

AN INTERVIEW WITH...

Vlad Alexandrescu, MD, PhD

Dr. Alexandrescu discusses the disparity between diabetic foot pathology treatment and global amputation rates, angiosome-targeted revascularization in CLTI, the new Global Anatomic Staging System for CLTI, and more.



Despite new awareness and technology in diabetic foot pathology treatment, why is the global amputation rate only slightly changing?

The global prevalence of diabetes mellitus has been continually rising despite proactive prevention and adequate therapy measures, from more than 420 million people in 2017 to an estimated 630 million by 2040.¹ Only about two-thirds of diabetic ulcers eventually heal, while another 28% will end in some sort of lower limb amputation, regardless of punctual therapy.^{2,3} In other words, every year, more than 1 million people with diabetes will lose part of or their entire leg due to diabetic neuroischemic complications.⁴

The truth that the global number of inferior limb amputations has only slightly changed in recent years despite huge progress in diabetic foot prevention and treatment (including revascularization) seems challenging at first glance. Nevertheless, from a much closer perspective, there is an effectively discrete yet conspicuous decrease in major amputations (particularly in higher-income countries) parallel to the steady or even worse limb salvage rates in lower-income countries.⁴ The percentage related to limb preservation, as an efficacy indicator for diabetic foot treatment, undeniably holds straightforward statistical information but requires cautious interpretation. The slight change in amputation rate can firstly be explained by unbalanced and faster diabetic pandemic dissemination as compared with much slower current therapeutic awareness and technologic progress. This discrepancy also reflects the different profiles of the diabetic population and diabetic foot care in different communities, which have different methods of prevention, screening, and multidisciplinary access to treatment.

Secondly, inasmuch as minor and major amputation rates (studied per world-specific regions) reflect irreversible limb- and life-threatening conditions, other variables such as judiciousness of the initial diagnostic exam (of diabetes and/or diabetic chronic limb-threatening ischemia [CLTI]), the patient's follow-up and social reintegration, and the association between prevention and concrete health costs per year can all influence interpretation.

Why has the benefit of angiosome-targeted revascularization in CLTI been so difficult to prove, particularly concerning the diabetic foot?

Angiosome-targeted revascularization in CLTI was initially described in 2001 but has only gained applicability in the last decade. It is a relatively recent and continuously evolving anatomic and physiologic concept in plastic surgery that also concerns current vascular applications. New questions are arising based on new clinical evidence and a better understanding of macro- and microcirculatory CLTI changes. This is particularly true in the context of the diabetic foot, where current ischemic features are affected by devastating neuropathic, septic, and hyperglycemic changes at the systemic and peripheral tissue levels. For effective diabetic foot limb preservation, arterial reperfusion is only one of at least five concomitant threatening risk factors for tissue loss to be controlled. Therefore, angiosome-targeted revascularization (with both anatomic and hemodynamic features) is not always easy to prove useful for limb preservation, because the neuroischemic diabetic foot remains at jeopardy as long as advanced local neuropathy, aggressive sepsis and osteomyelitis, extended necrotic wounds, local pressure lesions and bony deformations, lowered cardiac output (concurrent ischemic cardiopathy), and metabolic and immune disorders remain.

Other obstacles to correctly evaluating the benefit of angiosome-targeted (wound-oriented) revascularization are the lack of uniform definitions for *direct revascularization* and *topographic reperfusion*, standardized microcirculatory diagnostic methods for appropriate patient selection, and homogeneous postoperative protocols for treatment. For instance, most contemporary direct revascularization results exclusively focus on the angiosomal reperfusion of "source arteries," labeling the associated foot collaterals as "indirect revascularization." Other studies have labeled the foot arches, the direct arterial-arterial communicants, and the foot's regional large collaterals as "wound-directed revascularization" instead of angiosome-targeted revascularization.

