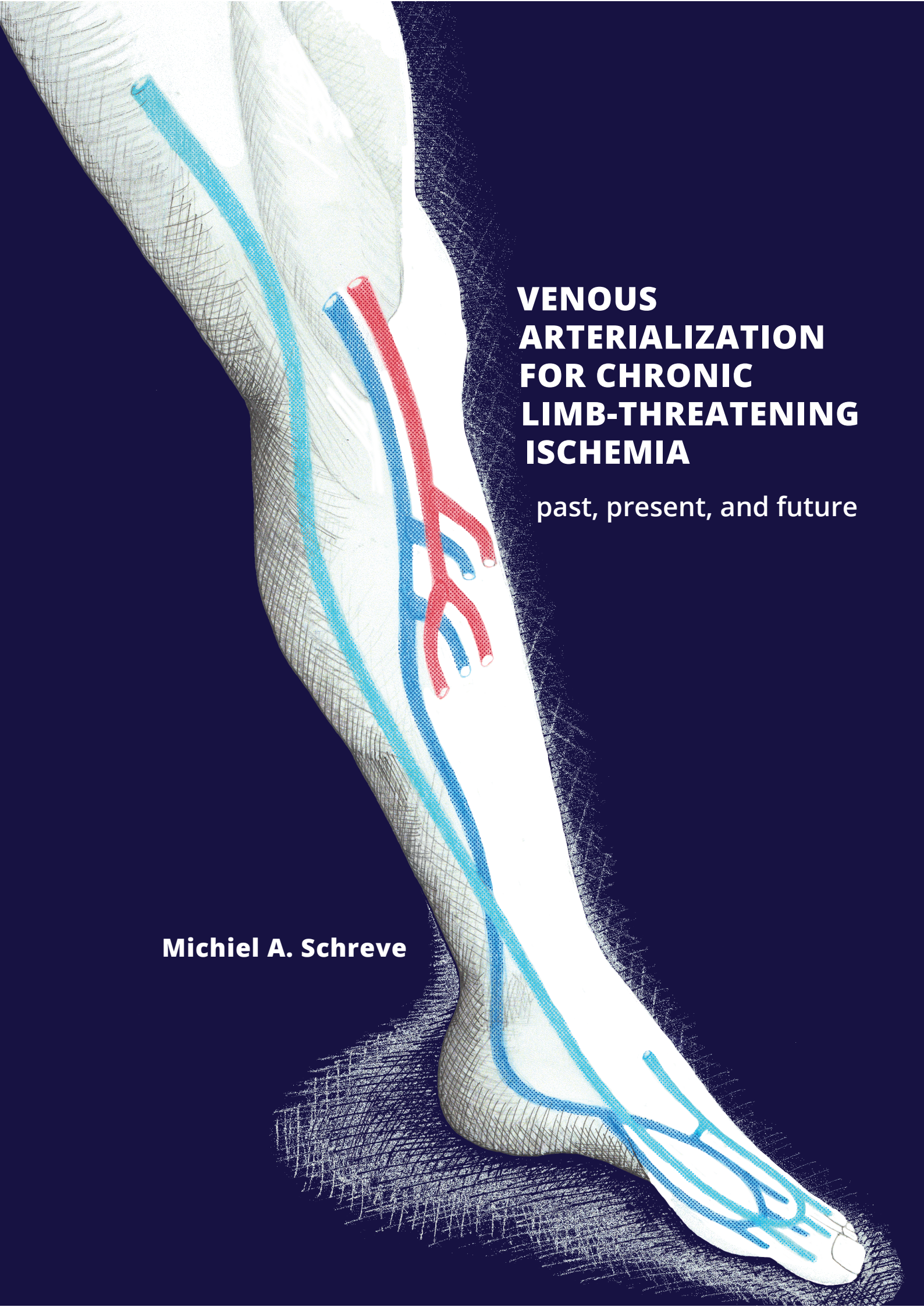

VENOUS ARTERIALIZATION FOR CHRONIC LIMB-THREATENING ISCHEMIA

past, present, and future

Michiel A. Schreve

Venous arterialization for chronic limb-threatening ischemia

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PhD thesis, University Medical Center Utrecht, with a summery in dutch

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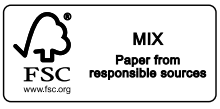

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Venous arterialization for chronic limb-threatening ischemia

past, present, and future

Veneuze arterialisatie bij patiënten met chronische kritieke ischemie van het been
verleden, heden en toekomst
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

woensdag 1 juni 2022 des middags te 2.15 uur

door

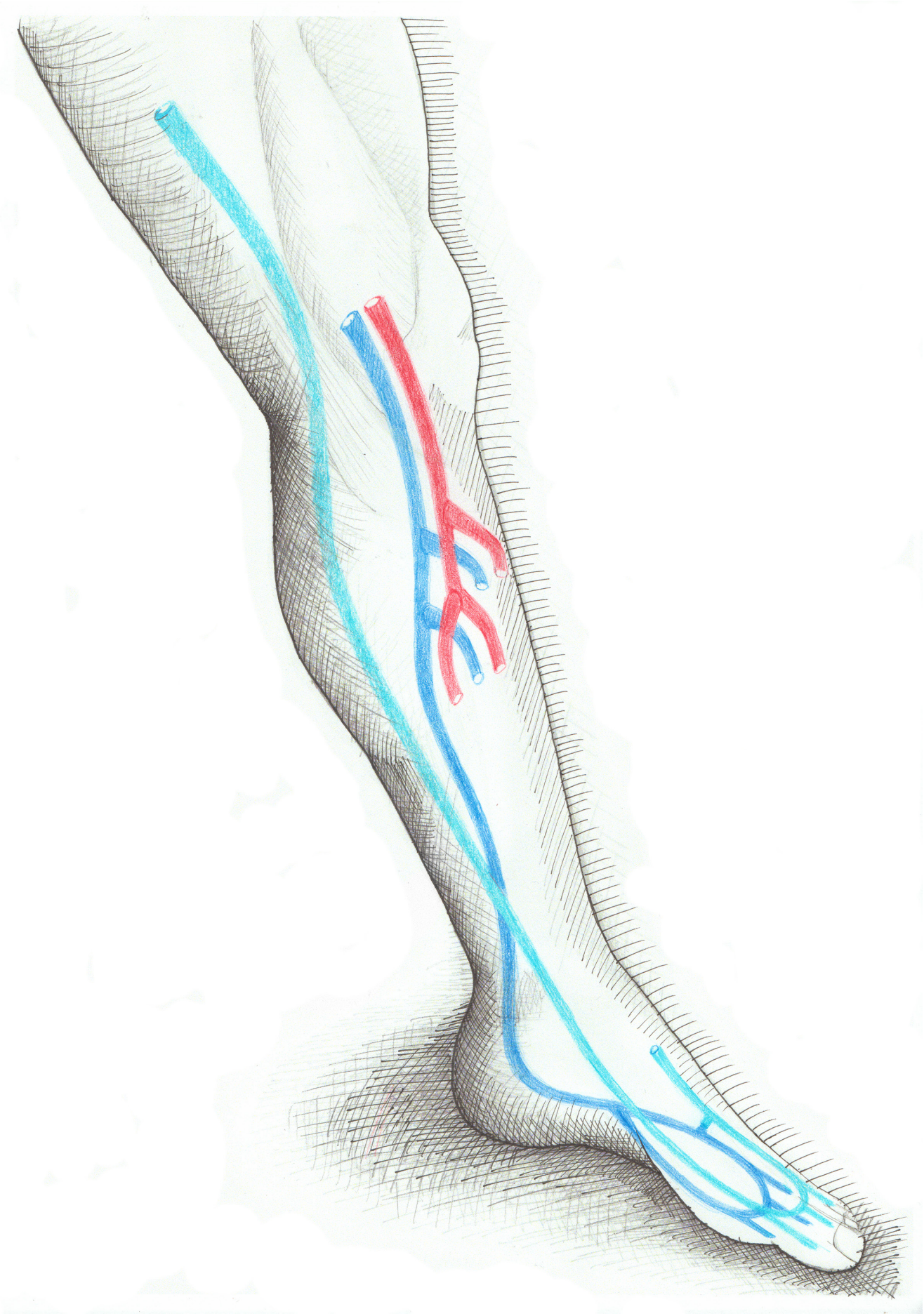
Michiel Alexander Schreve

geboren op 4 november 1973
te Leiden

Promotor:
Prof. dr. G.J. de Borst

Copromotor:
Dr. Ç. Ünlü

Table of Contents



Introduction

Chronic limb-threatening ischemia

Chronic limb-threatening ischemia (CLTI) is the clinical end stage of peripheral artery disease (PAD). CLTI will develop within 5 years in 5% to 10% of patients diagnosed with PAD aged older than 50 years.[1] These patients have a deplorable life expectancy, with a mortality rate of 20% after 1 year and 40% to 70% after 5 years.[2]

A tibial or pedal bypass operation or endovascular treatment may salvage the limb but depends on the presence of sufficient arterial outflow in the foot. Endovascular interventions with angioplasty and stenting have become the treatment of choice and are believed to be associated with a lower risk of morbidity and mortality compared with the classic open approach.[3]

Patients with CLTI, who are not suitable candidates for a vascular intervention are also referred to as no-option CLTI. When these patients are treated conservatively on a wait-and-see basis, the 1-year mortality and amputation rates are both approximately 20%. Spontaneous wound healing occurs in 10% to 20%, and 35% still have persisting wounds after 1 year.[4,5] Patients who need amputation and those with persisting wounds—jointly comprising 55%—could benefit from a suitable intervention but are not easily identified.

Different treatment options have been explored for patients with no-option CLTI, including stem cell therapy, spinal cord stimulation, and prostanoid therapy. A meta-analysis of placebo-controlled trials showed no advantageous effect of stem cell therapy on the primary outcome measures of amputation, survival, and amputation-free survival in patients with CLTI.[6] Another meta-analysis showed no benefit of prostanoid therapy or other types of medical treatment.[7] A Cochrane review concluded that spinal cord stimulation may be of some benefit in preventing amputation. However, evidence of these benefits is considered low, mainly because of imprecision and bias.[8]

For CLTI patients with no revascularization options, venous arterialization could be an alternative for limb salvage. Theoretical explanations for venous arterialization include direct nutrition of tissue[9] from reversed perfusion and increased flow, which stimulates angiogenesis.[10] The exact mechanism of action remains unclear. Attempts have been made to monitor these changes in microperfusion and pressure induced by reverse flow. It has been suggested that small connections between peripheral veins and arteries may open in response to the increased pressure.[11]

Historical background of venous arterialization

The first attempt to reverse flow was suggested and demonstrated by Carell and Guthrie in 1906, who performed a series of canine experiments to explore the possibility of an arteriovenous anastomosis in the groin.[12] The concept of using the disease-free venous bed as an alternative conduit for the perfusion of peripheral tissues with arterial blood was first proposed by Halstead and Vaughan in 1912.[13] The authors reviewed 42 cases and found only one patient in whom pulsation of the foot veins were observable on the day of surgery. The failure of the approach was primarily attributed to the formation of fistulae in the groin. The expectation of distal valves being destroyed by arterial pressure was proven incorrect. The operation was unpopular because of the difficulties of high-output cardiac failure, severe limb swelling, and progressive distal ischemia associated with proximal fistulae. In 1951, Szilagyi[14], using the technique of Halstead and Vaughan, reported failure in nine patients. Szilagyi showed that arterial pressure did not effectively destroy the valves, even if the latter were incompetent. As a result, this operation received very little interest until the end of the 1970s.

In 1977, Sheil[15] reported results of six patients who underwent venous arterialization of the great saphenous vein, highlighting the need for distal valve destruction and noting the lack of adequate perfusion to the forefoot when this step is omitted. In 1984, Lengua[16] reported a new concept with a more distal anastomosis on the superficial venous system, which yielded better results. Lengua described the outcome of the procedure in a series of 59 patients who were monitored for 15 years.[17]

Since then, the principle of arterialization has been used in different variations and under various conditions to improve tissue oxygenation in retrograde fashion. The key aspects of the success of the procedure are valve destruction and adequate blood flow to the forefoot. There was a revival of the technique, and many reports on venous arterialization have been published since, but with small numbers of patients. A systematic review and meta-analysis of these studies in 2017 concluded that venous arterialization could be a valuable treatment option in patients facing amputation, with a limb salvage rate of 75% after 1 year.[18]

The clinician's ability to identify patients with CLTI and recommend an optimal technique is rendered difficult by the variety of venous arterializations and low-volume studies.

Techniques of venous arterialization

Given the presence of a superficial and a deep venous system and the development of new techniques, different surgical and endovascular approaches are used for the venous arterialization.

Surgical techniques

The in situ superficial venous arterialization [Figure 1].

The superficial venous arch of the foot is used for arterialization. Separate incisions are performed to expose the infragenual great saphenous vein at the suitable site for the anastomosis and the median marginal vein of the foot for the treatment of valves. An anastomosis is created between the great saphenous vein and the appropriate inflow artery, which is usually the popliteal artery. A valvulotomy is performed by inserting an expandable valvulotome through a transverse venotomy at the median marginal vein. A small plastic or metal olive-shaped probe destroys, in antegrade fashion, the valves of the superficial venous arch. After the venotomy has been closed and all tributaries of the great saphenous vein have been ligated, a completion angiogram is performed to visualize the blood flow through the superficial venous arch in the foot.[19]

The superficial venous arterialization with a bypass [Figure 2]

The superficial venous arch of the foot is used for arterialization. An artificial bypass can be used or a vein is harvested, usually the great saphenous vein in the upper thigh. Separate incisions are used to expose the donor artery (femoral or popliteal artery) and the medial marginal vein at the foot. The conduit is tunnelled subcutaneously after a side-to-end anastomosis is created at the inflow artery. Through a venotomy in the medial marginal vein, the distal valves are destroyed with a probe, and an end-to-side anastomose is created. A completion angiogram is performed to visualize the blood flow through the superficial venous arch in the foot.[16]

FIGURE 1. The superficial venous arterialization

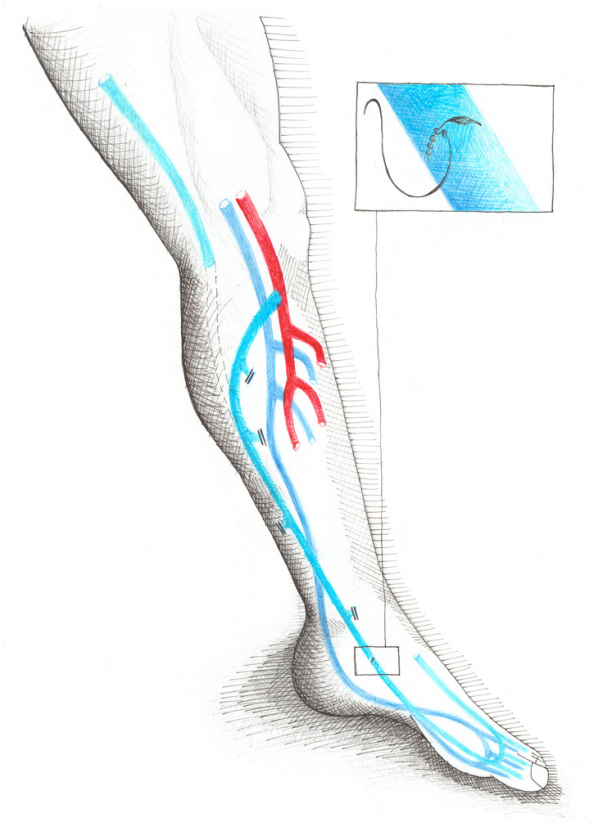
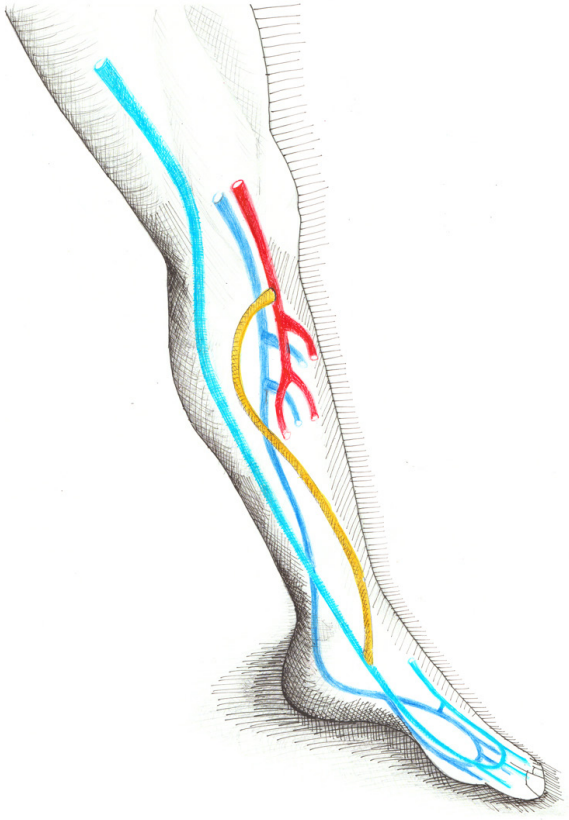


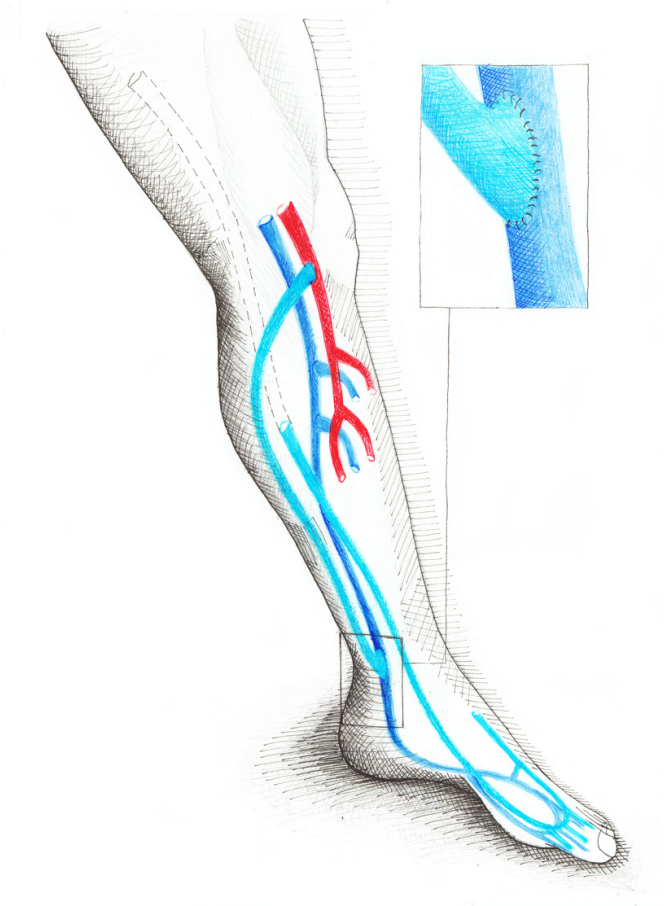
FIGURE 2. The superficial venous arterialization with a bypass



The deep venous arterialization [Figure 3]

The difference in this technique is that the outflow is directed toward one of the deep veins of the foot. An anastomosis to one of the concomitant veins of the posterior tibial artery at the malleolar level or even one of the concomitant veins of the plantar artery is commonly used. The deep venous arterialization can be performed with an in situ technique[20] or with any other bypass[21]. A theoretic advantage of deep venous arterialization is that it does not rely on the communications between the saphenous vein and the deep system below the ankle to perfuse the foot because the flow is directed to the foot through the deep system. A second advantage is that fewer valves need to be destroyed compared with superficial venous arterialization, as the last valve is located halfway in the foot. The distal anastomosis may prove to be a technical challenge.

FIGURE 3. The deep venous arterialization

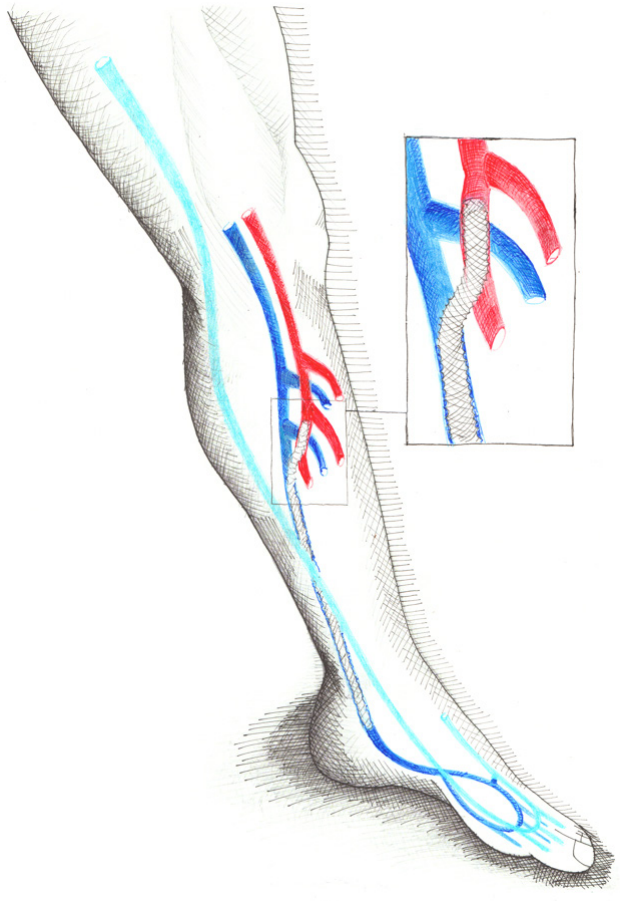


The endovascular technique of the venous arterialization

The percutaneous deep vein arterialization [Figure 4]

The percutaneous deep vein arterialization (pDVA) is an endovascular method to achieve venous arterialization. Arterial access is gained at the groin and venous access at the ankle or foot. A crossing device is used to make the connection between the artery and vein by creating an arteriovenous fistula. The crossing is usually at the proximal part of one of the tibial arteries, but more proximal or distal is also possible. After the crossing from artery to vein is established, the wire is secured in the target vein in the foot. Then, the valves are destroyed with an over-the-wire push valvulotome and balloon angioplasty. A covered crossover stent is placed to secure the arteriovenous fistula. The crossover stent is subsequently extended with multiple 5-mm self-expanding covered stents to the level of the ankle. The extension stents prevent the blood, returning to the heart by covering the multiple venous collaterals that may "bleed off" the flow to the foot.[22]

FIGURE 4. The endovascular technique of the venous arterialization



The alternative hybrid approach of the venous arterialization

The hybrid approach is a combination of a surgical bypass and an endovascular treatment of the distal part or outflow of the venous arterialization.[23] The hybrid approach can be performed on the superficial and the deep system.

Thesis Outline

The aim of this thesis is to study the clinical outcome of the venous arterialization in patients with no-option chronic limb-threatening ischemia.

The introduction and Chapter 1 of this thesis provides an update on the history and development of the venous arterialization.

The first part provides information about the open superficial venous arterialization. In Chapter 2, a superficial venous arterialization cohort of two Dutch hospitals is analysed. Chapter 3 contains a systematic review of literature and a meta-analysis that provides an update of all reported patient cohorts with a venous arterialization up to 2016.

The second part is about the percutaneous deep venous arterialization (pDVA) with the LimFlow procedure. In Chapter 4, the first experience of the pDVA in humans is published. The experience from four centers between 2014 and 2018 is analysed in Chapter 5. New studies have been developed and started. Chapter 6 contains the protocol of the PROMISE International study, an international multicenter study of the pDVA.

The last part of this thesis is about the postinterventional care and follow-up of the venous arterialization. In Chapter 7, we analyse postoperative duplex ultrasound measurements in a two-center cohort. Chapter 8 provides a guideline for post-pDVA wound care, based on literature and the clinical experience from two centers, Singapore and Alkmaar.

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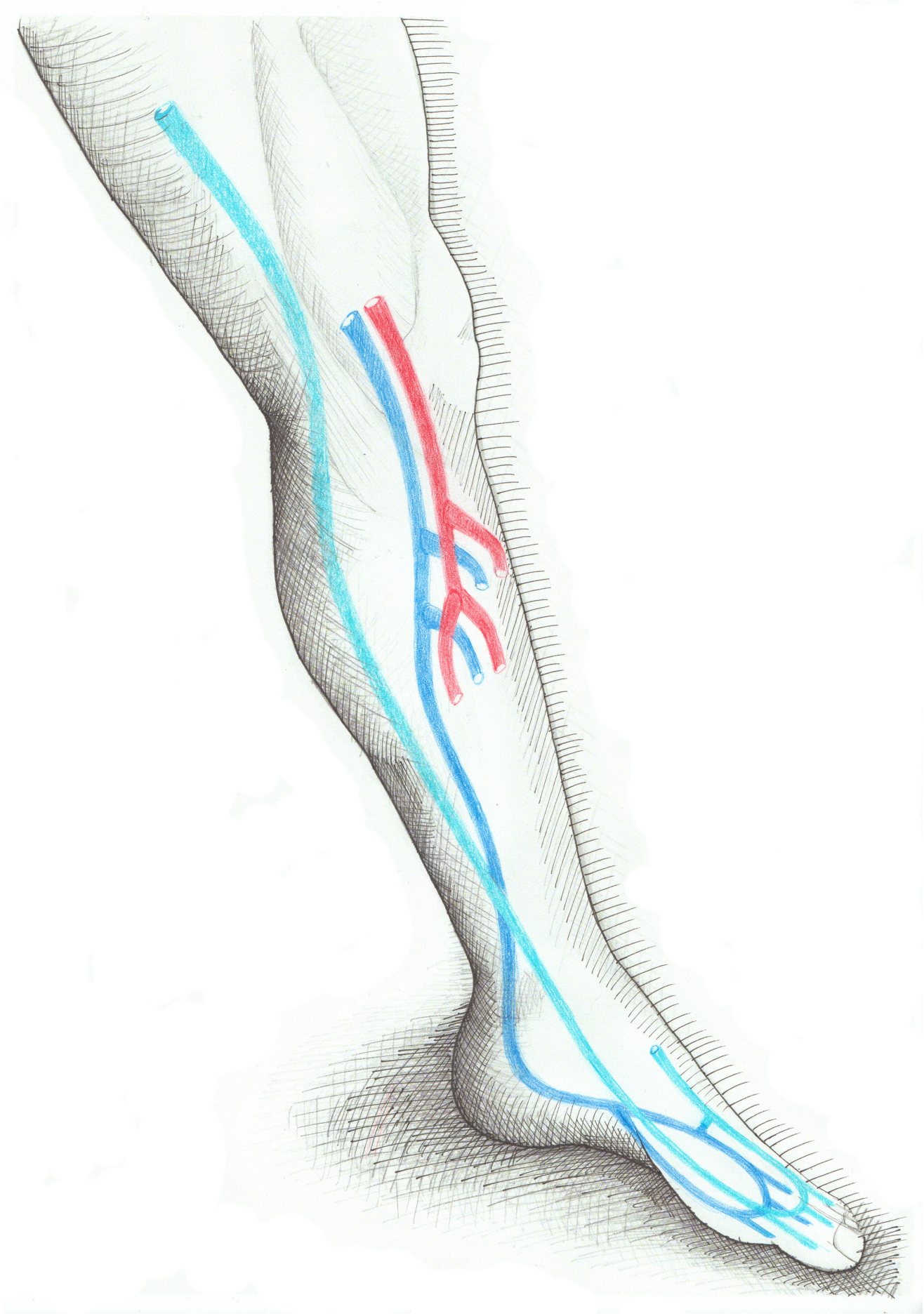


Chapter 1

Surgical and endovascular venous arterialization: ready to take the “desert” by storm?

Schreve MA, Ünlü Ç, Kum S, Tan YK

J Cardiovasc Surg (Torino). 2017 Jun;58(3):402-408.

Abstract

Patients with critical limb ischemia have a poor life expectancy, and aggressive revascularization is accepted to maintain their independence in the end stage of life. Bypass surgery and, more recently, endovascular interventions with angioplasty and stenting have become the treatment of choice to prevent amputation and resolve rest pain. Up to 20% of patients with critical limb ischemia are not suitable candidates for a vascular intervention because of extensive occlusions of the outflow in the crural and pedal vessels. This "desert foot" can be treated with a venous arterialization. In this review, we discuss the mechanism, the techniques, outcome, and complications of venous arterialization.

Introduction

Critical limb ischemia (CLI) is the clinical end stage of peripheral artery disease (PAD), and 5% to 10% of patients aged older than 50 years will develop critical limb ischemia (CLI) within 5 years.[1] Patients with CLI have a poor life expectancy, with a mortality rate of 20% after 1 year and 40% to 70% after 5 years.[2] Only 40% of all patients are mobile 2 years after a below-knee amputation, and even fewer are mobile outside their homes.[3]

Bypass surgery and, more recently, endovascular interventions with angioplasty and stenting have become the treatment of choice to prevent amputation and resolve rest pain. Endovascular interventions are thought to carry a lower risk of morbidity and mortality.[4]

In the last decade, new treatment options have been explored for patients with CLI for whom a surgical or endovascular revascularization is not an option. These include stem cell therapy, spinal cord stimulation, and prostanoids therapy. A meta-analysis of placebo-controlled trials showed no advantage of stem cell therapy on the primary outcome measures of amputation, survival, and amputation-free survival in patients with CLI.[5] Another meta-analysis showed no benefit for prostanoids treatment or other medical treatments. [6] A Cochrane review concluded that spinal cord stimulation may have some benefit for prevention of amputation; however, evidence is considered as very low grade, mainly as a result of imprecision and increased risk of bias.[7]

For CLI patients with no revascularization options, venous arterialization could be an alternative technique for limb salvage. It has been thought to improve the circulation of the leg when the recipient distal artery is too arteriosclerotic to allow a distal anastomosis of a bypass operation. The pedal capillaries are believed to fill up retrogradely through the venous system despite the steal effect produced by the connection of the artery to the venous system. Flow in existing collateral vessels will increase, and reversal of flow all the way through the capillaries improves tissue nutrition [8] and possibly stimulates angiogenesis.[9]

The concept of using the disease-free venous bed as an alternative conduit for perfusion of the peripheral tissues with arterial blood was first published by Halstead and Vaughan in 1912.[10] They reviewed 42 cases and found only one patient in whom the foot veins were seen to pulsate on the day of surgery. Lack of success was related primarily to construction of fistulae in the groin, and the

hope that the distal valves would be broken down by arterial pressure proved incorrect. The operation was unpopular because of the difficulties of high-output cardiac failure, severe limb swelling, and the progressive distal ischemia associated with the proximal fistulae. In 1951, Szilagyi [11] reported failure in nine patients using the same technique as Halstead. Such findings meant that little further interest was shown in this type of surgery until the end-1970s. Sheil [12] reported success in six patients, highlighting the requirement of valve destruction and noting the lack of adequate perfusion to the forefoot if this step was omitted. Since then, the principle of arterialization has been used in different varieties and conditions to improve tissue oxygenation retrogradely. The key of the succes is valve destruction and adequate perfusion to the forefoot. Many reports have been published since then on venous arterialization, however, with only small number of patients. A systematic review in 2006 of these studies concluded that venous arterialization may be considered a viable alternative before major amputation, with a limb salvage of 71% after 1 year.[13]

The ability of clinicians to recommend an optional technique for their patients is made harder by the variety of venous arterializations and low-volume studies. This review aims to inform clinicians about the outcomes and complications of all of the different modalities for venous arterializations and describes the various open techniques and new developments on percutanous technique.

Surgical technique of the superficial venous arterialization

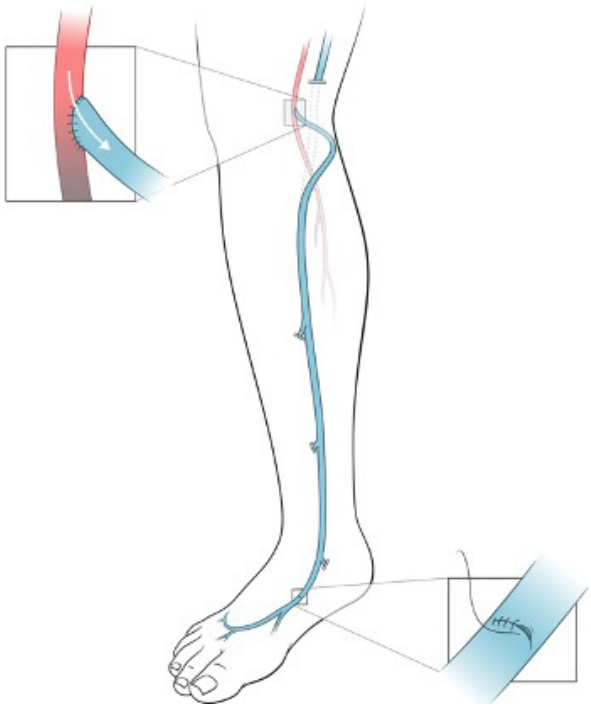
The operation is performed under anesthesia with prophylactic antibiotics. Using separate incisions, we expose the infragenual great saphenous vein at the suitable site for the anastomosis and the median marginal vein of the foot for treatment of the valves. After intravenous heparin administration, an anastomosis is created between the great saphenous vein and the appropriate inflow artery, normaly the popliteal artery (figure 1). A valvulotomy is performed by inserting an expandable valvulotome through a transversal venotomy at the median marginal vein. A small plastic probe destroys the distal valves of the hallux and superficial venous arcus. An angiogram is made after the venotomy is closed, and all tributaries of the great saphenous vein are ligated. A completion angiogram shows perfusion of the foot through the superficial venous arch.

Surgical technique of the deep venous arterialization

The difference in this technique is that the outflow is directed toward one of the deep veins of the foot. An anastomosis to one of the concomitant veins of

the posterior tibial artery at the malleolar level or even the plantar artery is common. A theoretic advantage of deep venous arterialization is that it does not rely on the communications between the saphenous vein and the deep system below the ankle to perfuse the foot. Rather the flow is directed first to the foot via the deep system and then subsequently to the saphenous system if the valves are properly destroyed. A second advantage is that there are fewer valves to be destroyed compared with superficial venous arterialization.

FIGURE 1. The superficial venous arterialization



Alternative hybrid approach

Another possibility is the hybrid approach where the distal anastomosis of an infragenual bypass is created at the level of the popliteal veins, followed by endovascular embolization of venous branches or covered stent placement. The valves of veins on the foot still have to be destroyed separately by an incision on the foot.[14]

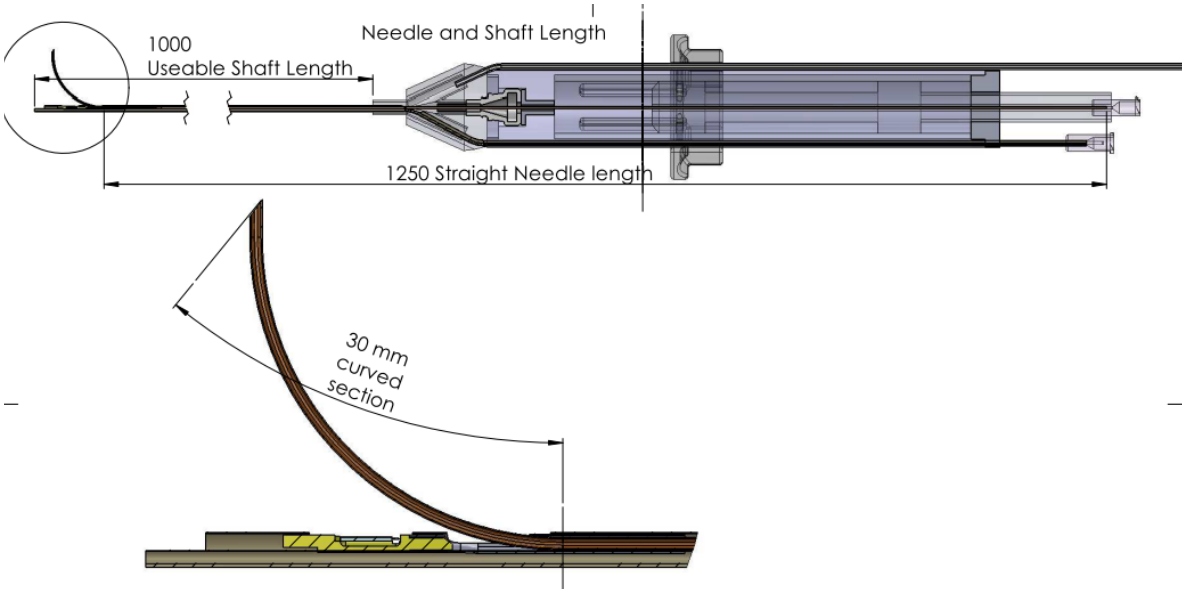
The endovascular technique of the venous arterialization

The novel endovascular or percutaneous deep vein arterialization uses an endovascular method to achieve venous arterialization. A novel system from Limflow (Limflow SA) has recently been CE marked for this indication. The endovascular system consists of four main components: an arterial ultrasound

catheter with needle, a venous ultrasound catheter, a covered nitinol stent in a 7F delivery system, and an ultrasound system with a laptop computer.

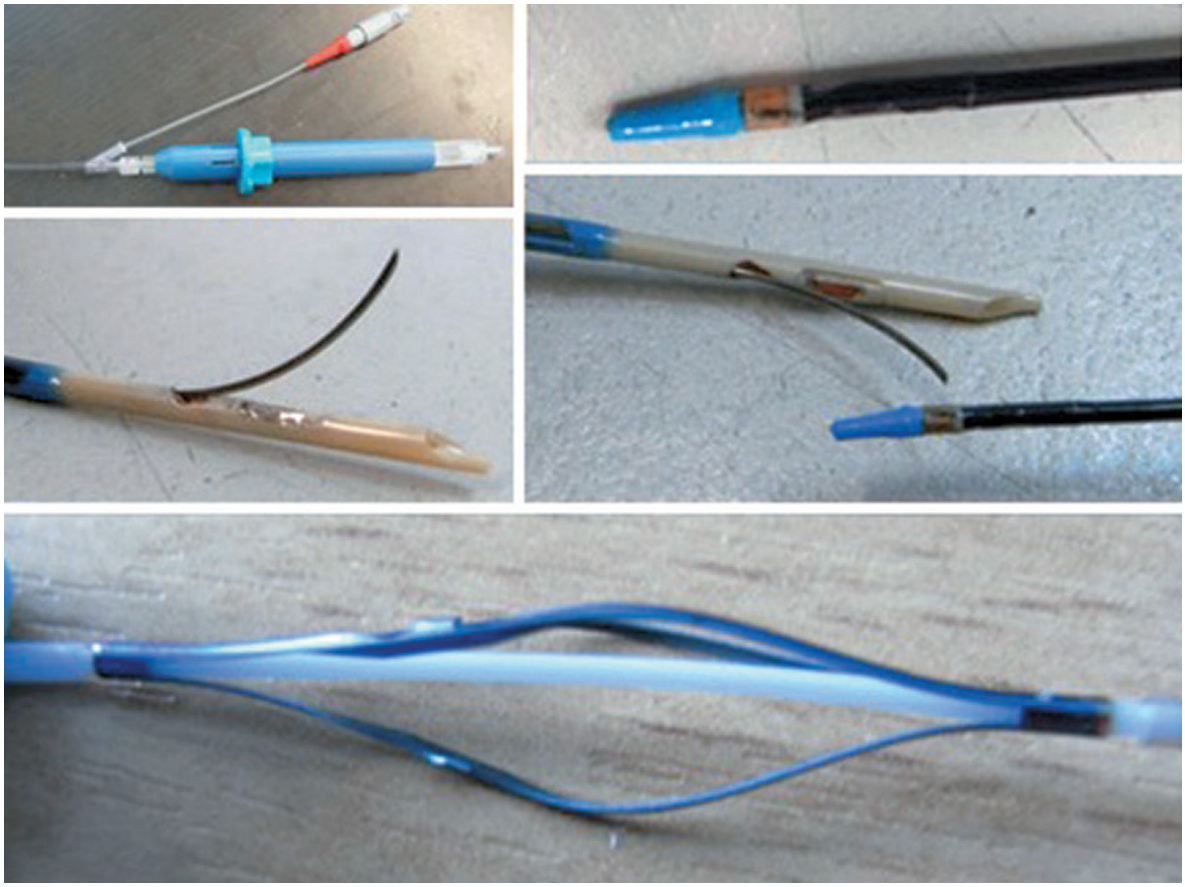
Figure 2 is a drawing of the arterial ultrasound catheter with needle. The catheter is placed over a standard 0.014-inch guidewire using a monorail system and is placed through a sheath in the femoral artery and advanced distally to the tibial artery up to the point of the intended crossing. The handle of the catheter has a pusher ring that advances the crossing needle from artery to vein. A standard 0.014-inch guidewire can be inserted through the needle from the proximal hub and is referred to as the crossing wire.

