ORIGINAL ARTICLE

Transcatheter Arterialization of Deep Veins in Chronic Limb-Threatening Ischemia

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ABSTRACT

BACKGROUND

Approximately 20% of patients with chronic limb-threatening ischemia have no revascularization options, leading to above-ankle amputation. Transcatheter arterialization of the deep veins is a percutaneous approach that creates an artery-to-vein connection for delivery of oxygenated blood by means of the venous system to the ischemic foot to prevent amputation.

METHODS

We conducted a prospective, single-group, multicenter study to evaluate the effect of transcatheter arterialization of the deep veins in patients with nonhealing ulcers and no surgical or endovascular revascularization treatment options. The composite primary end point was amputation-free survival (defined as freedom from above-ankle amputation or death from any cause) at 6 months, as compared with a performance goal of 54%. Secondary end points included limb salvage, wound healing, and technical success of the procedure.

RESULTS

We enrolled 105 patients who had chronic limb-threatening ischemia and were of a median age of 70 years (interquartile range, 38 to 89). Of the patients enrolled, 33 (31.4%) were women and 45 (42.8%) were Black, Hispanic, or Latino. Transcatheter arterialization of the deep veins was performed successfully in 104 patients (99.0%). At 6 months, 66.1% of the patients had amputation-free survival. According to Bayesian analysis, the posterior probability that amputation-free survival at 6 months exceeded a performance goal of 54% was 0.993, which exceeded the prespecified threshold of 0.977. Limb salvage (avoidance of above-ankle amputation) was attained in 67 patients (76.0% by Kaplan–Meier analysis). Wounds were completely healed in 16 of 63 patients (25%) and were in the process of healing in 32 of 63 patients (51%). No unanticipated device-related adverse events were reported.

CONCLUSIONS

We found that transcatheter arterialization of the deep veins was safe and could be performed successfully in patients with chronic limb-threatening ischemia and no conventional surgical or endovascular revascularization treatment options. (Funded by LimFlow; PROMISE II study ClinicalTrials.gov number, NCT03970538.)

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Arterial revascularization is standard care for patients with chronic limb-threatening ischemia, the most advanced form of peripheral artery disease.[1-3] In the United States, the annual prevalence and incidence of chronic limb-threatening ischemia in patients over the age of 40 years are estimated to be 1.33% and 0.35%, respectively, which translates to up to 1 million patients in the Medicare population alone.[4,5] Despite advances in surgical and endovascular treatment, up to 20% of patients with chronic limb-threatening ischemia are not candidates for revascularization (referred to here as no-option),[5-7] primarily owing to the lack of an arterial target for distal runoff or an appropriate conduit for surgical bypass. Without the restoration of blood flow, no-option chronic limb-threatening ischemia that is characterized by pain, nonhealing wounds, and gangrene will progress to major (above-ankle) amputation in most cases.[8,9] Major amputation for chronic limb-threatening ischemia is associated with 50% mortality within a year after amputation in patients over 65 years of age; mortality is higher among patients with coexisting cardiovascular conditions.[10]

Transcatheter arterialization of the deep veins is an endovascular revascularization procedure for the treatment of no-option chronic limb-threatening ischemia.[11] When the procedure is performed in the lower limbs, an arteriovenous fistula is created proximal to the diseased tibial arteries with the use of a covered stent. The oxygenated blood is then diverted from the tibial arteries to the tibial veins to bypass the severely diseased arterial vasculature. The venous system is leveraged to deliver oxygenated arterial blood to the foot through the pedal veins, which potentially averts major amputation and promotes wound healing. The PROMISE I study established the feasibility of transcatheter arterialization of the deep veins for the treatment of no-option chronic limb-threatening ischemia.[11] We performed the PROMISE II study to expand on this work to evaluate the effect of the procedure on amputation-free survival and limb salvage as compared with an objective performance goal.

METHODS

STUDY DESIGN

PROMISE II was a prospective, single-group, multicenter study to evaluate the safety and effectiveness of transcatheter arterialization of the deep veins against an objective performance goal. The protocol (available with the full text of this article at NEJM.org) was designed by the sponsor (LimFlow) with input from the principal investigators and 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.

Clinical events were adjudicated by an independent committee, and an independent data and safety monitoring committee provided oversight. An independent core laboratory reviewed all wound images. Analyses were performed by the North American Science Association (a contract research organization) and Paradigm Biostatistics (committees are described in the Supplementary Appendix, available at NEJM.org). The authors had unrestricted access to the data; the first author wrote the first draft of the manuscript, and all the authors provided critical review. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol. No agreements existed between the sponsor and the authors and their institutions regarding confidentiality of the data, and the outcomes were to be published regardless of the results.

PATIENT POPULATION

Patients with chronic limb-threatening ischemia with no option for arterial revascularization were recruited and screened for eligibility on the basis of lower-limb angiography, vein mapping, and prespecified study inclusion and exclusion criteria (described in the Supplementary Appendix). Before enrollment, an independent physician review committee confirmed each patient's no-option status, defined as either the absence of a pedal artery target for endovascular or surgical therapy or the absence of a viable single segment of an autogenous vein conduit despite the presence of a pedal artery target that could receive a graft. Follow-up visits were scheduled at 2 weeks; at 1, 2, 3, 6, 9, and 12 months for the first year; and annually to year 3. The study team at each site was multidisciplinary and included vascular specialists and wound-care experts working in collaboration.

Patients with Rutherford class 5 (tissue loss or focal gangrene) or 6 (extensive gangrene) chronic

limb-threatening ischemia were eligible for enrollment; scores on the Rutherford scale range from 0 to 6, with higher numbers indicating worse disease. Patients with dialysis-dependent chronic kidney disease were included if they had autogenous access or were receiving peritoneal dialysis and met the criteria for clinical stability. Patients with systemic infection, rapidly deteriorating wounds, or advanced heart failure were excluded. The index transcatheter arterialization procedure was not permitted within 30 days after an earlier revascularization procedure to prevent confounding; however, endovascular procedures to provide access to the arterial segment proximal to the transcatheter arterialization circuit were allowed during the index procedure.

TREATMENT AND PROCEDURAL STEPS

The procedure involved the use of the LimFlow System (LimFlow), and all study physicians who performed the procedure received didactic and hands-on training. Before undergoing the procedure, patients received dual antiplatelet therapy, and the patency, diameter, and tortuosity of the lateral plantar veins were assessed with the use of duplex ultrasound. The lateral plantar vein was accessed through the plantar surface with the use of ultrasound guidance and standard Seldinger technique (Fig. 1). A wire was advanced from the lateral plantar vein to the proximal posterior tibial vein adjacent to the tibial artery that would be used for arterialization in the leg. The ipsilateral common femoral artery was then accessed

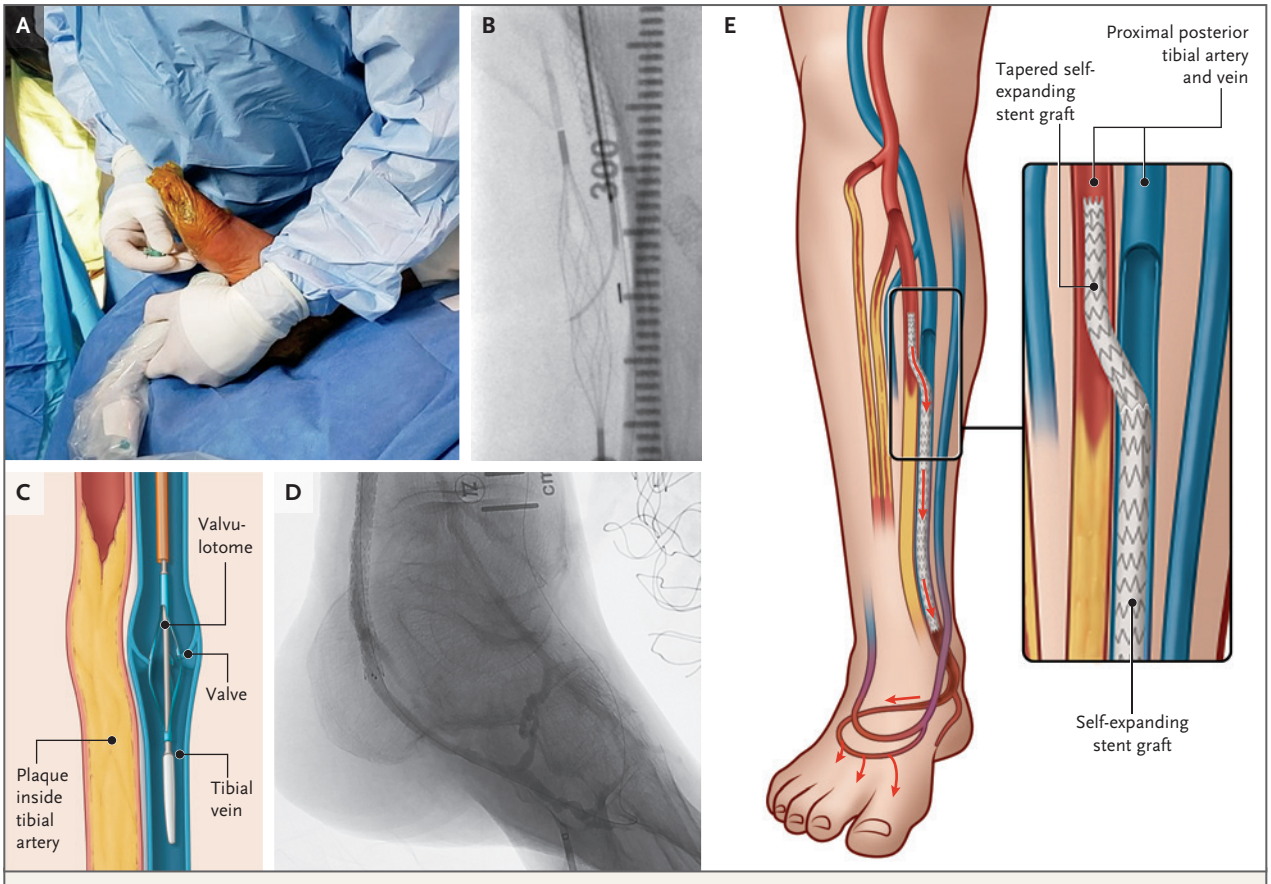


Figure 1. Key Procedural Steps for Transcatheter Arterialization of the Deep Veins.

