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Angiosome-Targeted Endovascular Revascularization in Chronic Limb-Threatening Ischemia

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Abstract

Background: Peripheral artery disease (PAD) is a prevalent manifestation of systemic atherosclerosis and a major contributor to cardiovascular morbidity and mortality worldwide. Chronic limb-threatening ischemia (CLTI), the most advanced stage of PAD, is characterized by rest pain, non-healing ulcers, and gangrene, carrying substantial risks of limb amputation and death. Traditional revascularization strategies often fail to account for the anatomical specificity of ischemic tissue zones, prompting growing interest in angiosome-targeted approaches. The angiosome model defines distinct vascular territories of the foot, each supplied by a specific source artery, and has been proposed as a framework for directing endovascular interventions to the precise arterial pathway supplying the ischemic wound. This review examines the pathophysiology, risk factors, and diagnostic modalities for PAD and CLTI, with particular emphasis on the clinical application, outcomes, and limitations of angiosome-guided endovascular revascularization in patients with tissue loss. Current evidence suggests that direct angiosome-targeted revascularization improves wound healing, enhances limb salvage, and reduces major adverse limb events compared to indirect approaches, although the evidence base remains largely observational and requires validation through large-scale randomized controlled trials.

Keywords: Peripheral artery disease; Chronic limb-threatening ischemia; Angiosome; Endovascular revascularization; Limb salvage; Ankle-brachial index; Diabetic foot ulcer; Infrapopliteal angioplasty; WIfI classification; Drug-coated balloon

Introduction

Peripheral artery disease (PAD) is a clinical manifestation of systemic atherosclerosis that remains a potent predictor of adverse cardiovascular outcomes. Individuals with PAD, especially those exhibiting an ankle-brachial index (ABI) below 0.90, face significantly heightened risks of myocardial infarction, stroke, and cardiovascular mortality, even in the absence of overt symptoms. Screening studies have confirmed that a reduced ABI independently stratifies patients into higher-risk categories, underscoring the importance of early detection in both symptomatic and asymptomatic populations [1].

The global burden of PAD is expected to surge significantly over the coming decades, with projections estimating over 360 million cases by 2050. This anticipated rise is driven largely by metabolic risk factors such as diabetes mellitus, which accelerates atherosclerotic progression and worsens limb-related outcomes [2].

A substantial proportion of individuals with an abnormal ABI may not exhibit classic symptoms such as intermittent claudication or chronic limb-threatening ischemia (CLTI). This phenomenon, often attributed to overlapping comorbidities including diabetic neuropathy, is termed chronic subclinical ischemia. Despite the

absence of overt symptoms, these patients remain at elevated risk for cardiovascular events and progressive limb deterioration [3].

Clinical Spectrum and Staging of Peripheral Artery Disease

PAD manifests along a wide clinical spectrum. In some individuals, the disease remains asymptomatic with silent plaque accumulation. Others develop intermittent claudication (IC), characterized by exertional leg pain that resolves with rest. More severe forms progress to CLTI, featuring persistent rest pain, non-healing ulcers, or gangrene. At its most acute, PAD may present as acute limb ischemia (ALI), a sudden and dramatic reduction in blood flow often triggered by embolism or thrombosis. Two well-established classification systems guide clinical staging: the Fontaine Classification, widely used in Europe and based solely on clinical symptoms ranging from Stage I (asymptomatic) through Stage IV (ulcers or gangrene), and the Rutherford Classification, more commonly applied in the United States, which combines clinical symptoms with objective findings across seven categories (Stage 0 through Stage 6) [4].

CLTI is the most critical manifestation of PAD, marked by severely reduced blood flow to the lower extremities persisting for more than two weeks. It is associated with high risks of limb amputation and cardiovascular mortality. Data from the DENEB study highlight that patients with CLTI undergoing endovascular therapy face significant challenges, with frailty and wound severity emerging as key predictors of poor prognosis [5].

Recent evidence supports the use of ABI screening in individuals over 40 years of age, particularly those with cardiovascular risk factors. Despite its diagnostic utility, revascularization is not recommended for asymptomatic PAD, as the procedural risks may outweigh benefits in the absence of limb-threatening symptoms. Clinical focus in such cases is directed toward intensive medical therapy to prevent systemic complications [6].