FIGURE 2. Arterial ultrasound catheter with needle



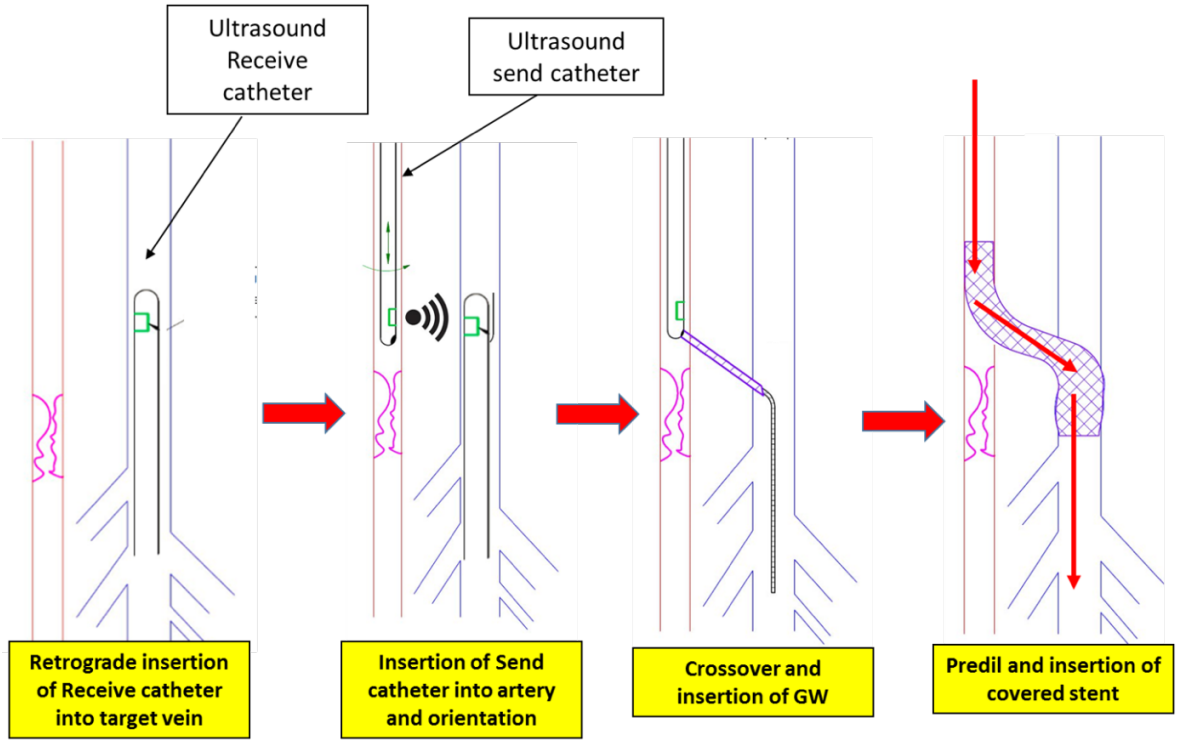
The venous access was achieved by ultrasound-guided puncture of the tibial vein around the ankle. The choice of target vein arterialization/access includes the size of the vein and the location of the wound based on the angiosome/"venosome" concept. The venous catheter is placed over a standard 0.014-inch guidewire and is placed through a 5F sheath positioned in the target vein at the distal extremity. The venous catheter is advanced from the ankle in a proximal direction up to and parallel to the arterial ultrasound catheter. The venous ultrasound catheter is a simple catheter that receives an ultrasound signal from the arterial catheter and acts as a target in the vein for aligning the needle of the arterial ultrasound catheter. The venous ultrasound catheter is left in place while the arterial ultrasound catheter is rotated and moved longitudinally to achieve a peak ultrasound signal (Figure 3).

FIGURE 3. (a) Arterial Catheter with Handle, (b) Arterial Catheter with crossing needle, (c) Venous Catheter, (d) Alignment of both catheters, (e) Over the wire Valvulotome



The procedure is summarized in Figure 4. After the peak ultrasound signal is achieved, indicating optimal alignment of the arterial and venous catheter, the needle of the arterial ultrasound catheter is advanced into the tibial vein. This is termed the "crossover procedure" at the "crossover point." A standard guidewire is installed through the crossing needle, which after predilatation allows for the deployment of a covered stent (the crossover stent), creating the arteriovenous fistula. Finally, both catheters are removed after stent dilation.

FIGURE 4. Step-by-Step Illustration of the PDVA Procedure.



The covered crossover stent creates the deep vein arterialization (DVA). It prevents leakage at the crossover point and also drives the blood distally, preventing the blood from returning toward the heart. The covered stent is a self-expanding tapered covered stent. The crossover stent is subsequently extended with multiple 5-mm self-expanding covered stents (the Extension Stents) to the level of the ankle. The extension stents serve as an endoconduit. They address the issue of the multiple valves in the tibial veins that may impede flow as well as cover the multiple venous collaterals that may "bleed off" the flow to the ankle. The extension stents also ensure a large caliber of flow to the ankle.

Distal to the covered stents at the ankle, a novel 4F over-the-wire forward-cutting valvulotome that destroys the valves distal to the covered stent, some occurring as distal as the midfoot. This is in contrast to a conventional surgical valvulotome that is pulled rather then pushed.

Patient selection

Patient selection is the key for successful outcome. Not all patients are candidates for venous arterialization, and even without intervention, a proportion of patients with CLI will be able to keep their limb. Comparative studies are lacking, although Matzke et al [15] showed that wound care and pain relief lead to a 50% limb salvage after 12 months, which suggests that not

all patients need revascularization. However, in the studies by Djoric et al [16, 17], 13% limb salvage was observed in patients treated by conservative means, whereas 83% and 93% limb salvage was obtained in the venous arterialization group. These findings and the differences in the limb salvage rate suggest that patient selection is important.

Patient selection should be based on radiologic and clinical criteria and concerns patients with CLI with no arterial revascularization options. If no pedal artery is available but the deep vein and venous arch of the foot are patent, a percutaneous deep vein arterialization can be performed. Clinically, the foot should have a wound, ischemia, and foot infection (WIfI) classification of W0-2, I3, and FI0-2 score, and the necrosis should not proceed to the metatarsal bones, thus, providing options for a forefoot amputation.

Outcome

Surgical Venous Arterialization

A critical appraisal and search of the current literature identified 418 studies. Excluding case reports and case series (n < 10), reviews, abstracts, animal studies, and in addition, studies not reporting limb salvage, wound healing, or amputation as outcome measures, 15 papers are included.

Limb salvage

Limb salvage was reported in all included studies. However, the exact definition of limb salvage varied and was not further defined in some studies. Seven studies reported limb salvage rates at 1 year that ranged from 57% to 79%.[14, 15, 18-22] Engelke et al [23] reported a limb salvage rate of 75% at 2 years and overall limb salvage of 83% with a mean follow-up of 25 months (range, 9-48 months).

The remaining seven studies reported limb salvage rates without specifying the postoperative interval at which limb salvage was measured.[16, 17, 24-26] Limb salvage ranged from 30% to 100% in these studies, and mean follow-up ranged from 4 to 23 months. The study by Wu et al [26] reported 100% limb salvage in 156 patients (212 limbs), with a mean follow-up of 10 months (range, 3-27 months). A comparative study between the conventional surgical pedal bypass and the superficial venous arterialization showed equivalent limb salvage results. [22]

Mortality, survival, and patency

The 30-day or in-hospital mortality was reported in 12 studies and ranged

from 0% to 10%.[14-16, 20, 21, 25] Survival at 12 months was reported in three studies and ranged from 85% to 93%.[24, 21, 22] Overall survival was reported in 10 studies and ranged from 54% to 100%, with a mean follow-up of 5 to 60 months.[14, 16-18, 21, 22, 24, 25]

Six studies reported the patency of the venous arterializations performed. The study by Mutirangura et al [21] described a primary patency of 59.0% ± 1.1% at 12 months and 49.2% ± 1.3% at 2 years. Alexandrescu et al [14] reported only secondary patency, which was 66% ± 9% at 12 months and 48% ± 14% at 3 years. Engelke et al [12] reported a primary and secondary pateny of 66% and 72%, respectively, with a mean follow-up of 25 months (range, 9-48 months). Two studies reported a mean patency of 8.5 and 15 months, respectively [18, 20], and another study reported a patency of 71% at 12 months.[22] In the latter three studies, patency was not further defined (ie, primary, primary assisted, or secondary patency).

Percutaneous DVA

In the case-series of Kum et al [27], percutaneous DVA (PDVA) was performed in seven patients with no-option CLI, defined as CLI with no traditional endovascular or surgical revascularization options. The primary safety end point was achieved in 100%, with no deaths, above-ankle amputations, or major reinterventions at 30 days. Also, the technical success rate was 100%. Two adverse cardiac events occurred within 30 days. All patients demonstrated symptomatic improvement, with formation of granulation tissue, resolution of rest pain, or both. Complete wound healing was achieved in 4 of 7 (57.1%) at 6 months and in 5 of 7 (71.4%) at 12 months, with a median healing time of 138 days (95% confidence interval, 84-192 days**).** The median postprocedural maximum transcutaneous oxygen measurement was 61.5 mm Hg compared with a preprocedure level of 8 mm Hg (p = 0.046). There were two major amputations (28.9%), one above the knee for infection and the other below the knee after PDVA graft thrombosis. This resulted in limb salvage rates of 85.7% at 6 months and 68.6% at 12 months. The mortality at 12 months was 42.9%, with each unrelated to the procedure or study device.[27]

Discussion

Objectively, one may consider classic CLI as a patient with a non-healing wound or distal gangrene associated with no distal pulses and a low TCPO2 of less than 40mmHg in the absence of confounding factors like edema or infection

that may falsely depress the TCPO2.[28]

The entity of no-option CLI is a poorly defined clinical condition that implies the lack of surgical or endovascular revascularization options in a patient who presents with CLI. Surgically, this implies the inability to perform a conventional distal bypass is usually due to the lack of a reasonable target vessel to bypass to. This may be due to the size of the surgical target or the quality of the vessel, which may be affected by severe calcification. For endovascular revascularization, it implies small distal target vessels of poor quality, resistant calcification and recoil, and the lack of an option for frequent below-the-knee restenosis. It is imperative that before a patient is labelled no-option CLI, a reasonable attempt at endovascular intervention by an experienced operator in contemporary techniques is performed. In this context, we feel that venous arterialization is a valuable treatment option.

Most patients with CLI are in an end-stage of their life. In a recent meta-analysis of no-option CLI studies, it was observed that the mortality rates ranged between 10 to 54.3% and the proportion of diabetics in these studies ranged from 19.2% to 54%.[29]

It is reasonable to assume that their functional reserves are poor and therefore imperative that medical comorbidities are optimised and an assessement of the "risk benefit ratio" of revascularisation is done. In addition, some have wounds that are unsalvageable or have infection so extensive that would preclude a reasonable attempt at limb salvage. These patients are better served with a primary amputation.

With regards to technical aspects, it is essential for the operator to understand the venous anatomy of the foot. Correct orientation and avoidance of twisting of the target segment of vein, meticulous handling of the vein segments and careful attention to the anastomosis. Another technical aspect is the need to address the issue of valves. Valves are a beauty of nature. However, their simplicity of construction can be deceiving when attempting to circumvent. It is widely believed that perfusion of the venous arch, of the foot, is the key to succes and associated with wound healing. A combination of probes, wires, balloons and even forward cutting over the wire push valvulotomes help to this end.

A common finding post procedure, is swelling of the leg. In our experience, the swelling can be managed conservatively with elevation and, occasionally, diuresis. Our impression is that the patient should be nursed with leg elevation

and off-loading measures if significant swelling is seen. Subsequently, the patient can be nursed with legs down to allow the hydrostatic pressure to encourage further formation of venous collaterals. AV formation can be seen even if the graft is occluded, and arterial flow is found with persistent high transcutaneous oxygen measurement.[21, 27]

In summary, chronic CLI is a significant facet of atherosclerotic disease that has significant medical and functional consequences. With the rise of diabetic patients, improved life expectancy, greater awareness and wider adoption of endovascular techniques, amputation rates continue to fall.[30,31,32] We expect that patients will be older, have more advanced comorbidities, will have had more prior interventions, limiting current options. This may translate to a greater proportion of them presenting with no-option CLI. Venous arterialisation may be a viable alternative to preserving limbs. The percutaneous approach shows promise and is a minimally invasive technique to reduce surgical stress in this vulnerable patient group.

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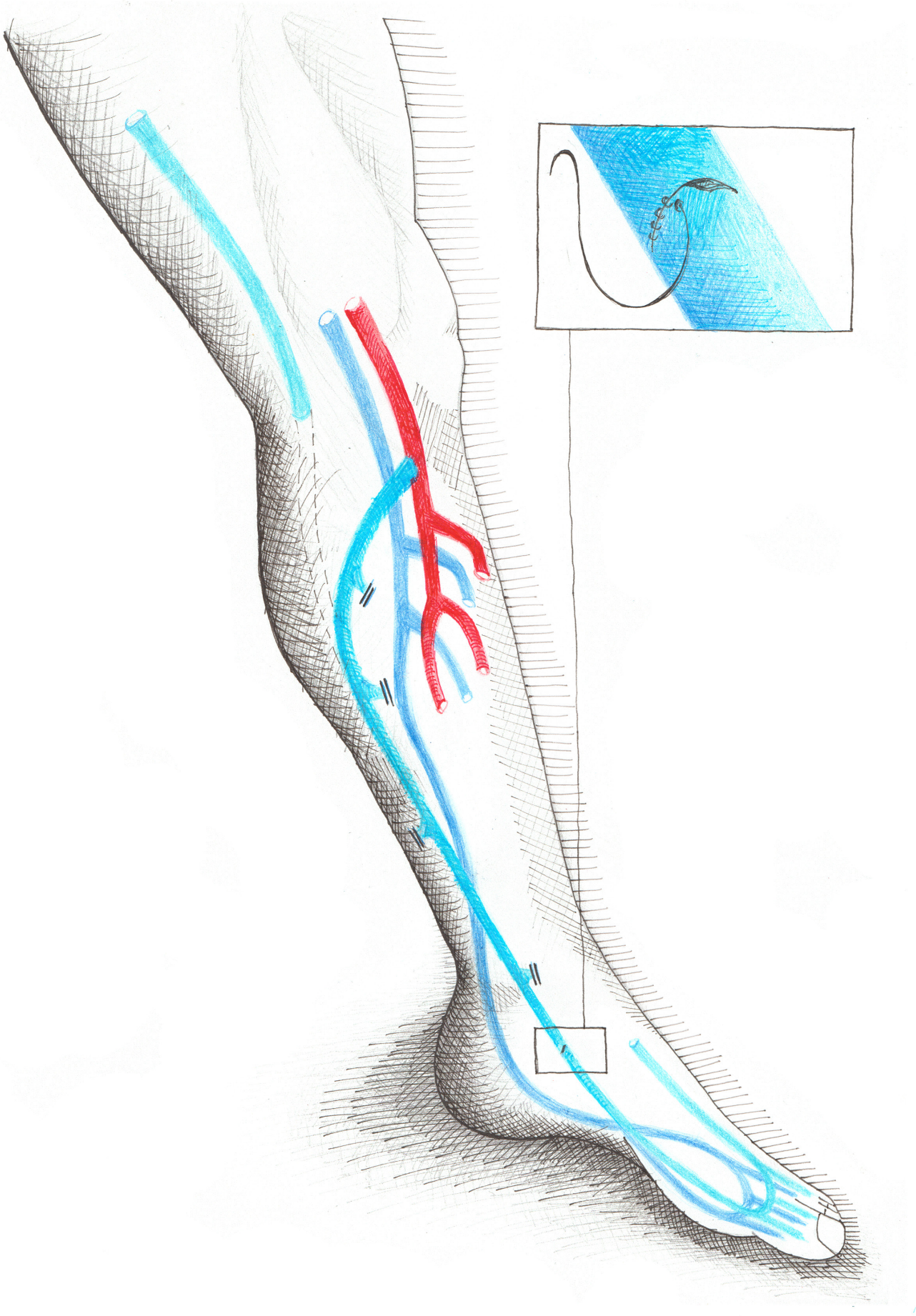
Part 1

Open venous arterialization



Chapter 2

Comparative study of venous arterialization and pedal bypass in a patient cohort with critical limb ischemia

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Ann Vasc Surg. 2014 Jul;28(5):1123-7

Abstract

Objectives

Patients with critical limb ischemia (CLI) have a poor life expectancy, and aggressive revascularization is accepted as a means to maintain their independence in the end stage of life. The goal of this case-control study was to evaluate the clinical outcome of distal venous arterialization and compare this with pedal bypass surgery in patients with CLI, and to identify potential risk factors that could be used to effectively identify patients at high risk of graft occlusion and amputation.

Methods

A retrospective cohort of patients was treated for CLI using venous arterialization or
pedal bypass between 2007 and 2012. Kaplan-Meier and Cox regression analyses were used to evaluate predictors for limb salvage and patency.

Results

In 40 patients with CLI, 21 venous arterializations and 19 pedal bypasses were performed.
In the venous arterialization group, early occlusion was 15%, 1-year patency was 71%, and limb salvage was 53%. In the PB group, early occlusion was 23%, one-year patency was 75% and limb salvage was 47%. The only independent risk factor for limb salvage in multivariate analysis was bypass occlusion ($P < 0.001$).

Conclusions

Limb salvage after venous arterialization was equal to limb salvage after pedal bypass surgery in this clinical comparative study.

Introduction

Patients with critical leg ischemia (CLI) have a poor life expectancy, with mortality rates of 20% after 1 year and 40e70% after 5 years.[1] The primary goal of aggressive revascularization in these patients is to maintain their independence in the end stage of life. Approximately 14-20% of patients with CLI have nonreconstructable distal arterial occlusive disease. Most of these patients must undergo a major amputation. Only 40% of all patients after a below-knee amputation are mobile after 2 years, and even fewer are mobile outside their homes.[2]

Alternative treatment options such as spinal cord stimulation or prostaglandins therapy have limited clinical effectiveness. However, a viable alternative is distal venous arterialization of the foot, which shows a secondary patency rate of 46% and limb salvage rate of 71% after 1 year.[3] Several theoretical reasons may explain why venous arterialization might be beneficial in patients with nonreconstructable CLI, including tissue nutrition, increased flow in existing collateral vessels, and stimulation of angiogenesis.

It has been questioned whether venous arterialization of the foot relieves distal critical ischemia and prevents amputation, because the underlying physiologic process is difficult to comprehend. Venous arterialization is not common practice, and the authors' hypothesis is that venous arterialization is a bypass with a higher flow compared with the pedal bypass, and therefore has a better patency. The authors question whether it provides better clinical results. Therefore, they performed a retrospective analysis to investigate the clinical effectiveness of venous arterialization for lower limb salvage and compared this with pedal bypass surgery. The goal of this study was to evaluate the outcome of distal venous arterialization compared with pedal bypass surgery in patients with CLI, and to identify potential risk factors that could be used to identify patients at high risk of graft occlusion and amputation.

Patients and Methods

A retrospective analysis was performed on a patient cohort of patients with CLI who underwent surgery between 2007 and 2012, in whom pedal bypass surgery was performed on either the venous or the arterial vasculature in the foot. Patients with crural revascularization procedures were excluded. All had severe ischemic persistent pain at rest and ulceration, gangrene, or both

(Fontaine classification 4). All patients had digital subtraction angiography of the arterial tree of the leg, including the arterial foot vessels distal to the ankle joint. Whenever possible, according to the angiographic findings, a pedal artery (posterior tibial or dorsal pedal artery) was used as the target vessel for distal anastomosis. When no pedal artery was available and the venous arch of the foot was still intact, a venous arterialization of the great saphenous vein on the dorsal foot was considered. For both procedures, sufficient autologous venous material had to be available (ipsilateral vein of sufficient length with a diameter > 2.5 mm). At the end of each procedure the volume flow in the bypass was measured. Postoperatively a synthetic Coumadin® (acenocoumarol) was administered for 2 years.[4]

Surgical Techniques for Venous Arterialization and Pedal Bypass

The procedures were performed under spinal or epidural anesthesia with prophylactic antibiotics and intravenous heparin administration (100 IU per kilogram of body weight) just before arterial clamping. Using separate incisions, the median marginal vein of the foot, the great saphenous vein, and the inflow artery were exposed. The proximal anastomosis was created between the great saphenous vein and the appropriate inflow artery. An in situ technique was applied. The disposable Expandable LeMaitre® Valvulotome (Sulzbach/Ts., Germany) was inserted through a transverse venotomy at the origin of the median marginal vein to cut the more proximal valves in the vein. A small plastic probe was inserted distally to cut the distal valves of the hallux and superficial venous arch. Indirect perfusion of the foot was established through the dorsal superficial venous arch by closing the venotomy and ligating the side branches of the great saphenous vein, which were found with the help of an intraoperative flow measurement device. At the end of the operation, completion Doppler and flow measurements were performed. For the pedal bypass, the posterior tibial or dorsal pedal artery at the foot was explored. The great saphenous vein was used as a conduit and an end-to-side anastomosis with the target artery was performed.

Postoperative Care

Postoperatively, all patients were treated equally with regard to pain regulation, mobilization, and postoperative care. Pain medication consisted of standard paracetamol, 500 mg 6 times per day or piritramide, 10 mg, or tramadol, 50 mg, 3 times per day. Acenocoumarol was administered to all patients with a target international normalized ratio between 2.5 and 3.5. All patients received preoperative and postoperative statins (simvastatin, 40 mg). All other medication was continued. The patient and physician determined timing of

discharge. Follow-up was on clinical basis, and with duplex graft surveillance at 6 weeks and 6 months. Hereafter duplex surveillance was performed on indication.

Statistical Analysis

Univariate and multivariate logistic regression analysis was performed to identify independent risk factors for limb salvage and patency. Multivariate logistic regression analysis was performed on all factors with a p-value of less than 0.20 in the univariate analysis. The variables included in the univariate analysis were male sex, smoking, diabetes, hypertension, heart disease, chronic kidney failure, ankle-brachial index, venous arterialization, wound infection, graft thrombosis, rebleeding, amputation, and bypass occlusion. The chi-squared test was used to analyze discrete data between groups. Survival analysis was performed using the Kaplan-Meier technique and the log-rank test. A p-value of less than 0.05 was considered statistically significant. Statistical analysis was done using SPSS version 18 (SPSS, Chicago, IL, USA).

Results

In 40 patients with CLI, 21 venous arterializations and 19 pedal bypasses were performed in the authors' hospital between 2007 and 2012. Patient characteristics are shown in Table I.

TABLE I. Patient characteristics

Variable	Venous arterialization (21)	Pedal bypass (19)	Univariate analysis *p*[1]
Age (mean±SD)	63.3 ± 16.8	66.8 ± 15.5	0.49
Male sex (no(%))	15 (71%)	12 (63%)	0.58
Smoking (no(%))	6 (29%)	7 (37%)	0.25
Hypertension (no(%))	16 (76%)	16 (84%)	0.53
Diabetes(no(%))	15 (71%)	15 (79%)	0.58
Heart disease (no(%))	10 (48%)	5 (26%)	0.17
Chronic renal failure (no(%))	7 (33%)	1 (5%)	0.012
Hospital stay (days, mean±SD)	27.6 ± 22.7	34.7 ± 29.8	0.40

[1]Chi-square test or Mann-Whitney *U* Test
SD, standard deviation.
aChi-squared test or Mann-Whitney U test used in the univariate analysis.

The most distal satisfactory artery was used as the inflow artery, and if possible the great saphenous vein (nonreversed) was used as a conduit. In the venous arterialization group, the popliteal artery was always used as the inflow artery, whereas in the pedal bypass group, the popliteal artery (n = 13), the distal superficial femoral artery (n = 3), and the common femoral artery (n = 3) were used. The distal anastomosis in the pedal bypass group was located on the posterior tibial artery below the ankle (n = 9) or the dorsal pedal artery (n = 10).

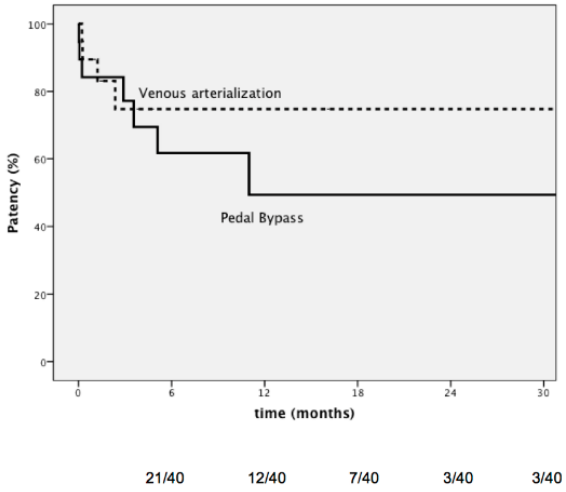
The average flow, perioperatively, was 38 mL/min in the pedal bypass group and 73 mL/min in the venous arterialization group (P = 0.03). Postoperative complications are shown in Table II. Mortality rates during follow-up were 24% in the venous arterialization group (n = 5) and 16% in the pedal bypass group (n = 3). The in-hospital mortality rate was 2.5% (1 patient in the venous arterialization group). The 1-month early occlusion rate in the venous arterialization group was 15% compared with 23% in the pedal bypass group (P = 0.325).

TABLE 2. Number of postoperative complications

	Venous arterialization (21)	**Pedal bypass (19)**	***p***
All postoperative complications	3 (14%)	5 (26%)	0.96
Postoperative bleeding	1	0	
Graft thrombosis	1	3	
Wound infection	1	2	
Amputations	19 (90%)	19 (100%)	0.87
Toe	4	6	
Transmetatarsal	6	3	
Transtibial	6	7	
Tranfemoral	3	3	

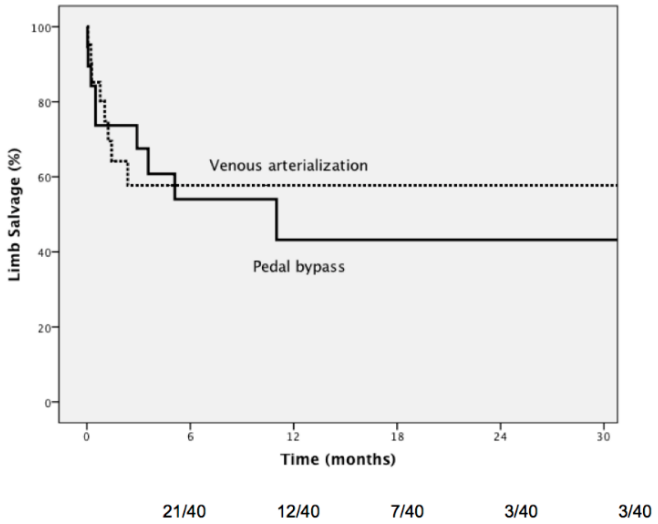
The 1-year patency rates in the venous arterialization and pedal bypass groups were 71% and 47%, respectively (P = 0.272) (Fig. 1). Limb salvage was 53% in the venous arterialization group and 47% in the pedal bypass group (P = 0.536) (Fig. 2). Multivariate analysis showed that bypass occlusion was an independent risk factor for limb salvage (P < 0.001) (Table III). However, no risk factors could be identified that were significantly associated with bypass occlusion.

FIGURE 1. Bypass patency



Log rank p = 0.557

FIGURE 2. Limb salvage



Log rank p = 0.933

TABLE 3. Univariate and multivariate analysis of risk factors for limb salvage

	No of patients (n=40)	Limb salvage (n=21)*	Univariate analysis		Multivariate analysis	
			Odds ratio[1]	*p*	Odds ratio[1]	*p*
Male sex	27	16 (59.3)	2.32 (0.60-9.03)	0.222		
Smoking	13	6 (46.3)	2.72 (0.48-15.47)	0.259		
Diabetes	30	17 (56.7)	0.51 (0.12-2.19)	0.365		
Hypertension	32	17 (53.1)	0.88 (0.19-4.16)	0.87		
Heart disease	32	17 (53.1)	0.39 (0.10-1.49)	0.169	1.65 (0.23-11.99)	0.621
Chronic kidney disease	8	5 (62.5)	0,60 (0,12-2,94)	0,53		
Venous arterialization	21	12 (57.1)	1.48 (0.43-5.16)	0.537		
Wound infection	3	1 (33.3)	2.35 (0.19-28.27)	0.500		
Graft thrombosis	4	1 (25)	3.75 (0.36-39.59)	0.272		
Rebleeding	1	1 (100)	N/A	0.335		
Bypass occlusion	14	0	N/A	<0.001	N/A	<0.001

Values in parentheses are * percentages or [1] 95 per cent confidence intervals

Discussion

The results of venous arterialization and pedal bypass were comparable, and no difference in short-term and long-term outcomes was noted. Postoperative complications were equally divided, and almost all patients needed a form of amputation.

The concept of using the disease-free venous bed as an alternative for perfusion of the peripheral tissues with arterial blood was first published by Halstead and Vaughan[5] in 1912. Since then, studies with both encouraging clinical outcomes and more pessimistic conclusions have been published. A review by Lu et al.[3] in 2006 reported a limb salvage rate of 71% after venous arterialization, and a recent study by Mutirangura et al.[6] reported a limb salvage rate of 76% after 1 year. The limb salvage rate after venous arterialization in the present study was lower than that reported in the literature (53% vs. 71%). Four patients who were amputated underwent an open bypass, because their wounds showed no healing tendency. Reasons for no healing tendency could be open side branches or insufficient distal valve destruction. An angiogram might be helpful to identify and treat these problems.[7]

A discussion remains regarding what group of patients with CLI should undergo revascularization. Varu et al.[8] suggested that functional outcome and quality of life (QoL) are better when revascularization is attempted instead

of amputation if patients are ambulating and living independently before the operation. Other studies show similar results if bypass surgery is successful, but QoL is deteriorated if bypass surgery fails, and therefore primary amputation is suggested if life expectancy is short and comorbidities are present.[9,10]

In a study comparing mortality after primary amputation or revascularization, Hobson et al.[11] found rates of 13% in the amputation group and 3% in the revascularization group. Five-year survival was 60%in both groups. Ouriel et al.[12] reported similar findings, with mortality rates of 7.6% and 2.9%, respectively. Bunt and Malone[13] showed no difference in mortality rates in patients younger than 70 years, but a 5-fold increase in mortality in patients older than 70 years who underwent reconstruction (revascularization, 8.0%; amputation, 1.5%).

No criteria exist to help determine when and in which patients bypass surgery or primary amputation should be performed. According to Djoric,[14] conservative treatment is not recommended, because it led to a limb salvage rate of 12.5% in patients with CLI and no arterial outflow, whereas venous arterialization resulted in a limb salvage rate of 91.7%. The limb salvage results reported in the present article are promising in a group of patients for whom no other reconstructive treatment options were available and who probably would have undergone amputation if treated conservatively. The mortality rate in the present group is higher compared with that reported in the literature, indicating that the present patient group was relatively frail. The patients who died underwent an open bypass. Although pedal bypass is still the gold standard treatment, distal venous arterialization is a good alternative because of its comparable results and simplicity. Venous arterialization should always be considered in patients with CLI and no distal arterial outflow vessels.

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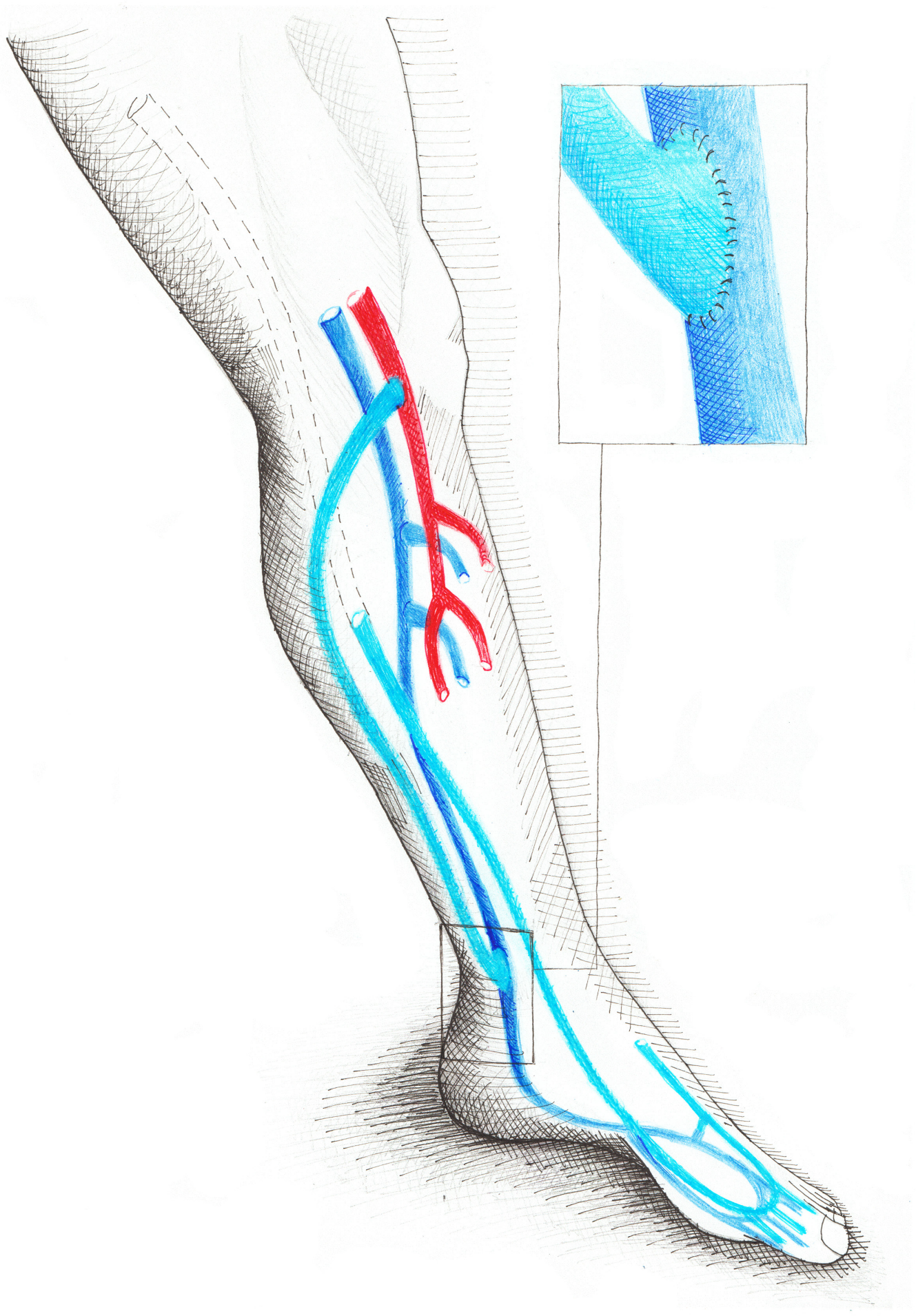

Chapter 3

Venous Arterialisation for Salvage of Critically Ischaemic Limbs: A Systematic Review and Meta-Analysis.

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What this paper adds

Critical limb ischaemia (CLI) is the clinical end stage of peripheral artery disease and is associated with high amputation and mortality rates, and poor quality of life. New treatment options are being explored for patients with CLI who have no option for surgical or endovascular revascularisation, with venous arterialisation considered to be a viable alternative before major amputation. This study reviews the literature and provides pooled data on the clinical effectiveness of venous arterialisation for lower limb salvage in CLI patients without revascularisation options.

Abstract

Background
Critical limb ischaemia (CLI) is the end stage of peripheral artery disease (PAD) and is associated with high amputation and mortality rates and poor quality of life. For CLI patients with no revascularisation options, venous arterialisation could be a last resort for limb salvage.

Objective
To review the literature on the clinical effectiveness of venous arterialisation for lower limb salvage in CLI patients with no revascularisation options.

Method
Different databases were searched for papers published between January 1966 and January 2016. The criteria for eligible articles were studies describing outcomes of venous arterialisation, published in English, human studies, and with the full text available. Additionally, studies were excluded if they did not report limb salvage, wound healing or amputation as outcome measures. The primary outcome measure was post-operative limb salvage at 12 months. Secondary outcome measures were 30 day or in-hospital mortality, survival, patency, technical success, and wound healing.

Results
Fifteen articles met the inclusion criteria. The included studies described 768 patients. According to the MINORS score, methodological quality was moderate to poor. The estimated pooled limb salvage rate at one year was 75% (0.75, 95% CI 0.70e0.81). Thirty day or in-hospital mortality was reported in 12 studies and ranged from 0 to 10%. Overall survival was reported in 10 studies and ranged from 54% to 100% with a mean follow-up ranging from 5 to 60 months. Six studies reported on patency of the venous arterialisations performed, with a range of 59e71% at 12 months.

Conclusion
In this systematic review on venous arterialisation in patients with non-reconstructable critical limb ischaemia, the pooled proportion of limb salvage at 12 months was 75%. Venous arterialisation could be a valuable treatment option in patients facing amputation of the affected limb; however, the current evidence is of low quality.

Keywords
Critical limb ischaemia, Venous arterialisation, Limb salvage

Introduction

Critical limb ischaemia (CLI) is the clinical end stage of peripheral artery disease (PAD) and is associated with high amputation and mortality rates, and poor quality of life.[1] It is estimated that 5-10% of patients with peripheral artery disease who are older than 50 years will develop severe or critical limb ischaemia (CLI) within 5 years.[2] Bypass surgery and more recently endovascular interventions with angioplasty and stenting have become the treatment of choice to prevent amputation and resolve rest pain. Endovascular interventions carry lower morbidity and mortality.[3] One prospective study 15 years ago showed that up to 50% of patients with CLI are not suitable candidates for vascular intervention because of extensive occlusions of the outflow in the crural and pedal vessels.[3] Nowadays more patients are suitable for vascular intervention because of progress in techniques and materials but when re-occlusion occurs, these patients will return.

In the past decade, new treatment options have been explored for patients with CLI with no option for surgical or endovascular revascularisation. These include stem cell therapy, spinal cord stimulation, and prostanoid therapy. A meta-analysis of placebo controlled trials showed no advan- tage for stem cell therapy on the primary outcome measures of amputation, survival, and amputation free survival in pa- tients with CLI.[4] Another meta-analysis showed no benefit for prostanoid treatment or other medical treatments.[5] A Cochrane review concluded that there may be some benefit from spinal cord stimulation for prevention of amputation; however, evidence is considered to be very low grade, mainly because of imprecision and increased risk of bias.[6]

For CLI patients with no revascularisation options, venous arterialisation could be an alternative technique for limb salvage. The concept of using the disease free venous bed as an alternative conduit for perfusion of the peripheral tissues with arterial blood was first published by Hal- stead and Vaughan in 1912.[7] Flow in existing collateral vessels will increase, reversal of flow all the way through the capillaries improves tissue nutrition[8] and possibly stimulates angiogenesis.[9]

A systematic review in 2006 concluded that venous arterialisation may be considered a viable alternative before major amputation.[10] Nevertheless, this technique is not being widely used. This could be because of the low quality of studies. Since 2006 the evidence has grown as the number of studies doubled and the number of included patients tripled. This study reviews the literature

on the clinical effectiveness of venous arterialisation for lower limb salvage in CLI patients without revascularisation options. Also, meta-analyses of the studies was conducted and pooled data provided on limb salvage.

Methods

This report was written in accordance with the PRISMA guidelines for reporting systematic reviews and meta- analyses.[11]

Literature search

Two authors (MS, CV) independently searched the literature to identify studies investigating venous arterialisation for critically ischaemic limbs. MEDLINE, EMBASE, and CINAHL databases and the Cochrane Database of Systematic Reviews were searched for papers published between January 1966 and February 2016, using the following keywords: (Vein OR veins OR venous OR venosome) AND (arterialization OR arterialisation) AND (ischemia OR ischaemia OR ischemic OR ischaemic OR gangrene OR necrosis OR tissue loss OR ulcus OR ulcer OR ulcera OR restpain OR limb salvage). Free text words were also used instead of MeSH terms to avoid missing recent publications that have not yet been given MeSH headings. The "related articles" function in PubMed and reference lists of retrieved articles were also used to identify articles not found in the original search. The search was not restricted to any language. However, studies published in Russian and Chinese were excluded. No unpublished data or abstracts were included. A full search strategy is available on request.

Validity assessment

After removal of duplicates, two authors (MS, CV) screened the titles and abstracts of the identified studies for relevance. Full texts of the remaining relevant studies were obtained and two authors (MS, CV) read the full text papers and made a final selection of relevant studies. Two authors (MS, CV) independently assessed the methodo- logical quality of the articles using the Methodological Index for Non-randomised Studies (MINORS) score, with a global ideal score of 16 for non-comparative studies and 24 for comparative studies.[12] The MINORS score was reported as a percentage of the global ideal score. For this review a score of ≤8 was considered to be poor quality, 9-14 moderate quality, and 15-16 good quality for non-comparative studies. Cutoff points were ≤14, 15-22, and 23-24, respectively, for comparative studies. Discrepancies between the authors during the search, selection, and quality

assessment were resolved by discussion. If agreement was not reached, a third author was consulted.

