

Healing of Diabetic Neuroischemic Foot Wounds With vs Without Wound-Targeted Revascularization: Preliminary Observations From an 8-Year Prospective Dual-Center Registry

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Abstract

Purpose: To assess the clinical efficacy of endovascular angiosome-oriented wound-targeted revascularization (WTR) vs indirect (wound-indifferent) revascularization (IR) in diabetic patients with neuroischemic foot ulcers. **Materials and Methods:** Between April 2009 and July 2017, 167 diabetic patients (mean age 72.8 years; 137 men) with chronic limb-threatening ischemia (Rutherford category 5) and foot wounds (Wagner 2–4) in 194 limbs were prospectively registered and scheduled for primary infragenicular endovascular treatment. Specific angiosome source artery reperfusion sustained by patent foot arches or arterial-arterial connections was attempted initially. If this approach failed, topographic revascularization via available collaterals (WTRc) and IR were sequentially attempted. **Results:** Reperfusion was successful in 176 (91%) of 194 limbs (113 with WTR, 28 with WTRc, and 35 with IR); the global angiosome-oriented technical success (WTR and WTRc) was 73% (141/194). The mean follow-up was 10.9 ± 0.7 months (range 3–12.5). Over 1 year, 102 (58%) of the 176 successfully treated limbs experienced wound healing [79/113 (70%) in the WTR group, 15/28 (54%) in the WTRc group, and 7/35 (20%) in the IR group; $p=0.011$]. The mean time to healing was 6.8 ± 0.4 months in the WTR group, 7.9 ± 0.6 months in the WTRc group, and 9.8 ± 0.7 months in the IR group ($p=0.001$). Relapses were noted in 18 (16%) WTR limbs, 5 (18%) WTRc limbs, and 6 (17%) IR limbs. Comparison between WTR and IR and WTRc vs IR showed improved cicatrization in the angiosome-oriented groups ($p<0.05$). Major adverse limb events (MALE) and limb salvage were different between WTR and WTRc and between WTR and IR groups ($p<0.05$), while WTRc vs IR was not. Amputation-free survival was not influenced by the revascularization strategy ($p=0.093$). **Conclusion:** Wound healing in diabetic patients with chronic limb-threatening ischemia appeared to be improved by intentional wound-targeted revascularization, but no uniform benefit concerning MALE or limb preservation was observed. IR still represents an alternative for limb salvage in cases in which angiosome-guided revascularization fails.

Keywords

amputation, angiosome, chronic limb-threatening ischemia, critical limb ischemia, diabetes, indirect revascularization, limb salvage, major adverse limb events, wound healing, wound-targeted revascularization

Introduction

In recent years, the implementation of the angiosome concept in daily vascular practice has generated novel clinical observations from studies concerning its utility in chronic limb-threatening ischemia (CLTI) treatment and limb salvage. Over the past 2 decades, the majority of investigations

involved nonrandomized, retrospective analyses in heterogeneous cohorts of patients, types of wounds, and associated risk factors for tissue regeneration.^{1,2}

The clinical benefit of direct revascularization with angiosome orientation is currently compared against indirect (wound-indifferent) revascularization without topographic

specificity.^{1,2} However, only a few of these comparative studies have included the foot collaterals as determinants of clinical success in angiosome-oriented foot reperfusion.^{3–6} Notably, associating the “choke vessels,”^{4,7} the large collaterals, foot arches, and arterial-arterial interconnections with direct or indirect revascularization may basically change clinical outcome interpretation.^{1–6} This can also explain a series of discrepancies in available angiosome-related clinical results.^{1,3–5} As a result, clear consensus about adding precise collateral stratification to the definitions of direct and indirect revascularization (IR) is still lacking.

The present prospective study compared direct revascularization using angiosome-source arteries or related collaterals, collectively identified as wound-targeted revascularization (WTR), to IR for wound healing in current CLTI treatment.⁸

Materials and Methods

Registry Design

A prospective dual-center registry was designed to assemble and compare homogeneous groups of diabetic CLTI patients treated under a well-defined protocol approved by the institutions' ethics committees. Under this institutional protocol, diabetic patients were thoroughly evaluated by a central multidisciplinary team for lower limb ischemia, peripheral neuropathy, and neuroischemic foot ulcers with or without adjacent skin and deep tissue infection using a variety of tools including the UK screening test scale,^{9,10} the Rutherford ischemia categorization,^{11,12} the Wagner grade,¹³ and the University of Texas (UT) grading system.¹⁴

By protocol, primary below-the-knee (BTK) tibial or pedal angioplasty was offered to diabetic CLTI patients exhibiting Rutherford category 5 ischemia and Wagner grade 2–4 or UT grade 1–3 neuroischemic foot ulcers. However, limbs presenting with thrombosed tibial trunks from their origin to the foot division branches or extensive occlusions with continuous circumferential calcifications (>25 cm) of 3 tibial arteries were ineligible, as were those exhibiting complete absence of foot collaterals (angiographic “desert foot”). Patients with extensive tissue necrosis or irreversible gangrene, that is, Wagner grade 5, UT grade 3 stage D, or Rutherford category 6 tissue loss

requiring major amputation, were also not recruited. Patients with additional common femoral artery lesions, infrainguinal aneurysmal disease, or recent arterial thrombosis, as well as all patients with acute ischemic presentations or those who underwent reinterventions after bypass surgery were not considered for an initial endovascular approach. Patients enrolled in the registry gave written informed consent to treatment; no consent was required for use of anonymized data for research purposes.

