The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 4, 2024 VOL. 390 NO. 1

Drug-Eluting Resorbable Scaffold versus Angioplasty for Infrapopliteal Artery Disease

Ramon L. Varcoe, M.B., B.S., Ph.D., M.Med. (Clin.Epi.), Brian G. DeRubertis, M.D., Raghu Kolluri, M.D., Prakash Krishnan, M.D., David C. Metzger, M.D., Marc P. Bonaca, M.D., M.P.H., Mehdi H. Shishehbor, D.O., M.P.H., Ph.D., Andrew H. Holden, M.B., Ch.B., Danielle R. Bajakian, M.D., Lawrence A. Garcia, M.D., Steven W.C. Kum, M.B., B.S., M.Med., John Rundback, M.D., Ehrin Armstrong, M.D., Jen-Kuang Lee, M.D., Yazan Khatib, M.D., Ido Weinberg, M.D., Hector M. Garcia-Garcia, M.D., Ph.D., Karine Ruster, Ph.D., Nutte T. Teraphongphom, Ph.D., Yan Zheng, M.S., Jin Wang, Ph.D., Jennifer M. Jones-McMeans, Ph.D., and Sahil A. Parikh, M.D., for the LIFE-BTK Investigators*

ABSTRACT

BACKGROUND

Among patients with chronic limb-threatening ischemia (CLTI) and infrapopliteal artery disease, angioplasty has been associated with frequent reintervention and adverse limb outcomes from restenosis. The effect of the use of drug-eluting resorbable scaffolds on these outcomes remains unknown.

METHODS

In this multicenter, randomized, controlled trial, 261 patients with CLTI and infrapopliteal artery disease were randomly assigned in a 2:1 ratio to receive treatment with an everolimus-eluting resorbable scaffold or angioplasty. The primary efficacy end point was freedom from the following events at 1 year: amputation above the ankle of the target limb, occlusion of the target vessel, clinically driven revascularization of the target lesion, and binary restenosis of the target lesion. The primary safety end point was freedom from major adverse limb events at 6 months and from perioperative death.

RESULTS

The primary efficacy end point was observed (i.e., no events occurred) in 135 of 173 patients in the scaffold group and 48 of 88 patients in the angioplasty group (Kaplan–Meier estimate, 74% vs. 44%; absolute difference, 30 percentage points; 95% confidence interval [CI], 15 to 46; one-sided $P<0.001$ for superiority). The primary safety end point was observed in 165 of 170 patients in the scaffold group and 90 of 90 patients in the angioplasty group (absolute difference, −3 percentage points; 95% CI, −6 to 0; one-sided $P<0.001$ for noninferiority). Serious adverse events related to the index procedure occurred in 2% of the patients in the scaffold group and 3% of those in the angioplasty group.

CONCLUSIONS

Among patients with CLTI due to infrapopliteal artery disease, the use of an everolimus-eluting resorbable scaffold was superior to angioplasty with respect to the primary efficacy end point. (Funded by Abbott; LIFE-BTK ClinicalTrials.gov number, NCT04227899.)

The authors' affiliations are listed in the Appendix. Dr. Parikh can be contacted at sap2196@cumc.columbia.edu or at Columbia University Irving Medical Center, 161 Fort Washington Ave., 6th Fl., New York, NY 10032.

*A complete list of the LIFE-BTK Investigators is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Varcoe, DeRubertis, and Parikh contributed equally to this article.

This article was published on October 25, 2023, at NEJM.org.

N Engl J Med 2024;390:9-19.
DOI: 10.1056/NEJMoa2305637

A Quick Take is available at NEJM.org

Peripheral artery disease is a global health epidemic estimated to affect more than 230 million people, including 7 to 12 million people in the United States alone.[1,2] The most severe manifestation is chronic limb-threatening ischemia (CLTI), which is characterized by ischemic rest pain and nonhealing ulceration or gangrene and is associated with a high risk of amputation. The adverse limb outcomes associated with CLTI affect quality of life and life expectancy; the prognosis is worse than that for most cancers.[3]

Open surgical revascularization with saphenous-vein bypass has been shown to increase the likelihood of limb salvage in highly selected patients with CLTI.[4] However, for the treatment of patients with CLTI and infrapopliteal artery disease (i.e., arterial disease below the knee), angioplasty has recently been shown to be superior to surgery.[5] Infrapopliteal angioplasty has limitations, such as elastic recoil, dissection, and restenosis, that reduce the durability of the procedure. Such limitations may be avoided with mechanical scaffolding.

The use of coronary drug-eluting stents has shown promise in below-the-knee interventions,[6-9] but stents can interfere with future reintervention. Drug-eluting resorbable scaffolds have potential advantages that may make them suitable for the treatment of infrapopliteal artery disease, and observational studies have shown promising results.[10-16] Drug-eluting resorbable scaffolds have unique scaffolding properties that allow them to overcome mechanical failure while acting as a delivery platform for an antiproliferative drug during the restenotic phase after intervention. These scaffolds also undergo resorption over time, which facilitates vessel remodeling and potentially reduces the late complications associated with permanent metal stents.

We conducted a single-blind, randomized, controlled trial (LIFE-BTK) to evaluate the safety and efficacy of a new everolimus-eluting resorbable scaffold (Esprit BTK, Abbott Vascular) for the treatment of infrapopliteal artery disease in patients with CLTI.

