Abstract: Lower extremity peripheral artery disease (PAD) is frequently underdiagnosed, in part because of the wide variety of leg symptoms manifested by patients with PAD and in part because of the high prevalence of asymptomatic PAD. In primary care medical practices, 30% to 60% of patients with PAD report no exertional leg symptoms and ≈45% to 50% report exertional leg symptoms that are not consistent with classic intermittent claudication. The prevalence and extent of functional impairment and functional decline in PAD may also be underappreciated. Functional impairment and functional decline are common in PAD, even among those who are asymptomatic. Lower extremity ischemia is also associated with pathophysiologic changes in calf skeletal muscle, including smaller calf muscle area, increased calf muscle fat content, impaired leg strength, and impaired metabolic function. People with severe PAD have poorer peroneal nerve conduction velocity compared with people with mild PAD or no PAD. The degree of ischemia-related pathophysiologic changes in lower extremity muscles and peripheral nerves of people with PAD are associated with the degree of functional impairment. New interventions are needed to improve functional performance and prevent mobility loss in the large number of patients with PAD, including in those who are asymptomatic or who have exertional leg symptoms other than claudication. (Circ Res. 2015;116:1540-1550. DOI: 10.1161/CIRCRESAHA.114.303517.)

Key Words: intermittent claudication ■ peripheral arterial disease
Nonstandard Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ABI</td>
<td>ankle brachial index</td>
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<td>CT</td>
<td>computed tomography</td>
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<td>PAD</td>
<td>peripheral artery disease</td>
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<td>PARTNERS</td>
<td>PAD Awareness, Risk, and Treatment: New Resources for Survival</td>
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<td>SILC</td>
<td>Study In Leg Circulation</td>
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<td>WALCS</td>
<td>Walking and Leg Circulation Study</td>
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<td>WHAS</td>
<td>Women’s Health and Aging Study</td>
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recorded systolic pressures in the lower and upper extremities. People without PAD have ABI values ranging from 1.00 to 1.30. An ABI < 0.90 is ≈ 70% sensitive and 95% specific for PAD.

Patients with PAD experience calf muscle ischemia during walking activity, when metabolic demands exceed oxygen supply, and calf muscle reperfusion during rest, when blood supply increases sufficiently to meet calf muscle oxygen requirements. This phenomenon of ischemia–reperfusion generates reactive oxygen species, such as superoxide anion and hydrogen peroxide, that damage muscle fibers, impair mitochondrial function, and promote apoptosis. Thus, walking impairment in people with PAD is related to both reduced vascular perfusion, from atherosclerotic blockages in lower extremity arteries, and skeletal muscle damage, most likely from ischemia–reperfusion injury to skeletal muscle.

During a 5-year period, only 1% to 2% of people with PAD will develop critical limb ischemia or require lower extremity amputation. Yet, even among patients without critical limb ischemia, chronic leg ischemia in PAD is associated with pathophysiologic changes in the lower extremities, impaired quality of life, and mobility loss. Adverse lower extremity outcomes associated with PAD include ischemic leg pain during walking activity, reduced leg strength, impaired balance, slow walking speed, impaired calf skeletal muscle mitochondrial function, ischemic peripheral neuropathy, and functional decline and mobility loss. Awareness of these lower extremity consequences of PAD will help clinicians better recognize the manifestations of PAD and will help scientists better identify interventions to reverse ischemia-related functional decline and mobility loss in people with PAD. This review summarizes lower extremity manifestations of PAD in people without critical limb ischemia. The spectrum of leg symptoms, the prevalence and significance of asymptomatic lower extremity ischemia, the associations of ischemia with pathophysiologic changes in peripheral muscle and nerves, and the functional consequences of PAD are discussed.

The 2005 clinical practice guidelines for PAD recommend both treadmill exercise testing (Class I Recommendation, Level of Evidence-B) and 6-minute walk testing (Class IIb Recommendation, Level of Evidence-B) to measure walking endurance in people with PAD. However, prospective natural history studies of lower extremity functioning in people with PAD have used serial 6-minute walk testing to objectively document the changes in functional performance over time in people with PAD. Thus, available evidence about the natural history of functional decline in people with PAD is primarily from the 6-minute walk test rather than from treadmill testing.

### Historical Perspective

The classic leg symptom of PAD, intermittent claudication, was originally described and characterized for the purposes of epidemiological study by Dr Geoffrey Rose, a London epidemiologist. The Rose Claudication Questionnaire was developed to facilitate the standardized measurement of the incidence, prevalence, and significance of claudication symptoms in epidemiological population studies and was based on observations of symptoms reported by patients with PAD identified in vascular surgery practices. Dr Rose’s definition of intermittent claudication consisted of exertional calf pain that does not begin at rest, does not resolve during walking activity, and resolves within 10 minutes of rest (Table 1). The Rose Claudication Questionnaire was used to establish the incidence and consequences of intermittent claudication among >5000 participants in the Framingham Study. The biennial incidence of intermittent claudication among participants in the Framingham Study was 7.1 per 1000 in men and 3.6 per 1000 in women.