The steps for transcatheter arterialization of the deep veins in the lower leg involve obtaining ultrasound-guided pedal vascular access (Panel A); advancing the needle into the mesh cage for establishment of arteriovenous crossing (the needle is in the arterial system and advances through the artery into the vein; the basket is in the vein) (Panel B); rendering venous valves incompetent with a push valvulotome (Panel C); deploying a straight covered stent at the level of the calcaneus (Panel D); and lining the vein with straight stents before placing a tapered, self-expanding, covered stent across the arteriovenous crossing to establish arterial blood flow in the venous system (Panel E).

with the use of an antegrade technique. The arterial and venous catheters were introduced into the common femoral artery and lateral plantar vein, respectively, and advanced to the desired crossing point, typically the proximal posterior tibial artery and a paired posterior tibial vein. With the use of a reentry catheter, the reentry needle was deployed from the artery into the mesh snare of the venous catheter that was positioned in parallel. A wire was then advanced and externalized through the pedal venous access site, which created through-and-through access. The arterial catheter was removed, and the artery-to-vein crossover point was dilated. The forward-cutting, coaxial valvulotome was inserted and advanced into the tibial vein to midfoot to render the venous valves incompetent. After successful valvulotomy, balloon dilatation of the tibial vein to the ankle was performed to avoid compression of the to-be-placed covered stent graft. The self-expanding stent grafts were deployed in the target vein from the cephalad calcaneal border to just distal of the crossover point. The procedure was completed with the placement of a tapered self-expanding stent graft across the artery-to-vein crossing point, and angiographic confirmation of adequate venous pedal outflow was obtained. Dilatation of the pedal venous loop was performed as needed to ensure adequate distal venous perfusion. Patients were prescribed dual antiplatelet or anticoagulant therapy for at least 3 months after undergoing the procedure.

PRIMARY AND SECONDARY END POINTS

The primary end point was amputation-free survival, defined as a composite of freedom from above-ankle amputation or death from any cause at 6 months. Secondary end points were primary patency of the transcatheter arterialization circuit (defined as the absence of occlusion of the endovascular intervention without the need for additional intervention), primary-assisted patency (the absence of occlusion of the endovascular intervention with the use of additional intervention, as long as occlusion of the primary treated site had not occurred), or secondary patency (absence of occlusion of the endovascular intervention that was maintained with the use of additional procedures after an occlusion occurred); limb salvage; change in Rutherford classification; technical and procedural success; healing of the target wound and all wounds; and wound area at 30 days and 6 months after the procedure. (Detailed descriptions of the secondary end points are provided in the Supplementary Appendix.) In addition, freedom from contrast-induced nephropathy, procedure time, radiation exposure, and contrast volume were collected periprocedurally. Serious adverse events (defined as events that were life-threatening; resulted in death, hospitalization, disability, or congenital abnormality; or necessitated an intervention) were reported by the investigators, reviewed by an independent medical monitor, and adjudicated by the clinical events committee.

STATISTICAL ANALYSIS

We used a Bayesian Goldilocks adaptive design for sample-size determination,[12] with possible sizes of 60, 75, 90, and 105 patients, which provided the study with at least 80% power when the probability of amputation-free survival was at least 0.68 and 90% power when the probability was at least 0.70. The statistical analysis plan allowed for early stopping of enrollment if amputation-free survival was very high or very low. Enrollment was concluded at 105 patients.

The primary end point of amputation-free survival at 6 months was evaluated against a prespecified performance goal of 54%, derived from the upper boundary of the confidence interval of 42% amputation-free survival reported among the patients with no-option chronic limb-threatening ischemia (descriptions of statistical analyses are provided in the Supplementary Appendix).[9] We assigned a uniform prior distribution for amputation-free survival at 6 months and updated that distribution on the basis of binary outcomes. We accounted for the effect of missing data with the use of multiple imputation. The standard of study success was a posterior probability exceeding 0.977, which controlled the false positive rate for the study at 0.025.

Prespecified subgroup analyses of sex, dialysis status, age (≤70 years or >70 years), presence of diabetes, race, ethnic group, and Rutherford class were performed. The effect of coronavirus disease 2019 (Covid-19) on patient mortality was considered, and a sensitivity analysis was performed. Baseline categorical variables were summarized with the use of descriptive statistics, including the number of observations and percentages. Continuous variables were summarized as medians with interquartile ranges. Kaplan–

Meier estimates were used to calculate time-to-event variables. Because the statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for secondary or other outcomes, results are reported as point estimates only. Data preparation and statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute), and R software, version 3.6.1 (R Project for Statistical Computing).

RESULTS

PATIENTS AND PROCEDURAL CHARACTERISTICS

Between December 2019 and March 2022, a total of 219 patients underwent screening, and 105 were enrolled in the study across 20 sites in the United States (Fig. S1 in the Supplementary Appendix). The median age of the patients was 70 years (interquartile range, 38 to 89), 33 (31.4%) were women, and 45 (42.8%) were Black, Hispanic, or Latino. Most patients had several preexisting conditions associated with chronic limb-threatening ischemia, including diabetes, hypertension, and dyslipidemia, and 78 patients (74.3%) had undergone previous revascularization procedures on the index limb (Table 1). All the patients presented with a nonhealing ulcer or frank gangrene and were classified as Rutherford class 5 (68 patients) or class 6 (37 patients). Our study included 19 patients with dialysis-dependent chronic kidney disease (18.1%) who had either a stable arteriovenous fistula or were receiving peritoneal dialysis. A total of 102 patients (97.1%) with no treatment option had no runoff target for traditional intervention, and 3 (2.9%) did not have a usable autogenous conduit.

The transcatheter arterialization procedure was technically successful in 104 of 105 patients (99.0%), with no unanticipated adverse device events. The patient who did not have a successful procedure was followed for safety through 6 months and withdrew from the study as prespecified in the protocol. The posterior tibial artery was the most common target for arteriovenous crossing location (75.2%), followed by the peroneal artery (19.0%) and the tibioperoneal trunk (5.7%) (Table 2).

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	All Patients (N=105)
Median age (range) — yr	70 (38–89)
Male sex — no. (%)	72 (68.6)
Race — no. (%)†	
White	64 (61.0)
Black or African descent	16 (15.2)
Asian	2 (1.9)
Unknown or declined to state	23 (21.9)
Ethnic group — no. (%)†	
Not Hispanic or Latino	76 (72.4)
Hispanic or Latino	29 (27.6)
Median body-mass index (range)‡	26.2 (18.0–48.8)
History of smoking — no. (%)	44 (41.9)
Current	6 (5.7)
Former	38 (36.2)
Previous stroke — no. (%)	9 (8.6)
Previous myocardial infarction — no. (%)	24 (22.9)
Hypertension — no. (%)	96 (91.4)
Dyslipidemia — no. (%)	73 (69.5)
Diabetes mellitus — no. (%)	81 (77.1)
Type I	11 (10.5)
Type II	70 (66.7)
Chronic kidney disease — no. (%)	41 (39.0)
Dialysis — no. (%)	19 (18.1)
Rutherford classification — no. (%)§	
Stage 5	68 (64.8)
Stage 6	37 (35.2)
Previous intervention in target limb — no. (%)	78 (74.3)

* Percentages may not total 100 because of rounding.
† Race and ethnic group were reported by the patient or abstracted from medical records.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The Rutherford scale ranges from 0 to 6, with higher numbers indicating worse disease.

END POINTS

Follow-up was completed in 102 of 105 patients (97.1%) at 6 months (1 patient was lost to follow-up, and 2 withdrew). A total of 23 patients underwent major amputation, and 12 died.

Amputation-free survival at 6 months (the primary end point) estimated by the mean of the posterior distribution was 0.66, with a 95% Bayesian credible interval of 0.565 to 0.745. The posterior probability that this rate exceeded the performance goal of 0.54 was 0.993, which was greater than the prespecified success criterion of 0.977. Amputation-free survival estimated with

Table 2. Procedural Characteristics of Transcatheter Arterialization of the Deep Veins.*

Characteristic	All Patients (N=105)
Technical success — no. (%)	104 (99.0)
Arteriovenous crossing target vein location — no. (%)	
Peroneal vein	6 (5.7)
Posterior tibial vein	99 (94.3)
Arteriovenous crossing target artery location — no. (%)	
Peroneal artery	20 (19.0)
Posterior tibial artery	79 (75.2)
Tibioperoneal trunk	6 (5.7)
Reintervention within 6 mo after procedure — no./total no. (%)	38/104 (36.5)

* Percentages may not total 100 because of rounding.

the use of the Kaplan–Meier method was 66.1%. The percentages of limb salvage and survival were 76.0% and 87.1%, respectively (Fig. 2).

Prespecified subgroup analyses showed no material differences between the groups (Fig. S2), with the exception that 19 patients with dialysis-dependent chronic kidney disease had amputation-free survival of 36.8%, whereas the 86 patients who did not have dialysis-dependent chronic kidney disease had amputation-free survival of 72.7%. The mortality among patients who had dialysis-dependent chronic kidney disease was 36.2% as compared with 8.6% among patients who did not have dialysis-dependent chronic kidney disease.

At 6 months, the percentages of primary patency, primary-assisted patency, and secondary patency were 25.9%, 45.4%, and 64.2%, respectively. Repeat interventions to address native arterial disease and flow optimization within the transcatheter arterialization circuit occurred in 38 patients (36.5%). A decrease in Rutherford class was observed in 27 of 64 patients (42%). The median procedure time was 199 minutes, the median radiation exposure was 195 mGy, and the median amount of iodinated contrast used in the procedures was 127 milliliters. At 72 hours postprocedure, 103 patients (98.1%) were free from contrast-induced nephropathy. Procedural success (technical success with absence of death, major amputation, or reintervention at 1 month) occurred in 80 patients (76.9%) (Table S1).

WOUND HEALING

The median primary wound area at baseline and at 6 months was 3.9 cm^2 (interquartile range, 1.7 to 9.3) and 1.0 cm^2 (interquartile range, 0.0 to 3.6), respectively. Since the study included patients with extensive gangrene and tissue loss, minor amputations, such as amputation of toes (40 amputations in 30 patients) and transmetatarsal amputations or revisions (51 in 41 patients) were allowed and expected. At 6 months, target wounds were completely healed in 16 of 63 patients (25%), and all wounds were completely healed in 24 of 86 patients (28%). Target wounds were categorized as being in the process of healing in 32 of 63 patients (51%) (Fig. 3 and Figs. S3, S4, and S5).

ADVERSE EVENTS

No unanticipated adverse device-related events were reported. A total of 98 of 105 patients (93.3%) had an adverse event (Table S2).

DISCUSSION

In this prospective study involving patients with chronic limb-threatening ischemia and no conventional surgical or endovascular revascularization treatment options, transcatheter arterialization of the deep veins was successfully performed in 104 of 105 patients (99.0%), was associated with 66.1% amputation-free survival, and improved wound healing with complete healing in 16 patients (25.4%) and partial wound healing in 32 patients (50.8%) at 6 months. Results appeared consistent among the subgroups, with the exception that among patients with dialysis-dependent chronic kidney disease, amputation-free survival occurred in a smaller proportion and death occurred in a greater proportion.

