JOURNAL OF ENDOVASCULAR THERAPY
A SAGE Publication
An official publication of the ISEVS

Journal of Endovascular Therapy
2020, Vol. 27(4) 658–665

DOI: 10.1177/1526602820922179
www.jevt.org
SAGE

Midterm Outcomes of Percutaneous Deep Venous Arterialization With a Dedicated System for Patients With No-Option Chronic Limb-Threatening Ischemia: The ALPS Multicenter Study

Andrej Schmidt, MD[1], Michiel A. Schreve, MD[2], Eline Huizing, MD[2], Costantino Del Giudice, MD[3], Daniela Branzan, MD[4], Çağdaş Ünlü, MD, PhD[2], Ramon L. Varcoe, MBBS, MS, FRACS, PhD[5], Roberto Ferraresi, MD[6], and Steven Kum, MMBS, FRCS[7]

Abstract

Purpose: To evaluate the midterm results of patients suffering from no-option chronic limb-threatening ischemia (CLTI) treated with a dedicated system for percutaneous deep venous arterialization (pDVA). **Materials and Methods:** Thirty-two consecutive CLTI patients (mean age 67±14 years; 20 men) treated with pDVA using the Limflow device at 4 centers between 11 July 2014 and 11 June 2018 were retrospectively analyzed. Of all patients, 21 (66%) had diabetes, 8 (25%) were on immunosuppression, 4 (16%) had dialysis-dependent renal failure, 9 (28%) had Rutherford category 6 ischemia, and 25 (78%) were deemed at high risk of amputation. The primary outcome was amputation-free survival (AFS) at 6 months. Secondary outcomes were wound healing, limb salvage, and survival at 6, 12, and 24 months. **Results:** Technical success was achieved in 31 patients (96.9%). The median follow-up was 34 months (range 16–63). At 6, 12, and 24 months, estimates were 83.9%, 71.0%, and 67.2% for AFS, 86.8%, 79.8% and 79.8% for limb salvage, and 36.6%, 68.2%, and 72.7% for complete wound healing, respectively. Median time to complete wound healing was 4.9 months (range 0.5–15). The DVA circuit occluded during follow-up in 21 patients; the median time to occlusion was 2.6 months. Reintervention for occlusion was performed in 17 patients: 16 because of unhealed wounds and 1 for a newly developed ulcer. **Conclusion:** This study represents the largest population of patients with no-option CLTI treated with pDVA using the LimFlow device with midterm results. In this complex group of patients, pDVA using the LimFlow device has been shown to be feasible, with a high technical success rate and AFS at 6 up to 24 months coupled with wound healing. In selected patients with no-option CLTI, pDVA could be a recommended treatment to prevent amputation and heal wounds.

Keywords

amputation, below-the-knee arteries, chronic limb-threatening ischemia, critical limb ischemia, desert foot, endovascular technique, infrapopliteal arteries, limb salvage, no-option CLTI, peripheral artery disease, wound healing

Introduction

Worldwide, more than 200 million people suffer from peripheral artery disease (PAD).[1] In a proportion of these patients, the disease evolves into chronic limb-threatening ischemia (CLTI) and tissue loss, which is associated with major amputation in 30% of the patients; only 20% will achieve wound healing at 1 year if left untreated.[2]

The need to prevent amputations is pressing. A systematic review confirmed improved limb salvage rates in CLTI patients undergoing revascularization compared with medically treated patients.[3] However, in patients with CLTI, revascularization can fail due to severe calcification, early recoil after angioplasty, or the absence of distal target vessels. Ferraresi et al[4] characterized the problem of large artery disease as a failure of "transmission" and small artery disease as a failure of "distribution." The most severe form of distribution failure may lead to a "desert foot" and result in a "no-option" scenario due to the lack of a viable target for either bypass or endovascular therapy.

The prevalence of no-option CLTI among all patients with CLTI has been estimated at around 20%, leaving major limb amputation as the only viable solution.[5] Patients with severe CLTI who are left untreated are at risk of having an all-cause mortality of 22% at 12 months and amputation rates as high as 42%.[6] Wound healing in this group is dismal and has been reported to be in the range of 10% to 20% at 1 year.[6,7]

The venous system is mostly disease free and could be considered as an alternative conduit for perfusion of the extremities with arterial blood. This procedure, venous arterialization, was shown to be a promising option for revascularizing the lower limb.[8–10] LimFlow SA (Paris, France) recently developed a dedicated set of tools to perform percutaneous deep venous arterialization (pDVA).[11] This endovascular technique showed promising 6-month results in the first-in-man study and in the early feasibility trial.[12,13] The aim of the ALPS study was to evaluate the midterm results of pDVA performed with the LimFlow device to treat no-option CLTI patients with tissue loss.