Kannel et al reported that men with intermittent claudication in the Framingham Study had an annual mortality rate of 39 per 1000 versus 10 per 1000 among men without intermittent claudication. In the Framingham Study, women with intermittent claudication had a 2-fold increased rate of mortality compared with women without intermittent claudication. Kannel et al concluded that because people with intermittent claudication could reduce their physical activity to avoid leg symptoms, the increased risk of mortality because of heart disease or stroke was a far greater concern for people with intermittent claudication. However, subsequent study has documented the adverse health consequences associated with reduced physical activity levels in people with PAD.

### Most People with PAD Do Not Have Classic Symptoms of Intermittent Claudication

Over the past 25 to 30 years, it has been established that most people with PAD do not have the classical symptoms of intermittent claudication as originally defined by Dr Rose. For example, in 1985, Criqui et al performed noninvasive vascular studies in 575 community dwelling men and women from Southern California who were participating in the Lipid Research Clinic study. Overall, 65 (11%) had lower extremity noninvasive studies that were consistent with PAD. Among the 65 participants with PAD, only 6 (9.2%) had classic symptoms of intermittent claudication. Thus, the sensitivity of
the rose claudication questionnaire for PAD in this population was 9.2%. Five of 510 participants without PAD also had symptoms of intermittent claudication, yielding a rose claudication questionnaire specificity of 99%. Criqui et al also defined a leg symptom category, possible claudication. Participants with possible claudication had exertional calf pain that did not begin at rest but that otherwise did not meet criteria for intermittent claudication. Twenty percent of the 65 participants with PAD in the lipid research clinical study had either classic rose claudication symptoms or possible claudication. In contrast, just 4.1% of the 510 participants without PAD met criteria for classic rose claudication symptoms or possible claudication. These findings were the first to demonstrate that a substantial proportion of individuals with PAD have exertional leg symptoms that are not consistent with classic intermittent claudication.

In 1991, Fowkes et al reported the prevalence of intermittent claudication in the Edinburgh artery study, in which 1592 community dwelling men and women aged 55 to 74 underwent an ABI and were administered the rose claudication questionnaire. Of the 1592 participants, 9% had an ABI<0.90, consistent with PAD. However, just 15% of those with PAD had classical symptoms of intermittent claudication and 35% of those with PAD reported no exertional leg symptoms, consistent with asymptomatic PAD. These results from the Edinburgh artery study were among the first to document the high prevalence of asymptomatic PAD. Fowkes et al concluded that the high prevalence of asymptomatic PAD is consistent with the high prevalence of asymptomatic atherosclerosis in other vascular beds, including asymptomatic coronary artery disease and asymptomatic cerebrovascular disease.

Since these original reports by Criqui et al and Fowkes et al, multiple studies have confirmed that most men and women with PAD do not have classic symptoms of intermittent claudication. In community dwelling populations and in primary care settings, 10% of people with PAD have classic symptoms of intermittent claudication (Table 2). In comparison, in community dwelling populations, 60% of people with PAD are asymptomatic and in primary care medical practices, 30% to 60% of PAD patients are asymptomatic (Table 2). The remainder has exertional leg symptoms that are not typical of intermittent claudication. In community dwelling settings, 30% of people with PAD have exertional leg symptoms other than intermittent claudication and in primary care medical practices, 50% of patients with PAD have exertional leg symptoms other than intermittent claudication.

Asymptomatic PAD and PAD with Atypical Symptoms May Contribute to Underdiagnosis of PAD

Asymptomatic leg ischemia and atypical leg symptoms may contribute to underdiagnoses of PAD. This phenomenon was illustrated in the PAD awareness, risk, and treatment: new resources for survival (PARTNERS) study, in which 6979 men and women in primary care practices across the United States were screened for PAD with the ABI. Participants in PARTNERS were aged ≥70 or were aged 50 to 69 with history of smoking or diabetes mellitus. Of the 6979 patients screened with the ABI, 1865 (29%) had an ABI<0.90 consistent with PAD. Among those in the PARTNERS study with PAD and no other clinically evident cardiovascular disease, 5.5% of those newly diagnosed with PAD had classical symptoms of intermittent claudication versus 12.6% of those with previously diagnosed PAD. Overall, 48% of those for whom PAD was newly diagnosed in the PARTNERS study were asymptomatic versus 25.8% of those with previously diagnosed PAD. Together, these data demonstrate that people with unrecognized PAD are more likely to be asymptomatic and less likely to have classic symptoms of intermittent claudication than people with previously established PAD.

