Lower-extremity peripheral artery disease (PAD) affects 8 million people in the United States and >200 million men and women worldwide.1,2 PAD will become increasingly common as the US population survives longer with chronic disease. Although intermittent claudication is the most frequent classic symptom of PAD, many patients with PAD are asymptomatic or have exertional leg symptoms other than intermittent claudication.3,4 Patients with PAD have slower walking speed, poorer walking endurance, and substantially lower physical activity levels compared with people without PAD.3,5 Patients with PAD also have a faster decline in lower-extremity functional performance and higher rates of mobility loss compared with individuals without PAD.6-8 Even patients with PAD who are asymptomatic or who have exertional leg symptoms other than intermittent claudication have greater functional impairment, faster functional decline, and higher rates of mobility loss than people without PAD.1,9-11 The functional limitations experienced by people with PAD are associated with loss of independence, loss of mobility in daily life, increased hospitalization rates, and increased mortality.3,12-14 Therefore, an important treatment goal in patients with PAD is improving walking performance and preventing mobility loss.

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Despite the functional limitations present in PAD, few medical therapies exist for improving walking performance and preventing mobility loss in patients with PAD. There are just 2 US Food and Drug Administration–approved medications, pentoxifylline and cilostazol, for improving walking performance in patients with PAD.15-17 Of these 2 medications, pentoxifylline is not substantially better than placebo.15,17 Cilostazol provides only modest improvement in treadmill walking performance.16,17 Although supervised treadmill exercise significantly improves walking performance in patients with PAD,18,19 medical insurance typically does not pay for costs of supervised exercise for patients with PAD. Thus, most patients with PAD do not participate in supervised treadmill exercise.20

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.
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This article is Part I of a 2-part article. Part II appears on p 69.
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New medical therapies are needed to improve walking performance and to prevent the adverse outcomes associated with PAD-related functional impairment such as mobility loss and the ability to continue living independently in one’s community. Emerging therapies for PAD must be tested in rigorous randomized, controlled, clinical trials. Traditionally, randomized trials have used treadmill walking performance as the primary outcome measure in clinical trials of therapeutic interventions in patients with PAD.\(^{21,22}\) However, there are significant limitations to treadmill walking as an outcome.

Increasingly, the 6-minute walk test has been validated as an outcome measure and is increasingly recognized as a meaningful outcome measure in patients with PAD. Among 156 people with PAD who completed both a 6-minute walk test and a treadmill test, the 6-minute walk test correlated more closely with physical activity levels in the community than treadmill testing.\(^{23}\) Additional evidence shows that the 6-minute walk test is not associated with a learning effect when repeated testing is performed in people with PAD.\(^{23,24}\) Changes in 6-minute walk performance have been linked to clinically meaningful outcomes such as mortality and mobility loss in patients with PAD.\(^{25}\) However, changes in treadmill walking performance have not been linked to clinically meaningful outcomes such as mortality or mobility loss in patients with PAD. This article provides evidence to support the assertion that the 6-minute walk is a better outcome than treadmill walking tests in clinical trials of therapeutic interventions in patients with PAD.

**Methods of Graded Treadmill Test**

A graded treadmill stress test has substantially better test-retest reliability than a constant-load treadmill stress test in patients with PAD.\(^{26}\) In the graded Gardner-Skinner stress test,\(^{26}\) participants begin walking on the treadmill at 2.0 mph. The grade begins at 0 and is increased by 2% every 2 minutes. Participants unable to walk at least 2.0 mph begin walking at 0.5 mph, and their speed is increased by 0.50 mph every 2 minutes until the participant reaches 2.0 mph. After the participant reaches 2.0 mph, the treadmill grade is increased by 2% every 2 minutes. The test is conducted by an exercise physiologist, and participants have continuous cardiac monitoring with ECG leads during testing. Participants are asked to continue walking without stopping until they cannot continue because of leg symptoms, exhaustion, or other symptoms. The test is also stopped if evidence of coronary ischemia develops during cardiac monitoring.