Patients with end-stage renal disease undergoing chronic dialysis were excluded from this analysis because of continuous, circumferential full-thickness calcifications (ossifications) of the tibial arteries.^{12,15} Cases in which recent endovascular drug-eluting technology was used (balloons or stents) were likewise excluded to maintain uniformity in treatment methods and results.

Preoperative Assessment

All eligible patients had a preoperative evaluation that included measurements of the ankle-brachial index (ABI) and transcutaneous oxygen pressure (TcPO₂), duplex ultrasound, and either computed tomography angiography (CTA) or magnetic resonance angiography (MRA) of the ischemic limbs. Digital subtraction angiography with run-off analysis (adding retarded blush collateral sequences) was additionally performed preoperatively in cases showing difficult tibial or pedal vessel morphology (huge calcifications or blurry distal flow beyond long occlusions) or postoperatively in cases showing an arrested healing process. All angiographic data were analyzed for angiosome source arteries, foot arches, full-channel arterial connections, appended visible branches, and collateral pattern. Calcifications were evaluated using a semiquantitative scoring system^{12,15} as intermittent or moderate calcifications (<50% lesion length) vs severe (>50% lesion length) continuous calcifications.

All tissue defects were evaluated by a thorough clinical examination that included assessments of the surface, depth, and bone contact; bacteriological samples; and the Semmes-Weinstein monofilament neuropathic information.^{9,15} Full-color, high-resolution photography was performed in each case and at every evaluation during follow-up.

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Endovascular Interventions

All patients were taking aspirin (160 mg/d) or clopidogrel (75 mg/d) at least 72 hours before the procedure. Primary infrapopliteal angioplasty (intra- or extraluminal; concomitant or staged) was performed in each patient, with upstream dilations in the superficial femoral artery and popliteal artery as needed. In the majority of cases, the tibial and foot vessels were catheterized using a 0.014-inch hydrophilic guidewire (Terumo, Tokyo, Japan) with a stiff 4- or 5-F support catheter. Long inflations (2–3 minutes) of various types of conventional low-profile balloons with diameters between 1.5 and 2.5 mm were applied. Nitinol stents were placed in the tibial trunks only as bailout for flow-limiting dissections. Subintimal procedures were carried out using a previously reported protocol.^{16,17}

WTR was performed for each wound according to the direct angiosome source arteries or by exploiting connected foot arches, direct connections, or large (>1 mm) metatarsal collaterals with respect to the wound zone.^{4–7} In cases in which the WTR was technically unachievable, alternative collateral-sustained perfusion (WTRc) utilizing available medium-to-small collaterals (including the choke vessels) or cutaneous perforators toward the angiosomes of the wound zone was employed. When neither WTR nor WTRc was technically possible and surviving collaterals toward the wounds were scarce, arterial limb flow was restored using IR, without deliberate angiosomal or collateral orientation. For the latter cases, the most accessible or technically feasible infragenicular vessel and remaining random collaterals were reperfused using a compulsory limb-salvage endovascular strategy.

Follow-up

Follow-up visits were scheduled every week during the first month and every month thereafter. All revascularized limbs were appraised by periodic clinical and duplex scan evaluations, including ABI and TcPO₂ measurement. CTA or MRA was performed in patients who lacked tissue improvement or for those showing clinical, ABI, and/or duplex deterioration. All patients received team evaluations for further treatment.

Wounds

All wounds were treated using a standardized multidisciplinary approach. The following fast-track algorithm^{15–17} was applied, including expeditious debridement, foot compartment release, ischemic and neuropathic assessment, prompt revascularization, culture-based infection treatment, specific podiatric treatment with osteomyelitis excision, negative pressure wound closure devices, and specific off-loading shoes and casts.

All treated wounds were independently reviewed every week during the first month after revascularization and every month up to 1 year until complete healing and/or pertinent trends toward cicatrization were noted. Cases showing relapsing wounds after initial healing were excluded from further analysis.

Patients

From April 2009 to July 2017, 167 diabetic patients (mean age 72.8 years; 137 men) with limb-threatening neuroischemic foot wounds were scheduled for infragenicular endovascular treatment and enrolled in the registry. Twenty-seven patients received staged bilateral revascularizations for ulcers located on both limbs (194 limbs treated). More than two-thirds of the patients had been diagnosed with diabetes for at least 10 years. Concomitant latent or manifested cardiac disease was present in 137 (82%) of the patients, while 51 (31%) had variable degrees of cardiac insufficiency (Table 1). Multilevel inferior limb atherosclerotic disease was a dominant finding. Two or three concomitantly treated tibial and/or foot arteries were noted in about half of the cases. Different stages of perceivable peripheral neuropathy were noted in all treated limbs.

