

# Peripheral Arterial Disease (PAD)

Subjects: **Pathology**

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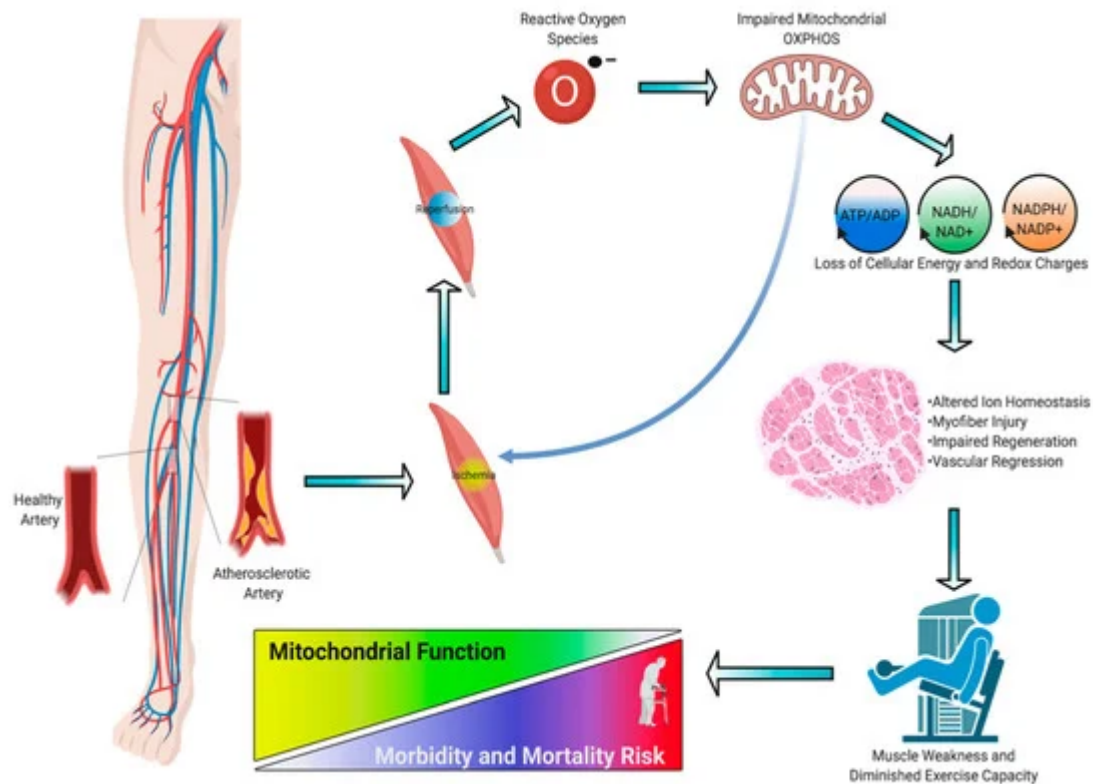
Peripheral artery disease (PAD) is caused by atherosclerosis in the lower extremities, which leads to a spectrum of life-altering symptomatology, including claudication, ischemic rest pain, and gangrene requiring limb amputation.

myopathy

peripheral vascular disease

## 1. Introduction

Peripheral artery disease (PAD) is a common manifestation of atherosclerosis that affects more than 200 million people worldwide and is the third leading cause of cardiovascular mortality <sup>[1]</sup>. PAD is caused by atherosclerotic narrowing or occlusion of blood vessels in the lower extremities that leads to a spectrum of life-altering symptomatology, including claudication, ischemic rest pain, and gangrene requiring limb amputation. Morbidity and mortality associated with PAD have increased over the last decade despite an increase in the number of lower extremity vascular procedures during that time. Current treatments for PAD are focused solely on re-establishing blood flow to the limb, implying that blood flow is the definitive factor that determines pathobiology. Unfortunately, failure rates of endovascular and revascularization procedures remain unacceptably high <sup>[2][3]</sup> and numerous cell- and gene-based vascular therapies have failed to demonstrate efficacy in clinical trials <sup>[4][5][6][7]</sup>. The low success of vascular-focused therapies implies that other non-vascular tissues must contribute to PAD pathobiology. Although atherosclerotic PAD manifests in the vascular system, there are significant consequences to skeletal muscle that result in impaired muscle health/function and exercise intolerance <sup>[8]</sup>. Several large clinical studies in PAD patients have demonstrated that muscle function/exercise capacity is the strongest predictor of morbidity/mortality <sup>[9][10][11][12][13][14][15]</sup>. Previous reports have documented evidence of skeletal muscle myopathies in PAD patients <sup>[16][17]</sup>, although its potential role in clinical pathology is not well understood. In this review, we analyze the evidence that PAD is associated with a skeletal muscle myopathy, including altered mitochondrial function and oxidative stress ([Figure 1](#)); discuss the risk factors that contribute to skeletal muscle myopathy; and review emerging therapeutic approaches that aim to mitigate these myopathic symptoms and have potential to improve outcomes for PAD patients.



