



Published in final edited form as:

Circ Cardiovasc Qual Outcomes. 2025 March ; 18(3): e000135. doi:10.1161/HCQ.0000000000000135.

Understanding the Pain Experience and Treatment Considerations Along the Spectrum of Peripheral Artery Disease: A Scientific Statement from the American Heart Association

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Abstract

Peripheral artery disease (PAD) is an atherosclerotic condition that affects a growing number of individuals worldwide, with estimates exceeding 220 million. One of the central hallmarks of PAD is lower extremity pain, which may present as intermittent claudication and atypical leg pain, and in more severe cases ischemic rest pain, neuropathic pain, and in those who underwent amputation, phantom limb pain. Although the majority of individuals with PAD may experience pain that is chronic in nature, the etiology and phenomenology of pain may differ.

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Nociceptive, inflammatory, and neuropathic mechanisms all play a role in the generation of pain. Pain in PAD results in severe disability and can co-present with distress, sickness behaviors such as avoidance and further deconditioning, and concomitant depression, anxiety, and addiction secondary to opioid use. These factors potentially lead to chronic pain interacting with a multitude of domains of functioning, including physical, emotional, and behavioral. While pain is a normal adaptive response, self-defeating behaviors and cognitions contribute to the persistence or worsening of the chronic pain experience, disability, and distress. Much is still unknown about the phenomenology of pain in PAD and its clinical subgroups and how it affects outcomes. Borrowing from other chronic pain syndromes, multimodal pain management strategies that emphasize a biopsychosocial model have generated a solid evidence-base for the use of cognitive behavioral approaches to manage pain. Multimodal pain management in PAD is not currently the norm, but theoretical pathways and roadmaps for further research, assessment, and clinical implementation are presented in this statement.

1. Pain in Peripheral Artery Disease: A Concern for Clinicians and Researchers

An estimated 8.5 million individuals in the United States, and over 220 million individuals worldwide are affected by peripheral artery disease (PAD), with numbers continuing to rise.^{1,2} The 2024 American Heart Association PAD guidelines establish the clinical subsets of PAD; asymptomatic PAD, chronic symptomatic PAD, chronic limb threatening ischemia (CLTI), and acute limb ischemia (ALI).³ A central hallmark of the experience of PAD is pain, which is often the initial symptom. On one end of the spectrum is intermittent claudication which may progress to tissue loss or even lower extremity amputation. Intermittent claudication is characterized by pain that is relieved upon rest, but which severely impacts individuals' function. On the other end, individuals may evolve to more extreme expressions of PAD, CLTI, which presents in 6.5 million individuals across industrialized nations.^{1,4,5} CLTI is an impactful condition which may be represented by extreme pain at rest, poorly healing wounds, and risk of amputation. Individuals may present with atypical symptoms of PAD, such as heaviness and leg discomfort, making the diagnosis at times difficult for clinicians. Thus, increased awareness of PAD and its risk factors are important upon encountering patients. The complexity of management at times involves additional comorbidities, such as spinal stenosis, osteoarthritis, diabetes, radiculopathy and other chronic diseases, which may delay appropriate diagnosis.

Both early-stage PAD as well as CLTI are associated with adverse cardiovascular outcomes, with CLTI having the worst prognosis for limb and life amongst individuals with PAD.⁶⁻⁹ Pain management is paramount as life expectancy exceeds one year after the diagnosis of PAD¹⁰⁻¹²

Living with PAD translates into severe disability where chronic pain may be a central part of the disease experience. Recently, there have been calls for person-centered outcome studies in PAD to shift from studying 'limbs' to 'individuals' perspectives, as well as the broader disease experience with psychological frameworks of illness in mind when looking at PAD treatment outcomes.¹³⁻¹⁵

The current statement further expands on this holistic view of the PAD experience and recognizes the need for an evidence-based understanding as well as treatment models that address pain and its associated clinical risk profiles.

This statement is written for any clinician who is part of the multidisciplinary PAD care team, as well as pain and addiction experts who aim to understand more about PAD, and how pain may interact with the clinical presentation, treatment pathway and outcomes in PAD. PAD researchers may also derive new insights from the current statement, as many gaps remain regarding the interplay of clinical factors, pain, and PAD. Lastly, this statement also aims to engage behavioral health specialists to address the problem of pain before it evolves into chronic pain syndromes and treat associated mental health conditions.

With no current dedicated programs for multimodal PAD pain management, this statement aims to lay the foundation that will translate into actionable insights that can guide research on the design of future holistic PAD pain management strategies, including psychological or psychologically informed interventions. Specifically, we will discuss, (a) the phenomenology of pain, its different presentations and high-risk populations; (b) a conceptual model of pain in the context of PAD; (c) current pain management strategies across the clinical PAD spectrum, interactions with PAD treatments, associated risks with adverse PAD outcomes, and risk of addiction, and specific clinical scenarios by Rutherford disease grading; (d) an overview of assessment tools for measuring pain in PAD. Next, (e) an overview of current gaps in pain management, (f) a model of multimodal pain management strategies, and (g) future directions.

