World Journal of Cardiovascular Diseases, 2019, 9, 168-192
http://www.scirp.org/journal/wjcd
ISSN Online: 2164-5337
ISSN Print: 2164-5329

Current Issues and Interrogations in Angiosome Wound Targeted Revascularization for Chronic Limb Threatening Ischemia: A Review

Vlad Adrian Alexandrescu, Tommy Sinatra, Coralie Maufroy

Department of Vascular and Thoracic Surgery, Princess Paola Hospital, Marche-en-Famenne, Belgium
Email: v.alex@skynet.be

How to cite this paper: Alexandrescu, V.A., Sinatra, T. and Maufroy, C. (2019) Current Issues and Interrogations in Angiosome Wound Targeted Revascularization for Chronic Limb Threatening Ischemia: A Review. *World Journal of Cardiovascular Diseases*, **9**, 168-192.
https://doi.org/10.4236/wjcd.2019.93016

Received: January 3, 2019
Accepted: March 12, 2019
Published: March 15, 2019

Abstract

Despite a lack of solid evidence in applying the angiosome concept (AC) in current chronic limb threatening ischemia (CLTI) treatment, several encouraging results for improved wound healing and less for limb preservation were reported in various consistency studies. Direct revascularization (DR) following the foot angiosomes distribution (whenever feasible) may afford better clinical results compared to angiosome indifferent, or indirect revascularization (IR), however without clear benefit on survival and for major adverse limb events (MALE). Inside this interrogation, the notable influence of the remnant collaterals, the foot arches, the wound characteristics, and the type of revascularization (bypass versus endovascular) still remain ardent topics. Current evidence suggests that applying DR in daily vascular practice requires practitioners to be committed to every individual hemodynamic variable in a thorough macro- and micro-vascular evaluation of the ischemic foot. It becomes clearer nowadays that not all CLTI foot ulcers hold same ischemic burden and seemingly need specific DR. In the same setting, a novel wound targeted revascularization (WTR) design was proposed assembling wider circulatory targets than genuine DR notion, as used by some authors. Beyond specific angiosomal artery reperfusion, WTR associates the available arches, the large- and medium-sized collaterals, and the arterial-arterial communicants, in an intentional "source artery" and "collateral" topographic foot revascularization. However, up to date, the notion of angiosome wound-guided revascularization (DR and WTR) detains only a reserved level of confirmation. As for DR, the WTR equally needs higher levels of evidence allowed by standardized definition, uniform indications, and pertinent results from multicenter larger prospective analysis, before large application.

Keywords

Critical Limb Ischemia, Wound Healing, Diabetic Foot, Angiosome, Balloon Angioplasty

1. Introduction

The effectiveness of the angiosome concept (AC) [1] [2] [3] has been initially documented in the plastic reconstructive surgery field to ensure success in tissue flap selection and tissue reconstruction strategy [2] [3] [4] [5]. The AC has also been applied for chronic limb threatening ischemia (CLTI) treatment as direct revascularization (DR) strategy and has yielded initiatory promising results in tissue healing and limb salvage [6] [7] [8] [9] [10]. These observations seem particularly to concern limb collateral-deprived subjects, such as diabetic and renal patients [7] [10]-[15]. Although there is currently a lack of solid evidence in angiosome-guided DR applications by classically following main angiosomal branches, recent publications suggest for adapting diagnostic and reperfusion strategies towards "wound-targeted revascularization" (WTR), if technically achievable [3] [14] [16] [17] [18] [19]. Always perceived as AC application, WTR proposes a wider apprehension of topographic arterial reperfusion, by including the available large collaterals, permeable foot arches (if present), and the arterial-arterial communicants between neighboring foot angiosomes [3] [10] [16] [17] [18] [19] (**Figure 1**). A few contemporary studies add the WTR notion to DR, or to "DR-collateral enhanced" according to the AC [3] [10] [18] [19] as primary intention to treat CLTI. These studies reveal several observational advantages of this theory [10] [17] [18] [19] and obviously, some inherent uncertainties [20] [21] [22] [23].

In these patients, parallel efforts were exerted to improve the mean time to limb tissue recovery and decrease amputation rates by implementing the DR/WTR strategies [16] [17] [18] [19] [24]. This hypothesis also focuses on specific foot wound topographic reperfusion either via specific angiosomal branches (DR) or by using available local collateral reserves (WTR) [5] [10] [17] [18] [19] [26] in each given CLTI pattern, if technically attainable.

The present review mainly focuses on current clinical issues that most vascular interventionist may encounter in his or her daily practice, since deliberately applying "angiosome-oriented" (DR), or topographically "wound-oriented" (WTR) revascularization for CLTI ulcer healing and limb salvage.

2. Methods of Selection

Data storage. A PubMed-Medline research focusing the AC applications in vascular surgery over the last two decades publications (1998-2018) was performed owning English language restriction. The designations "angiosome(s)"-"angiosomal" were primary analyzed, and secondary investigation was further performed

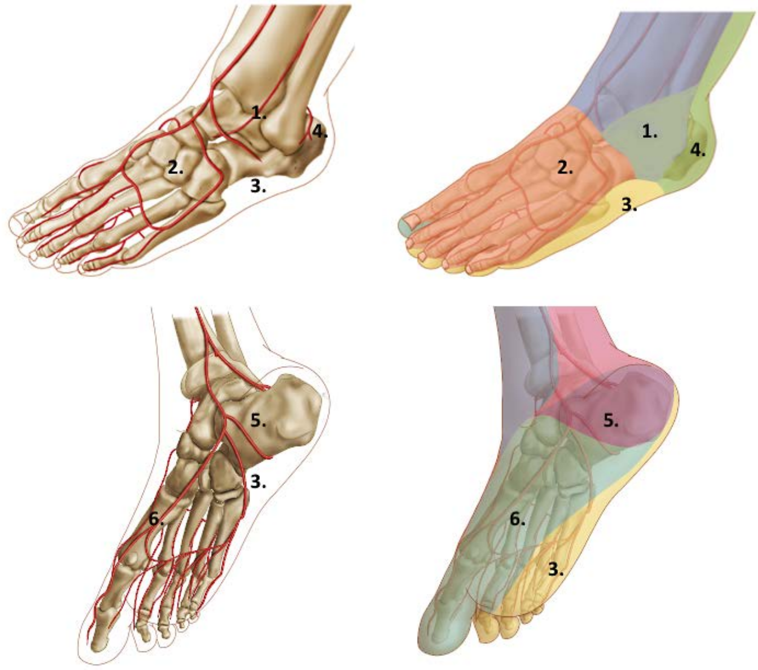

Figure 1. A global illustration of the currently described foot angiosomes: 1: The Anterior communicant's angiosome (from the Peroneal artery). 2: Dorsalis Pedis angiosome (from the Anterior Tibial artery). 3: Lateral Plantar angiosome (from the Posterior Tibial artery). 4: Lateral Calcaneal angiosome (from the Peroneal artery). 5: Medial Calcaneal angiosome (from the Posterior Tibial artery). 6: Medial Plantar angiosome (from the Posterior Tibial artery).

via "related articles" focusing "below the knee revascularization", "ulcer healing", "diabetic foot", and "limb-salvage terms". Papers without clear clinical protocol (inclusion-exclusion criteria, revascularization techniques, and follow-up) were excluded from this study. No restrictions were expressed concerning the type of study and the type of applied statistical analysis. The majority of remarks pointed on clinical directed applications, based on original observational data [6]-[14] [16]-[30]. Beyond standard clinical observations provided by the cited authors, no complementary statistical data reworking was attached at this inquiry phase.

Selection process. From the initial 1655 detected as potential fitting studies, after retrieval of unconnected topics, unfitting standardized research protocols, miscellaneous reviews, non-clinical outcomes, and inappreciable data, or conclusions, forty-three group analysis (forty-one paper cohorts and two conference presentations) were selected and evaluated.

3. Results

3.1. Contemporary Landmarks

Following meticulous macro- and micro-vascular preoperative diagnostic approaches, the CLTI treatment essentially involves endovascular technology (EVT) and open surgical interventions. The superiority/inferiority of these procedures in ensuring adequate limb salvage was, and still is currently debated in contemporary literature [11] [12] [24] [27]. The detailed apprehension of these controversies is however beyond the purpose of this paper. Nevertheless, for both strategies, chronic total occlusions (CTO) and heavy, continuous calcifications of tibial and pedal arteries, still remain huge obstacles for all revascularization techniques, including WTR options [5] [11] [12] [25] [27]. These disabilities mainly concern the technical success, associated patency, and limb salvage rates [9] [24]. Contemporary limb reperfusion technology is yet subject to tremendous changes owning, or not wound topographic orientation [11] [12] [13] [14]. As recently stated by Scott *et al.,* "nothing accentuates the benefits and limitations of an endovascular or surgical procedure more than using them frequently" in CLI practice [28]. Most likely, the most suitable WTR technique is the one that complements most individual anatomical and pathophysiological variables for each CLTI patient [17] [29] [30] [31] This, and any other particular technique (with, or without AC orientation) should be chosen in a flexible and balanced team deliberation, considering each method (bypass versus endovascular) as *complementary* and not as *concurrent* parts [3] [6] [7] [8] [9] [10] [17] [18] [19].

3.2. Current Endovascular Techniques

Contemporary clinical experience supports both, bypass and EVT as useful strategies in CLTI treatment [11] [12] [32] [33]. Owing low invasiveness, high feasibility, reproducibility and comparable limb salvage rate to bypass [6] [11] [12] [17] [28], the endovascular techniques continue to progress affording new low profile and high-performance devices in arterial reperfusion [11] [12] [34]. For most of the CLTI patients [11] [12], novel endovascular approaches offer personalized solutions for many arterial segments to be treated [26] [30] [33] [34].