Materials and Methods

Study Design and Patient Selection

A retrospective chart review was conducted of all consecutive patients treated with pDVA using the LimFlow device at 4 vascular centers in Alkmaar (Netherlands), Leipzig (Germany), Paris (France), and Singapore (ALPS) between 11 July 2014 and 11 June 2018. Inclusion criteria were Rutherford category 5 or 6 CLTI, no angiographically evident distal target artery for endovascular therapy or a distal bypass, and at least 1 patent tibial artery in the proximal segment. Exclusion criteria were acute limb ischemia, extensive tissue loss or infection that precluded limb salvage, known deep vein thrombosis, allergy to aspirin or clopidogrel, and/or contraindication to anticoagulation.

In total, 32 consecutive patients (mean age 67±14 years; 20 men) with tissue loss met the criteria and were eligible for analysis. Of these, 5 patients were treated in Alkmaar, 9 in Leipzig, 3 in Paris, and 15 in Singapore. Notable comorbidities were type 2 diabetes (21, 66%), renal insufficiency (17, 53%; 5 dialysis-dependent), and immunosuppression (8, 25%). All patients had tissue loss, and 9 patients (28%) had Rutherford category 6 ischemia. More than three-quarters of the patients (25, 78%) were deemed high risk according to the Society for Vascular Surgery (SVS) wound, ischemia, and foot infection (WIfI) classification.[14] Twenty-eight patients (88%) had undergone unsuccessful percutaneous intervention in the past. Patient characteristics are summarized in Table 1.

Table 1. Characteristics of the 32 Patients in the Study.[a]

Age, y	67±14
Men	20 (62)
Limb	
Left	16 (50)
Right	16 (50)
Body mass index, kg/m^2	24±4
Comorbidities	
Hypertension	27 (84)
Diabetes	21 (66)
Hyperlipidemia	20 (62)
Coronary artery disease	15 (47)
Chronic kidney disease	17 (53)
Dialysis dependent	5 (16)
Stroke	4 (12)
Smoking (n=30)	15 (50)
Immunosuppressant use	8 (25)
Serum creatinine, μmol/L	88 (67, 143)
Rutherford category	
5	23 (72)
6	9 (28)
SVS WIfI risk staging	
High	25 (78)
Moderate	6 (19)
Low	1 (3)

Abbreviations: SVS, Society for Vascular Surgery; WIfI, wound, ischemia, foot infection.
[a]Continuous data are presented as the mean ± standard deviation or median (interquartile range Q1, Q3); categorical data are given as the number (percentage).

This study was conducted according to the principles of the Declaration of Helsinki and in compliance with local regulatory requirements. Institutional review board approval was obtained when required, and consent was waived because of the retrospective nature of the study.

[1]Department of Interventional Angiology, University Hospital Leipzig, Germany
[2]Department of Surgery, Northwest Clinics, Alkmaar, the Netherlands
[3]Department of Interventional Radiology, Hôpital Européen Georges Pompidou, Paris, France
[4]Department of Vascular Surgery, University Hospital Leipzig, Germany
[5]Department of Surgery, Prince of Wales Hospital and University of New South Wales, Randwick, Sydney, New South Wales, Australia
[6]Peripheral Interventional Unit, Humanitas Gavazzeni, Bergamo, Italy
[7]Vascular Service, Department of Surgery, Changi General Hospital, Singapore

Corresponding Author:
Andrej Schmidt, Department of Interventional Angiology, University Hospital Leipzig, Liebigstraße 20, 04103 Leipzig, Germany.
Email: andrej.schmidt@medizin.uni-leipzig.de

Procedure

The suitability of the patient for the pDVA procedure was assessed by an interventionist and/or vascular surgeon with at least 5 years of interventional experience. The procedures were performed by angiologists, surgeons, or interventional radiologists. All patients were treated in a multidisciplinary setting with dedicated wound centers in all sites.