**Treadmill Walking Performance Has Limitations as an Outcome Measurement in PAD**

A summary of the advantages of the 6-minute walk test compared with treadmill testing is shown in the Table. Treadmill testing in patients with PAD has limitations. First, walking on a treadmill is not representative of walking in daily life.\(^{27-29}\) Second, there is a significant learning effect associated with treadmill walking in which even patients with PAD not receiving therapeutic interventions experience improvement in treadmill walking over time.\(^{26,30}\) This learning effect is particularly problematic for interventions that involve treadmill exercise. Third, meaningful change in treadmill walking performance has not been defined. The 6-minute walk circumvents all of these limitations.\(^{8,13,25,31}\) In the following sections, patients with PAD.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treadmill Walking Outcome</th>
<th>6-Minute Walk</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Represents walking during daily life, in the community</td>
<td>No</td>
<td>Yes</td>
<td>Treadmill walking requires balance and requires that the participant keep up with the pace of the treadmill test; the 6-minute walk test takes place in a corridor and is more representative of walking in daily life.</td>
</tr>
<tr>
<td>Test-related learning phenomenon</td>
<td>Yes</td>
<td>No</td>
<td>The learning phenomenon for treadmill testing is particularly problematic in studies that include a supervised treadmill exercise intervention, in which the participant is trained to the test outcome.</td>
</tr>
<tr>
<td>Meaningful, clinically important difference has been defined</td>
<td>No</td>
<td>Yes</td>
<td>Meaningful, clinically important difference has been defined for the 6-minute walk and helps determine whether a given change in the 6-minute walk represents a clinically meaningful difference.</td>
</tr>
<tr>
<td>Change in measure predicts mortality or mobility loss in patients with PAD</td>
<td>Unknown</td>
<td>Yes</td>
<td>Change in the 6-minute walk predicts all-cause mortality, cardiovascular disease mortality, and mobility loss in people with PAD.</td>
</tr>
</tbody>
</table>

PAD indicates peripheral artery disease.
Treadmill Walking Performance Does Not Represent Walking in Daily Life

Walking on a treadmill requires dynamic balance and the ability to maintain a constant rhythmic gait to keep up with the constant pace of the treadmill. Patients with PAD frequently touch or hold on to the treadmill rail to maintain balance. Importantly, these skills are intrinsically linked to treadmill walking but do not apply to walking in daily life. Furthermore, among patients with PAD, handrail support is associated with a greater learning effect and longer maximal walking distances compared with no handrail support. In addition, patients with PAD have specific impairments in balance and cognitive function compared with people without PAD that are likely to make the need for good balance and a rhythmic gait on the treadmill particularly difficult to achieve. For example, more severe PAD, as measured by the Rutherford classification, was associated with progressively increased difficulty with the Timed Up and Go test, a measure of dynamic balance. Lower ankle-brachial index (ABI) values, a measure of the presence and severity of PAD, are associated with poorer standing balance. In summary, patients with PAD have particular deficiencies in dynamic balance that are likely to make treadmill walking particularly challenging.

Furthermore, in a corridor walk such as the 6-minute walk test, patients with PAD who have difficulty walking can slow down but can keep going or even rest temporarily without stopping the test. In contrast, the treadmill test requires participants with PAD to maintain or even increase their walking speed. Participants with PAD who cannot keep up with the treadmill must stop walking, thereby simultaneously ending the treadmill test. This key difference between the 6-minute walk and treadmill walking performance is likely to result in longer walking distances in the 6-minute walk than on the treadmill, as observed previously in patients with heart failure.

Several studies of older people and people with chronic disease, similar to patients with PAD, have documented that treadmill walking performance does not accurately represent corridor walking such as that performed during the 6-minute walk test and during daily walking. For example, Swerts et al studied 12 healthy elderly men and women (age, 71–80 years) and 12 healthy young participants (age, 21–37 years). These 2 groups of participants underwent a self-paced 6-minute walk test and a treadmill walking test, respectively. The treadmill walking test was conducted so that it matched the walking velocity of the corridor walking test. The heart rate in younger participants when they walked on the treadmill was similar to that when they walked in a corridor at identical speed. In contrast, the elderly participants had higher heart rates when they walked on the treadmill compared with when they walked in a corridor at identical speed. Both the older and the younger participants had slower step rates, resulting in a longer stride, during treadmill walking compared with corridor walking performed at identical speed. In a separate study, Peters et al studied 37 patients (mean age, 81.3 years): 11 untrained control participants, 16 patients with New York Heart Association class II heart failure, and 10 patients with New York Heart Association class III heart failure. Participants completed a 6-minute walk and a treadmill exercise stress test on separate days, with the order of testing determined randomly. In this study, the treadmill stress test was not graded but started slowly at 1 km/h and increased in speed by 0.5 km/h every 2 minutes. All participants completed the 6-minute walk, but 22% were unable to perform the treadmill stress test. Six participants (17%) walked only very short distances on the treadmill test. On average, the distance achieved on the treadmill test was 27% shorter compared with that in the 6-minute walk. Although their sample sizes were small, together, these studies demonstrate that participants, particularly those who are older and have chronic diseases that limit their walking ability, alter their walking stride length and demonstrate physiological evidence of anxiety during treadmill walking. These changes are not present during corridor walking tests such as the 6-minute walk. However, the higher heart rates observed during treadmill walking may also be related to the fact that treadmill walking requires extra skills that are not necessary when walking in a corridor. Execution of these additional skills requires more energy, which may also explain the higher heart rate at a given speed during treadmill walking compared with corridor walking. An individual’s ability in the specific skills required for treadmill walking may also contribute to the observation that treadmill walking is less representative of walking in the natural environment than the 6-minute walk.