In a brief overview, the "drilling", the "subintimal", or the "parallel wire" techniques performed via ante- or retrograde accesses, can be associated to the pedal-plantar "loop", to the femoral-femoral, and the trans-tibial collaterals angioplasties with encouraging results reported in the last years [11] [12] [34] [35]. Synchronous advances in diabetic foot syndrome (DFS) topographic arterial and collateral reperfusion are soaring nowadays [11] [17] [35] [36]. Innovative tapered nitinol [37], drug-eluting stents (DES) [12] [38], and new generation drug-eluted balloon catheters (DEB) [34] [35] [36], were introduced and gain experience in current practice [34] [36].

Original or redesigned directional or rotational atherectomy devices [12] [39], adding latest "bioresorbable scaffolds" technologies [12] [34], represent complementary technological advances that today challenge ancient CTO revascularization barriers [11] [12] [35] [36]. According to this evolution, the technical feasibility of DR and WTR by EVT unceasingly changes and offers new perspectives for ischemic limb tissue preservation nowadays [27] [29] [30] [36].

3.3. Bypass surgery for Distal Foot Revascularization

Equivalent to the above-mentioned trans-catheter achievements, the common bypass for distal leg reperfusion still represents a fundamental procedure in CLTI diabetic foot revascularization [10] [11] [12] [32] [33] [40] [41], having, or not AC support for DR and WTR [3] [8] [10] [27]. Surgical reperfusion yet still detains recognized qualities for CLTI appropriate treatment, and limb preservation [11] [12] [40] [41], High-performance distal vein bypasses to the tibial [12] [42], pedal [41] [42] [43], and up to the plantar or tarsal foot arteries [44] were reported with remarkable clinical results. Other extreme techniques, exploiting even the remote branches of pedal arteries, were equally described, such as the publications of Brochado-Neto and co-workers regarding particular limb salvage bypass variants [45]. The distal foot run-off becomes then more approachable for extended bypass procedures with, or without topographic DR/WTR orientation [3] [8] [20] [27].

3.4. Specific Advantages of Each Method in WTR

As mentioned before, EVT is essentially reputed for minimal interventional aggression, wide accessibility, and high reproducibility since targeting one or multiple below-the-knee CTO vessels [10] [11] [26] [27]. These profits seem to match in particular with WTR, by allowing specific tibial and pedal arterial trunks to be selected for reperfusion [6] [25] [26] [27].

Distal foot run-off capacity can be also modulated by EVT, or hybrid reperfusion technologies [17] [46] [47].

Alternatively, bypass brings a much higher pressure to the distal foot arteries, adding a physiological and pulsatile blood flow along the collaterals to the wound zone [16] [31] [42] [43] [44] [48]. A physiological regained flow, owing higher "pressure and pulsatility" enhances additional dilatation of surrounding collaterals even without primary topographic orientation toward the foot wound zones [17] [31] [48]. By this good the bypass enhances a higher arterial-arterial collateral shear stress and increasing local arteriogenesis [17] [26] [31] [48]. Therefore, bypass was described to avail less profit from DR, or WTR compared to angioplasty [49].

It becomes obvious that surgical and endovascular techniques are more likely to afford *complementary* than *competitive* benefit to CLTI patients, since thoroughly selected [11] [12] [25] [26] [27] [40]. Without opponent means both techniques probably need to be further pondered in interactive multidisciplinary approaches and applied in an open-minded perspective [17] [30] [41].

Studying and proving potential WTR clinical benefits (for EVT or bypass) in CLTI treatment shows however to be a demanding task [16] [17] [18] [21]. This statement is mostly due to large heterogeneity of arterial lesions [25] [26] [27], numerous concurrent pathologies that accompany CLTI and DFS [11] [50] [51], inhomogeneous follow-up data [14] [24], and lack of concomitant *macro* and *microvascular* assessment of threatened hypoxic limbs [21] [22] [23] [24] [25].

Despite the lack of extended usage in revascularization, the AC has been validated in various clinical applications such as successful skin flaps reconstruction [2] [3] [4], targeted myocardial reperfusion [26] [52], specific neurosurgical, vascular interventions [53], selective arterial embolization [16], and topographically oriented incisions and levels of amputation, more detailed in the plastic reconstructive surgery domain [2] [3] [4].

During the last two decades, AC with DR, and more recently WTR have been increasingly associated with targeted inferior limb revascularizations (bypass or EVT) in CLTI treatment and limb salvage interventions [6] [7] [8] [9] [10] [16] [25] [26] [27]. Consequently, pressing questions in the field today are whether WTR promotes a better outcome in CLTI revascularization and whether the clinical outcomes—since WTR is being applied for tissue healing—may be better for limb preservation and for higher survival in these patients [26] [27] [30].

3.5. The Relevance of WTR in Current Vascular Practice

Current evidence suggests that applying the AC and WTR in daily clinical practice requires practitioners to be committed to ongoing learning curve [16]. True clinical application of the AC primarily implies thorough evaluation of the benefit allowed by targeted *macro*- and *microvasculature* reperfusion [17] [27]. Effective flow mapping toward the wound zone (**Figure 1**) requires open-minded judgment in adapting the best techniques for best achievable direct, or collateral-enhanced distal foot flow [25] [26] [27].

Every ischemic presentation is unique with regards to its anatomical pattern, specific local pathophysiological changes, and individual distinct risk factors for tissue healing [17] [54]. All concurrent pathologies must be recognized and managed in each CLTI subject, as unique combinations [16] [17] [18] [25] [26] [27]. The diabetic foot's multivariable pathology and collective specialists treatment represents an expressive example of this therapeutic convergence [14] [54].

Although the original *direct revascularization* description focused on specific BTK angiosomal branches [3] [6] [7] [8] [9] [10], other researchers have broadened this strategy by directly, or indirectly defining WTR concept [10] [16] [17] [18] [26].

Particularities of flow. WTR assembles wider therapeutic targets by including the large- and medium-sized arterial-arterial collaterals, in intentional topographic foot revascularization [17] [19] [26], In similar manner, Rachid *et al* [20] already revealed the clinical importance of foot arches in topographic reperfusion, while Osawa [19], Zheng [18], and Acin [55] observed similar clinical effects for analogous, collateral-enhanced revascularizations [3] [18] [55]. Large collaterals (around 1-mm diameter) and direct arterial-arterial interconnections seem to play a crucial role [17] [26] in appropriate ischemic foot reperfusion [17] [31] [55]. These findings seem to concern (in variable proportions) tissue regeneration and limb salvage rates for both, bypass and endovascular interventions [3] [8] [17] [18] [19]. Nevertheless, certain levels of clinical success have also been reported using the current practice for *indirect revascularization* (IR), without deliberate topographical orientation [20] [21] [22]. The importance of the notion "mean-time to tissue recovery" appears then to be ponderous in defining real benefits of DR/WTR versus IR [17] [26] [56].

Practicability of WTR. Original WTR benefits may appear less impressive in certain CLTI patients who avail less affected collateral network [2] [3] [10] [26]. Younger patients or those who benefit from unaffected arterial-arterial distal limb connections may express little differences in the healing process by specifically using DR instead of indirect revascularization (IR) [16] [19] [49]. These findings have previously been reported in angiosome-oriented bypass revascularization at mid- and long-term follow-up periods [3] [8] [10] [49]. Concerning EVT, Spillerova *et al.* observed in a 161 cases retrospective series that the feasibility of targeted DR was 69% for one, 86% for two, 85% for three, and only 25% for four affected angiosomes [27].

Potential indications. The best arterial path reopening towards the wound obviously depends on each individual anatomy and available collateral pattern [3] [25]. This approach relies on the most appropriate technique for foot revascularization selected for each case [3] [10] [16] [49]. As mentioned before, surgical bypass essentially stimulates collateral growth around the ischemic wound by direct arteriogenesis process [26] [31] [48]. This can be achieved by diligently reusing the good caliber remnant collaterals or available arterial-arterial interconnections [3] [10] [26] [30] [55]. According to contemporary bypass series of studies conducted by Neville *et al.* [8] Varela *et al.* [10] Kabra *et al.* [57] and Spillerova and colleagues [49], compared to IR effects, surgical DR results (when achievable) showed potential promise. However, the need for appropriate "angiosome-oriented" run-off vessels for successful distal bypass, as to judiciously compare DR/IR results in healing and limb salvage, still remains a controversial issue [3] [26] [30] [42]. Following different capacities for enhancing post-revascularization arteriogenesis, DR strategy may be less important for bypass than endovascular techniques, according to some clinical observation [49] and still notable for others [55] [56] [57]. Alternatively, endovascular technology may enable clinicians to recanalize the wound-oriented vessel(s) (when feasible) and to eventually improve parallel angiosome neighboring perfusion in the ischemic foot [6] [7] [18] [55] [56] [57] [58] [59]. Other researchers still remain reserved on this point [21] [22] [23]. Compared to bypass surgery, catheter-based techniques appear to fail to restore comparable high-pressure and "pulsatile" flow to the target tissue collaterals with lower mid- and long-term primary patency [16] [22] [28] [42].

Main WTR principles. Despite encouraging results obtained by applying DR and more recent WTR strategies in wound healing [16] [17] [18] [19] [24] [55], one major barrier of these applications represents their concrete technical limitations [27] [55] [56] [57]. Angiosome-targeted arteries have previously been shown to harbor severe atherosclerotic disease, such as multilevel tight stenoses, long chronic occlusions, and extended calcifications [17] [25] [27] [59]. These features may strongly relate to specific pathologies triggering CLTI, such as the metabolic and the renal syndromes [16] [17] [18] [19] [25] [26] [27].