2. The Etiology and Phenomenology of Pain in Peripheral Artery Disease

The Rutherford classification of PAD (or the Fontaine classification) distinguishes seven categories of disease severity with pain as one of the distinguishing features.¹⁶ Grade 0 is the asymptomatic phase. Grade 1 is characterized by mild claudication, with pain or cramping occurring in the hip, thigh, buttock or calf during strenuous physical activity. Grade 2 and 3 are characterized by moderate to severe claudication, with pain occurring during less strenuous activities such as walking. The pain is usually experienced one level distal to where the obstruction is situated.¹⁷ In this grade, pain may lead to significant functional limitations in daily life. Grade 4 is characterized by ischemic rest pain and is the threshold beyond which the limb is described as chronic limb threatening ischemia (CLTI). The pain is situated in the foot or toes and is mainly experienced when lying down. The pain can be profound and may seriously disrupt sleep. Grades 5 and 6 are additionally characterized by the presence of non-healing wounds and gangrene, which may ultimately lead to limb amputation, with Grade 7 classically described as ischemic wounds that are so severe as to merit major amputation. With the progression of PAD, pain becomes more profound and from intermittent (as in claudication) progresses to a chronic condition, often with nocturnal pain and pain at rest (Table 1).

Nociceptive, inflammatory, and neuropathic mechanisms may all play a role in the generation of pain. Claudication is the result of muscle ischemia and pain is mainly driven by nociceptive and inflammatory mechanisms. Reduced blood flow to the muscles

leads to an inadequate oxygen and nutrient supply. The resulting increased acidity of the muscle tissue stimulates acid-sensing ion channels on pain generating A δ and C fibers.¹⁸ Inflammatory mediators may also be released, leading to peripheral sensitization and hyperalgesia.¹⁹ There is a strong relationship between elevated serum or plasma levels of inflammatory markers and claudication severity (Figure 1).¹⁹ With the progression of PAD towards CLTI, the character and underlying mechanisms of pain change.²⁰ While claudication is experienced as pain originating from deep muscle tissue, ischemic rest pain is often felt more superficially in the skin. Moreover, ischemic rest pain may also have a neuropathic component (5,6).^{20,21} Prolonged ischemia can result in peripheral neuropathy,²² which causes pain through various mechanisms, including inflammatory processes and central sensitization from oversensitive or overactive nociceptors.^{18,23,24,25,26} The mechanisms related to sympathetic nervous system interaction and imbalances with the afferent neurons can all contribute to the pain syndrome.²⁷ Chronic ischemia may also lead to axonal degeneration resulting in somatic and autonomic nerve fibers injury.²⁸ Limb amputation can be a further source of pain. With disease progression, the risk of amputation increases²⁹ and may be especially prominent in individuals with PAD and concurrent diabetes.³⁰ Phantom limb pain is very common in amputees, with a lifetime prevalence as high as 80%.³¹ Chronic postsurgical pain (CPSP) can also develop after revascularization. Risk factors such as female gender, young adult age, amount of involved tissue, and surgical approach may increase the prevalence of CPSP.³²

Sex differences in symptom presentation have also been noted.³³ Women appear to have a lower prevalence of claudication but more often report rest pain or atypical leg symptoms with pain on exertion and rest. Moreover, women with PAD have greater disability and mobility loss than men.³⁴ In addition, women with PAD present with higher rates of mood disorders, and other pain-related disorders.³⁵

3. Conceptual model of Pain

Chronic pain needs to be understood as an experience that exceeds the ischemia pain, and is impacted by a multitude of factors including physical, emotional, and behavioral factors. Initially introduced by Melzack and Wall, the gate-control theory of pain posits that the experience of pain is both the result of nociceptive information ascending from the periphery, as well as through cortical input through descending pathways (Figure 2³⁶).³⁷ As both physical impacts, emotional factors such as depression and anxiety, as well as behavioral factors such as attending to the pain or avoiding painful movements, can instantly or with some delay “open the gate” for pain experience, these insights allowed for many chronic pain syndromes to be understood and managed through a biopsychosocial perspective.^{38,39} In this framework, pain is emphasized as a perception, and part of a motivational system that urges the individual to restore the body’s integrity by behavioral actions, where individuals play an active role and there is variability in pain sensations as a function of individual differences, and where pain is seen as both a physiological and psychological experience, acknowledging the mind-body interaction. More modern versions of this theoretical framework are summarized in biopsychosocial models of pain and pain management.³⁸