Relieving ischemia by arterializing the deep veins is not a new concept, having first been hypothesized and attempted more than 100 years ago and evaluated in multiple open surgical series.[13-15] However, the surgical technique was associated with several complications, including infection, deep incisions to create anastomosis, difficulty in lysing valves in the target vein, and difficulty in prevention of a steal phenomenon (diversion of blood flow away from the affected area) from venous branches at the calf and ankle.[16] Transcatheter arterialization addresses some of the limitations that resulted in failure in earlier surgical attempts. The transcatheter arteri-

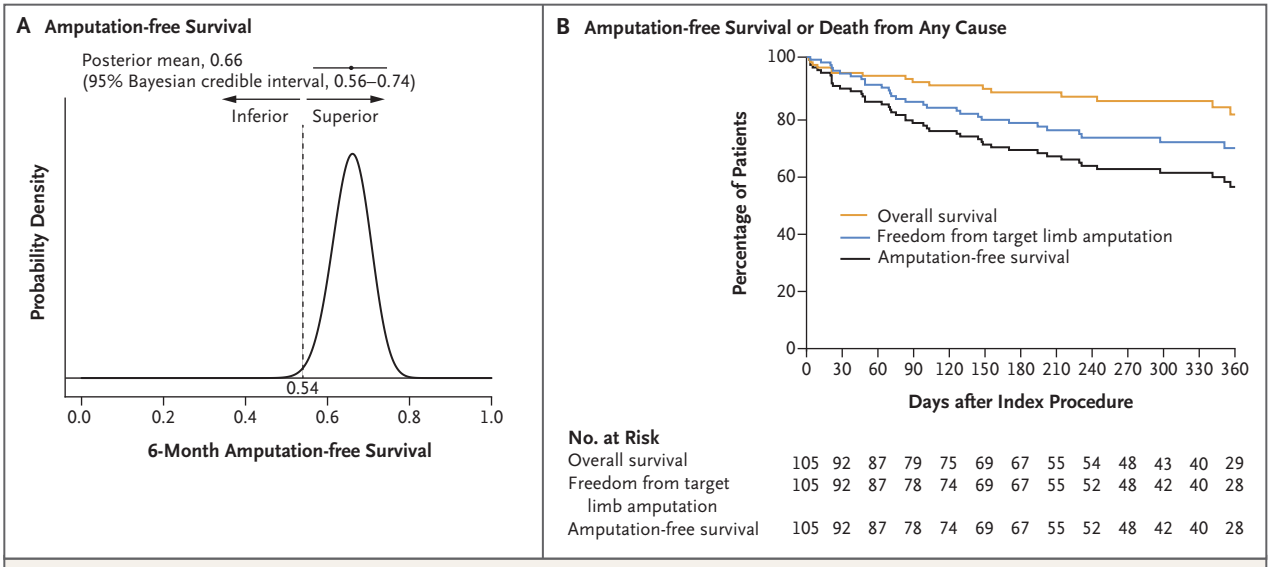


Figure 2. Survival and Freedom from Amputation.

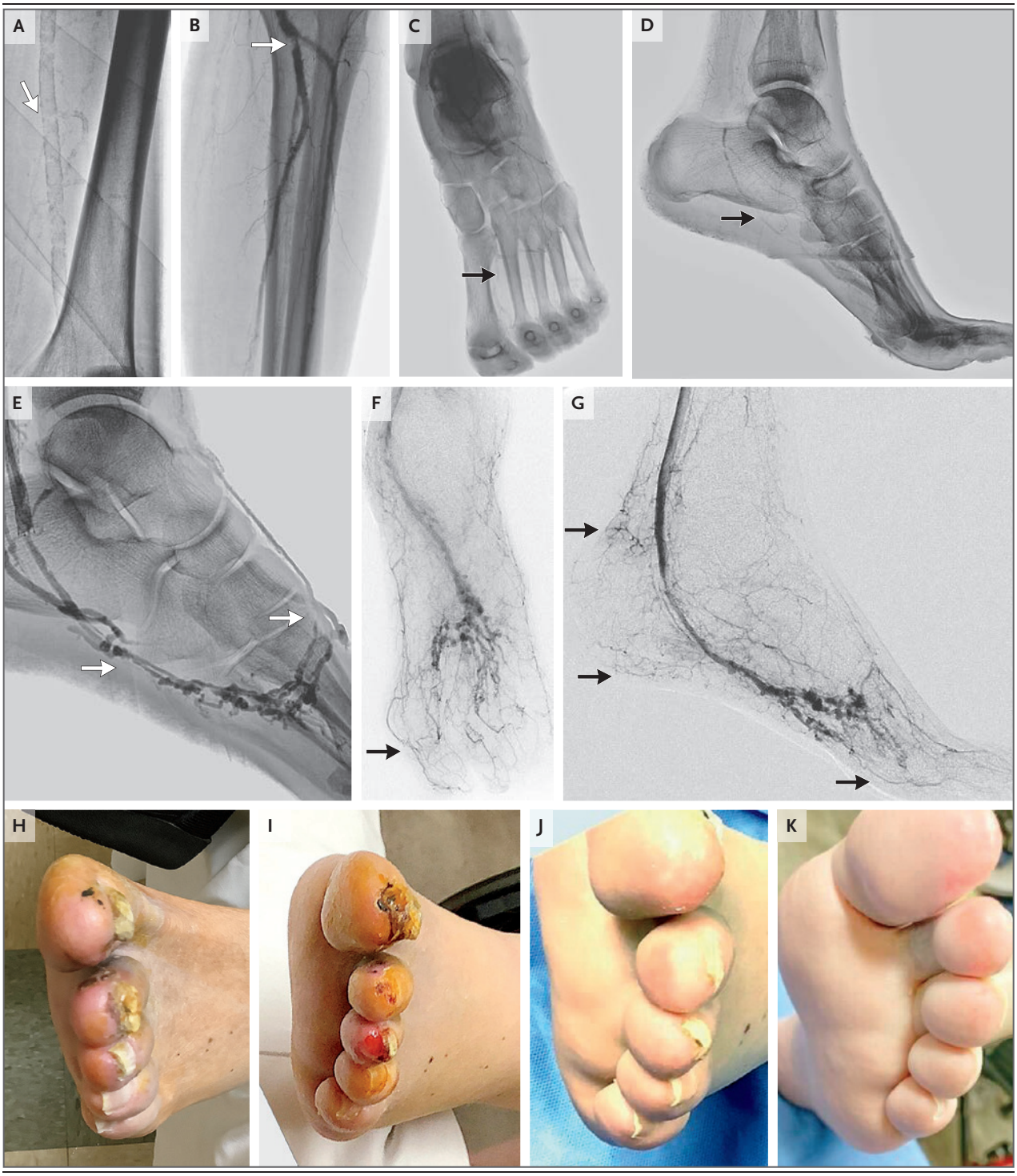
Panel A shows the posterior probability distribution for the primary end point of 6-month amputation-free survival (defined as freedom from amputation or death from any cause). The mean of the distribution is 0.66. The 95% Bayesian credible interval ranges from the 2.5th to the 97.5th percentiles of the distribution. The posterior probability that the 6-month amputation-free survival exceeds the performance goal of 0.54 was 0.993, represented by the area under the curve and to the right of 0.54. Panel B shows Kaplan–Meier estimates of the composite primary end point of amputation-free survival and its components.

alization endovascular technique circumvents an open incision and directs arterial blood to the pedal venous arch without diversion through the venous branches. Antegrade valvulotomy allows for the ablation of venous valves in the pedal loop that would otherwise hinder adequate blood flow to the distal foot. In addition, venous congestion as a side effect of the procedure has not been observed. The transcatheter arterialization procedure allows oxygenated blood to reach the distal foot by way of the venous system while addressing the limitations of surgical arterialization of deep veins.

Early prospective pilot studies in Singapore and Europe supported European Certificate of Conformity (known as the CE mark) approval and led to the PROMISE I early feasibility study in the United States.[17-19] Results across all studies were consistent, with the pilot studies that were performed outside the United States showing percentages of 6-month and 12-month amputation-free survival of 83.9% and 71.0%, respectively; 6- and 12-month amputation-free survival was 74% and 70%, respectively, in the PROMISE I study.[11,19,20] Patients who were enrolled in the PROMISE II study were representative of real-world patients (Table S3), including those with dialysis-dependent chronic kidney disease and Rutherford class 5 or 6 wounds, who are routinely excluded from vascular device studies. Beyond the presence of routine coexisting conditions, including diabetes, 74.3% of the patients had a history of previous unsuccessful revascularization procedures of the index limb, which indicated that this complex cohort of patients included those with limb pain, nonhealing wounds, and gangrene who were probably at risk for major amputation.

Results of a prespecified subgroup analysis were aligned with those of previously published outcomes indicating an increased risk of death after peripheral arterial revascularization procedures among patients who were undergoing dialysis.[21,22] Although the incidence of limb salvage was similar between patients who had dialysis-dependent chronic kidney disease and those who did not, mortality appeared to be greater in the population with dialysis-dependent disease. The decision to offer transcatheter arterialization of the deep veins to patients with dialysis-dependent chronic kidney disease should take into consideration life expectancy and patient preferences.

An important aspect of the PROMISE II study was the analysis of the independent multidisci-



plinary physician review committee, which confirmed the patient's no-option status before enrollment. However, the presence of no-option chronic limb-threatening ischemia is associated with several variables beyond anatomy alone. Access to subspecialty care, geographic location, and socioeconomic status all contribute to a real-world lack of peripheral artery revascularization and an increased incidence of major amputation. The transcatheter arterialization procedure may ad-

Figure 3 (facing page). Transcatheter Arterialization in a Patient with Chronic Limb-Threatening Ischemia.

A 72-year-old man with type II diabetes mellitus, hypertension, severely calcified peripheral arteries, and contralateral amputation due to chronic limb-threatening ischemia that was classified as Rutherford stage 5 (scale ranges from 0 to 6, with higher numbers indicating worse disease) with ulcers of the hallux and the second and third digits that were present for 24 months underwent transcatheter arterialization of the deep veins of his left foot. Panels A through D show baseline angiographic imaging that revealed calcified peripheral arteries (white arrows) and small-caliber plantar metatarsal vessels (black arrows) that were not amenable to traditional revascularization procedures. Panel E shows an angiogram obtained after the establishment of the transcatheter arterialization circuit, with some vessel spasm (white arrows) seen in the lateral plantar vein. Panels F and G show angiographic imaging at 24 months, which reveal newly appreciated vascular anatomy (black arrows) of the foot. Panels H through J show the progression of wound healing after transcatheter arterialization, and Panel K shows sustained healthy tissue at 24 months. Brightness was adjusted in the angiographic images to allow better visualization of the vasculature.

dress some of these issues by removing the anatomical barriers to revascularization by allowing for restoration of blood flow to the foot in patients who otherwise would have no option for treatment.