**Figure 1.** Pathogenesis of ischemic myopathy in peripheral artery disease (PAD). A graphical depiction of the pathogenesis of ischemic myopathy in PAD. This figure was created with Biorender.com.

## 2. Pathogenesis, Diagnosis, and Treatment of PAD

Before embarking upon an analysis of the role of skeletal muscle in PAD pathobiology, a brief discussion of pathogenesis, diagnosis, and treatment of PAD is required. The prevalence of PAD is estimated to be 1–4% in the general population; however, among selected subgroups of elderly patients, rates exceeding 20% have been reported [18]. Due to the frequent association of PAD with cardiovascular risk factors, such as smoking, diabetes, hypertension, dyslipidemia, and increasing age, approximately 200 million patients worldwide have some form of PAD [19]. The pathogenesis of PAD has been linked to several causes, including subendothelial dysfunction, aberrant platelet activity, hyperlipidemia, tobacco exposure, as well as a myriad of other immunologic and inflammatory factors [20][21][22][23][24][25][26]. The protean clinical presentation is underscored by subintimal accumulation of lipid and fibrous materials that form a fixed arterial stenosis and/or occlusion. Classically, lower extremity atherosclerotic occlusive disease involves either the aortoiliac, femoral-popliteal, or tibial vessels, and certain subpopulations, like diabetic patients and/or subjects with renal dysfunction, present with more distal disease [27][28][29]. The clinical manifestation of PAD occurs along a spectrum with some patients being asymptomatic while others describe disabling intermittent claudication (IC). Notably, 5–10% of patients have chronic limb-threatening ischemia (CLTI) and have significantly elevated risk of major limb amputation, adverse cardiac events, and mortality compared to age-matched controls [30][31][32]. The characterization of PAD severity is predominantly dependent upon the constellation of symptoms, with non-invasive studies corroborating the presence of disease. Reproducible exertional lower extremity muscle cramping that is relieved by rest and

associated with a fixed arterial stenosis/occlusion is the hallmark description of vasculogenic claudication. In contrast, CLTI may present as rest pain or tissue loss, which classically involves the forefoot. Initial evaluation includes a thorough history and physical with ankle-brachial index (ABI) assessment to confirm the diagnosis.

For patients with claudication, risk of major limb amputation is < 1% per year, but the 5-year major adverse cardiovascular event risk including death approached 30% [33][34]. Therefore, due to the non-limb-threatening nature of this PAD presentation, clinical practice guidelines and peer reviewed evidence strongly advocates that first-line therapy be medical, including smoking cessation, an exercise walking program, hypertension and blood glucose control, daily antiplatelet and statin therapy, as well as a trial of cilostazol [35][36][37]. Subjects that are compliant with initial medical management but have refractory symptoms generally undergo further imaging (e.g., computed tomographic arteriogram, magnetic resonance arteriogram, segmental doppler, and/or pulse volume recording) to delineate the anatomic extent of disease and identify potential treatment options. Most commonly, patients with claudication present with single-level aorto-iliac or superficial femoral artery atherosclerotic occlusive disease and revascularization is usually based upon endovascular strategies if anatomically eligible. However, long-segment occlusive disease is optimally treated with construction of an arterial bypass. Successful outcomes of endovascular or open surgical remediation are determined by improvement in absolute walking distance, patient quality of life, and augmented ABIs.

In contrast to claudication, PAD patients with CLTI require revascularization due to the significant risk of major limb amputation without restoration of limb perfusion [30]. An ankle pressure < 50mmHg, toe pressures < 30mmHg, monophasic Doppler waveforms, low-amplitude calf pulse volume recordings, transcutaneous oxygen pressure < 30mmHg, and/or tissue loss with any objective measurement of occlusive disease all strongly support the clinical diagnosis of CLTI [29]. Limb salvageability is determined using the Society for Vascular Surgery Wound, Ischemia, and foot Infection (WiFi) and Rutherford classification systems [38][39]. Tenets of revascularization include determination of the inflow vessel, the recipient outflow vessel, conduit choice, hemodynamic significance of the lesion, and characterization of the patient's functional and physiological status. These variables inform the clinician to optimally select the unique arterial reconstruction strategy for each patient. Generally, CLTI patients present with more complex patterns of PAD, so the probability of a durable outcome with endovascular recanalization is less compared to bypass but many providers subscribe to an 'endo first' approach [40][41][42]. For subjects undergoing infrainguinal arterial bypass, use of single-segment ipsilateral saphenous vein and clinical stage of the CLTI presentation are the most important determinants of limb salvage [43][44]. Clinical success is highlighted by freedom from major adverse limb events, such as unplanned re-intervention, thrombosis free graft function, and/or major limb amputation.