Learning Effect Associated With Treadmill Walking Performance

Another limitation of treadmill walking is that it is associated with a significant learning effect. Even without any therapeutic intervention, patients with PAD typically increase their maximum and pain-free walking distance between baseline and follow-up testing. Recent placebo-controlled drug therapeutic trials in patients with PAD have demonstrated increases in maximal walking time in the placebo or control groups ranging from 17% to 26%. This phenomenon likely occurs because treadmill walking is an unnatural form of walking. With the practice afforded by repeat treadmill tests at baseline and follow-up, patients with PAD improve their treadmill walking performance, even without receiving a therapeutic intervention.

The learning effect associated with treadmill walking is particularly problematic with interventions that include a treadmill exercise intervention. Treadmill exercise interventions train the participant to the treadmill outcome measure and allow participants to become more comfortable with treadmill walking during their treadmill exercise sessions. Consequently, participants with PAD get better on the
treadmill outcome measure in part because they have “prac-
ticed” the outcome as part of their exercise intervention. This
“training to the outcome” advantage likely explains some of
the gains reported on the treadmill outcome in groups random-
ized to supervised treadmill exercise interventions.

In contrast to treadmill walking performance, the 6-min-
ute walk is not associated with a learning effect when repeat
testing is performed in patients with PAD. McDermott et al23
reported the test-retest reliability of the 6-minute walk among
156 participants with PAD who completed the 6-minute walk
test = 1 to 2 weeks apart. In these PAD participants, the mean
value of the 6-minute walk during the first measurement was
312.7 ± 87.2 m, and the mean value during the second measure-
ment was 316.2 ± 87.7 m. The correlation coefficient between
the 2 measures was 0.90 (P<0.001),23 and the coefficient of
variation percent was 8.9%. In a separate study of 64 partici-
pants with PAD, the coefficient of variation for two 6-minute
walk tests performed ≈ 1 week apart was 10.4%.24 In summary,
the 6-minute walk test has excellent test-retest reliability.

Evidence of how participants with PAD in a supervised
treadmill exercise intervention achieve relatively greater
increases in the treadmill walking outcome than in the 6-min-
ute walk by training to the treadmill outcome is illustrated
in 2 previous trials of exercise interventions that measured
change in both treadmill walking and the 6-minute walk in
response to the exercise intervention.18,37 One of these trials
studied supervised treadmill exercise in patients with PAD;
the other studied home-based overground walking exercise in
patients with PAD. The study with treadmill walking exercise
interventions demonstrated greater gains in the treadmill out-
come measure than in the 6-minute walk test.18 However, the
study with a home-based walking exercise intervention that
encouraged overground walking exercise demonstrated rela-
tively greater gains in the 6-minute walk than in the tread-
mill walking measure (Figure). For example, the randomized,
controlled Study to Improve Leg Circulation (SILC) demon-
strated relative gains in maximal treadmill walking time of
51% among 61 patients with PAD who were randomized to
supervised treadmill exercise.18 However, the Group Oriented
Arterial Leg Study (GOALS) trial, in which patients with
PAD were randomized to home-based overground walking
exercise, demonstrated gains in maximal treadmill walking
time of only 19% (Figure).37 Relative gains in 6-minute walk
distance among PAD participants randomized to supervised
treadmill exercise were only 6.4% in the SILC trial and 12%
in the GOALS trial intervention of home-based overground
walking. Findings in the SILC trial were similar to results of
a randomized, controlled, clinical trial of 61 PAD participants
who were randomized to a treadmill exercise intervention ver-
sus a control group. PAD participants in the supervised exer-
cise intervention achieved an 80% improvement in treadmill
walking performance (P<0.001) but only a 10% improvement
in 6-minute walk performance (P=0.003) at the 18-month
follow-up.18 Together, these findings suggest that treadmill
walking exercise interventions that involve training to the
outcome measure of treadmill walking performance ensure
that participants become more familiar and comfortable with
treadmill walking because of the practice associated with their

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![Changes in Six-Minute Walk Performance](image1)

**Figure.** Relative changes in 6-minute walk and
treadmill maximal walking time in clinical trials of
exercise, according to whether the trial used tread-
mill walking exercise vs overground walking exer-
cise. GOALS indicates Group Oriented Arterial Leg
Study; and SILC, Study to Improve Leg Circulation.