According to the TransAtlantic Inter-Society Consensus classification,^{11,12} 12 (6%) of 194 limbs had a majority of type B lesions, 41 (22%) had a preponderance of type C, and 133 (71%) showed greater numbers of extensive type D infrapopliteal lesions. Sixty (31%) wounds initially presented as UT grade 1 stage B–D, 87 (45%) as grade 2 stage B–D, and 47 (24%) as grade 3 stage B–D trophic lesions.

Outcomes and Definitions

For analysis, the patient cohort was stratified according to treatment mode. The primary outcomes were wound healing and mean time to healing in successfully revascularized patients. Secondary outcomes were primary and secondary patency, major adverse limb events (MALE), limb salvage, and amputation-free survival defined according to current reporting guidelines.^{11,12,15,18,19}

Technical success was defined as patent revascularization providing direct arterial flow from the aorta toward the pedal arches, without residual stenosis $\geq 50\%$. Patency and healing were assessed in all instances by clinical evaluation, duplex scan, and TcPO₂ measurements in a standardized fashion. For CLTI wounds spreading in the forefoot (involving the toes and the metatarsal extremities), WTR was successful if reperfusion was achieved via the dorsal foot bundle (anterior tibial and dorsalis pedis arteries) or via the plantar vessels (posterior tibial and plantar arteries) with or without participation of foot arches, metatarsal perforators, or diagonal arteries. With regard to heel ulcers, WTR was successful if the medial calcaneal branch

Table 1. Characteristics for All Diabetic Patients and Subgroups According to Treatment.^a

Characteristics	All Patients (n=167)	WTR (n=125)	No WTR (n=42)	p ^b
Age >70 y	100 (60)	72 (58)	28 (67)	0.667
Men	137 (82)	87 (70)	32 (76)	0.784
Hypertension	146 (87)	110 (88)	36 (85)	>0.99
Type I diabetes	33 (20)	24 (19)	9 (21)	0.828
Smoking	72 (43)	52 (42)	20 (48)	0.748
Coronary disease	137 (82)	99 (79)	38 (90)	0.694
Cardiac insufficiency (LVEF <30%)	51 (31)	38 (30)	13 (31)	>0.99
Chronic renal insufficiency	65 (38)	51 (41)	14 (33)	0.612
Hypercholesterolemia	123 (74)	90 (72)	33 (78)	>0.99
Cerebrovascular disease	38 (22)	29 (23)	9 (21)	0.854
Chronic obstructive pulmonary disease	50 (30)	35 (28)	15 (36)	0.582
Hypoalbuminemia	51 (31)	36 (29)	15 (36)	0.586
C-reactive protein	135 (81)	102 (82)	37 (78)	>0.99
Associated venous insufficiency	16 (9%)	13 (10%)	3 (7%)	0.764
Corticosteroid or immunomodulator therapy	18 (11)	14 (11)	4 (9)	>0.99
Bedridden	15 (9)	9 (7)	6 (14)	0.227

Abbreviations: LVEF, left ventricular ejection fraction; WTR, wound-targeted revascularization.

^aData are given as the number (percentage).

^bComparing the WTR and no WTR groups.

from the posterior tibial or the lateral calcaneal branch from the peroneal artery was successfully reperfused.

Clinical success was defined as an ABI increase ≥ 0.10 ,¹¹ TcPO₂ improved ≥ 20 mm Hg,^{15,19} and wound regeneration (complete or significant trend toward healing) that yielded improvement by at least 2 Rutherford categories.^{11,18} Minor amputation referred to tissue ablation of the toes or forefoot with respect to the calcaneal standing pylon.^{15,18} Limb salvage implied that there was no major amputation (calf or thigh) and that functional autonomy was regained (walking or standing).^{11,20}

Statistical Analysis

Continuous data are presented as the mean $\pm$ standard deviation; categorical data are given as the number (percentage). Characteristics of successfully treated patients were evaluated for any relationship to healing using the 2-tailed chi-square test. The Kaplan-Meier method was utilized to estimate the wound healing rate and the secondary outcomes, such as MALE, primary and secondary patency, limb salvage, and amputation-free survival, in successfully revascularized patients over time; the curves were compared using the log-rank test. The estimates are reported with the 95% confidence intervals (CI). The time-to-event data were analyzed using Cox proportional hazards regression; the outcomes are reported as the hazard ratios (HR) and 95% CI. A $p < 0.05$ was defined as statistically significant. All analyses were performed using the MedCalc (Ostend, Belgium) and Prism (GraphPad, La Jolla, CA, USA) statistical software packages.

Results

Immediate Outcomes

Reperfusion was successful in 176 (91%) of 194 limbs: 113 were successfully treated with WTR, 28 with WTRc following failure to open the angiosome source arteries, and 35 with non-topographic IR (Table 2). The global angiosome-oriented technical success (WTR and WTRc) was 73% (141/194).

None of the current endovascular techniques were successful in 18 limbs, mainly because of heavy calcified and impassable infragenicular occlusions; 9 ultimately had amputations, 5 underwent infragenicular bypasses, 3 had distal venous arterializations, and 1 was treated medically. These initial technical failures were excluded from follow-up analysis.