As shown by previous research of our team [7] [16] [59], most angiosome-targeted arterial lesions were likely categorized as TASC Class "C" (32) (20% - 36%) and "D" [32] (68% - 73%) angiographic severity [7] [59]. Unsurprisingly, these topographically selected arteries also featured the heaviest infragenicular calcific burden (42% - 56%) [7] [25] [59]. Following the same observations in about 53% TASC "D" presentations, there was a correlation between wounds in the anterior tibial angiosome and the most severe anterior tibial lesions, while in 57% wounds dominating the posterior tibial angiosome(s) correlated with severe TASD "D" occlusions in the posterior tibial artery [7] [59]. Of note, the majority of the above observations can be mostly documented in cases with one predominant, or single angiosome ulcer location assessed in similar CLTI and "collateral-deprived" limbs [7] [25] [59].

Nearly 80% of the WTR interventions currently required multilevel tibiopedal angioplasties in the similar angiosomal axes [7] [59]. DR and WTR technical feasibility was achieved in our practice in a mean 70% (62% to 75%) of cases [7] [59]. According to current surgical and endovascular technology standards, global DR/WTR feasibility is reported to vary from 61% to 82% in different series [18] [19] [27] [55] [57]. Technical success appears to be statistically correlated with high-volume center interventions, patient age, duration of diabetes, wound's characteristics, and specific features of the targeted arterial occlusive disease [6] [7] [8] [9] [10] [25] [26] [27]. As previously emphasized in parallel studies, unlike "DR", the "WTR" may delineate a much larger perspective of treatment inside the global "angiosome-targeted" revascularization concept [17] [26] [55]. WTR additionally implies the diligent use of all available arterial-arterial interconnections, foot arches, metatarsal perforators, and medium-to-large collaterals by following "direct", also "indirect", yet collateral-sustained revascularization [3] [17] [18] [19] [55]. WTR equally implies intentional opening of neighboring angiosomal arterial axes (previously labeled as IR in several studies) that conduct the oxygenated blood via carefully selected collaterals towards the main wound territory of the threatened foot [17] [26] [60] [61].

Specific WTR feasibility rates compared to parallel DR achievement are not yet available.

3.6. New Approaches for WTR

The complex cascade of tissue regeneration requires precise circumstances to occur [62].

New revascularization strategies provide modern practitioners with more efficient tools for enhancing these stages of tissue reconstruction [17]. As emphasized by Elsayed *et al.* [63] and Chin *et al.* [46] key findings on hemodynamics and molecular mechanisms involved in the development of CLTI have been reported. This novel conceptualization of the ischemic threat clearly underlines the increasing role of clinical teams in preventing and applying the global limb salvage process [11] [12] [41] [63]. The modern knowledge of CLTI now belongs to a much larger and "integrated" multidisciplinary medicine [41] [63] [64]. based on more accurate arterial flow mapping [1] [2] [3] [25] and targeted tissue reperfusion for healing [29] [51] [55]-[60]. According to this redesigned strategy, beyond current bypass and trans-catheter revascularizations [11] [12] [33] novel "*hybrid*" surgical and endovascular procedures [11] [12] [63] afford complementary applications for increasing limb preservation. Parallel "extreme" limb revascularization techniques such as the venous arterialization [47] [65] [66] and the cell stem treatment [11] [12] [46] were included into the rising "multidisciplinary team" practice [11] [14] [17] [41]. Some of these innovative deep-veins arterialization methods propose WTR via still available "venosomes" of the threatened limb [66] although untouched by the ischemic and devastating atherosclerotic aggression [15] [66]. Inasmuch current evidence upon their real benefit in limb salvage and AC application still lacks, these audacious strategies seem but to upgrade previous paradigms of CLTI surgical and endovascular treatment [12] [14] [47] [65].

3.7. Current Literature Review Concerning DR/WTR Strategies

Angiosome-oriented revascularization (DR, DR via collaterals, or WTR) theoretically may offer improved chances for tissue regeneration [3] [6] [7] [8] [9] [10], and particularly in specific collateral-deprived ischemic wounds [7] [10] [14] [15] [16] [17]. These assertions still require complementary prospective validation in larger study groups gathering patients with equivalent CLTI pathologies and risk factors [17] [24] [26] [61]. The consistent implementation of the DR/WTR strategy in current distal bypass or transcatheter interventions has, however, only begun [16] [24].

Over the last ten years and despite inherent controversies, an increasing number of dedicated studies have emerged (**Table 1**) and focus on this subject [26]. While several analogous retrospective series appear to favor the DR hypothesis in endovascular analysis [6] [7] [8] [9] [10] [27] [58] or bypass groups [3] [8] [10] [57] other researchers have remained reserved [21] [22] [67] [68].

Macrocirculatory findings. In an initial single institutional study of 56 distal bypasses, Attinger and colleagues [69] noted that only 9.1% of healing treatments failed in wounds that were subjected to "direct" angiosome-related surgical revascularizations. These results contrast with the estimated 38.1% of treatments that lacked clinical success in wounds treated with "indirect" or non-angiosome-oriented bypasses [69]. Neville and colleagues [8] in a similar retrospective surgical series of 48 patients, found that the angiosome-related surgery (DR) group exhibited a 91% healing rate and 9% amputation rate compared to the 62% healing rate and 38% amputation rate in the non-angiosome (IR) structured subgroup. Moreover, in a 64 patients prospective study, Kabra *et al.* [57] documented a significant difference between the tissue healing success of

Table 1. Clinical and demographical features of main observational studies analyzing the benefit of angiosome-guided revascularization.

Author	Year	Period	Type of study	Vascular Technique	Type of patients: Diabetics (D), All pathologies	Ischemic stage	Treated limbs	Follow-up (months)	Clinical benefit of DR versus IR (p) - Healing (H) - Limb Salvage (LS)
Attinger	2006	-	Retrospective	Surgery	D.	Diabetic wounds Rutherford 5, 6.	56	6	$p = 0.0095$ (H) $p = 0.016$ (LS)
Neville	2009	-	Retrospective	Surgery	All pathologies	TP < 50, ischemic wounds	52	24	$p = 0.03$ (LS)
Varela	2010	2005-2008	Retrospective	Surgery + Endovascular	All pathologies	TP< 50, ischemic wounds	76	24	$p = 0.008$ (H) $p = 0.02$ (LS)
Iida	2012	2004-2010	Retrospective	Endovascular	All pathologies	TP < 50, ischemic wounds	326	48	$p = 0.002$ (H) $p = 0.03$ (LS)
Blanes	2011	-	Retrospective	Endovascular	All pathologies	Rutherford 5, 6.	34	21	$P > 0.05$ $P > 0.05$
Alexandrescu	2011	2001-2010	Retrospective	Endovascular	D.	Diabetic wounds Rutherford 5, 6.	232	54	$p = 0.018$ (H) $p = 0.030$ (LS)
Azuma	2012	2003-2009	Retrospective	Surgery	All pathologies	Rutherford 5, 6.	96	24	$p = 0.185$ (H)
Lejay	2013	2003-2009	Retrospective	Surgery	D.	Diabetic wounds Rutherford 5, 6	58	12	$p = 0.01$ (H) $p = 0.003$ (LS)
Kabra	2013	2007-2008	Prospective	Surgery + Endovascular	All pathologies	Rutherford 4-6.	64	6	$p = 0.021$ (H) $p = 0.06$
Söderström	2013	2007-2011	Retrospective	Endovascular	D.	Diabetic wounds Rutherford 5, 6.	168	12	$p = 0.001$ (H)
Jeon	2016	2011-2013	Retrospective	Surgery	D.	Diabetic wounds Rutherford 5, 6.	82	13	$P < 0.05$ (H)
Elbadawi	2018	2014-2016	Prospective	Endovascular	All pathologies	Rutherford 5, 6.	212	12	$p = 0.02$ (H) $p = 0.148$ (LS)

Abbreviations: Direct Revascularization (DR), Indirect Revascularization (IR), Toe Pressure (TP), Healing (H), Limb salvage (LS).

DR and IR ($p = 0.021$). However, the difference in the limb salvage between the groups was not significant (84% versus 75%) [57] Iida *et al.* [6] examined 203 consecutive ischemic limbs with tissue loss undergoing endovascular reconstructions and observed an 86% limb preservation rate in the angiosome-related subgroup, which was significantly higher than the 69% in the non-specific subgroup [6]. Consistent with these reports, in a similar 76 cases study of ischemic ulcers treated by both bypass and endovascular therapies, Varela *et al.* [10] documented significantly better results for wound healing (92% versus 73%) and limb salvage (93% versus 72%) in the angiosome-guided cohorts of patients [10] In an extended retrospective study of 744 consecutive patients, Spillerova *et al.* [49] observed that wound healing and limb salvage rates were both significantly improved after angiosome-targeted revascularization. In this setting, DR bypass surgery achieved significantly higher healing results than equivalent DR angioplasty [49].

In parallel studies conducted by Zheng [18] and Osawa [19] the authors similarly indicate that DR/WTR in intentional angiosome-oriented revascularization are both, technically achievable and offer superior clinical results than IR [18] [19]. Both authors also emphasize the importance of the collateral network surrounding the CLI wound [18] [19] which is consistent with reports by Varela *et* *al.* [10] Attinger *et al.* [69] Acin *et al.* [55] and by our team's previous observation [7] [59] Practical information about DR in surgical applications has been equally reported by Kret *et al.* in a study of 106 CLTI cases [70]. The authors concluded that DR may afford better clinical results than other methods, but this strategy is only applicable in 50% of common CLTI cases [70]. Similarly, in a recent retrospective analysis of 161 patients by Spillerova *et al.,* the technical success of DR seemed to depend on the number of involved and treated angiosomes [27]. Technical feasibility varied from 69% to 86% for one, up to three targeted angiosomes revascularization [27].

