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# Applicability of Intentional Topographic Revascularization Following the Angiosome Model in Patients with Chronic Limb-Threatening Ischemia: From Theory, to Current Clinical Challenges

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## Abstract

Since its first description almost four decades ago in the plastic surgery field, the angiosome theory has shown encouraging clinical success in Chronic Limb-Threatening Ischemia (CLTI) revascularization in recent years. Gradual scientific knowledge and evidence-based feedback are necessary to assess its usefulness and to overcome various challenges lingering in its practical application at the patient's bedside. Despite the increasing number of publications in recent years indicating its acceptable suitability in clinical practice, only a few provide conspicuous information regarding the applicability of angiosome-guided Direct Revascularization (DR) compared with the analysis of hurdles in the vascular approach, regardless of its clinical results. The current review aimed to provide an updated interpretation of DR applicability rates in daily practice, delineated through tangible assessments of feasibility, clinical match, and technical success (as previously mentioned). This analysis considered the applicability of DR, Indirect Revascularization *via* collaterals, (IRc), and "Wound-Targeted Revascularization" (WTR) within the broader perspective of "Intentional Topographic Revascularization" (ITR) in patients with CLTI foot. ITR affords a novel conceptualization of regional foot reperfusion *via* deliberate anatomical and functional orientation of the foot arterial flow to the ischemic zones (owing specific pedal arteries and regional collaterals). The analysis of data revealed significant differences in the current clinical definitions, interpretation, and application methods of TR. Inconsistent views on DR were also observed in the context of "wound-dependent" localization and the identification of the most suitable target foot artery for treatment. Unfortunately, a standardized definition of angiosome-oriented DR, IR, IRc, and WTR has not been established. Owing to the lack of a universally accepted definition and unified anatomical and functional foot arterial occlusive disease stratification, evidence supporting the applicability of ITR (by all its variants) is still awaited.

**Keywords: Chronic limb-threatening ischemia; Angioplasty; Atherosclerosis; Angiosome; Pedal arteries; Collateral circulation; Diabetic foot; Critical limb ischemia; Direct revascularization; Wound-targeted revascularization**

## Abbreviations

AG: Angiosomal; AT: Anterior Tibial; BTA: Below-The-Ankle; CLI: Critical Limb Ischemia; CLTI: Chronic Limb-Threatening Ischemia; DPN: Diabetic Peripheral Neuropathy; DR: Direct Revascularization; IR: Indirect Revascularization; IRc: Indirect Revascularization *via* collaterals; GVG: Global Vascular Guidelines; PT: Posterior Tibial; TAP: Target Artery Path; ITR: Intentional Topographic Revascularization; WIfI: Wound, Ischemia, and foot Infection classification; WDR: Wound-Directed Revascularization; WIR: Wound Indifferent Revascularization; WTR: Wound-Targeted Revascularization; WTRc: Wound-Targeted Revascularization *via* collaterals

## Introduction

Similar to any groundbreaking concept that requires gradual scientific interpretation, knowledge, and practical feedback; various challenges may persist in its current application. This

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holds true for Intentional Topographic Revascularization (ITR) in the treatment of ischemic foot wounds. This approach can be defined as intentional orientation of the revascularized blood flow toward the ischemic wound territory using all accessible arterial conduits (from the pedal trunks, the foot arches, to the large and small collaterals and their important connections). This approach can be also clinically formulated by employing "Angiosomal (AG)-guided reperfusion" through a specific "source artery," by utilizing characteristic regional foot collaterals, or by employing both methods [1-8]. This intentional approach finally encourages the nourishment of the targeted ischemic tissue, by joining previous "direct" or "indirect" flow anatomical connotations [1-6,9] to the functional aspects of collateral interconnections [7,10].

When analyzing various nomenclatures, interpretations, and applications from a wide range of studies investigating Chronic Limb-Threatening Ischemia (CLTI), [10] the purposeful restoration of blood flow to the wound zone (ITR) is often perceived as Direct Revascularization (DR), "Wound Directed Revascularization" (WDR), Indirect Revascularization *via* collaterals, (IRc), or "Wound-Targeted Revascularization" (WTR) [7] strategies. Despite the positive reports on tissue recovery and limb salvage results linked to ITR in the last decade [1-8], issues related to the current feasibility and technical success of this strategy in CLTI persist [9].

To date, the assessment of ITR suitability, indications, and management (regardless of the clinical results) relies predominantly on non-standardized observations [1-12]. As contemporary publications essentially focus on examining the specific ITR clinical outcomes, [1-8,11-14] there is a paucity of information concerning its practical feasibility and technical workability in routine clinical practice.

This mini review aimed to explore the current applicability of ITR (and the associated designations) in daily clinical practice. It also aimed to determine the interrelations between the characteristics of minimally ischemic or neuroischemic foot wounds, their specific locations on the foot, and the distribution of arterial flow in the region. This investigation corresponds to the anatomical AG and collateral assignments for Below-The-Ankle (BTA) arterial vasculature.

## Materials and Methods

A comprehensive review of literature spanning from 2006 to 2023, related to Critical Limb Ischemia (CLI) and CLTI, was conducted to assess the current feasibility and technical success of angiosome-guided Direct Revascularization (DR), Indirect Revascularization (IR), [1-6,11-15] Wound Targeted Revascularization (WTR), and Wound Targeted Revascularization *via* collaterals (WTRc) [7]. These terms were analyzed within a broader context of ITR perspective for treatment. Owing to the absence of universally standardized definitions and interpretations in the literature for these revascularization approaches, their clinical applicability (feasibility and technical success) was documented based on eventually specific mentions.