The increasing number of patients with chronic limb-threatening ischemia represents a large burden for the health care system and a reduced quality of life and life expectancy for patients. Major amputation results in loss of mobility and a host of secondary effects, including deconditioning, depression, and social isolation, and has been associated with an increased risk of death.[23] Revascularization and limb salvage avert this trajectory and have been shown to be more cost effective than amputation.[24] The introduction of transcatheter arterialization provides the possibility of revascularization in patients with no-option chronic limb-threatening ischemia who previously were consigned to primary amputation, thus potentially reducing the resulting illness, death, and economic burden of amputation.

Our study has several limitations, including the lack of a control group; however, random assignment of patients destined for major amputation was practically and ethically unfeasible. The study continuously enrolled patients during the Covid-19 pandemic, with 12 reported infections and 5 deaths adjudicated by the clinical events committee as being related to Covid-19. In addition, transcatheter arterialization was performed by experienced interventional cardiologists and vascular surgeons who underwent training to perform the procedures, and the procedure may be available only at a specialist center. In addition, follow-up was limited to 12 months, and the number of patients dependent on dialysis was small.

We found that transcatheter arterialization of the deep veins was safe and could be performed with a high degree of procedural success in patients with chronic limb-threatening ischemia and no conventional surgical or endovascular revascularization options to promote wound healing and prevent major amputation.

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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.

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Supplementary Appendix

Supplement to: Shishehbor MH, Powell RJ, Montero-Baker MF, et al. Transcatheter arterialization of deep veins in chronic limb-threatening ischemia. N Engl J Med 2023;388:1171-80. DOI: 10.1056/NEJMoa2212754

This appendix has been provided by the authors to give readers additional information about the work.

Table of Contents

PROMISE II Sites, Investigators, and Operators

Institution	Subjects Enrolled	Primary Investigator(s)	Primary Operators, Number of Procedures Performed
Baylor College of Medicine	12	Joseph Mills Miguel Montero-Baker	Miguel Montero-Baker, 12
Ponce Health Sciences University	12	Jorge Martínez-Trabal	Jorge Martinez-Trabal, 11 Rafael Santini, 1
Dartmouth-Hitchcock Medical Center	11	Richard Powell	Richard Powell, 11
Massachusetts General Hospital	9	Anahita Dua	Anahita Dua, 9
Coastal Carolina Surgery	7	David Weatherford	David Weatherford, 7
UH Cleveland Medical Center	7	Mehdi Shishehbor	Medhi Shishehbor, 7
The Cardiac and Vascular Institute	6	Arthur Lee	Arthur Lee, 6
Prisma Health Upstate and Midlands	6	Daniel Clair Bruce Gray Dimitrios Virvilis Sagar Gandhi	Bruce Gray, 1 Daniel Clair, 2 Dimitrios Virvilis, 2 Sagar Gandhi, 1
Saint Luke's Hospital of Kansas City	6	Matthew Bunte	Matthew Bunte, 6
Sanger Heart & Vascular Institute	5	Gregory Stanley	Gregory Stanley, 5
Vanderbilt University Medical Center	4	Patrick Stone Daniel Clair	Daniel Clair, 3 Mark Iafrati, 1
Harbor-UCLA Medical Center	4	Mark Archie	Mark Archie, 1 Nikhil Kansal, 2 Nina Bowens, 1

Boston Medical Center	4	Alik Farber	Alik Farber, 4
UnityPoint Health	3	Eric Scott	Eric Scott, 3
Seton Heart Institute	3	Lucas Ferrer	Lucas Ferrer, 3
Ochsner Medical Center	2	Zola N’Dandu	Zola N'Dandu, 2
University of California San Francisco	2	Michael Conte	Shant Vartanian, 2
New Mexico Heart Institute	1	Esteban Henao Trent Proffitt	Trent Proffitt, 1
Yale University	1	Cassius Iyad Ochoa Chaar	Jonathan Cardella, 1
University of Florida	0	Ben Jacobs	--

Study Committees

Committee:	**Contracted through:**
Independent Review Committee	NAMSA (formerly Syntactx) 4 World Trade Center; 44th Floor 150 Greenwich St. New York, NY 10006 https://namsa.com
Independent Clinical Events Committee	
Independent Data Monitoring Committee	
Independent Wound Core Lab	
Independent Statistical Analysis	

Committee:	**Contracted through:**
Independent Bayesian Statistical Analysis and Study Design	Paradigm Biostatistics, LLC 1288 Benton St Anoka, MN 55303 https://paradigm-biostat.com

Conflicts of Interest Disclosures

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MHS: Advisory and consultant for Abbott Vascular, Medtronic, Terumo, Boston Scientific, Philips, ANT, Inquis Medical.

RJP: No disclosures.

MMB: Educational consultant for Boston Scientific, Cook Medical, Veryan, LimFlow. Stock/Owner: HENDOLAT, HENDOSYN, Euphrates.

AD: Educational consultant for Boston Scientific, Abbott, Penumbra, Gore.

JMT: No disclosures.

MCB: Consultant for Abbott Vascular, Shockwave Medical, and Inari Medical. Institutional research support from Inari Medical.

ACL: No disclosures.

ASM: Statistical consulting and/or DSMB services for Abbott Vascular, Boston Scientific, Endospan, LimFlow, Medtronic, TriReme Medical.

JLM: Advisory Board for Xylocor.

AF: Consultant for Sanifit.

DGC: Advisory and consultant for Boston Scientific, Bard Peripheral Vascular, Medtronic, LimFlow.

Supplementary Methods

PROMISE II Inclusion and Exclusion Criteria

Inclusion Criteria:

1) Subject must be ≥ 18 and ≤ 95 years of age.

2) Clinical diagnosis of chronic limb-threatening ischemia, defined as any of the following clinical assessments: previous angiogram or hemodynamic evidence of severely diminished arterial inflow of the index limb (e.g., ankle-brachial index [ABI] ≤ 0.39, toe pressure [TP] / transcutaneous oximetry [TcPO2] < 30 mm Hg) and

    a) Rutherford Classification 5, ischemic ulceration or

    b) Rutherford Classification 6, ischemic gangrene

3) Subject has been assessed by the Principal Investigator, reviewed by the Independent Review Committee (IRC), and determined that no conventional distal bypass, surgical or endovascular therapy for limb salvage is feasible due to either a) absence of a usable pedal artery target (endovascular or surgical approach), or b) the presence of a pedal artery target with absence of a viable single-segment vein in either lower extremity or either arm that could be used for autogenous vein conduit.

4) Proximally, the target in-flow artery at the cross-over point must fall within the recommended vessel diameter ranges for the LimFlow stent graft by visual estimation.

5) Prior stent(s) to the infrainguinal arteries (e.g., iliac, superficial femoral artery, and popliteal) are allowed.

6) Planned minor amputation (e.g., partial toe, ray or proximal foot/transmetatarsal) of target

extremity within 30 days after the index procedure is allowed.

7) Subject is willing and able to sign the informed consent form.

8) Subject is enrolled in an acceptable wound care network and has an adequate support network to ensure that subject is compliant with medication regimen and follow-up study visits.

9) Prior to enrollment (7-day window), women of childbearing potential must have a negative pregnancy test.

10) Primary wound is stable (e.g., not rapidly deteriorating and/or showing signs of healing).

11) Stable glycemic control, HbA1C < 10% (<269mg/dL).

12) Subjects requiring dialysis may be included, provided they meet *all* the following requirements:

    - On dialysis for ≥ 6 months
    - Autologous arteriovenous (AV) fistula or peritoneal access used for hemodialysis
    - Serum albumin ≥ 30 g/liter
    - BMI ≥ 20

Exclusion Criteria:

Subjects will be excluded from participating in this study if they meet any of the following criteria prior to initiation of the endovascular procedure:

1) Concomitant hepatic insufficiency, thrombophlebitis in the target limb, or non-treatable coagulation disorder within the past 90 days.

2) Active immunodeficiency disorder or currently receiving immunosuppressant therapy for an immunodeficiency disorder.

3) Prior peripheral arterial bypass procedure above or below the knee which would inhibit proximal inflow to the stent graft or interventional revascularization procedure within 30 days.

4) Previous major amputation of the target limb or presence of a wound requiring a free flap or absence of adequate viable tissue.

5) Life expectancy less than 12 months.

6) Documented myocardial infarction or stroke within previous 90 days.

7) Active infection (e.g., fever, significantly elevated WBC count >20.0 x 10^9/L, and/or positive blood culture) at the time of the index procedure that may preclude insertion of a prosthesis or require major amputation (e.g., osteomyelitis proximal to metatarsals).

8) Known or suspected allergies or contraindications to aspirin or $P2Y_{12}$ inhibitors, heparin, stainless steel, nitinol, or contrast agent that cannot be adequately pre-treated.

9) Subject is currently taking anti-coagulants, which in the opinion of the investigator, interferes with the subject's ability to participate in the study (i.e., intermittent interruption of therapy for procedure may compromise subject's safety).

10) Lower extremity vascular disease that may inhibit the procedure and/or jeopardize wound healing (e.g., vasculitis, Buerger's disease, significant edema in the target limb, deep venous thrombus in the target vein, hyperpigmentation, or medial ulceration above the ankle).

11) Significant acute or chronic kidney disease with a serum creatinine of > 2.5 mg/dl in subjects

not undergoing dialysis.

12) Severe heart failure (e.g., New York Heart Association Class IV), which in the opinion of the investigator may compromise subject's ability to safely undergo a percutaneous procedure.

13) Any significant concurrent medical, psychological, or social condition, which may significantly interfere with the subject's optimal participation in the study, in the opinion of the investigator.

14) The subject is currently participating in another investigational drug or device study that has not completed the primary endpoint or that clinically interferes with the endpoints of this study.

15) Subject is unwilling, unable, or unlikely for cognitive or social reasons to comply with any of the protocol or follow-up requirements.

PROMISE II Primary and Secondary Endpoints

Primary Endpoint:

Amputation free survival defined as freedom from major amputation and death (defined below) at 6 months, compared to a historical performance goal.

Major Amputation: above-ankle amputation of the index limb *and*

Death: all-cause mortality

Secondary Endpoints:

Primary Patency: Defined as absence of occlusion of the endovascular intervention that is maintained without the need for additional or secondary surgical or endovascular procedures, at 30 days and 6 months.