Identifying PAD in People Without Classic Intermittent Claudication Symptoms

PAD can be identified noninvasively with the ABI, a ratio of Doppler recorded systolic pressures in the lower and upper extremities. However, medicare and most medical insurance companies do not reimburse for office-based ABI testing unless arterial waveforms are also measured and interpreted. Most medical practices do not routinely measure the ABI. The American heart association recommends ABI screening in patients with exertional leg symptoms, in patients with nonhealing wounds, in all patients aged ≥70, and in patients aged 50 to 69 with a history of diabetes mellitus or smoking. However, the US Preventive services task force recently concluded that there is insufficient evidence to recommend ABI screening in patients with PAD. Thus, identifying people with PAD who are asymptomatic or who have atypical leg symptoms remains challenging.

Types of Atypical Leg Symptoms Commonly Observed in PAD

Studies in defined clinical populations have characterized the types of leg symptoms other than intermittent claudication that are commonly observed in people with PAD. Two common types of atypical leg pain symptoms in PAD are leg pain on exertion and rest and leg pain/carry on. Leg pain on exertion and rest is exertional leg pain that sometimes begins at rest but is distinct from rest pain because of critical limb ischemia. Leg pain/carry on is exertional leg pain that does not cause the patient to stop walking. These leg symptom categories are important because they are associated with specific clinical characteristics and prognoses with regard to functional impairment and decline among people with PAD (Table 3). The walking and leg circulation study (WALCS) was a cohort of 460 prospectively followed men and women with PAD assembled from among consecutive patients diagnosed with PAD in 3 Chicago-area vascular laboratories. Of the 460 PAD participants in WALCS, 88 PAD participants (19%) reported exertional leg symptoms that sometimes began at rest (ie, leg pain on exertion and rest) and 46 PAD participants (9%) reported exertional leg symptoms that did not stop them from walking (ie, leg pain/carry on). None of the PAD participants in WALCS had critical limb ischemia at study entry.
<table>
<thead>
<tr>
<th>Study/Year of Publication</th>
<th>Characteristics of PAD Population</th>
<th>Total Sample Size/Prevalence of PAD</th>
<th>Mean Age, y (SD)*</th>
<th>Percent Female (%)</th>
<th>Study/Year of Publication</th>
<th>Characteristics of PAD Population</th>
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<th>Percent Female (%)</th>
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<tr>
<td>Community dwelling populations</td>
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<tr>
<td>Lipid Research Clinics (1985)</td>
<td>Community dwelling men and women in Southern California</td>
<td>n=575 total/n=65 (11%) with PAD</td>
<td>66 (range, 38–82)</td>
<td>59%</td>
<td>Cardiovascular Health Study (1993)</td>
<td>Men and women aged ≥65 from 4 US Communities</td>
<td>n=5084 total/n=629 (12.4%) with ABI&lt;0.90</td>
<td>71.7 for those with ABI 0.90 to 1.50; 75.5 for those with ABI&lt;0.80</td>
<td>ABI&lt;0.80: 54.1% ABI 0.90–1.50: 60%</td>
</tr>
<tr>
<td>Cardiovascular Health Study (1993)</td>
<td>Men and women aged ≥65 from 4 US Communities</td>
<td>n=933/n=328 (35%) with ABI&lt;0.90</td>
<td></td>
<td>100%</td>
<td>Women’s Health and Aging Study (2000)</td>
<td>Community dwelling women aged ≥65 with disability and without leg pain</td>
<td>n=933/n=328 (35%) with ABI&lt;0.90</td>
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<tr>
<td>Cardiovascular Health Study (2001)</td>
<td>Men and women aged ≥65 from 4 US Communities</td>
<td>n=5888 overall/ n=723 with ABI&lt;0.90 (12%)</td>
<td>Range from 72.7 (5.5) in people without leg pain to 74.9 (5.8) in those with intermittent claudication</td>
<td>54%</td>
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<td>Primary care medical practices</td>
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<tr>
<td>General Medicine Study (1999)</td>
<td>Patients aged ≥55 in a general medical practice with no prior history of PAD</td>
<td>n=174/n=26 with PAD (14.9%)</td>
<td>PAD: 69 (6.5) Non-PAD: 68 (7.2)</td>
<td>PAD: 31% Non-PAD: 65%</td>
<td>PARTNERS study (2001)</td>
<td>Primary care patients who were (a) aged ≥70 or (b) aged 50–69 with history of smoking or diabetes mellitus</td>
<td>n=6979 overall/n=1865 (27%) with ABI&lt;0.90</td>
<td>68.9* among those without PAD Mean age of PAD ranged from 70.8 (10.1) to 72.3 (9.1)</td>
<td>52% overall</td>
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<tr>
<td>Texas Primary Care Practices</td>
<td>Patients aged ≥50 in a Veterans Administration and 2 primary care practices in Houston</td>
<td>n=403 total sample/ n=67 with PAD</td>
<td>Non-PAD: 63.5 (7.3) PAD: 65.3 (7.0)</td>
<td>Non-PAD: 53% PAD: 49%</td>
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<tr>
<td>Get ABI Study (2009)</td>
<td>Patients aged ≥65 in primary care medical practices in Germany</td>
<td>n=6880 total sample size/ n=1429 (21%) with PAD</td>
<td>Non-PAD: 72.2 (5.1) PAD: 73.9 (5.6)</td>
<td>58%</td>
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<tr>
<td>Noninvasive vascular laboratory</td>
<td>WALCS Chicago cohort (2001)</td>
<td>Consecutive patients with PAD in a noninvasive vascular laboratory</td>
<td>460 PAD participants</td>
<td>71.9 (8.4)</td>
<td>41%</td>
<td></td>
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</tbody>
</table>