### Publications screening

A dual search was conducted in the Medline database, and unrestricted online data examinations were performed to identify all publications related to angiosome-guided DR/IR and its specific suitability in CLTI feet, over the last two decades. Twenty-one keywords were used during the database search including: "angiosome," "source artery" direct/indirect revascularization, "topographic perfusion," "functional angiosome," "wound directed," "wound targeted revascularization," applicability, feasibility, technical success, pedal arteries, foot arches, below-the-ankle angioplasty, collateral circulation, diabetic foot, etc. No restrictions were imposed on the study design and language.

### Data collection

Considering the significant heterogeneity observed in the profiles, study design, and diagnostic and treatment protocols mentioned in the selected studies, notable discrepancies were observed, especially in the definition and interpretation of DR/IR. Specific mentions of the feasibility and applicability of ITR (and its related terms) were limited, and the prospective data were scarce. Due to the absence of randomized and controlled data supporting an optimal level of evidence, the "Grading of Recommendations Assessment, Development, and Evaluation" was not employed in this succinct review analysis.

### Primary endpoint

In this mini review, we investigated the overall applicability of ITR in CLTI patients. We also evaluated the specific suitability, clinical alignment, and technical success of "AG-guided reperfusion" using various revascularization strategies (DR, IRc, WTR, and WTRc *vs.* IR), regardless of whether the clinical success results were mentioned.

The collected data were analyzed based on the contemporary research findings on DR/IR strategies and the recommendations outlined in the Global Vascular Guidelines [10]. Specific details, if mentioned, such as wound characteristics and topography, potential AG orientation, related Target Artery Path (TAP) [10] selection, and clinical correspondences for revascularization were also documented.

The authors did not intend to conduct a systematic review with independent statistical interpretation or an original meta-analysis. This decision was influenced by markedly reduced number of matching articles for analysis, aleatory applicability mentions and the low level of evidence that currently characterizes this topic.

## Results

### Preliminary observation

Despite the extensive number of initially detected publications (total: 1,844 papers, including 5 meta-analyses) indirectly suggesting a regular applicability level of ITR, only a few of these papers provided conspicuous information about specific DR, IRc, and WTR workability in current vascular practice (Figure 1).

Initially, this review showed a significant difference in the current clinical definitions, interpretation, and application methods of DR/IR. This primary finding further enhanced the inherent disparities related to the inclusion criteria, clinical results, and conclusions. The crucial concepts of "applicability," "feasibility," and "technical relevance" for DR were explicitly underscored, exposing divergent interpretations among distinct groups.

Different perceptions regarding DR, IRc, WTR, and IR were also observed in the context of "wound-dependent" localization [12-16] and the selection of the most suitable target foot artery for treatment [1-9,11-16]. The decisions made by local teams, whether associated with DR or the IRc subgroup, exhibited variations in defining the type of associated collaterals, eventual "true" arterial-arterial communicants [7], the interconnections of foot arches [7,17], and the sustained regional collateral run-off (IRc) [4,11,18] linked, or not to

**Table 1:** Capture: Various denominations including clinical applicability, feasibility, and analogous common practicality and technical success of DR, IRc, WTR, WTRc (inside the broader ITR perspective) in current CLTI treatment.

| Author | Year | Design | n | Applicability & Feasibility DR/IR | | Practicality &Technical success | | Clinical *vs.* Angiographical match |
|---|---|---|---|---|---|---|---|---|
| | | | | Endovascular technique | Bypass | Endovascular technique | Bypass | |
| Neville et al. [1] | 2009 | Retrospective | 52 | - | - | - | DR=51%<br>IR=49% | Regular clinical & angiographic correspondence |
| Iida et al. [2] | 2012 | Retrospective | 369 | - | DR=54%<br>IR=46% | - | Regular clinical & angiographic correspondence | - |
| Söderström et al. [25] | 2013 | Retrospective | 250 | - | - | DR=48%<br>IR=52% | - | - |
| Aerden et al. [16] | 2014 | Prospective | 185 | - | - | - | - | 345 wounds:<br>Toes=45%<br>Mitigate=18%<br>Unfit=9% |
| Bosanquet et al. [43] | 2014 | Review & Meta-analysis | 1868 | - | DR=47%-80% | | - | - |
| Acin F et al. [24] | 2014 | Retrospective | 101 | - | DR=54.1%<br>IR=20%<br>IRc=25.9% | - | - | - |
| Kretet al. (27) | 2014 | Retrospective | 106 | - | ATa= 27%<br>DP=39%<br>PTa=29% | - | DR=62%<br>IR=38% | Matching data:<br>1 AG= 36%<br>2 AG=56%<br>good arch= 33% |
| Špillerová et al. [15] | 2017 | Retrospective | 658 | 66.40% | 33.60% | Definition A=56%<br>Definition B=31% | | 1 AG=24%<br>>1 AG=76% |
| Elbadawy et al. [26] | 2018 | Prospective | 212 | DR=55%<br>IR=44.8% | - | ATa=43%<br>PTa=36%<br>PA=21% | | Regular clinical & angiographic correspondence |
| Stimpson et al. [28] | 2019 | Review & Meta-analysis | 2998 | - | - | DR=53%<br>IR=47% | DR=56%<br>IR=44% | - |
| Ceun et al. [19] | 2020 | Retrospective | 153 | DR=34%<br>IR=66% | - | DR+IR=81% | - | - |
| Alexandrescu et al. [7] | 2020 | Prospective | 167 | WTR=64%<br>WTRc=16%<br>IR=20% | - | WTR+WTRc=73% | - | - |
| Kim et al. [23] | 2021 | Review & Meta-analysis | 4252 | - | DR=52%<br>IR=41%<br>IRc=6% | | - | - |
| Bekeny et al. [18] | 2021 | Retrospective | 105 | DR=33%<br>IRc=36%<br>IR=31% | - | - | - | Regular clinical & angiographic correspondence |
| Alexandrescu et al. [17] | 2022 | Retrospective | 336 | TAAP lesions:<br>Grade A=95%<br>Grade B=88%<br>Grade C=70%<br>Grade D=12% | - | - | - | - |
| Špillerová et al. [29] | 2022 | Retrospective | 161 | 1 AG=69.2%<br>2 AG=86.7%<br>3 AG=85.7%<br>4 AG=25%<br>5 AG=0% | - | - | - | 1 AG=24%<br>>1 AG=76% |
| Hou et al. [45] | 2022 | Retrospective | 112 | - | | DR=63%<br>IR=37% | - | - |