Primary Assisted Patency: Defined as absence of occlusion of the endovascular intervention maintained with the use of additional or secondary surgical or endovascular procedures, as long as occlusion of the primary treated site has not occurred, at 30 days and 6 months.

Secondary Patency: Defined as absence of occlusion of the endovascular intervention that is maintained with the use of additional or secondary surgical or endovascular procedures after occlusion occurs, at 30 days and 6 months.

Limb Salvage: Defined as percentage of subjects with freedom from above-ankle amputation of the index limb, evaluated at 30 days, 3 and 6 months.

Technical Success: Defined as the successful creation of an arteriovenous fistula in the desired limb location with immediate morphological success.

Change in Rutherford Classification: Defined as a change of one class or greater, as evaluated

at 30 days, 3 and 6 months.

Procedural Success: Defined as the combination of technical success, and absence of all-cause death, above-ankle amputation or clinically driven major re-intervention (the creation of a new surgical bypass, the use of thrombectomy or thrombolysis [i.e., procedures done in the setting of lost primary-assisted patency], or major surgical revision such as a jump graft or an interposition graft performed for occlusion of the stent graft) of the stent graft at 30 days.

Target Wound Healing: Defined as complete healing of the patient's target wound as evaluated at 30 days; and 3, 6, and 9 months; and 1 year.

All Wound Healing: Defined as complete healing of the patient's wounds as evaluated at 30 days; and 3, 6, and 9 months; and 1 year

All Wound Area Reduction: Defined as reduction in area of the patient's wounds as evaluated at 30 days; and 3, 6, and 9 months; and 1 year.

Freedom from Contrast-Induced Nephropathy: Defined as subjects without acute (within 72 hours after intravenous contrast administration) impairment of renal function, measured as an absolute ≥0.5 mg/dL (44 μmol/L) increase compared to baseline serum creatinine value that results in a value above the upper limit of the normal range.

Procedure Time: Defined as the time of the first puncture (venous or arterial) to when the last catheter is removed.

Radiation Exposure: Defined as patient radiation exposure (in milligray) during the procedure.

Contrast Volume: Defined as the total volume of contrast media (in milliliters) given during the procedure.

Supplementary Statistical Analyses

Performance Goal Derivation

A literature search was performed by the Yale Clinical Research Group (YCRG) according to a pre-specified protocol, and the search methods and results have been documented in a Literature Search Report ("Literature Search Report for the LimFlow System" Version 1.0 dated 19 December 2017). The literature search identified 36 publications meeting inclusion criteria that reported amputation-free survival, the composite of all-cause death or major (above-the-knee) amputation, all-cause mortality, major amputation, or wound healing in no-option chronic limb-threatening ischemia subjects (patient with chronic limb-threatening ischemia Rutherford score > 4 that are inoperable) who were receiving the standard of care (medication) or placebo.

Of the 36 publications, 27 publications reported the 6- or 12-month rate of amputation-free survival (or the composite of all-cause mortality or major amputation, which was converted into amputation-free survival) and contributed to the meta-analysis. Of these, 23 studies reported amputation-free survival at 6 months, and 19 reported amputation-free survival at 12 months.

In a review of the studies used for developing the performance goal, some noted that the studies that used Fontaine IV for the classification of critical limb ischemia had the highest amputation-free survival rates. Fontaine IV is a clinical assessment only, and though it is associated with Rutherford 5 and 6, it is less specific (see the figure below).

The specificity of the Rutherford classification assures that the population enrolled in the studies will have the level of disease expected in the TADV clinical trial. In studies that used the Fontaine classification, the lack of specificity and objective criteria can lead to a broader population being included that might be considered Rutherford class 4 not included in the current study.

Comparison of Rutherford and Fontaine Classification Systems

Fontaine Grade	Symptoms	Grade	Category	Clinical Description	Objective Criteria
Stage I	Asymptomatic, incomplete blood vessel obstruction	0	0	Asymtomatic – no hemodinamically significant occlusive disease	Normal treadmill* or reactive hyperthermia test
			1	Mild claudication	
Stage II	Mild claudication pain in limb	I	2	Moderate claudication	Resting AP<60mmHg, ankle or metatarsal PVR flat or barely pulsatile; TP < 40mmHg
			3	Severe claudication	
Stage III	Rest pain, mostly in the feet	II	4	Ischemic rest pain	Complete treadmill exercise; AP after exercise >50 mmHg ≥20mmHg lower than resting value
Stage IV	Necrosis and/or gangrene of the limb	III	5	Minor tissue loss – nonhealing ulcer; focal gangrene with diffuse pedal ischemia	Resting AP<60mmHg, ankle or metatarsal PVR flat or barely pulsatile; TP < 40mmHg
			6	Major tissue loss – extending transmetatarsally; functional foot no longer salvageable	

Studies that only used the Fontaine classification were compared to those that only used the Rutherford classification (Table) using logistic regression. The SAS code was:

```
proc logistic data=limlos_adj;
class study status class;
freq num;
model status(event='no event')= class;
run;
```

where status is whether there was a death or major amputation event at 6 months or not, the class was the chronic limb-threatening ischemia classification system used (Rutherford or Fontaine classification system), and num is the variable that contains the number of subjects with or without an event.

Results of logistic regression predicting amputation-free survival using chronic limb-threatening ischemia classification method

The results of the logistic regression are shown in the table below. The classification system effect has a low p-value ($p < 0.0001$) and an odds ratio (Rutherford 5 or 6 versus Fontaine IV) of 2.891.

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	0.5020	0.0766	42.9900	<.0001
Class	**FIV**	1	0.5308	0.0766	48.0546	<.0001

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
Class FIV vs R56	2.891	2.141	3.903

DF denotes degrees of freedom, FIV Fontaine class IV, R56 is Rutherford class 5 or 6.

The 6-month amputation-free survival rates in studies shown in the Table (below; reprint from Yale Clinical Research Group) that used the Fontaine classification were adjusted in two ways: a) the average of the percentage of Rutherford class 5 or 6 in the other studies as reported in b) the odds ratio. The adjusted numbers were very similar between the two methods so for this document, the odds ratio adjusted numbers will be used. After the odds ratio adjustments, the final amputation-free survival rate point estimate was 42.0% with an upper 95% confidence limit of 51.2%. However, in acknowledgement of the Food and Drug Association's concern around the performance goal and the previous discussions since 2017, LimFlow is not proposing to change the previously communicated performance goal based on the prior work from the Yale Clinical

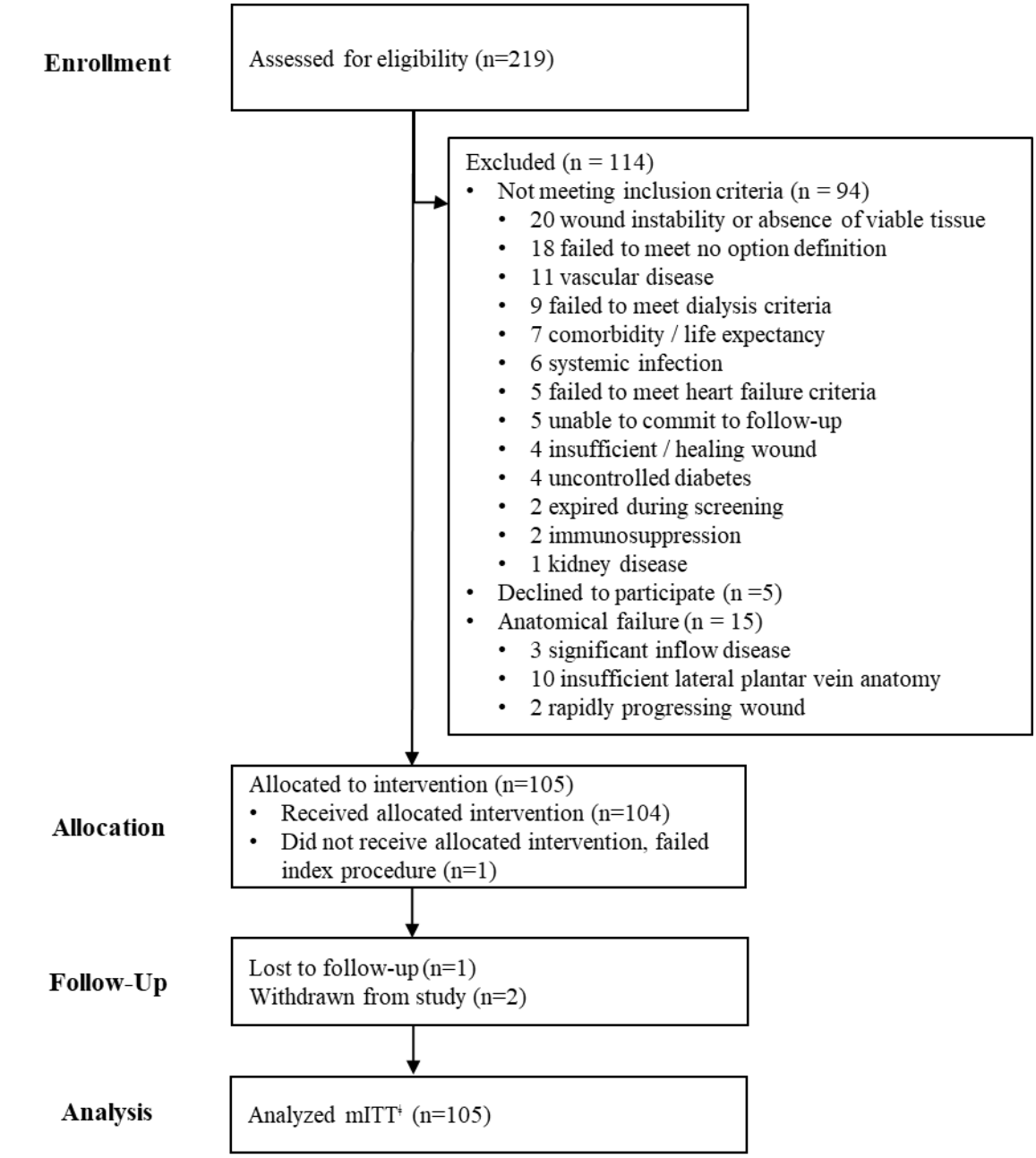
Research Group where the amputation-free survival rate point estimate was 43.7%, with an upper 95% confidence limit of 53.5%. Since the hypothesis test for this study is a test for superiority, the performance goal is set at the upper 95% confidence limit of 53.5%, rounded up to 54%.