Methods

Trial Design

The design of the LIFE-BTK trial has been described previously.[17] The protocol with the statistical analysis plan (available with the full text of this article at NEJM.org) was designed by the sponsor (Abbott) with input from the principal investigators (the first two authors and the last author). The protocol was then approved by the Food and Drug Administration (FDA) and the institutional review board at each site. An investigational device exemption was approved by the FDA. All the patients provided written informed consent. The trial was conducted at 50 sites in six countries. The list of clinical trial committees is provided in the Supplementary Appendix (available at NEJM.org), and the full list of investigators is provided in Table S1 in the Supplementary Appendix.

Data were managed by the sponsor and analyzed by the principal investigators and the sponsor. An independent data and safety monitoring board oversaw the conduct of the trial, and an independent committee adjudicated all the clinical events. The results of angiography, intravascular ultrasonography, optical coherence tomography, duplex ultrasonography, and quantitative wound assessment were adjudicated at core laboratories by assessors who were unaware of the trial-group assignments. The principal investigators wrote the first draft of the manuscript, and all the authors reviewed and edited the manuscript and approved the submitted version. The principal investigators vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Patients

Patients 18 years of age or older were eligible for inclusion in the trial if they presented with CLTI associated with either ischemic rest pain (Rutherford–Becker class 4) or minor tissue loss (Rutherford–Becker class 5) and had infrapopliteal artery stenosis or occlusion. A complete list of clinical and anatomical inclusion and exclusion criteria is provided in Table S2. Randomization was performed after all eligibility criteria had been met, inflow and nontarget lesions had been treated successfully, and the guidewire had crossed the target lesion.

Trial Procedures

Patients who met the eligibility criteria were randomly assigned in a 2:1 ratio to receive treatment with either the everolimus-eluting resorbable scaffold (Fig. S1) or angioplasty. As many as

two target lesions could be treated. Tandem lesions that were less than 3 cm apart were considered to be a single target lesion. The lesions could be de novo (previously untreated) or restenotic (previously treated). The lesions had to be located in separate arteries in the proximal two thirds of the lower leg and to have a runoff vessel to the ankle that was free of clinically significant disease.

Patients received aspirin (at a loading dose of ≥300 mg) and a P2Y12 receptor inhibitor (clopidogrel, prasugrel, or ticagrelor) between 24 hours before the index procedure and 1 hour after the procedure, if they were not already receiving these medications. Dual antiplatelet therapy was continued for at least 1 year in the scaffold group and for 1 month in the angioplasty group, and single-agent therapy was provided thereafter.

Planned minor amputation, such as toe or transmetatarsal amputation, was allowed at the time of the index procedure or within the first month after the procedure. In the scaffold group, predilation was a mandatory step; the use of a noncompliant balloon with a 1:1 ratio of balloon size to vessel size was preferred.[18] Successful predilation was defined as residual stenosis of less than 30% of the vessel diameter. The length of the scaffold was selected to cover a minimum of 2 mm of reference vessel at both the proximal edge and the distal edge. The maximum total length of the scaffold allowed over all target lesions was 170 mm. In the angioplasty group, the procedure was performed in accordance with the standard of care and at the discretion of the proceduralist.

The success of target-lesion treatment was assessed by means of angiography performed in magnified orthogonal views. Successful treatment immediately after the index procedure was defined as follows: residual stenosis of less than 30% of the vessel diameter, a final number of runoff vessels that was equal to or greater than the number on initial angiography, the absence of residual dissection (defined as the absence of a persistent or increased amount of contrast material outside the vessel lumen), and the absence of complications, such as distal embolization, perforation, or thrombosis.

Follow-up visits were performed at 30 days, 3 months, 6 months, and 1 year; data from these assessments are reported in this article. Additional follow-up is planned to be performed annually for 5 years. Details regarding follow-up are provided in Table S3.

END POINTS

The primary efficacy end point was freedom from the following events at 1 year: amputation above the ankle of the target limb, total (100%) occlusion of the target vessel, clinically driven revascularization of the target lesion, and binary restenosis of the target lesion. The original primary efficacy end point did not include freedom from binary restenosis of the target lesion. Before the completion of enrollment, this component was added, and the duration of observation was extended from 6 months to 1 year. This decision was made after consideration of the results of a prespecified interim analysis (described below), as well as consideration of the end points that had been used in recently completed randomized trials that had insufficient power to discern clinically relevant treatment effects of the test device as compared with the standard of care.

Binary restenosis was defined as the presence of restenosis of more than 50% of the vessel diameter on angiography or a peak systolic velocity ratio (PSVR) of 2.0 or more on duplex ultrasonography.[19] Each target lesion was interrogated. If the patient underwent both angiography and duplex ultrasonography at the same time point, the results of angiography were used as the primary determinant. The following secondary criteria were used at the duplex-ultrasonography core laboratories to confirm any target-lesion stenosis detected: visible stenosis on B-mode imaging, a focal increase in the absolute peak velocity, poststenotic turbulence, a change in waveform shape, or a reduction in velocity distal to the stenosis. If the PSVR could not be calculated, these secondary criteria were used to determine whether stenosis was present. When the results were indeterminate (discordant), the patient was excluded from the analysis.

The primary safety end point was freedom from major adverse limb events at 6 months and from perioperative death. Major adverse limb events were amputation above the ankle of the target limb and major reintervention, which was defined as new surgical bypass grafting, interposition grafting, thrombectomy, or thrombolysis.[20] Perioperative death was defined as death from any cause within 30 days after the index procedure.