AG: Angiosome; Ata: Anterior Tibial Artery; DR: Direct Revascularization; DP: Dorsalis Pedis; IR: Indirect Revascularization; IRc: Indirect Revascularization *via* Collaterals; PA: Peroneal Artery; PTa: Posterior Tibial Artery; WTR: Wound Targeted Revascularization; WTRc: Wound Targeted Revascularization *via* Collaterals

the main angiosomal source arteries [1-8,11-15]. With rare exceptions [7,17], none of the selected research articles added in their protocols or discussion the significance of the "functional angiosome" and its collateral network in defining the "anatomical DR, IRc, and WTR" entities.

However, following the comprehensive consolidation of data and in the absence of standardized definitions, some similarities emerged between DR, "Wound Directed Revascularization" (WDR), IRc and WTR protocols interpretations. Despite distinct DR/IR analyses, several analogies in basic ITR exposition were equally observed, all of which were further scrutinized from an "applicability" perspective.

## General concerns

The majority of gathered data were obtained from single-center studies with a small sample size. Consequently, the absence of a multicentric and controlled database poses a limitation for conducting a comprehensive analysis. Of the 1,844 relevant publications found (Figure 1), studies with inadequate data; duplicate studies; studies without clear protocols, endpoints, and indications; studies related to plastic reconstructive surgery, studies with no available English texts, conference papers, book chapters, and monographs were excluded. Following these exclusions, only 118 publications were deemed eligible for further analysis. Studies that analyzed the DR/IR clinical outcomes but failed to mention the applicability and/or technical success of its were also removed. Hence, 17 studies finally matched with the purpose of this research and provided a form of information for the primary endpoint were analyzed (Figure 1 and Table 1), including 3 prospective studies [7,16] and 3 meta-analysis.

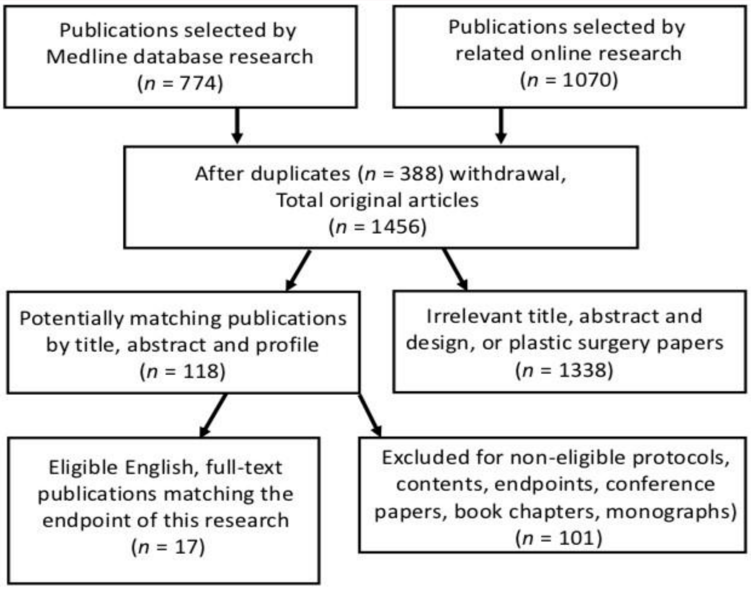


**Figure 1:** A simplified flow-chart representation of the study selection process:
Phase I: Identification of all publication fitting the keywords of this research.
Phase II: Duplicates retrieval and regrouping of unique articles data.
Phase III: Withdrawal of irrelevant papers by title, abstract, design of study, plastic surgery research, those with no available English texts, conference papers, book chapters, and final identification of 118 papers for study.
Phase IV: Specific analysis of topographic revascularization applicability in the remaining 17 studies, further detailed in Table 1.

