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Primary results of the SAVAL randomized trial of a paclitaxel-eluting nitinol stent versus percutaneous transluminal angioplasty in infrapopliteal arteries

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Abstract

Background: Effective and durable options for infrapopliteal artery revascularization for patients with chronic limb-threatening ischemia (CLTI) are limited. **Methods:** The SAVAL trial is a prospective, multicenter, randomized trial of patients with CLTI and infrapopliteal artery lesions with total lesion length ⩽ 140 mm, stenosis ⩾ 70%, and Rutherford category 4–5 assigned 2:1 to treatment with the SAVAL self-expandable paclitaxel drug-eluting stent (DES) or percutaneous transluminal angioplasty (PTA) with an uncoated balloon. The primary effectiveness endpoint was primary vessel patency (i.e., core lab-adjudicated duplex ultrasound-based flow at 12 months in the absence of clinically driven target lesion revascularization or surgical bypass of the target lesion). The primary safety endpoint was the 12-month major adverse event (MAE)-free rate; MAEs were defined as a composite of above-ankle index limb amputation, major reintervention, and 30-day mortality. The endpoints were prespecified for superiority (effectiveness) and noninferiority (safety) at a one-sided significance level of 2.5%. **Results:** A total of 201 patients were enrolled and randomly assigned to treatment ($N = 130$ DES, $N = 71$ PTA). Target lesion length was 68.1 ± 35.2 mm for the DES group and 68.7 ± 49.2 mm for the PTA group, and 31.0% and 27.6% of patients, respectively, had occlusions. The 12-month primary patency rates were 68.0% for the DES group and 76.0% for the PTA group ($P_{superiority} = 0.8552$). The MAE-free rates were 91.6% and 95.3%, respectively ($P_{noninferiority} = 0.0433$). **Conclusion:** The SAVAL trial did not show benefit related to effectiveness and safety with the nitinol DES compared with PTA in infrapopliteal artery lesions up to 140 mm in length. Continued innovation to provide optimal treatments for CLTI is needed. **(ClinicalTrials.gov Identifier: NCT03551496)**

Keywords

chronic limb-threatening ischemia (CLTI), endovascular therapy, peripheral artery disease (PAD), stent

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Background

Chronic limb-threatening ischemia (CLTI), often associated with disease of the infrapopliteal arteries, is a highly morbid and lethal condition.[1,2] Patients with CLTI are at significant risk for amputation, and have a poor survival and quality of life comparable to that of patients with other serious chronic conditions such as cancer.[1,3] Epidemiological and trial data have shown 10-year mortality of 75–80% for patients with CLTI.[2,4]

Despite the severity and significant ramifications of the condition, effective and durable endovascular options for infrapopliteal artery revascularization remain elusive. Various drug-coated balloons (DCBs) and off-label use of balloon expandable drug-eluting stents (DESs) designed and marketed for coronary arteries have been investigated (online Supplemental Table S1). DCB treatment has demonstrated mixed results in clinical trials, with at least three failed randomized controlled trials of paclitaxel-coated DCBs.[5–7] Balloon expandable DESs, with paclitaxel or sirolimus analogue antiproliferative agents, have shown efficacy in terms of restenosis or patency and clinical improvement, to some extent, in at least four randomized controlled trials.[8–12] However, due to limited length and flexibility, these coronary DESs are not optimal for longer crural lesions that are often encountered in patients with patients.

The SAVAL trial was conducted to investigate the effectiveness and safety of the SAVAL DES, a dedicated longer and flexible nitinol DES with paclitaxel for below-the-knee artery use. The study objective was to compare patency and safety rates between infrapopliteal artery lesions treated with the SAVAL DES or uncoated percutaneous transluminal angioplasty (PTA).

Methods

Study design and participants

SAVAL is a prospective, global, randomized, controlled, parallel-group trial of the SAVAL paclitaxel-eluting below-the-knee vascular stent versus PTA to treat infrapopliteal lesions in subjects with CLTI (ClinicalTrials.gov identifier NCT03551496).

The study was conducted in compliance with local regulations such as US FDA 21 CFR 812, ISO 14155, and principles originating in the Declaration of Helsinki. The protocol was approved by the applicable institutional review board or ethics committee for each site prior to commencing study activities. Patients were required to provide written informed consent prior to completion of trial-related procedures. The manuscript was prepared in accordance with CONSORT reporting guidelines.[13]