The 2024 European Society of Cardiology (ESC) guidelines endorse ABI measurement as a simple, non-invasive, and cost-effective tool for PAD detection. An ABI of 0.90 or below indicates significant arterial obstruction, while values exceeding 1.40 suggest arterial stiffness, often observed in diabetic or elderly patients [7].

Risk Factors for Peripheral Artery Disease

PAD arises from a complex interplay of demographic, behavioral, and metabolic factors shared with other forms of atherosclerotic cardiovascular disease. Age is the most significant non-modifiable risk factor; PAD is rare in individuals under 40 but affects up to 25% of those aged 80 and older. Diabetes mellitus is strongly linked to PAD prevalence, severity, and poor outcomes, including a fivefold increase in limb loss, and is especially associated with femoropopliteal and tibial-peroneal trunk disease patterns. Central obesity, linked to insulin resistance and metabolic syndrome, exacerbates the impact of diabetes and dyslipidemia on vascular health [8].

Cigarette smoking is a powerful and independent predictor of PAD, with both current and former smokers exhibiting elevated risk. Smoking is particularly associated with aortoiliac and femoropopliteal arterial involvement. Elevated homocysteine levels may impair endothelial function and promote arterial stiffness, while lower socioeconomic status correlates with increased PAD prevalence due to disparities in healthcare access and lifestyle [9].

Although hypertension is common among PAD patients, its independent association is less pronounced when adjusted for age and other variables. Elevated total cholesterol and reduced high-density lipoprotein levels are associated with PAD, though the relationship with low-density lipoprotein cholesterol is less consistent. Chronic systemic inflammation, reflected in biomarkers such as C-reactive protein, is consistently associated with atherosclerosis progression [10].

Diagnostic Assessment of PAD and CLTI

The diagnostic process for PAD and CLTI begins with a comprehensive clinical assessment, including a detailed history focusing on symptoms such as intermittent claudication, rest pain, non-healing ulcers, or gangrene.

Physical examination should assess pulse strength in the lower extremities, skin integrity, and signs of ischemia. Functional status, frailty, and previous vascular interventions are also critical in evaluating disease severity. Risk factors such as smoking, diabetes, hypertension, dyslipidemia, and chronic kidney disease should be documented, as they significantly influence disease progression and outcomes [11].

Foot ulcer evaluation begins with a structured clinical examination that considers ulcer location, depth, size, signs of infection, and perfusion status. Common classification systems such as the Wagner and University of Texas models are used to stage ulcers based on depth and the presence of infection or ischemia. A cross-sectional study from tertiary care hospitals found that patients with diabetes and cardiovascular comorbidities developed more severe ulcers, underscoring the need for integrated care approaches [12].

Emerging evidence highlights the role of inflammation and nutrition-based biomarkers in assessing ulcer severity and healing potential. Indicators such as the neutrophil-albumin ratio (NAR), monocyte-albumin ratio (MAR), red cell distribution width-albumin ratio (RAR), HALP score, and Prognostic Nutritional Index (PNI) have shown strong associations with diabetic foot ulcer prevalence and severity. These biomarkers help clinicians stratify risk and personalize treatment plans [13].

Validated scoring systems such as SINBAD (Site, Ischemia, Neuropathy, Bacterial infection, Area, Depth) and PEDIS (Perfusion, Extent, Depth, Infection, Sensation) are increasingly used to standardize ulcer assessment and predict outcomes. The 2023 IWGDF guidelines recommend the WIfI (Wound, Ischemia, Foot Infection) classification as an alternative when the necessary equipment and expertise are available, particularly for characterizing patients with PAD and diabetic foot ulcers [14].

WIfI staging correlates with healing outcomes and amputation risk, with Stage 1 patients achieving near-complete healing rates while Stage 4 patients face significantly higher rates of limb loss. The system evaluates three components graded from 0 to 3: wound severity, ischemia severity based on ABI and toe pressure values, and foot infection grade ranging from absent to systemically toxic [15].