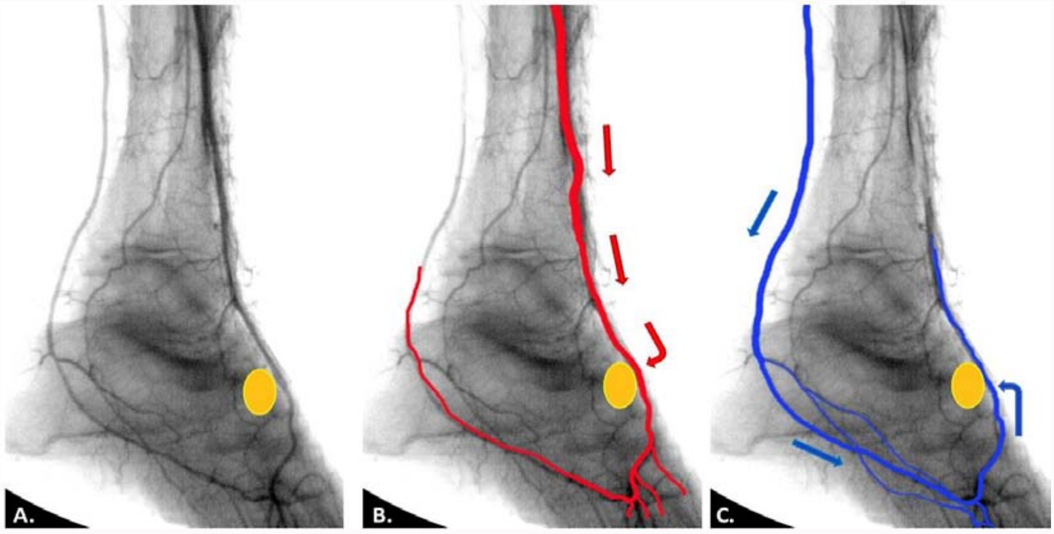


**Figure 2:** A schematic illustration of two distinct scenarios concerning angiosome-guided foot Intentional Topographic Revascularization (ITR). This can be applied either by Direct Revascularization (DR) or by analogous Wound Targeted Revascularization (WTR). It concerns a CLTI (Rutherford 5) foot presentation, showing a “W=grade 2”, “I=grade 3”, and “fI=grade 2” (WIfI 232-stage 2) ischemic and unique dorsal foot ulceration.
A) Shows the referent angiographic image; it gathers the Anterior Tibial (AT), the dorsalis pedis, the Posterior Tibial (PT) the plantar arteries, and the peroneal artery, all permeable foot arteries. The foot ulcer (in yellow) is conventionally designated in the dorsal foot’s region in this demonstrative example, as to evaluate all eventual ITR options.
B) Stands for the first ITR scenario: since the PT appears occluded, achievement of ITR implies specific antegrade revascularization of the AT and the dorsalis pedis angiosome, as anatomical direct “source artery” revascularization (DR), by following the red arrows to the wound zone (the dorsal foot angiosomes territory).
C) Sustains the second ITR scenario; in the context of AT occlusion and impossible antegrade (dorsalis pedis) reperfusion, the achievement of ITR is still feasible. It implies a specific WTR reflow of the dorsalis pedis this time in a specific retrograde manner, *via* the permeable PT, further following available plantar arteries, and additionally linked to permeable foot arches. All these succeeding levels of available arterial-arterial “high flow”, and same-caliber, “true” collaterals afford parallel hemodynamic compensatory capabilities to WTR and ITR. These large branches were labeled as “true collaterals” within the wider, (recently described) “functional angiosome” concept. This latest, may recruit the compensatory flow from one, or many neighboring anatomical “sources arteries” in a “*antegrade*”, or “*retrograde*”, “*direct*”, or “*indirect*” fashion, as long as this flow is shared *via* the “true” collaterals.
In the present Image C case, the plantar arteries *via* the permeable foot arches and available large, “true collaterals” (blue arrows), specifically afford dual anatomical and functional retrograde and redirected flow. This scenario unveils the wider apprehension and suitability that ITR may afford, by assembling various, yet analogous flow-directed strategies. Many of these methods (such as “Wound Directed Revascularization” (WDR), IRc, together with WTR, or WTRc), all theoretically appear as fundamentally opposed to current IR, or to “Wound Indifferent Revascularization” (WIR), despite their heterogeneous labeling.

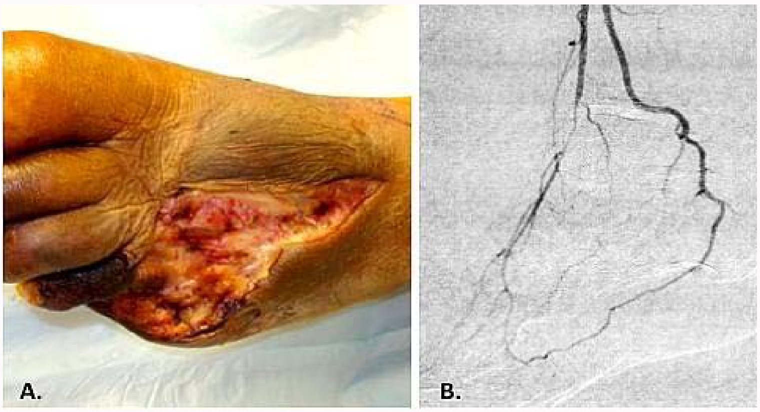


**Figure 3:** An example of ITR concerning a dorsal foot wound located in the Dorsalis Pedis angiosome (Image A).
ITR can be applied either by Direct Revascularization (DR) by treating the Dorsalis Pedis sub-occlusive lesion (Image B), or by Wound Targeted Revascularization (WTR) *via* the plantar arteries, by reestablishing an equivalent retrograde flow, since the foot arches "true collaterals" are permeable in this case.

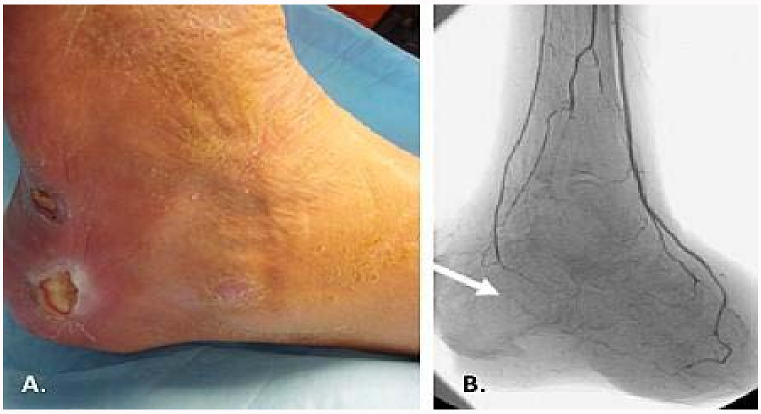


**Figure 4:** Another example for applying the ITR strategy this time for two wounds concerning the Posterior Tibial and the peroneal angiosomes (Image A). ITR can be completed in an antegrade fashion (*via* the posterior tibial, and the plantar arteries (if technically feasible), or by retrograde reflow *via* the Anterior Tibial assisted by large communicants, or "true collaterals" and associating the foot arches (Image B). In both cases, the "functional" flow to the targeted angiosomes can be achieved either by "anatomically" labeled "DR (*via* the Posterior Tibial and Peroneal arteries), or by comparable hemodynamic parameters resulting from "indirect revascularization *via* collaterals" (IRc, or WTRc).