Definition

Venous arterialisation was defined as the use of the disease free venous bed as an alternative conduit for perfusion of the peripheral tissues with arterial blood.

Chronic CLI was defined according to the transatlantic intersociety consensus document (TASC II 2007), which is based on the clinical symptoms predominantly caused by peripheral arterial disease (i.e. ischaemic rest pain and/or ulceration).[2]

Inclusion and exclusion criteria

Types of studies

The criteria for eligibility were studies describing outcomes of venous arterialisation, human studies, and full text availability. The exclusion criteria were case reports and case series (N<10), reviews, abstracts, animal studies, and studies published in Russian or Chinese. Additionally, studies were excluded if they did not report limb salvage, wound healing, or amputation as outcome measures.

Types of participants

All studies with patients who received venous arterialisation for critical lower limb ischaemia with no options for arterial revascularisation were included. Papers describing patients with upper limb ischaemia or venous arterialisation for indications other than critical lower limb ischaemia were excluded. There was no restriction for age, sex, socioeconomic status, method of diagnosis, or duration of symptoms.

Outcome measures

The primary outcome measure was post-procedural limb salvage at 12 months. Limb salvage was defined as preservation of the affected limb without any major amputation performed (transtibial, through the knee, or transfemoral amputation). Secondary outcome measures were 30 day or in-hospital mortality, survival, patency, wound healing, and clinical improvement of symptoms. Primary patency was defined as patent revascularisation without any re-interventions. Primary assisted patency was defined as patent revascularisation with percutaneous transluminal angioplasty only. Secondary patency was defined as patent revascularisation after any other re-intervention.

Data analysis

Data extraction was performed by two independent authors (MS, CV). Data extracted included study design, sample size, age, sex, comorbidities, disease stage according to Fontaine and/or Rutherford classification, type of operation, outcome measures as described above, and follow-up duration. Discrepancies were resolved by discussion and a third author was consulted in case of disagreement. Meta Analysist software version 3.1 was used for the meta-analysis. To provide reliable outcome, and to gain sufficient homogeneity of the pooled data, only studies reporting limb salvage at 1 year follow-up were used for pooled analyses. Rates were pooled using a random effects model. The presence of heterogeneity was determined between the studies using a forest plot and a X^2 heterogeneity test. The I^2-index was also calculated.

Results

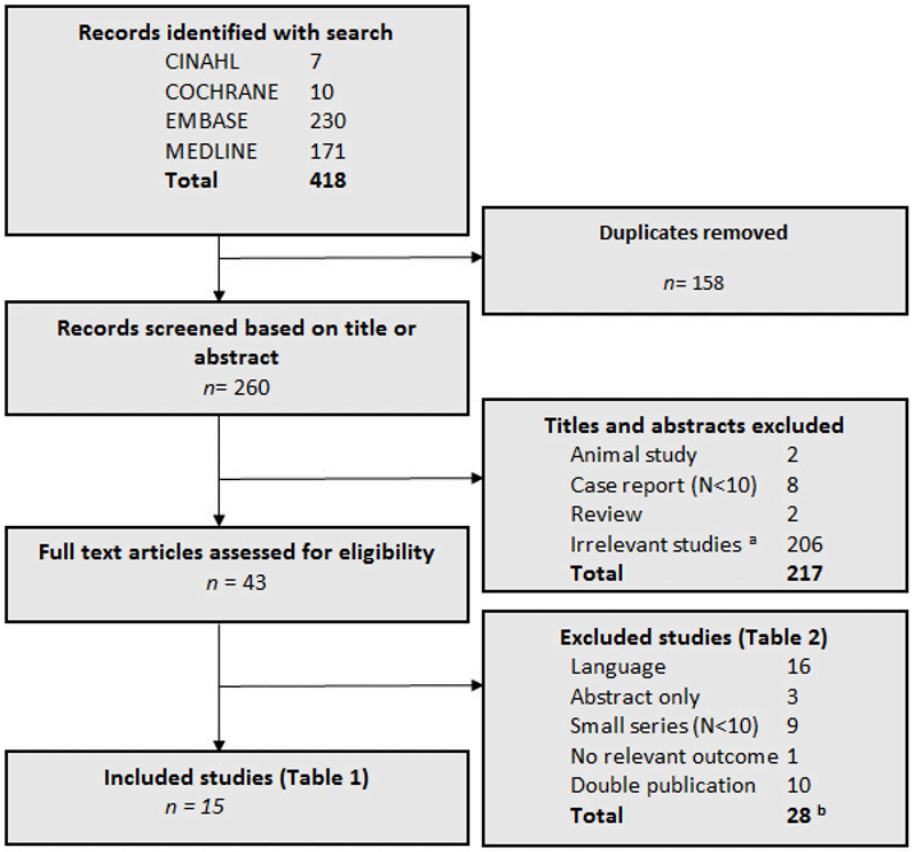
Description of studies

The search identified 418 studies, and after removal of duplicates and screening the titles and abstracts for rele- vance, 43 full text papers were assessed for eligibility. After application of the inclusion and exclusion criteria, 15 papers were finally included in this systematic review.[13-27] A flow chart of the complete selection procedure is shown in Fig. 1. Twenty-eight studies were excluded for the following reasons: article in Russian or Chinese (n=9), case reports or small series with <10 patients (n=9), double publication of the same data (n=10), and three studies were published as abstracts with no full text publication available.[28-55] Two studies did not report relevant outcome measures related to limb salvage.[53,54] Some studies were excluded for more than one reason.

The included studies described 768 patients. Twelve studies had a retrospective design,[13,14,17-22,24-27] and three were prospective observational studies.[15,16,23] Four articles were comparative studies.[15,16,22,24] Three compared surgery with conservative treatment[15,16,22] and one compared venous arterialisation with pedal bypass.[24] The included and excluded studies are summarised in Table 1 and Table 2, respectively. According to the MINORS scoring scale, ten studies[13-15,17,18,20,21,23,26,27] were of poor methodological quality (Fig. 2), and the quality of five studies was moderate.[16,19,22,24,25] Blinding and prospective calculation of study size were never reported, and loss to follow-up was higher than 5% in two studies[20,21] and not reported in nine.[13-18,22-24,26] One study scored 0 on all items of the MINORS scoring scale.[26] There was complete agreement between authors regarding the inclusion and exclusion of studies and the

assessment of methodological quality.

FIGURE 1. Flow chart of study selection



[a]Studies describing irrelevant topics including venous arterialization of prtal veins, arm veins and veins of the penis, studies on arteriovenous fistulas etc.
[b]Some papers had more than 1 reason to be excluded (for example: double publication of data in several languages other than English, or small series (N<10) and double publication and no English language).

Surgical technique

All included studies described the surgical technique used for venous arterialisation. The most distal patent artery was used for the proximal anastomosis in all studies. However, the distal anastomosis site and conduits used varied. In five studies an anastomosis between the great saphenous vein (GSV) and the most distal patent artery was created and the GSV was left in situ.[14-16,18,22] Side branches to ankle level were ligated and valvulotomy was performed in all but one study.[14-16,22] Gravrilenko et al. did not perform side branch ligation and stated that leaving the side branches led to improved patency and improved perfusion of the limb.[18]

TABLE 1. Included studies

First author	Sample size Patients (limbs)	Study design	Inclusion criteria	Patiënts					Intervention	Outcome	Follow-up (months)	MINORS
				Age mean (range)	M (%)	F3	F4	DM				
Alexandrescu 2011[14]	25 (26)	Retrospective cohort	Inclusion criteria: - Diabetes - Lower limb ischemic wound - tcPO2 < 30mmHg - no arterial revascularization options Exclusion criteria: - Extensive irrecoverable gangrene - severe cardiac insufficiency - patient disagreement	72 (56-84)	18 (72%)	0	25	25	Deep calf vein arterialization using PTFE bypass and endoluminal embolization of collaterals based on angiosome distribution. Aspirin 160mg/day or clopidogrel 75 mg/day ≥ 72 hours before intervention	Limb salvage 73±10% at 1 year 73±10% at 2 years 73±10% at 3 years 30-day mortality *0%* Primary patency Not reported Secondary patency *66±9% at 1 year* *60±10% at 2 years* *48±14% at 3 years* Technical success *21/26 (81%)* Patient survival *93% at 1 year* *67% at 2 years* *54% at 3 years* Clinical success[a] *68±10% at 1 year* *60±11% at 2 years* *60±11% at 3 years*	22 (1-62)	7
Busato 2010[15]	18 (18)	Retrospective cohort	CLI without arterial runoff	nr	nr	nr	nr	6	GSV arterialization with side-branch ligation until the anterior perforating vein of the malleolus.	Limb salvage *10/18 (56%)* Major amputation *7/18 (39%)* In-hospital mortality *1/18 (6%)* Overall morality *3/18 (17%)*	23 (7-33)	6

TABLE 1. Continued

First author	Sample size Patients (limbs)	Study design	Inclusion criteria	Patiënts					Intervention	Outcome	Follow-up (months)	MINORS
				Age mean (range)	M (%)	F3	F4	DM				
Djoric 2011[16]	36 (36)	Prospective cohort with matched controls	Inclusion criteria CLI and no arterial revascularization options Exclusion criteria - insufficient deep venous system or unsuitable GSV - extensive infection or necrosis up to the metatarsal level - poor prognosis of the patient	66 (36-82)	20 (55%)	16	20	26	GSV arterialization *vs* Antiplatelet therapy	Limb salvage *92% vs 13% (p<0.001)* Wound healing *78% vs 0% (p<0.001)* In-hospital mortality: *0%* *Mortality in conservative group 33% higher (p<0.05)* Survival *100% vs 67% (p<0.024)* Pain relief *75% vs 8% (p<0.001)*	5 (1-14)	12
Djoric 2012[17]	60 (60)	Prospective observational cohort	Inclusion criteria CLI and no arterial revascularization options Exclusion criteria - insufficient deep venous system or unsuitable GSV - extensive infection or necrosis up to the metatarsal level - poor prognosis of the patient	66 (nr)	38 (63%)	23	37	38	GSV arterialization *vs* Aspirin 100mg/day	Limb salvage *83 vs 13% (p< 0.001)* Wound healing *88 vs 0% (p< 0.001)* 30-day mortality *1/30 (3%)* Survival *97 vs 67% (p< 0.01)* Pain relief *83 vs 7% (p< 0.001)* Mean increase in TBI *0.254 (p<0.001)*	6 (nr)	15

TABLE 1. Continued

First author	Sample size Patients (limbs)	Study design	Inclusion criteria	Patiënts					Intervention	Outcome	Follow-up (months)	MINORS
				Age mean (range)	M (%)	F3	F4	DM				
Engelke 2001[18]	18 (18)	Retrospective cohort	CLI and no arterial revascularization options	69 (nr)	12 (67%)	0	18	nr	DVA using the GSV (n=11), Cephalic vein (n-1), SSV (n=2) or PTFE (n=4).	Limb salvage *75% at 2 years* *83% overall* Major amputation *3/18 (17%)* Primary patency *66%* Secondary patency *72%*	25 (9-48)	6
Gavrilenko 2007[19]	67 (67)	Retrospective cohort	CLI	57 (nr)	55 (82%)	42	25	15	GSV arterialization without ligation of side branches	Limb salvage *75% at 1 year* *70% at 2 years* *67% at 4 years* *64% at 5 years* Amputation *23 (34%)* Mortality at 5 years *9 (13%)* Patency (mean) *8.5 ± 1.5 months*	60 (nr)	6
Houlind 2013[20]	10 (10)	Retrospective cohort	CLI and no arterial revascularization options	70 (44-90)	8 (80%)	2	8	8	DVA based on angiosome distribution using the GSV or SSV (n=8) or PTFE (n=2).	Limb salvage *3/10 (30%)* Major amputation *7/10 (70%)* 30-day mortality *1/10 (10%)*	4 (1-11)	10
Lengua 1995[21]	25 (26)	Retrospective cohort	CLI	74 (49-95)	14 (56%)	2	23	10	GSV arterialization - reversed GSV (n=13) - in situ GSV (n=13)	Limb salvage *20/26 (77%) at 1 year* Patency (mean) *15 months*	41 (nr)	5

TABLE 1. Continued

First author	Sample size Patients (limbs)	Study design	Inclusion criteria	Patiënts					Intervention	Outcome	Follow-up (months)	MINORS
				Age mean (range)	M (%)	F3	F4	DM				
Lengua 2010[22]	59 (59)	Retrospective cohort	CLI, DM and no arterial revascularization options	71 (53-91)	44 (75%)	4	55	59	DVA using GSV (n=32), composed vein graft (n=18) and mixed graft (PTFE+vein; n=8).	Limb salvage *79% at 1 year* *69% at 1-5 years* *48% at ≥5 years* Major amputation *12/59 (20%)* 30-day mortality *1/59 (2%)*	52 (nr)	7
Matzke 1999[23]	28 (28)	Retrospective cohort with matched controls	CLI and no arterial revascularization options	73 (58-90)	nr	14	14	16	GSV arterialization (n=14) *vs* Conservative treatment (n=14)	Limb salvage *57 vs 54% at 1 year(NS)* 30-day mortality *0/28 (0%)* Survival *92 vs 64% at 1 year(NS)*	nr	15

TABLE 1. Continued

First author	Sample size Patients (limbs)	Study design	Inclusion criteria	Patiënts					Intervention	Outcome	Follow-up (months)	MINORS
				Age mean (range)	M (%)	F3	F4	DM				
Mutirangura 2011[24]	26 (26)	Prospective observational cohort	CLI and no arterial revascularization options Exclusion criteria - previous DVT - massive tissue loss beyond forefoot level - foot infection - compromised cardiopulmonary status	69 (37-91)	16 (62%)	2	24	22	DVA using a composite PTFE-GSV graft	Limb salvage *76.0*±8.6% *at 6 months* *76.0*±8.6% *at 1 year* *76.0*±8.6% *at 1.5 years* *76.0*±8.6% *at 2 years* Major amputation *6/26 (23%)* 30-day Mortality *1/26 (4%)* Survival *96.2*±3.8% *at 6 months* *85.4*±7.9% *at 1 year* *85.4*±7.9% *at 1.5 years* *85.4*±7.8% *at 2 years* Primary patency *72.1*±9.0% *at 6 months* *59.0*±1.1% *at 1 year* *59.0*±1.1% *at 1.5 years* *49.2*±1.3% *at 2 years*	nr (6-47)	8

TABLE 1. Continued

First author	Sample size Patients (limbs)	Study design	Inclusion criteria	Patiënts					Intervention	Outcome	Follow-up (months)	MINORS
				Age mean (range)	M (%)	F3	F4	DM				
Schreve 2014[25]	40 (40)	Retrospective cohort	CLI, venous arterialization was performed if no usable pedal artery was present Exclusion criteria Arterial revascularisation options at the crural level or higher.	65 (nr)	27 (68%)	0	40	30	DVA using GSV (n=21) *vs* Pedal bypass (n=19) Acenocoumarol for 2 years	Limb salvage *53% vs 47% (p=0.272)* Major amputation *9/21(43%) vs10/19(53%)* In-hospital mortality *1/21 (5%) vs 0%* Mortality *24% vs 16%* Patency at 1 year *71% vs 47% (p=0.325)*	nr	16
Taylor 1999[26]	18 (18)	Retrospective cohort	CLI and no arterial revascularization options			4	14	6	DVA using GSV (n=11), cephalic vein (n=3) or PTFE (n=4)	Limb salvage *75% at 1 year* *83% overall* 30-day mortality *1/18 (6%)* Overall mortality *3/18 (17%)*	17 (4-28)	10
Vira Reddi 1990[27]	182 (182)	Retrospective cohort	CLI and no arterial revascularization options	nr	Nr	nr	nr	nr	Popliteal vein arterialization	Limb salvage *149/182 (82%)* Major amputation *33/182 (18%)* Overall and 30-day mortality *0%*	nr	0

TABLE 1. Continued

First author	Sample size Patients (limbs)	Study design	Inclusion criteria	Patiënts					Intervention	Outcome	Follow-up (months)	MINORS
				Age mean (range)	M (%)	F3	F4	DM				
Wu 1993[28]	156 (212)	Retrospective cohort	CLI and no arterial revascularization options	43 (21-83)	151 (97%)	52	165	nr	Deep venous arterialization using reversed GSV, Brachial vein or prothetic graft or a direct arteriovenous fistula (side-to-side anastomosis) Deep vein proximally of anastomosis was constricted to 33% of original diameter using a suture. Ascal 100mg/day + persantin 50mg 3x/day for 30-90 days.	Limb salvage *212/212 (100%)* Wound healing *212/212 (100%)* 30-day mortality *0%* Overall mortality *3/156 (2%)*	10 (3-27)	6

CLI – critical (lower) limb ischemia; DM – Diabetes Mellitus; DVA – Distal vein arterialization; F3 – Fontaine stage 3; F4 – Fontaine stage 4; GSV – Great saphenous vein;M – Male nr – not reported; NS – not significant; RCT – Randomized controlled trial; SSV – Short saphenous vein; TBI – Toe-brachial index.

[a] clinical success was defined as marked healing without amputation and tcPO2 ≥ 30 mmHg

[b] No female patients in this cohort

TABLE 2. Excluded studies

First author	Sample size Patients (limbs)	Study design	Reason for exclusion
Djoric 2011[29]	36 (36)	RCT	Abstract only, no full-text or data available, overlapping data with other (included) publication by same author.
Dudanov 2011[30]	7 (7)	Retrospective cohort	Abstract only, no full-text or data available, venous arterialization not the topic of publication and performed in only 7 out of 317 patients described.
He 2002[31]	18 (18)	Retrospective cohort	Language: Chinese full-text available only
Jacob 1999[32]	15 (15)	Retrospective cohort	Abstract only, no full-text or data available
Jiang 2006[33]	11 (11)	Retrospective cohort	Language: Chinese full-text available only
Lengua 1982[34]	6 (6)	Retrospective cohort	Language: French full-text available only, overlapping data with other publications by same author, Small series, N < 10
Lengua 1984[35]	8 (8)	Retrospective cohort	Small series, N < 10, overlapping data with other publications by same author
Lengua 1993[36]	28 (28)	Retrospective cohort	Language: French full-text available only, overlapping data with other publications by same author
Lengua 1993[37]	28 (28)	Retrospective cohort	Language: German full-text available only, overlapping data with other publications by same author
Lengua 1994[38]	13 (14)	Retrospective cohort	Language: French full-text available only, overlapping data with other publications by same author
Lengua 2001[39]	59 (60)	Retrospective cohort	Language: French full-text available only, overlapping data with other publications by same author
Lengua 2010[40]	59 (59)	Retrospective cohort	Language: French full-text available only, overlapping data with other publications by same author
Li 2001[41]	49 (56)	Retrospective cohort	Language: Chinese full-text available only
Miasnik 2002[42]	77 (77)	Retrospective cohort	Language: Russian full-text available only
Ning 1998[43]	89 (89)	Retrospective cohort	Language: Chinese full-text available only
Ozbek 2005[44]	7 (7)	Retrospective cohort	Small series, N < 10
Pei 1985[45]	8 (8)	Retrospective cohort	Small series, N < 10
Pokrovskii 1990[46]	32 (32)	Retrospective cohort	Language: Russian full-text available only
Protsenko 1990[47]	13 (13)	Retrospective cohort	Language: Russian full-text available only
Rowe 2002[48]	6 (6)	Retrospective cohort	Small series, N < 10
Samodai 1999[49]	10 (10)	Retrospective cohort	Language: Russian full-text available only
Sasajima 2010[50]	9 (9)	Retrospective cohort	Small series, N < 10

TABLE 2. Continued

First author	Sample size Patients (limbs)	Study design	Reason for exclusion
Sasajima 2013[51]	1 (1)	Book chapter	Book chapter describing one case
Serra 2015[52]	9 (9)	Retrospective cohort	Small series, N < 10
Sheil 1977[53]	6 (6)	Retrospective cohort	Small series, N < 10
Van Dongen 1973[54]	60 (60)	Retrospective cohort	Language: German full-text available only
Vira Reddi 1980[55]	82 (82)	Retrospective cohort	No relevant outcome, overlapping data with other publication by same author
Wu 1993[56]	156 (212)	Retrospective cohort	Language: Chinese full-text available only, overlapping data with other publication by same author

FIGURE 2. Study quality assesment (MINORS score)

	Alexandrescu 2011	Busato 2010	Dioric 2011	Dioric 2012	Engelke 2001	Gavrilenko 2007	Houlind 2013	Lengua 1995	Lengua 2010	Matzke 1999	Mutirangura 2011	Schreve 2014	Taylor 1999	Vira Reddi 1990	Wu 1993
1. A clearly stated aim	2	2	2	2	2	0	2	0	0	2	2	2	2	0	0
2. Inclusion of consecutive patients	0	0	0	2	0	0	2	0	2	2	0	2	2	0	2
3. Prospective collection of data	1	0	0	0	0	0	0	0	0	0	2	0	0	0	0
4. Endpoints appropriate to the aim of the study	2	2	2	2	2	2	2	2	2	2	2	2	2	0	0
5. Unbiased assessment of the study endpoint	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6. Follow-up period appropriate to the aim of the study	2	2	1	2	2	2	2	2	2	2	2	2	2	0	2
7. Loss to follow-up less than 5%	0	0	0	0	0	2	2	1	1	0	0	0	2	0	2
8. Prospective calculation of the study size	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Item 9-12 only for comparative studies															
9. An adequate control group			2	2						2		2			
10. Contemporary groups			2	2						2		2			
11. Baseline equivalence of groups			2	2						2		2			
12. Adequate statistical analyses			1	1						1		2			
TOTAL MINORS score	**7**	**6**	**12**	**15**	**6**	**6**	**10**	**5**	**7**	**15**	**8**	**16**	**10**	**0**	**6**
Maximum possible score	16	16	24	24	16	16	16	16	16	24	16	24	16	16	16

Legend (Total MINORS score) moderate quality poor quality

Four studies performed a bypass procedure connecting the most distal patent artery to the medial marginal vein of the foot. The preferred conduit was the GSV in these studies.[20,21,23,24] In situ GSV[24] or reversed GSV[20] were used, and a third study reported the use of either in situ or reversed GSV or alternatively, composite vein, polytetrafluoroethylene (PTFE) or composite PTFE with vein as a conduit in cases where the GSV could not be used.[21] Mutirangura et al. always used a composite graft of a PTFE graft (proximally) with a GSV or an arm vein if the GSV could not be used.[23] In all of these studies valvulotomy of the foot veins was performed.

Three studies used the dorsal venous arch of the foot as the site for distal anastomosis and the GSV was the preferred conduit. A short saphenous vein,

cephalic vein or PTFE graft were used as a conduit in a minority of cases when no suitable GSV was available and in all cases valvulotomy of the veins in the foot was performed.[17,19,25] Side branch ligation was only described in the study by Engelke et al.[17]

Three studies described arterialisation of the deep venous system.[13,26,27] Alexandrescu et al. used a PTFE graft to connect the most distal patent artery to the popliteal vein or tibial vein.

The authors used only endovascular techniques for destruction of the distal valves and occluded side branches using coil embolisation to minimise wounds in those legs with compromised vascularisation. The choice of location for distal anastomosis was based on the angiosome theory.[13] In the other two studies the preferred technique was a direct anas- tomosis between the most distal patent artery and the adjacent deep vein.[26,27] While Vira Reddi et al. performed complete ligation of the deep vein proximal to the anastomosis,[26] Wu et al. ligated the vein proximal to the anastomosis to a third of the original diameter.[27] If direct anastomosis between adjacent vessels on the same level was not possible, the GSV was preferably used as a conduit between the most distal patent artery and distal deep vein. If the GSV could not be used, either arm veins or PTFE grafts were used.

The majority of studies did not report post-operative medication (i.e. anticoagulants or thrombocyte aggregation inhibitors), although regimens using acenocoumarol,[24] aspirin with heparin,[23] heparin followed by acetylsalicylic acid with dipyridamole,[27] or acetylsalicylic acid with clopidogrel[13] were reported. Duration of medical treatment was only reported by Wu et al. and ranged between 30 and 90 days.[27] Details of the operative techniques used are summarised in Table 3.

Limb salvage

Limb salvage was reported in all the studies. However, the exact definition of limb salvage varied and in some studies was not further defined. Seven studies reported limb salvage rates at 1 year that ranged from 57% to 79%.[13,18,20-23,25] Engelke et al. reported a limb salvage rate of 75% at 2 years and overall limb salvage of 83% with a mean follow-up of 25 months (range 9-48 months).[17]

TABLE 3. Operative techniques of venous arterialization

First author	Proximal anastomosis (n)	Distal anastomosis (n)	Conduit (n)	Other technical aspects	Postoperative medication
Alexandrescu 2011[14]	Most distal patent artery - CFA (20) - SFA (2) - PA (4)	Popliteal vein or tibial vein	PTFE (8mm)	- location of distal anastomosis chosen based on angiosome model - endovascular valvulotomy and coil-embolisation for side branches	- acetylsalicylic acid + clopidogrel
Busato 2010[15]	Most distal patent artery	n/a	GSV (in situ)	- Side branch ligation - Valvulotomy	nr
Djoric 2011[16]	Most distal patent artery	n/a	GSV (in situ)	- Side branch ligation - Valvulotomy	nr
Djoric 2012[17]	Most distal patent artery	n/a	GSV (in situ)	- Side branch ligation - Valvulotomy	nr
Engelke 2001[18]	Most distal patent artery	Dorsal venous arch of the foot or posterior tibial vein	- GSV in situ (3) - GSV reversed (8) - Cephalic (1) - LSV (2) - PTFE (4)	- Side branch ligation - Valvulotomy	nr
Gavrilenko 2007[19]	Most distal patent artery	n/a	GSV (in situ)	- No side branch ligation - Valvulotomy	nr
Houlind 2013[20]	Most distal patent artery	Dorsal venous arch of the foot (5) + CV PTA (3) + CV CPA (2)	- GSV (6) - LSV (2) - PTFE (2)	- Valvulotomy	nr
Lengua 1995[21]	Most distal patent artery - CFA (3) - SFA (14) - PA (8) - Fem-pop bypass (1)	Medial marginal vein	GSV	- Valvulotomy	nr
Lengua 2010[22]	Most distal patent artery - EIA (3) - CFA (3) - SFA (27) - PA (25)	Medial marginal vein	- GSV (in situ; 5) - GSV (reversed; 27) - Composite vein (18) - PTFE or Composite PTFE + vein (8)	- Valvulotomy	nr

TABLE 3. Continued

First author	Proximal anastomosis (n)	Distal anastomosis (n)	Conduit (n)	Other technical aspects	Postoperative medication
Matzke 1999[23]	Most distal patent artery - CFA or SFA	n/a	GSV (in situ)	- Side branch ligation - Valvulotomy	nr
Mutirangura 2011[24]	Most distal patent artery	Medial marginal vein	Composite graft of PTFE (proximal) and GSV or arm vein (distal)	- Valvulotomy	- aspirin + heparin
Schreve 2014[25]	Most distal patent artery	Medial marginal vein	GSV (in situ)	- Side branch ligation - Valvulotomy	- acenacoumarol
Taylor 1999[26]	Most distal patent artery - CFA (15) - PA (3)	- Dorsal venous arch of the foot (16) - CV PTA (2)	- GSV (11) - Cephalic vein (3) - PTFE (4)	- Valvulotomy	nr
Vira Reddi 1990[27]	Most distal patent artery - PA or CFA	Popliteal vein	PTFE in case of obstruction of the SFA	- Direct anastomosis between the popliteal artery and vein at the same level was preferred - In case of obstruction at the level of the SFA a PTFE graft was anastomosed between the CFA and popliteal vein	nr
Wu 1993[28]	Most distal patent artery	Superficial femoral vein or deep distal vein	GSV or arm vein or prosthesis if direct side-to-side of artery and adjacent deep vein was not possible	- Direct side-to-side anastomoses between distal patent artery and adjacent deep vein at the same level was preferred - Ligation of deep vein proximal to anastomosis to 1/3 of original diameter and side branch ligation - If anastomosis at the same level impossible a conduit was used for anastomosis of proximal artery to distal deep vein	- heparin for 5-7 days - acetylsalicylic acid + dipyridamole for 30-90 days

CFA – common femoral artery; CV PTA – concomitant vein of posterior tibial artery; CV CPA – concomitant vein of the common plantar artery; EIA – external iliac artery; GSV – great saphenous vein; LSV – lesser saphenous vein; n/a – not applicable; PA – popliteal artery; PTFE – polytetrafluoroethylene; SFA – superficial femoral artery.

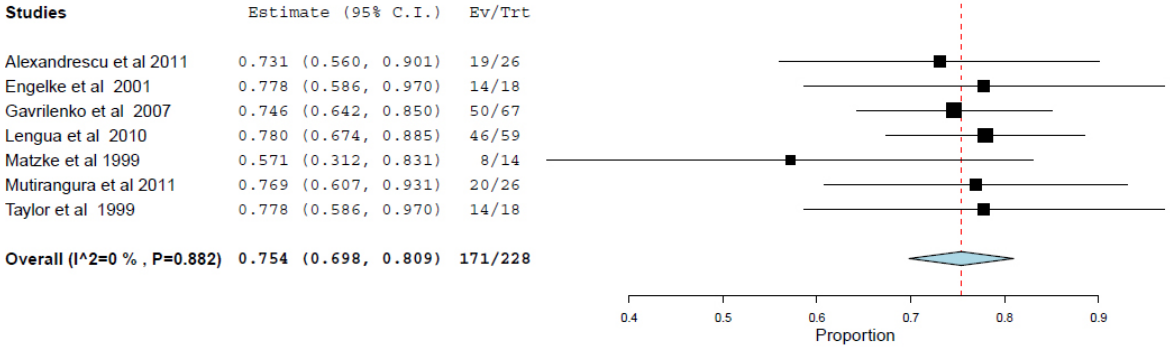
The remaining seven studies reported limb salvage rates without specifying the post-operative time interval at which limb salvage was measured.[14-16,19,24,26,27] Limb salvage ranged from 30% to 100% in these studies and mean follow-up ranged from 4 to 23 months, although mean follow-up was not reported in two studies.[24,26] The study by Wu et al. reported 100% limb salvage in a cohort of 156 patients (212 limbs), with a mean follow-up of 10 months (range 3-27 months).[27] All reported limb salvage rates and follow-up intervals are summarised in Table 1. The pooled analysis of limb salvage at 1 year was 0.75 (95% CI 0.70- 0.81), as shown in Fig. 3.

Mortality, survival, and patency

Thirty day or in-hospital mortality was reported in 12 studies and ranged from 0 to 10%.[13-16,19,21-27] Survival at 12 months was reported in three studies and ranged from 85% to 93%.[14,23,24] Overall survival was reported in 10 studies and ranged from 54% to 100% with a mean follow-up ranging from 5 to 60 months.[13-16,18,23-27]

Six studies reported the patency of the venous arterialisations performed. In the study by Mutirangura et al. a primary patency of 59.0±1.1% at 12 months and 49.2±1.3% at 2 years was described.[23] Alexandrescu et al. reported only secondary patency which was 66±9% at 12 months and 48±14% at 3 years.[13] Engelke et al. reported a primary and secondary patency of 66% and 72% respectively, with a mean follow-up of 25 months (range 9-48 months).[17] In two studies a mean patency of 8.5 and 15 months was reported respectively,[18,20] and another study reported a patency of 71% at 12 months.[24] In these last three studies patency was not further defined (i.e. primary, primary assisted, or secondary patency). Reported data on mortality, survival, patency, and other secondary outcome measures are listed in Table 1.

FIGURE 3. Pooled analyses of primary outcome (limb salvage)



Discussion

In this systematic review of venous arterialisation in patients with non-reconstructable critical limb ischaemia, the pooled proportion of limb salvage at 12 months was 75%. In the past decade several studies have been published with comparable results and the number of treated patients has grown considerably. Venous arterialisation could be a valuable treatment option in selected patients with no other option than amputation of the affected limb.

In 2006, Lu et al. performed a meta-analysis on the effectiveness of venous arterialisation for limb salvage in critical limb ischaemia.[10] The study had a design similar to the present study. They included seven studies comprising a total of 228 patients and found a pooled limb salvage rate of 71% at 12 months. The authors concluded that venous arterialisation can be a viable option to save the limb when no arterial reconstruction is possible. The present study confirms these findings in a larger population of 768 patients described in 15 studies, of which nine were published after the study by Lu et al.

A general limitation of the strength of the findings in this review is the poor methodological quality of the majority of the studies. Most were retrospective cohort studies or prospective observational studies of relatively small sample size. The description of the patients lost to follow-up is often poor or absent. Furthermore, there was considerable heterogeneity in terms of exclusion criteria, Fontaine stage, proportion of patients with diabetes, and the type and definition of outcomes reported. Additionally, in most studies information about peri-operative care and medication such as thrombocyte aggregation inhibitors or anticoagulants was not reported. Finally, there are important differences in the surgical technique applied between studies.

The donor artery for the proximal anastomosis was generally the most patent distal artery, preferably the popliteal artery. Using a more proximal donor artery requires a longer bypass that carries a higher risk for occlusion.[56] The distal anastomosis site and the conduits used, however, showed much greater variation. In nine studies a deep venous arterialisation was performed compared with six studies in which a superficial venous arterialisation of the GSV was performed. Limb salvage results between the two different techniques were comparable. There was a limb salvage rate of 76% in the deep venous arterialisation group and a 73% limb salvage rate in the superficial venous arterialisation group. Furthermore, the difference might be caused by other confounders, such as the donor artery or conduit used, peri-operative care, and medical treatment. The

majority of authors performed ligation of venous side branches to the level of the foot. In one study ligation of side branches was not performed and limb salvage was 75% at 12 months.[18] In three studies it was not reported whether side branches were ligated or not.[20,21,25] At this time, the optimal surgical technique is yet to be determined, as well as peri-operative measures and medical treatment and high quality studies addressing these issues are needed.

Not all patients are candidates for venous arterialisation and even without intervention a proportion of patients with CLI will keep their limb. There is a lack of comparative studies, although Matzke et al. showed that wound care and pain relief leads to 50% limb salvage after 12 months,[22] which suggests that not all patients need revascularisation. However, in the studies by Djoric et al. 13% limb salvage was observed in those patients treated by conservative means, while 83% and 93% limb salvage was obtained in the venous arterialisation group.[15,16] These findings and the differences in limb salvage rates in the studies included here suggest that patient selection might be important. Unfortunately, there are no data robust enough to support any recommendation on how to appropriately select patients for either venous arterialisation or conservative treatment or amputation.

A new development, percutaneous deep vein arterialisation (PDVA) is currently under investigation.[57] This procedure, called LimFlow, is a novel, minimally invasive, endovascular approach to perform a venous arterialisation procedure. A major advantage of this approach is the minimal invasiveness with lower peri-procedural risks and no creation of a wound in an already critically ischaemic leg. The first results in men are promising, although more research and long-term follow-up is needed to establish the efficacy of this new treatment modality.[57]

In conclusion, the currently available evidence suggests that venous arterialisation is a treatment option in selected patients with CLI and no arterial reconstructive options. These otherwise unsalvageable legs can be treated with acceptable morbidity and mortality. However, optimisation and standardisation of techniques are needed.

Conflict of interest
None.

Funding
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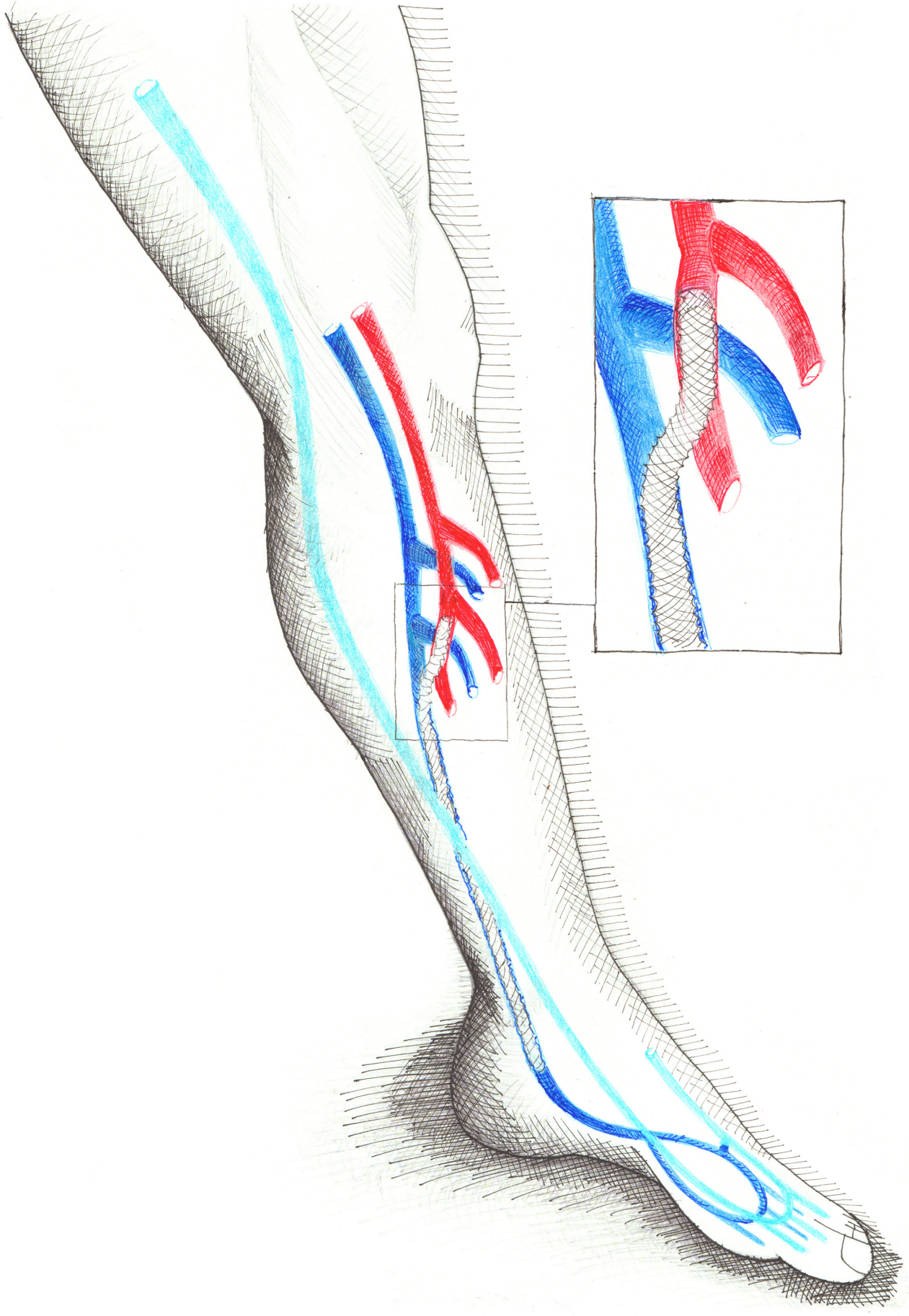
Part 2

The percutaneous deep venous arterialization
(pDVA, LimFlow procedure)



Chapter 4

Midterm Outcomes From a Pilot Study of Percutaneous Deep Vein Arterialization for the Treatment of No-Option Critical Limb Ischemia

Kum S, Tan YK, Schreve MA, Ferraresi R, Varcoe RL, Schmidt A, Scheinert D, Mustapha JA, Lim DM, Ho D, Tang TY, Alexandrescu VA, Mutirangura P. J.

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Abstract

Purpose

To report the initial clinical experience with percutaneous deep vein arterialization (PDVA) to treat critical limb ischemia (CLI) via the creation of an arteriovenous fistula.

Methods

Seven patients (median age 85 years; 5 women) with CLI and no traditional endovascular or surgical revascularization options (no-option CLI) were recruited in a pilot study to determine the safety of PDVA. All patients were diabetic; 4 had Rutherford category 6 ischemia. Six were classified at high risk of amputation based on the Society for Vascular Surgery WIfI (wound, ischemia, and foot infection) classification. The primary safety endpoints were major adverse limb events and major adverse coronary events through 30 days and serious adverse events through 6 months. Secondary objectives included clinical efficacy based on outcome measures including thermal measurement, transcutaneous partial pressure of oxygen ($TcPO_2$), clinical improvement at 6 months, and wound healing.