### 3. Skeletal Muscle Pathology in PAD

The pathogenesis of PAD is undoubtedly vascular in nature with a primary causative factor involving atherosclerosis. However, the ensuing limb muscle pathology appears to be intimately linked to patient outcomes [10][11][13][14][15][45][46][47][48][49]. A large body of literature from clinical human studies reports that altered skeletal muscle phenotype is prevalent in ischemic limbs and that patients with PAD present with reduced exercise capacity

and impaired lower extremity skeletal muscle function compared with age-matched healthy counterparts [49][50][51][52][53]. Longitudinal cohort studies determined that the exercise capacity and functional performance are strong predictors of mortality [15][54], implicating skeletal muscle health/function as an important clinical feature of PAD pathobiology.

Limb muscle pathology in PAD manifests as weakness and exercise intolerance. In addition, claudication and/or ischemic rest pain further reduce physical activity levels and negatively impact functional independence and quality of life [55]. The genesis of exercise intolerance in PAD is without doubt multifactorial [55][56]. Blockage of arteries that causes restricted blood flow to lower extremities is amongst the primary factors that negatively affects mobility and functional performance [57]. Further to limb perfusion limitations, walking performance in PAD patients is also related to muscle fiber size [48], and muscle size/strength is predictive of mortality [10][11][13]. Indeed, one of the most notable features of skeletal myopathy related to peripheral arterial insufficiency is lower extremity muscular atrophy. Data from computed tomographic (CT) imaging demonstrated that PAD patients have smaller calf muscle area with accumulated adipose tissue compared to the individuals without PAD [13][57][58]. Further investigation of morphology using histopathologic analysis revealed that a smaller cross-sectional area of both type I and II fibers as well as increased intramuscular collagen deposition [53][57][59]. The underlying mechanisms that explain these changes are complex and still require further examination, but a number of studies in human and animal studies suggest that impaired proteostasis (i.e., altered signaling pathways that regulate protein synthesis and degradation) plays a central role in muscle atrophy [60][61]. A dysfunctional peripheral nervous system, such as identified demyelination or focal denervation on the neuromuscular junction, will also likely stimulate the process of muscle atrophy and contribute to the weakness and functional impairment [62][63]. Skeletal muscle abnormalities also include capillary rarefaction and impaired microcirculation in PAD patients with IC and these findings are more obvious in people suffering from CLTI [59][64][65]. Considering the aspects of limited conduit artery blood flow and impaired endothelium-dependent vasodilation during physical activity in this population, there will probably be an increased reliance on the microcirculation to meet the metabolic demands of the contracting muscle. Therefore, novel strategies targeting skeletal muscle myopathy to reverse muscle atrophy [66][67] that can be used in addition to those targeting capillary rarefaction [68][69] hold great potential to produce greater and more sustainable clinical impact.

Interestingly, following progressive resistance training, PAD patients with intermittent claudication showed delayed onset of claudication time and improved maximum walking time during a graded treadmill test in addition to the increased leg muscle strength [68]. These changes occurred without improving limb hemodynamics (ABI), suggesting the perfusion-independent beneficial impact of resistance training may arise from changes in skeletal muscle. In support of this concept, invasive revascularization in symptomatic PAD patients does not effectively normalize exercise performance [70][71], and acute pharmacological administration of sildenafil, which enhances limb perfusion, did not alter walking capacity [72]. Taken together, these observations indicate that factors other than lower extremity perfusion must play a significant role [8].