## Preoperative assessment

Although several authors have questioned the relevance of clinical evaluation and the applicability of AG-oriented genuine DR in CLTI foot wounds [9,14,16], others advocate for a comprehensive vascular examination when planning DR, WDR, IRc, and WTR. This recommendation is also applicable in patients with intricate and/or overlapping tissue defects. The suggested approach involves the reperfusion of any (at least one) of the involved foot AGs [2,6,7,15,17,19]. The potential involvement of parallel non-ischemic tissue ulceration factors (such as infection, renal insufficiency, hypoalbuminemia, diabetes with associated peripheral neuropathy, and elevated levels of CRP) [10,20] could play a significant role in the assessment of AG applicability. These factors should be considered and documented in the current preoperative feasibility assessment.

Technical success is frequently equated with "feasibility" and "practicality" in the context of DR/IR strategies (Table 1). Although the topic appears infrequently discussed in contemporary literature [21-28], Neville et al. [1] reported a technical achievement rate of 51% for bypass DR, which was treated as an independent variable. In Acin et al. study [24] on EVT, the success rates were 54% for DR and 26% for IRc. Söderström et al. [25] documented a 48% success rate for DR. In our recent study, success rates were found to be 58% for WTR and 16% for WTRc [7]. Elbadawy et al. [26] study reported a 55% success rate for DR. Cheun et al. [19] noted an 81% success rate for DR. Lastly, Jeon et al. [8] observed a 91% success rate for DR.

In a recent, thorough review and meta-analysis conducted by Kim et al. [23] including 4,252 examined limbs, 53% of the DR procedures were successfully implemented. In a retrospective EVT study conducted by Bekeny et al. [18] involving 105 patients, 33%, 36%, and 31% of them were successfully treated with DR, IRc, and IR, respectively. In this study, the technical success of DR implied the restoration of the flow directly to the main AG source artery. IRc involved reperfusion *via* the adjacent source arteries connected by arterial-arterial connections and significant collaterals. By contrast, the use of IR did not restore the flow to deliberate tissue regions. Notably, no applicability discrepancies were observed between wound location and the target vessel selected.

In a parallel retrospective study by Spillerova et al. [29] involving 161 patients, the authors established peculiar clinical correlations, indicating that one angiosome was involved in 24.0% of cases, resulting in successful DR in 60.9% of limbs. In wounds associated with many angiosomes, the success of DR varied based on the number

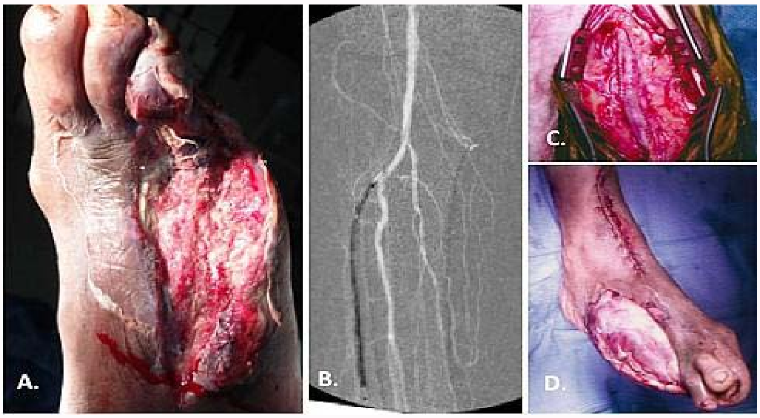


**Figure 5:** An example of hybrid (endovascular and surgical) angiosome-guided ITR for a complex wound that concerned the Dorsalis Pedis angiosome (A). A proximal Anterior Tibial artery angioplasty (B), was associating to a Dorsalis Pedis surgical endarterectomy plus venous patch (C), addressing an initially highly calcific occlusion, impassable by EVT. The early postoperative result is showed in D.

of angiosomes involved. Successful DR was achieved in 69.2% of wounds involving one angiosome, 86.7% of wounds involving two angiosomes, 85.7% of wounds involving three angiosomes, and 25.0% of wounds involving four angiosomes. Intriguingly, revascularization success was not quantifiable in wounds involving over five angiosomes [29].

In another 565-limb retrospective analysis of the same authors [15] the clinical implications of DR resulting from the various DR definitions were evaluated. The authors emphasized the potential dissimilarities that this disagreement might introduce in reporting technical success, clinical success, and correspondent applicability of DR/IR methods [15].

Related research was conducted by our vascular team in a prospective registry cohort of 167 diabetic patients treated for neuro-ischemic foot wounds [7]. The technical success for WTR implied reperfusion of the main angiosomal source artery, either directly by the main source artery, or through the connected permeable foot arches, by "true" arterial-arterial, equivalent caliber communicants, and by available large (>1 mm diameter) neighboring collaterals. If the WTR was unsuccessful, an alternative technique defined as WTR collateral-sustained perfusion (WTRc) was attempted. This strategy involved the use of all available medium-to-small arterial branches (including the choke vessels and cutaneous perforators), directed toward the topography of the wound zone [7].

These newly proposed definitions of WTR and WTRc are aimed at broadening the anatomical interpretation of AG source arteries distribution during the revascularization by adding a parallel, "collateral enhanced" hemodynamic aspect [7] (Figure 2).