Per the International Association for the Study of Pain (IASP), chronic pain is defined as persisting pain lasting longer than three months and negatively impacting an individual's wellbeing.⁴⁰ According to IASP's definition⁴⁰, pain is multifactorial, as pain can have different sources contributing to chronic pain and interacting with one another.⁴¹ For PAD, much of the pain is ischemic in nature, but it may coexist with chronic postsurgical or post-traumatic pain, and with chronic neuropathic pain. Preliminary evidence shows that most individuals with PAD, have been experiencing symptoms > 6–12 months, and by default, their pain would qualify as chronic pain. Yet, early stages of PAD-related pain, and even CLTI-related pain, are currently not conceptualized or treated as a chronic pain syndrome, but rather as episodic pain, with interventions intended to relieve pain focusing mostly upon ischemia relief.

An approach that comes closer to seeing PAD as a chronic pain syndrome, and a systemic condition, is the use of exercise therapy to improve pain-free and maximum walking distance.⁴² Exercise in this setting is seen as a way to promote our body's capabilities of adapting itself systemically (reduction of inflammation, improvement of cardiovascular fitness, angiogenesis, and mitochondrial function). Research in this setting has shown that the ischemic deprivation incompletely explains the PAD pain experience, as only 5–30% of pain-related improvements following exercise therapy can be explained by accompanying improvements in hemodynamic measurements. Underlying mechanisms are multifactorial in nature and challenging the traditional belief that new blood vessel formation and improved blood flow by exercise is the main driver of pain improvement in PAD. Candidate mechanisms that are the subject of ongoing research are improvements in cardiorespiratory fitness, endothelial function, mitochondrial number and activity, and muscle conditioning.⁴³

Along with insights still to be gained about the pain syndromes and mechanisms that underly PAD, are the relative unknowns with regards to the variability in pain manifestations, co-presenting motivational and emotional factors that may influence the pain experience. We know that women experience more pain and more atypical pain symptoms in PAD. There is also indirect evidence that pain in PAD may affect the younger population in a more prominent course, as there is a larger proportion of opioid use disorder and chronic pain syndromes.⁵

Whereas pain is a normal adaptive response, self-defeating behaviors and cognitions may contribute to the persistence or worsening of the chronic pain experience, disability, and distress.³⁸ Some of these insights have been studied in PAD, and illness perceptions and health beliefs that individuals hold about severity of the pain, duration of the pain, and beliefs in the efficacy of treatments, such as exercise therapy, are highly predictive of the experienced pain burden.⁴⁴

Increasingly, the role of early life-stress experiences and childhood adversity, have been recognized in the alternation of systems contributing to pain reports, and the development of chronic pain syndromes later in life. A variety of underlying neurological and biological factors involving these alterations in processing include the hypothalamic-pituitary-adrenal axis as well as monoaminergic, opioidergic, endocannabinoid and immune systems; and

epigenetic pathways.⁴⁶ The role of trauma, which may lead to hyperarousal and dissociation, have both been implicated in understanding and the persistence of pain syndromes like fibromyalgia and headache disorders, but have not been studied in individuals with PAD.⁴⁷

Finally, how and when claudication-related pain, which is more ischemic in nature, may transition to CLTI-related pain, which is more neuropathic in nature,²⁰ is also unknown. The clinical predictors, as well as wider factors related to the social determinants of health, or psychological make-up of the individual, still need to be uncovered. There is some evidence that for those dealing with post-amputation trajectories, significant pain reduction is reported following amputation, with individuals reporting the experience of phantom limb pain as less severe as the intense pain they experienced before.⁴⁸ However, replication of findings in large samples, reliable multifactorial prediction models, precision medicine intervention models, and rehabilitation trajectories that maximize pain relief strategies have yet to be realized.

4. Current pain management practices in PAD

Optimal medical therapy with smoking cessation, antithrombotic therapy (ex. aspirin and rivaroxaban), hyperglycemic medications (sodium-glucose transport protein-2, glucagon-like-peptide-1), HMG-CoA reductase inhibitors (statins), and anti-hypertensives contribute to the overall management of PAD as a chronic atherosclerotic disease.³ Similarly, control of atherosclerotic risk factors may mitigate chronic inflammation and hence, the pain pathways associated with inflammation. Cilostazol, a phosphodiesterase III inhibitor, has shown a benefit in patients with claudication or chronic symptomatic PAD.⁴⁹ A meta-analysis of patients treated with cilostazol, revealed an increase in maximal walking distance and ankle brachial index.⁵⁰ Exercise rehabilitation has shown benefit in the improvement of lower extremity nociceptive pain, specifically the pain-free and maximum walking distance, and individuals' overall functioning. With concurrent therapy, both nonopioid and opioid agents are used in the management of pain in PAD and in CLTI. Since pain is a mix of nociceptive and neuropathic symptoms, non-steroidal anti-inflammatories (NSAIDs), anti-neuropathic agents (such as gabapentin), and opioid therapy are being used in the management of pain in PAD. In patients with diabetes additional screening for neuropathy, may highlight intervention targets in the management of pain.²⁶ Treatments may include lifestyle changes, pharmacotherapies (neuropathic pain agents), or invasive management (anesthetic nerve blocks). Diabetes education and therapeutic footwear are options for consideration when diabetic neuropathy is present, in addition to medical management.³