Results

The primary safety endpoints were achieved in 100% of patients, with no deaths, above-the- ankle amputations, or major reinterventions at 30 days. The technical success rate was 100%. Two myocardial infarctions occurred within 30 days, each with minor clinical consequences. All patients demonstrated symptomatic improvement with formation of granulation tissue, resolution of rest pain, or both. Complete wound healing was achieved in 4 of 7 patients and 5 of 7 patients at 6 and 12 months, respectively, with a median healing time of 4.6 months (95% confidence interval 84–192). Median postprocedure peak $TcPO_2$ was 61 mm Hg compared to a preprocedure level of 8 mm Hg ($p=0.046$). At the time of wound healing, 4 of 5 of patients achieved $TcPO_2$ levels of >40 mm Hg. There were 2 major amputations, 1 above the knee after PDVA thrombosis and 1 below the knee for infection. Three patients died of causes unrelated to the procedure or study device at 6, 7, and 8 months, respectively. Limb salvage was 71% at 12 months.

Conclusion

PDVA is an innovative approach for treating no-option CLI and represents an alternative option for the “desert foot,” potentially avoiding major amputation. Our results demonstrate its safety and feasibility, with promising early clinical results in this small cohort.

Introduction

Critical limb ischemia (CLI), characterized by chronic pain and tissue loss, is an increasingly common problem in elderly individuals. The annual incidence of CLI is 50 to 100 cases per 100,000, and mortality rates are 20% at 6 months after onset.[1] An endovascular strategy for revascularization of the ischemic limb has become increasingly popular[2] and is often used as the first-line approach in preference to open surgery.[3] Endovascular therapy is suitable for multivessel, multilevel revascularization and is well tolerated in CLI patients, who often present with advanced comorbidities. Advancements in endovascular technology and technique have led to high technical success rates; however, failure may occur due to the absence of distal target vessels, severe calcification, and heavy plaque burden that results in elastic recoil and early restenosis after angioplasty. Advanced disease with occlusion of the pedal arteries commonly used for distal bypass or angioplasty targets (the "desert foot") also represents an end-stage pathology that commonly leads to failure of all conventional revascu- larization attempts and culminates in major amputation. This is termed no-option CLI (NOP-CLI).

Surgical arterialization of the deep veins to prevent limb loss has been performed since the early 20th century. Halstead and Vaughan[4] were the first to report their early results using healthy arterialized veins of the distal lower limb to deliver oxygenated blood in 1912. Several rationales have been suggested since then to explain the success that may be achieved with venous arterialization, including maximizing tissue perfusion through the capillary bed, improved venous return in the remaining vessels, and increased angiogenesis.[5–7]

A meta-analysis of 56 studies that evaluated surgical venous arterialization reported 71% limb salvage and 46% secondary patency at 12 months.[8] In addition, most patients avoided major amputation and serious adverse events (SAEs) and experienced successful wound healing and resolution of rest pain. This report concluded that venous arterialization may be considered before major amputation is undertaken in patients with inoperable CLI. A more recent publication compared the efficacy of surgical venous arterialization to conventional distal bypass.[9] In this retrospective study, 19 patients underwent conventional distal arterial bypass and 21 underwent open surgical venous arterialization to the great saphenous vein. Surgical venous arterialization was associated with 71% patency and 53% limb salvage at 12 months, which was comparable to the pedal bypass group (75% and 47%, respectively). Although these studies suggest a role for surgical venous arterialization in patients

with NOP-CLI, no known studies have evaluated venous arterialization via percutaneous access in this patient population. This study reports an initial clinical experience with a novel method of totally percutaneous deep venous arterialization (PDVA) used for the treatment of limb-threatening CLI in patients without conventional surgical or endovascular options.

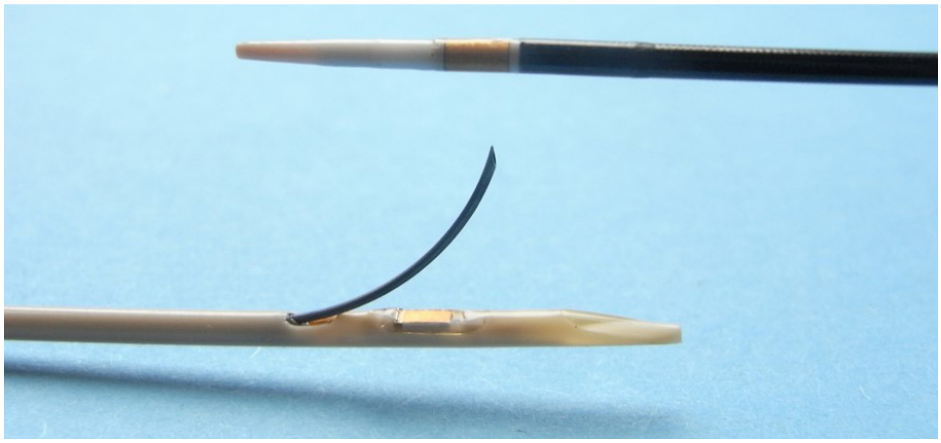
Methods

This prospective, open-label, single-arm study was performed at Changi General Hospital, Singapore, after extensive preliminary benchtop, animal, and cadaveric studies. The inclusion criteria allowed for enrollment of adult patients aged 21 to 100 years with CLI (Rutherford cate- gory 5 or 6) who were at risk of major amputation without revascularization, had at least 1 patent tibial vessel as an inflow vessel for PDVA, and had no conventional endovascular or surgical options for revascularization due to lesion recoil despite optimal balloon angioplasty and/or absence of a reasonable target foot vessel for bypass or angioplasty. Exclusion criteria included life expectancy <12 months, active life-threatening infection, aspirin and/or clopidogrel allergy, or contraindication to anticoagulation. All patients had undergone prior attempts at angioplasty. Angiograms were reviewed by at least 2 vascular interventionists, one of whom was not involved in the index procedure before PDVA. The SingHealth Centralised Institutional Review Board approved the study (reference 2013/828/C).

Device Description

The novel PDVA approach to treating CLI described in this report uses an endovascular method (LimFlow, Paris, France) to achieve venous arterialization. The system consists of 4 main components: an arterial catheter with a needle, a venous catheter (Figure 1), a covered nitinol stent in a 7-F delivery system, and an ultrasound alignment system with a laptop computer. The tips of the arterial and venous catheters have an ultrasound-emitting and ultrasound- receiving probe, respectively, which facilitates needle penetration from artery to vein. A nitinol stent is then used to create an arteriovenous fistula (AVF).

FIGURE 1. Arterial catheter with needle aligned next to venous catheter. Image courtesy of LimFlow SA.



Procedure

The target inflow vessel was accessed via an antegrade 7-F femoral sheath. A suitable inflow vessel below the knee was selected based on its caliber as well as the affected angiosome. An ultrasound-emitting arterial catheter with an embedded hollow crossing needle was placed over a standard 0.014-inch guidewire using a monorail system.

Venous access was achieved by percutaneous ultrasound-guided puncture of the corresponding target tibial vein near the ankle, chosen based on size and the location of the wound according to the angiosome/venosome concept. The venous catheter was placed over a standard 0.014-inch guidewire via a 5-F sheath in an over-the-wire system. The venous catheter was advanced proximally to the intended point of crossing, which was selected based on simultaneous digital subtraction venography and arteriography (ie, double injection) to determine where both vessels were in closest proximity.

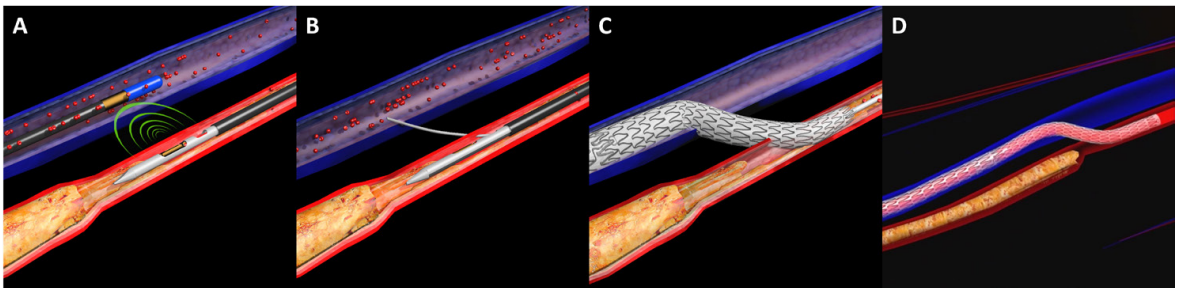
The venous “receive” catheter was initially placed at the selected crossing point. The arterial “send” catheter was then adjusted to achieve optimal alignment between the two as confirmed by maximum peak ultrasound signals. This allowed both catheters to be aligned at the same transverse level with the probes rotated toward each other (Figure 2A). The crossing needle was driven across the artery into the vein (Figure 2B) using the pusher ring at the handle of the arterial catheter. A 0.014-inch Spartacore guidewire (Abbott Vascular, Santa Clara, CA, USA) was then advanced through the needle into the vein.

A proprietary, tapered bare metal stent or a self-expand- ing covered stent (iCAST; Atrium Maquet Getinge Group, Hudson, NH, USA) with diameters of 3.5 mm at the proxi- mal aspect and 5 mm at the distal aspect was deployed

after predilation across the vein and artery to create an AVF (Figure 2C). The crossover stent is critical because it prevents leakage at the crossover point and also redirects blood distally, preventing it from immediately following the flow of the normal venous return back to the heart. The crossover stent was extended with multiple 5-mm Viabahn stentgrafts (W. L. Gore & Associates, Flagstaff, AZ, USA) to the ankle to serve as a conduit (Figure 2D). Apart from destroying the valves in the tibial vein by stenting, the reasonably large caliber ensured adequate flow down to the foot. These stentgrafts also covered multiple venous collaterals that could reduce flow to the forefoot.

Ancillary procedures were also performed to render the valves in the foot veins incompetent. Balloon angioplasty was used initially, with interwoven 4-mm nitinol stents (Supera; Abbott Vascular) implanted as needed after suboptimal distal vein angioplasty. Later, a proprietary, over-the- wire, forward-cutting 4-F valvulotome became available, which lysed the valves distal to the extension stents, some as far distal as the midfoot, in contrast to a conventional surgical valvulotome that is pulled rather then pushed.

FIGURE 2. Step-by-step illustration of percutaneous deep vein arterialization. (A) The venous "receive" catheter is initially placed at the selected crossing point, and the arterial "send" catheter transmits a signal to optimally align the devices. (B) The send catheter crossing needle is driven into the vein after the receive catheter is withdrawn. (C) A 0.014-inch guidewire is advanced through the needle into the vein. A self-expanding covered stent is deployed after predilation across the vein and artery. (D) Multiple extension stent-grafts are deployed in the vein down to the ankle to serve as a conduit. Image courtesy of LimFlow SA.



Assessments

Transcutaneous partial pressure of O_2 ($TcPO_2$) at the level of the capillary bed was recorded with the Periflux System 5000 (Perimed, Jarfalla, Sweden) in a room with constant temperature of 24°C; each measurement lasted ~25 minutes. Patients were supine, clinically well, and not on supplementary oxygen. Two readings were taken in every instance, one probe near the wound and another further from the wound. Probes were placed in the same locations at every measurement. $TcPO_2$ values ≥40 mm Hg are predicitive of wound healing.[10] $TcPO_2$

measurements were done every 2 weeks fort he first 2 months and here after monthly until wound healing was achieved or the leg was amputated.

Thermography was performed using an infrared camera (FLIR E30; FLIR Systems, FLIR Systems Co, Ltd, Hong Kong, China) and was interpreted subjectively. Thermography was done before the procedure and not more than 72 hours after the procedure by pointing the infrared camera at the foot in the anteroposterior, medial, and lateral projections. Areas of the foot that were detected as cool were visualized as yellow or blue, while warm areas were orange or red. A reduction in the cool areas by >50% after PDVA was considered an improvement in perfusion. Patient follow-up with duplex ultrasound to measure volume flow rate in particular was performed at 4 to 6 weeks and at 6 and 12 months; examinations were performed more often as clinically necessary.

Patient Enrollment

The study enrolled 7 patients (median age 85 years; 5 women) between September 2013 and November 2014. All patients were diabetic (Table 1); 4 presented with Rutherford category 6 ischemia (including 1 with heel gangrene). Six patients were classified at high risk of amputation based on the Society for Vascular Surgery WIfI (wound, ischemia, and foot infection) classification.[11] Five were treated with the LimFlow procedure and 2 underwent the procedure with off-the-shelf devices before the LimFlow system was developed. The main difference was that an Outback reentry catheter (Cordis Corporation, a Cardinal Health company, Milpitas, CA, USA) was used to puncture an inflated balloon catheter in the target vein after both catheters were visually aligned. Subsequent steps were identical to the LimFlow cases.

Outcomes

Safety endpoints were a major adverse limb event (MALE) and major adverse coronary event (MACE) through 30 days and SAEs through 6 months. A MALE was defined as major amputation (transtibial or above) or major vascular reinter- vention (bypass graft, thrombectomy, or thrombolysis) in the index limb but not including percutaneous reinterven- tions. A MACE included cardiac-related death, ST-elevation myocardial infarction (MI), or myocardial ischemia con- firmed biochemically regardless of the need for percutane- ous or open myocardial revascularization. SAE referred to any life-threatening event that resulted in death, persistent or significant disability/incapacity, or required/prolonged inpatient hospitalization.

Secondary objectives were technical success (the ability to position the artery and venous catheters and deploy the stent); clinical improvement (visible formation of granulation tissue, resolution of rest pain, or both) within 6 months; limb oxygenation assessed by $TcPO_2$; amputation-free sur- vival; limb salvage at 1 year; and wound status of the index limb, including time to wound healing (complete epithelialization of the index wound or successful incorporation of a split skin graft) and thermography of the affected limb.

Statistical Analysis

Patient data were collected on standardized case report forms. Device performance was evaluated by the principal investigator and treating physician. Descriptive data are presented as the number for categorical data and the median [interquartile range (IQR)] for continuous data. Differences between $TcPO_2$ levels were compared using the Wilcoxon signed rank test.

TABLE I. Patient and Procedure Characteristics[a]

Demographics and risk factors	
Age, y	85 (49-94)
Women	5
Coronary artery disease	2
Diabetes melitus	7
Obesity	1
Stroke	1
Dialysis dependent	0
MI withing 6 mo	0
Baseline clinical satus	
Rutherford category 5 / 6	3 / 4
Rest pain	2
Wifi risk	2 at W I I3fI0l; 1 at W313fI0; I at W3I3fI I; 2 at W3I3fI2; I at W3I3dl3
Procedure details	
Distal venous acces	5 PTV, 2 ATV
AVF location	4PTA-PTV; I ATA-ATV; I ATA-TPV; I PopA-PopV/PTV

Abbreviations: ATA, anterior tibial artery; ATV, anterior tibial vein; AVF, arteriovenous fistula; MI, myocardial infarction; PopA, popliteal artery; PopV, popliteal vein; PTA, posterior tibial artery; PTV, posterior tibial vein; TPV, tarsal pedal vein; WlfI, wound, ischemia, and foot infection. [a]Continuous data are presented as the median (absolute range); categorical data are given as the counts.

Results

Technical success was 100%, with flow to the plantar venous arch achieved in 5 of 7 cases. A tapered bare metal stent was used to create the AVF in 6 of 7 patients. Six patients had prior or simultaneous inflow treatment and received extension stent-grafts. Five patients also had inter- ventions to the foot veins (1 balloon dilation, 3 dilation + stent, and 1 valvulotome + dilation). The immediate angiographic appearance was dramatic (Figure 3A-D). One patient who had prior lumbar sympathectomy and was on high doses of opioids for chronic pain had a dramatic reso- lution of her pain within 48 hours and was opioid free. Negative pressure therapy was used to augment wound healing in 5 of 7 patients, and split skin grafting was used for wound closure in 3 of 7 patients.

No MALE was reported through 30 days, but 2 patients were treated medically for non–ST-elevation MIs. One patient was known to have right coronary artery disease deemed too diffuse for coronary intervention or bypass. There were no perioperative deaths associated with the procedure. Spontaneous retroperitoneal bleeding developed in 1 patient 8 weeks after the procedure, probably from anticoagulation; she was managed conservatively after cessation of the anticoagulation.

Median follow-up was 20 months (IQR 6–32). Clinical improvement was demonstrated in all patients with granulation, resolution of rest pain, or both. Five of 7 patients underwent minor amputation of one or more toes. At 6 months, 4 of 7 patients had achieved complete wound healing (Figure 3E-H) and were symptom free. By 12 months, 5 of 7 patients achieved complete wound healing, with a median healing time of 4.6 months (95% confidence interval 84 to 192). Thermography was also improved in all cases (Figure 4).

The median time to loss of primary patency was 3.3 months (IQR 1.9–6.8). Reinterventions were performed in 5 of 7 patients to maintain patency; occlusions were addressed using percutaneous mechanical thrombectomy (Rotarex; Straub Medical, Torrance, CA, USA) and drug-coated balloons to reestablish patency.

FIGURE 3. Angiograms before (A) and after (B-D) the procedure (C is magnified lateral, D is magnified anteroposterior). Wound status preoperatively (E) and after forefoot amputation at day 12 (F), day 91 (G), and day 164 (H, fully healed).

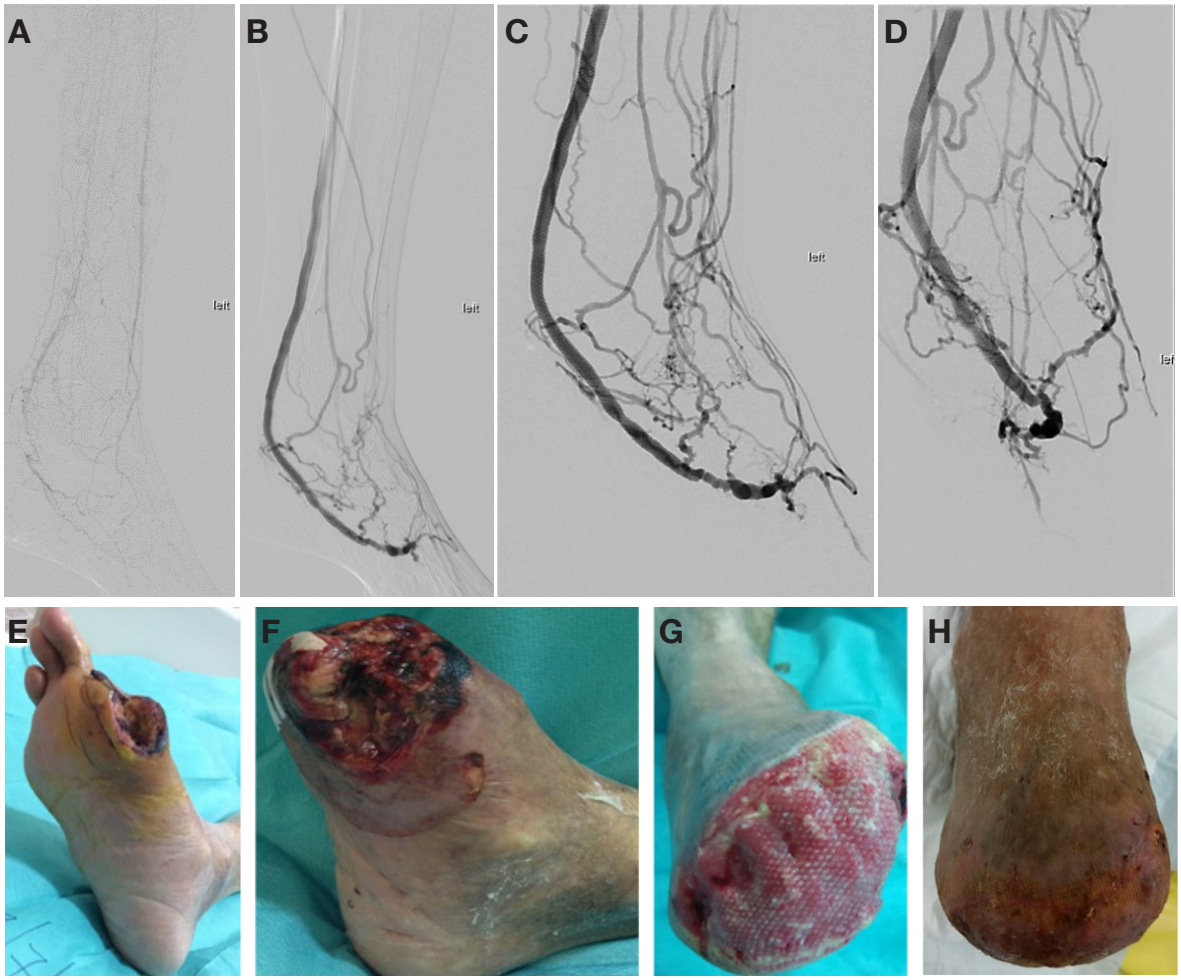
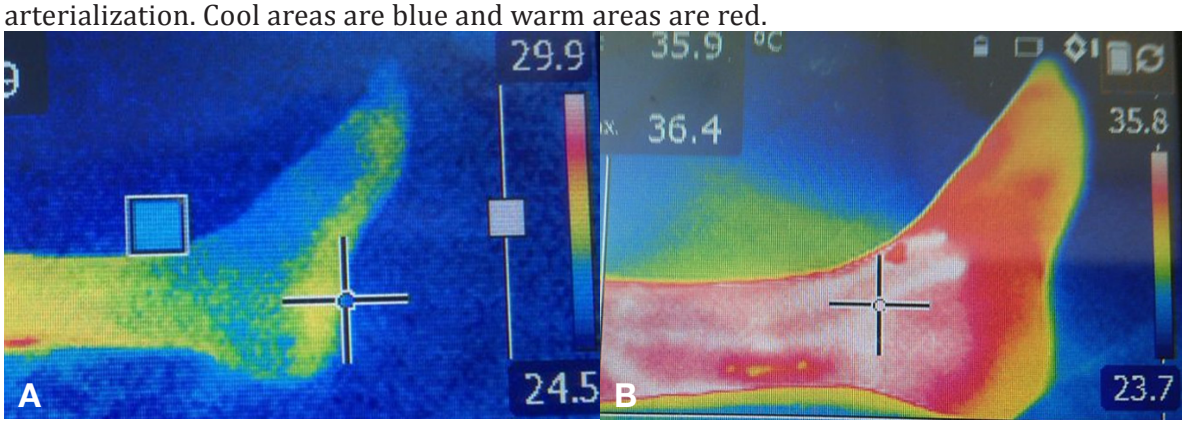


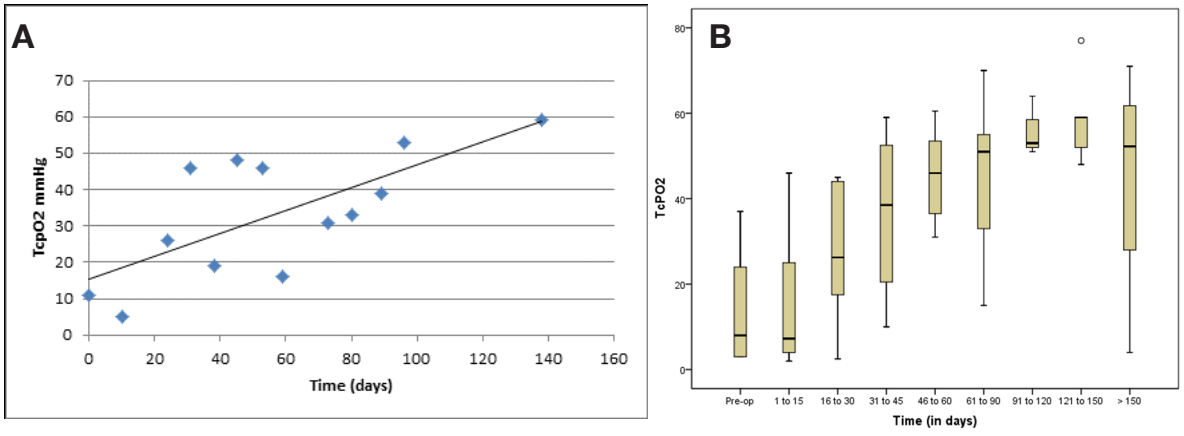
FIGURE 4. Improvement in thermography before (A) and after (B) percutaneous deep vein arterialization. Cool areas are blue and warm areas are red.



Two major amputations occurred within 12 months (limb salvage 71%). The first patient presented with Rutherford 6 heel gangrene and osteomyelitis, which was amputated at 61 days postprocedure owing to progressive symptoms of systemic infection. The PDVA was patent at the time of amputation. Bleeding of the heel wound was noted to be good in the preceding debridements. Another patient had severe ischemia with rest pain that resolved after the procedure. The PDVA occluded, and she required an above-knee amputation 7 months after the procedure. There were 3 deaths at 12 months, each unrelated to the device or procedure. Two patients died of pneumonia at 6 and 8 months, respectively. The previously mentioned patient with the above-knee amputation suffered a fatal MI 19 days after the amputation.

Tissue perfusion was recorded in 6 of 7 patients (Figure 5A). The median number of $TcPO_2$ measurements per patient was 13 (IQR 4–17). Median values rose from 8 mm Hg (IQR 3–27) before the procedure to 61 mm Hg (IQR 50–76) after (p=0.046); in 5 of the 6 patients, the value was >40 mm Hg. The $TcPO_2$ levels appeared to rise 2 to 4 weeks after treatment and were mostly >40 mm Hg at 6 to 8 weeks after treatment (Figure 5B). By the time of wound healing in 5 patients, the median $TcPO_2$ was 59 mm Hg (IQR 36– 67); 4 of these patients had values >40 mm Hg.

FIGURE 5. (A) Foot oxygenation against time in 1 patient from the day of the procedure. (B) Box-and-whisker plot of median transcutaneous pressure of oxygen ($TcPO_2$) values of all patients obtained from the probe adjacent to the wound. The top and bottom borders of the box mark the 75th and 25th percentiles, respectively; the horizontal line in the middle is the median. The whiskers are the 90th and 10th percentiles. The circle indicates an outlier.



Discussion

Percutaneous revascularization represents a revolution in the treatment of CLI. Novel techniques have increased the number of limbs being salvaged. However, there are multi- ple challenges yet to overcome, as well as the lack of alternatives for restenosis in below-the-knee vessels. These shortcomings and better survival from optimization of comorbidities have resulted in an increasing number of patients with NOP-CLI.

Different alternatives have been suggested for these patients, including cell-based therapies, which have shown some promise.[12] Other possible treatments include spinal cord stimulation and sequential pneumatic compression. Some of the earliest reports of surgical proximal venous arterialization by Halstead and Vaughan[4] and Bernheim[13] yielded mixed results. Lengua[14] and Taylor et al[15] reported their experience with distal venous arterializations. More contemporary series of surgical DVA[8,9] have been encouraging. The combination of interventional techniques to embolize the venous collaterals or to render valves incompetent[16,17] have been employed to improve the results and drive the arterialized blood distally.

To our knowledge, no one has yet reported a totally percutaneous approach to DVA. This pilot study indicates that the procedure is safe; none of the patients experienced peri- operative mortality or significant morbidity other than 2 MIs not resulting in any significant sequelae. It is important to understand that these patients were of an advanced age and had multiple cardiovascular comorbidities, some of which were poorly controlled, and multiorgan dysfunction. In every sense, when they presented with NOP-CLI they were also “end-stage” patients with poor organ reserves. It is not surprising that 3 deaths occurred within 12 months despite best medical treatment. A recent meta-analysis of NOP-CLI studies[18] reported mortality ranging between 10% and 54% in the 886 patients; notably, the proportion of diabetic patients in these studies (19%–54%) was lower than in our small cohort (100%), which could have accounted for higher mortality.

All our patients experienced clinical improvement as seen by the formation of granulation; 2 patients even had immediate resolution of rest pain. Most (71%) had achieved complete wound healing and improvement in Rutherford class by 1 year. The loss of 2 target limbs, in our opinion, is not unexpected given that all patients were diabetic and had NOP-CLI. These figures are comparable to a meta-analysis of surgical DVA,[8] in which the foot preservation rate at 1 year was 71%.

One of the outcomes specifically documented was the change in serial $TcPO_2$ measurements, which were systematically performed in a controlled environment. In our opinion, $TcPO_2$ levels represent the best available objective measurement of perfusion, but it can be influenced by swelling and the presence of infection, which may falsely depress the measurements. Conversely, shunting at the arteriole–venule level may not reflect oxygen tension at a cellular level.

The $TcPO_2$ readings increased dramatically in all patients, but it seemed to take >2 months for most of the patients to achieve the >40 mm Hg threshold, which seemed to lag behind clinical improvement. One possibility is that the swelling and edema commonly seen after the procedure may have falsely depressed the $TcPO_2$ levels. In our opinion, a rise in $TcPO_2$ represents an objective improvement in perfusion.

All of our patients experienced some degree of swelling, which was mostly managed conservatively with elevation and occasionally diuresis. Our impression is that the patient should be nursed with leg elevation and off-loading measures if significant swelling is seen. Subsequently, they can be nursed with legs down to allow the hydrostatic pressure to encourage further formation of venous collaterals, somewhat analogous to the maneuvers for the maturation of AVFs created in the arm.

Though the procedure was feasible in our early experience, challenges included the inconsistent vein anatomy, small vein diameters, and valve crossing in particular, which proved surprisingly difficult at times. We used a variety of 0.014-inch and 0.018-inch wires with dedicated support catheters to circumvent the valves. A combination of high-pressure balloon angioplasty and stents was also used as adjuncts to achieve flow to the foot. An over-the-wire reverse valvulotome that allows the operator to push and cut the valves after wire passage is now used routinely, obviating the need for high-pressure balloon angioplasty to address the valves. This represents a less traumatic approach to render the valves incompetent compared with the potentially damaging barotrauma associated with balloon angioplasty, which may ultimately lead to restenosis. In our opinion, the angiographic and clinical success of the procedure relies heavily on these measures to drive blood to the foot. Since these adjunctive interventions to address the valves were not available in the past, the limited success of early surgical series is not surprising.

The use of extension stent-grafts addresses not only the problem of venous bleed-offs via collaterals but also the valves in the calf. It allows a large-

caliber shunt and is analogous to a polytetrafluoroethylene surgical bypass to the deep veins. Reintervention for an occluded PDVA was usually due to restenosis distal to the extension stent-grafts. The use of these covered stents made reintervention relatively easy with dedicated pharmaceutical and mechanical thrombectomy devices to clear the thrombus, followed by treating the restenosis in the distal veins. These stent-grafts have also been surveyed with intravascular and transcutaneous ultrasound, documenting nearly full expansion.

Limitations

The small number of patients reported limits the conclusions with regard to the technique's general applicability. This pilot study, however, seems reasonable to demonstrate safety and feasibility.

Conclusion

PDVA, when applied to a cohort of patients with NOP-CLI, appears to be a safe and feasible procedure. The dual catheters, guided by ultrasound imaging, provide a reliable way to percutaneously create the AVF between a tibial artery and a deep tibial vein. Assisted by a percutaneously introduced valvulotome, arterial blood can now be directed to the veins of the foot. In this small cohort of patients, PDVA appears to be effective in improving limb oxygenation, encouraging wound healing and potentially avoiding major amputation. Although these initial results are promising, they need to be verified in larger studies, though it will remain challenging to prove the concept in this complex group of patients. Wound outcomes will continue to be important in future studies.

Authors' Note

This technique was presented at the VEITHsymposium (November 19, 2013; New York, NY, USA) and at the Amputation Prevention (AMP) Symposium (August 11–12, 2016; Chicago, IL, USA).

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Steven Kum is a consultant to Limflow and has received remuneration for travel expenses and consultancy services. Andrej Schmidt and Roberto Ferraresi are consultants to Limflow and have received remuneration for consultancy services. Yih Kai Tan

and Jihad Mustapha are uncompensated consultants to Limflow.

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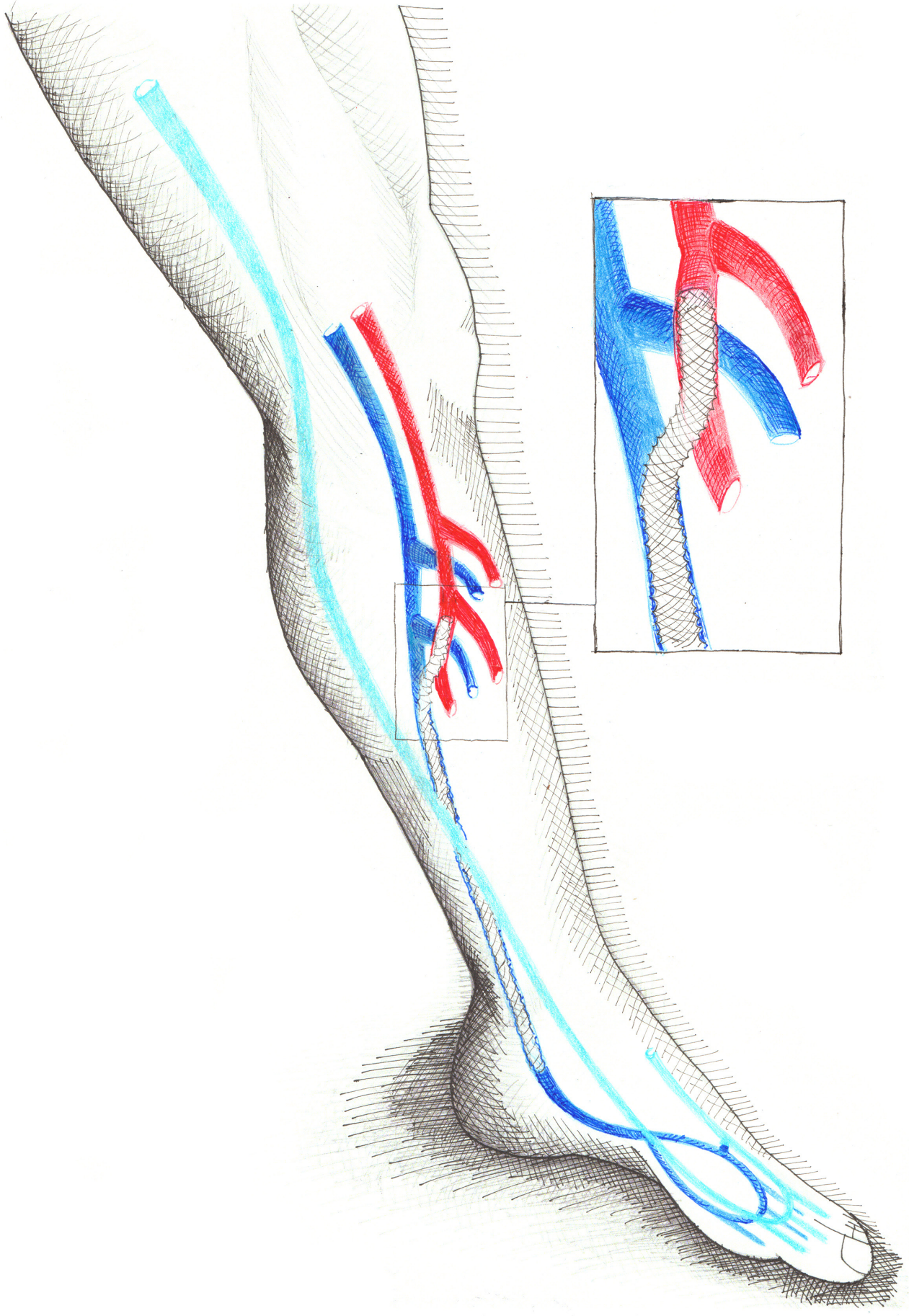


Chapter 5

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

Schmidt A, Schreve MA, Huizing E, Del Giudice C, Branzan D, Ünlü Ç, Varcoe RL, Ferraresi R, Kum S.

J Endovasc Ther. 2020 Aug;27(4):658-665.

Abstract

Purpose

To evaluate the mid to long-term results of patients suffering from no-option chronic limb threatening ischemia (NOP-CLTI) treated with a dedicated system for percutaneous deep venous arterialization (pDVA).

Methods

Consecutive patients treated with pDVA using the Limflow device (LimFlow SA) for CLTI between 11 July 2014 to 11 June 2018 in Alkmaar, Leipzig, Paris and Singapore were retrospectively analyzed. 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

A total of 32 patients with NOP-CLTI and tissue loss underwent pDVA with the LimFlow device. Of all patients, 65.6% had diabetes, 25.0% were on immunosuppression, 15.6% had dialysis dependent renal failure, 31.3% had Rutherford classification 6 and 78.1% deemed at high risk of amputation according to the Society of Vascular Surgery Wound Ischemia Foot infection (WIfI) classification. Technical success was achieved in 31 patients (96.9%). AFS was 83.9%, 71.0%, and 67.2% at 6,12 and 24 months respectively. Survival was 93.5%, 83.9% and 80.2% at 6, 12 and 24 months respectively. Limb salvage was 86.8%, 79.8% and 79.8% at 6, 12 and 24 months respectively. Complete wound healing was achieved with 36.6%, 68.2% and 72.7% of patients at 6,12 and 24 months respectively.

Conclusion

This study represents the largest population studied to date of patients with NOP-CLTI treated with pDVAusing the LimFlow device with mid and long-term results. In this complex group of patients, pDVA using the LimFlow device has shown to be feasible with high technical success rate and AFS at 6 up to 24 months coupled with wound healing. In selected patients with NOP-CLTI, pDVA could be a recommended treatment to prevent amputation and heal wounds.

Introduction

Worldwide, more than 200 million people suffer from peripheral arterial disease (PAD)(1).In a proportion of patients with PAD, the disease evolves into CLTI and tissue loss which is associated with major amputation in 30% of the patients and only 20% will achieve wound healing at 1 year when left untreated (2). The need to there fore prevent amputations is pressing. A systematic review confirmed improved limb salvage rates in 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. This concept was championed by Ferraresi et al.(4) who described the problem of big artery disease in the failure of 'transmission' and small artery disease in the failure of 'distribution'. The most severe form of distribution failure may lead to the '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 this NOP-CLTI has been reported to range between 10-50% of CLTI patients, leaving major limb amputation as the only viable solution (5,6). Severe untreated CLTI patients are at risk of having an all-cause mortality of 22% at 12 months and amputation rates as high as 42% (7). Dismal wound healing in severe untreated CLTI patients has been reported to be in the range of 10-20% at 1 year (7,8). 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 lowerl imb (9–11). LimFlow SA (Paris, France) recently developed a dedicated set of tools to perform pDVA (12). This endovascular technique showed promising 6-months resultsin the first-in-man study and in the early feasibility study (13,14). However, long-term follow-up has not been described.

The aim of this study is to evaluatethe mid and long-term results of pDVA performed with the LimFlow device in NOP-CLTI patients with tissue loss in 4 vascular centers.

Methods

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.

Patient selection

All consecutive patients treated with pDVA in Alkmaar (Netherlands), Leipzig (Germany), Paris (France), and Singapore (Singapore) from 11 July 2014 to 11 June 2018 were reviewed. Inclusion criteria were: Rutherford 5 or 6 NOP-CLTI, absence of distal target artery on the baseline angiogram, which precluded 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 which precluded limb salvage, known deep vein thrombosis, allergy to Aspirin or Clopidogrel or contraindication to anticoagulation. The suitability of the patient for the pDVA procedure was assessed by an interventionalist and/or vascular surgeon with both at least 5 years of interventional experience. All patients were treated in a multidisciplinary setting with dedicated wound centers in all sites.

Description of the procedure

The aim of the procedure is to create a connection between a tibial artery and a tibial vein to provide pressurized arterial flow to the venous system of the foot. The procedure was performed as described previously (14,15) and in accordance with the product instructions for use. In brief, antegrade arterial access was achieved via antegrade femoral puncture and the introduction of a 7-Fr sheath. Distal venous access was achieved by the ultrasound-guided puncture of the target tibial vein at the ankle. The crossing point was selected after simultaneous digital subtraction angiography with double contrast injection in both artery and vein. The crossing point was chosen to facilitate successful crossing between the artery and vein whilst preserving significant arterial collaterals. The arterial and venous catheter 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 artery to vein. A 0.14-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-Fr valvulotome was used to lyse the valves as distal as the midfoot, allowing antegrade flow into the deep venous system of the foot. Self-expanding stent grafts were implanted from the level of the ankle towards 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. Post-procedure, patients were prescribed lifelong antiplatelet therapy (aspirin 100 mg or clopidogrel 75 mg) in combination with anticoagulation for at least 3 months if possible.

Clinical follow-up

The follow-up was performed according to the institutional protocol and included clinical evaluation of the patient's 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 solely percutaneously with a thrombectomy device supplemented by drug balloon angioplasty or stenting.

TcPO2measurements

Assessment of the perfusion was performed as described previously (15). TcPO2 measurements were done every 2 weeks for the first 2 months and monthly thereafter until wound healing was achieved.

Data collection and study endpoints

Patient demographics, baseline risk factors, laboratory values, angiographic, and procedural data were retrospectively collected. Clinical and imaging datawere derived from electronic medical records.