Patients were recruited and treated at multiple centers including community, academic, and Veterans Affairs hospitals, and referral centers in Belgium, France, Japan, The Netherlands, and the United States. Study sites are listed in online Supplemental Table S2. Patients eligible for enrollment included adults with chronic, symptomatic lower-limb ischemia (Rutherford categories 4 or 5 in the target limb). Wounds were required to be confined to the toes or forefoot. Patients were further required to satisfy intraprocedural inclusion criteria. Specifically, target lesions located in the tibioperoneal trunk, anterior tibial, posterior tibial or peroneal arteries with a single target lesion per vessel, in up to two vessels in a single limb, were allowed. A target lesion originating in one vessel and extending into another vessel was considered one target vessel. Based on periprocedural angiographic assessment, target lesions were to have $\geqslant$ 70% stenosis, a reference vessel diameter of 2.5–3.25 mm, and to be at least 4 cm above the ankle joint. The total length of each target lesion (or lesion segment series) to be treated could be up to 70 mm or up to 140 mm after approval for stent overlap from the data monitoring committee. Lesions were to be fully covered with one or two stents for patients assigned to the stent group. Target lesions could be stenotic, restenotic or occlusive. Successful inflow lesion treatment and target lesion guidewire crossing were required prior to randomization and enrollment.

Key exclusion criteria were: life expectancy $<$ 1 year, renal failure (GFR $\leqslant$ 30 mL/min per 1.73 m^2 within 30 days prior to the procedure date), extremely calcified lesions, treatment required in more than two target vessels, or alternative therapy (e.g., atherectomy, cutting balloon, re-entry devices, laser, radiation therapy) use in the target vessels or lesions during the index procedure. Complete inclusion and exclusion criteria are listed in the online supplementary materials.

Randomization

Randomized treatment allocation occurred after successful guidewire crossing. Randomization was stratified by investigational center and lesion length. A computer-generated randomization schedule specific to each investigational center was used to assign subjects to treatments in a 2:1 ratio of SAVAL DES to PTA. Random permuted blocks of size 3 and size 6 within each stratum were employed.

Blinding of patients, investigators, and core labs was not practical given the stent and PTA allocation; however, wound assessors were blinded to treatment group. In addition, when determining whether target limb reintervention was warranted, treating physicians were requested to indicate whether there was clinical need (e.g., clinical symptoms, worsened Rutherford category or ankle-brachial index) prior to viewing imaging assessments. Study support personnel are listed in online Supplemental Table S3.

Procedures

The study device was the SAVAL Drug Eluting Vascular Stent (Boston Scientific, Marlborough, MA, USA). The SAVAL DES is a nitinol self-expanding stent designed for below-the-knee arterial anatomy with a small diameter and long length. One investigational stent size of 3.5 mm $\times$ 80 mm was available for use in the study. The stent has a polymer coating (i.e., poly[vinylidene fluoride-co-hexafluoropropylene]) with paclitaxel formulated for below-the-knee arterial lesions at a dose density of 0.24 $\mu g/mm^2$ stent surface area.

The control procedure was PTA performed with commercially available balloon catheters, chosen at the investigator's discretion and performed per the device instructions and standard of care. DCBs were not permitted. If flow-limiting dissection or recoil occurred following the index angioplasty, repeat balloon inflations (2–5 min, up to three inflations) with standard PTA balloons were required before bailout stent placement was permitted.

Additional interventions in the target limb were permitted for above-the-knee inflow treatment during the index procedure. Inflow lesions were treated according to the investigator's standard procedures using commercially available devices. Drug-eluting device use was permitted for inflow lesions. Interventions must have been deemed successful (e.g., absence of distal embolization, optimal inflow restoration) prior to randomization for the study treatment. Study treatment was assigned after successful guidewire crossing of all target lesions.

Outflow lesion treatment (i.e., lesions located in the target vessel segment distal to the target lesion) was not permitted. Procedural angiograms were provided to the angiographic core laboratory (Harvard Medical Faculty Physicians at Beth Israel Deaconess Medical Center, Boston, MA, United States) for assessment.

Anticoagulant and antiplatelet medications

Anticoagulant and antiplatelet medications were prescribed prior to and during the procedure according to the investigator's standard procedures. After the procedure, dual antiplatelet therapy was required through the 6-month visit and strongly recommended through the 12-month visit for patients who received the DES.

Follow up

Follow-up visits were scheduled for 1, 3, 6, and 12 months postprocedure, and will continue at 24 and 36 months. Telephone-based follow up is scheduled at 18 and 30 months postprocedure. Survival status will be assessed at 4 and 5 years via telephone, medical chart review, or publicly available records. Ultrasonography and radiography images obtained during the follow-up period were provided to the imaging core laboratory (VasCore, Boston, MA, United States) for stent patency and integrity assessment, respectively.

Health-related quality of life was assessed with the VascuQoL[14] and EQ-5D-5L[15] at each visit through 12 months. The 25-item VascuQoL is a disease-specific quality of life measure for patients with chronic lower-limb ischemia, which addresses five domains: pain, symptoms, activities, social, and emotional. A minimally important difference of 0.36 in the VascuQol sumscore has been reported to indicate a clinically meaningful change.[16] EQ-5D-5L index scores were based on the United States model.