The novel conceptualization of the critical neuroischemic diabetic foot includes both anatomic and hemodynamic characteristics. The conventional anatomic chart of the foot's angiosomes is now associated with the physiologic

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(hemodynamic) angiosome notion, which reunites one or more anatomic angiosomes that are connected by true arterial-arterial collaterals and available foot arches, and both have an equal role in regional foot perfusion. To summarize, in order to get a clearer idea of the benefit of angiosomal (or wound-oriented) revascularization, we need standardized definitions for direct/indirect revascularization, homogeneous treatment and patient selection guidelines, uniform arterial and collateral macro- and microcirculatory evaluation, and exclusive multidisciplinary follow-up protocols in multicenter and prospective future analysis.

What is your opinion on using limb salvage as a definitive indicator for clinical success after CLTI revascularization?

Limb salvage has been a highly used statistical endpoint for revascularization efficacy in CLTI since its first application as an indicator for initial critical limb ischemia in 1982. Although it has generic value for health efficacy, limb preservation per se has several limitations in expressing the precise role of arterial reperfusion among all risk factors of tissue loss in most CLTI presentations. This is true especially in the context of the multifaceted diabetic neuroischemic foot, as previously discussed. The CLTI-related diabetic foot is caused by critical tissue hypoxia related to at least one or more factors, which can affect the fate of successfully revascularized limbs. These factors currently include severe peripheral neuropathy, extensive sepsis, broad necrotic wounds, local pressure lesions, and the patient's systemic altered condition. Therefore, true assessment of limb salvage following diligent CLTI arterial reperfusion (with or without topographic orientation) should constantly be done using a multidisciplinary team approach with consistent follow-up.

Interestingly, in a recent meta-analysis on angiosome-directed revascularization, Dilaver et al found that only 18% of studies using limb salvage as a major indicator for successful revascularization involved a multidisciplinary team approach to reporting arterial flow results.⁵ It becomes evident that concomitant nonvascular causes for amputation can distort the value of this unexclusive vascular indicator among multifactorial CLTI issues. In addition, "saved limbs" from major amputation can still harbor distressing and painful chronic wounds for months, with poor social benefit and quality of life for the patient, as well as hospital costs, despite statistically and intuitively rather optimistic "limb salvage" percentages.

What are your thoughts on or key takeaways from the recently published study from Katsanos et al on the use of paclitaxel-coated balloons (PCBs) in patients with CLTI?⁶

Both meta-analyses by Katsanos et al continue to concern the medical vascular community and health care administrators.^{6,7} The finding that increased all-cause mortality and major amputation rates at 2 to 5 years of follow-up⁷ could be related to higher-dose PCBs persists up to recent days, but there is ambiguity in their liberal use for peripheral artery disease (PAD) and CLTI.⁷ However, available data seem to confirm improved drug-coated balloon (DCB) patency and comparable perioperative morbidity and mortality rates compared with classic percutaneous transluminal angioplasty, such as in LEVANT 1 and 2, the ILLUMINATE randomized controlled trial, CONSEQUENT, IN.PACT SFA, BIOLUX, and RANGER SFA. Each DCB is unique in its specific drug type, appended drug dose, crystallinity, excipients, downstream drug concentration, and secondary systemic interactions, and all may contribute to different clinical outcomes. We also know that not

all postoperative mortality can be exclusively ascribed to DCB treatment. More specifically, new clinical research and critical reviews based on the current use of PCBs and stents in PAD and CLTI continue to reveal new inferences for their utility and possible side effects. Nevertheless, I share the opinion that all creditable trials published to date have some discrepancies in primary or secondary endpoints and that homogeneous conclusions regarding each device's safety and efficacy compared to one another are not easy to draw.