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![Changes in Maximal Treadmill Walking Time](image2)
The 6-Minute Walk Test Methods

In contrast to a treadmill stress test, the 6-minute walk is inexpensive to perform and does not require highly specialized personnel or sophisticated equipment. However, the 6-minute walk requires a 100-ft corridor. The 6-minute walk also requires a research coordinator who is trained and certified in the administration of the 6-minute walk and a stopwatch. Participants receive standardized instructions by the certified study coordinator. Participants are advised by the coordinator that the goal of the 6-minute walk test is to achieve the greatest distance possible by walking back and forth along the 100-ft corridor for 6 minutes. Participants may not talk during the test except to notify the coordinator of any symptoms they develop. The coordinator calls out each passing minute during the test with a standardized phrase of encouragement. Participants are allowed to rest during the test, but the clock continues to run while the participant rests. At the end of the 6 minutes, the distance covered is measured. Certification requires that the research coordinator reads a study manual, practices administering the 6-minute walk, and demonstrates proficiency to another individual who has expertise in 6-minute walk testing. Use of a checklist for the certifier to document successful administration of each component of the 6-minute walk test is recommended.

The 6-Minute Walk Is Sensitive to Declines in Walking Endurance That Occur in Patients With PAD

In contrast to the learning effect associated with treadmill walking performance, observational studies demonstrate that the 6-minute walk detects and quantifies declines in walking endurance among patients with PAD who do not receive interventions. For example, in the Walking and Leg Circulation Study (WALCS), 676 individuals ≥55 years of age without PAD underwent a baseline 6-minute walk followed by annual 6-minute walk testing for 2 years.6 Average annual declines in 6-minute walk were 12.6 ft/y among participants without PAD (ABI, 0.90–1.50), 58.8 ft/y among participants with mild PAD (ABI, 0.51–<0.90), and 73.0 ft/y among participants with severe PAD (ABI <0.50). In addition, in randomized, clinical trials of participants with PAD that measured both the treadmill test and the 6-minute walk test at baseline and follow-up, those randomized to the control group who did not receive any therapeutic interventions experienced declines in the 6-minute walk of ≈11 to 15 m but simultaneously experienced gains in the treadmill test at the 6-month follow-up. Collectively, these findings demonstrate that the 6-minute walk is sensitive to declines in walking endurance that occur as part of the natural history of PAD in patients who do not receive therapeutic interventions. In contrast, the treadmill test tends to increase even among patients with PAD not receiving therapeutic interventions. This absence of a learning effect associated with the 6-minute walk in patients with PAD provides a distinct advantage compared with treadmill walking performance. The treadmill walking test simply does not reflect the natural history of declining walking performance over time in patients with PAD.
6-minute walk performance between baseline and the 2-year follow-up had significantly higher rates of all-cause mortality (HR=3.56; 95% CI=1.56–7.85), cardiovascular mortality (HR=2.45; 95% CI=1.08–5.54), and mobility loss (HR=3.50; 95% CI=1.56–7.85) compared with those with lesser declines in 6-minute walk between baseline and the 2-year follow-up.25 In summary, both a baseline 6-minute walk measurement and 2-year change in the 6-minute walk test predict clinically meaningful outcomes among individuals with PAD. In all of these analyses, the associations were independent of age, sex, race, PAD severity, comorbidities, and other potential confounders.8,13,25 To the best of our knowledge, only 1 prior longitudinal study related treadmill walking performance to subsequent outcomes.39 Although this study demonstrated that poorer baseline exercise capacity, measured by metabolic equivalents, was associated with higher rates of all-cause mortality in patients with PAD, the analyses were adjusted only for age. Most likely, the association is confounded by the severity of PAD and the presence of comorbid disease. However, the analyses did not adjust for ABI or comorbid disease.39

The 6-Minute Walk as a Measure of Improved Walking Endurance in Response to Medications

Clinical trials of exercise in participants with PAD demonstrate that the 6-minute walk test consistently successfully quantifies and documents improvement in walking endurance in responsive to exercise interventions. To the best of our knowledge, no prior clinical trials of therapeutic medications in patients with PAD have used the 6-minute walk test as an outcome measure. However, the 6-minute walk test is frequently used as a primary outcome measure in therapeutic trials of patients with chronic lung disease and pulmonary hypertension.40–42 The US Food and Drug Administration also considers the 6-minute walk a meaningful outcome measure in patients with PAD. An ongoing trial of granulocyte macrophage colony-stimulating factor combined with supervised treadmill exercise uses the 6-minute walk as a primary outcome measure.31 Future clinical trials of therapeutic medications in patients with PAD should include the 6-minute walk as an outcome.

