if a difference emerges over time in the BEST-SFA trial.

FIGURE 1 Distribution of Rutherford Clinical Categories at Baseline and 12 Months



The number at risk for each time point is given below each bar. No formal testing for changes across time in Rutherford scores was performed. SA = stent avoiding; SP = stent preferred.

With regard to the currently ongoing safety discussion concerning the clinical relevance of hypoechoic halos detected with duplex ultrasound after endovascular stent implantation, with the highest rates seen after a polymer PES, we also found this phenomenon frequently in our study, especially in the PES group, but no clinical sequelae were observed. In a recently published analysis focusing on prevalence, risk factors, and potential safety implications after stent implantation in the IMPERIAL and EMINENT (Trial Comparing ELUVIA Versus Bare Metal Stent in Treatment of Superficial Femoral and/or Proximal Popliteal Artery) trials, similar results were seen.[29] Halo prevalence ranged from 20% to 35% of patients in these studies and was present at all follow-up time points. Halos were noted around bare and paclitaxel-coated stents, as was the case in our study. No statistically significant correlation was also found between the presence of a halo phenomenon with respect to CD-TLR or primary patency after 1 year.[29]

Because of the heterogeneity of the interventions, the limited number of patients included, and the lack of the collection of detailed cost estimates, we did not conduct a formal cost efficacy analysis in our analysis. However, with ongoing challenges in health care policy and financing, clinicians increasingly need to consider both the cost and clinical effectiveness of therapeutic devices, and no clear benefit has yet been demonstrated for additional lesion preparation, which also highlights the need for further research in this area. Although our 1-year results are promising, it is unclear whether any potential benefit of lesion preparation justifies the additional cost of these devices. Ongoing follow-up in BEST-SFA through 5 years will give more insights, but larger studies are clearly needed to address this question.

STUDY LIMITATIONS. Because of the design of BEST-SFA as a pilot study, no formal sample size calculation was performed; thus, all results have to be seen as hypothesis generating only. For lesion preparation, various devices could be used by the operators, but intravascular lithotripsy was not reimbursed during the conduct of the trial in Germany and thus was not used in this trial. Similarly, the use of intravascular ultrasound (IVUS) is still very limited in Germany because of the lack of reimbursement, so no IVUS was used in any procedure of the BEST-SFA trial. We cannot exclude that the acute outcome (ie, the proportion of patients with a residual stenosis <30%) and restenosis rates could have been improved by the additional use of IVUS. The rate and type of lesion preparation differed significantly between the groups in favor of the SA arm, which may have influenced the observed results. A more extensive lesion preparation rate also in the SP arm could be associated with better patency results in this treatment arm.

CONCLUSIONS

We demonstrated that both treatment strategies had a promising primary patency and excellent freedom from CD-TLR at 1 year in complex, long lesions with a high grade of calcification. Ongoing follow-up for up to 5 years will show whether differing results will emerge over time.

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PERSPECTIVES

WHAT IS KNOWN? Many studies have demonstrated the superiority of paclitaxel-coated devices over uncoated technologies including plain old balloon angioplasty and bare-metal stents. However, there are limited data on the benefit of additional vessel preparation for lesion modification and debulking before treatment with paclitaxel-coated devices.

WHAT IS NEW? The BEST-SFA study evaluated the efficacy and safety of 2 different strategies for the endovascular treatment of complex femoropopliteal lesions comparing a stent-avoiding vs a stent-preferred option, promoting optimal lesion preparation and the use of drug-eluting devices in both arms. The pilot study showed promising primary patency rates and excellent freedom from CD-TLR for both treatment strategies.

WHAT IS NEXT? Further studies should continue to investigate the benefits of lesion preparation and the use of atherectomy systems to reduce bailout stenting and to improve primary patency and freedom from CD-TLR in the endovascular treatment of complex lesions of the superficial femoral artery to minimize the existing lack of evidence.

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KEY WORDS paclitaxel-eluting devices, patency, peripheral artery disease, restenosis, vessel preparation

APPENDIX For a list of the BEST SFA investigational sites and principal investigators and the members of the COMPARE Data Safety Monitoring Board and Clinical Events Committee as well as supplemental tables and a figure, please see the online version of this paper.