In contrast with the abovementioned data, another contemporary endovascular analysis conducted by Blanes *et al.* [67] revealed that, for 32 retrospectively reviewed Rutherford category 5 also category 6 patients (owning extensive tissue necrosis), there was no significant difference between the angiosome-targeted (direct) and non-targeted (indirect) percutaneous revascularizations. Analogous publications, either by analyzing the impact of DR in the paramalleolar bypass by Deguchi *et al.* [71] or by following the observations of Ricco and colleagues concerning DR compared to IR peroneal bypasses [72] the patency of foot arches and both peroneal terminal branches were more important predictive factors for healing than the angiosomal orientation itself [72]. Rachid and colleagues [20] reached parallel conclusions about the value of complete and permeable foot arches in angiosome-oriented infrapopliteal bypass [20].

All this complementary clinical expertise brings valuable issues in better defining and understanding real significance of DR, DR-collateral assisted, and WTR in current surgical and endovascular CLTI treatment [17] [18] [19] [26] (**Table 1**). It also appears more eloquent that all of these outwardly "opposing" findings instead contribute to a better understanding of collateral blood supply inside and between adjacent angiosomes touched by CLTI [17] [18] [19] [26] [61].

True value of the peroneal collaterals, the large foot arterial-arterial interconnections and the permeable foot arches has been consecutively documented as specific variants of DR-collateral assisted or WTR in CLTI [3] [10] [17] [18] [19] [55]. As mentioned before, these observations do not contradict the main principles of DR, and WTR conceived as topographic revascularization through available foot collaterals [3] [17] [26] [55]. These observations rather add complementary knowledge in daily practice that endorses with specific facets of the angiosome strategy [3] [10] [17] [18] [19] [26].

Microcirculatory observations. Parallel microcirculatory observations were reported by Rother *et al.* [22] Kawarada *et al.* [21] and Kagaya *et al.* [73] using tissue spectrometry, laser Doppler flowmetry, and tissue O_2 saturation foot mapping, respectively. Although without comparable and homogeneous design between series (inclusion-exclusion criteria), these studies however revealed few changes in angiosome-oriented (DR versus IR) tissue capillaries during the early stages of revascularization [21] [22] [73]. Ostensibly, these findings about the progression of capillary reperfusion after DR/WTR appear to contradict similar research by Iida *et al.* [6] by Shiraki *et al.* [51] by Zheng *et al.* [74] by Kawanishi *et al.* [75] and by Okamoto *et al.* [76] using parallel methods of analysis. However, beyond undeniable worth of all mentioned works, these studies all focused on the same microcirculatory skin changes post-CLTI retrieval, but in changeable collateral environments and patients, and at different sequences in reperfusion's follow-up [17] [18] [19] [26] [77]. Perhaps one of the most valuable findings of abovementioned data is that they highlight *timely skin flow redistribution stages* following arterial reconstruction [17] [26]. They express parallel "dormant collaterals" reopening after revascularization, inflammation retrieval, and rising angio- and arteriogenetic processes around the wound at sequential time intervals [29] [30] [31] [48]. Rather than being contradictory, these findings could be globally perceived as complementary pieces of a larger puzzle that merge well-timed microcirculatory events with well-timed macrocirculatory aspects of post-ischemic reperfusion [17] [26] [31]. The concrete effects of CLTI revascularization afford better analysis in a sequential and time-dependent approach method. It also becomes more and more eloquent the notable role that a multidisciplinary diabetic foot team plays in the treatment and parallel follow-up after revascularization [11] [14] [41] [64] for both, DR/WTR, or IR in current practice [26].

Modern meta-analyses concerning DR/WTR. Several thorough, recent meta-analyses on this subject revealed applicable information about potential WTR usefulness and the benefit of the AC in CLTI treatment [24] [29] [78] [79].

In a systematic literature review of 1290 CLTI cases, Biancari *et al.* [78] found that DR may enhance superior wound healing rates, if this strategy can be technically applied [78]. In the same analysis, DR limb salvage rates were, however, comparable to IR but with no statistical weight [78]. Two non-randomized retrospective studies conducted by Bosanquet *et al.* [24] and Huang *et al.* [29] revealed similar end-point examinations. These authors analyzed 1868 and 779 individually published cases, respectively, and their conclusions similarly suggested that DR may improve tissue regeneration and limb preservation better than IR (or random) distal foot reperfusion [24] [29]. Nevertheless, cumulative DR has not been shown to be superior to IR in terms of mortality, major adverse limb events (MALE), and reintervention rates [24].

It has also been shown that, in addition to the revascularization strategy, diabetic CLTI ulcer healing involves a multifaceted process. As described by Azuma *et al.* [68] the associated systemic factors, wound features, infections, wound management strategy, and revascularization technique, all additionally affect the wound healing process [68].

In a recent multicenter study of 871 limbs, Shiraki *et al.* [51] documented that the non-ambulatory status, decreased serum albumin, Rutherford category 6 presentations [32] local wound infection, lack of run-off foot vessels, and IR or non-application of the AC, were independent significant predictors for delayed wound healing [51].

These recent observations corroborating those of Serra *et al.* [80] Iida *et al.* [81]) Kret *et al.* [70] and Aydin *et al.* [82] indicate that, without coupled control of all concurrent risk factors for correct wound healing, and uniform diagnostic, treatment, or follow-up methods for WTR, all challenging claims "in favor" or "against" the use of the AC should be considered with caution [24] [26] [70] [80]. A new analysis and review made by Das *et al.* [83] in a 422 consecutive series of CLI patients, all treated by AC first-option strategy shows that beyond correct topographic foot flow reconstruction, the depths of ulcers, their duration, the albumin and the C-reactive protein levels, also the presence of local infection and gangrene represent independent factors to be carefully pondered in statistic evaluation [83]. Similar findings were reported by Lo *et al.* [84] in another 809 patients analysis a few months ago. The renal insufficiency, Rutherford 6, TASC "C" and "D" lesions, and the liability to perform IR (inadequacy for DR) were significant factors towards tissue decay and limb loss [84].

A remarkable 3932 patient review and meta-analysis of DR in CLI treatment was recently published by Jongsma *et al.* [85]. Over 306 screened abstracts, the Authors revealed significant improvement of healing and major amputation rates by using DR/WTR, in accordance with the AC. However, this significance tends to be lost for major amputation in bypass studies and no major difference was observed in global survival of patients [85]. Congruent observations were also provided by Bunte *et al.,* in a parallel review study focusing on AC applications in CLI [86]. A recent and conspicuous review and meta-analysis made by Dilaver *et al.* gathered an impressive 4146 limbs analysis from 22 selected publications on AC/CLTI treatment strategy [87]. The authors document global superior limb salvage and healing rates for DR versus IR however, with no effects on mortality and re-interventions in these patients [87].

Specific WTR applications in diabetic patients. Several contemporary publications suggest that applying the WTR strategy and the DR, particularly in diabetic subjects with critically neuro-ischemic foot wounds and notable loss of collaterals, could be rewarding [7] [11] [14] [17] [58].

The diabetic foot syndrome (DFS) has been shown to more frequently associate with distal atherosclerosis, "*functional microcirculatory impairment",* and global collateral depletion [11] [15] [54] [88]. In this setting, while O'Neal and colleagues [88] defined the concept of *diabetic* "end-artery occlusive disease" (*EAOD)* [88] parallel research established useful correlations with angiosome-guided revascularization [7] [11] [26] [59].

The EAOD theory focuses on the remaining blood flow to the diabetic foot [88] especially in cases when aggressive medium-sized collateral atherosclerosis [17] [88] is associated with *acute septic thrombosis* of "small arterioles" [54] [88] that is accompanied by wound sepsis, local inflammation, and neuropathic capillary shunting [17] [54] [88].

Thorough knowledge of the EAOD may help clinicians to better understand why blood flow from "a few millimeters of skin to the entire *diabetic foot* or leg"

[88] relies on specific nourishing vessels that are solely derived from one *angiosome-dependent* artery [7] [26] [59]. Similar to our findings [7] [14] [59], the EAOD may explain why patients with more distal and specific revascularization have a higher probability of adequate tissue recovery [7] [17] [26] [88].

Thirty years after its first description, the AC [1] [2] [3] [4] continues to interest the medical community in the search for better CLTI management.

In fact, it appears that WTR and EAOD theories together may both afford useful synergies in treating collateral deprived diabetic CLTI patients [17] [26].

Prospective analyses. Contemporary literature assembles only a few available prospective series or registries concerning DR and WTR, to date (**Table 1**). Beyond the above-mentioned initiatory *prospective* article of Kabra *et al.* [57] a recent 212 prospective analysis on AC-guided angioplasty in CLI conducted by Elbadawy *et al.* [89] was published the last year. This paper reveals better and quicker healing results for intentional endovascular DR, however with no significant difference in limb salvage and amputation free survival between groups [89]. In another up-to-date 40 cases prospective analysis, Rother *et al.* [90] found a notable difference in "time to healing" for bypass that was superior in DR against IR. The authors observed yet no meaningful significance in immediate microcirculation changes between the studied groups [90]. These two recent prospective studies seem but to confirm previous *retrospective* tissue healing observations about quicker *median time* to "tissue recovery" following DR/WTR [6] [7] [8] [9] [27] [59]. These findings open the doorway towards eventual benefits upon *the time for hospitalization*, *quality of life*, *social reintegration*, and health *costs* in future research, since obtaining faster tissue recovery mediated by WTR and DR [17] [26] [85].