The primary endpoint was amputation-free survival (AFS) at 6 months. Secondary endpoints were wound healing, limb salvage, and survival at 6, 12 and 24 months and AFS at 12 and 24 months. Wounds were considered healed if they were fully epithelized. Amputation-free survival was defined as avoidance of major amputation (above the ankle) of the index limb or death (any cause) (16). Limb salvage was defined as freedom from major amputation. Technical success was defined as the ability to cross from the artery in the vein with the LimFlow device and implantation of covered stents. Stent graft were considered patent whent here was flow detected within.

Statistical analysis

Patient- and physician-level characteristics were described using median (interquartile range [IQR], when nonnormally distributed), mean ± standard deviation (when normally distributed), and count (percentage). Quantile-quantile (Q-Q) plots were analyzed to determine whether continuous variables followed a normal distribution. If the points in the Q-Q plot lie on a straight diagonal line, the data was defined as normally distributed. AFS rate, limb salvage rate, survival rate, and wound healing rate were estimated by Kaplan-Meier analysis. In patients who died before complete wound healing, the date of death was defined as the cutoff date. In patients who underwent major amputation, the time to wound healing was considered to be infinite (17). TcPO2 data was compared using the paired *t* test. Statistical significance was

defined as $P < 0.05$. Statistical analysis was performed using SPSS 23 software (IBM, Armonk, NY, UnitedStates).

Results

Patient characteristics

A total of patients with tissue loss underwent the pDVA procedure with the LimFlow device. One patient with acute limb ischemia treated with the device was excluded from this study, leaving 32 patients with NOP-CLTI available for analyses. Of these, 5 patients were treated in Alkmaar, 9 in Leipzig, 3 in Paris and 15 in Singapore. Twenty patients (62.5%) were male and 12 female (37.5%), with an average age of 67 ± 14 years. Notable comorbidities included type 2 diabetes (65.6%), renal insufficiency (53.1%) (including dialysis-dependent renal failure in 15.6%) and immunosuppression (25.0%). Of note, all patients had tissue loss with 10 patients (31.3%) Rutherford 6 ischemia, and 25 patients (78.1%) were deemed high risk according to the SVS WIfI classification (18). As many as 87.5% had prior unsuccessful percutaneous intervention. Patients characteristics are summarized in Table 1.

Procedure

Technical success was achieved in 96.9% of the cases. In 1 patient, the pDVA procedure failed as the target vein did not respond to aggressive balloon dilatation which precluded stent graft implantation. This patient was excluded from subsequent 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 (86%) from the tibioperoneal trunk (17%) or posterior tibial artery (69%). The other crossings were performed from the anterior tibial artery to the anterior tibial vein (10%) or from the popliteal artery in the popliteal vein (4%).

30-day outcome

The median follow-up time was 34 months (range 16-63). During the first 30 days post-procedure, we observed 2 non-fatal myocardial infarctions and 2 deaths. One patient died secondary to sepsis of the foot that was present prior to the procedure. 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 procedure.

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

	Number (%)
Patients	32
Limbs	32
Men	20 (62.5)
Age, years	67 ± 14
Side of limb	
Left	16 (50.0)
Right	16 (50.0)
Comorbidities	
Body mass index (kg/m2)	24 ± 4
Hypertension	27 (84.4)
Diabetes	21 (65.6)
Hyperlipidemia	20 (62.5)
Coronary artery disease	15 (46.9)
Chronic kidney disease	17 (53.1)
Dialysis dependent	5 (15.6)
Cerebrovascular accident	4 (12.5)
Smoking*	15 (50.0)
Medication use	
Immunosuppressant	8 (25.0)
Lab results	
Serum creatinine (μmol/L)	88 (67-143)
Rutherford	
5	23 (71.9)
6	9 (28.1)
SVS Wifi risk staging	
High risk	25 (78.1)
Moderate risk	6 (18.8)
Low risk	1 (3.1)

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).

Subsequent follow-up

Beyond 30 days, 5 other deaths occurred due to myocardial infarction (n=2), pneumonia (n=2) and exacerbation of chronic obstructive pulmonary disease (n=1). There were several other adverse events. Onepatient developed bleeding from a superficial vein adjacent to the granulating wound 6 months post-procedure, which required surgical ligation.The graft thrombosed shortly after ligation.A secondpatient hadinfection of thestent graft10 weeks after the procedure. The primary wound on the 5thtoe had already healed. The stent graft was explanted andthe resultant large ankle wound continued to heal. A thirdpatient developed a new wound on the forefoot after the index

wound had healed 8 months post index procedure. This patient had an occluded DVA circuit and was treated with the Rotarexcatheter (Straub Medical AG, Wangs, Switzerland), thrombolysis and a Supera stent (Abbott, Chicago, United States)in the veins of the foot. Thisnew wound subsequently healed.
The AFS at 6,12 and 24 months was 83.9%, 71.0%, and 67.2% respectively. The corresponding survival was 93.5%, 83.9%, and 80.2% and the limb salvage was 86.8%, 79.8%, and 79.8% in the same period. All major amputations were performed within 9 months post-procedure. A total of 21 wounds were healed within 24 months, resulting in a wound healing estimate of 72.7% at 24 months with a median time to complete wound healing of 4.9 months (range 0.5 to 15.0). Amongst the patients who remained alive without amputation, 86.4% completely healed their wounds at 12 months. Kaplan-Meier curves are shown in Figures 1–4. An example of a typical case is shown in Figure 5. TcPO2 was measured at baseline and during follow-up in 13 patients. A total of 142 TcPO2 values were measured with an average number of 10.9 measurements per patient. Six patients had TcPO2 measurements that extended to two years and beyond. At baseline, the average TcPO2 measurement near the wound was 14.5±12.7 mmHg (median 11mmHg, range 3-37). As illustrated by Figure 6, TcPO2 levels increased after the pDVA procedure, reaching 56.1±11.9 mmHg (median 57.5mmHg, range 36-72) after 2 years. This became statistically significantly higher after 45 days (increase of +22.1mmHg, p=0.027) and remained statistically significant higher during follow-up (increase of + 41.7mmHg, p< 0.001) compared to baseline. The DVA circuit occluded during the period of follow-up in 21 patients and the median time to occlusion was 2.6 months (range 0.2–19.1). Reintervention for occlusion was performed in 18 patients, of which 17 were performed 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. Reinterventions for stenosis were performed in 1 other patient.

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

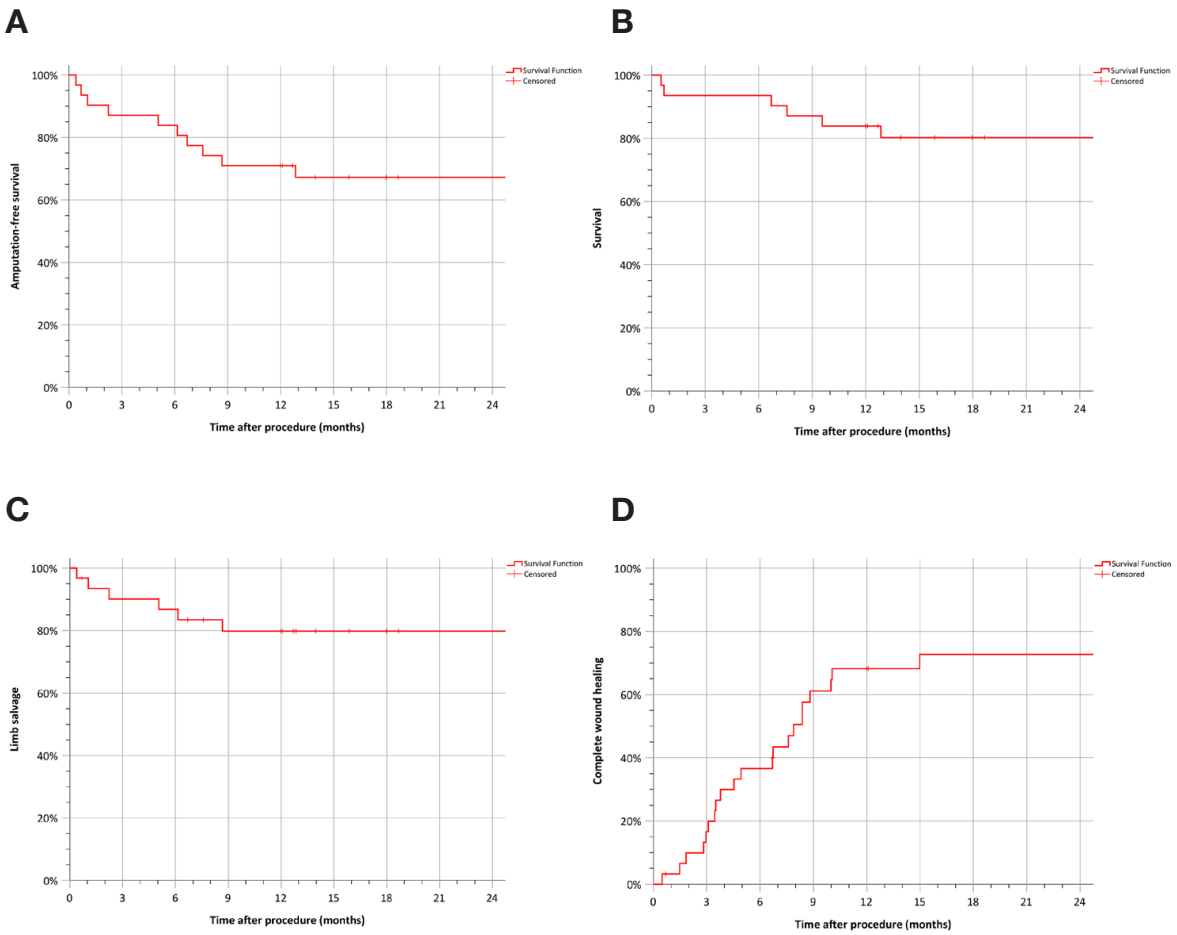


FIGURE 2. Transcutaneous oxygen pressure ($TcPO_2$) levels at baseline and follow-up.

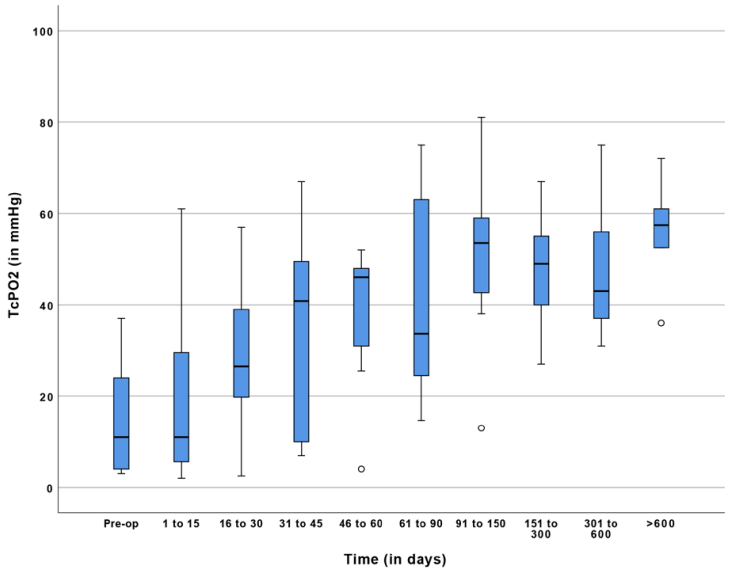
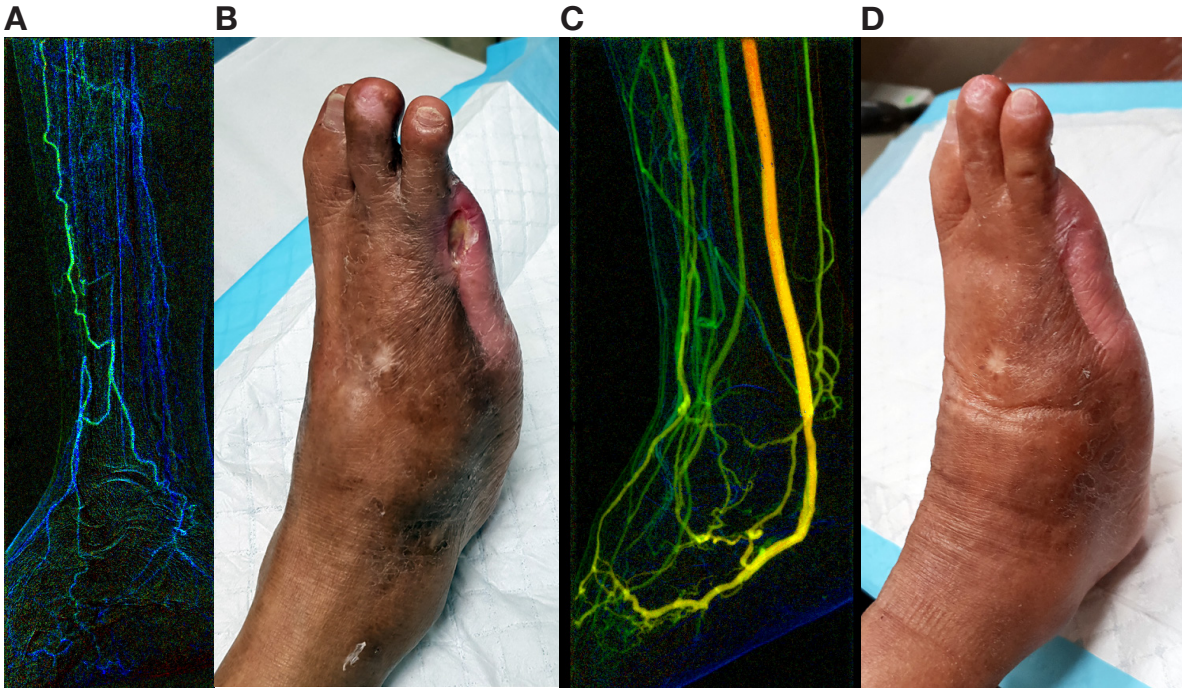


FIGURE 3. Angiographic and clinical results of percutaneous deep venous arterialization with the LimFlow device. (A) Perfusion angiogram of a patient with no-option chronic limb-threatening ischemia having failed conventional therapy. (B) Preprocedure photograph showing a wound that had failed to heal 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.



Discussion

This multicenter study represents the largest cohort of consecutive patients treated with pDVA by interventionalists from different sub-specialties followed-up to 2 years. Prior reports of surgical series (11) had shown venous arterializationto be a viable option in NOP-CLTI with technical success rates of approximately 81% (19). A high technical success rate of 97% was achieved with a percutaneous approach with the LimFlow device, mirroring the experience in the initial series (14,15). In a cohort of 312 patients treated by standard endovascular techniques, Iida et al. reported an AFS of 73.6% and 55.2% at 12 and 36 months respectively (20,21). Over 80% of these patients were treated by plain balloon angioplasty. Conversely, we were able to achieve AFS rates of 83.9%, 71.0%, and 67.2% at 6, 12 and 24 months, in NOP-CLTI patients with no further possibility of conventional revascularization. We obtained durable results up to 2 years with our cohort of patients, majority of whom had failed prior attempts at revascularization. Other investigators have suggested other treatments for NOP-CLTI. Benoit et al. (8) reviewed NOP-CLTI patients treated with vasoactive drugs and stem cell therapyand showed an AFS of between 53-55% in studies published after 2006, which were lower than those found in our study (8). Other treatment modalities exist for NOP-CLTI patients including spinal cord stimulation, lumbar sympathectomy, intermittent pneumatic compression and hyperbaric oxygen therapy (22). However, the efficacy of these treatment options remains low and they are therefore not recommended routinely for the treatmentof CLTI (22).

Wound healing rates are poorly reported in historic CLTI series. Specifically, wound healing rates are not often reported for NOP-CLTI patients. In a randomized controlled study of prostaglandins use for NOP-CLTI patients, Brass et al. (23) reported wound healing rates of less than 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 patients who remained alive without amputation healed their wounds at 12 months. Our wound healing rates and time to wound healing were reasonable compared to existing CLTI registries (21). In a large-scale registry of Japanese patients with CLTI (but not NOP-CLTI) wound healing rate of 86% at 1 year with a median time to wound healing of 97 days was reported. In our study, the median time to wound healing was 4.9 months i.e.150 days and we achieved reasonable wound healing rates of 68.2% at 1 year despite having patients on immunosuppression (25.0%), advanced ischemia with no other revascularization options, and a larger cohort of

Rutherford 6 wounds (31.3%).

We hypothesize that a remodeling process takes place after pDVA. Ferraresi et al. (9) reported the possibility of a remodeling process after DVA that was seen angiographically. This was associated with clinical wound healing and high TcPO2measurements. We believe that longer time to wound healing in our study could be related to this remodeling process. Our TcPO2 results seemed to rise to significant levels after 45 days which could be explained by this same phenomenon. TcPO2 has been shown to be a reliable predictor of wound healing (24).

Reintervention rates in patients with CLTI have been reported in several registries. At 1 year, Iida et al.(20) reported reintervention rates of 40% and Fernandez et al.(25) reported 50%. In our study, reintervention rates were comparable (59.4%) with the rates reported in the initial series (71%, (15)). The main cause of reinterventions was the venous outflow in the majority of the cases. Despite this study being the largest study of pDVA to date, the sample size is still relatively small, which is one of the weaknesses of the study. Due to the retrospective nature of the study, recall bias is possible.

Slight differences in treatment among the centers exist, especially in woundcare, which reduced the internal validity of the study. On the other hand, it is a multi-center study with a cohort of consecutively treated patient showing real world data which was mostly captured electronically. Further studies could include a larger sample size with longer follow-up data. A control group could be considered but would be difficult to implement due to small numbers and ethical considerations.

Conclusion

This study represents the largest population of patients to date with NOP-CLTI treated with pDVA using the LimFlow device with mid and long-term results. In this complex group of patients, pDVA using the LimFlow device has shown to be feasible and safe with high technical success and good AFS at 6-months up to 24 months coupled with good wound healing. In selected patients with NOP-CLTI, pDVA is a safe and effective treatment to prevent amputation and heal wounds.

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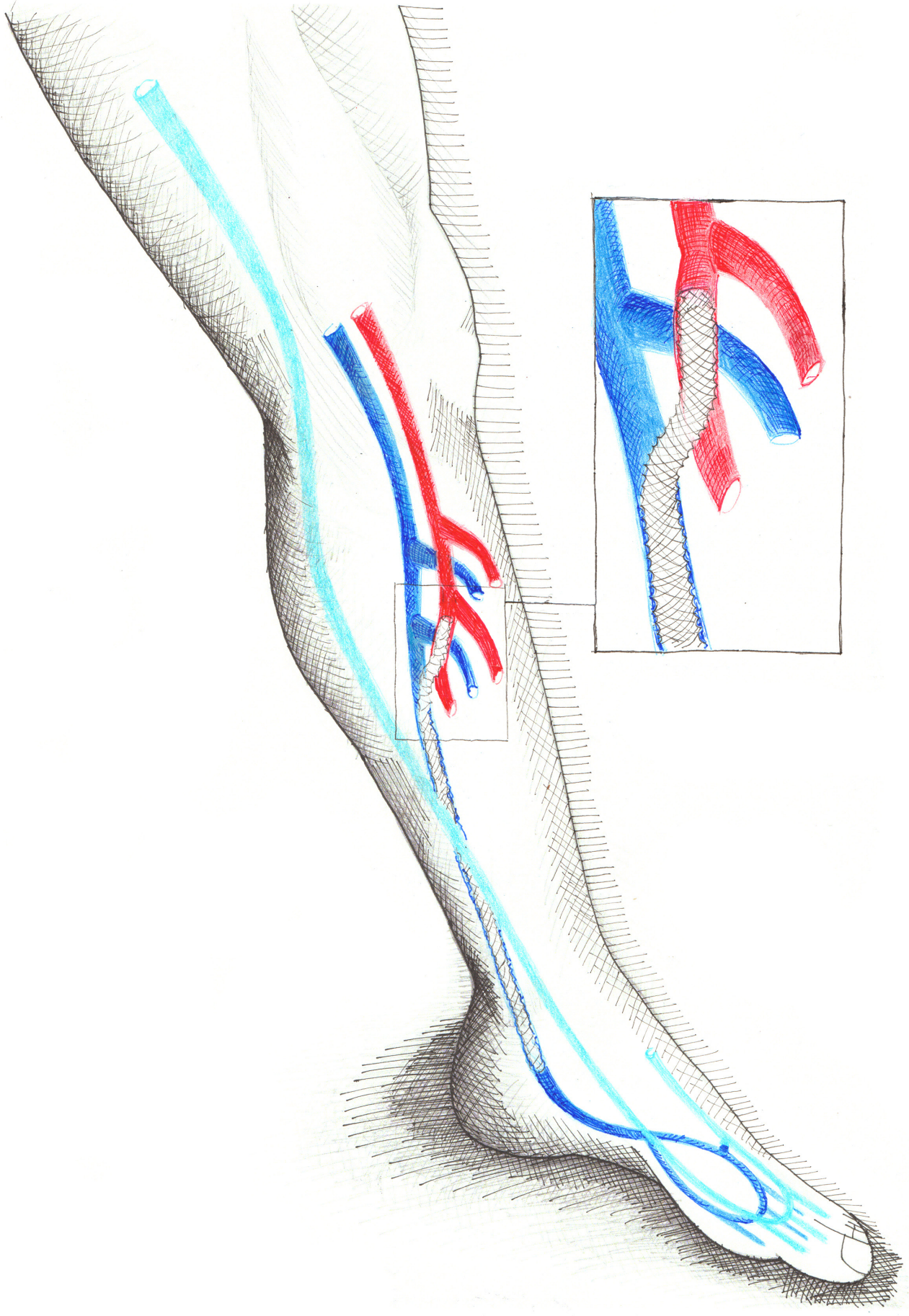

Chapter 6

PROMISE international; a clinical post marketing trial investigating the percutaneous deep vein arterialization (LimFlow) in the treatment of no-option chronic limb ischemia patient

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Abstract

Background

Critical limb ischemia (CLI) is the clinical end stage of peripheral artery disease and is associated with high amputation, mortality rates and poor quality of life. For CLI patients with no revascularization options, venous arterialization could be an alternative technique for limb salvage. A systematic review and meta-analysis published in 2017 concluded that venous arterialization may be considered a viable alternative. A recent development, is the Percutaneous Deep Vein Arterialization (pDVA), that is CE-marked and currently under investigation of the FDA. This procedure, called LimFlow, is a novel, minimally invasive, endovascular approach to perform a venous arterialization procedure. The limited evidence for its use necessitates a scientific judgement of the pDVA. Therefore, we initiated a prospective clinical post market trial to investigate the outcome of the pDVA in no-option critical limb ischemia.

Methods/design

The objective of this prospective study is to collect "real-life" clinical data among a population of patients treated with the pDVA in order to evaluate the clinical effectiveness and safety of the LimFlow System in patients with no-option critical limb ischemia. This study is a single-arm, open-label, prospective, post-market follow-up study to be conducted on up to fifty (50) eligible patients with a twelve-month follow-up period. The Primary endpoint is measured by amputation free survival. Secondary endpoints are complete wound healing, primary and secondary patency, limb salvage, renal function and technical and procedural success. Patients will be assessed at regular intervals during one year after the initial percutaneous deep vein arterialization procedure through clinical evaluation and self-completed questionnaires.

Discussion

The last decade several studies have been published with promising results and the number of treated patients has considerably grown. Venous arterialization could be a valuable treatment option in patients with often no other options than amputation of the affected limb. The first results in men are promising although more research and long term follow up is needed to establish the efficacy of this new treatment modality.

With this prospective study, we evaluate the clinical effectiveness and safety in patients with no-option CLI treated with the pDVA (LimFlow System).
Trial registration: NCT03321552.

Background

Critical limb ischemia (CLI) is the clinical end stage of peripheral artery disease (PAD) and is associated with high amputation, mortality rates and poor quality of life. (Sprengers et al., 2010) It is estimated that 5 to 10% of pa- tients with peripheral artery disease older than 50years will develop severe or critical limb ischemia (CLI) within 5 years and mortality rates are 20% at 6 months after on- set. (Norgren et al., 2007) Bypass surgery and more re- cently endovascular interventions with angioplasty and stenting have become the treatment of choice in order to prevent amputation and resolve rest pain. Endovascular interventions carry lower risk of morbidity and mortality and are often used as the first-line approach in preference to open surgery. (Adam et al., 2005; Katib et al., 2015)

Advancements in endovascular technology and tech- nique have led to high technical success rates; however, failure may occur due to the absence of distal target ves- sels, severe calcification, and heavy plaque burden that results in elastic recoil and early restenosis after angio- plasty. Advanced disease with occlusion of the pedal ar- teries or only small artery's (the "desert foot") represents an end-stage pathology that commonly leads to failure of all revascularization attempts and culminates in major amputation. This is termed no-option CLI.

In the last decade, new treatment options have been ex- plored as for patients with no-option CLI. These include stem cell therapy, spinal cord stimulation and prostanoids therapy. A meta-analysis of placebo controlled trials showed no advantage of stem cell therapy on the primary outcome measures of amputation, survival, and amputa- tion free survival in patients with CLI. (Peeters Weem et al., 2015) Another meta-analysis showed no benefit for prostanoids treatment or other medical treatments. (Abu Dabrh et al., 2015) A Cochrane review concluded that there may be some benefit with spinal cord stimulation for prevention of amputation, however evidence is consid- ered as very low grade, mainly due to imprecision and in- creased risk of bias. (Ubbink & Vermeulen, 2005)

For CLI patients with no revascularization options, venous arterialization could be an alternative technique for limb salvage. The concept of using the disease-free venous bed as an alternative conduit for perfusion of the peripheral tissues with arterial blood was first published by Halstead and Vaughan in 1912. (Halstead & Vaughan, 1912) Flow in existing collateral vessels will increase,

re- versal of flow all the way through the capillaries im- proves tissue nutrition (Ozek et al., 1997) and possibly stimulates angiogenesis. (Baffour et al., 1988)

A systematic review and meta-analysis published in 2017 concluded that venous arterialization may be con- sidered a viable alternative before major amputation. (Schreve et al., 2017) Nevertheless, this technique is not widely being used. This could be due to the low quality of studies together with the fact you have to compre- hend with wounds on the foot when performing a classic venous arterialization.

A recent development is the Percutaneous Deep Vein Arterialization (pDVA) that is CE-marked and currently under investigation of the FDA. This procedure, called LimFlow, is a novel, minimally invasive, endovascular approach to perform a venous arterialization procedure. A major advantage of this approach, is the minimal inva- siveness with lower periprocedural risks and no crea- tions of wounds in an already critically ischemic leg. The first in men results have recently been published, dem- onstrating safety and feasibility of the pDVA, with prom- ising early clinical outcome in this small cohort. Long term follow up is needed to establish the efficacy of this new treatment modality. (Kum et al., 2017)

The limited evidence for its use necessitates a scien- tific judgement of the pDVA. Therefore, we initiated a prospective clinical post market trial to investigate the outcome of pDVA in no-option critical limb ischemia.

Methods/design

Objective

The objective of this prospective study is to collect “real-life” clinical data among a population of patients treated with the pDVA (LimFlow System) in order to evaluate the clinical effectiveness and safety of the LimFlow System in creating a below-the-knee arterio- venous fistula for venous arterialization in subjects with critical limb ischemia.

Our hypothesis is that in patients with no-option critical limb ischemia, a treatment with pDVA is a feasible, safe, and clinically effective approach. This study is a single- arm, open-label, prospective, post-market follow-up study to be conducted on up to fifty (50) eligible patients with a twelve-month follow-up period. This study was designed and is to be conducted in compliance with

the ISO 14155: 2011 standard. Outcome is primarily measured as ampu- tation free survival. Results of the LimFlow System risk as- sessment indicated that device-related risks had been reduced to levels as low as reasonably practicable and comparable with the state of the art. However, although the risks associated with the use of the LimFlow System were comparable with the state-of-the-art, the clinical experience was insufficient to completely characterize the nature and incidence of device-related procedural complications or late clinical complications. The safety and clinical effectiveness has not been evaluated in large cohort. Therefore, post-market clinical follow-up was indicated to more precisely assess the clinical effect and incidence of potential risks or to confirm that their prevalence lied below the threshold of concern and that the safety and clinical outcome is good.

Study population

Inclusion criteria:

I-1. Subject must be > 21 and < 95 years of age

I-2. Clinical diagnosis of symptomatic critical limb ischemia, defined as Rutherford category 5 or 6

I-3. Assessment that no conventional surgical or endovascular treatment is possible

I-4. Proximally, the target in-flow artery at the cross-over point must be treatable with a 3.5–4.0 mm stent after pre-treatment (by visual estimate), and be < 50% stenosis

I-5. Subject is willing and has adequate support to comply with protocol requirements, including medication regimen and follow-up visits

Exclusion criteria:

E-1. Concomitant hepatic insufficiency, deep venous thrombus in target limb, uncorrected coagulation disorders, or current immunodeficiency disorder

E-2. Life expectancy less than 12 months

E-3. Patient currently taking coumarin/warfarin which, in the opinion of the attending physician, interferes with the patient's treatment

E-4. Any significant medical condition which, in the attending physician's opinion, my interfere with the patient's optimal treatment

E-5. Patient 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 treatment

E-6. Patient unable to give consent

E-7. Pregnant or breastfeeding women
E-8. Documented myocardial infarction or stroke within previous 90 days
E-9. Patients suffering from renal insufficiency (GFR value less than 30 ml/min/1.73 m^2) who are not on hemodialysis
E-10. Patients with vasculitis and/or untreated popliteal aneurysms
E-11. Patients with acute limb ischemia
E-12. Prior peripheral arterial bypass procedure above or below the knee which could inhibit proximal inflow to the stent graft
E-13. Lower extremity venous disease with significant oedema in the target limb that may inhibit the procedure and/or jeopardize wound healing, in the investigator's opinion
E-14. Known or suspected systemic or severe infection (e.g., WIfI foot Infection grade of 3)
E-15. Known or suspected allergies or contraindications to stainless steel, nickel, or contrast agent that cannot be adequately pre-treated, or patients who cannot receive anticoagulation or antiplatelet a ggregation therapy
E-16. Severe heart failure, which in the opinion of the investigator may compromise subject's ability to safely undergo a percutaneous procedure (e.g., known ejection fraction of < 40%, NYHA Classification III-IV)

Procedure

Device description

The LimFlow System comprises the following five (5) components:

Ultrasound system

The LimFlow ultrasound system consists of a power supply, a laptop computer, and a transceiver box. The system produces a short electrical pulse which is applied to the transmit catheter. The signal received by the receive catheter is amplified, filtered, and digitized. The received signal is then displayed on the laptop as a waveform, giving a visual display of the strength of the received pulse and hence permitting orientation of the two catheters. Software running on the laptop permits the gain of the receiver and other parameters to be adjusted.

Extension cable set

The LimFlow extension cables carry power between the LimFlow ultrasound system and the LimFlow arterial and venous catheters.

Arterial and venous catheter set

The arterial ultrasound catheter is a 6.5-Fr catheter with a usable length about 100 cm. It is placed over a standard 0.014" guide wire through a sheath in the femoral artery and advanced to the tibial artery up to the point of total arterial occlusion. The arterial ultrasound catheter has two functions:

1. Locating neighbouring veins: a small single directed ultrasonic transmitter as its tip allows to detect the venous catheter in a neighbouring vein. The handle design and the catheter body allow for an easy torque and push-pull to find the correct location.
2. Connecting to a neighbouring vein by advancing a crossing-needle: the catheter has a handle with a pusher ring, which advances the crossing needle from artery to vein. The catheter is placed into the artery with the needle retracted inside the catheter shaft. A standard 0.014" guide wire can be placed through the advanced needle from the proximal hub (this wire is referred to as the "crossing wire").

The venous ultrasound catheter is a simple ultrasound receiver catheter which acts as a target in the vein for aligning the needle of the arterial ultrasound catheter. The catheter tip features a 360° ultrasonic sensor which allows the catheter to detect the arterial ultrasound catheter at any circumference angle. The venous ultrasound catheter is a 5-Fr catheter with a usable length about 100-cm. The catheter is placed over a standard 0.014" guide wire and is placed through a sheath in the femoral vein and advanced to the tibial vein up to and parallel to the arterial ultrasound catheter. The venous ultrasound Catheter is left in place and the arterial ultrasound catheter is rotated and moved longitudinally to obtain an optimal ultrasound signal indicating that the needle is aligned with and in the direction of the venous ultrasound catheter in the tibial vein.

Both arterial and venous catheters are intended to be used in a catheterization laboratory in consenting patients under fluoroscopy guidance. Both catheters are supplied sterile, removed at the conclusion of the procedure, and intended for single use only.

Valvulotome

The valvulotome is intended to make venous valves incompetent. The valvulotome is a device that is inserted over the crossing wire, passing the crossing section into the venous vessel. A push-pull deployment mechanism allows to deploy a nitinol cutting basket mounted at the distal tip. This cutting element self-centers in the venous vessel up to a maximum diameter of 4.5 mm.

The actual cutting blades are arranged at a lower diameter as the maximum diameter of the cutting element, this prevents cutting the venous vessel but allows cutting of the vein vales ones the cutting element is pushed through the valves. The device (un-deployed cutting element) has a total outside diameter of 4 Fr. The valvulotome is sup- plied sterile and intended for single use only.

Stent grafts
To facilitate constant blood flow through the newly-created crossing from artery to vein, a stent graft needs to be inserted. The LimFlow stent grafts product line contains of different self-expanding stent graft sizes and shapes, in order to meet physiological variations in anatomy of patients, and one delivery system, which is compatible for each stent size. The blank laser-cut nickel-titanium alloy (nitinol) stent serves as basic for additional forming and electro spun PTFE encapsulation procedures to obtain final stent grafts.

The stent graft delivery system comprises of inner tubing, which serves as 0.018" guide wire lumen and a flushing lumen, which is proximal accessible through a check valve. Design input specifications require 7-Fr sheath compatibility for the delivery device. In order to achieve excellent mechanical properties and functional push ability the outer shaft was designed with special braid pattern. Two radiopaque markers are attached to the distal end of the delivery device where the stent is crimped in between. Unintended stent movement during sheath retraction is restricted by the delivery device.

Training and experienced needed
The procedure itself should be performed by vascular surgeons and/or interventionalists experienced in interventional techniques such as complex percutaneous transluminal angioplasty and stenting in the lower limb. Study investigators will be selected based on their ex- perience in performing below-the-knee interventions and duly trained by LimFlow SA on the percutaneous deep vein arterialization specific medical procedure. All study investigators will be required to perform at least one (1) successful revascularization prior to participating to the study. In addition, a LimFlow SA representative will attend the first treatments performed in each site in order to assist the physician on technical issues as well as to ensure that treatment characteristics and potential complications are duly recorded.

Medical procedures involved
The specific medical procedure involved in the use of the device is as follows:
1. Use sterile technique to carefully remove the catheters from the packaging.

Inspect the catheters to verify that they are undamaged.

2. Obtain femoral artery access using standard Seldinger[1] technique to place a 7-Fr introducer sheath.
3. Add tourniquet (pneumatic or Esmarch) above the knee to distend the veins and reduce the arterial flow.
4. Obtain tibial vein access using ultrasound-guided Seldinger[1] technique with an echogenic 2.9/4.0-Fr micropuncture set and place the sheath at or above the level of the ankle. Dotter up to a 5-Fr × 45 cm sheath for the venous catheter.
5. Insert a 0.014" guidewire through the arterial introducer sheath into the distal portion of the posterior or anterior tibial diseased artery. Advance the arterial catheter within a standard 7-Fr × 45/55 cm sheath in the artery.
6. Insert a 0.014" guidewire through the venous introducer sheath and advance antegrade until it is above the corresponding tibial diseased artery.
7. Set-up the ultrasound system by connecting red and blue sterile electrical extension cables to (1) color-coded electrical connectors from arterial and venous catheters, respectively, and (2) ultrasound system.
8. Flush (female luer port) and introduce the venous catheter into the venous 5-Fr sheath over the wire. Advance the catheter into the venous system until it is parallel to the corresponding tibial diseased artery.
9. Remove the protection stylet wire at the tip out of the arterial catheter, flush the central lumen (female luer port at handle) using a syringe up to 5 ml. Preload the 0.014" crossing wire in the arterial catheter. Advance the arterial catheter with the monorail 0.018" guide wire into the femoral sheath to the distal arterial target parallel to the venous catheter. Align the arterial and venous catheters using the ultrasound system.
10. Once aligned, advance the arterial catheter crossing needle from tibial artery to tibial vein by deactivating the "twist lock" (turning the thumb piece clockwise and advancing in distal direction).
11. Insert the 0.014" guidewire through the arterial catheter crossing needle and into the tibial vein going in a retrograde direction towards the foot.
12. Unplug the electrical connections from the ultrasound system.
13. Pull in the crossing needle by activating the "twist lock" (pulling thumb piece in proximal direction, thumb piece will flip back into lock position automatically). Ensure that the crossing needle is pulled back into the arterial catheter completely.
14. Remove the arterial catheter while leaving in place the guidewire going from the arterial target and into the tibial vein.
15. Advance a support catheter that accepts a 0.018" guidewire through the arterial sheath in the tibial vein (pre-dilatation of the crossing area may be

required) and advance wire and support catheter into and around the arch of the foot, anchoring the wire on the opposite tibial vein.
16. Exchange for a 0.018" guidewire through the support catheter.
17. Insert the valvulotome in the 7-Fr arterial sheath and advance to the level of the foot.
18. Venous valves distal to the cross over point have to be made incompetent using the valvulotome to allow blood to flow to the distal part of the venous circulation of the foot.
19. Place the stent graft delivery system over the 0.018" guidewire and advance through the arterio-venous crossing point.
20. Depending on patient anatomy, multiple stent grafts may be deployed. If not able to advance the first stent graft, remove the stent delivery system and advance a low profile over-the-wire PTA catheter to dilate the arterio-venous connection and place the stent delivery system again. The stented area should extend from the arterio-venous crossing area starting at the artery level and continuing into the tibial vein just above the ankle joint. Deploy stent grafts from distal to proximal, placing the crossing stent graph last. A minimum of 1-cm overlap is recommended between all placed stents grafts.
21. Once the stents are deployed, post-dilate extension and crossing stent grafts with a PTA catheter, choosing the diameter on the basis of the vessel size (3 to 6 mm).
22. Once the stent grafts are in place, the physician may decide to treat the inflow and/or outflow vessels.
23. Confirm placement of various catheters and stent grafts throughout the procedure under fluoroscopy using contrast injections.

Patients should receive adequate antiplatelet and antic- oagulation therapy for a minimum of three (3) months post-procedure as per institution practice.

Study outline

Screening and baseline

The subject screening and recruitment process will be performed by the site medical personnel and should follow the steps below:

1. Critical limb ischemia patients with no endovascular or surgical treatment options are initially identified by the site investigators
2. No-option CLI patients meeting the LimFlow System indications and contraindications (as provided in the instructions for use since the LimFlow System is commercially available) can be scheduled for a percutaneous deep vein arterialization

3. Patients scheduled for a LimFlow intervention are asked whether they would be willing to participate to the study (inclusion/exclusion criteria are aligned with the CE-marked indications/contraindications)
4. Patients candidate to the study are subsequently enrolled, treated, and followed as per standard of care (the study protocol does not require more visits than what is considered standard of care)

Once the patients have agreed to participate to the study (i.e., once the informed consent has been obtained), the following exams will be collected:

- Demographics, medical history, and peripheral assessment
- Infectious status, i.e., wound culture and/or blood analysis (WBC, CRP, ESR)
- Venous mapping of the foot, i.e., phlebography, duplex ultrasound, MRV, or CTV
- Arterial angiogram from the common femoral artery to the foot (two views)
- Serum creatinine level
- Rutherford classification
- WIfI (Wound – Ischemia – foot Infection) classification
- Wound pictures and assessment
- Pain assessment
- Perfusion assessment ($TcPO_2$, ICG i.v. injection, white-light spectroscopy with laser Doppler, etc.—optional)
- Quality of Life (EQ-5D)
- Review of medications (antiplatelets/anticoagulants and antibiotics regimen)

A dedicated website (decidemedical.com platform pro- vided by ClinFlows) will be used during the screening process to assess the eligibility of the candidates identified by the investigators. Baseline radiological images (e.g., ar- terial angiograms, phlebography, duplex ultrasound, MRV, or CTV) as well as wound pictures should be uploaded by the investigators in order for the patients' eligibility to be confirmed. An independent committee will review the data and judge the eligibility for the patient to be included in the study. The eligibility screening process that will be followed for this post-market study is presented in detail on Fig. 1 below.

Timing for performing visits and assessing variables during the study follow-up period are presented in Tables 1 and 2 below. Additional post-treatment evaluations performed outside of the follow-up window will be considered

"unscheduled".