Approximately 20% of the femoropopliteal angioplasties were performed 1 to 2 weeks prior to the main BTK revascularizations due to renal nephropathy and chronic renal insufficiency. In the same setting, concomitant supra-genicular angioplasties were rarely associated with main BTK interventions in these patients. These staged angioplasties were performed in 8 (7%) limbs in the WTR group, 3 (11%) in the WTRc group, and 4 (11%) in the IR group. Negative pressure wound closure devices were employed in 124 (70%) cases.

Complications

The overall perioperative complication rate in successfully treated patients was 14% (25/176). Nine major complications

Table 2. Characteristics of Patients With Successfully Revascularized Limbs.^a

Characteristics	Total Revascularized (n=176)	WTR (n=113)	WTRc (n=28)	IR (n=35)	p ^b
Age >70 y	109 (62)	68 (60)	18 (64)	23 (66)	0.099
Men	123 (70)	81 (72)	19 (68)	23 (66)	0.092
Hypertension	153 (87)	97 (86)	25 (89)	31 (89)	0.023
Type I diabetes	32 (18)	19 (17)	5 (18)	8 (23)	0.443
Smoking	67 (38)	44 (39)	10 (36)	13 (37)	0.974
Coronary disease	153 (87)	98 (87)	25 (89)	30 (86)	0.012
Cardiac insufficiency (LVEF <30%)	51 (29)	29 (26)	8 (29)	14 (40)	0.499
Chronic renal insufficiency	74 (42)	42 (37)	12 (43)	20 (57)	0.432
Hypercholesterolemia	126 (72)	80 (71)	20 (71)	26 (74)	0.987
Cerebrovascular disease	36 (20)	24 (21)	6 (21)	6 (17)	0.905
Chronic obstructive pulmonary disease	47 (27)	29 (26)	8 (29)	10 (29)	0.951
Hypoalbuminemia	63 (36)	36 (32)	11 (39)	16 (46)	0.577
C-reactive protein	137 (78)	88 (78)	19 (68)	30 (86)	0.833
Associated venous insufficiency	17 (10)	12 (11)	3 (11)	4 (11)	0.992
Corticosteroid or immunomodulator therapy	15 (9)	10 (9)	3 (11)	2 (6)	0.793
Bedridden	19 (11)	12 (11)	4 (14)	3 (9)	0.807

Abbreviations: IR, indirect revascularization; LVEF, left ventricular ejection fraction; WTR, wound-targeted revascularization; WTRc, wound-targeted revascularization with collateral-sustained perfusion.

^aData are given as the number (percentage).

^bComparing the WTR, WTRc, and IR groups.

included 3 flow-limiting dissections, 1 early myocardial infarction, 2 cases of transitory renal insufficiency requiring temporary dialysis, and 3 groin hematomas requiring prompt surgical hemostasis. The 16 minor complications with limited clinical sequelae included 9 flow-restricting arterial or collateral perforations, 1 distal embolism resolved by aspiration, and 6 superficial groin hematomas that resolved spontaneously.

Wound Healing

The mean follow-up was 10.9 ± 0.7 months (range 3–12.5), during which 11 patients died (9 WTR, 2 WTRc, and 4 IR limbs) and 4 limbs (2 WTR, 1 WTRc, and 1 IR) were lost to follow-up before 12 months. Over 1 year, 102 (58%) of the 176 successfully treated limbs experienced wound healing: 79/113 (70%) in the WTR group, 15/28 (54%) in the WTRc group, and 7/35 (20%) in the IR group [$p=0.011$ among all groups or $p=0.494$ for WTR vs WTRc (HR 0.903, 95% CI 0.704 to 1.159), $p=0.026$ for WTR vs IR (HR 0.831, 95% CI 0.744 to 0.927), and $p=0.043$ for WTRc vs IR (HR 0.622, 95% CI 0.422 to 0.915)]. The mean increases in TcPO₂ were 26.9 ± 2.5 mm Hg (range 25–44), 25.1 ± 3.8 mm Hg (range 21–50), and 21 ± 2.3 mm Hg (range 21–30 mm Hg), respectively.

The mean time to healing was 6.8 ± 0.4 months in the WTR group, 7.9 ± 0.6 months in the WTRc group, and 9.8 ± 0.7 months in the IR group ($p=0.001$). Of the 102 initially healed wounds, relapses were noted in 18 (16%) WTR

limbs, 5 (18%) WTRc limbs, and 6 (17%) IR limbs. These iterative ulcerations appeared mainly between months 7 and 10 and were associated with either severe concomitant peripheral neuropathy or poor patient compliance (inadequate walking habits, poor diet, high hemoglobin A1c levels, or smoking). Only 12 of 18 WTR cases, 3 of 5 WTRc cases, and 5 of the 6 IR cases were associated with iterative severe hemodynamic disturbances (recurrent occlusions or >70% restenosis).

Wound healing estimates (Figure 1) were 79% (95% CI 70% to 85%) and 66% (95% CI 55% to 77%) at 3 and 6 months in the WTR group, 70% (95% CI 47% to 84%) and 57% (95% CI 32% to 75%) at 3 and 6 months in the WTRc group, and 47% (95% CI 30% to 62%) and 31% (95% CI 16% to 46%) in the IR group at the same time intervals.