The aim of the procedure was to create a connection between a tibial artery and a tibial vein to provide pressurized arterial flow to the venous system of the foot. Prior to the procedure, patients were placed on at least aspirin and/or clopidogrel. The choice of performing a venous duplex ultrasound of the veins prior to the procedure was left to the discretion of the operator. The procedure was performed as described previously[13,15] and in accordance with the LimFlow instructions for use. In brief, antegrade arterial access was gained via a femoral artery puncture and the introduction of a 7-F sheath, while a distal venous access was obtained via an ultrasound-guided puncture of the target tibial vein at the ankle. Simultaneous digital subtraction angiography with contrast injection in both the artery and vein was performed to choose an appropriate crossing point that preserved significant arterial collaterals. The arterial and venous catheters were then advanced to the selected crossing point. After alignment using the proprietary ultrasound system, a needle from the arterial catheter was deployed to cross from the artery to the vein. A 0.014-inch guidewire was then passed through the needle into the vein all the way down to the foot. A proprietary, over-the-wire, forward-cutting 4-F valvulotome was used to lyse the valves as distal as the mid foot, allowing antegrade flow into the deep venous system of the foot. Self-expanding stent-grafts were implanted from the level of the ankle toward the crossing point, which was in turn covered by a dedicated tapered self-expanding stent-graft. The completion angiogram would then typically show rapid blood flow into the deep venous system of the foot. After the procedure, patients were prescribed lifelong antiplatelet therapy (daily aspirin 100 mg or clopidogrel 75 mg) in combination with anticoagulation for at least 3 months if possible.

Follow-up

Surveillance was performed according to the institutional protocol and included clinical evaluation of limb perfusion and wound status. Evaluation of stent-graft patency was performed using duplex ultrasound and angiography when required. In the case of occlusion, reintervention was performed percutaneously with a thrombectomy device supplemented by drug-coated balloon (DCB) angioplasty or stenting. Bailout stenting was deemed necessary if suboptimal angioplasty was performed. Edema was managed conservatively with elevation. Assessment of perfusion was performed as described previously.[15] Transcutaneous oxygen pressure ($TcPO_2$) measurements were done every 2 weeks for the first 2 months and monthly thereafter until wound healing was achieved.

Definitions and Study Outcomes

Technical success was defined as the ability to cross from the artery in the vein with the LimFlow device and implant the stent-grafts, which were considered patent when there was flow detected within.

The primary outcome was 6-month amputation-free survival (AFS), defined as no major (above the ankle) amputation of the index limb or death (any cause).[16] Secondary measures were wound healing, limb salvage (freedom from major amputation), and survival at 6, 12, and 24 months and AFS at 12 and 24 months. Wounds were considered healed if they were fully epithelialized.

Statistical Analysis

Continuous data are presented as the mean ± standard deviation or median [minimum–maximum or interquartile range (IQR) Q1, Q3] if nonnormally distributed according to quantile-quantile plots; categorical data are given as the number (percentage). Rates for AFS, limb salvage, survival, and wound healing were estimated using the Kaplan-Meier method. Patients who died before complete wound healing were censored on the date of death. In patients who underwent major amputation, the time to wound healing was considered to be infinite.[17] $TcPO_2$ data were compared using the paired *t* test. Statistical significance was defined at $p<0.05$. Statistical analyses were performed using IBM SPSS software (version 23; IBM Corporation, Armonk, NY, USA).

Results

Technical success was achieved in 31 of 32 cases (97%). In 1 patient, the pDVA procedure failed because the target vein did not respond to aggressive balloon dilation, which precluded stent-graft implantation. This patient was excluded from further analysis. General anesthesia was utilized in 40% of the cases. The average duration of the procedure was 3.5 hours. Crossings were predominantly performed to the posterior tibial vein (27, 87%) from the tibioperoneal trunk (5, 16%) or posterior tibial artery (22, 71%). The other crossings were performed from the anterior tibial artery to the anterior tibial vein (3, 10%) or from the popliteal artery to the popliteal vein (1, 3%).

During the first 30 days, there were 2 non-fatal myocardial infarctions and 2 deaths. One patient died from progression of foot sepsis. The second death occurred due to a perforated diverticulum of the bowel despite laparotomy.

Both deaths were deemed by the operator to be unrelated to the LimFlow procedure.

The median follow-up was 34 months (range 16–63), during which 5 other deaths occurred due to myocardial infarction (n=2), pneumonia (n=2), and exacerbation of chronic obstructive pulmonary disease (n=1). Among the adverse events, 1 patient developed bleeding from a superficial vein adjacent to the granulating wound at 6 months. Surgical ligation was performed, but the stent-graft thrombosed shortly after ligation. A second patient had infection of the stent-graft 10 weeks after the procedure; the primary wound on the fifth toe had already healed. The stent-graft was explanted, and the resultant large ankle wound continued to heal. A third patient developed a new wound on the forefoot 8 months post-procedure, after the index wound had healed. This patient had an occluded DVA circuit and was treated with the Rotarex catheter (Straub Medical AG, Wangs, Switzerland), thrombolysis, and a Supera stent (Abbott Vascular, Santa Clara, CA, USA) in the veins of the foot. This new wound subsequently healed.