FIGURE 1. Eligibility screening process for LimFlow cases

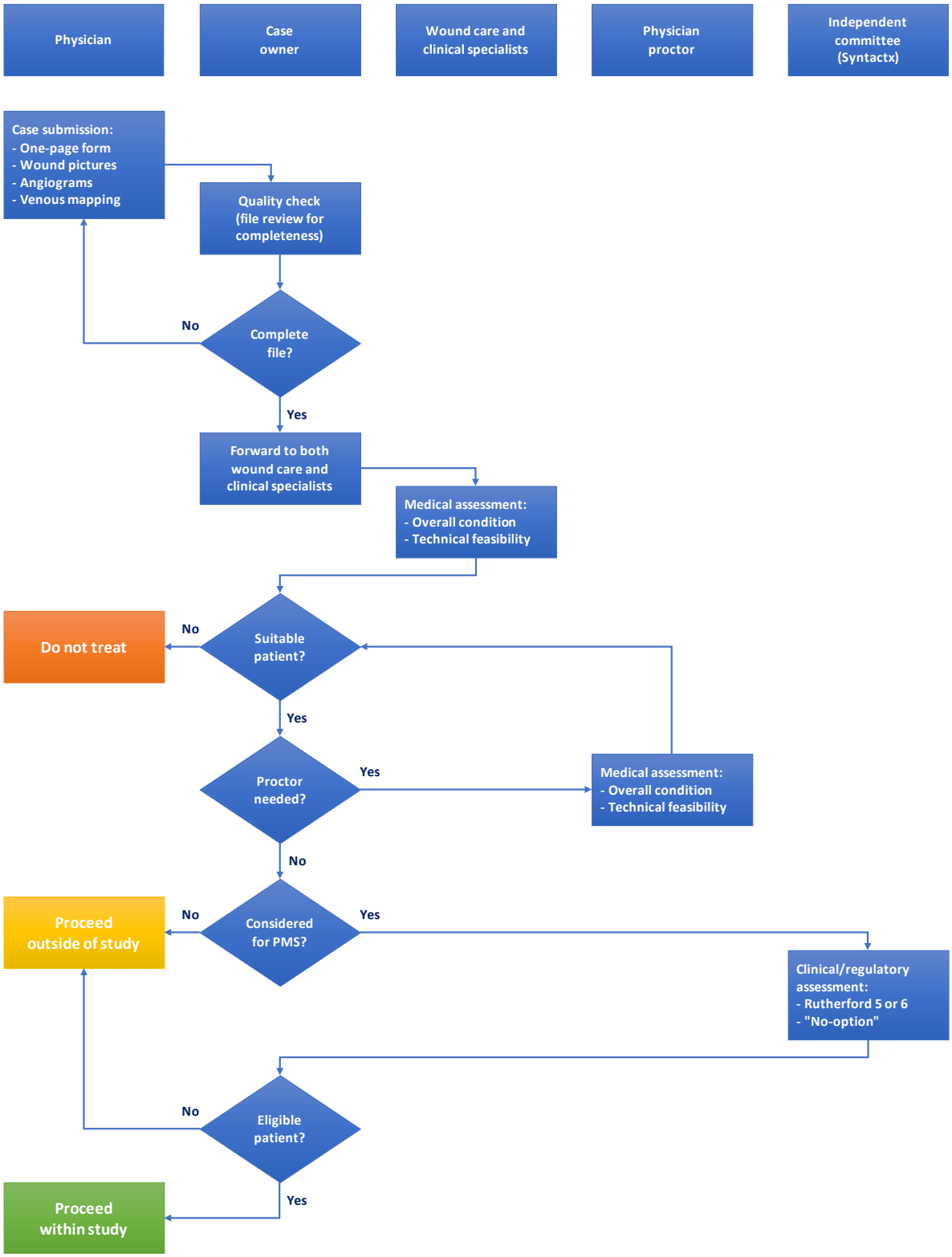

TABLE 1. Visits and exams

Patients should be followed at regular intervals during one year after the initial percutaneous deep vein arterialization procedure **in accordance with standard of care and local practice**. Visits and exams scheduled for this post-market study are presented in 1 below (keys: ■ mandatory, □ optional).

Exams	Baseline	Treatment	Week 02	Month 01	Month 02	Month 03	Month 06	Month 09	Month 12
Eligibility	■								
Demographics	■								
Infection status[†]	■								
Venous mapping[‡]	■								
Angiogram	■	■							
Ultrasound		Duplex		Duplex	Duplex	Duplex	Duplex	Duplex	Duplex
Medication	■	■	■	■	■	■	■	■	■
Creatinine	■			□			□		
Rutherford	■			■	■	■	■	■	■
WIfI	■			■	■	■	■	■	■
Wound pictures	■		■	■	■	■	■	■	■
Pain	■		■	■	■	■	■	■	■
Perfusion	□		□	□	□	□	□	□	□
Quality of Life	■					■	■	■	■
Adverse events		■	■	■	■	■	■	■	■

[†]Wound culture and/or blood analysis (WBC, CRP, ESR)

[‡]Phlebography, duplex ultrasound, MRV or CTV, depending on what is available

TABLE 2. Time windows

Visit	Target	Interval	Minimum	Maximum
Two (2) weeks	15 days	± 5 days	10 days	20 days
One (1) month	30 days	± 7 days	23 days	37 days
Two (2) months	60 days	± 10 days	50 days	70 days
Three (3) months	90 days	± 14 days	76 days	104 days
Six (6) months	180 days	± 14 days	166 days	194 days
Nine (9) months	270 days	± 14 days	256 days	284 days
Twelve (12) months	360 days	± 28 days	332 days	388 days

All variables will be recorded on electronic Case Report Forms (eCRFs) specifically designed for the study and provided by LimFlow SA to the investigational centers. Collected variables will be analyzed using IBM SPSS statistics software, version 17 or later.

Standard evaluation tools such as the Rutherford classification (Rutherford et al., 1997) or the SVS WIfI (Wound – Ischemia – foot Infection) classification system (Mills Sr. et al., 2014) will be used for the overall assessment of critical limb ischemia at baseline and follow-up visits. Pain will be evaluated using a numerical rating scale and the EuroQol (EQ-5D) questionnaire (EuroQol, 1990) will be used to assess the patients Quality of Life.

The eKare inSight (http://ekare.ai/) digital wound management platform (eKare, Inc., Fairfax, Virginia, United States of America) will be used for photographing, scanning, and assessing wounds at screening and follow-up visits. eKare inSight® is an FDA registered Class 1 medical device and is CE marked. Additionally, eKare is ISO 13485 certified and is fully compliant with FDA 21 CFR Part 820, Part 11.

Endpoints

Primary endpoint

- Amputation free survival

Secondary endpoints

- Complete wound healing
- Primary and secondary patency
- Limb salvage
- Renal function
- Technical and procedural success

Sample size calculation and date analysis

Sample size

In the absence of formal statistical hypotheses for this single-arm, post-market study, the planned sample size could not be derived statistically. It was however estimated that a cohort of approximately fifty (50) subjects would provide sufficient data in order to meet the objec- tives defined in the study.

Provision for an interim analysis

Interim analyses may be performed at any time if deemed necessary to fulfill the sponsor's or manufacturer's reporting requirements and/or update the evaluation of the side effects and of the acceptability of the benefit/risk ratio, as required in Council Directive 93/ 42/EEC of 14 June 1993 concerning medical devices.

Specification of subgroups for analysis

If relevant, subgroup analyses may be performed based on baseline or treatment parameters Student's (or Wilcox- on's according to the normality of the distribution) and Chi-2 (or Fisher's) between-group tests will then be used for quantitative and qualitative parameters, respectively.

In particular, renal function characteristics at baseline (GFR value and/or dialysis status) may be used to define subgroups for the purpose of the analysis. Specifically, patients on dialysis are excluded from the early feasibility study (EFS), which will be taken into consideration when pooling datasets from both cohorts. Safety and effectiveness results from dialysis and non-dialysis patients will be compared.

Risks and benefits

Anticipated clinical benefits

The patients designated for percutaneous deep vein arterialization have critical limb ischemia with no treatment option other than major amputation. These patients have had repeated percutaneous procedures to use angioplasty to open up the below-the-knee vessels, but the re-occlusion rate is high and once the foot is deserted (lack of blood circulation to the foot), ischemia and necrosis quickly set in. Necrotic tissue has to be cut away to allow healthy tissue a chance to heal. Infection is a major complication that can rapidly become systemic leading to mortality.

Critical limb ischemia patients are desperate as all medical experts have told them that there are no more possible treatments. The lack of options highlights percutaneous deep vein arterialization is a last hope treatment for these patients, who have exhausted all other possibilities. For this reason, the benefits of percutaneous deep vein arterialization with the LimFlow System far outweigh the known risks associated with this device and readily available percutaneous angioplasty equipment.

Anticipated adverse device effects

There is an independent medical monitor from Syntactx (NY) who will review all (severe) adverse events. The following adverse events are considered to be anticipated when performing any percutaneous catheterization:

- Allergic reaction, including anaphylactic shock and Quincke's oedema
- Vascular complications at access site, including bleeding events and hematoma
- Arterial and venous thromboembolic events, including angina or myocardial

infarction, stroke or transient ischemic event, pulmonary embolism, deep vein thrombosis, and limb ischemia
- Contrast-induced nephropathy and renal failure
- Local or systemic infection
- Pain

Residual risks associated with the investigational device

The LimFlow System was reviewed in accordance with a risk management process that complies with the international standard on the application of risk management to medical devices EN ISO 14971:2012.

The risk management process entailed an analysis of potential risks and an evaluation of their acceptability in the light of the intended therapeutic use of the system. The purpose of the risk analysis was to identify and characterize undesirable events that could result in harm. For each identified hazard the risks were estimated by factoring in the probability of occurrence and severity of the harm. The design verification report was reviewed to verify that all risk control measures identified as necessary to reduce risk to acceptable levels had been implemented and that no risks would arise from the implementation of control measures. It was concluded that all risks associated with the identified hazards had been reduced to acceptable levels and that the overall risk of the use of the LimFlow System was determined to be acceptable. The LimFlow System received CE-mark in October 2016.

Ethics

This study is conducted in accordance with the principles of the Declaration of Helsinki and 'good clinical practice' guidelines. The Medical Ethical Committee of the NorthWest Clinics in Alkmaar, the Netherlands, has approved the protocol. The Ethical Committees of the participating centers is applied for local feasibility. Prior to randomization, written informed consent will be obtained from all patients.

Discussion

Critical limb ischemia (CLI) is the end stage of peripheral artery disease (PAD) and is associated with high amputation and mortality rates. (Sprengers et al., 2010) The qual- ity of life is poor and data of patients with no-option CLI is significantly worse than scores previously obtained in patients with cancer, chronic heart disease, and chronic kidney disease underlining the need for improved treatment of these patients. (Sprengers et al., 2010)

Bypass surgery and the last decade endovascular interventions with angioplasty and stenting have become the treatment of choice. The percutaneous revascularization represents a revolution in the treatment of CLI. Novel techniques have increased the number of limbs being salvaged. However, when there is an absence of distal target vessels or only small artery's (the "desert foot") it often leads to failure of all revascularization attempts and culminates in major amputation. These are the no-option CLI patients where a venous arterialization can be a viable alternative.

A meta-analysis of the venous arterialization in patients with no-option CLI, show a pooled limb salvage rate at 12 months of 75%. (Schreve et al., 2017) The last decade several studies have been published with promising results and the number of treated patients has considerably grown. Venous arterialization could be a valuable treatment option in patients with often no other options than amputation of the affected limb.

However, the "classic" venous arterialization has a downside with the surgical wounds on already critical foot. A major advantage of the pDVA is the minimal invasiveness with lower periprocedural risks and no creations of wounds in an already critically ischemic leg. The first results in men are promising although more research and long term follow up is needed to establish the efficacy of this new treatment modality. (Kum et al., 2017)
With this prospective study, we evaluate the clinical effectiveness and safety in patients with no-option CLI treated with the pDVA (LimFlow System).

Abbreviations
CLI: Critical Limb Ischemia; GFR: Glomerular Filtration Rate; PAD: Peripheral Artery Disease; pDVA: percutaneous Deep Vein Arterialization; WIFi: Wound – Ischemia – Foot Infection

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Trial status
L017–088/ LimFlow Percutaneous, Post Market Study - Protocol version 4, September 13,2018. Start recruitment 29-11-2017, end recruitment 30-12-2019.

Authors' contributions
MS, ÇÜ and VC drafted the manuscript. MS, ÇÜ, ML, VC, MB, DH, SK participated

in the design of the study during a meeting. All authors edited the manuscript and read and approved the final manuscript.

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Availability of data and materials
All data will be collected and analysed by the authors.

Ethics approval and consent to participate
L017–088/ LimFlow Percutaneous, Post Market Study - Protocol version 4, September 13,2018. Start recruitment 29-11-2017, end recruitment 30-12-2019.

Competing interests
The author(s) declare that they have no competing interests.

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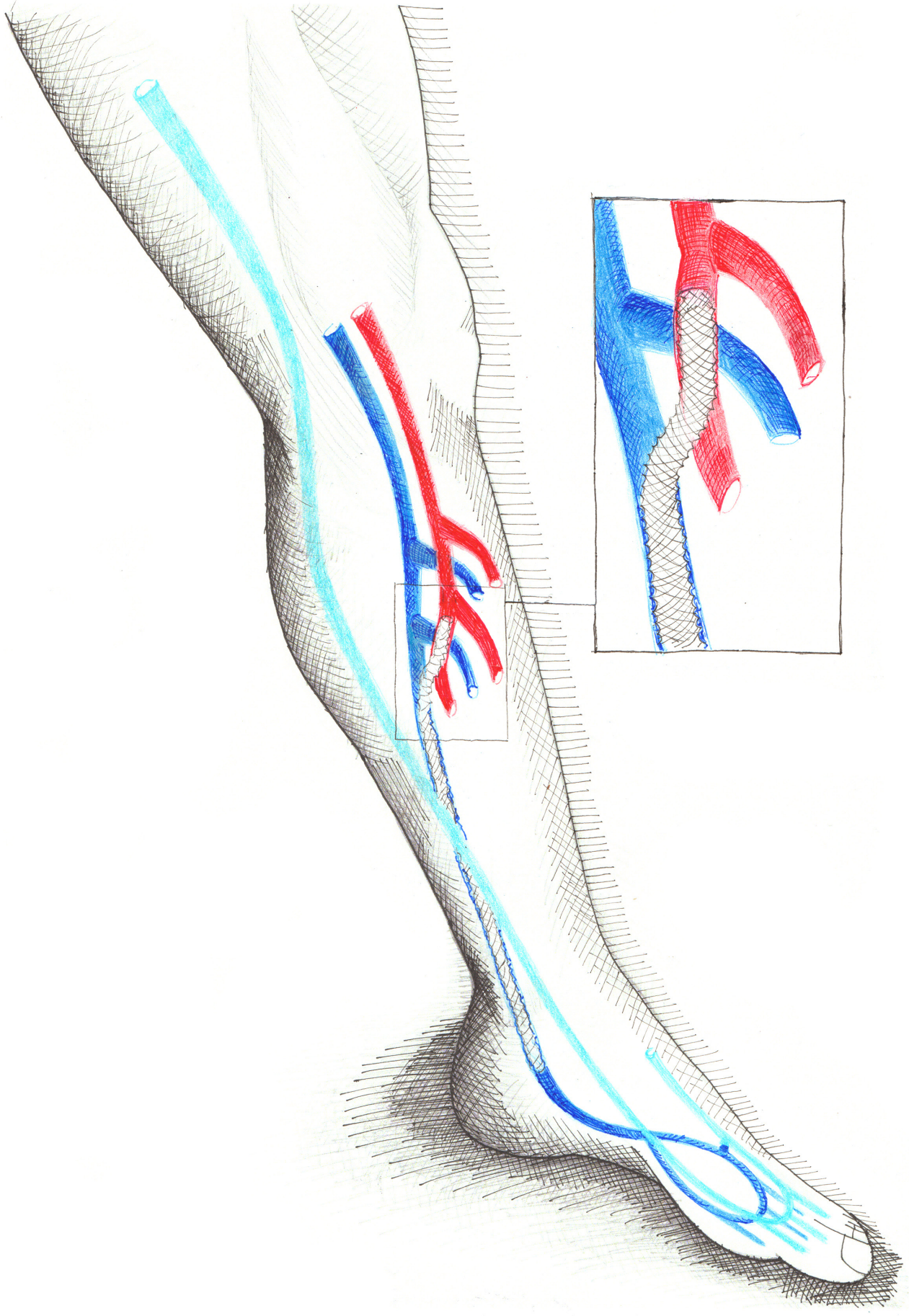
Part 3

The postoperative care and follow-up
of the venous arterialization



Chapter 7

Volume Flow and Peak Systolic Velocity of the Arteriovenous Circuit in patients after Percutaneous Deep Venous Arterialization.

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Abstract

Percutaneous deep venous arterialization (pDVA) is a developing technique for limbsalvage in patients with chronic limb-threatening ischemia by creating an arteriovenous (AV)circuit. After pDVA, patency of the AV circuit is evaluated using duplex ultrasound (DUS) imaging. Peak systolic velocity (PSV) and volume flow (VF) values for maintaining a patent AV circuitare undefined; therefore, guidance about when a reintervention should be performed is lacking. The objective of this study was to interpret post-pDVA PSV and VF values in relation to AV circuitpreservation. This was performed by analyzing DUS results of 22 post-pDVA patients. A total of670 PSV and 623 VF measurements were collected. A PSV value of ≤55 cm/s and a VF value of ≤195 mL/min were found predictive for failure. The reliability of PSV and VF measurements in patent AV-circuits was good (intraclass correlation coefficient; PSV, 0.85; VF, 0.88). In conclusion, this study is the first to analyze DUS measurements in post-pDVA patients and showed that DUS can be used to anticipate for failure. The thresholds found can be used to help interpret DUS measurements in post-pDVA patients. More research in a larger patient population is needed to prospectively validate these thresholds.

Keywords
chronic limb threatening ischemia; peripheral arterial disease; endovascular; venous arterialization; duplex ultrasound; peak systolic velocity; volume flow

Introduction

Chronic limb-threatening ischemia (CLTI) is the clinical end stage of peripheral artery disease(PAD), which is associated with severe ischemia and has an amputation risk of 25% at 1 year when untreated [1]. The cornerstone to prevent amputation in CLTI patients is the combination of medication and revascularization [2]. Endovascular interventions and bypass surgery are the most performed techniques for revascularization, but sometimes technically unsuitable due to extensiveness of the disease. As a result, up to 20% of patients with severe limb ischemia are unsuitable for bypass surgery or angioplasty [3]. For these patients, percutaneous deep venous arterialization (pDVA) could be an alternative technique for limb salvage. In this procedure, a connection is made between a tibial artery and a tibial vein creating an arteriovenous (AF) fistula, after which the valves in the vein are destroyed, and the side branches are covered with a covered stent to provide pressurized arterial flow to the venous system of the foot. We call this the arteriovenous (AV) circuit [4].

Duplex ultrasound (DUS) surveillance after the procedure is indicated to detect any inflow or outflow problems of the AV circuit. DUS measurements include peak systolic velocity (PSV), as recommended for regular infrainguinal bypasses, and volume flow (VF) measurements as done for AV fistulas [5,6]. However, determining when the AV circuit is at risk for occlusion or when a reintervention should be performed is difficult because DUS imaging criteria for failed and patent AV circuits are lacking. Therefore, the aim of this study was to interpret the post-pDVA PSV and VF values by specifying these values in a patent and failed AV circuit and by selecting optimal thresholds for detecting a stenosis or occlusion anywhere in the AV circuit.

Materials and Methods

This study was conducted according to the principles of the Declaration of Helsinki and approved by the Institutional Board of Directors of Northwest Clinics, Alkmaar, the Netherlands on 20 May 2016, and Changi General Hospital, Singapore in 2013, with reference code 2013/828/C. All patients provided written informed consent for the procedure.

Patient Selection

All consecutive patients treated by pDVA using the LimFlow device (LimFlow SA, Paris, France) between July 2014 and June 2018 for CLTI in the Northwest

Clinics in Alkmaar and Changi GeneralHospital in Singapore were eligible for the present study. CLTI was defined as the presence of PAD in combination with gangrene, a lower limb ulceration >2 weeks' duration, or rest pain with affirmative hemodynamic studies [2]. Patients without DUS measurements at follow-up due to early amputation or death were excluded.

Inclusion criteria for the pDVA procedure were Rutherford category≥4, 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 [7]. Patient suitability for the pDVA procedure was assessed by an independent committee from Syntactx, including an experienced vascular surgeon and interventionalist.

pDVA Procedure

The procedure was performed using the LimFlow device, as described in detail previously [4,7]. In brief, antegrade arterial access and distal venous access were achieved by ultrasound-guided puncture of the femoral artery and target tibial vein at the ankle, respectively. The arterial and venous catheters were inserted and advanced to the crossing point. A needle from the arterial catheter was deployed to cross from the artery to the vein to create the AV fistula. A 0.14-inch guidewire was thenpassed through the needle into the vein all the way down to the foot. A valvulotome was inserted to lyse the valves in the vein. Stent grafts were implanted in the vein from the level of the ankle toward the crossing point, which was in turn covered by a tapered self-expanding stent graft. The tapered crossing stent secures the AV fistula, and the stents in the vein and outflow in the foot are considered to be the AV circuit. Postprocedure, patients were prescribed lifelong antiplatelet therapy (aspirin 100 mg or clopidogrel75 mg) in combination with therapeutic low-molecular-weight heparin (LMWH) for at least 3 months. Both hospitals used the same procedure protocol and patient selection criteria.

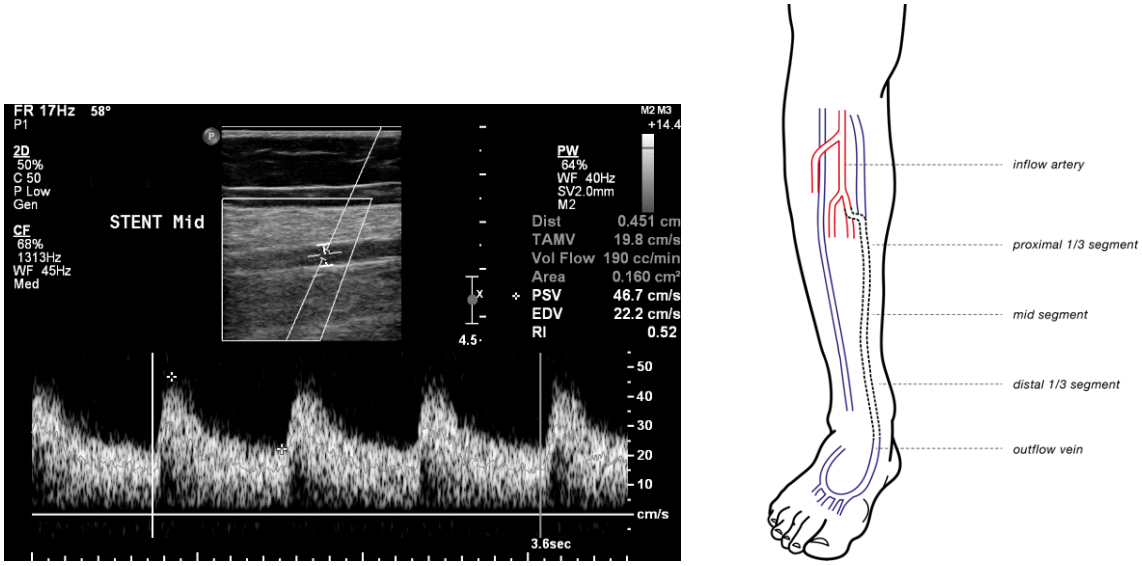
DUS Measurements

All DUS measurements were performed in the hospitals by trained vascular ultrasound technologists. The measurements were done using Philips ultrasound scanners: Affiniti 70G inAmsterdam, The Netherlands, and IU22 at Changi General Hospital, Singapore.

The patient was examined supine with the hip of the measured leg rotated

externally and the knee slightly flexed. A L12-3 linear array transducer was placed behind the knee in the transverse plane and moved distally along the posteromedial or anterolateral aspect of the calf to locate the popliteal artery, tibial vessels, stent, and anastomoses. Grayscale and color Doppler imaging was used to check the vessel lumen and flow direction in transverse and longitudinal views for any abnormalities. PSV andVF measurements were recorded with the vessels in longitudinal views using the duplex Dopplermode. A ≤60◦ Doppler angle with the cursor parallel to the vessel wall was used when the PSV was measured. The sample volume was positioned in the center and completely encompassed the vessellumen. On the Doppler trace, the baseline was lowered and the velocity scale adjusted appropriately to avoid aliasing. A low wall filter setting was used.

To obtain the VF, the diameter of the vessel was measured with the calipers at right angles to thesample volume. Three pulse cycles on the spectral trace were selected, and the system automatically estimated the time-averaged mean and calculated the VF in milliliters/minute (Figure1a).



(a) (b)

FIGURE 1. Image of duplex ultrasound measurement and measurement points. (a) Duplex ultrasoundimage of measuring the volume flow in the mid-segment of the stented vein. (b) Schematic image of thevarious duplex ultrasounds measuring points in patients after percutaneous deep venous arterialization.

Measurements consisting of diameter, PSV, and volume flow, were recorded at 5 points, over straight segments (Figure 1b):

- At the inflow artery (popliteal artery, P3)
- At the proximal one-third segment, middle segment, and distal one-third

segment of the stented vein, and
- At the distal outflow vein, >3 cm distal to the lowest point of the covered stent (e.g., lateral plantar vein).

The surveillance protocol included measurements every 2 weeks for the first 2 months postprocedural and at 3-, 6-,and 12-months postprocedural, when possible. Deviations from the protocol and additional measurements were depending on the condition of the patient. Indications for additional measurements included aberrant findingson DUS, impaired wound healing, aberrant pain,or other signs of ischemia. Extra measurements were also performed after a reintervention.

Reinterventions and Digital Subtraction Angiography
The decision to perform a reintervention was left at the operator's discretion and primarily basedon the condition of the patient, e.g., pain, new or persistent wounds, or other signs of ischemia. When there was any doubt of the patency of the AV circuit on DUS, a digital subtraction angiography (DSA) was performed preemptively.

The angiograms performed during reinterventions were collected and stored for postintervention analysis in detail if the DSAs were performed ≤1 month after DUS. DSAs performed >1 month after DUS were not associated, because the time between the two imaging techniques was considered too long. Duplex values followed by a stenosis ≥50% seen on angiography or an occlusion as seen on DUS were marked as failed. If no stenosis ≥50% was seen on angiogram or if no occlusion was seen on DUS, DUS values were reported as patent.

Optimal Threshold Selection for Predicting ≥50% Stenosis or Occlusion
To determine a range of values that indicated a failed AV circuit (≥50% stenosis or occlusion anywhere in the AV circuit) and a patent AV circuit (absence of ≥50% stenosis or occlusion anywhere in the AV circuit), receiver operating characteristic (ROC) curves with corresponding sensitivity and specificity were calculated. Two cutoff values for each measuring point were selected. The first value with a specificity of >80% was selected as the cutoff point of the lowest value to ensure that false positives for occlusion were low. The first value with a sensitivity of >80% was selected for the cutoff point of the highest value to ensure that the false negatives for occlusion were low. In this way, it was possible to determine a low PSV/VF cutoff point, which indicated that under this specific value, flow problems are likely to occur, and to determine a high PSV/VF cutoff point, which indicates that flow problems are unlikely to occur.

Reliability of the PSV and VF Measurements

Test–retest analyses were performed to explore the reliability of the DUS measurements. Measurements were included in the analysis if they were considered patent, succeeded each other within 30 days, and if both PSV and VF measurements were performed during the same consultation. In this way, the chance for equal conditions between the two succeeded measurements and between PSV and VF measurements was considered highest. Consecutive measurements were performed using the same ultrasound scanners. The analyses were performed using the intraclass correlation coefficient. Values <0.5 were considered as poor reliability, between 0.5 and 0.74 as moderate reliability, between 0.75 and 0.90 as good reliability, and values >0.90 were considered as excellent reliability [8].

Data Collection, End Points, and Definitions

Patient demographics, baseline risk factors, and PSV and VF measurements were retrospectively collected. Data were derived from electronic medical records, clinical records, and imaging reports. Follow-up visits for the patients were based on their clinical condition.

The primary outcome was the optimal thresholds for detecting stenosis of ≥50% or occlusion within the first 3 months postprocedure. Secondary outcomes were the reliability of the measurements, the mean of post-pDVA PSV and VF values in patent and failed AV circuits, and the predictive value of PSV and VF values for major amputation and wound healing.

The AV circuit consists of the inflow artery, the AV fistula, the stented vein, and the outflow veins in the foot. Major amputation was defined as amputation above the ankle [2]. Wounds were asassessed by the treating physician and considered healed if they were fully epithelized. Reintervention was defined as repeat percutaneous intervention. Reliability of the measurements was defined as the consistency of successive measurements.

Statistical Analysis

Statistical analysis was performed using SPSS software (version 23, IBM, Armonk, NY, USA). Quantile–quantile plots were analyzed to determine whether continuous variables followed a normal distribution. If the points in the quantile–quantile plot lie on a straight diagonal line, the data were defined as normally distributed. Normally distributed continuous variables are expressed as mean ± standard deviation. Nonnormally distributed data were presented as median with theinterquartile range (IQR) and were log transformed to normally

distributed data for comparison. Log-transformed normally distributed data were compared using the independent t test. The means calculated from log-transformed data were transformed back to normal values and are reported as geometric means. Categorical variables are expressed as numbers with percentages.

Kaplan–Meier analyses were performed to estimate the amputation-free survival, defined as avoidance of major amputation (above the ankle) of the index limb or death (any cause) and wound healing at 12 months. Wounds were considered healed if they were fully epithelized. For patients who died before complete wound healing, the date of death was defined as the cutoff date. For patients who underwent major amputation, the time to wound healing was considered to be infinite [9].

Reliability analyses were performed using the intraclass correlation coefficient using the alpha two-way random effects model with absolute agreement. Single measures values were used.

ROC curves were calculated to establish a threshold for PSV and VF values. Statistical significance was defined as $p < 0.05$.

Results

Patient Characteristics

Between July 2014 and June 2018, 27 patients underwent the pDVA procedure in the Changi General Hospital in Singapore (n=19) and in the North West Clinics in Alkmaar, the Netherlands (n=8). Of the 27 patients, 22 had DUS measurements at follow-up (from July 2014 to December 2019) and were included in the study. The other five patients were lost to follow-up because of an early amputation (n=3), death (n=1), or living abroad (n=1). Patient characteristics are summarized in Table 1. Of all patients, seven patients were classified as Rutherford stage 6. These patients were eligible for the procedure as the ischemic ulcers or gangrene affected slightly more than just the digits of the foot and therefore did not deemed unsalvageable in the operator's opinion. The target arteries included the posterior tibial artery (n=14), tibioperoneal trunk (n=4), anterior tibial artery (n=2), and popliteal artery (n=2). Target veins were posterior tibial vein (n=18), tibioperoneal trunk (n=1), anterior tibial vein (n=2), and popliteal vein (n=1).

Five patients (23%) required a major amputation, and six patients (27%) died during follow-up. Rutherford category 6, coronary artery disease, and renal insufficiency was found in three of the five patients requiring amputation. Reasons to perform a major amputation included a combination of new wounds and occluded graft (34 months postprocedural), an occluded graft and occluded femoral popliteal bypass (7 months postprocedural), infection ((n=2), 6 and 9 months postprocedural), and worsening of tissue loss (1 month post procedural). The median time between the intervention and major amputations was 6.7 (3.4–21.3) months. The estimated amputation-free survival and wound healing at 12 months was 71.6% and 64.5%, respectively. The median follow-up was 5 months (IQR, 0.6–35 months).

TABLE 1. Baseline characteristics

Variable	Values
Patients	22
Men	9 (40.9)
Age, years	67 ± 17
Comorbidities	
Hypertension	18 (81.8)
Diabetes	15 (68.2)
Hyperlipidemia	17 (77.3)
Cerebrovascular accident	4 (18.2)
Coronary artery disease	7 (31.8)
Dialysis dependent	2 (9.1)
Body mass index, kg/m^2	22 ± 5
Laboratory results	
Creatinine, mg/dL	85 (66-145)
eGFR <30 mL/min/1.73m^2	5 (22.7)
Rutherford	
4	1 (4.5)
5	14 (63.6)
6	7 (31.8)
SVS WIfI risk staging	
Low risk	1 (4.5)
Moderate risk	5 (22.7)
High risk	16 (72.7)

Continuous data are presented as mean ± standard deviation or median (interquartile range), and categorical data are presented as number (%).
eGFR, estimated glomerular filtration rate; *SVS Wifi*, Society for Vascular Surgery risk system based on Wound, Ischemia, and foot Infection.

Reinterventions

A total of 47 DSAs were performed in 19 patients. Reasons to perform a DSA were pain, new or persistent wounds, preemptive, or stenosis or occlusion identified with DUS. Of these 47 DSAs, two AV circuits were found patent and one stenosis in the outflow vein was found and left untreated because of adequate foot perfusion and a healed wound. In the other 45 DSAs, the lesions found were locatedin the inflow arteries (n=18), in the stented vein (n=12), and, most often, in the outflow veins (n=31).

Of all lesions, 45 were stenoses (74%) and 16 occlusions (26%). Treatment modalities for thrombosis included thrombolysis with or without mechanical thrombectomy. Occlusions were treated with athrombectomy device in combination with percutaneous transluminal angioplasty (PTA) using plainold balloon angioplasty (POBA) or drug eluting balloons (DEB). Stenoses were treated using POBA or DEB and stents when necessary. A stealing outflow vein was found twice and treated by embolizationor ligation.

The difference between the PSV and VF values before and after reintervention were statistically significant: the geometric mean PSV was 54±2 cm/s before and 77±2 cm/s after ($p<0.001$), and the geometric mean VF was 121±3 mL/min before and 178±2 mL/min after ($p=0.005$).

Continuous data are presented as mean ± standard deviation or median (interquartile range), and categorical data are presented as number (%). eGFR, estimated glomerular filtration rate; SVS WIfI, Society for Vascular Surgery risksystem based on Wound, Ischemia, and foot Infection.

PSV and VF Measurements

The 22 patients had a total of 670 PSV and 623 VF measurements with a median of 27 PSV measurements (IQR, 8–91 measurements) and 25 VF measurements (IQR, 4–77 measurements) per person. Of these, 487 PSV and 464 VF measurements were reported as patent and 183 PSV and 159 VF measurements as failed.

Test–Retest Reliability

The results of the reliability test of the PSV and VF values are shown in Table 2. Per measuring point, two consecutive measurements were used. The mean time between the measurements was 14±8 days. The mean time point for first reliability measurement was at 36 days postprocedural. The ICC were found highest in the distal 1/3 segment and middle segment for the PSV and VF

values, respectively.

Table 2. Reliability of consecutively measured peak systolic velocity (PSV) and volume flow (VF) values.

TABLE 2. Difference in mean between values in patent and failed arteriovenous (*AV*) circuits

Measurement point	PSV			VF		
	No.	ICC	95% CI	No.	ICC	95% CI
Inflow artery	8	0.747	0.17-0.94	5	0.367	−0.80 to 0.91
Proximal 1/3 segment	10	0.588	0.02-0.88	10	0.549	−0.80 to 0.87
Middle segment	10	0.652	0.13-0.90	10	0.875	0.58-0.97
Distal 1/3 segment	10	0.846	0.37-0.96	10	0.771	0.33-0.94
Outflow vein	10	0.354	−0.39 to 0.80	10	0.647	0.08-0.90

CI, confidence interval; ICC, intraclass correlation coefficient; No, number of patients included in the analysis.

Predictive Value for Failed AV Circuits

The diagnostic accuracy of the PSV values to predict failure anywhere in the AV circuit was highest for the measurements performed in the proximal one-third and middle part of the stented vein and for VF values at the inflow artery and middle segment in the stent (Table3).

TABLE 3. Area under the curve (AUC) values for evaluating failed arteriovenous circuits by the peaksystolic velocity (PSV) and volume flow (VF) values of various measuring points.

Measurement point	PSV				VF			
	No.	AUC	95% CI	P	No.	AUC	95% CI	P
Inflow artery	50	0.691	0.51-0.88	.048	32	0.859	0.73-0.99	.003
Proximal 1/3 segment	68	0.747	0.63-0.87	.001	60	0.693	0.54-0.84	.019
Middle segment	72	0.710	0.58-0.84	.005	65	0.704	0.57-0.84	.010
Distal 1/3 segment	69	0.707	0.57-0.84	.006	66	0.644	0.49-0.80	.068
Outflow vein	68	0.552	0.40-0.70	.498	62	0.583	0.43-0.74	.303

CI, confidence interval; No., number of measurements included in the analysis.

Optimal PSV and VF Threshold for Predicting Failed AV Circuits ≤3 Months Postprocedure

The optimal cutoff values for detecting a failed AV-circuit are summarized in Table 4. The accuracy was highest for the cutoff values in the proximal 1/3 segment and middle segment of the stented veinfor the PSV values and in the inflow artery and middle segment of the stented vein for the VF values.

TABLE 4. Optimal cutoff point (COP) for evaluating failed arteriovenous circuits by the peak systolicvelocity (PSV) and volume flow (VF) values of various measuring points.

	Measurement point	COP	Sensitivity	Specificity	YI	PPV	NPV	Accuracy
PSV, cm/s	Inflow artery	≤96	41.7	81.6	0.233	41.7	81.6	72.0
		≤162	83.3	34.2	0.175	28.6	86.6	46.0
	Proximal 1/3 segment	≤90	54.5	80.4	0.349	57.1	78.7	72.0
		≤120	81.8	54.3	0.361	46.1	86.2	63.2
	Middle segment	≤55	40.9	84.0	0.249	52.9	76.4	70.8
		≤99	81.8	52.0	0.338	42.9	86.7	61.1
	Distal 1/3 segment	≤58	45.5	80.9	0.264	52.7	76.0	69.6
		≤104	81.1	48.9	0.307	42.8	85.2	59.4
	Outflow vein	≤49	23.8	83.0	0.068	38.5	70.9	64.7
		≤163	81.0	27.7	0.087	33.4	76.5	44.2
VF, mL/min	Inflow artery	≤206	75.0	83.3	0.583	60.0	90.9	81.2
		≤239	87.5	79.2	0.667	58.4	95.0	81.3
	Proximal 1/3 segment	≤175	38.9	81.0	0.199	46.7	75.6	68.4
		≤452	83.3	38.1	0.214	36.6	84.2	51.7
	Middle segment	≤195	42.1	80.4	0.225	47.0	77.1	69.2
		≤364	84.2	55.2	0.364	42.1	88.9	61.6
	Distal 1/3 segment	≤166	42.1	80.9	0.230	47.1	77.6	69.7
		≤339	84.2	42.6	0.268	37.2	87.0	54.6
	Outflow vein	≤105	42.1	81.4	0.235	50.0	76.1	69.4
		≤367	84.2	27.9	0.121	34.0	80.0	45.2

COP, cutoffpoint; NPV, negative predictive value; PPV, positive predictive value; YI, Youden Index.

Discussion

The pDVA procedure seems to be a promising option for patients with no-option CLTI [7,10]. Early detection of flow problems is required to prevent failure of the AV circuit. Current guidelines support DUS surveillance and prophylactic intervention for asymptomatic vein graft stenosis to promote long-term patency [2]. DUS PSV measurements have a sufficiently high sensitivity and specificity in the femoropopliteal region but poor correlation in the tibial vessels [11]. In venous access surgery, the dialysis AV shunt is monitored by DUS using PSV and VF measurements. A PSV value of 400 cm/s has good discrimination to predict >50% stenosis, and a threshold of a PSV value >500 cm/s will reliably identify graft-threatening lesions [12]. A VF value of <300 mL/min predicts failure of the graft [13]. The VF is measured in the artery, which creates a more reliable outcome because the diameter is predictable and the flow has less turbulence.

In this study, the accuracy of the cutoff points and the diagnostic accuracy was found highest for the measurements performed in the middle of the stented

vein for both PSV and VF measurements. The variation between the measuring points was not expected to occur for the VF measurements, as the VF values are expected to be the same at every measuring point. The variation could be explained by the occurrence of turbulent flow within the AV circuit. VF is most accurately measured when laminar flow is present. Turbulent flow occurs when the direction of the flow is disrupted, which occurs by the curves in the crossing stent and in the veins in the foot. Flow in the middle and distal segments in the stent should therefore be the most laminar, and thus, the most accurate point to measure the VF, which was also found in the reliability tests. The measurements performed in the middle and distal segments in the stent had the highest intraclass correlation coefficient scores.