A comparison of the 6-month Kaplan-Meier wound healing estimates between the WTR and WTRc groups was not significant (HR 0.67, 95% CI 0.315 to 1.464, $p=0.323$), but significant differences emerged when comparing the WTR (HR 0.25, 95% CI 0.133 to 0.475, $p<0.001$) and the WTRc groups (HR 0.47, 95% CI 0.245 to 0.912, $p=0.025$) with the IR group.

The risk factors associated with wound healing (Tables 3 and 4) were cardiac disease ($p<0.001$), the C-reactive protein level ($p<0.001$), long occlusions ($p<0.001$), severe calcification ($p<0.001$), incomplete or diseased foot arches ($p<0.001$), poor collateral foot appearances ($p<0.001$), and TASC (TransAtlantic Inter-Society Consensus) D lesions ($p<0.001$).

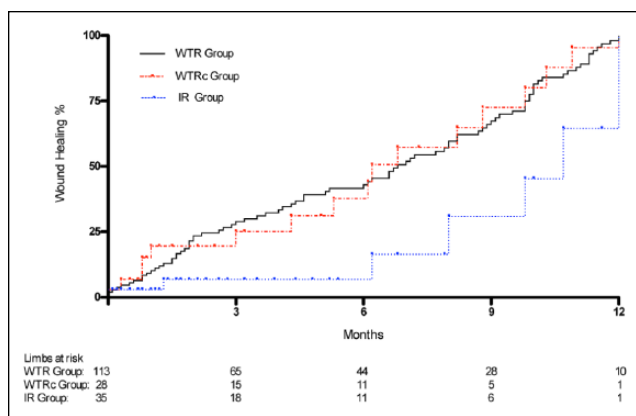


Figure 1. Kaplan-Meier estimates of the wound healing rates in successfully treated patients per treatment group at time points with at least 10 patients remaining. Healing rates were 66% and 62% in the wound-targeted revascularization (WTR) group at 6 and 12 months, 57% in the wound-targeted revascularization with collateral-sustained perfusion (WTRc) group at 6 months, and 31% in the indirect revascularization (IR) group at 6 months ($p=0.323$ for WTR vs WTRc, $p<0.001$ for WTR vs IR, and $p=0.025$ for WTRc vs IR).

Event Analysis in Successfully Treated Patients

Primary patency estimates were 90% (95% CI 82% to 94%) and 78% (95% CI 67% to 85%) at 3 and 6 months for the WTR group, 81% (95% CI 58% to 92%) and 76% (95% CI 52% to 89%) at 3 and 6 months for the WTRc group, and 78% (95% CI 58% to 89%) and 64% (95% CI 43% to 78%) at 3 and 6 months for the IR group ($p=0.458$). Secondary patency estimates were 94% (95% CI 87% to 97%) and 87% (95% CI 77% to 93%) at 3 and 6 months for the WTR group, 89% (95% CI 64% to 96%) for the WTRc group at 3 and 6 months, and 87% (95% CI 66% to 79%) and 75% (95% CI 49% to 88%) at 3 and 6 months for the IR group ($p=0.686$).

Rates of freedom from amputation (ie, limb salvage, Figure 2) were estimated as 91% (95% CI 86% to 96%) and 86% (95% CI 79% to 93%) at 3 and 6 months for the WTR group, 83% (95% CI 68% to 98%) and 61% (95% CI 33% to 89%) at 3 and 6 months for the WTRc group, and 79% (95% CI 64% to 94%) and 58% (95% CI 35% to 81%) at 3 and 6 months for the IR group. Comparison of the limb salvage estimates between the WTR and WTRc groups ($p=0.041$, HR 0.26, 95% CI 0.075 to 0.948) and the WTR vs IR groups ($p=0.003$, HR 5.37, 95% CI 1.758 to 16.41) were significant, but not between the WTRc and IR groups.

MALE estimates were 86% (95% CI 80% to 92%) and 77% (95% CI 69% to 85%) at 3 and 6 months for the WTR group, 71% (95% CI 53% to 89%) and 52% (95% CI 26% to 78%) at 3 and 6 months for the WTRc group, and 73% (95% CI 57% to 89%) and 42% (95% CI 20% to 64%) at 3 and 6 months for the IR group. Significant differences were apparent between the WTR and WTRc groups ($p=0.027$,

HR 0.32, 95% CI 0.120 to 0.882) and the WTR vs IR groups ($p=0.002$, HR 3.76, 95% CI 1.576 to 8.998) but not between the WTRc and IR groups.

Amputation-free survival (Figure 3) was not influenced by the revascularization strategy ($p=0.093$). Survival estimates were 96% (95% CI 89% to 98%) and 90% (95% CI 80% to 95%) at 3 and 6 months, respectively, in the WTR group, 88% (95% CI 62% to 96%) and 80% (95% CI 50% to 92%) in the WTRc group at 3 and 6 months, and 78% (95% CI 56% to 89%) in the IR group at 3 and 6 months.

Discussion

Contemporary literature still needs uniform consensus and standardized definitions about direct vs indirect types of revascularization in CLTI treatment.¹⁻³ In their original descriptions, Attinger et al⁴ and Taylor and Palmer⁷ identified the angiosome source arteries as main branches for perfusion of specific vascular territories. Under ischemic conditions, direct interangiosomal arterial-arterial connections (the foot arches, the metatarsal connections, and other large collaterals) have a pivotal role in direct flow compensation.^{4,7} The surrounding choke vessels, although initially labeled as indirect compensators,^{4,7} likewise supply perfusion between angiosomes.