The AFS estimates at 6, 12, and 24 months were 83.9% (95% CI 71.9% to 97.9%), 71.0% (95% CI 56.7% to 88.9%), and 67.2% (95% CI 52.4% to 86.2%), respectively. The corresponding survival estimates were 93.5% (95% CI 85.3% to 100%), 83.9% (95% CI 71.9% to 97.9%), and 80.2% (95% CI 67.2% to 95.8%). The limb salvage estimates were 86.8% (95% CI 75.5% to 99.7%), 79.8% (95% CI 66.6% to 95.7%), and 79.8% (95% CI 66.6% to 95.7%) in the same period. All major amputations were performed within 9 months of the procedure.

A total of 21 wounds were healed within 24 months; the estimated wound healing rate was 72.7% (95% CI 49.6% to 85.3%) at 24 months with a median time to complete wound healing of 4.9 months (range 0.5–15). Among the 21 patients who remained alive without amputation, the majority (18, 85.7%) had completely healed wounds at 12 months. Kaplan-Meier curves are shown in Figure 1. An example of a typical case is shown in Figure 2.

$TcPO_2$ was measured at baseline and during follow-up in 13 patients. A total of 142 $TcPO_2$ values were measured (mean 10.9 measurements per patient). Six patients had $TcPO_2$ measurements that extended to 2 years and beyond. At baseline, the average $TcPO_2$ measurement near the wound was 14.5 ± 12.7 mm Hg (median 11, range 3–37). As illustrated in Figure 3, $TcPO_2$ levels increased after the pDVA procedure, reaching 56.1 ± 11.9 mm Hg (median 57.5, range 36–72) after 2 years. This became statistically significantly higher after 45 days (increase of +22.1 mm Hg, p=0.027) and remained statistically significantly higher during follow-up (increase of +41.7 mm Hg, $p<0.001$) compared with baseline.

The DVA circuit occluded during follow-up in 21 patients; median time to occlusion was 2.6 months (range 0.2–19.1). Reintervention for occlusion was performed in 17 patients: 16 because of unhealed wounds and 1 for a newly developed ulcer. In 4 patients no further revascularization was done because the wound had healed or healing was imminent. Reintervention for asymptomatic stenosis found on surveillance was performed in 2 other patients. A variety of techniques and devices were used during reintervention, including thrombolysis (n=6), mechenical thrombectomy (n=9), DCB angioplasty (n=10), and stenting (n=5).

Discussion

The multicenter ALPS study represents the largest cohort of consecutive no-option CLTI patients treated with pDVA by interventionists from different subspecialties and followed to 2 years. Prior reports of surgical series[10] had shown venous arterialization to be a viable therapy in no-option CLTI, with technical success rates of ~81%.[18] In the current study, a high technical success rate of 97% was achieved with a percutaneous approach using the LimFlow device, mirroring the experiences in the initial LimFlow series.[13,15]

In several cohorts of >300 patients treated by standard endovascular techniques, AFS rates of 74% to 76% and 52% to 55% at 12 and 36 months, respectively, were reported.[19–22] In the majority of cases, patients were treated using plain balloon angioplasty. In the current study, AFS rates of 83.9%, 71.0%, and 67.2% were achieved at 6, 12, and 24 months, respectively, in CLTI patients with no further possibility of conventional revascularization. The results were durable up to 2 years despite the high rate of prior failed revascularization attempts in these patients.

Alternate techniques of venous arterialization have been reported.[23–25] In these studies, the arteriovenous fistula was created as distal in the tibial artery as possible. Technical success varied from 77% to 100%, with clinical success rates from 29% to 75% at various time points. The techniques used in these studies varied, and there was no definite way to assess the continued presence of an arteriovenous fistula without the use of a covered stent. In addition, Gandini et al[25] reported wound healing rates in 6 of 9 patients with a mean time to wound healing of 20 weeks despite a relatively modest $TcPO_2$ of 30 mm Hg compared with the higher $TcPO_2$ levels found in our patients. As such it is difficult to draw any conclusions regarding the different techniques. In our study, good technical success was achieved across all centers and different subspecialties.

Some investigators have suggested other treatments for no-option CLTI. Benoit et al[7] reviewed no-option CLTI patients treated with vasoactive drugs and stem cell therapy and showed an AFS of between 53% and 55% in studies published after 2006, which were lower than the rate in our study. Other treatment modalities exist for no-option CLTI patients, including spinal cord stimulation, lumbar sympathectomy, intermittent pneumatic compression, and