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## References

1. Fowkes, F.; Rudan, D.; Rudan, I.; Aboyans, V.; Denenberg, J.O.; McDermott, M.M.; Norman, P.E.; Sampson, U.K.A.; Williams, L.J.; Mensah, G.A.; et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: A systematic review and analysis. *Lancet* 2013, 382, 1329–1340.
2. Tsai, T.T.; Rehring, T.F.; Rogers, R.K.; Shetterly, S.M.; Wagner, N.M.; Gupta, R.; Jazaeri, O.; Hedayati, N.; Jones, W.S.; Patel, M.R.; et al. The Contemporary Safety and Effectiveness of Lower Extremity Bypass Surgery and Peripheral Endovascular Interventions in the Treatment of Symptomatic Peripheral Arterial Disease. *Circulation* 2015, 132, 1999–2011.
3. Taylor, S.M.; Kalbaugh, C.A.; Blackhurst, D.W.; Cass, A.L.; Trent, E.A.; Langan, E.M.; Youkey, J.R. Determinants of functional outcome after revascularization for critical limb ischemia: An analysis of 1000 consecutive vascular interventions. *J. Vasc. Surg.* 2006, 44, 747–756.
4. Rajagopalan, S.; Mohler, E.R.; Lederman, R.J.; Mendelsohn, F.O.; Saucedo, J.F.; Goldman, C.K.; Blebea, J.; Macko, J.; Kessler, P.D.; Rasmussen, H.S.; et al. Regional Angiogenesis With Vascular Endothelial Growth Factor in Peripheral Arterial Disease. *Circulation* 2003, 108, 1933–1938.
5. Van Royen, N.; Schirmer, S.H.; Atasever, B.; Behrens, C.Y.; Ubbink, D.; Buschmann, E.E.; Voskuil, M.; Bot, P.; Hoefer, I.; Schlingemann, R.O.; et al. START Trial. *Circulation* 2005, 112, 1040–1046.
6. Creager, M.A.; Olin, J.W.; Belch, J.J.F.; Moneta, G.L.; Henry, T.D.; Rajagopalan, S.; Annex, B.H.; Hiatt, W.R. Effect of Hypoxia-Inducible Factor-1 $\alpha$  Gene Therapy on Walking Performance in Patients With Intermittent Claudication. *Circulation* 2011, 124, 1765–1773.
7. Hammer, A.; Steiner, S. Gene therapy for therapeutic angiogenesis in peripheral arterial disease—systematic review and meta-analysis of randomized, controlled trials. *Vasa* 2013, 42, 331–339.
8. McDermott, M.M. Functional Impairment in Peripheral Artery Disease and How to Improve It in 2013. *Curr. Cardiol. Rep.* 2013, 15, 1–8.
9. Gardner, A.W.; Montgomery, P.S.; Parker, D.E. Physical activity is a predictor of all-cause mortality in patients with intermittent claudication. *J. Vasc. Surg.* 2008, 47, 117–122.
10. Singh, N.; Liu, K.; Tian, L.; Criqui, M.H.; Guralnik, J.M.; Ferrucci, L.; Liao, Y.; McDermott, M.M. Leg strength predicts mortality in men but not in women with peripheral arterial disease. *J. Vasc. Surg.* 2010, 52, 624–631.
11. McDermott, M.M.; Liu, K.; Ferrucci, L.; Tian, L.; Guralnik, J.M.; Liao, Y.; Criqui, M.H. Decline in Functional Performance Predicts Later Increased Mobility Loss and Mortality in Peripheral Arterial Disease. *J. Am. Coll. Cardiol.* 2011, 57, 962–970.
12. Jain, A.; Liu, K.; Ferrucci, L.; Criqui, M.H.; Tian, L.; Guralnik, J.M.; Tao, H.; McDermott, M.M. The Walking Impairment Questionnaire stair-climbing score predicts mortality in men and women with