However, the reliability results found in the present study should be interpreted carefully as the values of the measurements were collected retrospectively and therefore not performed understrict protocol. In addition, some consecutive measurements could have been performed by different vascular ultrasound technologists, which preferably would be the same technician to correctly analyze the accuracy of the test–retest measurements. However, a recent study investigated the inter-rater reliability of VF measurements performed in the posterior tibial artery and found an ICC of 0.7 for mean VF values and an ICC of 0.87 for maximum VF values [14]. Thus, the effect of the various ultrasound technicians performing the measurements may be limited.

In this study, a low cutoffpoint was found to be predictive for failure. This is in line in bypass graft DUS surveillance studies that associated >70% stenosis with mid-graft PSV<45 cm/s [15,16] and PSV<60 cm/s with flow problems [17]. In the present study, a cutoffpoint of ≤55 cm/s was found to be predictive for failure in the middle segment of the stented vein.

However, in most patients with vascular problems, high PSV values are used to indicate a stenosis and thus a problem. This is only possible when measured close to the stenosis. However, stenosis and occlusions are sometimes difficult to detect, and it would be more helpful to provide thresholds that indicates flow problems without the necessity to measure at a specific spot. This is important for patients after pDVA specifically, because flow problems that occur due to stenosis or occlusions occur more frequently in the inflow arteries or outflow veins of the foot and less frequent in the stented vein. The present study showed that the flow and the velocity of blood in the stented vein decreased because of a stenosis or occlusion in the inflow arteries or outflow veins in the foot. Therefore, the measurementsin the stented vein are helpful to identify flow

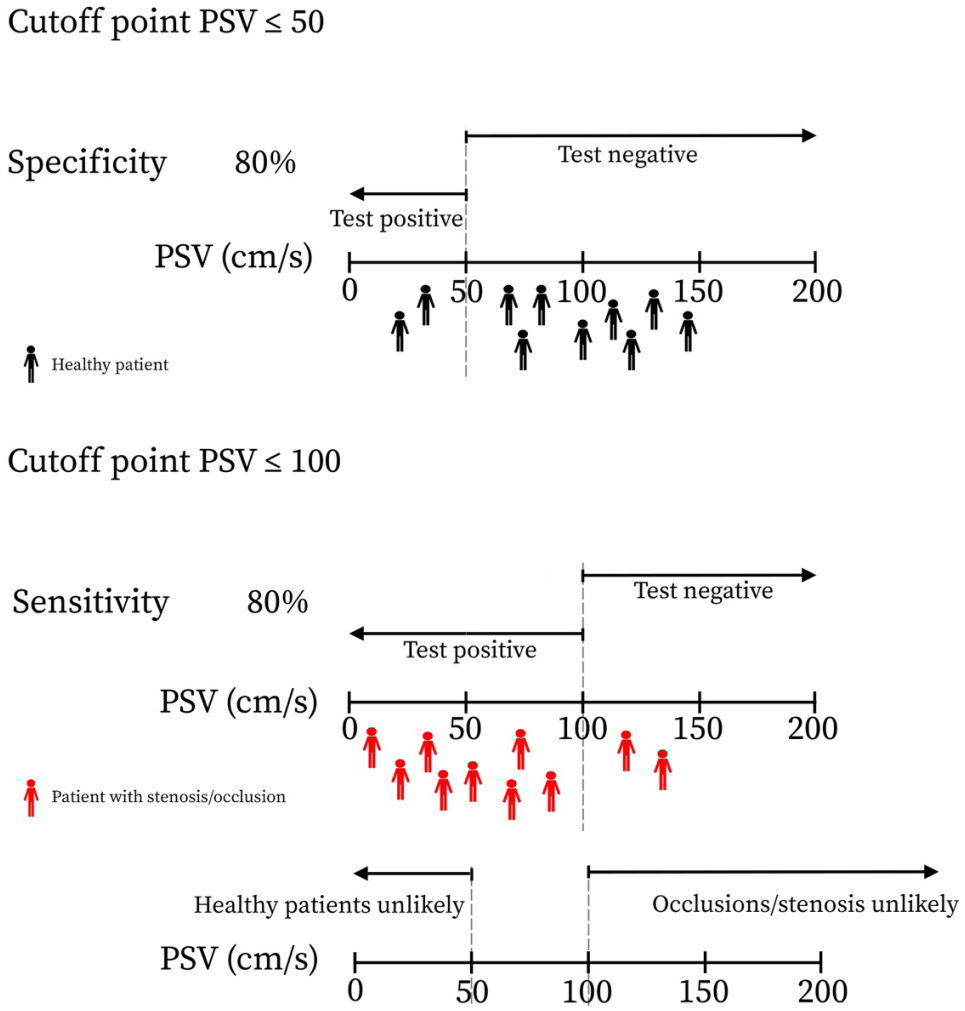
problems in the inflow arteries and outflow veins. The occurrence of a decrease in PSV values in patients with flow problems has also been reported in a recent study where the PSV values of patients with PAD and healthy controls were compared. At the anterior tibial artery, PSV values of 43.7 vs. 65.4 ($p<0.001$) were found in patients with PAD and healthy controls, respectively, and comparable results were found when measured in the posterior tibial artery (43.4 vs. 74.1;$p<0.001$) [18].

The predictability of PSV and VF values for stenosis or occlusion was determined by ROC analysis. The lower cutoff point was selected according to a high specificity (>80%) to determine a point on which the PSV values below this point are unlikely to be found within healthy patients. The higher cutoff point was selected according to a high sensitivity (>80%) to determine a cutoff point in which PSV values higher than this point are unlikely to be found in patients with a stenosis or occlusion (Figure2). In between these values, there is a gray area in which no hard conclusion can be made. The analysis showed that a VF value of <195 mL/min was predictive for failure and >364 mL/min was defined as patent measured in the middle of the stent. For a PSV value, <55 cm/s was found to be predictive for failure and >99 cm/s as an indication for patency measured in the middle of the stent. These values could be a helpful contribution for current clinical practice while waiting for more and prospective studies with a larger cohort of patients.

Limitations

The present study is not without limitations. In this cohort, not every DUS value was compared with angiography. Therefore, DUS values could have been incorrectly considered as patent. In addition, as mentioned earlier, the interrater reliability was not assessed, leaving any bias in this area unknown. In addition, because of the novelty of the technique, the studied patient population is small, resulting in broad confidence intervals and less reliable results. Final, normal PSV,and VF of the bypass do not always represent a good perfusion of the foot. Side branches can evolve, which do not influence the flow in the AV circuit but give a poor distal foot perfusion.

FIGURE 2. Illustration of the meaning of a high specificity and sensitivity for the selected cutoff points.



(a) Illustrates that in 80% of all healthy patients, a peak systolic velocity (PSV) value of > 50 cm/s was found. (b) Illustrates that in 80% of the patients with an occlusion or stenosis, a PSV ≤ 100 cm/s was found. (c) Illustrates that taking into account figures (a) and (b), this means that if in a patient a PSV value ≤ 50 is found, it is unlikely that the patient is healthy and if in a patient a PSV value of>100 cm/s is found, the patient is unlikely to have an occlusion or stenosis.

Conclusions

This study is the first to analyze DUS measurements in post-pDVA patients. Because of the frequent occurrence of stenosis and occlusions in this specific patient population, there is a high need for more insight in DUS interpretation to detect failure of the AV-circuit and preserve the limb. This study showed that surveillance of the AV circuit can be performed by DUS to anticipate for failure, but the small sample size of the study does not allow firm conclusions

to be drawn. One could consider the possibility of stenosis or occlusions that could occur when PSV values of <55 cm/s and VF valuesof <195 mL/min are found, but a final judgment about the perfusion of the foot and an indication for reintervention should be based on a combination between the clinical evaluation, the DUS findings with PSV and VF values, and transcutaneous oxygen measurements pending further research to prospectively validate these thresholds.

Author Contributions

Conceptualization, M.A.S., E.H., S.K., J.-P.P.M.d.V., G.J.d.B., and Ç.Ü.; data curation, M.A.S., E.H., and S.K.; formal analysis, E.H.; investigation, M.A.S., E.H., and S.K.; methodology, M.A.S. and E.H.; project administration, M.A.S. and E.H.; resources, M.A.S. and S.K.; software, E.H.; supervision, J.-P.P.M.d.V.,G.J.d.B., and Ç.Ü.; validation, M.A.S., E.H., S.K., J.-P.P.M.d.V., G.J.d.B., and Ç.Ü.; visualization, M.A.S. and E.H.;writing–original draft, M.A.S. and E.H.; writing–review and editing, M.A.S., E.H., S.K., J.-P.P.M.d.V., G.J.d.B.,and Ç.Ü. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

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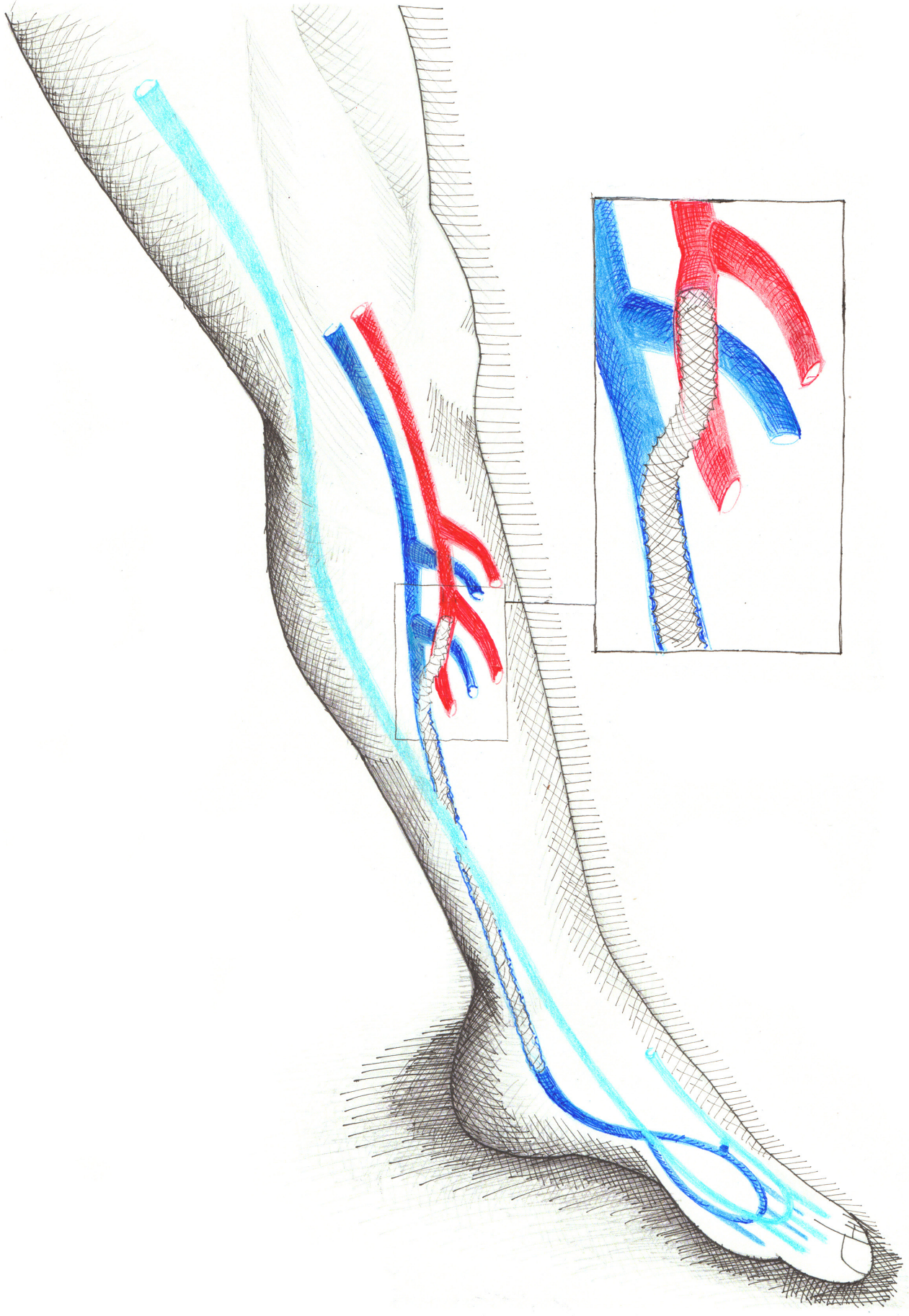

Chapter 8

Postprocedural management in patients after percutaneous deep venous arterialization: an expert opinion

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Abstract

Deep venous arterialization (DVA) is a new and developing technique with promising outcomes. The DVA procedure can be performed surgically, in a hybrid fashion or percutaneously. Over the last years, the hybrid and percutaneous techniques have been further developed and have become a focus of many DVA studies. Between 2017 and 2021, five different percutaneous DVA (pDVA) techniques, and 2 hybrid procedures have been investigated. In total, 9 cohort studies, and 2 case reports have been performed to evaluate their outcomes. Understandably, these studies mainly focused on the technique, patency, and outcomes after DVA. However, postprocedural management can be as challenging as the procedure itself but has not been a priority for further investigation. This article summarizes the different techniques proposed, and the follow-up care provided in literature. Follow-up care includes postoperative medication, edema occurrence and treatment, pain management, patency assessment, reintervention techniques, a staged amputation strategy if necessary, and appropriate wound care. Evidence from literature and own clinical experience were combined to provide recommendations for care after DVA.

Keywords
Chronic limb-threatening ischemia, peripheral arterial disease, venous arterialization, percutaneous deep venous arterialization, revascularization, limb salvage, wound healing, follow-up care

Introduction

Venous arterialization for the treatment of severe peripheral arterial disease was first postulated more than a century ago.[1] The rationale is to use the disease-free venous bed as an alternative conduit for distal perfusion with arterial blood. Many studies have been published and the procedure has developed and evolved from a surgical approach to a hybrid and even entirely percutaneous procedure.[2]

The surgical approach is becoming less popular because of the need to create surgical wounds in a mal perfused area. In the hybrid approach, the anastomosis is performed in an open fashion, but valve disruption is established endovascularly.[3,4] Usually, a great saphenous vein (GSV) or polytetrafluoroethylene (PTFE) graft is used to create a bypass between the popliteal artery and a tibial vein. Finally, venous collaterals are coiled or ligated to improve inflow to the foot. Limb salvages rates of 69-73% have been reported, but the hybrid procedure has not gained as much attention as the percutaneous techniques.[3,4]

Percutaneous approaches have the advantage of avoiding surgical wounds. Between 2017 and 2021, five different percutaneous deep venous arterialization (pDVA) techniques have been published.[5–9] As the principles of these five approaches are similar (arteriovenous crossing, valve impairment, and distal flow achievement), the differences lie in the arteriovenous crossing point and, the devices and techniques used to cross from the artery into the vein and secure the arteriovenous fistula (AVF).

All approaches have their advantages and disadvantages, and a preferred method is primarily personally based then scientifically. Nevertheless, follow-up management may be similar as a new conduit has been created using the venous system in all techniques. However, a comprehensive follow-up summary for post DVA patients is lacking. Subsequently, this article aims to provide an overview of all aspects regarding postprocedural management and present an expert opinion based on clinical experience of the topics on which current knowledge is limited.

Literature search

A search in EMBASE, Medline, and cross-references identified 14 studies to be included in this article to assess postprocedural management after DVA. Two of the included studies investigated the results of a hybrid DVA procedure,[3,4] while

the other 12 studies focused on a pDVA procedure.[5–16] Surgical DVA procedures were excluded to reduce the clinical heterogeneity between the studies. Further, letter to the editors,[17–19] editorials,[20] commentaries[21] and reviews[2,22–24] were also excluded. However, although these studies were not included to evaluate postoperative care, they all have been read to gain more insights in the hypothesis, thoughts and rationale of the authors performing DVA procedures. This information was taken into consideration for providing well thoroughly recommendations.

An overview of the included studies is presented in Table 1, and involves cohort studies (N=8), technical notes (N=4), case reports (N=2). The methodological quality of the cohort studies was assessed using the Methodological Index for Non-Randomized Studies (MINORS) score, with a global ideal score of 16.[25] For this article, a score of ≤8 was considered poor quality, 9–14 moderate quality, and ≥15 good quality. All included studies were of moderate quality (Figure 1a). The quality of case reports was assessed using the Joanna Briggs Institute Critical Appraisal Checklist.[26] The case reports were considered as sufficient to be included in this article (Figure 1b).

The 12 pDVA studies were performed using 5 different techniques and devices. Kum et al.,[8,14] was the first to describe an entirely percutaneous technique, in which ultrasonic catheters (LimFlow, Paris, France) were used to create the AVF in the proximal part of the tibial vessels. Covered stents were used from the crossing point to the ankle to mature the AVF and redirecting flow distally. This technique is now known as the LimFlow procedure.

An alternative technique[9] performed the AV crossover in the plantar vessels by a guidewire., while angioplasty of the arteriovenous anastomosis was performed to secure the AVF. Valve disruption was not required, and no stents were used.[9]

Another technique.,[5,16,20] used the Pioneer Plus IVUS-guided re-entry catheter (Philips, Amsterdam, The Netherlands) to cross at the level of proximal tibial vessels (PIPER technique). Valvulotomy was performed by a semi-compliant balloon. Finally, covered stents were placed from the AVF to the foot. Venous collaterals were embolized 6 weeks later to focalize flow into the forefoot.

TABLE 1. Summary of studies and their reported postoperative management aspects

Study	Article type	No.	Technique	Devices/ materials	Crossing*	Med	Edema	Pain	Duplex	$TcPO_2$	RI	Amp	WC	FU
Alexandrescu 2011	Cohort	25	Hybrid	PTFE bypass	Both	Y	Y	NR	Y	Y	NR	Y	NR	36
Cangiano 2020	Cohort	14	pDVA	Pioneer Plus + IVUS	Proximal	Y	Y	NR	Y	Y	Y	Y	NR	12
Del Guidice 2018	Cohort	5	pDVA	LimFlow	Proximal	Y	NR	NR	Y	Y	Y	NR	NR	6
Ferraresi 2018	Cohort	35	Hybrid	GSV/PTFE	Distal	NR	Y	Y	Y	Y	Y	Y	Y	11
Gandini 2017	Technical note	9	pDVA	Regular devices	Distal	Y	Y	NR	Y	Y	NP	NR	NR	6
Ichihashi 2019	Case report	1	pDVA	Regular devices (AV spear technique)	Distal	NR	NR	NR	NR	Y	NR	Y	Y	NR
Kum 2017	Cohort	7	pDVA	LimFlow	Proximal	NR	Y	NR	Y	Y	Y	Y	Y	20
Kum 2018	Cohort	7	pDVA	LimFlow	Proximal	Y	NR	NR	Y	NR	Y	Y	Y	20
Mustapha 2019	Cohort	10	pDVA	LimFlow	Proximal	NR	Y	Y	NR	NR	Y	Y	NR	6
Migliara 2018	Technical note	7	pDVA	Pioneer Plus + IVUS (PIPER)	Proximal	NR	NR	NR	NR	NR	NR	NR	NR	7
Migliara 2020	Case report	1	pDVA	Pioneer Plus + IVUS (PIPER)	Proximal	NR	Y	Y	NR	NR	Y	Y	Y	6
Schmidt 2020	Cohort	32	pDVA	LimFlow	Proximal	Y	Y	NR	Y	Y	Y	NR	NR	24
Schreve 2020	Cohort	22	pDVA	LimFlow	Proximal	Y	NR	NR	Y	NR	Y	NR	NR	12
Ysa 2019	Technical note	5	pDVA	Homemade devices (VAST technique)	Distal	Y	NR	NR	Y	NR	Y	Y	Y	6

No.: number of patients included in the studies; pDVA: percutaneous deep venous arterialization; PTFE: polytetrafluoroethylene; AV spear technique: simplified technique by Ichihashi; VAST: venous arterialization simplified technique by Ysa; Med: postoperative antiplatelet or anticoagulation medication; RI: reinterventions; Amp: minor amputations; WC: wound care including vacuum assisted therapy, split skin grafts, epidermal substitutes, and debridements; NR: not reported; Y: yes, topics in follow-up care are reported/mentioned in the study; proximal: proximal part of the tibial vessels; FU: follow-up time in months.
*crossing point in hybrid DVA studies specifies the location of the outflow AVF.

FIGURE 1. Quality assessment of included studies. (a) MINORS score of included cohort studies. (b) Joanna Briggs Institute Critical Appraisal Checklist for the case reports.

	Alexandrescu 2011	Cangiano 2020	Del Guidice 2018	Ferraresi 2018	Kum 2017	Kum 2018	Mustapha 2019	Schmidt 2020	Schreve 2020
1. A clearly stated aim	2	2	2	2	2	2	2	2	2
2. Inclusion of consecutive patients	2	2	2	2	2	2	2	2	2
3. Prospective collection of data	1	2	2	1	2	2	2	1	1
4. Endpoint appropriate to the aim of the study	2	2	2	2	2	2	2	2	2
5. Unbiased assessment of the study endpoint	0	0	0	0	0	0	0	0	0
6. Follow-up period appropriate to the aim of the study	2	2	1	2	2	2	1	2	2
7. Loss to follow-up less then 5%	0	0	0	0	0	0	0	0	0
8. Prospective calculation of the study size	0	0	0	0	0	0	0	0	0
Total MINORS score	**9**	**10**	**9**	**9**	**10**	**10**	**9**	**9**	**9**
Maximum possible score	16	16	16	16	16	16	16	16	16

moderate quality poor quality

(a)

JBI Critial Appraisal Case Reports Questions	Ichihashi 2019	Migliara 2020
1. Were patient's demographic characteristics clearly described?	No	Yes
2. Was the patient's history clearly described and presented as a timeline?	No	Yes
3. Was the current clinical condition of the patient on presentation clearly described?	Yes	Yes
4. Were diagnostic tests or assessment methods and the results clearly described?	Yes	Yes
5. Was the intervention(s) or treatment procedure(s) clearly described?	Yes	Yes
6. Was the post-intervention clinical condition clearly described?	Yes	Yes
7. Were adverse events (harms) or unanticipated events identified and described?	Yes	No
8. Does the case report provide takeaway lessons?	No	Yes

(b)

The venous arterialization simplified technique (VAST) used a low-profile balloon catheter and a snare to facilitate the AVF.[6] The AVF was created in the distal tibial vessels and no stents were placed. Others performed the pDVA by the simplified technique (AV spear). In that technique, distal tibial vessels were crossed by direct percutaneous puncture under ultrasound guidance and a stent was used to secure the AVF.

The LimFlow device was used in 6 studies,[8,10,11,13–15] the Pioneer Plus catheter with intravascular ultrasound (PIPER technique) in 3,[5,12,16] a homemade device (VAST technique) in 1,[6] the AV spear technique in 1,[7] and the pDVA technique using regular devices in 1.[9] One cohort study[8] contained the same patient population as described in a technical note.[14] Therefore, these two studies were counted as one in follow-up care analysis further in this study.

Antiplatelet and anticoagulation medication

Postprocedural medication has been described in several pDVA studies, but consensus has not been achieved. Most studies used single antiplatelet therapy in combination with anticoagulation therapy for 3-6 months[6,10,11,13,14] followed by indefinite single antiplatelet therapy.[10,11,13] In 3 studies, dual antiplatelet therapy was used for at least 3 months,[3,9,12] followed by lifelong aspirin (Table 2).[3,12]

TABLE 2. Overview of studies reporting on postprocedural antiplatelet and anticoagulation medication and their outcomes on reintervention rates and bleeding.

Study:	No.	DVA Technique	Device	Stents/ PTFE	First 3-6 mo	FU med	# Duplex	RR (%)	Bleeding
Del Guidice 2018	5	pDVA	LimFlow	Yes	SAPT+AC	SAPT	3	60	NR
Kum 2018	7	pDVA	LimFlow	Yes	SAPT+AC	DAPT	3	NR	1 case (minor)
Schmidt 2020	32	pDVA	LimFlow	Yes	SAPT+AC	SAPT	NR	61	1 case (minor)
Schreve 2020	22	pDVA	LimFlow	Yes	SAPT+AC	SAPT	6	86	NR
Alexandrescu 2011	25	Hybrid	PTFE bypass	Yes	DAPT	SAPT	3	NR	NR
Cangiano 2020	14	pDVA	Pioneer plus with IVUS	Yes	DAPT	SAPT	5	NR	NR
Gandini 2017	9	pDVA	Regular devices	No	DAPT	DAPT	0	14	NR
Ysa 2019	5	pDVA	Homemade (VAST)	No	SAPT+AC	SAPT	1	25	NR

DVA: deep venous arterialization; pDVA: percutaneous deep venous arterialization; PTFE: polytetrafluoroethylene; SAPT: single antiplatelet therapy; DAPT: dual antiplatelet therapy; AC: anticoagulation; No.: number of patients included in the studies; mo; months; FU med; follow-up medication after 3-6 months postprocedural; # Duplex: number of duplex measurements performed within 6 months of follow-up; RR: Reintervention rates at 6 months of follow-up; NR: not reported

Restenosis and reinterventions

Primary patency rates were only reported in 2 studies,[3,13] which was 66% at both 6 months follow-up. The reported reintervention rates for the studies using a combination of antiplatelet and anticoagulation therapy ranges from 25-86%, with a mean of 61% at 6 months follow-up. In the study which prescribed dual antiplatelet therapy and assessed the reintervention rate, the reintervention rate was 14% at 6 months follow-up.[9]

Pharmacological viewpoint

From a more pharmacological viewpoint, it is known that arterial thrombosis mainly consists of clotted thrombocytes due to activation by a damaged

endothelial layer.[27] In patients with PAD, where the endothelial layer is often injured by a rupture of the atherosclerotic plaque, it is therefore necessary to use antiplatelet therapy to prevent the thrombocytes from clotting.[28] However, in post-pDVA patients, the venous system is also involved, and venous thrombosis typically exists from fibrin.[27] The formation of fibrin can effectively be prevented by anticoagulation medication as vitamin K antagonists or heparins.[29] However, it is uncertain if the occlusions that occur in post-pDVA patients, can be attributed to arterial or venous thrombosis or a combination of both. In AVF studies for vascular access in patients with chronic kidney disease, the use of single or double antiplatelet therapy has not shown to reduce thrombosis rates or improve maturation. Likewise for the use of anticoagulation therapy.[30] However, it is unknown if these results can be extrapolated to post-pDVA patients.

Covered stents

Covered stents were used in most (p)DVA treatment techniques. When considering the appropriate medical treatment, the use of covered stents should also be taken into account.[31] A previous study evaluated the efficacy of various antiplatelet/anticoagulation regimes in patients with a Viabahn stent graft for femoropopliteal occlusive disease.[31] Three treatment groups were compared: i) triple therapy including aspirin, clopidogrel and warfarin ii) indefinite dual antiplatelet therapy (aspirin and clopidogrel), and iii) indefinite aspirin with a temporarily 6 weeks clopidogrel. The triple therapy group showed the highest primary patency rates (68%, 56%, and 21%, for the three groups respectively), but bleeding events also occurred more frequently (12%, 0%, and 0%, respectively). The indefinite dual antiplatelet therapy group showed similar outcomes as the triple therapy group with less bleeding events. The 12-month results from the temporarily dual therapy group were significantly worse compared to the other two treatment groups in all aspects including, freedom from reintervention (76%, 59%, and 21%), freedom from major adverse limb events (75%, 74%, and 62%), and freedom from thrombolysis (85%, 78% and, 63% for group i, ii, and iii, respectively).

Expert opinion

Based on existing literature on various domains, it is difficult to draw firm conclusions about the optimal medical treatment regime in post-pDVA patients. We consider low-molecular-weight heparin (LMWH) 2 times daily 0.6-0.8 ml depending on body weight, and clopidogrel 75 mg daily for at least 3 months, followed by lifelong dual antiplatelet therapy (clopidogrel 75 mg and Aspirin 100 mg daily). Therapeutic anticoagulation can be continued for other indications if necessary.

Edema, cyanosis and necrosis

The occurrence of edema was described in 9 articles,[3,4,8–10,12,15,16] of which 2 used a hybrid DVA approach[3,4] and 7 a percutaneous DVA technique.[8–10,12,15,16] Out of the 9 studies only three studies[4,8,10] reported the treatment given, which included elevation of the leg. In one paper, occasionally diuretics were prescribed.[8] In addition, off-loading and hanging the legs down was advised to allow the hydrostatic pressure to encourage further formation of venous collaterals.[8]

Purple coloring of the foot

Beside edema, cyanosis or purple coloring of the forefoot was described by two studies[9,16] and was suggested to be a result of venous hypertension.[16] The purple coloring disappeared within the first week postprocedural.[9]

Necrosis

Superficial necrosis has been mentioned to become apparent in the first postprocedural period.[3,4,16] Intentional demarcation of the affected toes was the preferred treatment option.[3,4]

Clinical experience and expert opinion

In our experience with a cohort of 23 post-pDVA patients treated with the LimFlow system in Singapore and The Netherlands, edema occurred in all patients. Edema was mild and effectively treated by leg elevation, which is in line with previous literature. Also, to prevent excessive edema, we advised to elevate the leg for at least 24 hours postprocedural and off-loading of the heel was ensured to prevent pressure related wounds. In case of minor edema, the patient was allowed to hang the foot down for 2 hours followed by elevation for another 2 hours to encourage hydrostatic pressurization of the AV-circuit.

No studies mentioned the use of stockings to treat edema. It is uncertain if they were not used or not reported as only 3 studies reported their edema treatments given. In our cohort, thromboembolic foot pump and thromboembolic stockings were avoided as a precaution for the concern of compromising the venous outflow. Also, compressive bandages for wound care were discouraged and stocking net dressings like Tubifast (Mölnlycke Health Care, Gothenburg, Sweden) were used instead, fixated with tape.

Purple coloring of the foot was also noticed by our team and was deemed as a normal reaction on the pDVA procedure.

Progression of gangrene occurred in 13 patients (57%). Similar to the options discussed in the other studies,[3,4] progressive necrotic tissue was left to demarcate and further assessed during follow-up visits in the outpatient clinic. Eventually, minor amputations were performed in case of wet gangrene.

Based on published literature and own experience, swelling and coloring of the foot is regularly seen after a pDVA and is a positive sign of venous perfusion. Keep the leg elevated for 24 hours can be considered, and after this on indication. Progression of necrosis can occur due to steal from existing arterial collaterals. Demarcation of necrotic tissue should be strived for in order to wait with amputation until the AV-circuit has matured. Necrotectomy or a minor amputation can be considered in case of wet gangrene.

Pain management

Only 3 articles reported the occurrence of postprocedural pain.[4,15,16] However, none of the articles mentioned management of postprocedural pain. One study reported an increase in pain when the AV-circuit was occluded.[4] The other studies described pain as a postprocedural effect.[15,16]

Clinical experience and expert opinion

In all patients in our cohort, the character of the pain changed from the typical ischemic pain type to a more engorgement type of pain. Pain management was handled by the primary team, and in case of more severe pain, pain specialists were consulted. Consultation of the APS was necessary 5 patients (22%). In addition, patients were examined to identify the cause of the pain. Inflammation, reperfusion, ulceration, persistent ischemia, neuropathy, and a combination of the previously mentioned causes were considered and examined. Examination included clinical evaluation of the necrotic tissue or ulcer, $TcPO_2$ measurements and DUS measurements. As ischemic pain post-pDVA may result from threatened patency of the circuit, examination could also include repeat angiography to accurately determine lack of distal perfusion and to assess if there was evidence of excessive shunting. In 3 patients, the pain was deemed related to an occlusion of the AV-circuit. Further causes were infection (N=1) and a stealing collateral (N=1).

We believe that the change of postprocedural pain from ischemic to engorgement is due to venous pressure and can be considered a result of the procedure. However, persisting, or an increase pain has in our experience always been a sign of mal perfusion of the foot. Therefore, we recommend analyzing the AV-circuit with duplex ultrasound to detect stealing side branches or flow limiting

stenosis, in combination with a $TcPO_2$ measurement of the foot when the pain is persistent or severe. An angiogram can be considered to resolve the cause and create a better forefoot perfusion.

Patency assessment

Duplex ultrasound

Patency by duplex ultrasound was assessed in 9 studies.[3,4,6,8–13] Patency evaluations varied between the studies. Three studies[4,11,12] evaluated patency frequently by duplex which was generally performed immediately after the procedure, at 1 week, 4 weeks and 3-, 6-, and 12-months post-procedural (Table 3).

TABLE 3. Studies reporting on duplex measurements* and their outcomes on reintervention rates, major amputation, and wound healing.

Study	#pt	DVA Technique	Device	# Duplex	Crossing	RR (%)	MA (%)	WH (%)
Alexandrescu 2011	25	Hybrid	PTFE bypass	3	Both	NR	14	NR
Cangiano 2020	14	pDVA	Pioneer plus with IVUS	5	Proximal	NR	21	64
Del Guidice 2018	5	pDVA	LimFlow	3	Proximal	60	20	40
Ferraresi 2019	35	Hybrid	GSV/PTFE bypass	7	Distal	NR	31	NR
Gandini 2017	9	pDVA	Regular devices	0	Distal	14	29	71
Kum 2017	7	pDVA	LimFlow	3	Proximal	71	14	NR
Schreve 2020	22	pDVA	LimFlow	6	Proximal	86	9	NR
Ysa 2019	5	pDVA	Homemade (VAST)	1	Distal	25	25	75

DVA: deep venous arterialization; pDVA: percutaneous deep venous arterialization; PTFE: polytetrafluoroethylene; GSV: great saphenous vein; IVUS: intravascular ultrasound; # duplex: number of duplex measurements within 6 months of follow-up; MA: major amputation at 6 months of follow-up; WH: wound healing rate at 6 months of follow-up.
*The study by Schmidt et al., did not perform duplex measurements in a regular basis (when necessary) and were therefore not included in the Table.

One study determined optimal threshold selection for peak systolic velocity (PSV) values in cm/s and volume flow (VF) values in ml/min for patent and AV-circuits at risk. Measurements were performed at 5 different points: i) at the inflow arteries, ii) proximal 1/3 segment of the stented vein, iii) mid-segment of the stented vein, iv) distal 1/3 segment, and v) the outflow vein. The PSV and VF measurements had the highest combination of reliable and diagnostically

accurate. PSV ≤ 55 cm/s and VF ≤ 195 ml/min measured mid stent were found predictive of failure.[11]

$TcPO_2$ measurements

$TcPO_2$ was used to evaluate distal perfusion in eight studies perioperatively but also including interval measurements.[3,4,7,9,10,12,13] Intervals varied from every 2 weeks for the first 2 months and monthly after until wound healing was achieved or a major amputation was performed[8,10,12] to 1-, 6- and 12-months postprocedural.[3,13] All studies reported that a mean increase in oxygen pressure was noticed after the procedure. Generally, $TcPO_2$ values ≥ 40 mmHg were considered sufficient for wound healing.[8,12] Details regarding treatment when a drop in oxygen pressure or stagnation of improvement was seen, were not reported in any of the studies.

Clinical experience and expert opinion

A more liberal approach concerning duplex measurements was used in our clinic, especially the first 3 months postprocedural when most stenosis or occlusions were found. The median time to perform the first reintervention was 5 weeks (IQR, 3-9 weeks) and was performed for clinically relevant stenosis, occlusions, and stealing collaterals. The indication for the reinterventions was based on lesions found on duplex surveillance in 78%. Other indications included pain (11%) and persistent wounds (11%). Therefore, we would advise to assess patency frequently. At the first day postprocedural, patency of the AV-circuit can be evaluated by doppler. The AV-circuit can be considered patent if a pulsating flow sound is heard on the plantar surface of the calcaneus. Duplex ultrasound measurements should be planned in the first week postprocedural in which the peak systolic velocity (PSV) and volume flow (VF) should be measured at least at mid stent and at more points of the AV-circuit, if possible. Further follow-up visits can be planned at 2-, 4-, 6-, 8-weeks, and 3-, 6-, 12-months postprocedural. In addition, $TcPO_2$ measurements can be performed pre-procedural, and at 1-, 3-, 6-, 12-months postprocedural to evaluate distal perfusion.

Reinterventions

Reinterventions after DVA are often necessary to reestablish patency. Almost all identified studies on DVA reported the necessity of reinterventions in one or multiple patients.[4,6,8,10–13,15,16] In fact, reinterventions are mentioned in 2 studies as part of the procedure as maintenance of the AV-circuit.[4,16] the hybrid-DVA procedure was described as a vascular procedure with multiple staged endovascular steps. After the initial bypass procedure, focalization of blood flow to the wound was performed 2-4 weeks later to create forward pressure.

Additional procedures were performed as maintenance to reestablish patency when impairment was detected by duplex scan.[4] An angiography has been proposed at 4-6 weeks postprocedural to treat possible lesions, and to focalize the arterial flow into the venous system, based on the venosome concept and wound lesion location.[16] In other studies,[6,10,12] stealing collaterals were also embolized or ligated to increase forward pressure, however, it was not performed on a regular base [4,16] In another study embolization of stealing veins is performed during the primary procedure.[3]

Reintervention techniques

A total of 6 studies discussed the devices used during reinterventions. Thrombectomy for occlusion was necessary in 5 studies,[8,10–13] of which 4 reported the device used, including AngioJet (N=2)[12,13] and Rotarex (N=2).[8,10] In 2 studies, additional medical thrombolysis was given.[10,11] PTA for (re)stenosis was performed using a plain old balloon (POBA) or a drug coated balloon (DCB).[6,8,10,11,13] Stents were used in 2 studies in case of a suboptimal balloon angioplasty result.[8,10] Reported indications to perform a reintervention were stenosis or occlusion as seen on duplex surveillance in the majority of cases, and pain, a new wound or stagnant wound healing in the minority of cases.[4,6,10–13]

Clinical experience and expert opinion

The venous arterialization seems to be a multiple staged procedure as the AV circuit needs time to develop and reinterventions are often necessary to increase forward flow and pressure. Reintervention procedures performed in our clinics are similar as described in literature. Based on both, we advise the following: The indication for reintervention should be based on a combination of the $TcPO_2$ measurements, DUS results and patient's clinics. In case of an occlusion, percutaneous mechanical thrombectomy should be applied first, to create flow and unmask the cause of the occlusion followed by thrombolysis. When a stenosis is present, this can be treated by a high-pressure balloon or a cutting balloon, and drug coated balloons or (drug eluting) stents, if necessary. Stealing side branches preventing distal pressurization can be ligated or coiled.

Amputation strategy

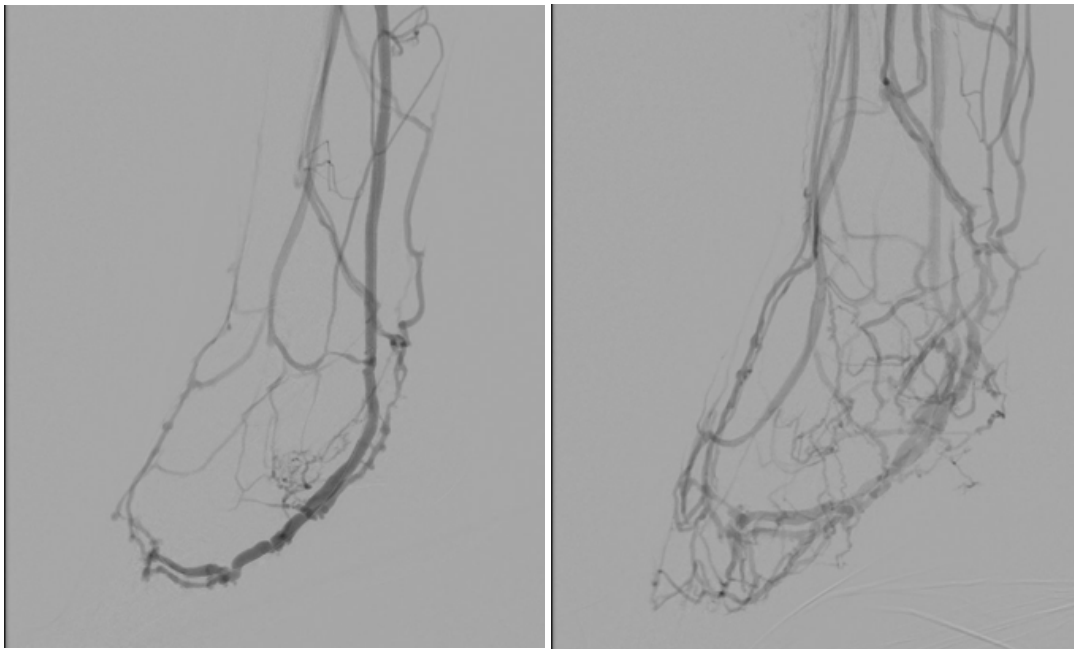
Performing minor amputations is almost inescapable in the DVA patient population in which many suffer from Rutherford 5 or 6 ischemia. This is also reflected in literature: a total of 8 studies reported the necessity of minor amputations. The minor amputation rate varied from 50-100% between the studies. Toes were amputated most often, followed by transmetatarsal amputations (TMA),[3,6,8,12,15] Lisfranc, and Chopart amputations.[4,7] The technique

and timing of the minor amputations has been discussed in 3 studies.[4,14,16] Despite the different techniques used in the studies, their minor amputation approach is similar. A guillotine amputation to drain severe infection has been suggested before the DVA procedure. Definite amputation was considered after 6-8 weeks postprocedural. The rationale was that it takes time to develop retrograde tissue nutrition by veins and stimulation of the angiogenesis process that leads to a remodeling of the vascular distribution system of the foot.[14] Tension-free foot surgery has been suggested after the focalizing embolization procedure, so 6 weeks post-DVA. This was argued by the similar hypothesis that it takes time to arterialize the forefoot.[4,16] Regarding skin closure, secondary healing was recommended, and sometimes a dermal substitute or dermo-epidermal graft was used to cover exposed bone and enhance wound healing.[4,16]

Clinical experience and expert opinion

Minor amputations are crucial in the follow-up after DVA. As mentioned earlier, progression of ischemia can be seen in the first weeks postprocedural, because the blood will flow into the veins and will directly return to the heart after DVA. During maturation of the AV-circuit, a distal perfusion of the forefoot arises through "new" vascular branches. This was also noticed in our cases, of which an example is shown in Figure 2. Therefore, we recommend to avoid definitive foot surgery at the initial period.