Wound care and assessments

Wound care was recommended to follow the Wound Healing Society 2014 update on guidelines for arterial ulcers.[17] Target limb wound images were collected at each follow-up visit and provided to independent, blinded, experienced wound image reviewers (online Supplemental Table S3). Reviewers assessed characteristics including size, healing status, presence of infection, and whether new wounds developed. For the wound assessment summary, observations from the Japan-based assessor were used for patients in Japan and observations from the USA-based assessor were used for patients based in the USA or Europe.

Endpoints and definitions

The technical success definition was the same for both study arms; that is, delivery and deployment of the assigned study therapy to the target lesion with residual angiographic stenosis no greater than 30% by visual assessment. Procedural success was a subject-based measure, defined as technical success with no major adverse events (MAEs) within 24 hours of the index procedure.

The primary effectiveness endpoint, 12-month primary vessel patency, was defined as a binary endpoint based on core lab-adjudicated duplex ultrasound (DUS) flow in the absence of clinically driven target lesion revascularization (CD-TLR) or surgical bypass of the target lesion. The endpoint was prespecified for superiority. Diagnostic DUS imaging from the 12-month visit was used for flow assessment, or, if DUS was not performed or was nondiagnostic, computed tomography angiography or digital subtraction angiography were substituted if available. If none of these modalities was available for assessment from the 12-month visit window, patent DUS from a later visit was used, providing no TLR or bypass was performed in the intervening period. A TLR was considered 'clinically driven' if the clinical events committee determined that it occurred for diameter stenosis $\geqslant$ 50% by quantitative angiography within 5 mm proximal or distal to the original treatment segment and the patient had recurrent symptoms, defined as an increase in Rutherford Classification by at least one category, or associated with an ankle–brachial index decrease of at least 0.15 or 20% compared with the baseline measure in the treated segment. The toe–brachial index was allowed in cases of incompressible vessels.

The primary safety endpoint was designed for noninferiority and defined as the MAE-free rate at 12 months postprocedure. MAEs were defined as a composite of: above-ankle index limb amputation as assessed by the clinical events committee, major reintervention, or perioperative (30-day) mortality. Major reinterventions were defined as new bypass graft, jump or interposition graft, or thrombectomy or thrombolysis.

The primary endpoints were originally intended to be assessed at 6 months postprocedure; timing was changed to 12 months due to regulatory guidance during the COVID-19 pandemic.[18]

The CD-TLR rate, changes in wound characteristics, Rutherford Classification, and health-related quality of life based on the VascuQoL and EQ-5D-5L questionnaires were considered additional endpoints.

Statistical analysis

A minimum sample size of 150 evaluable patients was targeted to preserve adequate statistical power for both the primary effectiveness and safety endpoints. The sample size was based on the primary effectiveness hypothesis, which tested whether 12-month primary patency among patients treated with the DESs was superior to that of patients treated with PTA. A 40% patency rate for PTA based on the results of a meta-analysis[10,19–22] and a 25% treatment effect for DESs was assumed. With a 25% annual attrition rate, and given a one-sided significance level (alpha) of 2.5% with at least 80% power and 2:1 allocation ratio, 201 patients were recruited.

The subject-level intention-to-treat population comprised the analysis set for the primary endpoint analysis. If a patient had more than one lesion treated but at least one failed, it was considered a patency failure in this subject-based analysis. Patients in the PTA group with stent bailout were considered treatment failures.

Success criteria for both the effectiveness and safety endpoints were based on one-sided 97.5% CI, corresponding with one-sided p-values (i.e., significance required $p < 0.025$). The superiority criterion for the effectiveness endpoint was that the lower bound of the one-sided 97.5% CI of the between-group difference in 12-month primary patency rates was greater than zero. The noninferiority criterion for the safety endpoint was that the lower bound of the one-sided 97.5% CI of the between-group difference in 12-month MAE-free rates was greater than the noninferiority margin of –10%. The p-values and CIs for the differences are from the Wald z-test. The primary effectiveness and safety hypotheses were tested simultaneously without adjustment.

The p-values for comparisons of baseline characteristics, procedure characteristics, and additional endpoints were two-sided from two-sample t-tests for continuous variables, or Fisher's exact or chi-squared tests for categorical variables. Statistical comparisons for additional endpoints were considered exploratory. The 12-month survival rate was estimated using the Kaplan–Meier method considering all-cause death reported via the study and adjudicated by the clinical events committee, as well as additional vital status information obtained from other sources such as public databases. Statistical analyses were performed with SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patients

From August 2018 to March 2021, 201 patients (130 in the DES group and 71 in the PTA group) with 218 target lesions (142 lesions in the DES group and 76 in the PTA group) were enrolled at 39 study centers. The CONSORT diagram for 12-month follow up is shown in Figure 1.