ABI indicates ankle brachial index; PAD, peripheral artery disease; PARTNERS, PAD Awareness, Risk, and Treatment: New Resources for Survival; and WALCS, Walking and Leg Circulation Study.

*SD provided when available.
Leg Pain on Exertion and Rest

As compared with PAD patients with classical symptoms of intermittent claudication, PAD patients with leg pain on exertion and rest in the WALCS cohort had poorer lower extremity nerve sensation, a higher prevalence of diabetes mellitus, a higher prevalence of spinal stenosis, and a higher burden of comorbid disease.\(^{18}\) ABI values were higher among PAD participants with leg pain on exertion and rest compared with those with intermittent claudication, suggesting less severe PAD among those with leg pain on exertion and rest. Despite this, PAD participants with leg pain on exertion and rest had poorer 6-minute walk performance, poorer balance, and slower walking speed than PAD participants with intermittent claudication.\(^{18}\) In a separate study, Gardner et al\(^{40}\) reported that PAD participants with leg pain on exertion and rest had poorer 6-minute walk performance compared with PAD participants with intermittent claudication. Collins et al\(^{37}\) reported that PAD participants with leg pain on exertion and rest had poorer scores on the self-reported Walking Impairment Questionnaire domains of walking distance, walking speed, and stair climbing compared with PAD participants with intermittent claudication. Comorbid diseases, particularly spinal stenosis and peripheral neuropathy, may contribute to the type of leg symptoms reported by people with PAD who have leg pain on exertion and rest. Ain et al\(^{41}\) reported that 75.7% of 107 patients found to have PAD in a noninvasive vascular laboratory also had lumbar degenerative disease on a MRI or computed tomographic test performed within 6 months of their lower extremity arterial testing. However, the extent to which comorbid disease causes atypical leg symptoms in patients with PAD has not been specifically delineated.

Leg Pain/Carry On

Compared with PAD participants with classical symptoms of intermittent claudication, PAD participants with leg pain/carry on in the WALCS cohort had fewer depressive symptoms, a higher ABI, and a lower prevalence of prior lower extremity revascularization.\(^ {18}\) PAD participants with leg pain/carry on also had a better 6-minute walk performance and were less likely to stop during the 6-minute walk than those with intermittent claudication.\(^ {18}\) However, Gardner et al\(^ {40}\) reported no difference in treadmill walking or 6-minute walk performance among PAD participants with leg pain/carry on compared with PAD participants with intermittent claudication. Similarly, Collins et al reported no significant differences in the Walking Impairment Questionnaire scores in PAD participants with leg pain/carry on compared with PAD participants with intermittent claudication, although the sample sizes in the study by Collins et al\(^ {37}\) were small.