This view was aimed by incorporating a parallel interpretation of the physiological inter-angiosomal flow, according to the novel comprehensive concept of the "functional AG" recently introduced by Taylor et al. [30]. This broader functional AG comprises one or multiple anatomical "sources arteries" that associate neighboring angiosomes, as long as they are connected by available "true" (equivalent caliber) [30] arterial-arterial communicants and collaterals between neighboring arterial bundles [30]. WTR captures this extended functional unit, bringing together multiple anatomical "source arteries" with similar hemodynamic characteristics (warranted by the presence of these "true" collaterals) [7].

From this perspective, the technical feasibility rates documented in our analysis were 64% for WTR, 16% for WTRc, and 20% for IR [7].

Our observation revealed that the collateral involvement, judiciously identified in the literature (labeled as IRc or parallel WTRc), seemed to confer distinct capabilities for hemodynamic flow compensation [3,6,7,11,12,18]. This distinction is particularly useful as each of these approaches can be deliberately applied either as an initial technique in revascularization or as a contingency "secondary" solution in cases where the initiation of DR or WTR was unsuccessful (Figure 2). Consequently, the anticipated applicability of DR or WTR and technical success may manifest different values and outcomes.

### Clinical applicability and current match

Although some authors are reluctant about the applicability of DR/IR in the "real-world" setting, [9,16] others demonstrate greater confidence in establishing clinical match between the "classical" anatomical distribution of AG and the current characteristics and topography of foot wounds in a majority of cases, albeit with cautious considerations for Rutherford 6 presentations [1-8,17-19]. The present study revealed a paradox. Although data on the fundamental applicability of DR/IR are limited, data on the clinical outcomes of DR/IR are conversely on the rise. Subsequently, a second paradox appeared by this analysis. Contemporary interventionists are confronted by conflicting opinions, either opposing, or supporting the practicality of DR, IRc, and WTR [1-9], without establishing unanimously accepted "basic definitions" and "consensual applicability" recommendations in clinical practice [15,22,28].

Ten years ago, Aerden et al. [16] conducted an initiatory single-center analysis focusing on 185 diabetic feet. The study examined 345 distinctive diabetic multifactorial foot wounds in diabetic patients. A single tissue defect was identified in 50%, two in 23%, and three or more wounds in 27% of the studied feet. Additionally, 45% of the wounds exclusively involved the toes. However, the study did not employ a standardized classification of diabetic foot wounds. Approximately 18% of patients, diagnosed solely based on the findings of clinical examinations, were deemed with unsuitable applicability for AG-guided revascularization. In 9% of patients, this correlation was considered impossible [16]. Although this comprehensive analysis provided valuable insights, it lacked specific details regarding the prevalence of parallel Diabetic Peripheral Neuropathy (DPN), the ratio of dominant neuropathic or pressure ulcers, and the presence and extent of local sepsis. These variables, easily accessible in an initial clinical examination, could enhance the depth of the study's findings.

Recent selected publications, benefiting from advancements in macro- and microvascular diagnostic methods, presented different clinical feasibility rates of DR related based on the topographical distribution of foot wounds. This variability ranged from 69% (for DR and IRc) [18] to 81% (for cumulated DR, IRc, and IR) [19]. Notably, Kret et al. [27] observed a comprehensive alignment in applicability, attributing 36% to exercises involving single-targeted arterial graft angiosome and 56% for those involving dual-targeted angiosomes.

In our multidisciplinary team's experience, we investigated the applicability of DR and the technical success of EVT based on a four-grade (A-D), Below-The-Ankle (BTA) arterial angiographic lesions stratification [17]. For grade A lesions with solitary angiosome affliction and single wounds, the technical success and DR applicability rate were noted at 95%. In grade B lesions, which involved single or twin wounds and one or two angiosomal diseases, we observed an 88% completion rate. Grade C lesions, characterized by at least one targeted angiosomal artery in complex or multiple wounds that were successfully treated, showing variable angiosomal correlation, demonstrated a 70% match. Grade D lesions only exhibited a 12% associated technical success rate, with poor angiosomal applicability and correlations [17].

## Discussion

ITR may afford a novel conceptualization of regional foot reperfusion by intentional anatomical and functional orientation of the territorial foot flow to the ischemic zones (owing specific permeable pedal arteries and regional collaterals). While DR, IRc, and WTR hold a deliberate topographic orientation of the arterial flow *via* selected foot "source arteries" or specific "groups of collaterals", IR does not [1-8].

### Recognition of angiosome guided revascularization

In the last two decades, angiosome-guided revascularization has gained increasing attention as clinical observations and research focus on the comparative clinical benefits of DR *vs.* IR in CLTI wound healing [1-8]. The consideration involves adherence to, or deviation from the foot's six angiosomal "source arteries" [1-11]. However, studies reporting the accurate applicability rates of angiosome-oriented DR, IR, IRc, and WTR methods in routine vascular practice are notably limited [15,22] and often inaccessible.

Although the anatomical allocation of the main "nourishing" AG source arteries in the foot has been openly established, the inclusion or exclusion of foot arches as "true" arterial-arterial functional inter-angiosomal communicants and the main groups of collaterals (from large-to-small branches and "choke vessels") in the definitions of DR, IRc, and WTR need to be explored further [7,15].

The diameter, density, and flow resistances of these distinct levels of arterial ramifications [22] are seldom specified in the literature, despite their importance in the assessment and potential applicability of the ITR strategy in CLTI treatment [17,19,27]. In terms of the angiographic evaluation of the main AG source arteries, only a few publications have proposed a simultaneous assessment of the foot arches [10,17,31,32]. Moreover, a smaller number of studies have evaluated the main groups of collaterals [7,17,18] or specific "run-off patterns" to aid in the development of an individualized ITR method [19,27].