Demographic and medical history were similar between the treatment groups, with high proportions of comorbid diabetes, hyperlipidemia, and hypertension (Table 1). Target lesion characteristics were similar (Table 2), with the exception of a significantly greater proportion of patients in the DES group with core-lab assessed moderate or severe calcification (57.0% [81/142] vs 40.8% [31/76]; $p = 0.0221$).

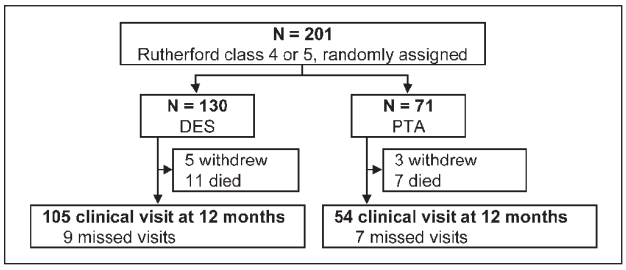

Figure 1. SAVAL trial CONSORT diagram.
DES, drug-eluting stent; PTA, percutaneous transluminal angioplasty.

Procedures

Target limb inflow lesions were treated during the index procedure for 42.6% of patients in the DES group and 34.3% of patients in the PTA group ($p = 0.2503$), and all of these interventions were successful prior to SAVAL trial target lesion treatment. The majority of inflow treatment procedures in both study arms included the superficial femoral artery (DES 74.5% [41/55] and PTA 83.3% [20/24]), with popliteal artery treatment in about one-third (DES 34.5% [19/55] and PTA 33.3% [8/24]).

Intravascular ultrasound (IVUS) was used during treatment in 36.6% (52/142) and 28.9% (22/76) of lesions in the DES and PTA groups, respectively. Predilation was performed for 95.1% (135/142) of lesions in the DES group; a mean of 1.7 ± 1.1 predilation balloon inflations with a maximum inflation duration of 76 ± 52 seconds was reported. The mean maximum balloon diameter was 2.8 ± 0.3 mm and the mean maximum balloon length was 69.2 ± 36.6 mm. In the PTA arm, a mean of 1.5 ± 0.6 balloon inflations (range 1–4) were performed with a maximum inflation duration of 158.3 ± 68.8 seconds (per balloon); the mean PTA balloon diameter was 3.0 ± 0.4 mm and length was 83.7 ± 50.6 mm.

Technical and procedural success were both 100% in the DES group. In the PTA group, technical success was 98.7% (75/76 lesions) and procedural success was 98.6% (69/70 patients). One patient in the PTA arm received a bailout stent. Technical ($p = 0.3486$) and procedural ($p = 0.3518$) success rates did not differ significantly between the treatment groups.

Antiplatelet medications

Dual antiplatelet therapy was reported for a significantly greater percentage of patients in the DES group: 85.7% (108/126) versus 72.3% (47/65) at 1 month ($p = 0.0248$); 82.6% (100/121) versus 64.5% (40/62) at 6 months ($p = 0.0062$); and 72.4% (76/105) versus 51.9% (28/54) at 12 months ($p = 0.0100$). At 12 months, 92.4% (97/105) versus 75.9% (41/54) reported clopidogrel, ticlopidine, prasugrel, ticagrelor, or cilostazol use ($p = 0.0037$), and acetylsalicylic

Table 1. Baseline patient characteristics.

	DES ($N = 130$)	PTA ($N = 71$)	p-value
Age, years	73.27 ± 9.61	72.58 ± 10.14	0.6328
Men	73.1% (95/130)	77.5% (55/71)	0.4944
Women	26.9% (35/130)	22.5% (16/71)	0.4944
Race/ethnicity[a]			
White	53.1% (69/130)	49.3% (35/71)	0.6081
Asian	25.4% (33/130)	25.4% (18/71)	0.9960
Japanese	100.0% (33/33)	94.4% (17/18)	0.3529
Korean	0.0% (0/33)	5.6% (1/18)	0.3529
Black	11.5% (15/130)	14.1% (10/71)	0.6011
Hispanic or Latino	5.4% (7/130)	5.6% (4/71)	> 0.99
American Indian or Alaska Native	0.8% (1/130)	1.4% (1/71)	> 0.99
Other	1.5% (2/130)	1.4% (1/71)	> 0.99
Not disclosed	2.3% (3/130)	2.8% (2/71)	> 0.99
Smoking history			
Current	20.8% (27/130)	25.4% (18/71)	0.4563
Previous	50.8% (66/130)	49.3% (35/71)	0.8417
Medically treated diabetes	63.8% (83/130)	62.0% (44/71)	0.7923
History of hyperlipidemia[b]	77.7% (101/130)	73.2% (52/71)	0.4791
History of hypertension[b]	88.5% (115/130)	83.1% (59/71)	0.2865
Renal insufficiency	17.7% (23/130)	15.5% (11/71)	0.6910
Rutherford category			
4	50.8% (66/130)	58.6% (41/70)	0.2914
5	49.2% (64/130)	41.4% (29/70)	
Prior lower-limb amputation	21.5% (28/130)	22.5% (16/71)	0.8702
Target limb	35.7% (10/28)	25.0% (4/16)	0.4629
Nontarget limb	57.1% (16/28)	56.3% (9/16)	0.9541
Both	7.1% (2/28)	18.8% (3/16)	0.3364
Minor	82.1% (23/28)	81.3% (13/16)	> 0.99
Major	21.4% (6/28)	25.0% (4/16)	> 0.99
Ankle–brachial index	0.9 ± 0.3 ($n = 115$)	0.9 ± 0.3 ($n = 65$)	0.9180
Toe–brachial index	0.4 ± 0.2 ($n = 89$)	0.5 ± 0.2 ($n = 49$)	0.0787