Hemodynamic Assessment and Imaging Modalities

ABI measurement is the cornerstone of PAD diagnosis, calculated by dividing the systolic blood pressure at the ankle by that at the brachial artery. An ABI below 0.90 confirms PAD, while values below 0.40 are indicative of severe ischemia often seen in CLTI. In patients with non-compressible arteries due to medial calcinosis, toe pressure and toe-brachial index (TBI) offer more reliable indicators of perfusion. Transcutaneous oxygen pressure (TcPO2) assesses skin oxygenation and is a valuable tool for evaluating wound healing potential, with values below 20 mmHg strongly associated with critical ischemia [11].

Duplex ultrasound combines B-mode imaging with Doppler flow analysis to visualize arterial anatomy and assess blood flow velocity. It is non-invasive, widely available, and effective for identifying stenosis, occlusions, and post-intervention patency. Computed tomography angiography (CTA) provides high-resolution images of the arterial tree and is useful for evaluating complex or calcified lesions, though it requires iodinated contrast and exposes patients to radiation. Magnetic resonance angiography (MRA) offers detailed vascular imaging without ionizing radiation and is preferred for patients with renal dysfunction [17].

Digital subtraction angiography (DSA) remains the gold standard for vascular imaging and is typically reserved for patients undergoing endovascular procedures, allowing real-time visualization and immediate therapeutic intervention. Emerging technologies such as laser Doppler, skin perfusion pressure, and photoplethysmography are gaining traction in microvascular assessment, particularly for patients with CLTI and diabetic foot ulcers [18].

Medical Management of Peripheral Artery Disease

Management of PAD should be comprehensive and individualized to reduce systemic atherosclerotic burden. Daily administration of aspirin or clopidogrel is recommended for all patients with PAD to reduce thrombotic risk, and in select patients with low bleeding risk, low-dose rivaroxaban may be added for enhanced protection. Aggressive lipid-lowering therapy aims to reduce LDL cholesterol to below 100 mg/dL, or below 70 mg/dL in very high-risk individuals, using high-intensity statins. Antihypertensive therapy should target values below 130/80 mmHg, with ACE inhibitors or angiotensin receptor blockers preferred for their vascular protective effects [19].

Structured physical activity, particularly supervised walking programs, is the cornerstone of initial management for patients with intermittent claudication. Evidence from more than 20 randomized controlled trials has consistently demonstrated that exercise therapy significantly improves pain-free walking distance and overall functional capacity. The standard protocol involves walking sessions lasting 30 to 45 minutes, performed three to four times per week over a minimum of 12 weeks [20].

According to the 2025 Society for Vascular Surgery update, supervised exercise therapy (SET) is a Class IA recommendation for claudication management. Despite its proven efficacy, approximately one-third of patients are unable to participate due to comorbidities, while another third decline therapy due to logistical or motivational barriers. Recent innovations, including pilot programs integrating mobile applications with remote monitoring, show promise in enhancing adherence and expanding access to SET [21].

Among pharmacologic agents for claudication, only cilostazol and pentoxifylline have received FDA approval. Cilostazol consistently ranks highest in improving walking distance and functional outcomes, while pentoxifylline shows more modest and variable results across trials [23].

Pain Management and Wound Care in CLTI

Ischemic rest pain and ulceration are hallmark features of CLTI, and effective pain management is a critical component of patient care. While definitive relief is typically achieved through restoration of perfusion, interim pain control remains essential. Initial pharmacologic strategies may include acetaminophen or non-steroidal anti-inflammatory drugs, though COX-2 inhibitors should be used cautiously due to the frequent presence of renal impairment. In more severe cases, opioid analgesics may be required, and adjunctive antidepressants with neuropathic pain-modulating properties may further enhance symptom control [24].

For patients with ischemic foot ulcers, a multidisciplinary approach is strongly recommended, including optimizing perfusion, implementing advanced wound care techniques, offloading pressure, treating infections, and managing underlying conditions. Emerging evidence supports the use of negative pressure wound therapy and dermal substitutes as part of limb salvage strategies in patients with limited revascularization options [25].

Prognostic data reveal that within one year of CLTI diagnosis, approximately 25% of patients undergo major limb amputation, while a similar proportion experiences cardiovascular events including myocardial infarction and stroke. Evidence from placebo-controlled trials indicates that conservative medical management alone yields poor outcomes, with major limb amputation rates approaching 40% within six months in patients with non-reconstructable vascular disease [27].