Recent clinical correlations. In a 2017 editorial article, Varela *et al.* [77] highlights the new paradigm shift for vascular practitioners that represents the introduction of AC in CLI treatment. This novel trend in current revascularization can be more specifically sustained nowadays because of the new understanding for that the major role that collaterals play in DR, and WTR [17] [18] [19] [26] [77].

Another remarkable 225 diabetic foot wounds analysis for healing was newly provided by Weaver *et al.* [91]. The authors compare the SVS-"WIfI" wound classification [92] versus direct angiosome reperfusion (DR) [6] [7] [8] [9] [10] and pedal arch patency [20] as predictors of ulcer healing in diabetic patients with PAD. They seemingly observe that specific *hemodynamic indicators* like «direct angiosome perfusion» [49] [50] [51] [52] or «pedal arch patency» [20] (as variants of DR) studied alone, had lower predictive significance for tissue recovery than the multivariable *risk factors* "WIfI" (Wound, Infection, Ischemia) classification [92]. The authors further recommend that each wound's specific features should systematically accompany individual hemodynamic data in every revascularization strategy analysis towards *wound healing* [92]. This approach brings more clarity in defining and predicting «clinical success» rates than «major amputation» notion does [64] [92].

From 2010 to the present, larger studies of CLI patients continue to provide new insights into better understanding and applying DR and WTR strategies [6] [7] [8] [9] [10] [17] [18] [19] [83] [84] [85] [86].

However concomitant and new inquiries unceasingly unfold concerning this theory, alike those for any soaring interest research field [17].

3.8. New Interrogations in Angiosome-Oriented Revascularization

In light of increasing clinical information, several new questions confront researchers and clinicians regarding the applicability of the AC in CLTI. These interrogations, and at this level of CLTI understanding and treatment can be summarized [93] as:

1) What specifically *defines today* the term "direct revascularization" (DR), wound-directed, or "angiosome-guided" revascularization? Beyond targeting the principal angiosomal arteries (**Figure 1**), should the main regional collaterals, the arterial-arterial communicants and the foot arches also be included in a broader WTR strategy? [3] [17] [18] [19] [77] Does a wider vascular topographic view of the ischemic foot replace previous concepts and afford better clinical results?

2) What is the best *diagnostic method* for accurately applying WTR? [17] [25] [26] It becomes obvious that single macro, or micro-vascular evaluation can only poorly define the whole regional hemodynamic changes of DR/WTR versus IR in the CLTI context [18] [26].

3) Does wound oriented revascularization rely on the *type* of arterial reconstruction (bypass versus angioplasty)? [16] [26] [49] Should we consider these two techniques as concurrent, or rather complementary ways of treatment for specific CLTI patterns and patients? [26]

4) How to *assess* successful tissue recovery and clinical success among the five described *phases of tissue healing* [50] [51] [52] [62] and the three *stages of flow redistribution* [26] [62] following CLTI reperfusion?

Does the heterogeneous "limb salvage" indicator still holds accurate ischemic meanings?

Do the classical "primary patency" and "limb preservation" rates thoroughly reflect efficient tissue regeneration effects in the multifaceted CLTI environment? [17] [26] [91]

5) What is the best *follow-up* indicator for DR/WTR efficacy (if any)?

6) What remains lastly the biggest challenge in performing angiosome-guided wound targeted revascularization?

Despite undeniable progress in better understanding the "macrocirculatory" and "microcirculatory" angiosomal flow [6] [7] [8] [9] [14]-[19], there is still a lack of consensus concerning quantitative and qualitative collateral support in AC definition [17] [26]. The related clinical success following DR/WTR needs similar standardization [17] [26].

Concerning *the first question*, while a majority of authors define DR as successful reperfusion of main foot angiosomal branches (the "source arteries" alone) [6] [7] [8] [27] [67] [68], others describe equivalent results by including *Indirect* "collateral-enhanced" reperfusion through remnant arterial-arterial interconnections [10] [17] [18] [19] [55] [69] or *Direct* "collateral-mediated" revascularization via the foot arches and the metatarsal communicants [16] [30] While some authors analyze pedal arches patency and DR as separate (and competitor) hemodynamic entities in CLTI [20] [94] others assemble both notions in a broader regional perfusion vision as to intentionally target topographic revascularization towards the wound zone [16] [17] [18] [19] [26] [77].

Thereafter, a precise and widely accepted definition of DR is still pending [26] It is probably not conceivable to judge any further DR/IR analysis without preliminary solid ground consensus about truly definition of DR [85] [93] [95].

Regarding *the second question*, it has recently become more apparent that only the combination of *micro*- and *macrocirculatory* diagnostic methods can improve regional foot flow assessment regardless of the CLTI collateral pattern of distribution [17] [18] [19] [21] [26]. Future investigations are certainly needed to prove this perspective [25].

Concerning *the third question*, while several contemporary series observed improvements in clinical results by using directed angioplasty [6] [58] [59] [81] topographic bypasses [8] [69] or both [10] [27] [49] [55] in the targeted foot angiosome(s) [24] [56] other researchers noted no differences between *DR* and *IR* in "limb salvage rates" [20] [21] [22] [72].

Based on available contemporary literature, it has become apparent that the arterial-arterial connections between different foot perfusion zones may play a crucial role in flow redistribution [3] [14] [15] [16] [17] [18] [19] [77] following bypass or angioplasty [49] [77] and with or without angiosomal consideration [11] [14] [25].

Focusing *the next two questions*, although widely used as therapeutic success indicator, "patency" and/or "limb preservation" are independently considered by different authors and may poorly reflect the real limb tissue benefits following WTR [12] [26] [54] [93]. This observation seems particularly true in diabetic multifactorial CLTI wounds [14] [15] [16] [17] [88]. It is known that for these patients the recently and successfully revascularized limb is still at jeopardy for tissue loss by concomitant neuropathy, infection, systemic factors, etc. [17] [41] [93] [95].

Future prospective databases and analyses may bring new clarification on topographic revascularization subject.

For the last interrogation the answer remains more complex. Performing WTR implies supervision of precise diagnostic and therapeutic stages, each gathering specific challenges and individual defiance factors. From a pragmatic perspective the high frequency of severe atherosclerotic disease, long occlusions and dense calcifications currently encountered in specific angiosomal "source arteries" to treat [26] [27] still represents a daily challenge for every committed interventionist.

3.9. What Is Still Needed?

Similar to other developing theories of interdisciplinary interest, the limited current evidence has fueled an expected debate concerning the advantages and downsides of the AC oriented DR/WTR in CLTI [16] [30].

The implementation of the AC in current CLTI therapy represents a rational hypothesis but still remains theoretical and without practical validation at the present time. Although currently successfully employed in specific myocardial revascularization [52] neurosurgery [53] and plastic reconstructive skin flap surgery [2] [3] [4] its usefulness in treating critical ischemic feet wounds undoubtedly needs complementary documentation in an evidence-based practice [14] [26] [30] [93] [94] [95] [96]. Unlike other new thesis, its judiciousness depend on simultaneous control of parallel hemodynamic, local tissue, and systemic risk factors that round off the multifaceted CLTI milieu. Thus, additional larger series with controlled multicenter, randomized, multidisciplinary and prospective analysis (level "A" of evidence) [64] are mandatory to fulfill the present understanding of the WTR applications in CLTI (available level "C" of evidence) [64] as to provide concrete proofs and algorithms for its clinical utility [24] [25] [26] [29] [30] [85] [95] [96].

Limitations. The majority of current notifications in this review are based on clinical observational data. Therefore, the level of evidence is low because of the lack of available randomized, prospective, and multicentric variable analysis. Due to relative scarcity of consistent standardized series, no complementary study quality scoring at the inclusion of documents, and no statistical data reworking were attached in this discussion.

Further stratification of information in accordance to Cochrane recommendations, in a meta-analysis profile is scheduled in a near stage of this work.

4. Conclusion

The notion of angiosome wound-guided revascularization (via DR or WTR) detains only a reserved level of confirmation at the present time. As for DR, the WTR equally needs higher levels of evidence allowed by *standardized definition*, *uniform indications*, and pertinent *multicenter and prospective results*, before larger applications.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Taylor, G.I. and Palmer, J.H. (1987) The Vascular Territories (Angiosomes) of the Body: Experimental Study and Clinical Applications. *British Journal of Plastic Surgery*, **40**, 113-141. https://doi.org/10.1016/0007-1226(87)90185-8

[2] Taylor, G.I. and Pan, W.R. (1998) Angiosomes of the Leg: Anatomic Study and

Clinical Implications. *Plastic and Reconstructive Surgery*, **102**, 599-616. https://doi.org/10.1097/00006534-199809010-00001

[3] Attinger, C.E., Evans, K.K. and Mesbahi, E. (2006) Using the Angiosome Principle in Planning the Optimal Revascularization, Chapter 8. In: Sidawy, A.N., Ed., *Diabetic Foot Lower Extremity Arterial Disease and Limb Salvage*, Lippincott Williams & Wilkins, Philadelphia, 104-107.