### Role of collaterals in DR/IR applicability

It appears that any successful DR proves however partially useful, unless a correct collateral framework and run-off proves available, as to conduct blood flow to the targeted tissue [17-19,23]. The appropriate application of AG-guided revascularization does not entail the rigid reperfusion of only one or multiple foot's source arteries (if eventually permeable) [7,11,17-19,24]. The overall individual collateral reserve of the foot and the persistent regional arterial branches serve as the "true redeemers" for each threatened ischemic inferior limb [7,11,17,18,24,27,32]. It is the profile, density, and functional fitness of these surviving collaterals that ultimately determine the likelihood of tissue recovery and perhaps limb salvage [3,6,7,11,17,32-34]. The "reinsuring" restoration of adequate angiographic flow in the targeted AG source artery alone does not always indicate the correct redemption of ischemic tissues without anatomically and functionally viable flow distribution to the tissue by the regional collaterals. Regardless of the assigned label (DR, IRc, WTR, or WTRc), the applicability of AG-related ITR cannot be evaluated without a centralized assessment of the collateral flow [7,17,18,27,32,33].

Although different study protocols may present varying claims, upon closer examination, all DR, IRc, WTR, and WTRc appear to have conceptual similarities. They share a common objective: to enhance the anatomical and physiological collateral flow around the wound zone. Regardless of their labels, this objective is attempted by selecting one of the three alternative paths to the wound zone: a) by utilizing DR as a successful reperfusion origin *via* the regional angiosome and its unique source artery [1-8,17-19,24-29,32]; b) by incorporating the available large arterial-arterial communicants and permeable foot arches to the main AG source artery, toward the wound zone, perceived as WTR [7]; and c) by applying IRc (or a similar WTRc method) assisted by the available collateral network (based on the diameter and topography) [4,6,11,18,24]. Despite their apparent differences, all these strategies hold equal value in the context of ITR-oriented thinking.

Given that the current intentional IRc, WTR, or WTRc definitions [7,18] link various diameter collaterals in the limbs with different run-off patterns [21,27,33] and unknown regional hemodynamic flow-parameters (vascular peripheral resistances), an ambiguous interpretation of AG-applicability can be anticipated [21,22].

As an exhaustive and unanimously recognized BTA atherosclerotic occlusive disease classification (including the pedal arteries, foot arches, and distinct classes of collaterals) is still awaited [6,10,17], the true nature of these collaterals "conventionally" incorporated in WTR, WTRc [7,22] and IRc [3,6,8,11,18] remains poorly understood. Two patients benefitting from two distinct "technically successful" IRc methods or two WTRc methods do not necessarily have similar tissue recovery capacities. This discrepancy arises from the differences in functional characteristics (peripheral resistances), variability in diameter, varying severity of the atherosclerotic disease, diverse calcification burden, and different types of connections with neighboring source arteries [21,28].

For instance, previous research has demonstrated that approximately "16 collaterals with a 0.25 cm diameter" equivalent to "625 collaterals with a 0.1 cm diameter" may be required to achieve a correct compensation of an unobstructed artery measuring 5 mm in diameter [34]. It was equally estimated that "a few large collaterals appear far more effective for flow compensation compared with hundreds of small collaterals, choke vessels, and capillaries [22,34].

Recently, Taylor et al. [30] introduced a novel functional interpretation of the AG theory, which integrates the angiographic and anatomical assessments of the ischemic foot and ITR applicability [28,30].

This novel "dualistic" (anatomical and functional) definition of the "angiosomal entity" surpasses the initial limitations imposed by the sole anatomical description [33] of the main foot arterial bundles of vasculature and the connected collateral network [11,33]. Concerning the present study, with three exceptions [7,17,28], none of the selected papers considered the significance of the "functional angiosome" and its collateral network implications [30] in completing the "anatomical" DR, IRc, and WTR relevance in CLTI.

Moreover, this complementary notion introduced new perspectives for the current deployment and applicability of ITR, as highlighted in a recent comprehensive meta-analysis by Stimpson et al. [28].

The "functional-AG" represents a larger volume of tissue (inclusive of one or many "anatomical-AGs") dependent on a main nourishing "source vessel." It incorporates additional territories connected to various individual hemodynamically significant branches (including equal caliber "true" collaterals, and large, arterial-arterial "communicants") [8,30] (Figure 2). It has a flexible and personalized collateral-dependent shape that can be widened by the eventual reopening of the inter-angiosomal "dormant collaterals" [28,30]. Finally, it transcends the previously "rigid" anatomical demarcations of the six foot's AG [28,30,33], enabling the capture of additional remote foot territories irrigated by adequate "choke" vessels and "true" collateral branch anastomoses [8,11,28,30].

The "functional-AG" introduces novel perspectives for a comprehensive flow assessment in CLTI revascularization (Figure 2, 3). It unfolds new interpretation and applicability challenges for DR, IRc, TWR, and TWRc in limb salvage [7,11,22,28,30]. Furthermore, it provides insights into the reasons behind the variations in the evaluation of DR/IR applicability and treatment interpretations associated with the AG theory [9,14,31] (Figures 2-4).

## Multiple identities of DR *vs.* IR

Various challenges arise in the current assessment of DR/IR applicability that undoubtedly, highlighting the lack of uniform consensus and standardized definitions for these CLTI treatment methods. Unfortunately, the current level of evidence concerning the suitability of DR and IR remains low, given the use of diverse study protocols, inclusion criteria, primary endpoints, and methods for accesses and techniques for revascularization [11,22,23,28].