The efficacy of escalating analgesia in PAD for pain relief, improved walking distance, and QOL remains uncertain.⁵¹ Non-steroidal anti-inflammatory drugs are promising, but entail renal and cardiac risks. Antidepressants and gabapentinoids target neuropathic pain, reducing opioid use, with inconclusive evidence supporting their prevention of phantom limb pain.⁵² Various drugs, such as prostanoids, cilostazol, naftidrofuryl, pentoxifylline, buflomedil, carnitine, and propionyl-L-carnitine, demonstrate limited benefits.^{53–55} Thus, the treatment of pain in PAD should initiate with the recommendation of supervised exercise therapy, followed by cilostazol, both class I indications. Although, other therapies are

suggested for the treatment of pain, neither nonopioid or opioid agents are recommended nor mentioned in the 2024 AHA PAD guidelines.³

While revascularization in CLTI, (either open surgical or endovascular) remains the mainstay to alleviate ischemic pain, a significant number of patients may benefit from non-revascularization options.³⁰ Common approaches include spinal cord stimulation (SCS),^{31–37} lumbar sympathectomy (LS),^{38–43} intermittent pneumatic compression (IPC),^{44–48} and hyperbaric oxygen therapy (HBOT).^{49–52} Guidelines and consensus documents weakly advocate their use to mitigate amputation risk and alleviate pain in carefully selected patients.^{53,3}

As an extension, in chronic pain syndromes overall, both medical (serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and gabapentinoids, opioid medications) and psychological interventions (cognitive-behavioral interventions) have shown to be effective options to manage chronic pain in medical populations, resulting in multimodal pain management programs.^{38,39,56,57} As approaches involving opioid medications are associated with clear risks and harms, including overdosing, dependency and addiction, depression, and death, alternative approaches to chronic pain management are indicated.

Currently, there are no standards for pain management in individuals with PAD, thus most recommendations are based on expert experience and outcomes data is still emerging. Recent preliminary data suggest that individuals with PAD are at particular risk of high opioid use following their revascularization trajectories.⁵⁸ The use of opioids in PAD is used disproportionately in individuals with advanced disease. Opioid use increases in those with a history of revascularizations and with worsening severity of PAD, with individuals diagnosed with CLTI having a > 60% odds of high opioid use.^{52,59} Continued high opioid use, defined as >2 opioid prescriptions are present in 1 in 4 individuals with PAD, this includes those with and without a history of opioid use. Garnering reports from other conditions, the use of opioids is demonstrated to result in a greater risk of adverse outcomes, such as addiction, incident depression, hyperalgesia, and mortality. In PAD, specifically, it has been associated with a higher risk of post-operative complications following lower-extremity bypass surgery,⁶⁰ higher admission costs, length of stay, addiction,⁶¹ and higher risk of amputation.^{60,62} At present, there is no sufficient data in the best treatment for phantom limb pain.

5. Assessment of Pain Questionnaires/Scales in PAD

Although multiple tools exist to evaluate the presence, severity, and quality of pain in other chronic conditions,⁶³ there are no disease-specific measures to assess the multifaceted pain experience in PAD or CLTI. Studies evaluating the efficacy of treatment for PAD or CLTI consistently include outcomes related to technical success of revascularization, major adverse cardiovascular or limb events, functional ability, and in some cases, patient-reported outcomes covering aspects related to health status.⁶¹ Multiple reviews have evaluated the use and quality of functional and quality of life patient reported outcome measures (PROM) in PAD^{14,64} and CLTI,⁶⁵ and a comprehensive review of these tools is outside the scope of this

statement. Patient reported outcome measures in PAD help assist in further understanding the symptoms, satisfaction with care, and further continue to educate the clinician in how the current disease is affecting the patients' physical, mental, and social well-being. Thus, this would continue to build the optimal management plan for the individual patient, improving the quality of care and planning the best treatment regimen.