Asymptomatic PAD and Functional Impairment and Decline

People with asymptomatic PAD have significantly greater functional impairment and faster functional decline than people without PAD.\(^ {18-21,42}\) The Women’s Health and Aging Study (WHAS), a cohort of 933 community-dwelling women aged \( \geq 65\) with disability, included 328 (35%) participants with an ABI <0.90, consistent with PAD. Of WHAS participants with an ABI <0.90, 63% reported no exertional leg pain and therefore were classified as asymptomatic.\(^ {34}\) Among all of the WHAS participants who reported no exertional leg symptoms, women with ABI values <0.90 performed more poorly on multiple subjective and objective measures of lower extremity functioning than asymptomatic women with normal ABI values. Asymptomatic women with PAD had lower physical activity levels, were more likely to report difficulty walking up 1 flight of steps or walking ½ mile, had slower walking velocity, were slower during a timed repeated stand from a seated position, and had poorer balance than asymptomatic women without PAD.\(^ {34}\) In the WALCS cohort, asymptomatic PAD participants had an average annual decline in 6-minute walk performance of \(-76.8\) feet per year at 2-year follow-up compared with \(-8.7\) feet per year among WALCS participants without PAD at baseline.\(^ {30}\) Asymptomatic PAD participants in the WALCS cohort, who did not develop leg symptoms during the 6-minute walk test at baseline, had an increased rate of mobility loss at 5-year follow-up compared with participants without PAD (hazard ratio, 2.94 [95% confidence interval, 1.39–6.19]).\(^ {21}\)

Future study is needed to identify interventions that improve walking performance and prevent mobility loss in people with asymptomatic PAD. The 2 medications that are Food and Drug Administration approved for treating walking impairment in people with PAD, cilostazol and pentoxifylline, have been studied only in PAD patients with intermittent claudication symptoms. Only 2 randomized trials of PAD patients have included PAD patients who are asymptomatic.\(^ {43,44}\) These 2 randomized trials suggest that exercise therapy is beneficial.

### Table 3. Atypical Leg Pain Categories Commonly Experienced by Patients With PAD

<table>
<thead>
<tr>
<th>Leg symptom features</th>
<th>Leg Pain/Carry On</th>
<th>Leg Pain on Exertion and Rest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exertional leg pain that does not stop the patient from continuing to walk</td>
<td>Exertional leg pain that sometimes begins at rest among PAD patients without critical limb ischemia</td>
<td></td>
</tr>
<tr>
<td>Prevalence among people with PAD</td>
<td>( \approx 10% )</td>
<td>( \approx 20% )</td>
</tr>
<tr>
<td>Clinical characteristics when compared with people with intermittent claudication</td>
<td>Fewer depressive symptoms</td>
<td>Higher prevalence of diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Higher ABI values</td>
<td>Higher prevalence of spinal stenosis</td>
</tr>
<tr>
<td>Functional impairment when compared with patients with classic intermittent claudication</td>
<td>Data are mixed with some evidence for less functional impairment and some showing no difference compared with PAD patients with claudication</td>
<td>Greater functional impairment</td>
</tr>
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<td></td>
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<td>Faster functional decline</td>
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ABI indicates ankle brachial index; and PAD, peripheral artery disease.
even within the subset of PAD patients who are asymptomatic. Because asymptomatic PAD patients do not have exertional leg pain, improvement in walking performance cannot be measured by patient report of improved leg symptoms. Objective outcomes, such as a graded treadmill test, the 6-minute walk test, or physical activity levels during daily life, are helpful to objectively document improved walking performance in response to interventions.

Although the cause of functional limitations in people with asymptomatic PAD has not been fully delineated, pathophysiologic skeletal muscle and peripheral nerve changes, including reduced calf muscle mass, increased calf muscle fat content, and reduced lower extremity peripheral nerve function, have been documented in PAD patients without exertional leg symptoms. For example, in the WAlCS cohort, PAD participants who were asymptomatic had lower lower extremity peripheral nerve function, than PAD participants with classic symptoms of intermittent claudication. In the WAlCS II cohort, PAD participants who were asymptomatic and did not develop leg pain during the 6-minute walk had significantly lower calf muscle area and increased calf muscle percent fat compared with PAD participants with symptoms of intermittent claudication. Based on pathophysiologic abnormalities documented in calf skeletal muscle mitochondrial dysfunction of PAD patients with intermittent claudication, it is possible that impaired skeletal muscle mitochondrial function also contributes to functional impairment in people with asymptomatic PAD. However, mitochondrial function in calf skeletal muscle of PAD participants who are asymptomatic has not been studied.

Why Do Some PAD Patients Lack Ischemic Leg Symptoms?

There are at least 2 potential explanations for absence of exertional leg symptoms in patients with PAD. First, some PAD patients limit their walking activity during daily life to avoid leg symptoms. This phenomenon is illustrated by people with PAD who report that they have no exertional leg symptoms but develop leg pain during a 6-minute walk test. In the WAlCS cohort, 42 of 91 PAD participants (46%) who reported absence of exertional leg symptoms developed leg symptoms during the 6-minute walk test. In addition, asymptomatic PAD participants in the WAlCS cohort were categorized according to their physical activity level. An asymptomatic/inactive group of PAD participants consisted of asymptomatic PAD participants who walked ≤6 blocks per week. An asymptomatic/active group of PAD participants consisted of asymptomatic people with PAD who walked >6 blocks per week. Thirty-three percent of PAD participants in the asymptomatic/active group developed leg pain during the 6-minute walk test versus 89% of PAD participants who were asymptomatic/inactive. In summary, asymptomatic PAD participants who were less physically active were more likely to develop leg symptoms during a 6-minute walk test than asymptomatic PAD participants who were more physically active. A second potential explanation for asymptomatic PAD is that some PAD patients may slow their walking speed to avoid exertional leg symptoms.