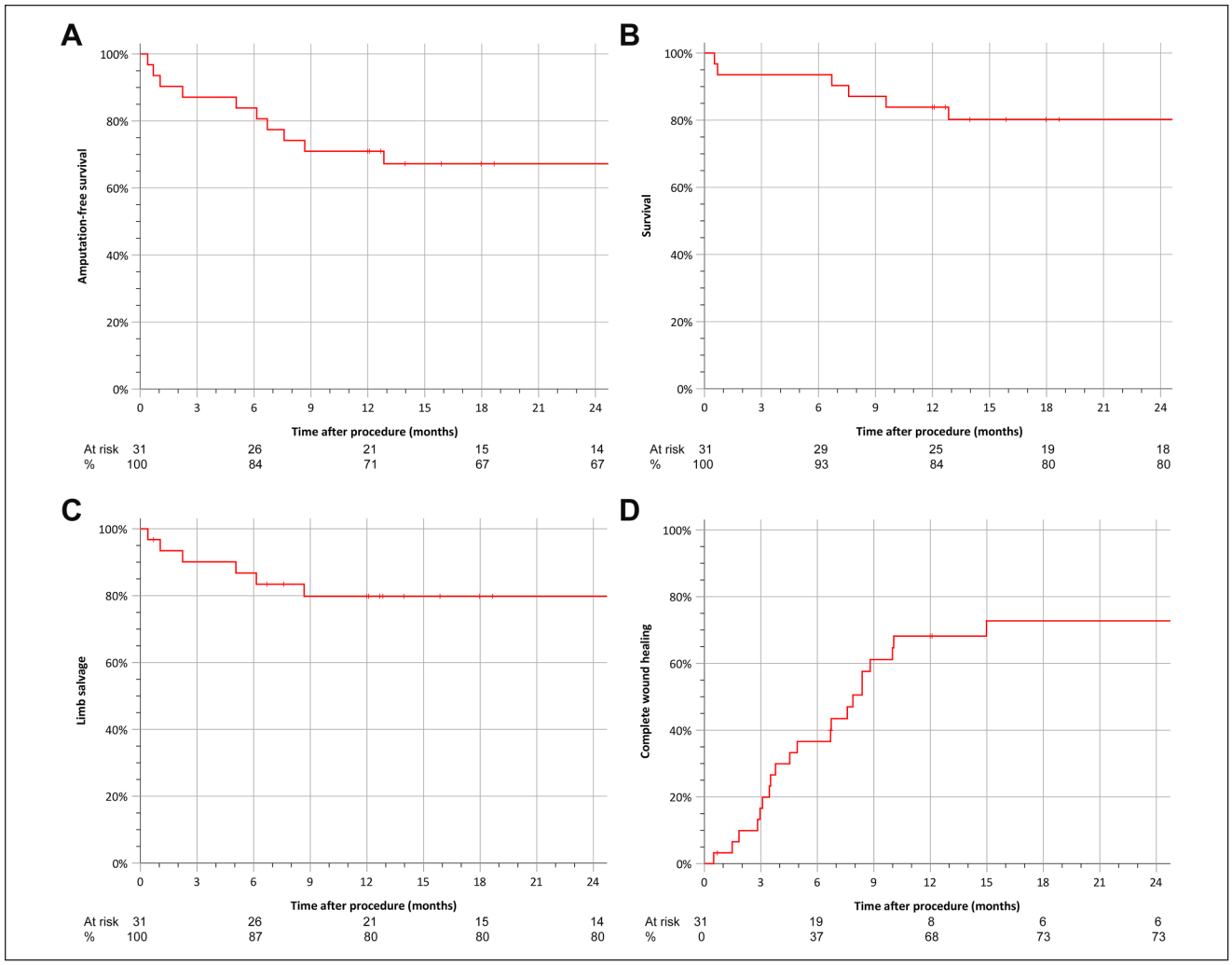

Figure 1. Kaplan-Meier curves for (A) amputation-free survival, (B) survival, (C) limb salvage, and (D) wound healing.

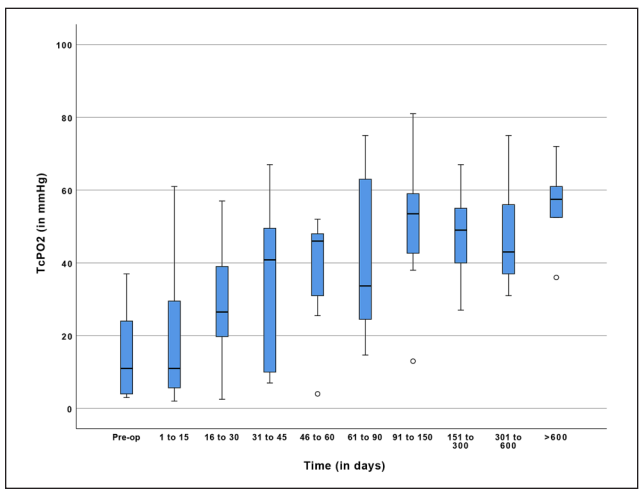

Figure 2. Transcutaneous oxygen pressure ($TcPO_2$) levels at baseline and follow-up.