The trial was powered to assess two secondary end points, both of which were adjudicated at 1 year. The first was the original primary efficacy end point (freedom from amputation above the ankle of the target limb, occlusion of the target vessel, and clinically driven revascularization of the target lesion), and the second was binary restenosis of the target lesion. A complete list of end points and their definitions is provided in Tables S4 and S5.

STATISTICAL ANALYSIS

A prespecified interim analysis was performed during the enrollment period by an independent statistician on May 12, 2022. On September 7, 2022, the following components of the adaptive trial design were implemented by the principal investigators and the sponsor, in consultation with the FDA: the sample size was increased, the primary efficacy end point was modified to include freedom from binary restenosis of the target lesion, and the duration of observation was extended from 6 months to 1 year. The investigators and trial statisticians remained unaware of the trial-group assignments. For the analysis of the primary efficacy end point, the alpha level was adjusted by 0.0001 (from 0.025 to 0.0249). The original primary efficacy end point was preserved as a powered secondary end point, and binary restenosis of the target lesion at 1 year was also added as a powered secondary end point. The analyses of these powered secondary end points were conducted at a one-sided alpha level of 0.025 because they were performed only after the threshold for significance for the primary efficacy and safety end points had been met. Data were unblinded on July 7, 2023.

We estimated that a sample of 261 patients would provide the trial with more than 80% power to show the superiority of the use of the scaffold to angioplasty with respect to the primary efficacy end point. The sample size was estimated on the basis of a difference between the scaffold group and the angioplasty group (i.e., treatment effect) of approximately 20 percentage points that was seen in previous data.[6,9,21,22] We initially estimated that a sample of 222 patients (148 in the scaffold group and 74 in the angioplasty group) would provide the trial with more than 80% power to show a treatment effect of the scaffold; we then adjusted the sample size to account for 15% attrition at 1 year.

The primary efficacy end point was evaluated in a superiority analysis performed with the use of Pearson's chi-square test at a one-sided trial-wise alpha level of 0.0249. The primary safety end point was evaluated in a noninferiority analysis (noninferiority margin, –10 percentage points) performed with the use of the Farrington–Manning method at a one-sided alpha level of 0.025. It was assumed that the primary safety end point would be observed in 95% of the patients in each trial group. The two powered secondary end points were evaluated in superiority analyses performed at a one-sided alpha level of 0.025. Assumptions were based on published data.[6,8,9,21,23] For the superiority analyses, a between-group difference of approximately 15 percentage points was required to show superiority.

The primary efficacy end point and the two powered secondary end points were assessed in the intention-to-treat population, which included all the patients who underwent randomization. The primary safety end point was assessed in the as-treated population, which included all the patients who received the randomly assigned treatment. For these end points, Kaplan–Meier estimates are reported. Kaplan–Meier time-to-event analyses for efficacy and safety from baseline through the prespecified follow-up time point were performed as sensitivity analyses. Treatment effects were estimated with the use of Cox proportional-hazards regression and are presented as hazard ratios with 95% confidence intervals. If the proportional-hazards assumption was violated, the Com–Nougue method was used; this method involves the use of estimates from the Kaplan–Meier analyses together with variance estimated with the Greenwood method.

Missing data were handled with multiple imputation. The Markov chain Monte Carlo method was used to impute missing values for the end points and prespecified baseline variables with an arbitrary missing pattern from data under the assumption of multivariate normal distribution. A final assessment of the treatment effect was performed by combining the results for the treatment assessments across the five imputed data sets with Rubin's combination rules.

If the threshold for significance for the primary efficacy and safety end points was met, the two powered secondary end points were to be tested in a hierarchical fashion until the threshold for significance was not met; if an end point

remained, it was to be tested in an exploratory fashion. One-sided P values are reported. For other analyses, 95% confidence intervals are presented without adjustment for multiplicity. Thus, the confidence intervals should not be used to infer definitive treatment effects. Details regarding the statistical analysis are provided in the Supplementary Appendix. All analyses were conducted with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS AND PROCEDURES

From July 2020 through September 2022, a total of 7837 patients were assessed for eligibility at 50 clinical sites with 66 unique operators, and 635 patients provided consent. Subsequently, 365 patients had a screening failure before or during the index procedure, 8 withdrew consent before randomization, and 1 provided consent but the site closed and the patient did not undergo randomization; 261 patients underwent randomization.

A total of 173 patients (with 179 target lesions) were randomly assigned to receive the scaffold, and 88 patients (with 92 target lesions) were randomly assigned to undergo angioplasty (Fig. S2). The characteristics of the patients at baseline are shown in Table 1. The representativeness of the trial population is shown in Table S6. The mean (±SD) age of the patients was 72.6±10.1 years, and 32% were female. Rutherford–Becker class 4 disease (associated with ischemic rest pain) was present in 135 patients (52%), and Rutherford–Becker class 5 disease (associated with minor tissue loss) was present in 126 patients (48%). There was a wound on the target limb in 130 patients (50%), and the mean ankle–brachial index of the target limb was 0.88±0.32.

The characteristics of the target lesions are shown in Table 2. The mean lesion length at baseline was 43.8±31.8 mm in the scaffold group and 44.8±29.1 mm in the angioplasty group. On the basis of angiography performed at the angiography core laboratory, successful treatment immediately after the index procedure occurred in 91% of the patients in the scaffold group and in 70% of the patients in the angioplasty group. Bailout stenting was performed in 5 patients (6%) in the angioplasty group. Additional data regarding characteristics of the patients and target lesions at baseline and the procedures are provided in Tables S7 through S12. Results for procedural end points are shown in Table S13.