Contemporary endovascular or surgical studies agree that direct revascularization mainly influences source artery flow.^{3,4,21-27} Some also include direct arterial-arterial metatarsal connections,^{4,5,8,28} patent foot arches,^{4,8,28} or surrounding large collaterals and runoff branches^{6,17,29} in the definition of wound-oriented revascularization while others do not.^{30,31} IR is represented in various ways in the literature, appearing as either angiosomal branch nonoriented revascularization^{21-29,32} or indirect reperfusion via the choke vessels toward specific foot zones.^{4,6} A classic example is represented by diabetic ischemic heel ulcers.^{17,25} This critical anatomical foot zone has terminal flow from only 2 isolated angiosome branches.^{4,7,8} The heel is also deprived of other arterial-arterial connections, collaterals, or important anterior tibial connections.^{4,7,8,33} All reperfusion attempts via the anterior foot circulation will indisputably be indirect and have only poor chances for promoting tissue healing, particularly in diabetic limbs.^{4,17,21-26}

Based on previous assumptions,^{4-8,21-29} the present study proposes a wider interpretation of direct revascularization as WTR. WTR expresses an intentional flow reconstruction through available angiosomal pedicles, arterial-arterial connections, permeable arches, and accessible foot collaterals (WTRc). This strategy includes the choke vessels and the cutaneous perforators as directed branches down to specific foot wounds in ischemic territories.^{8,34} IR, on the other hand, involves compulsory or nontopographic use of persisting arterial branches directed toward the globally ischemic foot.

Table 3. Comparison of Clinical Features Among Treatment Groups for Successfully Treated Limbs With Wound Healing.^a

Characteristics	WTR (n=79/113)	WTRc (n=15/28)	IR (n=8/35)	p ^b
Age >70 y	38/68 (56)	8/18 (44)	7/23 (30)	0.10
Men	55/81 (68)	12/19 (73)	8/23 (35)	0.066
Hypertension	68/97 (70)	14/25 (56)	8/31 (26)	0.090
Type I diabetes	8/19 (42)	3/5 (60)	2/8 (25)	0.448
Type II diabetes	48/63 (76)	8/15 (53)	4/13 (31)	0.124
Other forms of diabetes	23/31 (74)	4/8 (50)	2/14 (14)	0.071
Smoking	20/44 (45)	3/10 (30)	5/13 (38)	0.646
Coronary disease	71/98 (72)	13/25 (52)	8/30 (27)	<0.001
Cardiac insufficiency (LVEF <30%)	10/29 (34)	2/8 (25)	4/14 (29)	0.847
Chronic renal insufficiency	15/42 (36)	3/12 (25)	4/20 (20)	0.416
Hypercholesterolemia	52/80 (65)	8/20 (40)	8/26 (31)	0.074
Cerebrovascular disease	11/24 (46)	2/6 (33)	3/6 (50)	0.821
Chronic obstructive pulmonary disease	14/29 (48)	4/8 (50)	4/10 (40)	0.885
Hypoalbuminemia	12/36 (33)	3/11 (27)	3/16 (19)	0.558
C-reactive protein	66/88 (75)	7/19 (37)	7/30 (23)	<0.001
Associated venous insufficiency	7/12 (58)	2/3 (67)	1/4 (25)	0.445
Corticosteroid or immunomodulator therapy	4/10 (40)	1/3 (33)	0/2	0.549
Bedridden	6/12 (50)	1/4 (25)	1/3 (33)	0.644

Abbreviations: IR, indirect revascularization; LVEF, left ventricular ejection fraction; WTR, wound-targeted revascularization; WTRc, wound-targeted revascularization with collateral-sustained perfusion.

^aData are given as the number (percentage).

^bComparing the WTR, WTRc, and IR groups.

Table 4. Comparison of Procedure Details Among Treatment Groups for Successfully Treated Limbs With Wound Healing.^a

Characteristics	WTR (n=79/113)	WTRc (n=15/28)	IR (n=8/35)	p ^b
CTO >15 cm	59/70 (84)	9/16 (56)	1/21 (5)	<0.001
Severe calcifications ^c	41/61 (67)	6/15 (40)	2/27 (7)	<0.001
Tibial trunks targeted				
1	44/60 (73)	8/14 (57)	5/26 (19)	0.013
2	28/42 (67)	6/11 (55)	2/9 (22)	0.374
3	7/11 (64)	1/3 (33)	0/0	>0.990
Diseased or incomplete foot arches	28/42 (67)	6/13 (46)	2/19 (11)	<0.001
Globally inadequate foot collateral reserve	70/82 (85)	12/20 (60)	3/23 (13)	<0.001
Patent tibial trunks post PTA				
3	8/9 (89)	0/0	0/0	—
2	24/32 (75)	5/8 (56)	0/0	—
1	38/41 (93)	5/8 (62)	7/21 (33)	0.100
Dominant TASC lesion				
B	6/8 (75)	0/0	0/0	—
C	18/24 (75)	4/6 (67)	1/6 (17)	0.229
D	55/81 (68)	8/18 (44)	7/29 (24)	<0.001
Tibial artery diameter <3 mm	10/16 (63)	3/5 (60)	1/7 (14)	0.092
Previous infrapopliteal PTA	18/23 (78)	4/6 (67)	1/6 (17)	0.069
Angiographic anatomic variations	5/10 (50)	1/3 (33)	0/3	0.288

Abbreviations: CTO, chronic total occlusion; IR, indirect revascularization; PTA, percutaneous transluminal angioplasty; TASC, TransAtlantic Inter-Society Consensus; WTR, wound-targeted revascularization; WTRc, wound-targeted revascularization with collateral-sustained perfusion.