Meta-analysis of 6-month amputation-free survival rate in no-option patients with Rutherford category 5 or 6 chronic limb ischemia

Study	N	Event-free survivors (n)	Observed AFS Rate	Included Rutherford Categories	Observed Proportion R4	Observed Proportion R 5/6	Imputed Proportion R 5/6	Adjusted AFS Rate
Brass et al 2006[1]	177	146	82.5%	4, 5, 6	NR	NR	66.9%	59.3%
Teraa et al. 2015[2]	79	66	83.5%	3, 4, 5, 6	31.6%	63.3%	NA	58.3%
Dubsky et al. 2013[3]	22	10	45.5%	4, 5, 6	NR	NR	66.9%	32.7%
Iafrati et al. 2016[4]	34	22	64.7%	5	0.0%	100.0%	NA	64.7%
Anghel et al. 2011[5]	14	3	21.4%	4,5	50.0%	50.0%	NA	13.5%
Li et al. 2013[6]	29	23	79.3%	4, 5, 6	NR	NR	66.9%	57.0%
Benoit et al. 2011[7]	14	9	64.3%	4,5	50.0%	50.0%	NA	40.4%
Gupta et al. 2013[8]	10	8	80.0%	4, 5, 6	20.0%	80.0%	NA	64.7%
Szabo et al 2013[9]	10	4	40.0%	4, 5, 6	NR	NR	66.9%	28.8%
Belch et al. 2011[10]	259	196	75.7%	4, 5, 6	NR	NR	66.9%	54.4%
Losordo et al. 2012[11]	12	8	66.7%	4,5	41.7%	58.3%	NA	44.7%
Nikol et al. 2008[12]	56	34	60.7%	4, 5, 6	NR	NR	66.9%	43.7%
Powell et al. 2012[13]	24	17	70.8%	4, 5, 6	NR	NR	66.9%	50.9%
Idei et al. 2011[14]	30	3	10.0%	4, 5, 6	27.0%	73.0%	NA	7.6%
Pignon et al. 2017[15]	19	14	73.7%	4,5	35.0%	65.0%	NA	52.1%
Wang et al. 2018[16]	36	28	77.8%	4,5	66.7%	33.3%	NA	43.5%
Faglia et al. 2010[17]	27	3	11.1%	4,5,6	37.0%	63.0%	NA	7.7%
Dalla Paola et al. 2019[18]	84	50	59.5%	4,5,6	NR	NR	66.9%	42.8%
Dubsky et al. 2019[19]	44	31	70.5%	4,5,6	NR	NR	66.9%	50.7%
Faglia et al. 2012[20]	12	3	25.0%	5.6	0.0%	100.0%	NA	25.0%
Simple Average			58.1%				**Simple Average**	42.1%
Weighted Average			68.3%				**Weighted Average**	49.2%
Meta-Analytic Average			**58.6 %**				**Meta-Analytic Average**	**42.0 %**
Min			10.0%				**Min**	7.6%
Max			83.5%				**Max**	64.7%
SD			24.1%				**SD**	17.7%

Statistical methods used for the meta-analysis are reported in Ghare et al.[21]

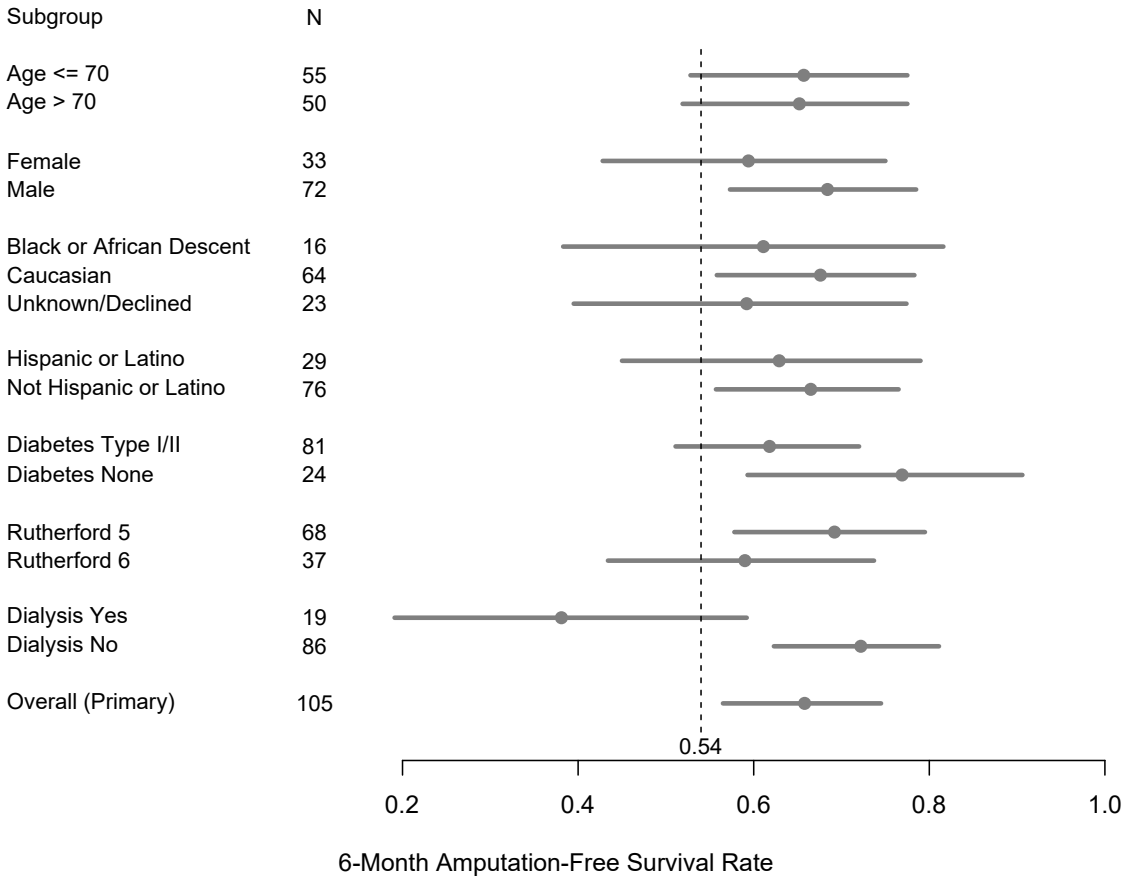
Figure S1. CONSORT Diagram



mITT denotes modified intention-to-treat analysis

Randomization, Treatment, and Follow-up. Patients with Rutherford Class V or VI no-option chronic limb-threatening ischemia were enrolled in a nonrandomized fashion.

Figure S2. Forest Plot of 6-Month Amputation-Free Rate by Subgroups



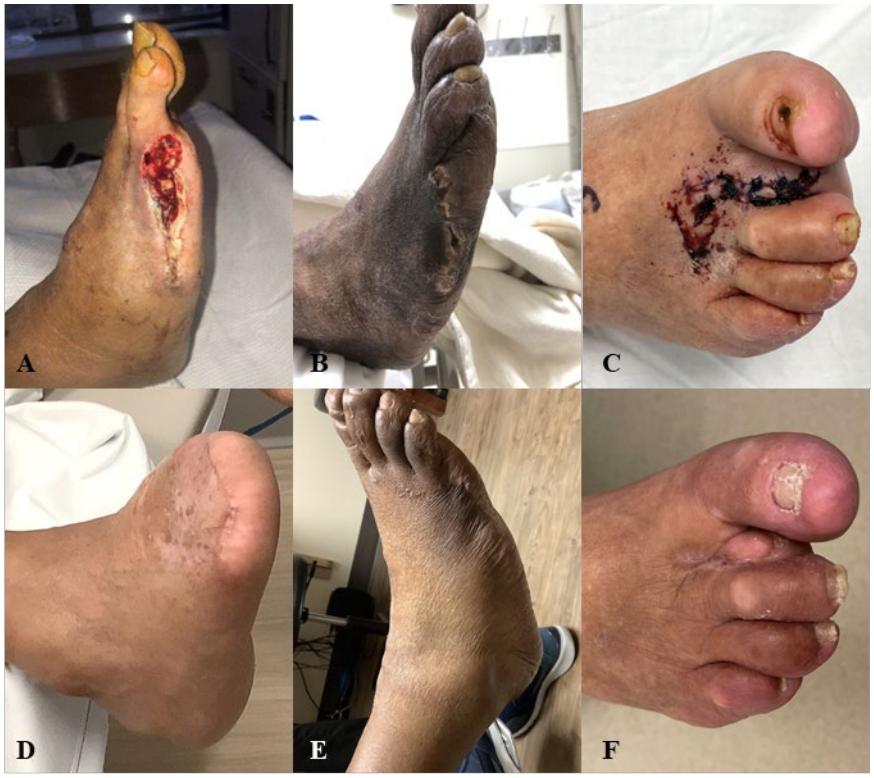
Point estimates and line segments indicate posterior mean and central 95% Bayesian credible intervals, respectively, for each subgroup. Statistical methods are identical to that of the primary analysis other than restricting the analysis to subgroups. The widths of the credible intervals have not been adjusted for the multiplicity of subgroups and should not be used to infer definitive treatment effects for subgroups.

Figure S3. Transcatheter Arterialization of Deep Veins Case Example

A 76-year-old male with Type II diabetes mellitus, hypertension, and planned transmetatarsal amputation due to Rutherford stage VI chronic limb-threatening ischemia. Baseline forefoot transcutaneous oxygen pressure (TcPO2) was 3mmHg. At a 6-month follow-up visit, the transcatheter arterialization of deep veins (TADV) circuit was patent and the $TcPO_2$ was 58mmHg. At 9-month follow-up, the TADV circuit was occluded and the $TcPO_2$ was 51mmHg. **A)** Baseline angiogram of the lower extremity showing diffusely diseased arterial vessels and poor perfusion of the foot. **B)** Angiogram after establishment of the index TADV circuit showing increased