- peripheral arterial disease. *J. Vasc. Surg.* 2012, 55, 1662–1673.e2.
13. McDermott, M.M.; Liu, K.; Tian, L.; Guralnik, J.M.; Criqui, M.H.; Liao, Y.; Ferrucci, L. Calf Muscle Characteristics, Strength Measures, and Mortality in Peripheral Arterial Disease. *J. Am. Coll. Cardiol.* 2012, 59, 1159–1167.
  14. Jain, A.; Liu, K.; Ferrucci, L.; Criqui, M.H.; Tian, L.; Guralnik, J.M.; Tao, H.; McDermott, M.M. Declining Walking Impairment Questionnaire Scores Are Associated With Subsequent Increased Mortality in Peripheral Artery Disease. *J. Am. Coll. Cardiol.* 2013, 61, 1820–1829.
  15. Leeper, N.J.; Myers, J.; Zhou, M.; Nead, K.T.; Syed, A.; Kojima, Y.; Caceres, R.D.; Cooke, J.P. Exercise capacity is the strongest predictor of mortality in patients with peripheral arterial disease. *J. Vasc. Surg.* 2013, 57, 728–733.
  16. Rissanen, T.T.; Vajanto, I.; Hiltunen, M.O.; Rutanen, J.; Kettunen, M.; Niemi, M.; Leppanen, P.; Turunen, M.P.; Markkanen, J.E.; Arve, K.; et al. Expression of Vascular Endothelial Growth Factor and Vascular Endothelial Growth Factor Receptor-2 (KDR/Flk-1) in Ischemic Skeletal Muscle and Its Regeneration. *Am. J. Pathol.* 2002, 160, 1393–1403.
  17. Pipinos, I.I.; Judge, S.M.; Selsby, J.T.; Zhu, Z.; Swanson, S.A.; Nella, A.A.; Dodd, S.L. Basic Science Review: The Myopathy of Peripheral Arterial Occlusive Disease: Part 2. Oxidative Stress, Neuropathy, and Shift in Muscle Fiber Type. *Vasc. Endovasc. Surg.* 2008, 42, 101–112.
  18. Criqui, M.H.; Aboyans, V. Epidemiology of Peripheral Artery Disease. *Circ. Res.* 2015, 116, 1509–1526.
  19. Fowkes, F.G.R.; Aboyans, V.; McDermott, M.M.; Sampson, U.K.A.; Criqui, M.H. Peripheral artery disease: Epidemiology and global perspectives. *Nat. Rev. Cardiol.* 2017, 14, 156–170.
  20. Krishna, S.M.; Moxon, J.V.; Golledge, J. A Review of the Pathophysiology and Potential Biomarkers for Peripheral Artery Disease. *Int. J. Mol. Sci.* 2015, 16, 11294–11322.
  21. Tsiara, S.; Elisaf, M.; Jagroop, I.A.; Mikhailidis, D.P. Platelets as Predictors of Vascular Risk: Is There a Practical Index of Platelet Activity? *Clin. Appl. Thromb.* 2003, 9, 177–190.
  22. Brevetti, G.; Giugliano, G.; Brevetti, L.; Hiatt, W.R. Inflammation in Peripheral Artery Disease. *Circulation* 2010, 122, 1862–1875.
  23. Hamburg, N.M.; Creager, M.A. Pathophysiology of Intermittent Claudication in Peripheral Artery Disease. *Circ. J.* 2017, 81, 281–289.
  24. Gimbrone, M.A., Jr.; García-Cardena, G. Endothelial Cell Dysfunction and the Pathobiology of Atherosclerosis. *Circ. Res.* 2016, 118, 620–636.
  25. Gimbrone, M.A.; García-Cardena, G. Vascular endothelium, hemodynamics, and the pathobiology of atherosclerosis. *Cardiovasc. Pathol.* 2013, 22, 9–15.

26. Hansson, G.K.; Hermansson, A. The immune system in atherosclerosis. *Nat. Immunol.* 2011, 12, 204–212.
27. Garimella, P.S.; Hart, P.D.; O'Hare, A.; Deloach, S.; Herzog, C.A.; Hirsch, A.T. Peripheral Artery Disease and CKD: A Focus on Peripheral Artery Disease as a Critical Component of CKD Care. *Am. J. Kidney Dis.* 2012, 60, 641–654.
28. Jude, E.B.; Oyibo, S.O.; Chalmers, N.; Boulton, A.J. Peripheral Arterial Disease in Diabetic and Nondiabetic Patients: A comparison of severity and outcome. *Diabetes Care* 2001, 24, 1433–1437.
29. Conte, M.S.; Bradbury, A.W.; Kolh, P.; White, J.V.; Dick, F.; Fitridge, R.; Mills, J.L.; Ricco, J.-B.; Suresh, K.R.; Murad, M.H.; et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. *J. Vasc. Surg.* 2019, 69, 3S–125S.e40.
30. Abu Dabrh, A.M.; Steffen, M.W.; Undavalli, C.; Asi, N.; Wang, Z.; Elamin, M.B.; Conte, M.S.; Murad, M.H. The natural history of untreated severe or critical limb ischemia. *J. Vasc. Surg.* 2015, 62, 1642–1651.e3.
31. Sigvant, B.; Kragsternan, B.; Falkenberg, M.; Hasvold, P.; Johansson, S.; Thuresson, M.; Nordanstig, J. Contemporary cardiovascular risk and secondary preventive drug treatment patterns in peripheral artery disease patients undergoing revascularization. *J. Vasc. Surg.* 2016, 64, 1009–1017.e3.
32. Fridh, E.B.; Andersson, M.; Thuresson, M.; Sigvant, B.; Kragsternan, B.; Johansson, S.; Hasvold, P.; Falkenberg, M.; Nordanstig, J. Amputation Rates, Mortality, and Pre-operative Comorbidities in Patients Revascularised for Intermittent Claudication or Critical Limb Ischaemia: A Population Based Study. *Eur. J. Vasc. Endovasc. Surg.* 2017, 54, 480–486.
33. Rantner, B.; Kollerits, B.; Pohlhammer, J.; Stadler, M.; Lamina, C.; Peric, S.; Klein-Weigel, P.; Mühlthaler, H.; Fraedrich, G.; Kronenberg, F. The fate of patients with intermittent claudication in the 21st century revisited—results from the CAVASIC Study. *Sci. Rep.* 2017, 7, 45833.
34. Norgren, L.; Hiatt, W.R.; Dormandy, J.A.; Nehler, M.R.; Harris, K.A.; Fowkes, F.G.R. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J. Vasc. Surg.* 2007, 45, S5–S67.
35. Bevan, G.H.; Solaru, K.T.W. Evidence-Based Medical Management of Peripheral Artery Disease. *Arter. Thromb. Vasc. Biol.* 2020, 40, 541–553.
36. Conte, M.S.; Pomposelli, F.B.; Clair, D.G.; Geraghty, P.J.; McKinsey, J.F.; Mills, J.L.; Moneta, G.L.; Murad, M.H.; Powell, R.J.; Reed, A.B.; et al. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: Management of asymptomatic disease and claudication. *J. Vasc. Surg.* 2015, 61, 2S–41S.e1.