Lower Extremity Functional Impairment and Decline in PAD

The natural history of lower extremity outcomes in people with PAD has been described as benign. This is in part because only a small proportion of patients with PAD develop gangrene, require amputation, or undergo surgical revascularization. Furthermore, in some studies of PAD patients identified from vascular surgery practices, patients with claudication report no change or even improvement in claudication symptoms during a 5-year follow-up period. As described above, this phenomenon of stabilization or improvement in claudication symptoms is explained in part by reducing physical activity levels to avoid ischemic leg symptoms. Yet PAD patients with lower levels of physical activity have faster rates of functional decline and increased rates of mortality than those more physically active. For these reasons, improvement or absence of ischemic leg symptoms should not necessarily be equated with improvement in PAD.

Magnitude of Functional Impairment in People With PAD

In the WALCS cohort, the 6-minute walk and other objective functional performance measures were assessed annually in 460 men and women with PAD and also in 240 without PAD, enabling objective assessment of functioning over time, independently of patient-reported leg symptoms. At baseline, patients with PAD achieved shorter distance in the 6-minute walk test had slower walking velocity, were more likely to stop to rest during the 6-minute walk, had lower physical activity levels, and had poorer balance than people without PAD. People with more severe PAD, measured by lower ABI values, had even poorer functional performance than people with mild PAD. When compared with participants without PAD, those with an ABI<0.50 walked 523 feet fewer and had slower 4-m walking velocity by 0.21 m/s even after adjusting for age, sex, race, body mass index, smoking, and comorbidities. Fifty feet and 0.10 m/s, respectively, represent clinically meaningful changes in 6-minute walk and 4-m walking velocity. Therefore, these differences in walking endurance and walking speed between people with mild versus severe PAD represent clinically important differences.

At 2-year follow-up in the WALCS cohort, participants with the most severe PAD (ABI<0.50) had an average annual decline in 6-minute walk of −73 feet per year, those with mild to moderate PAD (ABI 0.50–0.89) had an average annual decline in 6-minute walk of −58.8 feet per year, and those without PAD (ABI 0.90–1.50) had an average annual decline in 6-minute walk of −26.6 feet per year. Among participants who completed the 6-minute walk without stopping at baseline, those with ABI<0.50 at baseline were nearly 13× more likely to become unable to walk for 6 minutes without stopping at 2-year follow-up. These associations were independent of age, sex, race, comorbidities, smoking history, and body mass index. In summary, PAD is associated with greater functional impairment than absence of PAD, and more severe PAD is associated with greater impairment and faster decline than less severe PAD.
Lower Extremity Ischemia and Calf Skeletal Muscle

Although the pathophysiologic mechanisms causing functional impairment and functional decline in PAD are not fully delineated, available evidence suggests that both impaired vasculature and skeletal muscle pathophysiologic changes contribute to the lower extremity functional impairment and functional decline that is present in PAD. People with PAD have smaller calf muscle area and increased calf muscle percent fat, as measured by computed tomography (CT), than people without PAD. These ischemia-related adverse changes in calf skeletal muscle are independent of differences in physical activity level between people with mild versus severe PAD. In 92 men and women with PAD without history of lower extremity revascularization whose left and right leg ABI values differed by >0.20, consistent with clinically important differences in leg ischemia between the left and right legs, legs with more severe ischemia had a CT scan measured average calf muscle area of 5283 mm² and legs with highest ABI had a CT scan measured average calf muscle area of 5511 mm². Similarly, average calf muscle percent fat was higher in the leg with more severe ischemia (11.4% versus 9.5%). By comparing calf muscle characteristics between legs with higher versus lower ABI, these analyses controlled fully for ischemia-associated differences in physical activity and demonstrate that greater ischemia is associated with smaller muscle area and higher calf muscle fat content.

