When Nerves and Arteries Collide: Shared Biology, Diagnostic Pitfalls, and Integrated Care for Neuropathy and Peripheral Artery Disease

Lidan Chen[1,*], Bowen Zhang[1]

[1] Peking Union Medical College, Chinese Academy of Medical Science, Beijing, China

***Correspondence:** Lidan Chen, Peking Union Medical College, Chinese Academy of Medical Science, Beijing 100730, China.
E-Mail: lidan.chan@foxmail.com

Abstract

Peripheral artery disease (PAD) and diabetic neuropathy frequently coexist, blunting symptom reporting, complicating diagnosis, and increasing limb threat. In classic PAD, ischemic pain reflects atherosclerotic obstruction severity due to intact nociception, while diabetes or advanced age-related neuropathy masks ischemia, enabling unrecognized tissue necrosis. Based on literature searches through November 2025 (validated via randomized trials, cohorts, and consensus statements), this review synthesizes their shared biology and diagnostic pitfalls, noting they share metabolic roots but differ clinically. PAD involves macrovascular flow limitation, while neuropathic feet develop ulcers from lost protective sensation. Effective therapy requires multimodal care; an integrated, multidisciplinary approach is needed to interrupt ischemia, denervation, ulceration, and amputation cycles.

Keywords: Peripheral arterial disease; Neuropathy; Diabetic peripheral neuropathy

Introduction

Peripheral artery disease (PAD) is increasingly common worldwide and confers major adverse cardiovascular events (MACE) and major adverse limb events (MALE). People with diabetes are at increased risk for ulcerations and amputations when diagnosed with PAD[1–3].

In diabetes and aging populations, neuropathy frequently coexists, converting many foot ulcers into neuro-ischemic lesions that require both perfusion restoration and pressure redistribution[3,6]. Half of diabetic peripheral neuropathy (DPN) may be asymptomatic. Without recognition and preventive foot care, people with diabetes are vulnerable to injuries as well as diabetic foot ulcers (DFUs) and amputations[1].

PAD-associated ischemic neuropathy can be independent from DPN, while diabetes mellitus (DM) has an additive effect on sensory changes which are observed in PAD. However, it is difficult to distinguish them from each other in clinic[4]. It is also reported neuropathic sensory loss can blunt classic ischemic symptoms, promoting late recognition of PAD. Recent multisociety PAD and IWGDF guidelines bring long-needed specificity to testing and revascularization thresholds, while

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neurology guidelines clarify painful diabetic neuropathy (PDN) therapy; it is therefore timely to gain a deeper understanding of the relationship between PAD and neuropathy, and generalize a unified, cross-specialty app roach[1,2,5–8].

In this review, we analyze the similarities, differences, and relationships between PAD and neuropathy with regard to pathophysiology, diagnostics, and therapy.

Methods

The literature searches in PubMed, Embase, and major guideline repositories (AHA/ACC 2024, IWGDF 2023, ADA 2024, AAN 2022) were performed. Search items comprised PAD, peripheral arterial disease, neuropathy, diabetic peripheral neuropathy, DPN, revascularization. Individual publications were checked for initially unidentified researches.

Epidemiology and shared risk factors

PAD is a growing public health concern worldwide, with more than 200 million people affected[9]. Over 20% of people over the age of 65 suffer from PAD[10]. The population of DM globally is expected to reach 783 million by 2045, and 1.31 billion by 2050[11–13]. Approximately 50% of people with diabetes and foot ulcer have PAD[6]. Neuropathy occurs in more than 2% of the general population and approximately 15% in those over the age of 40[14–16]. The prevalence of neuropathy in patients with diabetes is approximately 30%, and up to 50% will finally develop neuropathy during the course of the disease[12]. Diabetic distal symmetric polyneuropathy (DSP) is the most common neuropathy subtype, also named diabetic neuropathy interchangeably.