CLINICAL OUTCOMES

At 1 year, follow-up data were available for 231 patients (89%, including 88% in the scaffold group and 89% in the angioplasty group). The median follow-up was 390 days (range, 0 to 1012) in the scaffold group and 397 days (range, 35 to 884) in the angioplasty group. The use of concomitant medical therapy is shown in Table S14. The use of dual antiplatelet therapy at 30 days and at 1 year is shown in Table S15.

For the primary efficacy end point (freedom from amputation above the ankle of the target limb, occlusion of the target vessel, clinically driven revascularization of the target lesion, and binary restenosis of the target lesion at 1 year), the Kaplan–Meier estimate was 74% in the scaffold group and 44% in the angioplasty group, with an absolute difference of 30 percentage points (95% confidence interval [CI], 15 to 46; one-sided P<0.001 for superiority) (Table 3). The results for freedom from clinically driven revascularization of the target lesion at 1 year and freedom from binary restenosis of the target lesion at 1 year appeared to be consistent with the results for the primary efficacy end point. Results for subgroup analyses of the primary efficacy end point are shown in Figure S7.

The primary safety end point (freedom from major adverse limb events at 6 months and perioperative death) was observed in 165 of 170 patients in the scaffold group and 90 of 90 patients in the angioplasty group, with an absolute difference of −3 percentage points (95% CI, −6 to 0; one-sided P<0.001 for noninferiority). Results for the prespecified analysis of binary data are shown in Table S16, and results for the imputation analysis are shown in Table S17.

The first powered secondary end point (freedom from amputation above the ankle of the target limb, occlusion of the target vessel, and clinically driven revascularization of the target lesion at 1 year) was observed in 148 of 173 patients in the scaffold group and 66 of 88 patients in the angioplasty group. The second powered secondary end point (binary restenosis of the target lesion at 1 year) was observed in 35 of 173 patients in the scaffold group and 35 of 88 pa-

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Scaffold (N=173)	Angioplasty (N=88)	Total (N=261)
Age — yr	73.3±9.9	71.1±10.4	72.6±10.1
Sex — no. (%)			
Male	117 (68)	61 (69)	178 (68)
Female	56 (32)	27 (31)	83 (32)
Race or ethnic group — no. (%)†			
White	98 (57)	56 (64)	154 (59)
American Indian or Alaska Native	0	1 (1)	1 (<1)
Asian	36 (21)	11 (12)	47 (18)
Black	21 (12)	11 (12)	32 (12)
Native Hawaiian or Pacific Islander	1 (1)	2 (2)	3 (1)
Declined or unable to disclose	18 (10)	7 (8)	25 (10)
Hispanic ethnic group — no. (%)†			
Hispanic or Latinx	31 (18)	12 (14)	43 (16)
Not Hispanic or Latinx	132 (76)	70 (80)	202 (77)
Declined or unable to disclose	10 (6)	6 (7)	16 (6)
Body-mass index‡	27.85±5.47	28.94±5.77	28.21±5.58
Risk factors — no. (%)			
Tobacco use	91 (53)	47 (53)	138 (53)
Hypertension	163 (94)	80 (91)	243 (93)
Hyperlipidemia	140 (81)	72 (82)	212 (81)
Diabetes mellitus	123 (71)	61 (69)	184 (70)
Previous minor amputation of target limb — no. (%)	16 (9)	7 (8)	23 (9)
Rutherford–Becker classification — no. (%)§			
Class 4	90 (52)	45 (51)	135 (52)
Class 5	83 (48)	43 (49)	126 (48)
Wound on target limb — no. (%)	85 (49)	45 (51)	130 (50)
Ankle–brachial index of target limb¶	0.87±0.32	0.91±0.33	0.88±0.32
Toe–brachial index of target limb‖	0.51±0.31	0.46±0.24	0.49±0.29

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Race or ethnic group was reported by the patient.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Rutherford–Becker class 4 disease is associated with ischemic rest pain, and Rutherford–Becker class 5 disease is associated with minor tissue loss.
¶ Data for the ankle–brachial index of the target limb are shown for 227 patients (87%). The ankle–brachial index is the ratio of ankle pressure to arm pressure; a value of 0.9 to 1.4 is considered to be borderline or normal, a value lower than 0.9 indicates peripheral artery disease, and a value higher than 1.4 suggests a noncompressible artery. When the ankle–brachial index was higher than 1.4 or could not be measured reliably, a toe-pressure measurement was obtained and the toe–brachial index was used.
‖ Data for the toe–brachial index of the target limb are shown for 79 patients (30%). The toe–brachial index is the ratio of toe pressure to arm pressure; a value of 0.7 or higher is considered to be normal, and a value lower than 0.7 indicates peripheral artery disease.