Some researchers have compared the clinical success rate of angiosome-oriented DR and foot arches reperfusion, clearly delineating them as separate entities. These comparisons were conducted within the realms of infragenicular bypass [35] and endovascular BTA approaches [36]. These investigations provided valuable insights, suggesting that the clinical outcomes are more likely to benefit from the morphological integrity and functional appropriateness of the pedal arch's flow connections, rather than by adhering strictly to the distribution chart of the six foot's angiosomal "source arteries" (Figure 3, 4).

Alternatively, simultaneous studies emphasized the significant role played by the pedal arch's anatomical [1-5,11,18,23] and functional [21-23,28,30] status (and generally by all types of foot collaterals) [3,11,12,17-19,27,28].

This goes beyond merely ensuring the patency of source arteries, contributing to a broader understanding, definition, and application of anatomical-functional DR/IR [3,4,6-8,11,18,21,22,32] (Figures 3-5).

Unfortunately, a universally accepted and standardized definition of AG-oriented DR and IR is still lacking [11,15,22,28].

Some authors suggested that the inclusion of effective collaterals in IRc [18] or the addition of "true" [30] collateral ramifications such as the foot arches in WTR [7,32] could enhance the overall fitness for ITR, leading to superior applicability and clinical success.

The evaluation of ITR applicability becomes challenging due to the heterogeneous variants of collateral anatomical indexation and the absence of parallel functional evaluation. Given that the DR, IR, IRc, WTR, and WTRc methods have independent applicability challenges and lack uniform definitions, drawing pertinent conclusions from this review proves to be difficult.

Discrepancies in DR and IR study protocols inevitably lead to dissimilar feasibility mentions [29] due to the differing foundations on which these protocols are established. Addressing this essential priority should be the primary focus before contemplating the pros or cons of real-world ITR utility [15,22].

## Current challenges in ITR applicability

Several authors have described significant challenges in planning DR, emphasizing the necessity of accurately identifying AG-targeted territories, especially in cases involving complex foot wounds spanning multiple "anatomical" angiosomes [16,22]. In a recent article, Ferraresi et al. [9] pointed out that the conventional recognition of the "classical" anatomical AG distribution chart, when applied to the distorted CLTI vascular anatomy, remains controversial. This is particularly relevant in extended diabetic neuroischemic foot wounds that encompass parallel neuropathic or pressure ulcers in neighboring territories, with possible involvement of the multiple AG source arteries [9,16]. It also appears that in planning revascularization of a limb for CLTI, the proper angiosome is only one factor to consider. Many other factors are involved in the decision, and angiosome-based revascularization is only rarely the primary and sole consideration [10] (Figures 3-5).

As previously mentioned, the combined use of angiographic and hemodynamic mapping of pedal arteries and collaterals, [11,17,21,28,30] coupled with AG-guided topographic necrotic tissue debridement [7,10,37,38], has significantly improved the foundational vascular orientation required for the implementation of ITR.

Interestingly, although some authors express skepticism regarding the feasibility of ITR in complex and multifactorial CLTI wounds [9,13,14,16], others recommend DR for "any" of the involved AGs in these complex and "overlapping wounds" [7,19,23,27,29,39] as a primary therapeutic approach.

Enlarging contemporary clinical experience suggests that angiosome based revascularization is more applicable to endovascular intervention than bypass where options are often more limited based on arterial anatomy and the available graft conduit [28,40] (Figure 5).

### Anatomical variations

Various challenges in the current applicability of ITR were attributed to potential anatomical variants in foot arterial distribution.

In the context of CLTI, true ITR requires diligent utilization of all available arterial trunks and collaterals, that includes the eventual existence of inherent anatomical arterial variants [7,17-19,39]. This approach initially involves a meticulous identification of each remaining permeable arterial trunk, the entire or suspended segments of "source arteries," leading to the dorsal or plantar arterial network. It also includes the recognition of complete or partially visible foot arches, along with all enduring regional branches, arterial-arterial communicants, and potential "dormant" collaterals identified during the intervention [7,39].

Various anatomical patterns of foot arteries have been described in approximately 10% to 12% of the general population [41,42]. Although not always easily recognizable, the foot generally maintains a rather harmonious and distinct dorsal *vs.* plantar blueprint of vascularization, with different compensatory connections and collaterals [17,18,21,39,41]. The identification of these patterns requires meticulous angiographic and foot flow mapping [7,19,22,39].

## Limitations

This study has several limitations that need to be acknowledged. These include the presence of multiple non-standardized definitions of DR, IRc, WTR, and WTRc, the limited number of applicability mentions (most patients primarily treated in single-center and retrospective cohorts), the notable heterogeneity in the selection and study protocols, the diverse revascularization methods used, and the varied interpretations given to DR/IR, with sporadic feasibility mentions. These factors collectively hindered the attainment of more consistent information in this survey.

## Perspectives

The integrated anatomical and functional understanding of CLTI provides a dynamic perspective on the interpretation, understanding, and applicability of ITR. According to several modern meta-analysis [23,28,43] and AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: Executive summary [44], the angiosome concept should be considered in planning revascularization since DR does result in increased healing [6,8,26,45]. At this level of knowledge, it also appears that applying DR (or related ITR) may be most important for endovascular therapy [28,40], diabetic patients [2,7,17,19] and wounds in a single or dual angiosomes [17,27,29].

Future developments in ITR strategy may appoint novel interpretations in wound treatment such as the "woundosomes" theory [46], and obviously introduce new challenges and opportunities in advancing knowledge about CLTI.

## Conclusion

The current applicability of ITR demonstrates significant variations influenced by local team interpretations, the type of revascularization method used, and the specific characteristics of targeted wounds and arterial lesions. The absence of standardized DR/IR definitions, coupled with the lack of a unified anatomical and functional stratification for inframalleolar atherosclerotic disease, requires complementary evidence for ITR applicability. ITR based on the angiosome concept matters when it can be utilized without sacrifice of other principles of revascularization.

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