Diabetes, age, hypertension, chronic kidney disease, Atherosclerotic Cardiovascular Disease (ASCVD), and low body mass index (< 18.5 kg/m^2), jointly drive both neuropathy and PAD. In community and clinic cohorts, asymptomatic or atypically symptomatic PAD is common, especially when neuropathy is present[2,6,17]. Contemporary guidance now categorizes PAD across asymptomatic, chronic symptomatic, chronic limb-threatening ischemia (CLTI), and acute limb ischemia—reflecting the spectrum that clinicians encounter[2]. The clinical burden is compounded by polyvascular disease and microvascular comorbidities (e.g. retinopathy, neuropathy, nephropathy), which amplify MACE and MALE risks. Foot ulcers and amputation caused by PAD or DPN are major causes of death and potential mortality in patients with these conditions. The recent PAD guideline emphasizes annual foot risk assessment, neuropathy screening, and prevention[6,18–20].

A recent study shows a significant proportion of PAD patients have undiagnosed neuropathy[21]. One study showed that approximately 12% of patients with DPN had never mentioned the condition to their doctors[22]. A large cohort (approximately 125 674; median follow-up about 9.3 years) showed that microvascular disease (retinopathy, nephropathy, or neuropathy) increased amputation risk about 3.7-fold; PAD alone about 13.9-fold; and the combination about 22.7-fold—highlighting the macro- and microcirculatory interplay that drives limb loss[23]. The significant clinical meanings of PAD and neuropathy and the under estimated prevalence indicate the importance of further coordinated international researches.

Pathophysiology—shared biology and distinct lesions

DPN and PAD arise in different target tissues, yet they are driven by a shared metabolic–vascular–immune engine. Chronic hyperglycemia and dyslipidemia activate the polyol, advanced glycation end products (AEGs) and AEG receptors (AGE–RAGE), protein kinase C (PKC), and hexosamine routes, tipping redox balance, damaging mitochondria, and inciting endothelial dysfunction and low-grade inflammation. In nerves, this network injures axons and Schwann cells; in arteries and the limb microcirculation, it hardens intima, fosters thrombosis, and blunts angiogenic repair. A recent state-of-the-art neuropathy review distills these converging threads and emphasizes mitochondrial failure, immune activation, and microvascular injury as the “core triad” to target[24–27].

On the vascular side, PAD is not only stenotic conduit-artery disease. Diabetes superimposes endothelial dysfunction, impaired arteriogenesis/angiogenesis, pro-

thrombotic signaling, and skeletal-muscle bioenergetic failure, which together explain diffuse, distal disease and poor limb outcomes even after technically adequate revascularization[28,29].

Shared biological modules

Metabolic and mitochondrial stress

Glucose and lipid oversupply propel reactive oxygen species (ROS)/reactive nitrogen species (RNS) production and mitochondrial dysfunction in both neurons/Schwann cells and endothelium/smooth muscle, reducing axonal transport and excitability on one side and nitric-oxide bioavailability and adaptive remodeling on the other. These defects are central in DPN and are equally evident in PAD skeletal muscle ("ischemic myopathy") with impaired oxidative phosphorylation and mtDNA damage[24,30].

Microvascular disease as a system-wide amplifier

Diabetes thickens capillary basement membrane, perturbs pericytes, and increases permeability—features that compromise endoneurial oxygen delivery (vasa nervorum) and limb nutritive flow. This pan-microvascular dysfunction links nerve ischemia to malperfusion of skin and muscle—two tissues that ultimately determine wound healing and walking capacity in PAD[31,32].

Inflammation and thrombosis at the neurovascular interface

Sterile inflammation, platelet activation, and neutrophil–endothelial interactions feed atherogenesis and microvascular plugging in PAD; analogous immune activation participates in DPN progression and pain phenotypes. These pathways are now mapped as central to modern PAD biology[28].

Neuroimmune–vascular circuitries (NICIs) and perivascular nerves

Human and murine atherosclerosis exhibit neuroimmune cardiovascular interfaces (NICIs) in the adventitia—dense axonal networks apposed to artery tertiary lymphoid structures and smooth muscle, creating structural "artery–brain" circuits that can sense and modulate local inflammation. This provides a mechanistic bridge between neural inputs and vascular remodeling, and a conceptual scaffold for neuropathy–PAD crosstalk in the limb[33,34].