37. Gerhard-Herman, M.D.; Gornik, H.L.; Barrett, C.; Barshes, N.R.; Corriere, M.A.; Drachman, D.E.; Fleisher, L.A.; Fowkes, F.G.R.; Hamburg, N.M.; Kinlay, S.; et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2017, 135, e686–e725.
38. Mills, J.L.; Conte, M.S.; Armstrong, D.G.; Pomposelli, F.B.; Schanzer, A.; Sidawy, A.N.; Andros, G. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: Risk stratification based on Wound, Ischemia, and foot Infection (WIFI). *J. Vasc. Surg.* 2014, 59, 220–234.e2.
39. Stoner, M.C.; Calligaro, K.D.; Chaer, R.A.; Dietzek, A.M.; Farber, A.; Guzman, R.J.; Hamdan, A.D.; Landry, G.J.; Yamaguchi, D.J. Reporting standards of the Society for Vascular Surgery for endovascular treatment of chronic lower extremity peripheral artery disease. *J. Vasc. Surg.* 2016, 64, e1–e21.
40. Mills, J.L. BEST-CLI trial on the homestretch. *J. Vasc. Surg.* 2019, 69, 313–314.
41. Tokuda, T.; Oba, Y.; Koshida, R.; Suzuki, Y.; Murata, A.; Ito, T. Prediction of the Technical Success of Endovascular Therapy in Patients with Critical Limb Threatening Ischaemia Using the Global Limb Anatomical Staging System. *Eur. J. Vasc. Endovasc. Surg.* 2020, 60, 696–702.
42. Bradbury, A.W.; Adam, D.J.; Bell, J.; Forbes, J.F.; Fowkes, F.G.R.; Gillespie, I.; Ruckley, C.V.; Raab, G.M. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: An intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy. *J. Vasc. Surg.* 2010, 51, 5S–17S.
43. Robinson, W.P.; Loretz, L.; Hanesian, C.; Flahive, J.; Bostrom, J.; Lunig, N.; Schanzer, A.; Messina, L. Society for Vascular Surgery Wound, Ischemia, foot Infection (WIFI) score correlates with the intensity of multimodal limb treatment and patient-centered outcomes in patients with threatened limbs managed in a limb preservation center. *J. Vasc. Surg.* 2017, 66, 488–498.e2.
44. Almasri, J.; Adusumalli, J.; Asi, N.; Lakis, S.; Alsawas, M.; Prokop, L.J.; Bradbury, A.; Kolh, P.; Conte, M.S.; Murad, M.H. A systematic review and meta-analysis of revascularization outcomes of infrainguinal chronic limb-threatening ischemia. *J. Vasc. Surg.* 2018, 68, 624–633.
45. Matsubara, Y.; Matsumoto, T.; Aoyagi, Y.; Tanaka, S.; Okadome, J.; Morisaki, K.; Shirabe, K.; Maehara, Y. Sarcopenia is a prognostic factor for overall survival in patients with critical limb ischemia. *J. Vasc. Surg.* 2015, 61, 945–950.
46. McDermott, M.M.; Peterson, C.A.; Sufit, R.; Ferrucci, L.; Guralnik, J.; Kibbe, M.R.; Polonsky, T.S.; Tian, L.; Criqui, M.H.; Zhao, L.; et al. Peripheral artery disease, calf skeletal muscle mitochondrial DNA copy number, and functional performance. *Vasc. Med.* 2018, 23, 340–348.