PAD-specific instruments designed to assess patient burden and experience include only limited evaluation of pain. For example, the San Diego Claudication Questionnaire,⁶⁶ is frequently used to classify an individual's symptoms as either 'typical' or 'atypical.' This measure includes a single item related to pain "Do you get pain in either leg or buttock on walking", but there is no evaluation of pain severity or impact. Similarly, the PAD Quality of Life Questionnaire (PADQOL)⁶⁷ is a PAD specific measure of health-related quality of life and includes two items specific to pain in PAD "My legs hurt a lot when I walk because of my PAD" and "My PAD causes me a lot of pain." As individuals are provided with the option to respond on a 6-point scale from strongly agree to strongly disagree, some information on the burden or severity of pain can be gleaned from this scale. The Vascular Quality of Life 6 (VascuQOL-6)⁶⁸ is also commonly used in PAD but does not directly capture pain severity or experience. The Peripheral Artery Questionnaire (PAQ) has items on pain frequency, pain intensity, and nocturnal pain.⁶⁹

Presence of ischemic rest pain is a clinical indicator of CLTI, but pain is not always assessed. In CLTI, the focus is typically on limb salvage, and managing pain is typically a secondary outcome.⁷⁰ The World Union of Wound Healing Society guidelines recommend the use of simple pain assessments, such as visual, numerical, or verbal scales, or pain diaries in individuals with chronic wounds.⁷¹ Studies that have evaluated the effects of various interventions specifically on PAD/CLTI-related pain have commonly used simple numeric rating scales or visual analogue scales.⁷² Although effective in classifying pain severity, simple numeric or visual rating scales lack detail on the location and quality of pain. The Short Form McGill Pain Questionnaire,⁷³ which was originally validated in post-surgical, obstetric, and dental populations⁷³ includes 15 pain descriptors (11 sensory; 4 affective) that individuals are asked to rate on an intensity scale from 'none' to 'severe.' The Neuropathic Pain Questionnaire (NPQ) is a 12-item instrument designed to distinguish between neuropathic and nonneuropathic pain conditions,⁷⁴ but questions related to how 'unpleasant' and 'overwhelming' the pain is may also be useful in monitoring the effect of pain treatments and outcomes in individuals with PAD. (Table 2)

There are challenges related to the more comprehensive assessment of pain in PAD, however. Differentiating between pain and functional ability is challenging as they are tightly linked in many PAD assessments that assess degree of difficulty completing various activities or walking different distances and speeds via behavioral tasks (e.g., 6-minute walking, maximal treadmill distance⁷⁶) or self-report assessment (e.g., Walking Impairment Questionnaire⁷⁴). Instruments such as the Walking Impairment Questionnaire, or the Peripheral Artery Questionnaire,⁶⁹ do mention pain, but often simultaneously with other symptoms or the degree of disability combined. Often, the wording of the items group that are used in these instruments include functioning and as such, they would not allow us to

measure pain frequency, intensity, and pain quality in a more targeted way, and additional pain instruments may be advisable to be used.

Documentation of pain severity, location, and quality is also challenging in clinical practice. Limitations to the International Classification of Diseases-10 (ICD) include that the criteria are not aligned with the widely accepted biopsychosocial model of pain and did not include diagnoses related to important types of chronic pain, including chronic neuropathic pain.⁷⁷ The changes made in the ICD 11 classification system provide an opportunity for health care professional to more comprehensively assess and document chronic pain severity in PAD. Using chronic primary and chronic secondary pain diagnoses, clinicians can add extension codes related to pain severity, temporal features (continuous, episodic or continuous with additional flare-ups), and severity (none, mild, moderate, severe).⁷⁸ These options enable clinicians to provide a more complete picture of the chronic pain and how the individual experiences both pain and the effects of pain management strategies.

7. Multimodal pain management

The gate theory of pain advanced our understanding of the pain experience as having a physical impact, with emotional, and behavioral factors regulating the pain experience. Expansion of these insights have led to the study of moderating and mediating factors related to self-control and self-regulation of the pain experience, and resultant psychological interventions^{44,79,80} for chronic pain management in chronic back pain, migraine, and musculoskeletal disorders.^{38,39} Borrowing from insights gathered from other pain disorders, and reflecting on what components a multimodal pain management intervention might consist of, there are potential ways on how to integrate psychological interventions into the overall PAD management.

Cognitive-behavioral treatment, for example, is a non-pharmacological and non-invasive treatment that aims to improve accomplishing life goals that individuals value (e.g., social relationships, work goals). This multimodal and psychologically informed treatment consists of three key ingredients: risk identification, clarification, and exposure-based treatments³⁸.