Sensory neuropeptides and transient receptor potential (TRP) channels as shared regulators

Sensory fibers (e.g. transient receptor potential vanilloid-1 [TRPV1]-positive nociceptors) release calcitonin gene-related peptide (CGRP), a potent vasodilator with pro-angiogenic and endothelial-protective actions; CGRP/endothelial nitric oxide synthasee (NOS)/Vascular endothelial growth factor (VEGF) coupling supports vascular regeneration in several tissues. These same pathways plausibly influence vasa nervorum perfusion and collateral formation in the ischemic limb[35,36].

Distinct lesions

Neuropathy

DPN shows a length-dependent distal axonopathy with early small-fiber loss, variable demyelination, and neuroinflammation. Microvascular remodeling of the endoneurial bed—basement-membrane thickening, endothelial hypertrophy, and impaired diffusion—correlates with severity and supports an ischemic component to nerve injury[24,37].

PAD

PAD features intimal atherosclerotic plaque with superimposed thrombosis/embolization, but symptoms and tissue loss track to microcirculatory failure: endothelial dysfunction, capillary rarefaction/plugging, poor arteriogenesis, and a metabolically inflexible skeletal muscle with mitochondrial dysfunction. These downstream lesions limit reperfusion and healing even when upstream stenoses are fixed[29,38]. The pathophysiological comparison of neuropthy and PAD is shown in Table 1.

Do PAD and neuropathy influence each other?

PAD → neuropathy (ischemic nerve injury)

Lower extremity ischemia associates with worse nerve function across ABI strata, and PAD cohorts show

Table 1: Pathophysiological comparison

Axis	Neuropathy (DSP/PDN)	PAD (LE atherosclerosis)	Shared
Initiating drivers	Chronic hyperglycemia, dyslipidemia	Classical ASCVD risks + diabetes	Metabolic stress, AGEs/RAGE, ROS
Primary lesion	Axonal degeneration, small-fiber loss; microvascular dysregulation of vasa nervorum	Endothelial dysfunction → plaque; distal tibial/pedal predominance; medial calcification	Endothelial dysfunction, oxidative/ inflammatory signaling
Clinical meaning	LOPS, gait imbalance, deformity; variable pain	Claudication to CLTI; atypical symptoms common	Neuro-ischemic ulcers when both coexist
Diagnostic impact	Pain under-reported; need annual sensory testing	ABI may be false-normal/high; need TBI/$TcPO_2$	Multimodal testing required
Therapeutic anchors	Glycemic optimization; AAN-endorsed analgesics; SCS for refractory PDN	GDMT (antithrombotic, statin, BP, smoking cessation); SET; revascularization	Team-based limb salvage (offloading, infection control, perfusion)

Abbreviations: AAN: American Academy of Neurology; ABI: ankle-brachial index; AGEs: Advanced Glycation End-products; ASCVD: Atherosclerotic Cardiovascular Disease; BP: blood pressure; CLTI: Chronic Limb-Threatening Ischemia; DSP: Distal Symmetric Polyneuropathy; GDMT: Guideline-Directed Medical Therapy; LE: Lower Extremity; LOPS: Loss of Protective Sensation; PAD: Peripheral Artery Disease; PDN: Painful Diabetic Neuropathy; RAGE: Receptor for Advanced Glycation End-products; ROS: Reactive Oxygen Species; SCS: Spinal Cord Stimulation; SET: Supervised Exercise Therapy; TBI: toe–brachial index; $TcPO_2$: transcutaneous oxygen pressure.

neuropathy and myopathy consistent with chronic ischemic injury. Diabetes likely heightens this vulnerability by remodeling the vasa nervorum[16,39].

Neuropathy → PAD biology (neurovascular tone and inflammation)

Loss/dysfunction of peptidergic nociceptors and autonomic fibers may reduce CGRP-mediated vasodilation, blunt microvascular recruitment, and alter NICI signaling in the adventitia—mechanisms that could hinder collateral growth or wound angiogenesis. While direct clinical proof in PAD is limited, the NICI framework and CGRP biology support this bidirectional hypothesis[33,36].