Advanced wound care modalities, including negative-pressure wound therapy, aggressive surgical debridement, and targeted antibiotic regimens, have achieved healing rates exceeding 50% in multidisciplinary centers. However, pharmacologic therapies such as prostanoids, vasodilators, and hyperbaric oxygen have shown limited and inconsistent efficacy in randomized trials and have not demonstrated robust limb salvage benefits [28].

Revascularization Strategy Selection

The process of selecting an appropriate revascularization strategy in PAD is inherently complex and requires a multidimensional approach. Anatomical classification systems like the Global Limb Anatomic Staging System (GLASS) and the Trans-Atlantic Inter-Society Consensus II (TASC II) provide valuable frameworks for assessing lesion severity and distribution. GLASS evaluates lesion complexity based on the Target Artery Path (TAP) and Limb-Based Patency (LBP), grading infrapopliteal disease from Grade 0 through Grade 4. TASC II categorizes infra-popliteal lesions into Types A through D based on lesion length, number, and complexity [30].

Effective management demands a nuanced understanding of the patient's overall health, goals of care, and risk tolerance. The therapeutic approach must be tailored not only to anatomical findings but also to the clinical presentation, as intermittent claudication and CLTI differ significantly in treatment objectives. Procedural success, often defined by technical endpoints such as vessel patency, does not always correlate with meaningful clinical improvement, underscoring the importance of shared decision-making [33].

Recent guidelines from the American Heart Association and American College of Cardiology emphasize individualized care pathways incorporating lesion complexity, patient frailty, and anticipated functional recovery. Emerging technologies such as perfusion imaging, biomimetic stents, and drug-coated devices are reshaping the therapeutic landscape, offering new options for patients with advanced disease [32].

Open Surgical Versus Endovascular Revascularization

Historically, open bypass surgery has been the gold standard for managing CLTI, particularly in patients with multilevel arterial occlusions. Autologous vein grafts, most notably using the great saphenous vein, have demonstrated superior long-term patency and durability compared to prosthetic conduits. The landmark BEST-CLI study demonstrated that in patients with suitable anatomy and available vein conduit, open surgery showed significantly better long-term outcomes, including lower rates of major adverse limb events and amputations [34].

Endovascular therapy offers reduced morbidity, shorter recovery times, and is often feasible in outpatient settings, making it attractive for high-risk patients. However, prior failed endovascular interventions may compromise the success of subsequent surgical bypass, leading to higher rates of graft failure and limb loss. This challenges the notion of a low-risk endovascular-first approach and reinforces the importance of individualized strategy based on conduit availability and lesion complexity [35].

The great saphenous vein remains the preferred conduit for lower extremity bypass due to its superior long-term patency. In cases where it is unavailable, alternative autogenous veins may be considered, although outcomes are more variable. Preoperative vein mapping using duplex ultrasound is essential to assess conduit suitability and guide the decision between open surgical and endovascular therapy [38].

The Global Vascular Guidelines introduced the PLAN framework, a structured model integrating patient risk estimation, limb staging using the WIfI classification, and anatomic disease characterization through GLASS. This approach emphasizes patient-centered care, moving beyond anatomy alone to guide treatment decisions. Validated prediction models further stratify postoperative survival risk and support shared clinical decision-making [31].

Infrapopliteal Angioplasty in Limb Salvage

Infrapopliteal angioplasty has become a cornerstone in the management of CLTI, especially in patients with complex below-the-knee arterial disease. The primary aim is to reestablish direct blood flow to the foot arches whenever feasible. Advances in endovascular technology have enabled innovative strategies for managing infrapopliteal arterial occlusive disease [40].

In patients with CLTI, infrapopliteal arterial occlusions are commonly encountered and present significant challenges. Although long-term outcomes remain variable, conventional guidewire recanalization techniques can

achieve high technical success and favorable limb salvage rates in appropriately selected cases. Transluminal and subintimal angioplasty techniques are applicable to crural arteries, with ipsilateral antegrade access offering enhanced procedural precision [41].