The early identification of individuals at risk of becoming disabled might lead to more effective interventions. Screening tools have been developed to help clinicians assess the risk of chronic pain and its related disability in individuals seeking pain relief. For example, the Örebro Musculoskeletal Pain Screening Questionnaire predicts long-term disability and work absenteeism in working people suffering from acute and chronic musculoskeletal pain.⁷⁵ Pain education⁸¹ consists of unambiguously providing new information that that pain can be self-managed and that avoiding painful movement can be adaptive in acute pain but may have paradoxical negative effects when pain persists. Information not necessarily leads to behavior change and patients are encouraged to re-engage in valued activities that were identified as painful or potentially harmful. In such an exposure treatment, individuals receive the opportunity to experience that they may have overestimated the harmfulness of valued activities in daily life.⁵³ Expanding the behavioral repertoire enables the restoration of function and the discovery of novel ways to enrich the person's life. The exposure-

based treatment can be facilitated by lifestyle modification approaches³, supervised exercise training,⁵⁵ emotion regulation, and physiological self-regulation strategies.⁸²

8. Future Directions & Conclusion [awareness] [research] [assessment] [management]

Paving the way for comprehensive and patient-centered pain management in PAD, we highlight key areas for future focus and action:

Awareness:

Multiple gaps in our understanding of pain and its role in PAD management persist. Awareness needs to be raised regarding the phenomenology and multidimensionality of pain across the PAD spectrum, with a focus on risk stratification based upon PAD severity, psychological distress, pain beliefs, and dysfunctional behaviors. In addition, co-presenting pain syndromes and how this may impact the pain experience and outcomes in PAD are areas for future research.

Education:

Unawareness of pain models and underlying theories among PAD care team members and individuals with PAD can hinder effective management. Further educational efforts targeting PAD clinicians and individuals with PAD on effective pain management strategies are necessary to address these gaps and promote a biopsychosocial approach to pain in PAD care.

Research:

Insights into mechanisms and pathophysiological aspects of pain in PAD are still evolving, highlighting the need for a deeper understanding of nociceptive, inflammatory, and neuropathic pain pathways. Variability in pain expression and disparities in pain burden across subgroups need further investigation, particularly in high-risk individuals prone to amputation due to factors such as age, sex, race, ethnicity, and comorbidities like opioid use disorder. Research into the social determinants of health and policies at regional, state, and national levels is crucial for understanding and addressing these disparities comprehensively.

Assessment:

PAD should be recognized as a complex pain syndrome, requiring further exploration of its association with outcomes and identification of intervention targets. Novel methods of assessment, incorporating a biopsychosocial framework, are essential for developing precision-medicine models of pain management tailored to the PAD population.

Management:

Standards for pain management in PAD are lacking, but ideally, such standards would be leading to documented rates of opioid use and associated risks for prolonged use and PAD complications. Integration of pain specialists into future team-based PAD care is imperative

for addressing chronic pain needs both related to PAD and other conditions effectively and minimizing opioid-related risks.

Quality Metrics & Patient-Centered Care:

Evidence-based, multi-modal pain management strategies addressing pain from a biopsychosocial perspective are needed in PAD management. Standardization in assessment and the development of quality metrics for PAD care, including pain management targets, will enhance patient-centered care and outcomes.

In conclusion, addressing the gaps in understanding, research, assessment, and management of pain in PAD requires a comprehensive, multidisciplinary approach that integrates biopsychosocial perspectives, fosters collaboration among health care professionals, and empowers patients to actively participate in their care. By prioritizing awareness, research, assessment, management, quality metrics, and education, we can enhance the delivery of patient-centered care and improve outcomes for individuals with PAD.