hyperbaric oxygen therapy.[26] However, the efficacy of these treatment options remains low, and they are therefore not recommended routinely for the treatment of CLTI.[26]

Wound healing rates are poorly reported in historical CLTI series and not at all for no-option CLTI patients. In a randomized controlled study of prostaglandins used in no-option CLTI patients, Brass et al[27] reported wound healing rates of <25% in both treatment and placebo arms at 6 months (n=181 in each arm). However, wound healing rates at 1 year were not reported. In our study, Kaplan-Meier estimates of complete wound healing were 36.6%, 68.2%, and 72.7% at 6, 12, and 24 months, respectively. Eighty-six percent of the survivors without amputation had healed wounds at 12 months.

Our wound healing rates and time to wound healing were reasonable compared with existing CLTI registries.[19] For example, a large-scale registry of Japanese patients

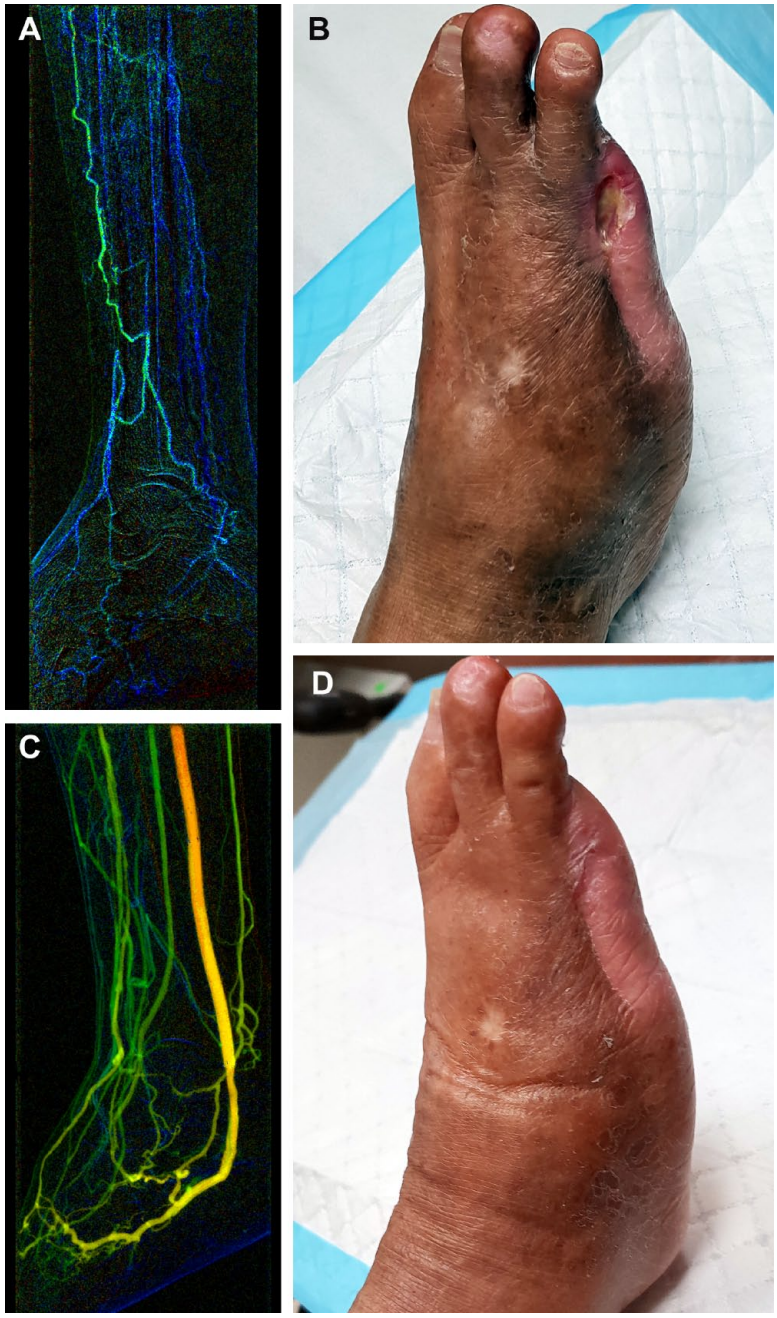

Figure 3. Angiographic and clinical results of percutaneous deep venous arterialization with the LimFlow device. (A) Perfusion angiogram of a patient with no-option chronic limb-threatening ischemia having failed conventional therapy. (B) Preprocedure photograph showing a wound that had failed to heal for 6 months. (C) Perfusion angiogram of the same patient treated with the LimFlow device showing rapid flow of blood into the venous circulation of the foot. (D) Complete wound healing of the same patient was achieved after 3 months.

with CLTI (but not no-option CLTI) reported a wound healing rate of 86% at 1 year with a median time to wound healing of 97 days. In our study, the median time to wound healing was 150 days, and a reasonable wound healing rate of 68.2% was achieved at 1 year despite having patients with advanced ischemia and no other revascularization options, in addition to a quarter of patients on immunosuppression and 28% with Rutherford category 6 wounds.