Despite the frequent presence of incomplete pedal arch anatomy in diabetic patients, targeted tibial artery revascularization remains feasible and effective in relieving ischemia. The anterior tibial artery is preferred for forefoot ischemia, while the posterior tibial artery is targeted for heel lesions. If both are inaccessible, the peroneal artery may serve as a viable alternative, and patients with isolated peroneal artery runoff have shown comparable outcomes in 12-month patency and limb preservation [43].

The core endovascular techniques include percutaneous transluminal angioplasty (PTA) using balloon dilation, drug-coated balloon (DCB) angioplasty with paclitaxel-coated devices that reduce restenosis, and atherectomy that mechanically removes plaque to enhance vessel compliance. Evidence indicates that atherectomy improves technical success and reduces bailout stenting in lesions shorter than 10 cm [46].

Post-Revascularization Care and Surveillance

Hemodynamic success following endovascular angioplasty is typically assessed by improvement in the ABI. A post-procedural increase in ABI of 0.15 or more has been associated with reduced rates of reintervention and major amputation, serving as a reliable predictor of procedural efficacy [49].

Maintaining vessel patency and preventing thrombotic complications are essential following lower limb revascularization. Dual antiplatelet therapy (DAPT), consisting of aspirin combined with clopidogrel, is recommended for one to three months after endovascular procedures involving stent placement. Dual pathway inhibition using low-dose rivaroxaban with aspirin has shown superior efficacy in reducing major adverse limb and cardiovascular events [48].

Effective wound management following revascularization is essential for limb salvage. Central to this approach is regular debridement, negative pressure wound therapy, targeted antibiotic therapy guided by culture results, and offloading techniques with advanced dressings. Multidisciplinary strategies in specialized centers have demonstrated healing rates exceeding 60% [26].

Routine duplex ultrasound surveillance is recommended at 1, 3, 6, and 12 months post-intervention to monitor vascular integrity and identify complications. Supervised exercise therapy after angioplasty enhances functional recovery, lowers restenosis rates, and improves limb salvage outcomes when combined with medical therapy [22].

Limitations and Challenges of Infrapopliteal Angioplasty

One of the most persistent limitations is the high rate of restenosis following conventional PTA. Studies show that up to 40% of treated vessels re-narrow within 12 months, particularly in long or calcified lesions. Although drug-coated balloons have demonstrated improved patency, their efficacy is reduced in heavily calcified vessels [47].

Long-segment occlusions exceeding 10 cm are associated with lower technical success and higher complication rates, including dissection and elastic recoil. Severe arterial calcification impairs balloon expansion and increases the risk of procedural failure, while poor distal runoff and compromised pedal arch circulation further limit the success of revascularization [63].

Patient-specific factors such as diabetes, renal insufficiency, and systemic inflammation impair wound healing and increase the risk of graft failure. Meta-analyses confirm that diabetic patients have significantly lower limb salvage rates regardless of the revascularization technique used [54].

The Angiosome Concept and Its Anatomical Basis

The concept of angiosomes was first introduced by Taylor and Palmer in 1987, who conducted extensive cadaveric studies using ink injections and radiographic analysis to map the blood supply to the skin and underlying tissues. Angiosomes are three-dimensional blocks of tissue supplied by specific source arteries and veins, with adjacent angiosomes connected by a network of collateral vessels known as choke vessels [51].

Each angiosome functions as a distinct anatomical region with a dedicated arterial (arteriosome) and venous (venosome) network, operating together as a unified perfusion unit. Neighboring angiosomes are interconnected through multiple vascular channels that facilitate collateral circulation. These vascular links form a robust collateral network that can help maintain tissue perfusion under ischemic stress, particularly in non-atherosclerotic limbs [52].

Severe loss of collateral circulation, commonly seen in below-the-knee arterial disease associated with diabetes and advanced renal failure, can significantly impair the body's intrinsic compensatory mechanism between neighboring angiosomes. The human body is divided into 40 angiosomes, with 18 localized to the lower limbs. Within the foot, six distinct angiosomes are described, each supplied by branches of the three crural arteries [53].

The posterior tibial artery provides blood to three angiosomes through its branches: the medial calcaneal artery supplying the medial and plantar heel, the medial plantar artery supplying the medial instep, and the lateral plantar artery supplying the lateral plantar surface and the plantar aspect of the toes. The anterior tibial artery continues as the dorsalis pedis artery, supplying the dorsum of the foot. The peroneal artery contributes two angiosomes, with its lateral calcaneal branch supplying the lateral and plantar aspects of the heel [44].