NONSTANDAR ABBREVIATIONS AND ACRONYMS

CLTI	chronic limb-threatening ischemia
PAD	peripheral artery disease

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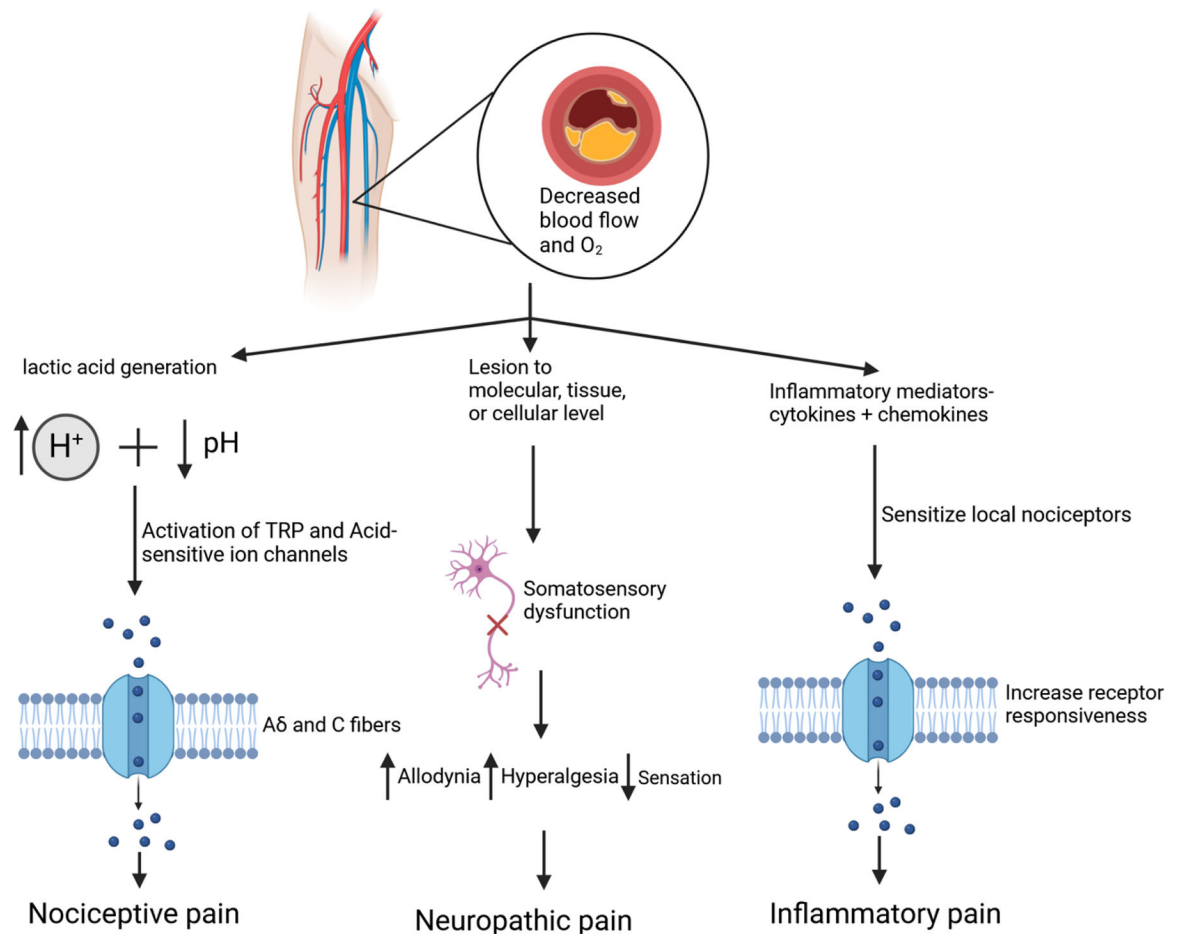


Figure 1. Conceptual Model Underlying Pain Mechanisms Related to Different Pain Manifestations in Peripheral Artery Disease and Critical Limb Threatening Ischemia in the Periphery.^{18–24}