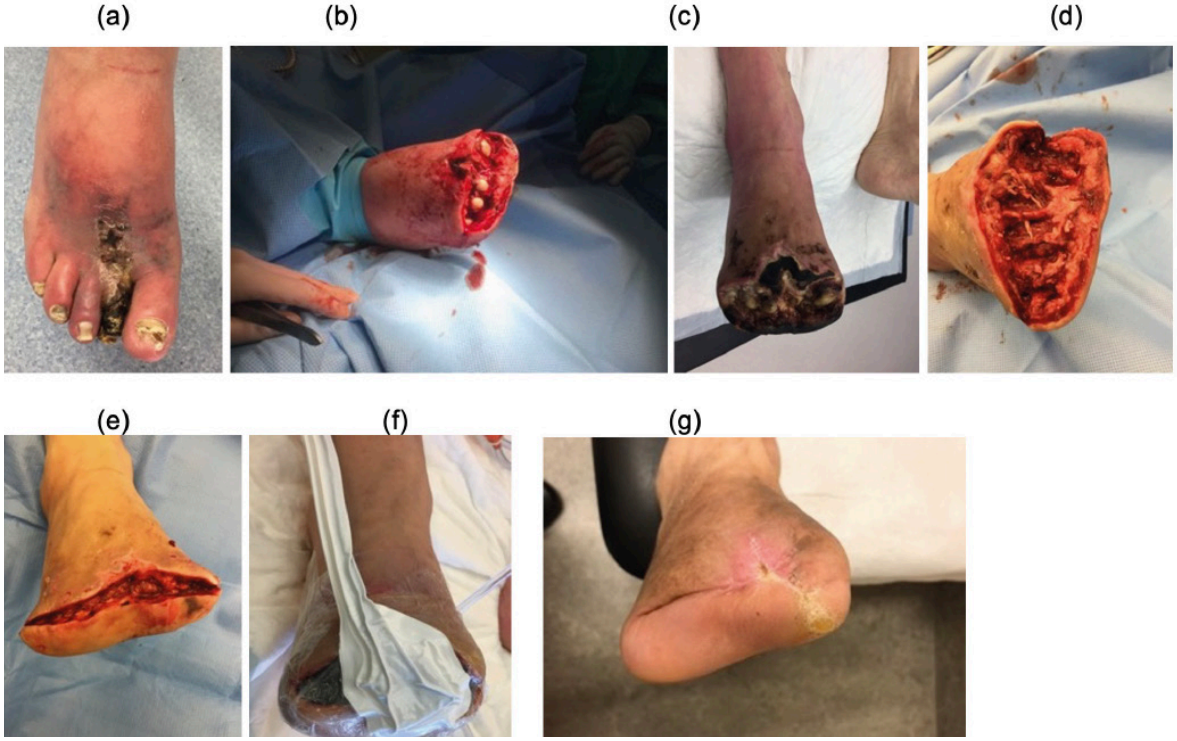
FIGURE 2. Image of two angiograms of the same patient. (a) Angiogram after the index procedure showing blood flow into the venous arch. (b) Angiogram 7 weeks later showing forward flow distal in the foot.



(a) (b)

In addition, a staged amputation strategy is preferred to firstly drain the infection and secondly allow the AV-circuit to develop. A subsequent definitive amputation can be planned at least after 6 weeks post-DVA. In our cohort, minor amputations deemed necessary in 13 patients (57%). An example of the staged amputation approach is shown in Figure 3. In one of our first cases, the skin was closed after a TMA. Wound dehiscence was seen a month later (Figure 4). In the following patients, the strategy was changed, and the skin was left open.

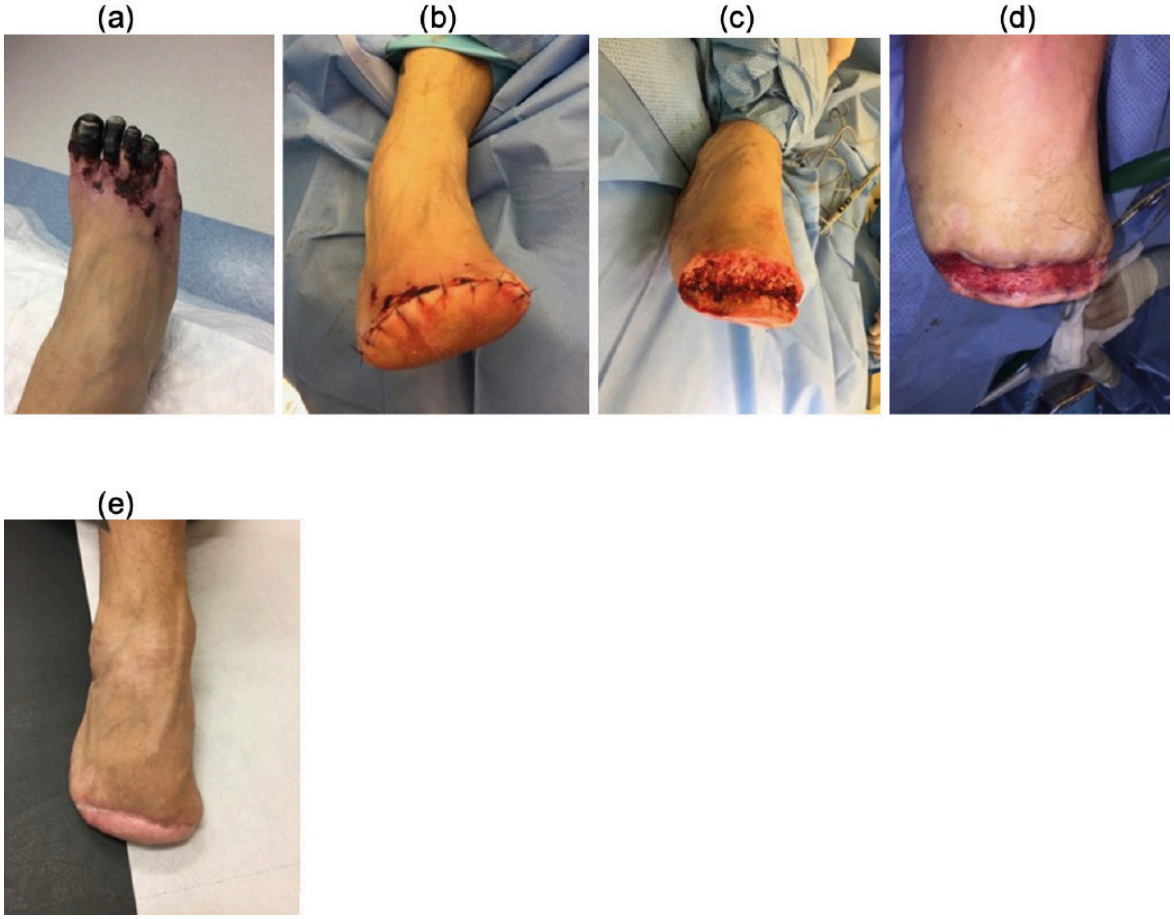
FIGURE 3. A staged amputation approach in a 63-year-old male. (a) Photograph showing affected tissue 6 weeks post-pDVA. (b) Around 8 weeks postprocedural, the forefoot was amputated without removing the metatarsal cartilage. (c) Progression of necrosis was seen two weeks later. (d, e) Necrotic tissue and metatarsal heads were removed during the next amputation stage and the fascia was approximated. (f) VAC therapy was applied to accelerate wound healing. (g) Photograph of the fully healed wound.



Concerning the above, we advise to perform a staged amputation strategy as follows: the initial foot surgery should consist of necrotectomy of the gangrenous tissue and minor amputations in cases with a high risk of infection, leaving the skin open. When the amputation is through the metatarsal-phalangeal joint, the metatarsal heads should be left in place to prevent exposure of the cancellous bone. The second stage can include cleaning the wound surface, removing metatarsal heads and approximate the fascia to cover the underlying bone. Further wound care after DVA or minor amputations will be discussed in

the following paragraph.

FIGURE 4. A 28-year-old male in which a forefoot amputation was performed with primary closure. (a) Necrosis was left to demarcate after the pDVA procedure. (b) A forefoot amputation was performed a month later, in which the skin was closed by sutures. (c) Necrosis started to develop at the site of the sutures a few days later, followed by wound dehiscence. Necrotectomy was performed in the operating theatre to improve wound healing. (d) A split skin graft was placed after stagnant wound healing. (e) Wound healing was achieved at 8 months postprocedural.



Wound care

Wound care was briefly discussed in five studies.[3,4,14,16] The use of vacuum assisted therapy (VAC) was used in 23-100% of the cases.[3,7,14] The use of split skin grafts was only described in one study[14] and was applied in 43% of the cases. Biosynthetic skin substitutes and rotational skin flaps were used in 7% and 3% of the cases, respectively.[3] Also dermal substitutes and dermo-epidermal grafts were used to enhance healing.[4,16] Sole epithelialization-stimulating dressings were applied in 38% of the cases in one study.[3] Patients underwent debridements in two studies to improve healing potential.[6,14]

Clinical experience and expert opinion

In our clinic, wound care was led by a multidisciplinary team including wound specialty nurses, physicians, and a podiatrist. We advise to treat dry gangrene conservatively with iodine in the initial 6 weeks. After a minor amputation, the wound can be covered with a gauze and netting. Compressive bandages should be discouraged. In case of wound debris during follow-up, special cleaning wound dressings as Prontosan® (B Braun, Melsungen, Germany) or Eusol can be used for debridement. Open wounds should be dressed with Hydrogels or Hydrofibre e.g. Aquacel to keep them moist. VAC dressing can only be used when the wound bed is showing pink granulation and should generally be avoided in the first 6 weeks. In our first patient in which VAC therapy was applied, the pressure was 120 mmHg in a continuous setting. This was too intensive as the food colored white and the VAC was subsequently stopped after 3 days. In the following patients, the settings were changed to a pressure of 60-75 mmHg with an intermittent suction frequency. This resulted in progression of wound healing in the following patients. Therefore, we recommend to apply VAC therapy intermittent with a low pressure of 60-70 mmHg. In case of worsening infection or necrosis, the patient can be planned for surgical debridement in the operating theatre. Necrotectomy can be performed using a knife and/or using the VERSAJET Hydrosurgery Xystem (Smith & Nephew, London, United Kingdom).

Discussion

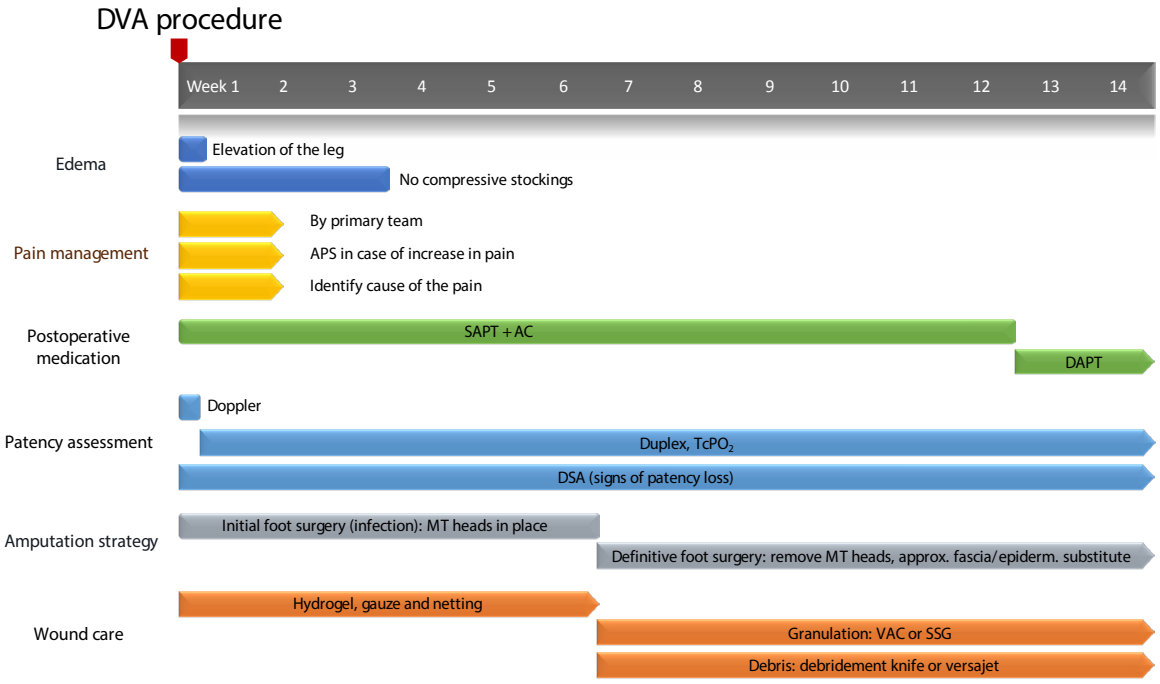
The advances in DVA over the last years have been impressive. Especially the percutaneous approach has shown most developments with promising results.[6,10,12,13,15,16] The technique is becoming more accepted and applied in the treatment of patients with no-option CLTI, but there are still uncertainties on several aspects in the postprocedural management. A multimodal approach can be considered in the treatment of post-DVA patients.

Based on literature and clinical experience, we propose an algorithm for the challenges that interventionalists can face in the follow-up period after a DVA (Figure 5).

Edema and pain are the first events that can occur postprocedural and can be treated by elevation of the leg. A sudden increase in pain should be treated by pain specialists and the cause should be identified. Postprocedural antiplatelet and anticoagulation therapy can include clopidogrel and heparin

for the first 3 months postprocedural followed by lifelong dual antiplatelet therapy (clopidogrel and aspirin). Doppler can be performed in the first 48 hours postprocedural as this can be done at the ward and provides sufficient information about an open or occluded AV-circuit. Further, we advise to evaluate patency by duplex ultrasound and assess foreward pressure by $TcPO_2$ measurements. Definitive foot surgery, debridements and wound enhancing therapies should be avoided within the first 6 weeks postprocedural as forward flow and pressure is unsufficient and evolving during that period.

FIGURE 5. Timeline of postprocedural management. Six main subjects are shown.



APS = acute pain services; SAPT = single antiplatelet therapy; AC = anticoagulation; DAPT = dual antiplatelet therapy; $TcPO_2$ = transcutaneous oxygen pressure; DSA = digital subtraction angiography; MT heads = metatarsal heads; VAC = vacuum assisted therapy; SSG = split skin grafts

With all developments in the technique and knowledge, the role of DVA for the treatment of no-option CLTI patients will become more important. The suggested recommendations were based on the reviewed studies and our experience with a cohort of 23 post-pDVA patients. The reviewed studies included cohort studies of moderate quality, case reports and technical notes. Therefore, the level of evidence on which the recommendations were based can be considered moderate to low. In addition, the differences in (p)DVA techniques and procedures could affect postprocedural care and limit the

generalizability of the propositions. Thus, we advocate for further research for this continuously developing revascularization method.

Conclusions

There are still many debated topics about postprocedural management in DVA patients. This article provides an overview of the current literature and suggests recommendations based on literature and clinical experience. Key elements in follow-up care are the acknowledgment that the DVA needs 6 weeks to develop before becoming effective, and a multimodal approach including surveillance, wound care, and a staged amputation strategy. The recommendations proposed may help future interventionalist in the present gap of knowledge in follow-up care of post-DVA patients. However, it is based on moderate to low quality evidence and therefore, further research is needed to draw firm conclusions.

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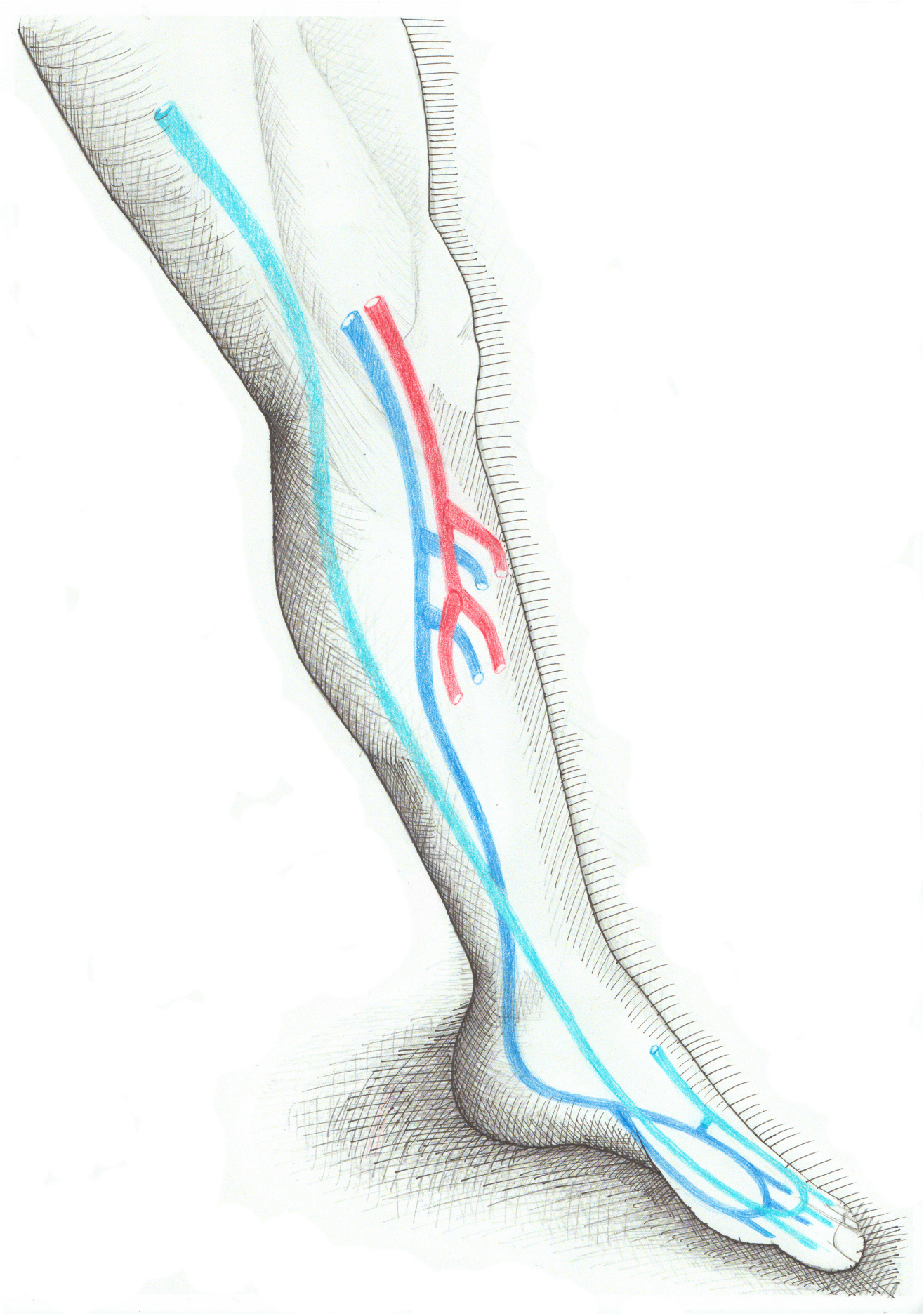

Chapter 9

Summary, general discussion,
and future perspectives

Summary

Chronic limb-threatening ischemia (CLTI) is a significant facet of atherosclerotic disease that has major medical and functional consequences. With the number of diabetic patients on the rise and improved life expectancy, has also come a greater awareness and wider adoption of endovascular techniques; thus, amputation rates continue to fall.[1-3] We expect that patients will be older, have more advanced comorbidities, and will have had more prior interventions. This may translate to a greater proportion of them presenting with no-option CLTI. Venous arterialization may be a viable alternative to preserving these limbs. This thesis starts with a general introduction that provides an update on the history and development of the venous arterialization. After this the thesis consists of three parts:

Part 1 is entitled; the open venous arterialization
Part 2 is entitled; percutaneous deep venous arterialization (pDVA, LimFlow procedure)
Part 3 is entitled; postoperative care and follow-up of the venous arterialization

The first part provides information about the open superficial venous arterialization. In **Chapter 2**, a superficial venous arterialization cohort and pedal bypass cohort of two Dutch hospitals is analysed, with promising results in a group of patients for whom no other reconstructive treatment options were available. Although the pedal bypass is still the gold standard (if a target artery is present), distal venous arterialization is a good alternative due to comparable results and its simplicity. The current evidence was analysed in a systematic review and meta-analysis in **Chapter 3** and suggests that venous arterialization is a valuable treatment option in selected patients with no-option CLTI. These otherwise unsalvageable legs can be treated with acceptable morbidity and mortality. However, optimization and standardization of techniques are needed. The venous arterialization should always be considered in patients without distal arterial outflow vessels.

The second part is about the percutaneous deep venous arterialization (pDVA). In **Chapter 4**, the first experience with the pDVA in humans is published, applied to a cohort of patients with no-option CLTI. The dual catheters, guided by ultrasound imaging, provide a reliable way to percutaneously create the AVF between a tibial artery and a deep tibial vein. Assisted by a percutaneously introduced valvulotome, arterial blood can now be directed to the veins of the

foot. In this small cohort of patients, pDVA appears to be a safe and feasible procedure that effectively improves limb oxygenation, encourages wound healing, and potentially, avoids major amputation.

The experience, after this first publication, from four centers between 2014 and 2018, is analysed in **Chapter 5**. 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 amputation-free survival rates of 67% 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. A new international multicenter prospective study, PROMISE International, has been started to validate these outcomes in a larger cohort, and the protocol is described in **Chapter 6**.

The last part of this thesis is about the postinterventional care of the venous arterialization. **Chapter 7** is the first analysis of duplex ultrasound (DUS) measurements in post-pDVA patients. The venous arterialization needs time to mature before becoming effective. Stenoses or occlusions can frequently occur during this period, and therefore, there is a high need for more insight in DUS interpretation to detect failure of the arteriovenous circuit and preserve the limb. This study showed that surveillance of the arteriovenous circuit can be performed by DUS and we determined cut-off values to define the presence of stenosis or occlusions, but the small sample size of the study does not allow firm conclusions to be drawn.

A guideline for post-pDVA care is given in **Chapter 8**. Based on literature and clinical experience of 24 patients from Alkmaar and Singapore, we summarize the different techniques proposed and provide an algorithm for the challenges that interventionalists can face in the follow-up period after a pDVA. The most important, is the acknowledgement that the pDVA needs 6 weeks to develop before becoming effective. Other key elements are edema treatment, pain control, wound care and a staged amputation strategy.

The postprocedural management can be as challenging as the procedure itself but has not been a priority for further investigation.

General discussion

The aim of this thesis is to study the clinical outcome of the venous arterialization in patients with no-option CLTI. In this chapter, we will discuss the contents of this thesis and try to position the use of a venous arterialization.

In the late 1800s, the first experiments connecting an artery with a vein were performed. Key figures in the development of the venous arterialization are Halstead and Vaughan in 1912,[4] with the description of the first experience in humans. Sheil confirmed in 1977[5] the need for distal valve destruction and noted the lack of adequate perfusion to the forefoot when this step was omitted. Lengua has dedicated his life's work to the venous arterialization and can be regarded as the godfather. He introduced a new concept with a more distal anastomosis on the deep or superficial venous system, with better results. His book; 'Arterializacion del pie por isquemia', has explanations about the venous system of the foot and the mechanism of the venous arterialization.[6]

Patient selection is challenging. Until now, only patients with no-option CLTI were candidates for a venous arterialization. The natural history of these patients shows high morbidity and mortality rates in a vulnerable patient group. After amputation, a minority will be mobile, and most patients cannot return home and need extensive care. Therefore, we strive for limb salvage.

Different techniques of venous arterialization are described; however, after the initial procedure it was not well investigated, how the bypass evolved.[9] Studies do not mention postinterventional angiograms searching for side-branch development and adequate distal foot perfusion. This is maybe why in some studies, legs were amputated with an open venous arterialization, but without any clinical effect. With the development of the hybrid venous arterialization by Ferraresi[10] and the pDVA by Kum,[11] postinterventional angiograms were made, resulting in a better understanding of the development of the venous arterialization in the first 6 weeks after the initial procedure. It shows there is a need to treat side branches and stenosis in the outflow to get adequate distal foot perfusion.

The concept of the venous arterialization is different than that of a regular arterial bypass. Blood flows into the capillary bed from the venous side, and there is some tissue nutrition from reverse perfusion through capillaries, collaterals, and arteriovenous shunts,[12,13] but angiogenesis is generally believed to be the key to perfusion.[14] Mutirangura described that connections

are made between the pressurized veins and the existing arterial collaterals as the phenomenon of the venous arterialization.[15] This was confirmed by Lenqua and Ferraresi, who published images demonstrating a remodeling of the distal vascular network suggesting a plausible direct tissue feeding. These images, alongside the persistent healing and high TcPO2 values of patients with an occluded bypass, support the hypothesis of a neoangiogenesis process triggered by the arterialized circuit.[10,16]

Our experience is that the venous arterialization is a dynamic bypass that needs guidance in the first 6 weeks to become effective. Side branches can develop, leading to a fast return of blood to the heart, and stenoses can occur in the outflow vein, both resulting in an inadequate forefoot perfusion. If we regularly control the bypass in the first period, we can control and treat these threats to establish an adequate foot perfusion.

Postinterventional wound care and amputation strategy are described in this thesis. Based on our experience, we think a different strategy should be chosen than that used after regular bypass surgery. We have to wait for the venous arterialization to develop, which means we do not primarily perform the amputation at the index procedure but advise a staged amputation strategy. Primary wound closure seems to have a negative outcome on wound healing due to pressure on the developing veins and should be avoided. Secondary wound healing supported with intermittent vacuum assisted closure therapy is advised. The key of this procedure is not the procedure itself but lies in the aftercare.[17]

Future perspectives

The venous arterialization is going through a second revival after the 70s with the percutaneous procedure. The pDVA has become a safe and reliable procedure and evidence is building, but is it going to deserve its place in the treatment of CLTI?

At this moment, different trials are being conducted in Asia, Europe, and in the USA (The PROMISE International and the PROMISE II U.S.A. Pivotal trial). These studies should provide us with more information. A registry has started in the Netherlands that includes every patient with no-option CLTI receiving a pDVA. The design of this Dutch registry differs from other studies because every patient is included. The aim is a cohort of 50 patients within 2 years with

seven dedicated hospitals.

Patient selection remains a main issue, because patients with CLTI and no-option CLTI come in a wide variety. Patients have different comorbidities and etiologies, patients present with large-artery disease or small-artery disease,[18] and the progression of their disease differs in time and extent. The natural history of these patients shows spontaneous wound healing and major amputation in the same patient group, without the ability to predict this beforehand.[7,8] If we could predict which patients' wounds will heal spontaneously, we could reserve venous arterialization for patients who need it. This will have to come from big data registries and a better interpretation of our diagnostic possibilities.

Among the current limitations of the technology are that only a few arteries can be used as a donor vessel. Future developments will have to overcome these limitations so a wider variety of arteries can be used and existing collaterals can be preserved. This will mean that anatomically higher and lower crossings will be possible. At this moment, different techniques are explored using off-the-shelf devices. These techniques include the venous arterialization simplified technique (VAST) by Ysa,[19] the wire perforation technique by Gandini,[20] or the percutaneous deep venous foot arterialization, or Pioneer Peschiera Revascularization (PiPeR) technique, using an intravascular ultrasound-guided catheter technique by Migliara.[21] These developments show that there is a need for venous arterialization in patients in whom no other options are available.

The most important step at this moment is a better understanding of the mechanism and knowledge of the development of the venous arterialization at the foot. When this becomes clear, the patient journey from procedure to wound healing will become predictable. This will result in treating a wider variety of patients, with success.

Speculations are made about Pramook Mutirangura's theory of the phenomenon of the venous arterialization, which says that connections are made between the existing collaterals and the new developing branches of the venous arterialization. When these connections are made, a closure of the bypass will not lead to ischemia because blood will flow through the new connections and provide the foot with enough blood. When proven to be true, the venous arterialization can be considered as a temporary bypass that will be effective even after an occlusion. Evidence is not yet available, but we hope this will be provided by the new trials.

If the mechanism is further understood and the phenomenon is proven to be true, the venous arterialization will deserve its place in the treatment of CLTI and be a valuable treatment option because it is not temporary.

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Nederlandse samenvatting

Veneuze arterialisatie bij patiënten met kritieke ischemie van het been (verleden, heden en toekomst)

Chronische kritieke ischemie van het been is een belangrijk onderdeel van perifeer arterieel vaatlijden. Doordat het aantal diabetes patiënten toeneemt en de levensverwachting stijgt wordt deze groep steeds groter. De ontwikkeling van de (endovasculaire) behandeltechnieken gaat enorm snel waardoor amputaties voorkomen kunnen worden. De groep van patiënten met kritieke ischemie van het been waarbij geen dotter procedure of het aanleggen van een bypass meer mogelijk is zal ook toenemen en vanwege de uitgebreidheid van de ziekte is er een hoog risico op amputatie. De veneuze arterialisatie is een mogelijk alternatief en zou een amputatie kunnen voorkomen.

Bij een veneuze arterialisatie wordt er een verbinding gemaakt tussen de slagader en de ader om het zuurstofrijke bloed via de gezonde aders naar de voet te laten stromen. Hierbij moeten de kleppen in de ader uitgeschakeld worden en de zijtakken afgedicht zodat het bloed de juiste kant op stroomt. De veneuze arterialisatie kan op verschillende manieren uitgevoerd worden en op het diepe of het oppervlakkige veneuze systeem in de voet worden aangesloten. In de inleiding van dit proefschrift wordt de geschiedenis van de veneuze arterialisatie en de verschillende technieken beschreven. Hierna bestaat het proefschrift uit drie delen:

Deel 1 is getiteld; de open veneuze arterialisatie
Deel 2 is getiteld; de percutaan diep veneuze arterialisatie (pDVA, LimFlow-procedure)
Deel 3 is getiteld; de postoperatieve zorg en follow-up van de veneuze arterialistie

Het eerste deel geeft informatie over de verschillende open veneuze arterialisatie technieken. In **Hoofdstuk 2**, wordt een cohort van patienten uit twee ziekenhuizen geanalyseerd; patienten die een oppervlakkige veneuze arterialisatie ondergaan worden vergeleken met patiënten die een pedale-bypass krijgen. Alhoewel de pedale-bypass nog steeds de gouden standaard is (indien er een slagader op de voet aanwezig is), is de oppervlakkige veneuze arterialisatie een goed alternatief vanwege vergelijkbare resultaten en zijn eenvoud. De literatuur werd geanalyseerd in een systematische review en meta-analyse in **Hoofdstuk 3** en suggereert dat de veneuze arterialisatie een

waardevolle behandeloptie is bij patiënten met chronische kritieke ischemie van het been zonder andere revascularisatie mogelijkheden. Deze anders verloren benen kunnen worden behandeld met een aanvaardbare morbiditeit en mortaliteit. Er is echter wel optimalisatie en standaardisatie van de technieken nodig. Er wordt geconcludeerd dat de veneuze arterialisatie altijd overwogen zou moeten worden, bij patiënten met chronisch kritieke ischemie zonder andere revascularisatie mogelijkheden.

Het tweede deel gaat over de percutane diep veneuze arterialisatie (pDVA). In **Hoofdstuk 4**, wordt de eerste ervaring met de pDVA in de mens gepubliceerd. De percutane techniek waarbij de arterio-veneuze fistel (AVF) wordt aangelegd doormiddel van twee katheters en ondersteund door echogeleide beeldvorming, geeft een betrouwbare manier om een verbinding te maken tussen de tibiale arterie en de tibiale vene. Met behulp van een percutaan ingebracht valvulotoom kunnen de kleppen worden uitgeschakeld en kan arterieel bloed via de diepe vene naar de voet worden geleid. In deze kleine groep patiënten, blijkt de pDVA een veilige en haalbare procedure te zijn, die zuurstofrijk bloed naar het weefsel kan brengen, wondgenezing bevordert en grote amputaties kan voorkomen.

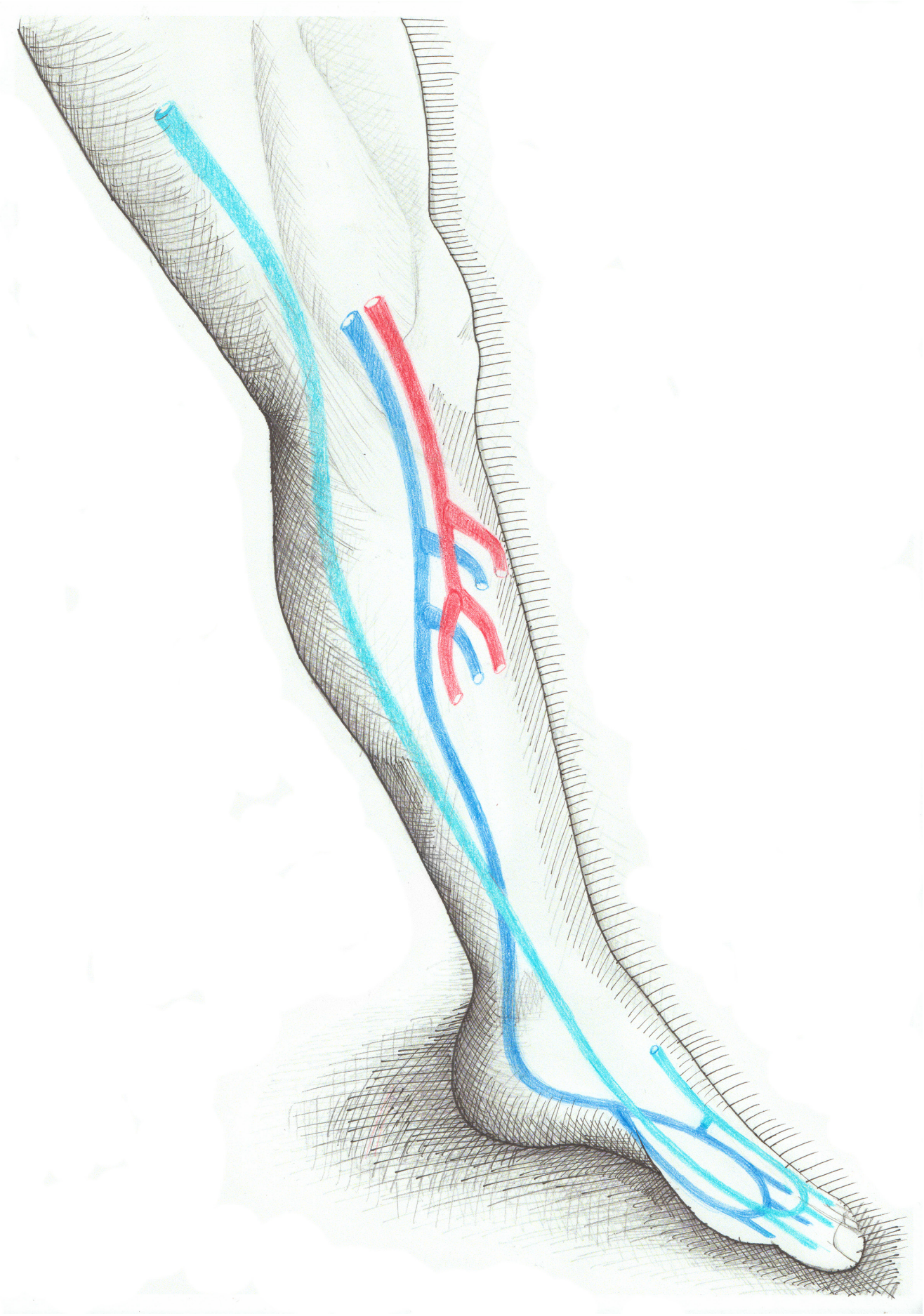
De ervaring van vier centra tussen 2014 en 2018 is geanalyseerd in **Hoofdstuk 5**. Dit is het grootste cohort patiënten met chronische kritieke ischemie van het been zonder revascularisatie mogelijkheden die werden behandeld met een pDVA, volgens de LimFlow techniek. In deze complexe patiëntengroep is er een hoog technisch succes en een goede wondgenezing na 2 jaar met een amputatie vrije overleving van 67%. Een nieuwe prospectieve internationale multicenter studie, de PROMISE International, is gestart om deze resultaten te valideren in een groter patiënten cohort. Het protocol wordt beschreven in **Hoofdstuk 6**.

Het laatste deel van dit proefschrift gaat over de nazorg, na een pDVA. Hoewel er steeds meer inzicht wordt verkregen in de pDVA procedure zelf, blijven de restenosen en occlusies die kunnen ontstaan tijdens de ontwikkelingsfase, een uitdaging. Om vernauwingen en occlusies vroegtijdig te identificeren wordt gebruik gemaakt van monitoring via duplexonderzoek. Met het duplexonderzoek kunnen bloedstroomsnelheden en bloedvolumes gemeten worden, echter de betekenis van de waarden zijn nog onbekend. Daarom hebben we in **Hoofdstuk 7** de duplexwaarden van de post-pDVA patiënten geanalyseerd en afkapwaarden bepaald om de aan of afwezigheid van vernauwingen of occlusies in het arterioveneuze circuit (AV-circuit) te definiëren. Deze studie toont aan dat surveillance van het AV-circuit goed kan worden uitgevoerd met een

duplexonderzoek maar door de kleine steekproefomvang van de studie kunnen geen harde conclusies getrokken worden en is verder prospectief onderzoek noodzakelijk om de gevonden waarden te valideren.

Monitoring van het AV-circuit via duplex is een belangrijk onderdeel van de post-pDVA zorg maar andere essentiële onderdelen zoals oedeem bestrijding, antistolling, wondzorg en de amputatiestrategie zijn essentieel voor succes. Een richtlijn voor post-pDVA zorg wordt beschreven in **Hoofdstuk 8**. Dit is gebaseerd op literatuuronderzoek en onze eigen ervaringen met 24 pDVA patiënten uit Alkmaar en Singapore. Er wordt een algoritme aangeboden waarin de uitdagingen worden beschreven waarmee de behandelaars te maken kunnen krijgen. Het belangrijkste element is, dat er wordt erkend dat het 6 weken duurt voordat de veneuze arterialisatie zich ontwikkeld heeft en effectief wordt.

De post pDVA zorg kan net zo uitdagend zijn als de procedure zelf, maar is in eerder onderzoek nooit een prioriteit geweest.



Chapter 10

Review committee
Acknowledgements - Dankwoord
List of publications
Curriculum Vitae

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About the Author

Michiel Schreve was born on November 4, 1973 in Leiden, the Netherlands. His family moved to Zambia for 3 years at the age of 2 and when returning to the Netherlands they settled in Rotterdam. At the age of 11 they moved to Zutphen were his father got a permanent position as a general surgeon. Michiel attended secondary school at the Stedelijk Lyceum in Zutphen from 1986 till 1992. After secondary school Michiel studied Economics for three years, at the Erasmus University in Rotterdam. He was accepted for Medical school at the same University in 1996 and obtained his medical degree in 2003. During his studies he was a member of the Rotterdamse Student Corps (RSC) and played field-hockey on national level.

In 2004 he started his general surgical training in affiliation of the Amsterdam Medical Center. From 2004 till 2008 in the Albert Schweitzer hospital in Dordrecht and from 2008 till 2010 in the Amsterdam Medical Center. His vascular surgery training was continued in the Onze Lieve Vrouwe Gasthuis in Amsterdam and was completed in 2011. After this he got a permanent position as a vascular surgeon in the chirurgennoordwest group, a collaboration between surgeons from the Red Cross Hospital in Beverwijk and the Northwest Clinics in Alkmaar and Den Helder.

He lives with his wife Ariadne Steensma and his two daughters, Amelie and Philippine (Pia) in Bentveld.