[4] Rozen, W.M., Grinsell, D., Koshima, I., *et al.* (2010) Dominance between Angiosome and Perforator Territories: A New Anatomical Model for the Design of Perforator Flaps. *Journal of Reconstructive Microsurgery*, **26**, 539-545. https://doi.org/10.1055/s-0030-1262947

[5] McGregor, A.D. (1992) The Angiosome: An *in Vivo* Study by Fluorescein Angiography. *British Journal of Plastic Surgery*, **45**, 219-221. https://doi.org/10.1016/0007-1226(92)90081-8

[6] Iida, O., Nanto, S., Uematsu, M., *et al.* (2010) Importance of the Angiosome Concept for Endovascular Therapy in Patients with Critical Limb Ischemia. *Catheterization and Cardiovascular Interventions*, **75**, 830-836. https://doi.org/10.1002/ccd.22319

[7] Alexandrescu, V.A., Hubermont, G., Philips, Y., *et al.* (2008) Selective Primary Angioplasty Following an Angiosome Model of Reperfusion in the Treatment of Wagner 1 - 4 Diabetic Foot Lesions: Practice in a Multidisciplinary Diabetic Limb Service. *Journal of Endovascular Therapy*, **15**, 580-593. https://doi.org/10.1583/08-2460.1

[8] Neville, R.F., Attinger, C.E., Bulan, E.J., *et al.* (2009) Revascularization of a Specific Angiosome for Limb Salvage: Does the Target Artery Matter? *Annals of Vascular Surgery*, **23**, 367-373. https://doi.org/10.1016/j.avsg.2008.08.022

[9] Biancari, F. and Juvonen, T. (2014) Angiosome-Targeted Lower Limb Revascularization for Ischemic Foot Wounds: Systematic Review and Meta-Analysis. *European Journal of Vascular and Endovascular Surgery*, **47**, 517-522. https://doi.org/10.1016/j.ejvs.2013.12.010

[10] Varela, C., Acin, N.F., Haro, J.D., *et al.* (2010) The Role of Foot Collateral Vessels on Ulcer Healing and Limb Salvage after Successful Endovascular and Surgical Distal Procedures according to an Angiosome Model. *Vascular and Endovascular Surgery*, **44**, 654-660. https://doi.org/10.1177/1538574410376601

[11] Marso, S.P. and Hiatt, W.R. (2006) Peripheral Arterial Disease in Patients with Diabetes. *Journal of the American College of Cardiology*, **47**, 921-929. https://doi.org/10.1016/j.jacc.2005.09.065

[12] Gulati, A., Botnaru, I. and Garcia, L.A. (2015) Critical Limb Ischemia and Its Treatments: A Review. *Journal of Cardiovascular Surgery* (*Torino*), **56**, 775-785.

[13] Toursarkissian, B., D'Ayala, M., Stefanidis, D., *et al.* (2002) Angiographic Scoring of Vascular Occlusive Disease in the Diabetic Foot: Relevance to Bypass Graft Patency and Limb Salvage. *Journal of Vascular Surgery*, **35**, 494-500. https://doi.org/10.1067/mva.2002.120046

[14] Alexandrescu, V. and Letawe, A. (2015) Critical Limb Ischemia Strategies in Diabetics: Present Deeds and Future Challenges. *Current Research in Diabetes & Obesity Journal*, **1**, 553-555.

[15] Waltenberg, J. (2001) Impaired Collateral Vessel Development in Diabetes: Potential Cellular Mechanisms and Therapeutic Implications. *Cardiovascular Research*, **49**, 554-560. https://doi.org/10.1016/S0008-6363(00)00228-5

[16] Alexandrescu, V.A. (2012) Angiosomes Applications in Critical Limb Ischemia: In

Search for Relevance. Minerva Medica, Torino, 1-30, 71-88.

[17] Alexandrescu, V.A. and Triffaux, F. (2016) Ischemic Ulcer Healing: Does Appropriate Flow Reconstruction Stand for All That We Need? In: Alexandrescu, V.A., Ed., *Wound Healing*: *New Insights into Ancient Challenges*, InTech Publ., Rijeka, 251-282. https://doi.org/10.5772/64834

[18] Zheng, X.T., Zeng, R.C., Huang, J.Y., *et al.* (2016) The Use of the Angiosome Concept for Treating Infrapopliteal Critical Limb Ischemia through Interventional Therapy and Determining the Clinical Significance of Collateral Vessels. *Annals of Vascular Surgery*, **32**, 41-49. https://doi.org/10.1016/j.avsg.2015.09.021

[19] Osawa, S., Terashi, H., Tsuji, Y., Kitano, I. and Sugimoto, K. (2013) Importance of the Six Angiosomes Concept through Arterial-Arterial Connections in CLI. *International Angiology*, **32**, 375-385.

[20] Rashid, H., Slim, H., Zayed, H., *et al.* (2013) The Impact of Arterial Pedal Arch Quality and Angiosome Revascularization on Foot Tissue Loss Healing and Infrapopliteal Bypass Outcome. *Journal of Vascular Surgery*, **57**, 1219-1226. https://doi.org/10.1016/j.jvs.2012.10.129

[21] Kawarada, O., Yokoi, Y., Higashimori, A., *et al.* (2011) Assessment of Macro- and Microcirculation in Contemporary Critical Limb Ischemia. *Catheterization and Cardiovascular Interventions*, **78**, 1051-1058. https://doi.org/10.1002/ccd.23086

[22] Rothe,r U., Krenz, K., Lang, W., *et al.* (2017) Immediate Changes of Angiosome Perfusion during Tibial Angioplasty. *Journal of Vascular Surgery*, **65**, 422-430. https://doi.org/10.1016/j.jvs.2016.08.099

[23] Aerden, D., Denecker, N., Gallala, S., *et al.* (2014) Wound Morphology and Topography in the Diabetic Foot: Hurdles in Implementing Angiosome-Guided Revascularization. *International Journal of Vascular Medicine*, **2014**, Article ID: 672897. https://doi.org/10.1155/2014/672897

[24] Bosanquet, D.C., Glasbey, J.C., Williams, I.M. and Twine, C.P. (2014) Systematic Review and Meta-Analysis of Direct versus Indirect Angiosomal Revascularization of Infrapopliteal Arteries. *European Journal of Vascular and Endovascular Surgery*, **48**, 88-97. https://doi.org/10.1016/j.ejvs.2014.04.002

[25] Alexandrescu, V.A. and London, V. (2015) Angiosomes: The Cutaneous and Arterial Evaluation in CLI Patients. In: Mustapha, J.A., Ed., *Critical Limb Ischemia*: *CLI Diagnosis and Interventions*, Chapter 5, HMP, Chicago, 71-88.

[26] Alexandrescu, V.A. and Defraigne, J.O. (2018) Angiosome System and Principle. In: Lanzer, P., Ed., *Textbook of Catheter-Based Cardiovascular Interventions*, Chapter 77, Springer, Berlin, 1344-1358. https://doi.org/10.1007/978-3-319-55994-0_77

[27] Spillerova, K., Sörderström, M., Albäck, A., *et al.* (2015) The Feasibility of Angiosome-Targeted Endovascular Treatment in Patients with Critical Limb Ischaemia and Foot Ulcer. *Annals of Vascular Surgery*, **30**, 270-276. https://doi.org/10.1016/j.avsg.2015.07.020

[28] Scott, E.C. (2015) Surgical versus Endovascular Revascularization in the Critical Limb Ischemia Patient. *Endovascular Today*, **5**, 42-46.

[29] Huang, T.Y., Huang, T.S., Wang, Y.C., *et al.* (2015) Direct Revascularization with the Angiosome Concept for Lower Limb Ischemia: A Systematic Review and Meta-Analysis. *Medicine*, **94**, 1427. https://doi.org/10.1097/MD.0000000000001427

[30] Alexandrescu, V.A. (2014) Myths and Proofs of Angiosome Applications in CLI: Where Do We Stand? *Journal of Endovascular Therapy*, **21**, 616-624. https://doi.org/10.1583/14-4692C.1

[31] Schaper, W. (2009) Collateral Circulation, Past and Present. *Basic Research in Car-*

diology, **104**, 5-21. https://doi.org/10.1007/s00395-008-0760-x

[32] Norgreen, L., Hiatt, W.R., Dormandy, J.A., Nehler, M.R., Harris, K.A., *et al.* (2007) Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *European Journal of Vascular and Endovascular Surgery*, **33**, S1-S75. https://doi.org/10.1016/j.ejvs.2006.09.024

[33] Hinchliffe, R.J., Andros, G., Apelqvist, J., Bakker, S.F., Friederichs, S., *et al.* (2012) A Systematic Review of the Effectiveness of Revascularization of the Ulcerated Foot in Patients with Diabetes and Peripheral Disease. *Diabetes-Metabolism Research and Reviews*, **28**, 179-217. https://doi.org/10.1002/dmrr.2249

[34] Zeller, T., Rastan, A., Macharzina, R., Beschorner, U. and Noory, E. (2015) Novel Approaches to the Management of Advanced Peripheral Artery Disease: Perspectives on Drug-Coated Balloons, Drug-Eluting Stents, and Bioresorbable Scaffolds. *Current Cardiology Reports,* **17**, 624-627. https://doi.org/10.1007/s11886-015-0624-6

[35] Park, S.W., Kim, J.S., Yun, I.J., *et al.* (2013) Clinical Outcomes of Endovascular Treatments for Critical Limb Ischemia with Chronic Total Occlusive Lesions Limited to Below-The-Knee Arteries. *Acta Radiologica*, **54**, 785-789. https://doi.org/10.1258/ar.2012.120217

[36] Palena, L.M., Diaz-Sandoval, L.J., Gomez Jabalera, E., *et al.* (2017) Drug-Coated Balloon Angioplasty for the Management of Recurring Infrapopliteal Disease in Diabetic Patients with Critical Limb Ischemia. *Cardiovascular Revascularization Medicine*, **19**, 83-87. https://doi.org/10.1016/j.carrev.2017.06.006

[37] Taneja, M., Tay, K.H., Dewan, A., *et al.* (2010) Bare Nitinol Stent Enabled Recanalization of Long-Segment, Chronic Total Occlusion of Superficial Femoral and Adjacent Proximal Popliteal Artery in Diabetic Patients Presenting with Critical Limb Ischemia. *Cardiovascular Revascularization Medicine*, **11**, 232-235. https://doi.org/10.1016/j.carrev.2009.10.002

[38] Spiliopoulos, S., Theodosiadou, V., Katsanos, K., *et al.* (2015) Long-Term Clinical Outcomes of Infrapopliteal Drug-Eluting Stent Placement for Critical Limb Ischemia in Diabetic Patients. *Journal of Vascular and Interventional Radiology*, **26**, 1423-1430. https://doi.org/10.1016/j.jvir.2015.06.034

[39] Pernès, J.M., Auguste, M., Borie, H., *et al.* (2015) Infrapopliteal Artery Recanalization: A True Advance for Limb Salvage in Diabetics. *Diagnostic and Interventional Imaging*, **96**, 423-434. https://doi.org/10.1016/j.diii.2014.09.002

[40] Jaff, M.R., White, C.J., Hiatt, W.R., *et al.* (2015) An Update on Methods for Revascularization and Expansion of the TASC Lesion Classification to Include Below-The-Knee Arteries: A Supplement to the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Journal of Vascular Surgery*, **22**, 663-677.