Table 2. Baseline, Procedural, and Postprocedural Characteristics of the Target Lesions.*

Characteristic	Scaffold (N=173)	Angioplasty (N=88)	Difference (95% CI)†	Total (N=261)
Baseline characteristics reported by trial sites				
Target lesions treated				
No. of target lesions	1.0±0.2	1.0±0.2	0.0 (–0.0 to 0.1)	1.0±0.2
One target lesion — no. (%)	165 (95)	85 (97)	–1 (–5 to 6)	250 (96)
Two target lesions — no. (%)	7 (4)	3 (3)	1 (–6 to 5)	10 (4)
Calcification of target lesion — no./total no. of target lesions (%)				
None or mild	124/179 (69)	64/92 (70)	0 (–11 to 12)	188/271 (69)
Moderate	49/179 (27)	26/92 (28)	–1 (–12 to 10)	75/271 (28)
Severe	6/179 (3)	2/92 (2)	1 (–5 to 5)	8/271 (3)
Baseline characteristics reported by core laboratory‡				
Diameter of reference vessel before treatment — mm	2.94±0.77	2.82±0.74	0.12 (–0.09 to 0.32)	2.90±0.76
Length of target lesion — mm	43.8±31.8	44.8±29.1	–1.0 (–8.7 to 6.8)	44.1±30.9
Absence of thrombus — no. (%)	172 (100)	89 (100)	0 (–2 to 4)	261 (100)
Location of target lesion — no. (%)				
Anterior tibial artery	59 (34)	24 (27)	7 (–5 to 18)	83 (32)
Posterior tibial artery	26 (15)	16 (18)	–3 (–13 to 6)	42 (16)
Peroneal artery	28 (16)	21 (24)	–7 (–18 to 3)	49 (19)
Tibioperoneal trunk	26 (15)	15 (17)	–2 (–12 to 7)	41 (16)
Tibioperoneal trunk to posterior tibial artery	15 (9)	8 (9)	0 (–9 to 6)	23 (9)
Tibioperoneal trunk to peroneal artery	18 (10)	5 (6)	5 (–3 to 11)	23 (9)
TASC II classification — no. (%)§				
Class A	83 (48)	47 (53)	–5 (–17 to 8)	130 (50)
Class B	61 (35)	23 (26)	10 (–2 to 20)	84 (32)
Class C	28 (16)	19 (22)	–5 (–16 to 5)	47 (18)
Stenosis before treatment — % of vessel diameter	72.6±18.9	73.7±21.0	–1.1 (–6.3 to 4.1)	73.0±19.6
Procedural characteristics reported by trial sites				
Predilation performed — no./total no. of target lesions (%)	179/179 (100)	92/92 (100)	0 (–2 to 4)	271/271 (100)
Postdilation performed without complications — no./total no. of target lesions (%)	176/179 (98)	NA	NA	NA
Bailout devices used — no. (%)	0	5 (6)	–6 (–13 to 2)	5 (2)
Postprocedural characteristics reported by core laboratory¶				
Residual stenosis after predilation — % of vessel diameter	30.0±12.6	25.0±8.7	5.0 (–14.8 to 24.8)	29.8±12.5
Residual stenosis after index procedure — % of vessel diameter	17.0±9.3	22.8±11.2	–5.8 (–8.6 to –3.0)	19.0±10.3
Residual stenosis after index procedure <30% of vessel diameter — no./total no. (%)	163/170 (96)	61/84 (73)	23 (14 to 34)	224/254 (88)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. CI denotes confidence interval and NA not applicable.
† Differences in percentages are shown in percentage points.
‡ No patients had ulceration or aneurysm of the target lesion at baseline.
§ The Trans-Atlantic Inter-Society Consensus (TASC) II classification indicates the anatomical pattern of atherosclerotic disease severity. No patients had class D.
¶ No patients had residual flow-limiting dissection after the index procedure.

Table 3. Efficacy and Safety End Points.

End Point	Scaffold		Angioplasty		Difference (95% CI)*	P Value†
	no./total no.	*Kaplan–Meier %*	*no./total no.*	*Kaplan–Meier %*		
Primary efficacy end point‡						
Freedom from amputation above ankle of target limb, occlusion of target vessel, clinically driven revascularization of target lesion, and binary restenosis of target lesion at 1 yr	135/173	74	48/88	44	30 (15 to 46)	<0.001
Freedom from amputation above ankle of target limb at 1 yr	169/173	98	88/88	100	—	—
Freedom from occlusion of target vessel at 1 yr	155/173	87	76/88	83	—	—
Freedom from clinically driven revascularization of target lesion at 1 yr	162/173	93	77/88	87	—	—
Freedom from binary restenosis of target lesion at 1 yr	138/173	76	53/88	50	—	—
Powered secondary end points						
Original primary efficacy end point: freedom from amputation above ankle of target limb, occlusion of target vessel, and clinically driven revascularization of target lesion at 1 yr	148/173	83	66/88	70	0.56 (0.32 to 0.99)	0.03
Binary restenosis of target lesion at 1 yr	35/173	24	35/88	50	−26 (−41 to −11)	<0.001
Primary safety end point§						
Freedom from major adverse limb events at 6 mo and perioperative death	165/170	97	90/90	100	−3 (−6 to 0)	<0.001
Freedom from major adverse limb events at 6 mo	167/170	98	90/90	100	—	—
Freedom from amputation above ankle of target limb	168/170	99	90/90	100	—	—
Freedom from major reintervention of target limb	169/170	99	90/90	100	—	—
Freedom from perioperative death	168/170	99	90/90	100	—	—

* For the primary efficacy end point, the difference in percentages (shown in percentage points) and 95.02% confidence interval are provided. For the original primary efficacy end point (the first powered secondary end point), the hazard ratio and 95% confidence interval are provided. For binary restenosis of the target lesion at 1 year (the second powered secondary end point) and for the primary safety end point, differences in percentages (shown in percentage points) and 95% confidence intervals are provided.