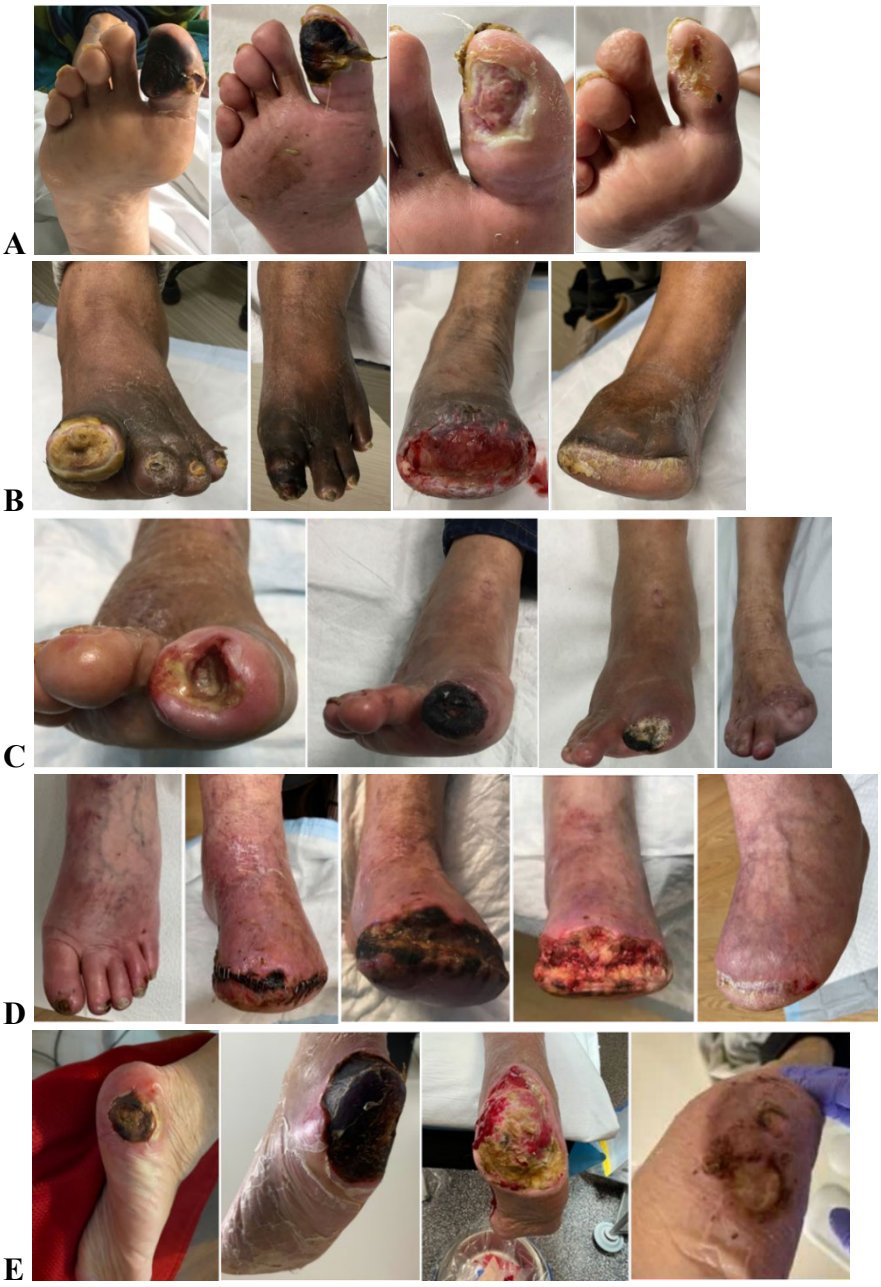
perfusion of the foot. **C)** At day 17 after establishing the TADV circuit, the patient underwent repeat intervention, thrombectomy and angioplasty to open the circuit, which had occluded. **D)** The angiogram shows the reintervention day 210, balloon angioplasty to circuit, **E,F)** 9-month duplex imaging showing occluded TADV stents with patent LPV fed by arterial collateral to lateral plantar venous connection. Wound progression from **G)** baseline to **H)** 6-months, and **I)** 9-months.

Figure S4. Case Examples of Healed Minor Amputations at 6 Months after TADV



Subjects that presented with non-healing chronic ulcers at baseline that underwent TADV and reached complete healing by the 6-month timepoint. **A-C)** baseline wounds that progressed to a fully healed; **D)** transmetatarsal, **E)** partial ray, and **F)** toe minor amputation.

Figure S5. Wound Images from PROMISE II Trial Subjects



A. Hallux wound healing progression at baseline, 2-months, 4-months, and 7-months follow-up. **B**. Initial hallux wound to transmetatarsal amputation at baseline, 1-month, 2-months, 9-weeks, and 6-months follow-up. **C.** Hallux wound healing progression at baseline, 1-month, 3-months, 4-months, and 12-months follow-up. **D.** Toe wounds to transmetatarsal amputation with primary

closure at baseline, 6-weeks, 2-months, 9-weeks, and 8-months follow-up. **E.** Heel wound progression with calcanectomy at baseline, 2-months, 4-months, and 8-months follow-up.

Table S1. Secondary Endpoints

	Procedure	30-Day **Follow-up**	3-Months **Follow-up**	6-Months **Follow-up**
Primary Patency – no./total no. (%)[*]	--	73/105 (67.7)	--	19/23 (25.9)
Primary Assisted Patency – no./total no. (%)[†]	--	90/105 (85.0)	--	34/44 (45.4)
Secondary Patency – no./total no. (%)[‡]	--	100/105 (94.9)	--	50/59 (64.2)
Limb Salvage – (%)	--	94.0	83.7	76.0
Change in Rutherford Class – no./total no. (%)[§]	--	14/77 (18.2)	24/74 (32.4)	27/64 (42.2)
Technical Success – no./total no. (%)[‖]	104/105 (99.0)	--	--	--
Procedural Success – no./total no. (%)[¶]	--	80/104 (76.9)	--	--
Target Wound Complete Healing – no./total no. (%)	--	3/76 (3.9)	6/72 (8.3)	16/63 (25.4)
All Wound Complete Healing – no./total no. (%)	--	4/93 (4.3)	6/100 (6.0)	24/86 (27.9)
Target Wound Area (cm^2) — interquartile range	3.9 (1.7, 9.3)	7.0 (1.4, 12.9)	7.0 (0.6, 25.5)	1.0 (0.0, 3.6)
All Wound Area (cm^2) — interquartile range	3.7 (1.4, 8.7)	6.0 (1.1, 11.6)	3.8 (0.9, 18.6)	0.1 (0.0, 2.8)
Freedom from Contrast-Induced Nephropathy – (%)[**]	103/105 (98.1)	--	--	--
Procedure Time (minutes) — interquartile range	199 (151, 260)	--	--	--
Radiation Exposure (milligray) — interquartile range	195 (88, 343)	--	--	--
Contrast Volume (milliliters) — interquartile range	127 (83, 178)	--	--	--

Data are presented as number and percentage of the total number or median and interquartile range.

*Defined as absence of occlusion of the endovascular intervention that is maintained without the need for additional or secondary surgical or endovascular procedures at 30 days and 6 months.
† Defined as absence of occlusion of the endovascular intervention maintained with the use of additional or secondary surgical or endovascular procedures, as long as occlusion of the primary treated site has not occurred at 30 days and 6 months.
‡ Defined as absence of occlusion of the endovascular intervention that is maintained with the use of additional or secondary surgical or endovascular procedures after occlusion occurs at 30 days and 6 months.
§Defined as a change of one class or greater, as evaluated at 30 days, 3 and 6 months.
‖ Defined as the successful creation of an arteriovenous fistula in the desired limb location with immediate morphological success.
¶Defined as the combination of technical success, and absence of all-cause death, above-ankle amputation or clinically driven major re-intervention of the stent graft at 30 days.
** Defined as subjects without acute (within 72 hours after intravenous contrast administration) impairment of renal function, measured as an absolute ≥0.5 mg/dL (44 μmol/L) increase compared to baseline serum creatinine value that results in a value above the upper limit of the normal range.

Table S2. Serious Adverse Events by MedDRA System-Organ Class and Preferred Term

Adverse Event	TADV (N=105 Subjects)
Subjects with one or more serious adverse events	98/105 (93.3%)
Total number of Serious Adverse Events	350
Blood and lymphatic system disorders[a]	8/105 (7.6%)
Anemia	3/105 (2.9%)
Anemia postoperative	1/105 (1.0%)
Blood loss anemia	4/105 (3.8%)
Cardiac disorders[a]	19/105 (18.1%)
Acute left ventricular failure	1/105 (1.0%)
Acute myocardial infarction	4/105 (3.8%)
Angina pectoris	1/105 (1.0%)
Arrhythmia	1/105 (1.0%)
Cardiac arrest	2/105 (1.9%)
Cardiac failure	1/105 (1.0%)
Cardiac failure acute	1/105 (1.0%)
Cardiac failure congestive	4/105 (3.8%)
Cardio-respiratory arrest	1/105 (1.0%)
Cardiovascular disorder	1/105 (1.0%)
Chest pain	2/105 (1.9%)
Fluid overload	1/105 (1.0%)
Myocardial infarction	2/105 (1.9%)
Pulmonary oedema	1/105 (1.0%)
Pulseless electrical activity	1/105 (1.0%)
Endocrine disorders[a]	2/105 (1.9%)
Hyperglycemia	1/105 (1.0%)
Hypoglycemia	1/105 (1.0%)
Gastrointestinal disorders[a]	11/105 (10.5%)
Diarrhea	1/105 (1.0%)

Adverse Event	TADV (N=105 Subjects)
Gastrointestinal hemorrhage	7/105 (6.7%)
Hematochezia	1/105 (1.0%)
Perihepatic abscess	1/105 (1.0%)
Rectal hemorrhage	1/105 (1.0%)
Retroperitoneal hematoma	1/105 (1.0%)
Small intestinal obstruction	1/105 (1.0%)
Vomiting	1/105 (1.0%)
General disorders and administration site conditions[a]	27/105 (25.7%)
Asthenia	1/105 (1.0%)
Death	5/105 (4.8%)
Impaired healing	5/105 (4.8%)
Incision site impaired healing	6/105 (5.7%)
Incision site pain	1/105 (1.0%)
Pain	1/105 (1.0%)
Procedural pain	1/105 (1.0%)
Tissue discoloration	1/105 (1.0%)
Vascular access site pseudoaneurysm	1/105 (1.0%)
Vascular stent occlusion	5/105 (4.8%)
Wound necrosis	2/105 (1.9%)
Wound secretion	1/105 (1.0%)
Hepatobiliary disorders[a]	1/105 (1.0%)
Cholecystitis	1/105 (1.0%)
Immune system disorders[a]	1/105 (1.0%)
Anaphylactic reaction	1/105 (1.0%)
Infections and infestations[a]	36/105 (34.3%)
Abscess limb	1/105 (1.0%)
Bacteremia	1/105 (1.0%)
Cellulitis	5/105 (4.8%)