Frontier inference from neuron–tissue crosstalk

Two latest studies in cancer show that neuronal activity can organize local tissue programs, including synapse-like neuron–cancer interactions and activity-dependent growth advantages. Although derived from oncology, these data validate a general principle: peripheral neurons are not passive bystanders; they can instruct non-neuronal cells. Extrapolated to the ischemic limb, this supports testing whether neuronal activity (and neuropeptides) modulate vascular inflammation, angiogenesis, and muscle remodeling in PAD and DPN[40,41].

In a murine hindlimb ischemia model, Diao et al. showed that *NGF* gene transfer increased NGF and VEGF protein levels in gastrocnemius, boosted $CD34^+$ capillary density and endothelial proliferation, improved limb function, and shifted muscle toward type I fibers—a metabolic remodeling favorable for endurance and oxidative capacity. These data link a neurotrophin to angiogenesis and myofiber phenotype in ischemic muscle, illustrating a direct neuron-vessel-muscle axis highly relevant to PAD with coexisting neuropathy[42].

We propose that DPN and PAD are two phenotypes of one systems disorder: metabolism-driven, mitochondria-centered stress acting on a dysfunctional microcirculation, embedded within neuroimmune–vascular circuits. In this model: 1) Common drivers (hyperglycemia, dyslipidemia) → mitochondrial injury + endothelial dysfunction → impaired perfusion and tissue repair[24]; 2) PAD aggravates DPN via chronic endoneurial hypoxia from limb ischemia[43]; 3) DPN aggravates PAD by loss of neuropeptidergic support (e.g. CGRP, NGF) and maladaptive NICI signaling that restrain angiogenesis/collateralization and skew inflammation[33,35].

Clinical presentation—how neuropathy obscures PAD

Neuropathy attenuates claudication and rest pain, so PAD often first appears as nonhealing wounds, infection,

or gangrene. In non-neuropathic legs, exercise-induced ischemia produces calf pain that resolves at rest. In diabetes/older adults, sensory neuropathy blocks or distorts nociception, so PAD more often presents with "silent ischemia," atypical leg symptoms, or sudden tissue loss rather than claudication or rest pain. The 2024 ACC/AHA guideline explicitly warns that many patients have atypical or no leg symptoms—warranting objective testing despite a bland history.[1,2,44].

Neuropathy frequently masks ischemic symptoms, delays referral, and results in higher WIfI stages at presentation. Consequently, the absence of classical ischemic pain should not preclude vascular evaluation. The combination of neuropathy and PAD requires a lower threshold for objective perfusion testing and warrants earlier vascular consultation—even when classical ischemic pain is absent.

Diagnostic approach—what to test, in what order

Screen for neuropathy (annual minimum)

Follow ADA: in type 2 diabetes at diagnosis and in type 1 diabetes ≥ 5 years after onset, then at least annually. Document Loss of Protective Sensation (LOPS), deformities, and prior ulcer/amputation; risk-stratify follow-up accordingly[1].

First-line hemodynamics for PAD (2024 ACC/AHA)

Resting ABI (bands): abnormal ≤ 0.90, borderline 0.91–0.99, normal 1.00–1.40, noncompressible > 1.40. If ABI is > 1.40 or clinical suspicion remains high with normal/borderline ABI, obtain toe-brachial index (TBI) with waveforms; for exertional symptoms and normal/borderline ABI, obtain exercise ABI[2]. Recognize that neuropathy and calcification increase the prevalence of noncompressible ABIs; TBI and waveforms are crucial in diabetes[2,6].

Local tissue perfusion tests for ulcers and CLTI (2023 IWGDF)

Toe pressure: ≥ 30 mmHg increases healing probability; < 30 mmHg increases the probability of major amputation—an urgent signal. Transcutaneous oxygen pressure ($TcPO_2$): ≥ 25 mmHg increases healing probability; < 30 mmHg denotes severe ischemia. Skin perfusion pressure (SPP) ≥ 40 mmHg also predicts healing[6,45] (Table 2).

Imaging—map for therapy, not for screening

Use duplex ultrasound for segmental disease mapping and surveillance; however, Computed Tomography Angiography (CTA) or Magnetic Resonance Angiography (MRA) is preferred for detailed anatomical mapping when revascularization is planned. Accurate definition of the pedal target is essential in CLTI planning[6].

Risk staging—who benefits from revascularization?