† The one-sided P values were calculated on the basis of the Com–Nougue method against a one-sided alpha level of 0.025, except the P value for the primary efficacy end point, which was calculated against a one-sided alpha level of 0.0249.

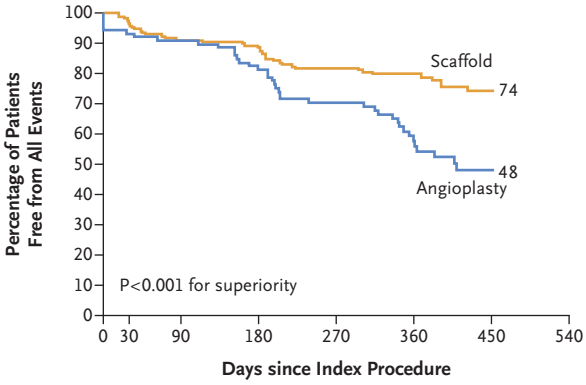
‡ Patients were included in the analysis of the primary efficacy end point if they had data from duplex ultrasonography (or data from angiography, if both angiographic and duplex ultrasonographic data were available) from a qualified core laboratory at 1 year or had had a clinical event. Clinical events were adjudicated by the clinical events committee through 365 days, whereas angiographic data through 423 days and duplex ultrasonographic data through 453 days were used to evaluate patency.

§ Major reintervention was defined as new surgical bypass grafting, interposition grafting, thrombectomy, or thrombolysis. Perioperative death was defined as death from any cause within 30 days after the index procedure.

tients in the angioplasty group. Additional results for primary and secondary end points, as well as results of an analysis performed according to lesion-length terciles, subgroup analyses, sensitivity analyses, and a center-effects analysis, are provided in Tables S16 through S21. The Kaplan–Meier curve for efficacy is shown in Figure 1.

Four patients in the scaffold group had undergone amputation above the ankle by 1 year. Three of these patients had patent scaffolds. The other patient had evidence suggestive of scaffold occlusion on duplex ultrasonography reported by the trial site, but the scaffold was found to be patent on follow-up angiography. Of those four patients, two had undergone clinically driven revascularization of the target lesion by 1 year, including the aforementioned patient and a patient with 57% stenosis of the vessel diameter as adjudicated by the core laboratory.

Wound healing was observed in 37 of 83 patients (45%) in the scaffold group by 1 year, with a mean time to healing of 196.7±130.1 days. Wound healing was observed in 25 of 45 patients (56%) in the angioplasty group by 1 year, with a mean time to healing of 187.6±122.7 days. The mean ankle–brachial index at 1 year is shown in Table S22; the percentage of patients with an abnormal ankle–brachial index and with an abnormal toe–brachial index at various time points between baseline and 1 year is shown in Tables S23 and S24, respectively. Serious adverse events related to the index procedure occurred in 2% of the patients in the scaffold group and 3% of those in the angioplasty group. A summary of serious and nonserious adverse events reported by the trial sites is shown in Tables S25, S26, and S27.



Days	0	30	90	180	365	453
No. at Risk						
Scaffold	173	163	152	142	95	42
Angioplasty	88	82	78	67	33	15
Patients Free from All Events (%)						
Scaffold	100	96	91	89	80	74
Angioplasty	94	93	91	81	54	48

Figure 1. Kaplan–Meier Curve for Efficacy.

The primary efficacy end point was freedom from the following events at 1 year: amputation above the ankle of the target limb, occlusion of the target vessel, clinically driven revascularization of the target lesion, and binary restenosis of the target lesion. The Kaplan–Meier curve shows the percentage of patients free from all events from baseline through day 453. Patients were included in the analysis of the primary efficacy end point if they had data from duplex ultrasonography (or data from angiography, if both angiographic and duplex ultrasonographic data were available) from a qualified core laboratory at 1 year or had had a clinical event. Clinical events were adjudicated by the clinical events committee through 365 days, whereas angiographic data through 423 days and duplex ultrasonographic data through 453 days were used to evaluate patency. One event in the angioplasty group that was based on duplex ultrasonographic data obtained after 453 days was excluded from the Kaplan–Meier analysis but was included in the analysis of the primary efficacy end point. The one-sided P value for the primary efficacy end point was calculated on the basis of the Com–Nougue method against a one-sided alpha level of 0.0249.

DISCUSSION

The results of this randomized, controlled trial showed that among patients with CLTI and infrapopliteal artery disease, the incidence of freedom from amputation above the ankle of the target limb, occlusion of the target vessel, and clinically driven revascularization of the target lesion (the original primary efficacy end point) at 1 year was higher among patients who received an everolimus-eluting resorbable scaffold than among those who received angioplasty — and the magnitude of the effect was increased when freedom from binary restenosis of the target lesion was included in the end point (the primary efficacy end point). With respect to freedom from major adverse limb events at 6 months and perioperative death (the primary safety end point), the use of the scaffold was noninferior to angioplasty.

Several trials have evaluated methods for revascularization in the infrapopliteal circulation in an attempt to avoid the poor patency outcomes seen with angioplasty. However, most of these methods have failed because of the complex nature of the atherosclerotic disease and the difficulty of maintaining patency in both the

short term and the long term.[22-26] The challenges associated with infrapopliteal artery revascularization include extensive medial calcinosis, long lesion lengths, acute lesion recoil, and a predilection for flow-limiting dissection after angioplasty. Various methods have not shown efficacy with respect to the maintenance of long-term patency and the reduction of undesirable long-term clinical events, such as reintervention and amputation. The findings suggest that device success may require both the mechanical properties of a stent and an antiproliferative coating.