Data are presented as mean ± SD unless otherwise noted.
[a]Patients with more than one race were considered only once in the subcategory where comparatively fewer subjects are available.
[b]Requiring medication.
DES, drug-eluting stent; PTA, percutaneous transluminal angioplasty.

acid (with or without other medication) was reported for 79.0% (83/105) versus 74.1% (40/54) of patients in the DES and PTA groups, respectively ($p = 0.4779$).

Effectiveness and safety

A total of 153 patients were evaluable for the primary effectiveness endpoint. The 12-month primary patency rates are shown in Table 3. The difference between DES and PTA groups was –8.0% (95% CI –22.9%, 6.8%). Superiority testing yielded a p-value of 0.8552, thus the primary effectiveness superiority endpoint was not met.

A total of 183 patients had follow up to 335 days (i.e., the lower limit of the 12-month visit window) or MAE occurrence and were included in the primary safety evaluation. The difference in MAE-free rates between DES and PTA groups was –3.7% (95% CI –10.9%, 3.5%). The noninferiority p-value for the primary safety endpoint at a one-sided significance level of 2.5% was 0.0433, thus the primary safety endpoint was not met (Table 3). The MAE rate was driven by the major reintervention component (Table 4). The major reinterventions were represented as thrombectomy or thrombolytic therapy and these occurred at a mean of 107 ± 59 days (approximately 3.6 months) postrandomization. Five of the seven patients undergoing thrombectomy or thrombolysis were prescribed dual antiplatelet therapy at the time of the event. No new bypass graft or jump/interposition graft procedures were performed. Above-ankle amputation and perioperative mortality rates were low and did not differ significantly between groups (Table 4).

The 12-month CD-TLR rates, an additional endpoint, did not differ significantly between study groups (15.0% [19/127] DES vs 13.0% [9/69] PTA; $p = 0.7141$). Twelve-month survival did not differ between treatment groups (Figure 2).

Wounds

At baseline, 54 patients in the DES group had 79 diagnostic wounds and 24 patients in the PTA group had 32 diagnostic wounds. The progression of healing for wounds present at

Table 2. Baseline lesion characteristics (angiographic core labortory).

	DES (N = 142 lesions)	PTA (N = 76 lesions)	p-value
Treated limb – right	54.2% (77/142)	50.0% (38/76)	0.5515
Lesion location[a]			
Anterior tibial	33.8% (48/142)	36.8% (28/76)	0.6536
Posterior tibial	30.3% (43/142)	30.3% (23/76)	0.9977
Peroneal	29.6% (42/142)	28.9% (22/76)	0.9224
Tibioperoneal trunk	22.5% (32/142)	23.7% (18/76)	0.8475
Lesion length (mm)	68.1 ± 35.2	68.7 ± 49.2	0.9158
Reference vessel diameter (mm)			
Proximal	3.1 ± 0.7	3.0 ± 0.6	0.4398
Distal	2.4 ± 0.5	2.5 ± 0.5	0.0566
Calcification			
None/mild	41.5% (59/142)	55.3% (42/76)	0.0530
Moderate	25.4% (36/142)	15.8% (12/76)	0.1044
Severe	31.7% (45/142)	25.0% (19/76)	0.3013
Not available	1.4% (2/142)	3.9% (3/76)	0.3452
% Diameter stenosis	78.6 ± 17.5	76.6 ± 16.7	0.4178
100% Stenosis (occlusion)	31.0% (44/142)	27.6% (21/76)	0.6059
Run-off vessel patency			
Anterior tibial	7.0% (10/142)	14.5% (11/76)	0.0764
Posterior tibial	13.4% (19/142)	18.4% (14/76)	0.3224
Peroneal	24.6% (35/142)	38.2% (29/76)	0.0369
⩾ 1 pedal artery	83.1% (118/142)	72.4% (55/76)	0.0621

Data are presented as mean ± SD unless otherwise noted.
[a]Patients could have lesions in more than one location.
DES, drug-eluting stent; PTA, percutaneous transluminal angioplasty.