^aData are given as the number (percentage).

^bComparing the WTR, WTRc, and IR groups.

^cDefined as calcium deposits covering >50% of the lesion length.

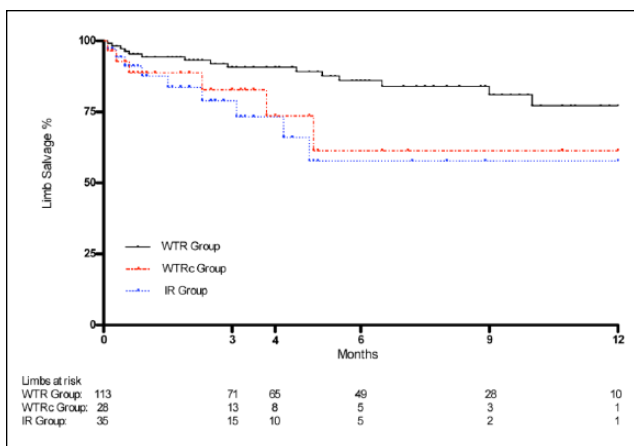


Figure 2. Kaplan-Meier estimates of the limb salvage rates in successfully treated patients per treatment group at time points with at least 10 patients remaining. Limb salvage rates were 91% and 86% in the wound-targeted revascularization (WTR) group at 3 and 6 months, 83% and 61% in the wound-targeted revascularization with collateral-sustained perfusion (WTRc) group at 3 and 6 months, and 73% in the indirect revascularization (IR) group at 4 months ($p=0.041$ for WTR vs WTRc, $p=0.003$ for WTR vs IR, and $p=0.695$ for WTRc vs IR).

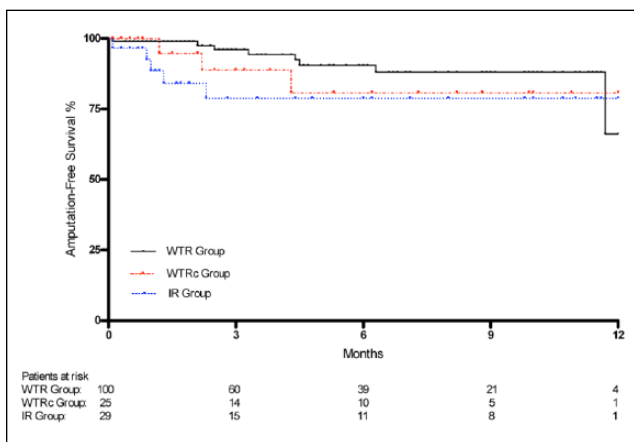


Figure 3. Kaplan-Meier estimates of the amputation-free survival rates in successfully treated patients per treatment group at time points with at least 10 patients remaining. Survival estimates at 3 and 6 months were 96% and 90%, respectively, in the WTR group, 88% and 80% in the WTRc group, and 78% at both times in the IR group. IR, indirect revascularization; WTR, wound-targeted revascularization; WTRc, wound-targeted revascularization with collateral-sustained perfusion.

Recent publications highlight the potential benefit of direct revascularization in CLTI wound healing, particularly the use of endovascular techniques.^{1,2,35} These applications seem enhanced when dealing with diabetic patients.^{17,21,34,36} However, purely diabetic CLTI studies comparing direct vs indirect revascularization are quite rare and generally

retrospective,^{1,35} which makes the present prospective, diabetic CLTI registry more distinct. In a retrospective study of 70 diabetic patients, Jeon et al³⁷ observed a significant difference in healing (87% vs 47%, $p<0.05$) in the direct revascularization or angiosome-oriented subgroup vs IR interventions. Similarly, Khor et al³⁶ reviewed the literature on 280 diabetic subjects with critical limb ischemia treated by direct vs indirect revascularization strategy, finding not only better wound healing outcomes but also a nearly 2-fold increase in the probability of wound healing within 12 months (HR 1.97, 95% CI 1.34 to 2.90) for direct revascularization.