47. Thompson, J.R.; Swanson, S.A.; Haynatzki, G.; Koutakis, P.; Johanning, J.M.; Reppert, P.R.; Papoutsis, E.; Miserlis, D.; Zhu, Z.; Casale, G.P.; et al. Protein Concentration and Mitochondrial Content in the Gastrocnemius Predicts Mortality Rates in Patients With Peripheral Arterial Disease. *Ann. Surg.* 2015, 261, 605–610.
48. White, S.H.; McDermott, M.M.; Sufit, R.L.; Kosmac, K.; Bugg, A.W.; Gonzalez-Freire, M.; Ferrucci, L.; Tian, L.; Zhao, L.; Gao, Y.; et al. Walking performance is positively correlated to calf muscle fiber size in peripheral artery disease subjects, but fibers show aberrant mitophagy: An observational study. *J. Transl. Med.* 2016, 14, 1–15.
49. McDermott, M.M.; Hoff, F.; Ferrucci, L.; Pearce, W.H.; Guralnik, J.M.; Tian, L.; Liu, K.; Schneider, J.R.; Sharma, L.; Tan, J.; et al. Lower Extremity Ischemia, Calf Skeletal Muscle Characteristics, and Functional Impairment in Peripheral Arterial Disease. *J. Am. Geriatr. Soc.* 2007, 55, 400–406.
50. Gasparini, M.; Šabovič, M.; Gregoric, I.; Simunic, B.; Pisot, R. Increased Fatigability of the Gastrocnemius Medialis Muscle in Individuals with Intermittent Claudication. *Eur. J. Vasc. Endovasc. Surg.* 2012, 44, 170–176.
51. Scott-Okafor, H.R.; Silver, K.K.C.; Parker, J.; Almy-Albert, T.; Gardner, A.W. Lower extremity strength deficits in peripheral arterial occlusive disease patients with intermittent claudication. *Angiology* 2001, 52, 7–14.
52. McDermott, M.M.; Ferrucci, L.; Guralnik, J.; Tian, L.; Liu, K.; Hoff, F.; Liao, Y.; Criqui, M.H. Pathophysiological Changes in Calf Muscle Predict Mobility Loss at 2-Year Follow-Up in Men and Women With Peripheral Arterial Disease. *Circulation* 2009, 120, 1048–1055.
53. Koutakis, P.; Myers, S.A.; Cluff, K.; Ha, D.M.; Haynatzki, G.; McComb, R.D.; Uchida, K.; Miserlis, D.; Papoutsis, E.; Johanning, J.M.; et al. Abnormal myofiber morphology and limb dysfunction in claudication. *J. Surg. Res.* 2015, 196, 172–179.
54. Morris, D.R.; Skalina, T.A.; Singh, T.P.; Moxon, J.V.; Golledge, J. Association of Computed Tomographic Leg Muscle Characteristics With Lower Limb and Cardiovascular Events in Patients With Peripheral Artery Disease. *J. Am. Hear. Assoc.* 2018, 7, e009943.
55. McDermott, M.M. Lower Extremity Manifestations of Peripheral Artery Disease. *Circ. Res.* 2015, 116, 1540–1550.
56. Anderson, J.D.; Epstein, F.H.; Meyer, C.H.; Hagspiel, K.D.; Wang, H.; Berr, S.S.; Harthun, N.L.; Weltman, A.; Dimaria, J.M.; West, A.M.; et al. Multifactorial determinants of functional capacity in peripheral arterial disease: Uncoupling of calf muscle perfusion and metabolism. *J. Am. Coll. Cardiol.* 2009, 54, 628–635.
57. Regensteiner, J.G.; Wolfel, E.E.; Brass, E.P.; Carry, M.R.; Ringel, S.P.; Hargarten, M.E.; Stamm, E.R.; Hiatt, W.R. Chronic changes in skeletal muscle histology and function in peripheral arterial disease. *Circulation* 1993, 87, 413–421.