[41] Hingorani, A., LaMuraglia, G.M., Henke, P., *et al.* (2016) The Management of the Diabetic Foot: A Clinical Practice Guideline by the Society for Vascular Surgery in Collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. *Journal of Vascular Surgery*, **63**, 3S-21S. https://doi.org/10.1016/j.jvs.2015.10.003

[42] Abu Dabrh, A.M., Steffen, M.W., Asi, N., *et al.* (2015) Bypass Surgery versus Endovascular Interventions in Severe or Critical Limb Ischemia. *Journal of Vascular Surgery*, **63**, 244-253.e11. https://doi.org/10.1016/j.jvs.2015.07.068

[43] Good, D.W., Al Chalabi, H., Hameed, F., *et al.* (2011) Popliteo-Pedal Bypass Surgery for Critical Limb Ischemia. *Iranian Journal of Medical Sciences*, **180**, 829-835.

https://doi.org/10.1007/s11845-011-0740-2

[44] Hughes, K., Domenig, C.M., Hamdan, A.D., *et al.* (2004) Bypass to Plantar and Tarsal Arteries: An Acceptable Approach to Limb Salvage. *Journal of Vascular Surgery*, **40**, 1149-1157. https://doi.org/10.1016/j.jvs.2004.08.037

[45] Brochado-Neto, F.C., Cury, M.V., Bonadiman, S.S., *et al.* (2012) Vein Bypass to Branches of Pedal Arteries. *Journal of Vascular Surgery*, **55**, 746-752. https://doi.org/10.1016/j.jvs.2011.10.006

[46] Chin, J.A. and Sumpio, B.E. (2014) New Advances in Limb Salvage. *Surgical Technology International*, **25**, 212-216.

[47] Kum, S., Tan, Y.K., Schreve, M.A., *et al.* (2017) Midterm Outcomes from a Pilot Study of Percutaneous Deep Vein Arterialization for the Treatment of No-Option Critical Limb Ischemia. *Journal of Endovascular Therapy*, **24**, 619-626. https://doi.org/10.1177/1526602817719283

[48] Lehoux, S. and Lévi, B.I. (2006) Collateral Artery Growth: Making the Most of What You Have. *Circulation Research*, **99**, 567-569. https://doi.org/10.1161/01.RES.0000243585.97392.95

[49] Spillerova, K., Biancari, F., Leppäniemi, A., *et al.* (2015) Differential Impact of Bypass Surgery and Angioplasty on Angiosome-Targeted Infrapopliteal Revascularization. *European Journal of Vascular and Endovascular Surgery*, **49**, 412-419. https://doi.org/10.1016/j.ejvs.2014.12.023

[50] Brownrigg, J.R., Hinchliffe, R.J., Apelqvist, J., *et al.* (2016) Performance of Prognostic Markers in the Prediction of Wound Healing or Amputation among Patients with Foot Ulcers in Diabetes: A Systematic Review. *Diabetes-Metabolism Research and Reviews*, **32**, 128-135. https://doi.org/10.1002/dmrr.2704

[51] Shiraki, T., Iida, O., Takahara, M., *et al.* (2015) Predictors of Delayed Wound Healing after Endovascular Therapy of Isolated Infrapopliteal Lesions Underlying Critical Limb Ischemia in Patients with High Prevalence of Diabetes Mellitus and Hemodialysis. *European Journal of Vascular and Endovascular Surgery*, **49**, 565-573. https://doi.org/10.1016/j.ejvs.2015.01.017

[52] Brodmann, M. (2013) The Angiosome Concept in Clinical Practice: Implications for Patient-Specific Recanalization Procedures. *Journal of Cardiovascular Surgery*, **54**, 567-571.

[53] Hong, M.K., Pan, W.R., Wallace, D., *et al.* (2008) The Angiosome Territories of the Spinal Cord: Exploring the Issue of Preoperative Spinal Angiography. Laboratory Investigation. *Journal of Neurosurgery: Spine*, **4**, 352-364. https://doi.org/10.3171/SPI/2008/8/4/352

[54] Jörneskog, G. (2012) Why Critical Limb Ischemia Criteria Are Not Applicable to Diabetic Foot and What the Consequences Are. *Scandinavian Journal of Surgery*, **101**, 114-118. https://doi.org/10.1177/145749691210100207

[55] Acin, F., Varela, C., de Maturana, I.L., *et al.* (2014) Results of Infrapopliteal Endovascular Procedures Performed in Diabetic Patients with Critical Limb Ischemia and Tissue Loss from the Perspective of an Angiosome-Oriented Revascularization Strategy. *International Journal of Vascular Medicine*, **10**, 2-15.

[56] Elraiyah, T., Apostolos, T., Prutsky, G., *et al.* (2016) A Systematic Review and Meta-Analysis of Adjunctive Therapies in Diabetic Foot Ulcers. *Journal of Vascular Surgery*, **63**, 46S-58S. https://doi.org/10.1016/j.jvs.2015.10.007

[57] Kabra, A., Suresh, K.R., Vivekanand, V., Sumanth, R. and Nekkanti, M. (2013) Outcome of Angiosome and Non-Angiosome Targeted Revascularization in Critical

Lower Limb Ischemia. *Journal of Vascular Surgery*, **57**, 44-49. https://doi.org/10.1016/j.jvs.2012.07.042

[58] Faglia, E., Clerici, G., Caminiti, M., Vincenzo, C. and Cetta, F. (2013) Heel Ulcer and Blood Flow: The Importance of the Angiosome Concept. *International Journal of Lower Extremity Wounds*, **12**, 226-230. https://doi.org/10.1177/1534734613502043

[59] Alexandrescu, V., Vincent, G., Azdad, K., *et al.* (2011) A Reliable Approach to Diabetic Neuroischemic Foot Wounds: Below-The-Knee Angiosome-Oriented Angioplasty. *Journal of Endovascular Therapy*, **18**, 376-387. https://doi.org/10.1583/10-3260.1

[60] Orhan, E. and Ozçaglayan, O. (2018) Collateral Circulation between Angiosomes in the Feet of Diabetic Patients. *Vascular*, **26**, 432-439. https://doi.org/10.1177/1708538118759250

[61] Alexandrescu, V.A. (2012) Is the Angiosome Concept Useful? In: Greenhalgh, R.M., Ed., *Vasc Endovasc Controversies Update*, Biba Publ. Ltd., London, 469-482.

[62] Shai, A. and Maibach, H. (2005) Etiology and Mechanisms of Cutaneous Ulcer Formation. In: Shai, A. and Maibach, H.I., Eds., *Wound Healing and Ulcers of the Skin*, *Diagnosis and Therapy*, Springer, San Francisco, 30-52.

[63] Elsayed, S. and Clavijo, L.C. (2015) Critical Limb Ischemia. *Cardiology Clinics*, **33**, 37-47. https://doi.org/10.1016/j.ccl.2014.09.008

[64] Hirsch, A.T., Haskal, Z.J., Hertzer, N.R., *et al.* (2006) ACC/AHA 2005 Practice Guidelines for Management of Patients with Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic): A Collaborative Report from the American Association for Vascular Surgery/Raphy and Interventions, Society for Vascular Medicine and Biology, Society for Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines. *Circulation*, **113**, 1474-1547. https://doi.org/10.1161/CIRCULATIONAHA.106.174526

[65] Vos, C.G., Schreve, M.A., Vahl, A.C., *et al.* (2016) Venous Arterialization for Salvage of Critically Ischemic Limbs: A Systematic Review and Meta-Analysis. *Vascular*, **24**, 68-69.

[66] Alexandrescu, V., Ngongang, C., Vincent, G., Gilles, L. and Gérard, H. (2011) Deep Calf Veins Arterialization for Inferior Limb Preservation in Diabetic Patients with Extended Ischaemic Wounds, Unfit for Direct Arterial Reconstruction: Preliminary Results According to an Angiosome Model of Perfusion. *Cardiovascular Revascularization Medicine*, **12**, 10-19. https://doi.org/10.1016/j.carrev.2009.12.002

[67] Blanes, O., Riera, V., Puigmacia, L., *et al.* (2011) Percutaneous Revascularization of Specific Angiosome in Critical Limb Ischemia. *Angeologia*, **63**, 11-17.

[68] Azuma, N, Uchida, H., Kokubo, T., *et al.* (2012) Factors Influencing Wound Healing of Critical Ischaemic Foot after Bypass Surgery: Is the Angiosome Important in Selecting Bypass Target Artery? *European Journal of Vascular and Endovascular Surgery*, **43**, 322-328. https://doi.org/10.1016/j.ejvs.2011.12.001

[69] Attinger, C., Evans, K.K. and Mesbahi, A. (2006) Angiosomes of the Foot and Angiosome-Dependent Healing. In: Sidawy, A.N., Ed., *Diabetic Foot*, *Lower Extremity Arterial Disease and Limb Salvage*, Lippincott Williams & Wilkins, Philadelphia, 75-107.