Drug-eluting devices that inhibit neointimal hyperplasia have not been used routinely for the treatment of infrapopliteal artery disease. In numerous trials of drug-coated balloons and drug-eluting scaffolds and stents, the treatment has not resulted in greater patency than angioplasty or has had practical limitations.[22-24,26,27] Of all the available approaches, the use of coronary drug-eluting stents with sirolimus analogues in below-the-knee interventions has shown the most promise for maintaining primary patency.[6-9,28] However, the permanent nature of these metal implants has made some clinicians wary of their routine use.

This trial had several limitations that should be considered during the interpretation of the data. First, after the interim analysis was conducted, the primary efficacy end point of the trial was changed to include freedom from binary restenosis of the target lesion. However, this change was made during the enrollment period, and the investigators and other personnel conducting the trial remained unaware of the trial-group assignments. In addition, the original primary efficacy end point was preserved as a powered secondary end point, and the results for that end point were significant, although the magnitude of the effect was smaller than that for the primary efficacy end point. Second, the trial population was highly selected, with patients having shorter lesions than those commonly encountered in clinical practice. Nevertheless, patients in the two trial groups had coexisting conditions that were evenly matched and were consistent with those of the population of patients with CLTI in clinical practice.

Third, the prescribed predilation in the scaffold group may have influenced the results to some extent, but this technique is known to be an important consideration in attaining the best results with these scaffolds. Fourth, as with most clinical trials, participation in the trial conferred close supervision of the patients, and the expected incidences of amputation and clinically driven revascularization of the target lesion were substantially lower than the incidences that might be expected in clinical practice. Fifth, the use of the scaffolds in the trial was restricted to the proximal two thirds of the infrapopliteal arteries. Caution must be used in extrapolating these findings to other anatomical locations.

Among patients with CLTI due to infrapopliteal artery disease, the use of an everolimus-eluting resorbable scaffold was superior to angioplasty with respect to the primary efficacy end point. With respect to the primary safety end point, the use of the scaffold was noninferior to angioplasty.

Supported by Abbott.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

The authors' affiliations are as follows: the Prince of Wales Hospital and University of New South Wales, Randwick, Australia (R.L.V.); New York Presbyterian–Weill Cornell Medical Center (B.G.D.), Mount Sinai Hospital (P.K.), and Columbia University Irving Medical Center and Columbia Vagelos College of Physicians and Surgeons (D.R.B., S.A.P.), New York, and Catholic Health Services, St. Francis Hospital and Heart Center, Roslyn (L.A.G.) — all in New York; Syntropic Core Lab and OhioHealth Heart and Vascular, Columbus (R.K.), and University Hospitals Harrington Heart and Vascular Institute, Cleveland (M.H.S.) — both in Ohio; Ballad Health, Kingsport, TN (D.C.M.); CPC Clinical Research, Cardiovascular Division, University of Colorado School of Medicine, Aurora (M.P.B.), and Advanced Heart and Vein Center, Denver (E.A.) — both in Colorado; Auckland Hospital and Auckland University, Grafton, Auckland, New Zealand (A.H.H.); the Department of Surgery, Changi General Hospital, Singapore (S.W.C.K.); Advanced Interventional and Vascular Services, Teaneck, NJ (J.R.); National Taiwan University Hospital, Taipei City, Taiwan (J.-K.L.); First Coast Cardiovascular Institute, Jacksonville, FL (Y.K.); VasCore, Boston (I.W.); MedStar Washington Hospital Center, Washington, DC (H.M.G.-G.); and Abbott Vascular, Santa Clara, CA (K.R., N.T.T., Y.Z., J.W., J.M.J.-M.).