It is known that the ischemic diabetic foot syndrome hides specific collateral destruction inflicted by CLTI.^{8,17,34-36} In this context, direct revascularization as a primary treatment strategy seems to hold even more potential for wound healing.^{17,25,33,34,38} However, according to Kret et al²⁹ and other data from a recent systematic review and meta-analysis,³⁹ the residual runoff in the critical diabetic foot may not follow the classical angiosome model. Therefore, the application of WTR to maximally utilize all surviving collaterals with topographic weight may gain in interest.⁸ This documented diabetic foot collateral decay^{33,38} appears proportional to the longevity and severity of individual hyperglycemic disorders.^{17,38,40}

Two prospective series^{23,26} also noted improved healing results for intentional direct revascularization but no significant difference in limb salvage and amputation-free survival between direct vs indirect revascularization groups. Similar results for WTR and direct revascularization came from large population meta-analyses^{34,41} and from retrospective^{2,24,29,36} and prospective^{23,26} studies. These observations seem to match our preliminary findings of shorter mean time to healing and better outcomes for angiosome-guided angioplasties. Limb salvage and MALE were, however, not uniformly improved by topographic revascularization, with a significant benefit for WTR in only some comparisons. Furthermore, there were no improvements concerning reinterventions (secondary patency) or survival among groups.

Are all foot collaterals (from broad arterial-arterial connections to small choke vessels) similarly involved in direct^{5,8,28,34} vs indirect^{4,6} angiosomal compensation? Table 4 shows a clear difference in healing among the 3 groups following specific angiographic features, which supports the fact that different types of collaterals have different hemodynamic roles in tissue regeneration.^{5,8,17,42} A few types of interangiosomal connections have been described, starting from tiny choke vessels to the small-to-large visible collaterals, cutaneous perforators, and broader arterial-arterial connections.^{4,7,8,42-44} All these structures seem harmoniously ranked in distinct levels of limb perfusion.^{8,34,42} Different sizes and numbers of the inferior limb cutaneous collaterals, or “skin module perforators,”⁴⁴ vary between

and within each source artery.^{7,44} It becomes evident that not all collaterals are able to share the same capacity, flow, and hemodynamic function during CLTI progression,^{34,42,43} particularly in diabetic patients.^{17,33,34,38} From a straight hemodynamic perspective, Summers et al⁴⁵ documented in normal subjects that about “16 collaterals with a 0.25-cm diameter may equal 625 collaterals with 0.1-cm diameter” and compensate for “an unobstructed artery of 0.5 cm diameter.” This observation may also explain why a few large collaterals appear more efficient in CLTI flow redistribution than hundreds of small collaterals and other interangiosomal choke vessels during similar ischemic threats.^{8,44,45} The present study sustains this hypothesis by reporting significant variations between WTR/IR and WTRc/IR groups in terms of healing and limb preservation.

Aiming to standardize different individual collateral patterns, a few classification systems have been proposed in the contemporary literature.^{4,8,42,45} One of these is a 6-level digressive inferior limb arterial ramification scale, including the angiosomal, the appended collateral, and the choke vessels arrangements.^{8,34} As for direct vs indirect revascularization definitions, this research also highlights the need for uniform “collateral” and “source artery” reporting standards,^{8,46} particularly for current CLTI revascularization.⁴⁶ Forthcoming homogeneous and comparable results may probably elucidate several of the discrepancies reported in healing and limb salvage outcomes.^{21–28,30,31,34,35,38}

To the best of our knowledge, this prospective registry is distinctive owing to its homogeneous CLTI population with diabetes, neuroischemic wounds, and Rutherford category-5 ischemia. By choosing sequential approaches from WTR to IR according to technical feasibility, more difficult atherosclerotic patterns with a higher burden of occlusive disease would have been expected in the IR group. Yet, with one exception (concomitant cardiac disease), no significant differences among the groups were detected.

Consistent with other publications in this field,^{1–3,23,24,26–29} the present study also indicates that indirect wound revascularization still has a role in limb salvage. Even though tissue recovery is slower and may increase wound exposure to bacterial and mechanical jeopardy, IR appears to produce degrees of tissue regeneration and finally limb preservation.^{1–3,23,24,34,36} Non-wound-oriented revascularization should be considered as a bailout if intentional WTR and WTRc prove technically infeasible.^{1–3,34,35,39}

Limitations

The present research was affected by the relatively small number of patients available for the analysis and the considerable loss to follow-up. The patients were enrolled over an 8-year period, so the clinical results might have been influenced by the evolving skill of the vascular interventionists

and other health professionals involved in the diabetic foot team and by the technological advances in equipment.

Inherent restrictions in interpretation of standard DSA hinder evaluation of the distal foot collaterals, particularly in collaterally deprived CLTI subjects, as well as diabetic and renal patients.^{17,33,34,38,40,43} In these cases scarce “dormant” or “latent” foot collaterals distal to long and highly calcified tibial occlusions may foster suboptimal interpretation.⁴⁷

It should also be noted that about a third of cases enrolled in this study had a distal “low-flow” limb owing to severe cardiac insufficiency, which may have added hurdles in precisely evaluating small arterial branches.

According to contemporary observation,^{19,47} DSA still represents a purely luminographic imaging modality that is impacted by the individual hemodynamic situation of the patient and the position of the sheath.⁴⁷ Perfusion iconography based on flow-contrast technology can just barely depict tiny circulatory changes inside the severely diseased diabetic ischemic foot.^{8,19,34,40,47}

Conclusion

Wound healing and the mean time to healing in CLTI diabetic patients appeared to be improved by intentional WTR, though there was no uniform benefit for MALE, limb preservation, or survival between the topographic and non-topographic groups. IR still represents an alternative for limb salvage in cases in which angiosome-guided revascularization fails.

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