Adverse Event	TADV (N=105 Subjects)
Fungal peritonitis	1/105 (1.0%)
Gangrene	10/105 (9.5%)
Gas gangrene	1/105 (1.0%)
Infection	1/105 (1.0%)
Localized infection	3/105 (2.9%)
Necrotizing soft tissue infection	1/105 (1.0%)
Osteomyelitis	8/105 (7.6%)
Pneumonia	2/105 (1.9%)
Post procedural infection	1/105 (1.0%)
Psoas abscess	1/105 (1.0%)
Sepsis	7/105 (6.7%)
Septic shock	1/105 (1.0%)
Staphylococcal sepsis	1/105 (1.0%)
Urinary tract infection	1/105 (1.0%)
Wound infection	7/105 (6.7%)
Injury, poisoning and procedural complications[a]	20/105 (19.0%)
Arteriovenous fistula thrombosis	1/105 (1.0%)
Hip fracture	1/105 (1.0%)
Limb injury	1/105 (1.0%)
Post procedural hematoma	1/105 (1.0%)
Postoperative wound complication	3/105 (2.9%)
Rib fracture	1/105 (1.0%)
Subarachnoid hemorrhage	1/105 (1.0%)
Subdural hematoma	1/105 (1.0%)
Toxic encephalopathy	1/105 (1.0%)
Vascular pseudoaneurysm	1/105 (1.0%)
Vessel perforation	1/105 (1.0%)
Wound complication	7/105 (6.7%)

Adverse Event	TADV (N=105 Subjects)
Wound hemorrhage	2/105 (1.9%)
Investigations[a]	5/105 (4.8%)
Blood glucose decreased	1/105 (1.0%)
Diagnostic procedure	1/105 (1.0%)
SARS-CoV-2 test positive	2/105 (1.9%)
Troponin increased	1/105 (1.0%)
Metabolism and nutrition disorders[a]	6/105 (5.7%)
Decreased appetite	1/105 (1.0%)
Diabetic ketoacidosis	1/105 (1.0%)
Hyperkalemia	1/105 (1.0%)
Metabolic encephalopathy	2/105 (1.9%)
Respiratory failure	1/105 (1.0%)
Shock hemorrhagic	1/105 (1.0%)
Musculoskeletal and connective tissue disorders[a]	7/105 (6.7%)
Pain in extremity	7/105 (6.7%)
Nervous system disorders[a]	4/105 (3.8%)
Cerebrovascular accident	1/105 (1.0%)
Headache	1/105 (1.0%)
Status epilepticus	2/105 (1.9%)
Product issues[a]	4/105 (3.8%)
Device breakage	2/105 (1.9%)
Device occlusion	2/105 (1.9%)
Psychiatric disorders[a]	2/105 (1.9%)
Mental disorder	1/105 (1.0%)
Mental status changes	1/105 (1.0%)
Renal and urinary disorders[a]	9/105 (8.6%)
Acute kidney injury	6/105 (5.7%)
End stage renal disease	2/105 (1.9%)

Adverse Event	TADV (N=105 Subjects)
Nephropathy	1/105 (1.0%)
Respiratory, thoracic, and mediastinal disorders[a]	9/105 (8.6%)
COVID-19	5/105 (4.8%)
Epistaxis	1/105 (1.0%)
Hypoxia	2/105 (1.9%)
Pleural effusion	1/105 (1.0%)
Pneumonia aspiration	1/105 (1.0%)
Pulmonary oedema	1/105 (1.0%)
Skin and subcutaneous tissue disorders[a]	12/105 (11.4%)
Decubitus ulcer	1/105 (1.0%)
Diabetic wound	1/105 (1.0%)
Dry gangrene	2/105 (1.9%)
Gangrene	4/105 (3.8%)
Ischemic skin ulcer	3/105 (2.9%)
Skin ulcer	1/105 (1.0%)
Surgical and medical procedures[a]	32/105 (30.5%)
Amputation	1/105 (1.0%)
Angioplasty	2/105 (1.9%)
Debridement	6/105 (5.7%)
Foot amputation	10/105 (9.5%)
Leg amputation	12/105 (11.4%)
Peripheral revascularization	3/105 (2.9%)
Skin graft	1/105 (1.0%)
Therapeutic embolization	1/105 (1.0%)
Toe amputation	6/105 (5.7%)
Vascular disorders[a]	42/105 (40.0%)
Aortic stenosis	1/105 (1.0%)
Arteriosclerosis	1/105 (1.0%)

Adverse Event	TADV (N=105 Subjects)
Deep vein thrombosis	1/105 (1.0%)
Hematoma	2/105 (1.9%)
Hemorrhage	1/105 (1.0%)
Hypotension	1/105 (1.0%)
Internal hemorrhage	1/105 (1.0%)
Ischemic limb pain	3/105 (2.9%)
Peripheral arterial occlusive disease	2/105 (1.9%)
Peripheral artery occlusion	1/105 (1.0%)
Peripheral artery stenosis	3/105 (2.9%)
Peripheral ischemia	7/105 (6.7%)
Peripheral vein stenosis	3/105 (2.9%)
Peripheral venous disease	1/105 (1.0%)
Shock	1/105 (1.0%)
Steal syndrome	1/105 (1.0%)
Vascular stenosis	3/105 (2.9%)
Vascular stent occlusion	20/105 (19.0%)
Vascular stent stenosis	5/105 (4.8%)
Vascular stent thrombosis	2/105 (1.9%)

[a]Event verbatim terms are reported by sites. The events listed in this table are then coded using MedDRA version 21.0 and then stratified by System-Organ Class (SOC) and Preferred Term. Patients may be counted in this table more than once by Preferred Term but are only counted once in the SOC summary line.
Numbers are counts/sample size (%) unless otherwise stated.

Table S3. Representativeness of PROMISE II Study Participants

Category	Example
Disease under investigation	Chronic Limb-Threatening Ischemia (CLTI)
Special considerations related to	
Sex and gender	CLTI affects more men than women (ratio of 3:1).
Age	Prevalence increases with age; individuals between 51-84 years old are more likely to suffer from CLTI.
Race or ethnic group	CLTI affects Black, Hispanic, and Latino persons at a higher rate than Whites in the United States.
Overall representativeness of this trial	The participants in the PROMISE II study demonstrated the expected ratio of men to women. The median age of this study population was 70 which is consistent with available CLTI registry data. The proportion of Black, Hispanic, or Latino patients enrolled was slightly higher (42.8%) than the same racial and ethnic compositions reported in the United States. The proportion of Black, Hispanic, or Latino study participants is congruent with the distribution found in other CLTI-focused trials.

To determine representativeness of the PROMISE II trial based on a series of metrics (sex, age, race), the population of all individuals who have the health condition studied in the trial, chronic limb-threatening ischemia, was reviewed in a search of PubMed and Census data and information from appropriate sources condensed into the above table.[22-25]

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Arterial Gerrymandering — Converting Veins to Arteries to Save Ischemic Limbs

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Peripheral artery disease affects more than 200 million persons worldwide and is associated with substantial morbidity and mortality.[1] More than 1 million persons in the United States have chronic limb-threatening ischemia, the most severe manifestation of peripheral artery disease, with a substantial risk of amputation and death 1 year after onset that exceeds 20%.[2] Key treatments for chronic limb-threatening ischemia include guideline-directed medical therapy to address risk factors for systemic cardiovascular disease and revascularization of the affected leg to restore straight-line arterial flow to the foot and facilitate wound healing.[3-5]

Two major revascularization approaches can be pursued in patients with limb ischemia. Surgical bypass, ideally performed with the use of an autogenous vein, can circumnavigate arterial obstruction and carry blood flow from proximal sites to distal arterial targets that are free of or have limited atherosclerotic disease. Alternatively, minimally invasive endovascular techniques can be used to open blocked segments of the peripheral arteries to restore antegrade arterial blood flow.[6] Both surgical and percutaneous approaches to critical limb ischemia are techniques that connect artery to artery and require a downstream target of an unobstructed vessel in the lower leg or foot on which to "land" the treatment. However, in as many as 15 to 20% of persons with chronic limb-threatening ischemia, there is no landing point, owing to diffuse distal arterial disease, which precludes conventional revascularization.[7]

It is for these specific no-option patients that Shishehbor and colleagues present their findings from the PROMISE II study in this issue of the *Journal*.[8] Using a novel — if not audacious — approach, the investigators connect arterial flow in the leg to the downstream deep-venous segments instead of to an arterial target, thereby reversing flow in the veins and perfusing the distal limb through the venous rather than the arterial system. This redistricting of the circulation, which diverts red oxygenated arterial blood flow into inherently blue deoxygenated veins, runs opposite to our understanding of how body circulation works; however, the findings of the study indicate that this technique may offer substantial promise.

The procedure of transcatheter arterialization of the deep veins is conceptually simple and elegant but requires significant technical expertise. One catheter is advanced in the artery from the groin to the knee; another catheter is advanced in the vein from the foot to the knee. At this rendezvous point behind the knee, the artery and vein are mechanically connected with the use of a needle, a guide wire, and covered stents. This creates a straight pathway from the upper-leg arterial system to the venous circulation of the foot, effectively "arterializing" the venous flow and providing oxygenated blood to the ischemic tissues.

In the PROMISE II study, the investigators prospectively enrolled 105 patients with advanced chronic limb-threatening ischemia who were deemed by a multidisciplinary review board to

have no revascularization options and to face a likely prospect of major amputation. The primary end point of this nonrandomized, single-group study was 6-month amputation-free survival, defined as freedom from above-ankle amputation or death from any cause. The investigators reported procedural success in 99% of the patients and 6-month amputation-free survival in 66.1%, which exceeded the prespecified performance goal of 54.0%. Complete wound healing was noted in 25% of the patients and partial healing in half. Outcomes were worse for patients who were receiving dialysis than for those without renal failure: amputation-free survival in that subgroup was 36.8% and 72.7%, respectively, and death from any cause was 36.2% and 8.6%. In addition, 12 patients in the total study population contracted coronavirus disease 2019 (Covid-19), 5 of whom died as a result of sequelae of the disease.

Although the PROMISE II investigators advance a new endovascular strategy to treat no-option chronic limb-threatening ischemia, further exploration may be warranted to determine which patients may benefit most from this exceptional approach. In the study, patients who were undergoing dialysis appeared to fare poorly after deep-vein arterialization; this finding may warrant additional study. In addition, as other revascularization techniques evolve, what constitutes no-option arterial anatomy today may be surmounted in future years.

The authors report favorable 6-month outcomes after deep-vein arterialization, but nearly three fourths of the patients had undergone repeat endovascular treatment to maintain patency of the arteriovenous circuit. Whether ongoing vessel patency may be necessary to maintain limb salvage and whether venous congestion in the treated limb will attenuate long-term benefit are unknown. Similarly, construction of the arterialized venous circuit requires a highly specialized technique that was performed by exceptionally proficient operators in this study. Will these findings be generalizable under conditions more akin to the real world with regard to operators, patients, and health care systems?

Unresolved questions notwithstanding, the establishment of a new option for reperfusion in advanced chronic limb-threatening ischemia offers potential promise for patients who would otherwise often be relegated to amputation. Bringing arterial blood into venous vessels may be considered a unique version of gerrymandering by means of reclassifying the composition of circulation to the foot. We hope that this procedure to reconfigure lower-limb perfusion reduces the need for amputation in many patients who historically have had no other options.

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

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