58. Garg, P.K.; Liu, K.; Ferrucci, L.; Guralnik, J.M.; Criqui, M.H.; Tian, L.; Sufit, R.; Nishida, T.; Tao, H.; Liao, Y.; et al. Lower Extremity Nerve Function, Calf Skeletal Muscle Characteristics, and Functional Performance in Peripheral Arterial Disease. *J. Am. Geriatr. Soc.* 2011, 59, 1855–1863.
59. Askew, C.D.; Green, S.C.; Walker, P.J.; Kerr, G.K.; Green, A.A.; Williams, A.D.; Febbraio, M.A. Skeletal muscle phenotype is associated with exercise tolerance in patients with peripheral arterial disease. *J. Vasc. Surg.* 2005, 41, 802–807.
60. Tuomisto, T.T.; Rissanen, T.T.; Vajanto, I.; Korkeela, A.; Rutanen, J.; Ylä-Herttuala, S. HIF-VEGF-VEGFR-2, TNF- $\alpha$  and IGF pathways are upregulated in critical human skeletal muscle ischemia as studied with DNA array. *Atherosclerosis* 2004, 174, 111–120.
61. Sugo, T.; Terada, M.; Oikawa, T.; Miyata, K.; Nishimura, S.; Kenjo, E.; Ogasawara-Shimizu, M.; Makita, Y.; Imaichi, S.; Murata, S.; et al. Development of antibody-siRNA conjugate targeted to cardiac and skeletal muscles. *J. Control. Release* 2016, 237, 1–13.
62. Ugalde, V.; Wineinger, M.A.; Kappagoda, C.T.; Kilmer, D.D.; Pevec, W.C.; Rosen, W.S.; Rubner, D. SENSORY AXONOPATHY IN MILD TO MODERATE PERIPHERAL ARTERIAL DISEASE. *Am. J. Phys. Med. Rehabil.* 1998, 77, 59–68.
63. Mäkitie, J.; Teräväinen, H. Histochemical changes in striated muscle in patients with intermittent claudication. *Arch. Pathol. Lab. Med.* 1977, 101, 658–663.
64. Robbins, J.L.; Jones, W.S.; Duscha, B.D.; Allen, J.D.; Kraus, W.E.; Regensteiner, J.G.; Hiatt, W.R.; Annex, B.H. Relationship between leg muscle capillary density and peak hyperemic blood flow with endurance capacity in peripheral artery disease. *J. Appl. Physiol.* 2011, 111, 81–86.
65. McGuigan, M.R.; Bronks, R.; Newton, R.U.; Sharman, M.J.; Graham, J.C.; Cody, D.V.; Kraemer, W.J. Muscle fiber characteristics in patients with peripheral arterial disease. *Med. Sci. Sports Exerc.* 2001, 33, 2016–2021.
66. Kim, K.; Reid, B.A.; Ro, B.; Casey, C.A.; Song, Q.; Kuang, S.; Roseguini, B.T. Heat therapy improves soleus muscle force in a model of ischemia-induced muscle damage. *J. Appl. Physiol.* 2019, 127, 215–228.
67. Kim, K.; Ro, B.; Damen, F.W.; Gramling, D.P.; Lehr, T.D.; Song, Q.; Goergen, C.J.; Roseguini, B.T. Heat therapy improves body composition and muscle function, but does not affect capillary or collateral growth in a model of obesity and hindlimb ischemia. *J. Appl. Physiol.* 2020, LID.
68. McGuigan, M.R.M.; Bronks, R.; Newton, R.U.; Sharman, M.J.; Graham, J.C.; Cody, D.V.; Kraemer, W.J. Resistance Training in Patients With Peripheral Arterial Disease: Effects on Myosin Isoforms, Fiber Type Distribution, and Capillary Supply to Skeletal Muscle. *J. Gerontol. Ser. A: Boil. Sci. Med. Sci.* 2001, 56, B302–B310.
69. Wang, J.; Bronks, R.; Graham, J.; Myers, S. Effects of Supervised Treadmill Walking Training on Calf Muscle Capillarization in Patients with Intermittent Claudication. *Angiology* 2009, 60, 36–41.

70. Gardner, A.W.; Killewich, L.A. Lack of functional benefits following infrainguinal bypass in peripheral arterial occlusive disease patients. *Vasc. Med.* 2001, 6, 9–14.
  71. West, A.M.; Anderson, J.D.; Epstein, F.H.; Meyer, C.H.; Hagspiel, K.D.; Berr, S.S.; Harthun, N.L.; Weltman, A.L.; Annex, B.H.; Kramer, C.M. Percutaneous intervention in peripheral artery disease improves calf muscle phosphocreatine recovery kinetics: A pilot study. *Vasc. Med.* 2012, 17, 3–9.
  72. Roseguini, B.T.; Hirai, D.M.; Alencar, M.C.; Ramos, R.P.; Silva, B.M.; Wolosker, N.; Neder, J.A.; Nery, L.E. Sildenafil improves skeletal muscle oxygenation during exercise in men with intermittent claudication. *Am. J. Physiol. Integr. Comp. Physiol.* 2014, 307, R396–R404.
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