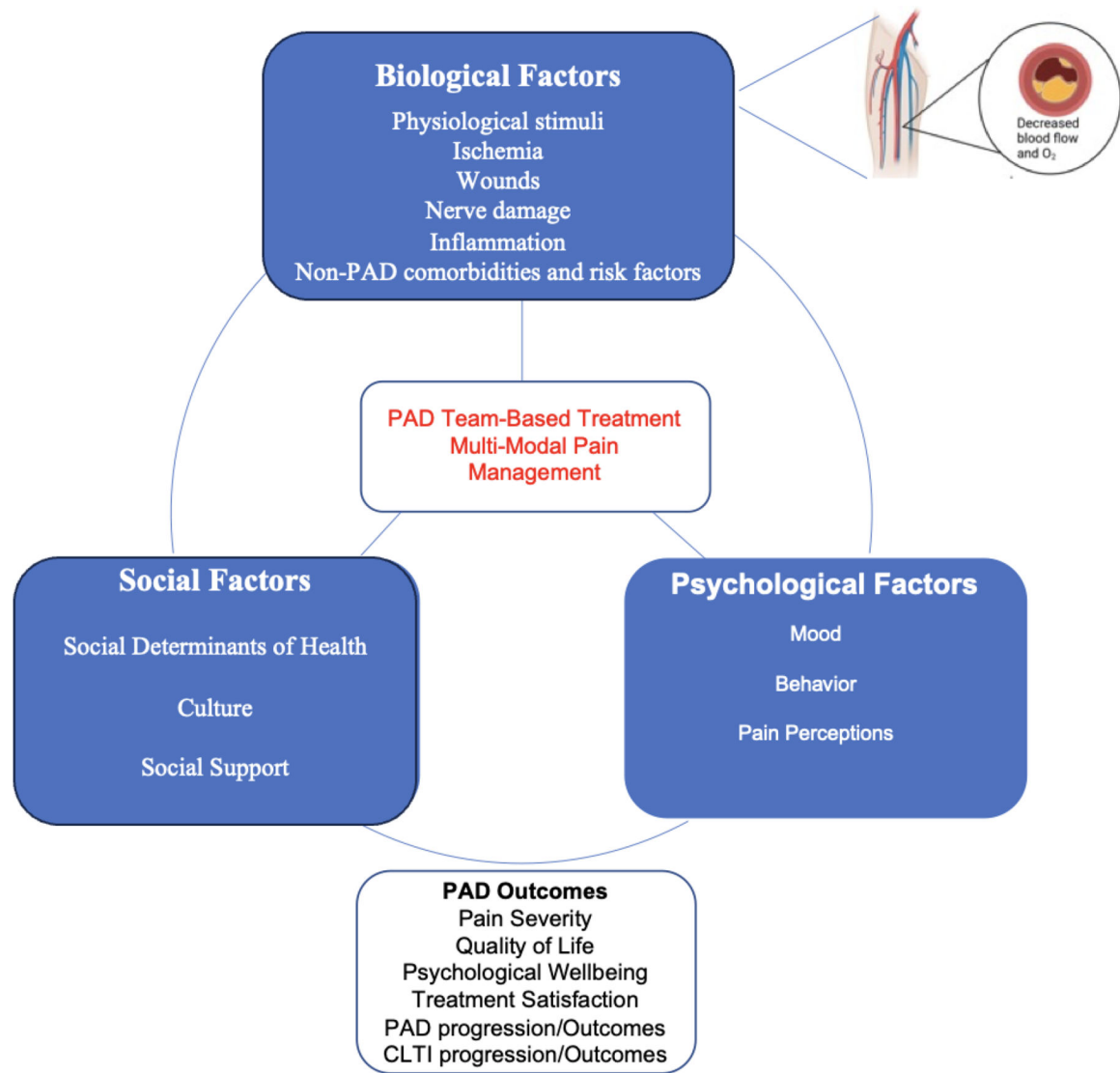


Figure 2. Biopsychosocial Model of PAD Pain.

Adapted from Miaskowski C, Blyth F, Nicosia F, Haan M, Keefe F, Smith A and Ritchie C. A Biopsychosocial Model of Chronic Pain for Older Adults. *Pain Med.* 2020;21:1793–1805.

Table 1.

Overview of Pain Symptoms by Nature, Location, and Intensity by Rutherford/Fontaine Classification.

Adapted from Rutherford et al. 1997¹⁶

Fontaine		Rutherford	
Stage	Clinical presentation	Category	Clinical presentation
I	Asymptomatic	0	Asymptomatic
IIa	Claudication at walking distances >200m	1	Mild claudication
IIb	Claudication at walking distances <200m	2	Moderate claudication
		3	Severe Claudication
III	Rest pain	4	Rest pain
IV	Ulceration or gangrene	5	Minor tissue loss
		6	Major tissue loss

Table 2. Overview of Assessment Instruments and Domains Assessed to Measure Pain in Peripheral Artery Disease.

Abbreviations: PAD, peripheral artery disease.

Assessment Tool	Pain Constructs Measured	Length
PAD-Specific Health Status Instruments		
San Diego Claudication Questionnaire ⁶⁶	Assesses presence or absence of leg-specific symptoms for thigh, buttock, and calf pain. Classification as typical Rose claudication, atypical symptoms, rest pain	9 items
Peripheral Artery Disease Quality of Life Questionnaire ⁶⁷	Includes 2 items specific to pain in PAD “My legs hurt a lot when I walk because of my PAD” and “My PAD causes me a lot of pain.” Answered on a 6-point scale from strongly agree to strongly disagree	38 items Multi-dimensional health status instrument
Peripheral Artery Questionnaire ⁶⁹	Symptom scale has 3 items on pain frequency, pain intensity, and nocturnal pain answered along various Likert scales	20 items questionnaire Multi-dimensional health status instrument
Walking Impairment Questionnaire ⁷⁴	Includes 3 items assessing location of pain in calves/buttocks, thighs, and joints and the degree of difficulty	22 items Health status instrument assessing walking impairment, distance, and speed
Pain Instruments to be Considered for PAD		
Short form McGill Pain Questionnaire ⁷³	15 descriptors (11 sensory; 4 affective) rated on an intensity scale, includes 3 pain scores	22 items, originally validated in post-surgical, obstetric, and dental populations
Neuropathic Pain Questionnaire ⁷⁴	Designed to distinguish between neuropathic and non-neuropathic pain conditions	12 items
the Örebro Musculoskeletal Pain Screening Questionnaire ⁷⁵	Predicts long-term disability and work absenteeism in working people suffering from acute and chronic musculoskeletal pain	25 items