Adopt the SVS WIfI classification (Wound, Ischemia, foot Infection) to estimate 1-year amputation risk and revascularization benefit; it is now embedded in modern guidance[7].

Management pillars—treat the artery, the nerve, and the foot

Global cardiovascular and limb risk reduction (2024 ACC/AHA)

Antithrombotic therapy. Most symptomatic PAD patients warrant single antiplatelet therapy. In appropriate patients with acceptable bleeding risk, dual-pathway inhibition—rivaroxaban 2.5 mg twice daily + aspirin—reduces MACE and MALE, including after lower-extremity revascularization (VOYAGER-PAD) and in stable polyvascular disease (COMPASS); decisions must individualize bleeding risk[2,46–48].

Lipid, blood pressure (BP), tobacco, glycemia. High-intensity statin, guideline-directed BP control, smoking abstinence, and individualized glycemic goals align with PAD and diabetes standards. Supervised exercise therapy (SET) improves walking distance and quality of life and is a Class I recommendation; structured home-based programs are reasonable when SET access is limited[2,49]. Cilostazol improves claudication walking distances and health status; contraindicated in heart failure[2].

Table 2: ABI/TBI/toe pressure/$TcPO_2$ cutoffs and indications

Test	When to use	Key cutoffs	Action Threshold (WIfI correlation)	Common Pitfalls
Resting ankle–brachial index (ABI)	Screening; walking limitation; nonhealing ulcer	≤ 0.90 PAD; 0.91–0.99 borderline; 1.00–1.40 normal; >1.40 noncompressible	ABI < 0.4 suggests severe ischemia (WIfI Ischemia Grade 3)	Medial calcification leads to "false-normal" or elevated ABI (> 1.40). Avoid in isolation for diabetic foot.
Exercise ABI	Exertional leg symptoms with normal/borderline ABI	≥ 20% fall or ≥ 30 mmHg drop post-exercise	Confirms functional PAD when resting ABI is normal	Contraindicated in patients with critical ischemia, active wounds, or severe cardiac limits.
Toe-brachial index (TBI) with waveforms	ABI > 1.40 or suspected calcified arteries	< 0.70 abnormal	TBI < 0.25 suggests severe ischemia (WIfI Ischemia Grade 3)	Cold digits or vasospasm can cause false low readings; requires waveforms for accuracy.
Toe pressure (TP)	CLTI evaluation; noncompressible ABI	≥ 30 mmHg: healing likely; < 30 mmHg: severe ischemia	TP < 30 mmHg: Urgent revascularization consideration (WIfI Ischemia Grade 3)	Edema or thick nails affect sensors; not reliable if toe is gangrenous/amputated.
Transcutaneous oxygen tension ($TcPO_2$)	Predicting wound healing; CLTI	≥ 25 mmHg: healing likely; < 30 mmHg: severe ischemia	$TcPO_2$ < 30 mmHg: Severe ischemia (WIfI Ischemia Grade 3)	Values fluctuate with edema, infection (local hyperemia), or improper temperature control.
Skin perfusion pressure (SPP)	When $TcPO_2$ unavailable or for confirmation	≥ 40 mmHg = better healing potential	SPP < 30 mmHg: Severe ischemia (WIfI Ischemia Grade 3)	Limited device access; interpret with context

Revascularization strategy for CLTI & function

In CLTI (ischemic rest pain, tissue loss, or gangrene corroborated by hemodynamics), revascularization is limb-salvaging. IWGDF intersocietal PAD guidance recommends restoring in-line flow to at least one foot artery and, when feasible, angiosome-directed targets[6].

BEST-CLI showed that among patients suitable for either approach with an adequate great saphenous vein, a bypass-first strategy reduced MALE or death versus endovascular therapy (Cohort 1). Outcomes were more similar when good conduit was unavailable (Cohort 2); therefore, conduit and anatomy should guide choice. However, in patients with diabetes, multilevel tibial and pedal disease is frequent. In these cases, the revascularization strategy is often dictated by the quality of the distal target, tibial runoff, and the necessity of pedal-arch reconstruction, rather than conduit availability alone[50,51].