Table 3. Primary effectiveness and safety endpoints (12 months).

	DES (N = 130)	PTA (N = 71)	Difference (95% CI)	One-sided lower 97.5% CI	p-value
Primary patency	68.0% (70/103)	76.0% (38/50)	–8.0% (–22.9%, 6.8%)	–22.92%	0.8552[a]
Freedom from MAE	91.6% (109/119)	95.3% (61/64)	–3.7% (–10.9%, 3.5%)	–10.90%	0.0433[b]

[a]Superiority p-value.
[b]Noninferiority p-value.
DES, drug-eluting stent; MAE, major adverse event; PTA, percutaneous transluminal angioplasty.

Table 4. Major adverse events (MAEs) through a 12-month follow up.

	DES (N = 130)	PTA (N = 71)	p-value
Composite MAE rate	8.4% (10/119)	4.7% (3/64)	0.5475
Above-ankle amputation	2.5% (3/119)	1.6% (1/64)	> 0.99
Major reintervention	5.9% (7/119)	0% (0/64)	0.0981
30-day mortality	0.0% (0/119)	3.1% (2/64)	0.1211

DES, drug-eluting stent; PTA, percutaneous transluminal angioplasty.

baseline across follow-up visits is shown in Figure 3. A total of 43.0% (34/79) and 46.9% (15/32) of wounds in the DES and PTA groups, respectively, healed by 12 months. Twenty-four patients in the DES group (18.5%) and 10 (14.1%) in the PTA group developed new wounds over a 1-year follow up.

Rutherford changes

The distribution of Rutherford categories at each follow-up visit is shown in Figure 4. The majority of patients in both groups presented as a Rutherford category of 3 or less by 3 months. At 12 months, 78.4% in the DES group and 73.5% in the PTA group (p = 0.4987) demonstrated a category improvement of at least one level without undergoing TLR.

Quality of life results

Mean baseline VascuQol summary scores were 3.8 ± 1.4 and 4.1 ± 1.4 for DES and PTA groups, respectively. At 12 months, mean scores were 5.0 ± 1.3 and 5.0 ± 1.4. VascuQoL scores improved significantly across all domains and all timepoints for the DES group and all except the social domain for the PTA group (online Supplemental Table S4).

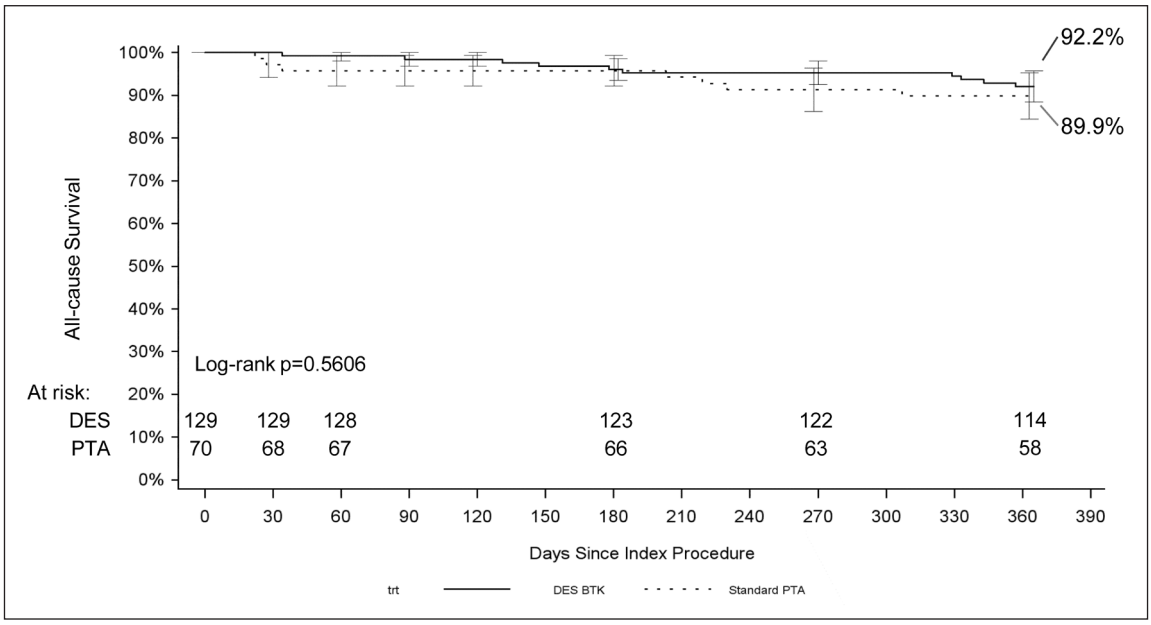

Figure 2. Kaplan–Meier analysis of all-cause survival in the SAVAL trial (with standard error bars). Subjects event-free at later than 365 days are censored at 366 days.
DES, drug-eluting stent; PTA, percutaneous transluminal angioplasty.