Recently published data from the COMPARE 1 trial, a prospective, randomized, and noninferiority analysis of DCB applications in femoropopliteal lesions, provide new insights into these previous challenges. In this 414-patient multicenter study comparing high-dose (In.Pact DCB, Medtronic) versus low-dose (Ranger, Boston Scientific Corporation) DCBs with different coating characteristics (nominal paclitaxel densities of 3.5 $\mu\text{g}/\text{mm}^2$ vs 2 $\mu\text{g}/\text{mm}^2$), clinical results were "comparable" with "excellent effectiveness and safety through 12 months for femoropopliteal interventions including a wide range of lesion lengths."⁸

In the same setting, the novel meta-analysis published in February 2020 by Dinh et al, owing to a predominantly CLTI study population and mean follow-up of 25 months, failed to evince consistent statistical differences in short-to-midterm mortality for PCBs or stents compared with uncoated controls.⁹

In daily practice, we need concrete applications for DCBs and are still waiting for confirmation of broader applicability. The recent Global Vascular Guidelines provided a dedicated statement on the safety of paclitaxel-eluting devices for the treatment of CLTI, noting that controlled, prospective studies dedicated to CLTI are needed to examine the appropriateness of drug-eluting

devices, with adapted safety monitoring and regulatory oversights, to inform the vascular community.¹⁰ From the patient's point of view, such future analysis should help inform appropriate consent discussions, including mortality risk compared with the advantages of DCBs.

What was the impetus behind creating the newly proposed Global Anatomic Staging System (GLASS) as part of the Global Vascular Guidelines released last summer?¹⁰

The new Global Vascular Guidelines intersociety (Society for Vascular Surgery and European Society for Vascular Surgery) document published in 2019 represents the quintessence of more than 4 years of sustained work by many vascular specialists and offers a modern look at the complex CLTI syndrome.

The guideline document casts an ambitious challenge to redefine major traits, prognostics, and treatments of this multifaceted pathology, according to best available evidence-based revascularization (EBR) principles to date. In addition to outlining novel CLTI terminology, the document also analyzes threatening inferior limb condition as a more complex pathologic entity, beyond rigid anatomic levels and singular critical flow determinants. The new "PLAN" (Patient, Limb, ANatomy) strategy aims to optimize the decision-making algorithm to better provide individual treatment. Therefore, although relief of pain, tissue regeneration, limb preservation, and functional rehabilitation remain major goals in the EBR/PLAN concept, a new way to stage vascular anatomy (GLASS), coupled with novel hemodynamic and prognostic features (different from the Trans-Atlantic Inter-Society Consensus scale), is proposed. A new atherosclerotic anatomic delineation (four degrees of femoropopliteal lesions combined with four others at infrapopliteal level) results in three important stages of

morphologic (the target artery path) and predictive functional patterns (the limb-based patency) in a clearer, original view. From the same PLAN perspective, each patient's individual therapy matches to specific interventional indications. In my opinion, the GLASS scale is more flexible in terms of decision-making because it provides adaptations between "typical" CLTI cases and complex ischemic presentations in frail, high-risk patients who have significant morbidity and mortality risks.

I also believe that, owing to the WIfI (Wound, Ischemia, and foot Infection) classification for wound/limb evaluation, the PLAN strategy distinguishes between "low ischemic" (dominant neuropathic) and "severely ischemic" foot ulcers, which have different prognostic and revascularization indications. Although the WIfI classification has its advantages, I value the utility of an elaborated clinical categorization, such as the GLASS score and PLAN strategy, despite criticism regarding the complexity and "heaviness."

What advice would you give to those with a passion for limb salvage who seek to obtain a level of mastery in their skill set?

I have three suggestions:

- **Promote teamwork at all stages to save a limb—from diagnosis to treatment to follow-up.** A CLTI patient has myriad clinical presentations that result from multiple concurrent pathologies beyond severe ischemia, and management continually requires a common effort of committed specialists.
- **Adapt revascularization to each anatomic and hemodynamic arterial and collateral pattern.** Perform the vascular role in a flexible manner, using unceasing dialogue and good clinical sense; adapt the most suitable technique in targeting

lasting arterial segments and groups of collaterals, as well as according to the wound's location, sepsis features, and patient's individual frailties.

- **The CLTI patient is never a "one-shot" therapeutic target.** Peripheral tissue disorders are a small part of systemic hidden vascular disease. Anticipate reinterventions, and when performing initial revascularization, prepare future second options for flow. Include iterative debridement as the rule for effective tissue salvage. ■

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