Ischemia-related calf muscle pathophysiologic changes in people with PAD are likely to be in the biological pathway of functional decline in people with PAD. In the WALCS II cohort, including 380 PAD participants who were followed prospectively after baseline measurement of calf muscle characteristics, PAD participants with greater CT-measured calf muscle percent fat and lower CT-measured calf muscle density at baseline each had an increased incidence of mobility loss at 2-year follow-up. PAD participants in the lowest tertile of calf muscle percent fat at baseline had a 0.18 hazard for developing mobility loss compared with PAD participants in the highest tertile of calf muscle percent fat at baseline. PAD participants in the lowest tertile of calf muscle density had a 3.50-fold increased hazard of mobility loss at 2-year follow-up compared with PAD participants in the highest tertile of calf muscle density at baseline. These associations were independent of age, sex, race, comorbidities, smoking, body mass index, and ABI. Together, these data demonstrate that ischemia-related pathophysiologic changes in lower extremity calf skeletal muscle predict increased rates of mobility loss (Figure 1).

Mitochondrial Impairment in Lower Extremity Skeletal Muscle of Patients With PAD

PAD patients experience calf muscle ischemia during walking activity, when metabolic demands exceed oxygen supply. Patients with PAD experience calf muscle reperfusion during rest, when blood supply increases sufficiently to meet calf muscle oxygen requirements. This phenomenon of ischemia–reperfusion generates reactive oxygen species, such as superoxide anion and hydrogen peroxide, that can damage muscle fibers, impair mitochondrial function, and promote apoptosis. Electron microscopy of calf muscle from patients with PAD shows distorted mitochondria consistent with a severe qualitative dysfunction. Growing evidence also demonstrates a quantitative mitochondria impairment in calf muscle among individuals with PAD, resulting in reduced energy production (Figure 2). In a study of 34 participants with PAD and 21 without PAD who underwent calf muscle biopsy, PAD participants had higher protein carbonyl content (695 grayscale units±1.32 versus 486 grayscale units±135) and higher 4-hydroxy-2-nonenal levels (436 grayscale units±119 versus 261 grayscale units±101; P<0.001) than those without PAD, indicating higher calf muscle levels of oxidative stress in the PAD participants. Higher quantities of oxidative stress were associated...
Peripheral nerve function is impaired in people with PAD. Poorer peroneal nerve conduction velocity among people with PAD was also similar between PAD participants who were asymptomatic and those with exertional leg symptoms other than intermittent Claudication. Supervised treadmill exercise significantly improved 6-minute walk performance, treadmill walking performance, and quality of life in PAD participants with and without intermittent claudication. Supervised resistance training significantly improved treadmill walking performance and quality of life in PAD participants with and without intermittent claudication. The magnitude of improvement in response to study interventions was also similar between PAD participants who were asymptomatic and those with exertional leg symptoms. Second, the Group Oriented Arterial Leg Study (GOALS) randomized trial without diabetes mellitus, severe PAD (ABI<0.50) was associated with poorer peroneal nerve conduction velocity compared with participants without PAD (ABI 0.90–1.50) and when compared with participants with mild PAD (ABI 0.70–0.90) or moderate PAD (ABI 0.50–0.70). In participants with diabetes mellitus, the presence of PAD was associated with poorer peroneal nerve conduction velocity and poorer sural nerve amplitude compared with the absence of PAD, even after adjustment for known and potential confounders. The WALCS II cohort is the largest to evaluate the association of lower extremity ischemia with lower extremity peripheral nerve function. Results suggest that among people without critical limb ischemia, severe PAD (ie, ABI<0.50) is associated with impaired lower extremity peripheral nerve function. Additional findings from the WALCS II cohort demonstrated that greater impairment in lower extremity nerve function is associated with poorer 6-minute walk performance and slower walking velocity among people with PAD.

**Lower Extremity Nerve Function in PAD**

Ischemia-related damage to lower extremity nerves may also cause functional impairment and functional decline in people with PAD. The inferior gluteal artery supplies the lumbosacral nerve plexus and the popliteal artery supplies the common peroneal nerve. Cross-sectional studies about PAD and lower extremity nerve function have reported conflicting results, with some studies demonstrating no difference in peroneal or femoral nerve function between people with versus without PAD and another reporting poorer peroneal and tibial nerve function in people with PAD. However, these studies included small sample sizes. In a study of 25 patients with PAD and 37 age-matched controls without PAD, Weber et al identified an axonal lower extremity neuropathy affecting the sural, peroneal, and tibial nerves. However, this study included PAD participants with critical limb ischemia and the most severe findings were observed in PAD patients with critical limb ischemia-related rest pain.

The WALCS II cohort studied the association of PAD and lower extremity nerve function in 478 participants with PAD and 292 without PAD using lower extremity electrodiagnostic testing to measure peripheral nerve function. In participants with fewer myofibers in participants with PAD, in 2 cross-sectional studies, poorer mitochondrial function, measured by respirometry from muscle biopsy specimens or magnetic resonance spectroscopy, was associated with poorer treadmill walking in people with PAD.