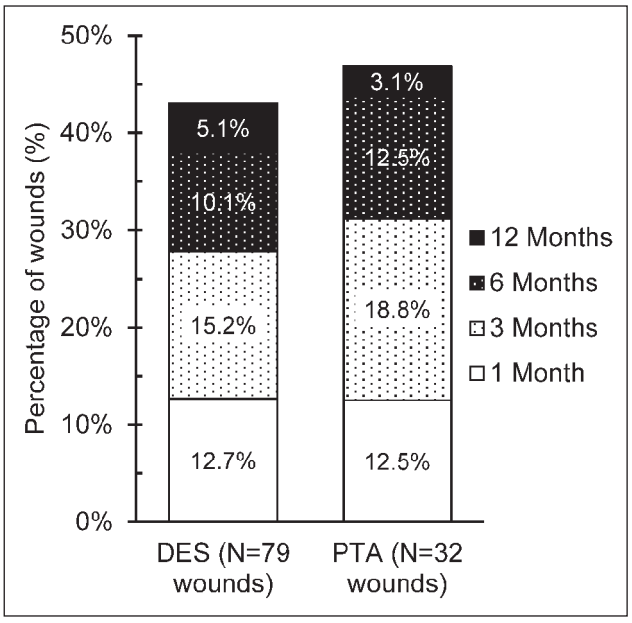

Figure 3. The proportion of wounds present at baseline that healed over time.
DES, drug-eluting stent; PTA, percutaneous transluminal angioplasty.

EQ-5D-5L index scores were 0.6 ± 0.2 for the DES group and 0.7 ± 0.2 for the PTA group at baseline, and 0.7 ± 0.2 and 0.7 ± 0.3, respectively, at 12 months. EQ-5D-5L dimension improvement is summarized in online Supplemental Table S5. Dimensions with the greatest frequency of improvements in both groups were mobility and pain/discomfort.

Discussion

The SAVAL nitinol DES was designed for below-the-knee artery treatment to improve the morphological and clinical results among patients with CLTI. The SAVAL trial, however, did not meet its primary effectiveness and safety endpoints. Thus, this randomized controlled trial did not provide clinical evidence to show a benefit of using a longer nitinol stent below the knee compared with PTA alone.

Prior studies of infrapopliteal use of DESs, summarized in online Supplemental Table S1, have suggested a patency benefit compared with PTA or bare metal stents. In previous DES randomized trials, relatively short lesions (mean length range for DES arms 15.9–30.0 mm)[8–11] were treated with coronary balloon-expandable DESs, whereas in this trial, relatively long DESs were used for longer lesions (i.e., mean length 68.1 mm in the DES arm). In addition to the differences in antiproliferative agents employed, nitinol stents, as used in this trial, have greater wall thickness and other geometric differences compared with balloon-expandable metallic coronary stents used below the knee, which may affect endothelialization[23] and thus clinical outcomes.[24]

The technical and effectiveness results for PTA in our study were better than anticipated. This may have been caused by the aggressive PTA protocol requiring additional prolonged balloon inflations in case of suboptimal angiographic results. Indeed, bailout stenting was performed in only one patient, which is less than would be expected in ordinary daily practice, and the 12-month primary patency rate for the PTA arm was greater than that reported for PTA arms of prior randomized studies.[6,10,22]

The availability of only one stent size for the trial may have contributed to suboptimal size-matching between target vessels and the stent. Although IVUS use was documented for 37% of stent procedures, IVUS-guided DES treatment was limited as stent size adjustment was not possible due to the availability of the study device in only one diameter.

Calcification is increasingly recognized as an independent severity factor in CLTI, which may also negatively affect stent patency.[25,26] The significantly greater prevalence of