Neuropathy management: screening, disease modification, pain control

Glycemic optimization and cardiometabolic risk control remain foundational; annual neuropathy/foot risk assessment is necessary[1]. Intensive glycemic control is vital in reducing the incidence and progression of DPN in patients with Type 1 Diabetes Mellitus (T1DM). In Type 2 Diabetes Mellitus (T2DM), the role of glycemic control in preventing neuropathy is more complex. Intensive glycemic control may slow the progression of neuropathy, but can not significantly prevent its onset[24,52].

It is necessary for PDN patients suffer from neuropathic pain to obtain pain relief therapy[53]. The AAN 2022 practice guideline endorses SNRIs (e.g. duloxetine), gabapentinoids (pregabalin/gabapentin), TCAs, and topical capsaicin 8%; it advises against chronic opioid therapy for PDN[24,44]. High-frequency (10-kHz) spinal cord stimulation (SENZA-PDN) added to conventional

management yielded substantial pain relief and improved quality of life with durability to 24 months in randomized and extension reports, which informed shared decision-making in selected, refractory PDN[54].

Gene therapy and gut microbiota modulation are emerging directions in the treatment of PDN. Preliminary studies using gene delivery of neurotrophic or angiogenic factors (such as *HGF* or *VEGF*) have shown potential in relieving neuropathic pain and promoting peripheral nerve repair[55,56].In parallel, growing evidence links gut microbial dysbiosis to altered metabolism, inflammation, and pain signaling in diabetes. Modifying the gut microbiota through probiotics, fecal microbiota transplantation, or metabolite-based interventions may help restore neuroimmune balance and improve neuropathic symptoms[57,58]. Although these strategies remain in early investigation, they suggest a future shift in PDN therapy from symptomatic pain control toward neural restoration and metabolic modulation, paving the way for more integrated, multimodal treatments.

Foot-focused care (the decisive local therapy)

Offloading. For non-infected plantar ulcers, use a non-removable knee-high device or total contact cast; alternatives when contraindicated. The 2023 IWGDF offloading guideline provides graded recommendations and cost-practical options[45].

Infection control. Follow IWGDF/IDSA 2023 guidance for diagnosis, severity grading, imaging for osteomyelitis when indicated, surgical source control, and antibiotic stewardship[59].

Follow-up and education. Intensify surveillance for individuals with prior ulcer/amputation, PAD, or LOPS; instruct on daily inspection, prompt reporting of skin breaks, and footwear management—principles embedded in ADA and IWGDF practical guidance[1,6,45,59,60].

Special topics & controversies

Medial arterial calcification and "normal" ABI in diabetes. In diabetes and chronic kidney disease (CKD), noncompressible arteries can produce falsely elevated or normal ABIs despite limb ischemia. The 2024 guideline explicitly recommends TBI with waveforms (and exercise ABI for exertional symptoms with normal/borderline ABI). Clinicians should maintain a low threshold to escalate testing when neuropathy blunts symptoms[2,6,61].

SGLT2 inhibitors and limb events. The FDA removed the boxed amputation warning for canagliflozin in 2020; the risk now appears lower than first estimated and is captured in Warnings/Precautions. Regardless of agent, emphasize foot surveillance and prompt care in high-risk PAD populations[62].

Practical diagnostic–therapeutic pathway (Narrative Algorithm) (Box 1)

• Annual neuropathy & foot risk screen (monofilament, vibration, reflexes, deformity, skin) in all diabetes; immediate screen in those with walking limitation or wounds[1].

• If PAD suspected (diminished pulses, nonhealing ulcer, exertional leg symptoms—even atypical): obtain ABI[2].

• If ABI 0.91–1.40 but suspicion persists, or ABI > 1.40/noncompressible: obtain TBI with waveforms; for exertional symptoms with normal/borderline ABI, obtain exercise ABI[2].

• For ulcers or suspected CLTI, obtain toe pressure and/or $TcPO_2$; if toe pressure < 30 mmHg or $TcPO_2$ < 30 mmHg, treat as severe ischemia → urgent vascular consult[1,45].

• Stage limb threat with WIfI and plan revascularization; visualize pedal targets; aim for in-line flow to at least one foot artery; consider angiosome-directed revascularization when feasible[6,7].