![Figure 2. Association of the ankle brachial index with the 6-minute walk in people with and without peripheral artery disease. Reprinted from McDermott et al with permission of the publisher. Copyright ©2002, the American College of Physicians.](image)

**Table 4. Pathophysiological Findings in the Lower Extremities of Patients With PAD**

<table>
<thead>
<tr>
<th>Calf skeletal muscle</th>
<th>Peripheral nerve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced calf muscle area</td>
<td>Poorer peroneal nerve conduction velocity among people with ABI&lt;0.50</td>
</tr>
<tr>
<td>Increased calf muscle percent fat</td>
<td></td>
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<tr>
<td>Increased calf muscle oxidative stress</td>
<td></td>
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<tr>
<td>Impaired ATP production</td>
<td></td>
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</tbody>
</table>

ABI indicates ankle brachial index; ATP, adenosine triphosphate; and PAD, peripheral artery disease.

*Results reported in Table 4 are limited to PAD patients without critical limb ischemia.
tested the ability of a home-based exercise intervention that used a group-mediated cognitive behavioral intervention to improve walking performance in people with PAD, including participants with and without symptoms of intermittent claudication. The group-mediated cognitive-behavioral home-based exercise intervention significantly improved walking endurance, measured by the 6-minute walk and by treadmill walking performance. In subgroup analyses, the group-mediated cognitive behavioral home-based walking exercise intervention improved 6-minute walk performance in the subset of PAD participants who did not have classical symptoms of intermittent claudication. Together, these data demonstrate that walking exercise interventions benefit PAD patients even among PAD patients without classical symptoms of intermittent claudication. However, Medicare and most other medical insurance companies typically do not pay for supervised exercise programs in people with PAD.

Measuring Change in Walking Performance and Quality of Life in People with PAD

Treadmill exercise testing is the most commonly used objective outcome measure in randomized trials studying interventions to improve walking performance in people with PAD. Treadmill testing is conducted in a tightly controlled setting and measures maximal walking performance. The 6-minute walk test is an objective measure of walking endurance that simulates walking in the community because it is performed in a hall corridor. The 6-minute walk test has been well validated in patients with PAD and improves in response to effective exercise interventions. The 2005 American Heart Association/American College of Cardiology clinical practice guidelines for PAD recommend both treadmill exercise testing (Class I recommendation, Level of Evidence-B) and 6-minute walk testing (Class Ib recommendation, Level of Evidence-B) for objective assessment of changes in walking performance in patients with PAD. Since 2005, new evidence has been accrued demonstrating the validity of the 6-minute walk test as an objective measure of walking performance in PAD. Validated questionnaires for measuring change in patient-reported walking performance and quality of life include the Walking Impairment Questionnaire, the Short-Form-36 Physical Functioning Score, the Peripheral Artery Questionnaire, and the PAD Quality of Life Questionnaire. These outcomes are not interchangeable. Each outcome measures a different aspect or dimension of walking performance or quality of life. PAD patients’ perceptions of walking performance do not fully correlate with objective measures of their walking performance. For example, in a randomized trial of cilostazol to improve walking performance in PAD patients with intermittent claudication, the correlation between improvement in treadmill walking performance and improvement in the patient-reported Walking Impairment Questionnaire distance score was only 0.34. In the Claudication: Exercise versus Endovascular Revascularization (CLEFT) randomized trial in PAD patients with intermittent claudication, treadmill walking performance and patient-reported change in walking performance and quality of life were only modestly correlated among participants who received the exercise intervention. In summary, objective and subjective assessments of walking performance, quality of life, and physical activity used in randomized trials of therapeutic interventions measure distinct aspects of walking performance and functioning in people with PAD. Researchers and clinicians should be cognizant that these outcome measures are complementary and not interchangeable.

In conclusion, most people with PAD do not have classical symptoms of intermittent claudication. Lower extremity pathophysiologic changes associated with PAD include reduced calf skeletal muscle mass, increased calf skeletal muscle fatty infiltration, reduced calf skeletal muscle density, impaired lower extremity peroneal nerve function, impaired calf muscle mitochondrial function, impaired functional performance, and increased rates of mobility loss and functional decline. Functional impairment and functional decline are observed even among PAD patients who are asymptomatic or who have atypical leg symptoms other than intermittent claudication. Future studies should identify therapeutic interventions to improve functional performance and prevent functional decline and mobility loss among people with PAD, including the large proportion without classical symptoms of intermittent claudication.

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Disclosures

None.

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Limb Manifestations in Peripheral Artery Disease


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