[70] Kret, M.R., Cheng, D., Azarbal, A.F., *et al.* (2014) Utility of Direct Angiosome Revascularization and Runoff Scores in Predicting Outcomes in Patients Undergoing Revascularization for Critical Limb Ischemia. *Journal of Vascular Surgery*, **59**, 121-128. https://doi.org/10.1016/j.jvs.2013.06.075

[71] Deguchi, J., Kitaoka, T., Yamamoto, K., *et al.* (2010) Impact of Angiosome on Treatment of Diabetic Foot with Paramalleolar Bypass. *Japanese College of Angiology*, **50**, 687-691.

[72] Ricco, J.B., Gargiulo, M., Stella, A., *et al.* (2017) Impact of Angiosome- and Nonangiosome-Targeted Peroneal Bypass on Limb Salvage and Healing in Patients with Chronic Limb-Threatening Ischemia. *Journal of Vascular Surgery*, **66**, 1479-1487. https://doi.org/10.1016/j.jvs.2017.04.074

[73] Kagaya, Y., Ohura, H., Suga, H., *et al.* (2014) Real Angiosome Assessment from Peripheral Tissue Perfusion Using Tissue Oxygen Saturation Foot Mapping in Patients with Critical Limb Ischemia. *European Journal of Vascular and Endovascular Surgery*, **47**, 433-441. https://doi.org/10.1016/j.ejvs.2013.11.011

[74] Zheng, J., Muccigrosso, D., Zhang, X., *et al.* (2016) Oximetric Angiosome Imaging in Diabetic Feet. *Journal of Magnetic Resonance Imaging*, **44**, 940-946. https://doi.org/10.1002/jmri.25220

[75] Kawanishi, J., Ohta, T., Ishibashi, H., Sugimoto, I., Iwata, H., Takahashi, M., Yamada, T. and Hida, N. (2009) Quantitative Assessment of Therapeutic Effects in the Critically Ischemic Limb Using ^{99m}Tc-Diethylene-Triamine-Pentaacetic Acid Serum Albumin. *Surgery Today*, **39**, 14-20. https://doi.org/10.1007/s00595-008-3778-7

[76] Okamoto, S., Iida, O., Nakamura, M., *et al.* (2015) Postprocedural Skin Perfusion Pressure Correlates with Clinical Outcomes I Year after Endovascular Therapy for Patients with Critical Limb Ischemia. *Angiology*, **66**, 862-866. https://doi.org/10.1177/0003319715569907

[77] Varela, C., Acin, F., De Haro, J. and Michel, I. (2017) The Role of Foot Collateral Vessels on Angiosome-Oriented Revascularization. *Annals of Translational Medicine*, **5**, 431-436. https://doi.org/10.21037/atm.2017.08.41

[78] Biancari, F. and Juvonen, T. (2014) Angiosome-Targeted Lower Limb Revascularization for Ischemic Foot Wounds: Systematic Review and Meta-Analysis. *European Journal of Vascular and Endovascular Surgery*, **47**, 517-522. https://doi.org/10.1016/j.ejvs.2013.12.010

[79] Jens, S., Conijn, A.P., Koelemay, M.J., *et al.* (2014) Randomized Trials for Endovascular Treatment of Infrainguinal Arterial Disease: Systematic Review and Meta-Analysis (Part 2: Below the Knee). *European Journal of Vascular and Endovascular Surgery*, **47**, 536-544. https://doi.org/10.1016/j.ejvs.2014.02.012

[80] Serra, R., Grande, R., Scarcello, E., *et al.* (2013) Angiosome-Targeted Revascularization in Diabetic Foot Ulcers. *International Wound Journal*, **7**, 110-116.

[81] Iida, O., Takahara, M., Soga, Y., *et al.* (2014) Impact of Angiosome-Oriented Revascularization on Clinical Outcomes in Critical Limb Ischemia Patients without Concurrent Wound Infection and Diabetes. *Journal of Endovascular Therapy*, **21**, 607-615. https://doi.org/10.1583/14-4692R.1

[82] Aydin, K., Isildak, M., Karakaya, J. and Gürlek, A. (2010) Change in Amputation Predictors in Diabetic Foot Disease: Effect of Multidisciplinary Approach. *Endocrine*, **38**, 87-92. https://doi.org/10.1007/s12020-010-9355-z

[83] Das, S.K., Yuan, Y.F. and Li, M.Q. (2018) Predictors of Delayed Wound Healing after Successful Isolated Below-The-Knee Endovascular Intervention in Patients with Ischemic Foot Ulcers. *Journal of Vascular Surgery*, **67**, 1181-1190. https://doi.org/10.1016/j.jvs.2017.08.077

[84] Lo, Z.J., Lin, Z., Pua, U., *et al.* (2018) Diabetic Foot Limb Salvage—A Series of 809 Attempts and Predictors for Endovascular Limb Salvage Failure. *Annals of Vascular*

Surgery, **49**, 9-16. https://doi.org/10.1016/j.avsg.2018.01.061

[85] Jongsma, H., Bekken, J.A., Akkersdijk, G.P., *et al.* (2017) Angiosome-Directed Revascularization in Patients with Critical Limb Ischemia. *Journal of Vascular Surgery*, **65**, 1208-1219. https://doi.org/10.1016/j.jvs.2016.10.100

[86] Bunte, M.C. and Shishehbor, M.H. (2017) Angiosome-Guided Intervention in Critical Limb Ischemia. *Interventional Cardiology Clinics*, **2**, 271-277. https://doi.org/10.1016/j.iccl.2016.12.010

[87] Dilaver, N., Twine, C.P. and Bosanquet, D.C. (2018) Direct vs Indirect Angiosomal Revascularization of Infrapopliteal Arteries: An Updated Systematic Review and Meta-Analysis. *European Journal of Vascular and Endovascular Surgery*, **56**, 834-848. https://doi.org/10.1016/j.ejvs.2018.07.017

[88] O'Neal, L.W. (2007) Surgical Pathology of the Foot and Clinicopathologic Correlations. In: Bowker, J.H. and Pfeifer, M.A., Ed., *Levin and O'Neal's the Diabetic Foot*, 7th Edition, Mosby Elsevier, Philadelphia, 367-401.

[89] Elbadawy, A., Ali, H., Salem, M. and Hasaballah, A. (2018) A Prospective Study to Evaluate Complete Wound Healing and Limb Salvage Rates after Angiosome Targeted Infrapopliteal Balloon Angioplasty in Patients with Critical Limb Ischaemia. *European Journal of Vascular and Endovascular Surgery*, **55**, 392-397. https://doi.org/10.1016/j.ejvs.2017.12.003

[90] Rother, U., Lang, W., Horch, R.E., *et al.* (2018) Pilot Assessment of the Angiosome Concept by Intra-Operative Fluorescence Angiography after Tibial Bypass Surgery. *European Journal of Vascular and Endovascular Surgery*, **55**, 215-221. https://doi.org/10.1016/j.ejvs.2017.11.024

[91] Weaver, M.L., Hicks, C.W., Canner, J.K., *et al.* (2018) The SVS WIfI Classification System Predicts Wound Healing Better than Direct Angiosome Perfusion in Diabetic Foot Wounds. *Journal of Vascular Surgery*, **68**, 1473-1481. https://doi.org/10.1016/j.jvs.2018.01.060

[92] Mills, J.L., Conte, M.S., Armstrong, D.G., *et al.* (2014) The Society for Vascular Surgery Lower Extremity Threatened Classification System: Risk Stratification Based on Wound, Ischemia, and Foot Infection (WIFI). *Journal of Vascular Surgery*, **59**, 220-234. https://doi.org/10.1016/j.jvs.2013.08.003

[93] Alexandrescu, V.A. (2018) Contributions of the Angiosome Concept in the Management of the Ischemic Diabetic Foot. PhD Thesis University of Liège, Thomas & Chabot, Liège, 167-181.

[94] Troisi, N., Turini, F., Chisci, E., *et al.* (2017) Pedal Arch Patency and Not Direct-Angiosome Revascularization Predicts Outcomes of Endovascular Interventions in Diabetic Patients with Critical Limb Ischemia. *International Angiology*, **5**, 438-444.

[95] Jeon, E.Y., Cho, Y.K., Yoon, D.Y., Kim, D.J. and Woo, J.J. (2016) Clinical Outcome of Angiosome-Oriented Infrapopliteal Percutaneous Transluminal Angioplasty for Isolated Infrapopliteal Lesions in Patients with Critical Limb Ischemia. *Diagnostic and Interventional Radiology*, **22**, 52-58. https://doi.org/10.5152/dir.2015.15129

[96] Lejay, A., Georg, Y., Tartaglia, E., *et al.* (2014) Long-Term Outcomes of Direct and Indirect Below—The-Knee Open Revascularization Based on the Angiosomeconcept in Diabetic Patients with Critical Limb Ischemia. *Annals of Vascular Surgery*, **28**, 983-989. https://doi.org/10.1016/j.avsg.2013.08.026

Abbreviations

Angiosome concept (AC), below-the-knee (BTK), critical limb ischemia (CLI), chronic limb threatening ischemia (CLTI), chronic total occlusion (CTO), diabetic foot syndrome (DFS), direct revascularization (DR), end-artery occlusive disease" (EAOD), endovascular technology (EVT), indirect revascularization (IR), major adverse limb events (MALE), wound targeted revascularization (WTR).