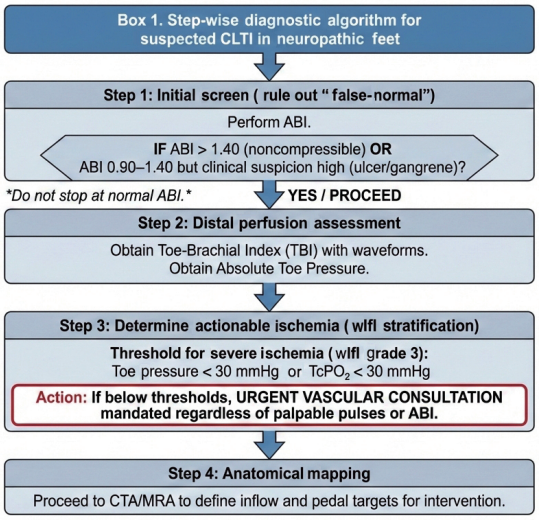
• Start GDMT (antiplatelet; consider rivaroxaban 2.5 mg bid + aspirin if appropriate), statin, BP control, smoking cessation, glycemic optimization, and SET; cilostazol if no heart failure and claudication persists[2,46,49].

• In CLTI, revascularize; when adequate single-segment saphenous vein and suitable anatomy exist, bypass-first offers fewer MALE/death events (BEST-CLI)[50].

• Concurrently treat neuropathic pain per AAN (SNRIs,

gabapentinoids, TCAs; topical capsaicin; avoid chronic opioids). Consider 10-kHz SCS for refractory PDN[44,54].

• Offload ulcers per IWGDF and manage infection per IWGDF/IDSA; re-assess vascular status if a wound fails to reduce by ≥ 50% in about 4 weeks despite optimal care[45,59].



Therapeutics in focus

Dual-pathway inhibition (rivaroxaban 2.5 mg bid + aspirin). In VOYAGER-PAD, rivaroxaban + aspirin reduced a composite of acute limb ischemia, major amputation for vascular causes, MI, ischemic stroke, or CV death *vs.* aspirin alone after revascularization (absolute risk reduction approximately 2.6% at 3 years), with more bleeding but no significant increase in fatal/critical organ bleeding; in COMPASS, the same regimen reduced MACE and mortality in stable atherosclerotic disease, including PAD. Consider in PAD patients with acceptable bleeding risk[47,49].

Supervised exercise therapy (SET). High-quality evidence supports SET for improving pain-free and maximal walking distance, function, and quality of life; it is guideline-endorsed as a cornerstone of care. Barriers include access and reimbursement, with structured home-based programs as alternatives[49].

Surgical *vs.* endovascular revascularization (BEST-CLI, plus guideline context). In CLTI patients with usable great saphenous vein and suitable anatomy, bypass-first strategy reduced MALE or death versus best endovascular therapy; when no suitable vein, outcomes were broadly similar—so conduit and anatomy should guide choice. These findings are reflected in IWGDF recommendations emphasizing in-line foot flow and center expertise[6,50].

Painful diabetic neuropathy (PDN) pharmacotherapy and neuromodulation. AAN 2022 endorses duloxetine, pregabalin/gabapentin, TCAs, and topical capsaicin 8%; it recommends against chronic opioid therapy. For refractory cases, 10-kHz SCS produced large, durable improvements *vs.* conventional medical management in randomized trials, with benefits sustained to 24 months[44,54].

Practical takeaways for clinicians

• Do not trust symptoms alone in neuropathic feet; test perfusion[1,2].

• Toe pressure and $TcPO_2$ convert uncertainty into action; know the 30/25–30 mmHg thresholds[6,61].

• SET for everyone who can walk, revascularization for CLTI (bypass-first when vein and anatomy permit), and dual-pathway inhibition in selected patients improve limb and cardiovascular outcomes[2,46,49,50].

• Treat pain without opioids when possible; escalate to 10-kHz SCS for refractory PDN after shared decision-making[44,54].

• Team sport: vascular surgery/interventional, cardiology, endocrinology/diabetes, podiatry, wound care, pain/Physical medicine and rehabilitation (PM&R), infectious diseases—around the patient's goals.

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Conflicts of interest

The authors declare no conflict of interest.

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