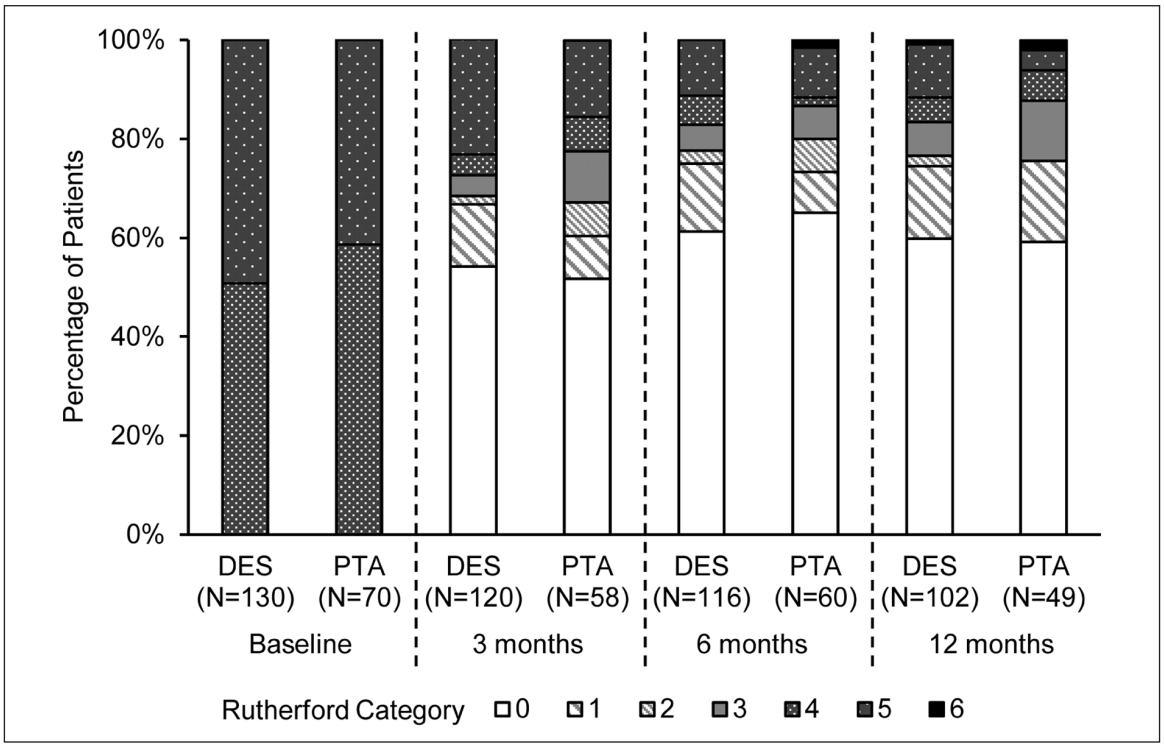

Figure 4. Rutherford categories of patients in the SAVAL trial at baseline and follow-up.
DES, drug-eluting stent; PTA, percutaneous transluminal angioplasty.

moderate or severe calcification in the DES arm as assessed by the angiographic core lab could have influenced the SAVAL trial outcomes.

The ability to discern a difference in outcomes could be attenuated by a relatively less severe or unstable CLTI presentation. A Rutherford category 4 presentation accounted for more than half of study patients and could show improvement less objectively than among patients with Rutherford category 5 presentation initially. The remarkably low major amputation rate in this trial of 1.6–2.5% at 12 months may be partly explained by the fact that only patients with Rutherford 4 and 5 disease were included, with the aforementioned predominance of Rutherford category 4 patients.

Another trial design-related limitation relates to the 2:1 randomization scheme, in which small data variances could influence the primary analyses, and meeting the minimum requirement for evaluable subjects was an additional challenge with follow-up occurring during the COVID-19 pandemic.

In general, patients with CLTI are at high risk.[27] In the PADI trial, which included Rutherford categories 4, 5, and 6, the overall 5-year rate of major amputation or death was approximately 74%,[28] and the 10-year mortality rate was 79.6%.[2] In the recently published BEST-CLI trial,[29] CLTI was associated with major adverse limb events or death in 43–48% of patients without adequate saphenous vein conduit—a common clinical reality—after a median of 1.6 years. Further underscoring the need for consistent, durable clinical benefits from below-the-knee endovascular therapies is the poor quality of life associated with CLTI.[3] Thus, further efforts should be undertaken to improve both the medical and interventional treatment of patients with CLTI.

Conclusion

The SAVAL trial did not show benefit related to effectiveness and safety with a paclitaxel-eluting, nitinol DES compared with PTA in below-the-knee lesions up to 140 mm in length. Given the impact of CLTI on limb and life, continued innovation to provide optimal treatments is needed.

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Data availability statement

Inquiries for data sharing may be submitted via https://www.bostonscientific.com/en-US/data-sharing-requests.html. Individual participant data will not be shared.

Declaration of conflicting interests

Hans van Overhagen, MD, PhD, serves as a consultant for Boston Scientific and Cordis. Masato Nakamura, MD, PhD, serves as a consultant for Terumo Co. and Boston Scientific; has received honoraria from Boston Scientific and Terumo Co. Patrick J Geraghty, MD, holds stock or stock options in MedAlliance SA, Aveera, Protexa, and Pulse Therapeutics. Sid Rao, MD, serves as a consultant for Cardiovascular Systems, Inc. and Philips. Max Arroyo, MD, has no conflicts of interest to declare. Yoshimitsu Soga, MD, serves as an advisor to Boston Scientific. Osamu Iida, MD, serves as a consultant for Boston Scientific. Ehrin Armstrong, MD, serves as a consultant for Abbott Vascular, Boston Scientific, Gore, Medtronic, Philips, and Shockwave Medical. Tatsuya Nakama, MD, serves as a consultant for Boston Scientific, BD,

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Supplementary material

The supplementary material is available online with the article.

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