We hypothesize that a remodeling process takes place after pDVA. Ferraresi et al[8] reported the possibility of an angiographically detected remodeling process after DVA associated with clinical wound healing and high $TcPO_2$ measurements.

We believe that longer time to wound healing in our study could be related to this remodeling process. Our $TcPO_2$ results seemed to rise to significant levels after 45 days, which could be explained by this same phenomenon. $TcPO_2$ has been shown to be a reliable predictor of wound healing.[28]

Reintervention rates in patients with CLTI have been reported in several registries. At 1 year, Iida et al[20] had a 40% reintervention rate and Fernandez et al[29] reported 50%. In our study, reintervention rates were comparable (59.4%) to the rates reported in the initial series (71%).[5] The main cause of reinterventions was the venous outflow in the majority of cases.

Limitations

Although the ALPS study is the largest evaluation of pDVA to date, the sample size is still relatively small, which is one of the weaknesses of the study. Due to its retrospective nature, recall bias is possible. Slight differences in treatment among the centers existed, especially in wound care, which reduced the internal validity of the study. On the other hand, it was a multicenter study with a cohort of consecutively treated patients. Further studies could include a larger sample size with longer follow-up. A control group could be considered but would be difficult to implement due to small numbers and ethical considerations.

Conclusion

This study presents midterm results from the largest population of patients with no-option CLTI treated with pDVA using the LimFlow device. In this complex group of patients, the LimFlow device demonstrated high technical success and AFS rates coupled with good wound healing at up to 24 months. In selected patients with no-option CLTI, pDVA is a safe and effective treatment to prevent amputation and heal wounds.

Acknowledgments

The authors are very grateful to Vincent Cabane for his original contribution and his valuable assistance with data retrieval and support during the preparation of this report.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Andrej Schmidt is a paid consultant to LimFlow. Roberto Ferraresi and Steven Kum are paid consultants to LimFlow and hold co-inventor patents and stock in the company.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Eline Huizing https://orcid.org/0000-0002-5297-2640
Ramon L. Varcoe https://orcid.org/0000-0001-5611-6991
Steven Kum https://orcid.org/0000-0003-0883-0829

References

1. Fowkes FGR, Aboyans V, Fowkes FJI, et al. Peripheral artery disease: epidemiology and global perspectives. *Nat Rev Cardiol*. 2017;14:156–170.
2. Boccalon H, Braga A, Breddin K, et al. Two randomised and placebo-controlled studies of an oral prostacyclin analogue (Iloprost) in severe leg ischaemia. The Oral Iloprost in severe Leg Ischaemia Study Group. *Eur J Vasc Endovasc Surg*. 2000;20:358–362.
3. Hinchliffe RJ, Brownrigg JRW, Andros G, et al. Effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral artery disease: a systematic review. *Diabetes Metab Res Rev*. 2016;32(suppl 1):136–144.
4. Ferraresi R, Mauri G, Losurdo F, et al. BAD transmission and SAD distribution: a new scenario for critical limb ischemia. *J Cardiovasc Surg (Torino)*. 2018;59:655–664.
5. Schreve MA, Unlu C, Kum S, et al. Surgical and endovascular venous arterialization: ready to take the "desert" by storm? *J Cardiovasc Surg (Torino)*. 2017;58:402–408.
6. Abu Dabrh AM, Steffen MW, Undavalli C, et al. The natural history of untreated severe or critical limb ischemia. *J Vasc Surg*. 2015;62:1642–1651.e3.
7. Benoit E, O'Donnell TFJ, Kitsios GD, et al. Improved amputation-free survival in unreconstructable critical limb ischemia and its implications for clinical trial design and quality measurement. *J Vasc Surg*. 2012;55:781–789.
8. Ferraresi R, Casini A, Losurdo F, et al. Hybrid foot vein arterialization in no-option patients with critical limb ischemia: a preliminary report. *J Endovasc Ther*. 2019;26:7–17.
9. Lichtenberg M, Schreve MA, Ferraresi R, et al. Surgical and endovascular venous arterialization for treatment of critical limb ischaemia. *Vasa*. 2018;47:17–22.
10. Schreve MA, Vos CG, Vahl AC, et al. Venous arterialisation for salvage of critically ischaemic limbs: a systematic review and meta-analysis. *Eur J Vasc Endovasc Surg*. 2017;53:387–402.
11. Kum S, Huizing E, Schreve MA, et al. Percutaneous deep venous arterialization in patients with critical limb ischemia: a technical note. *J Cardiovasc Surg (Torino)*. 2018;59:665–669.
12. Del Giudice C, Van Den Heuvel D, Wille J, et al. Percutaneous deep venous arterialization for severe critical limb ischemia in patients with no option of revascularization: early experience from two European centers. *Cardiovasc Intervent Radiol*. 2018;41:1474–1480.
13. Mustapha JA, Saab FA, Clair D, et al. Interim results of the PROMISE I trial to investigate the LimFlow system of percutaneous deep vein arterialization for the treatment of critical limb ischemia. *J Invasive Cardiol*. 2019;31:57–63.
14. Mills JLS, Conte MS, Armstrong DG, et al. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIfI). *J Vasc Surg*. 2014;59:220–222.