Numerous normal arterial-to-arterial connections exist between the tibial vessels, contributing to the rich collateral circulation of the lower limb. The deep plantar arch, formed by the lateral plantar artery, connects with the deep branch of the dorsalis pedis artery in the first intermetatarsal space. In the absence of direct anastomoses between adjacent angiosomes, connection is maintained through small-caliber choke vessels that can enlarge in response to vascular compromise, underpinning the delay phenomenon utilized in reconstructive surgery [60].

Angiosome-Targeted Revascularization: Clinical Application and Outcomes

In CLTI, reduced blood flow compromises tissue viability, leading to pain, ulcers, and potential limb loss. Understanding angiosomes helps vascular surgeons plan revascularization procedures effectively. Angiosome-targeted angioplasty (direct revascularization) involves restoring blood flow directly to the ischemic tissue by targeting the artery supplying the affected angiosome. Indirect revascularization, by contrast, restores perfusion via collateral vessels from adjacent angiosomes without directly targeting the ischemic zone [55].

Direct revascularization is associated with significantly better wound healing and limb salvage when technically feasible, and is especially beneficial in diabetic patients with localized ischemic ulcers. Meta-analyses have shown a reduced risk of major amputation (relative risk 0.44; 95% confidence interval 0.26 to 0.75) and superior one- and two-year limb salvage rates of 86.2% and 84.9%, respectively, with angiosome-targeted approaches [54].

This technique supports a personalized treatment strategy by integrating anatomical mapping with wound location and individual patient factors, allowing clinicians to select the optimal target artery path to maximize perfusion and minimize procedural risk. Direct revascularization not only promotes tissue healing but also alleviates rest pain and enhances quality of life when pulsatile flow is restored to the ulcerated zone [47].

While indirect revascularization may still achieve acceptable outcomes when collateral circulation is robust, patients with poor collateralization or advanced atherosclerosis often experience suboptimal results. The Intentional Topographic Revascularization model expands the angiosome concept by incorporating foot arches and collateral networks to optimize perfusion [57].

Current Evidence and Knowledge Gaps

A comprehensive review emphasized the theoretical benefits of angiosome-targeted revascularization in enhancing wound healing and limb preservation but cautioned that clinical application remains inconsistent due to the absence of standardized definitions and multicenter prospective trials. To address these limitations, the concept of Wound-Targeted Revascularization has been proposed, expanding beyond strict angiosomal boundaries to incorporate collateral networks as a more adaptable strategy [57].

Several important gaps remain in the existing literature. Heterogeneity of patient populations across studies makes it difficult to interpret outcomes and generalize findings. Significant variability in how direct versus indirect revascularization is defined, the imaging modalities employed, and wound classification systems used hinders comparative analysis [65].

Most studies report outcomes within 6 to 12 months, while long-term data on durability, reintervention rates, and functional recovery remain sparse. Overlapping angiosomes and inconsistent arterial dominance can undermine targeted interventions, while few studies systematically evaluate how collateral flow and pedal arch integrity influence the effectiveness of angiosome-guided strategies [68].

Limited evidence in specific high-risk subgroups, such as patients with diabetes, renal insufficiency, or advanced frailty, further complicates clinical decision-making. These populations are disproportionately affected by CLTI but remain underexplored in targeted revascularization trials [69].

Conclusion

Current evidence suggests that direct angiosome-targeted interventions improve wound healing, enhance limb salvage, and reduce major adverse limb events compared to indirect approaches; however, the evidence base is predominantly observational and characterized by heterogeneous methodologies. Future research should prioritize large-scale multicenter randomized controlled trials with standardized protocols, long-term follow-up, and inclusion of high-risk subgroups to validate and refine angiosome-guided strategies. Integration of advanced imaging, artificial intelligence-assisted diagnostic tools, and predictive outcome models may further optimize patient selection and individualize revascularization planning. A multidisciplinary approach incorporating vascular surgery, wound care, cardiology, and rehabilitation will remain essential for optimizing long-term prognosis and reducing morbidity in this challenging patient population [70].

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