REFERENCES

1. Allison MA, Ho E, Denenberg JO, et al. Ethnic-specific prevalence of peripheral arterial disease in the United States. Am J Prev Med 2007;32:328-33.
2. Song P, Rudan D, Zhu Y, et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. Lancet Glob Health 2019;7(8): e1020-e1030.
3. Mustapha JA, Katzen BT, Neville RF, et al. Determinants of long-term outcomes and costs in the management of critical limb ischemia: a population-based cohort study. J Am Heart Assoc 2018;7(16): e009724.
4. Farber A, Menard MT, Conte MS, et al. Surgery or endovascular therapy for chronic limb-threatening ischemia. N Engl J Med 2022;387:2305-16.
5. Bradbury AW, Moakes CA, Popplewell M, et al. A vein bypass first versus a best endovascular treatment first revascularisation strategy for patients with chronic limb threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal revascularisation procedure to restore limb perfusion (BASIL-2): an open-label, randomised, multicentre, phase 3 trial. Lancet 2023;401:1798-809.
6. Bosiers M, Scheinert D, Peeters P, et al. Randomized comparison of everolimus-eluting versus bare-metal stents in patients with critical limb ischemia and infrapopliteal arterial occlusive disease. J Vasc Surg 2012;55:390-8.
7. Rastan A, Brechtel K, Krankenberg H, et al. Sirolimus-eluting stents for treatment of infrapopliteal arteries reduce clinical event rate compared to bare-metal stents: long-term results from a randomized trial. J Am Coll Cardiol 2012;60:587-91.
8. Rastan A, Tepe G, Krankenberg H, et al. Sirolimus-eluting stents vs. bare-metal stents for treatment of focal lesions in infrapopliteal arteries: a double-blind, multi-centre, randomized clinical trial. Eur Heart J 2011;32:2274-81.
9. Scheinert D, Katsanos K, Zeller T, et al. 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. J Am Coll Cardiol 2012;60:2290-5.
10. Dia A, Venturini JM, Kalathiya R, et al. Single arm retrospective study of bioresorbable vascular scaffolds to treat patients with severe infrapopliteal arterial disease. Catheter Cardiovasc Interv 2019; 94:1028-33.
11. Ipema J, Kum S, Huizing E, et al. A systematic review and meta-analysis of bioresorbable vascular scaffolds for below-the-knee arterial disease. Int Angiol 2021; 40:42-51.
12. Varcoe RL, Menting TP, Thomas SD, Lennox AF. Long-term results of a prospective, single-arm evaluation of everolimus-eluting bioresorbable vascular scaffolds in infrapopliteal arteries. Catheter Cardiovasc Interv 2021;97:142-9.
13. Varcoe RL, Schouten O, Thomas SD, Lennox AF. Initial experience with the absorb bioresorbable vascular scaffold below the knee: six-month clinical and imaging outcomes. J Endovasc Ther 2015; 22:226-32.
14. Varcoe RL, Thomas SD, Lennox AF. Three-year results of the absorb everolimus-eluting bioresorbable vascular scaffold in infrapopliteal arteries. J Endovasc Ther 2018;25:694-701.
15. Kum S, Ipema J, Chun-Yin DH, et al. Early and midterm experience with the Absorb everolimus-eluting bioresorbable vascular scaffold in Asian patients with chronic limb-threatening ischemia: one-year clinical and imaging outcomes from the DISAPEAR Registry. J Endovasc Ther 2020;27:616-22.
16. Huizing E, Kum S, Ipema J, et al. Mid-term outcomes of an everolimus-eluting bioresorbable vascular scaffold in patients with below-the-knee arterial disease: a pooled analysis of individual patient data. Vasc Med 2021;26:195-9.
17. Varcoe RL, Parikh SA, DeRubertis BG, et al. Evaluation of an infrapopliteal drug-eluting resorbable scaffold: design methodology for the LIFE-BTK randomized controlled trial. J Soc Cardiovasc Angiogr Interv 2023;2:100964 (https://doi.org/10.1016/j.jscai.2023.100964).
18. Varcoe RL, Thomas SD, Rapoza RJ, Kum S. Lessons learned regarding handling and deployment of the absorb bioresorbable vascular scaffold in infrapopliteal arteries. J Endovasc Ther 2017;24: 337-41.
19. Eiberg JP, Grønvall Rasmussen JB, Hansen MA, Schroeder TV. Duplex ultrasound scanning of peripheral arterial disease of the lower limb. Eur J Vasc Endovasc Surg 2010;40:507-12.
20. Conte MS, Geraghty PJ, Bradbury AW, et al. Suggested objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia. J Vasc Surg 2009;50(6): 1462-73.e1.
21. Romiti M, Albers M, Brochado-Neto FC, Durazzo AES, Pereira CAB, De Luccia N. Meta-analysis of infrapopliteal angioplasty for chronic critical limb ischemia. J Vasc Surg 2008;47:975-81.
22. Zeller T, Baumgartner I, Scheinert D, et al. Drug-eluting balloon versus standard balloon angioplasty for infrapopliteal arterial revascularization in critical limb ischemia: 12-month results from the IN.PACT DEEP randomized trial. J Am Coll Cardiol 2014;64:1568-76.
23. Mustapha JA, Brodmann M, Geraghty PJ, Saab F, Settlage RA, Jaff MR; Lutonix BTK Study Investigators. Drug-coated vs uncoated percutaneous transluminal angioplasty in infrapopliteal arteries: six-month results of the Lutonix BTK Trial. J Invasive Cardiol 2019;31:205-11.
24. Liistro F, Weinberg I, Almonacid Popma A, Shishehbor MH, Deckers S, Micari A. Paclitaxel-coated balloons versus percutaneous transluminal angioplasty for infrapopliteal chronic total occlusions: the IN.PACT BTK randomised trial. EuroIntervention 2022;17(17):e1445-e1454.
25. Zeller T, Beschorner U, Pilger E, et al. Paclitaxel-coated balloon in infrapopliteal arteries: 12-month results from the BIOLUX P-II randomized trial (BIOTRONIK'S-First in Man study of the Passeo-18 LUX drug releasing PTA balloon catheter vs. the uncoated Passeo-18 PTA balloon catheter in subjects requiring revascularization of infrapopliteal arteries). JACC Cardiovasc Interv 2015;8:1614-22.
26. Zeller T, Micari A, Scheinert D, et al. The IN.PACT DEEP clinical drug-coated balloon trial: 5-year outcomes. JACC Cardiovasc Interv 2020;13:431-43.
27. van Overhagen H, Nakamura M, Geraghty PJ, et al. Primary results of the SAVAL randomized trial of a paclitaxel-eluting nitinol stent versus percutaneous transluminal angioplasty in infrapopliteal arteries. Vasc Med 2023 October 16 (Epub ahead of print).
28. Taeymans K, Bosiers M, Deloose K, et al. One-year outcome of the everolimus-eluting, balloon-expandable Promus Element and Promus Element Plus stent in the treatment of below-the-knee lesions in CLI patients. J Cardiovasc Surg (Torino) 2020;61:445-50.