15. Kum S, Tan YK, Schreve MA, et al. Midterm outcomes from a pilot study of percutaneous deep vein arterialization for the treatment of no-option critical limb ischemia. *J Endovasc Ther*. 2017;24:619–626.
16. 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;50:1462–1463.
17. Nakama T, Watanabe N, Kimura T, et al. Clinical implications of additional pedal artery angioplasty in critical limb ischemia patients with infrapopliteal and pedal artery disease. *J Endovasc Ther*. 2016;23:83–91.
18. Alexandrescu V, Ngongang C, Vincent G, et al. Deep calf veins arterialization for inferior limb preservation in diabetic patients with extended ischaemic wounds, unfit for direct arterial reconstruction: preliminary results according to an angiosome model of perfusion. *Cardiovasc Revasc Med*. 2011;12:10–19.
19. Iida O, Nakamura M, Yamauchi Y, et al. Endovascular treatment for infrainguinal vessels in patients with critical limb ischemia: OLIVE registry, a prospective, multicenter study in Japan with 12-month follow-up. *Circ Cardiovasc Interv*. 2013; 6:68–76.
20. Iida O, Nakamura M, Yamauchi Y, et al. 3-Year outcomes of the OLIVE registry, a prospective multicenter study of patients with critical limb ischemia: a prospective, multi-center, three-year follow-up study on endovascular treatment for infra-inguinal vessel in patients with critical limb ischemia. *JACC Cardiovasc Interv*. 2015;8:1493–1502.
21. Iida O, Takahara M, Soga Y, et al. Three-year outcomes of surgical versus endovascular revascularization for critical limb ischemia: The SPINACH study (Surgical Reconstruction Versus Peripheral Intervention in Patients With Critical Limb Ischemia). *Circ Cardiovasc Interv*. 2017;10:e005531. doi:10.1161/CIRCINTERVENTIONS.117.005531
22. Stavroulakis K, Borowski M, Torsello G, et al. One-year results of first-line treatment strategies in patients with critical limb ischemia (CRITISCH Registry). *J Endovasc Ther*. 2018;25:320–329.
23. Migliara B, Cappellari TF. A novel technique to create an arteriovenous fistula during total percutaneous deep foot venous arterialisation using an IVUS guided catheter [letter]. *Eur J Vasc Endovasc Surg*. 2018;55:735.
24. Ysa A, Lobato M, Mikelarena E, et al. Homemade device to facilitate percutaneous venous arterialization in patients with no-option critical limb ischemia. *J Endovasc Ther*. 2019;26: 213–218.
25. Gandini R, Merolla S, Scaggiante J, et al. Endovascular distal plantar vein arterialization in dialysis patients with no-option critical limb ischemia and posterior tibial artery occlusion: a technique for limb salvage in a challenging patient subset. *J Endovasc Ther*. 2018;25:127–132.
26. Conte MS, Bradbury AW, Kolh P, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. *J Vasc Surg*. 2019;69(6S):3S–125S.e40.
27. Brass EP, Anthony R, Dormandy J, et al. Parenteral therapy with lipo-ecraprost, a lipid-based formulation of a PGE1 analog, does not alter six-month outcomes in patients with critical leg ischemia. *J Vasc Surg*. 2006;43:752–759.
28. Wang Z, Hasan R, Firwana B, et al. A systematic review and meta-analysis of tests to predict wound healing in diabetic foot. *J Vasc Surg*. 2016;63(2 suppl):29S–36S.e1-2.
29. Fernandez N, McEnaney R, Marone LK, et al. Predictors of failure and success of tibial interventions for critical limb ischemia. *J Vasc Surg*. 2010;52:834–842.