Meaningful Changes in the 6-Minute Walk Have Been Defined

Clinically meaningful change in the 6-minute walk test has been defined by relating changes in 6-minute walk over time to corresponding rates of mobility loss and declines in quality of life across several studies of older people with and without chronic diseases.31 This study combined a distribution-based method and an anchor-based method to define clinically meaningful change in the 6-minute walk.31 Distribution-based methods rely on the psychometric properties of the 6-minute walk to determine small and large effect sizes. Anchor-based methods define a clinical standard to link with a meaningful change, measured with the use of small and large effect sizes in the 6-minute walk. With the use of these methods, a small meaningful change in 6-minute walk was defined as a change of 20 m, and a large meaningful change in 6-minute walk was defined as a change of 50 m.31 These defined clinically meaningful changes in the 6-minute walk can be used to interpret results of clinical trials that use the 6-minute walk as an outcome. In contrast, to the best of our knowledge, no prior studies have defined clinically meaningful changes for treadmill walking performance.

Safety and Other Considerations

To the best of our knowledge, data on the safety of the 6-minute walk and treadmill testing in people with PAD have not been reported. However, in our experience conducting >7900 six-minute walk tests in people with PAD, we have had only 1 serious adverse event: a fall resulting in a forearm fracture. In our experience conducting >1300 treadmill tests in participants with PAD, we have had 2 participants who required immediate referral to the emergency department. Of these, 1 patient developed ventricular tachycardia during the treadmill test, and 1 patient developed hypotension during the treadmill test. Although treadmill testing can be used as a diagnostic test for PAD,41 the 6-minute walk has not been studied as a diagnostic tool. Finally, there is currently insufficient evidence to calculate the statistical efficiency of the treadmill test versus the 6-minute walk.

Conclusions

Available evidence in patients with PAD demonstrates that walking performance measured by the 6-minute walk test better represents walking in daily life than treadmill walking performance. Among patients with PAD, the 6-minute walk has excellent test-retest reliability, predicts risk for mortality and mobility loss, is sensitive to the natural history of declines in walking endurance, and detects improved walking endurance in response to therapeutic interventions. Treadmill testing is particularly problematic for clinical trials that use supervised treadmill exercise as a therapeutic intervention because these trials are training patients with PAD specifically to the outcome measurement. Future therapeutic trials of new medications for patients with PAD should preferentially use the 6-minute walk, rather than treadmill walking performance, as an outcome measure.

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Disclosures

None.

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treadmill testing should continue to be the testing modality of choice in clinical trials for interventions in PAD. With a variety of interventions, excellent test characteristics, strong clinical correlates, and wide acceptance suggest that not been established in PAD. Thus, the physiological foundations, demonstrated ability to detect changes in performance and various clinical parameters, these correlations are based largely on cross-sectional studies and thus do not establish a scientific statement from the American Heart Association. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. Circulation. 2012;126:2890–2909.

Response to McDermott
William R. Hiatt, MD; R. Kevin Rogers, MD; Eric P. Brass, MD, PhD

As we acknowledge and document in our article, the 6-minute walk test has value and demonstrated utility in some situations. Unfortunately, the experience in multicenter intervention clinical trials for peripheral artery disease is substantially more limited; the variance of any performance test is greater than when assessed at a single site. McDermott et al cite performance characteristics for the 6-minute walk test in peripheral artery disease derived exclusively from single-site studies of exercise training. Exercise has a large treatment effect size that is easily detected by either a treadmill or 6-minute walk test. There is no published information on the 6-minute walk test in any multicenter trial; therefore, the variance of the test under these conditions is not known, in contrast to the well-described test characteristics of the graded treadmill across sites and countries that form the basis for our recommendations. Although McDermott et al cite correlations between 6-minute walk test and various clinical parameters, these correlations are based largely on cross-sectional studies and thus do not establish that change in 6-minute walk test performance with an intervention will translate to other clinically important benefits. Furthermore, the minimal clinically important difference defined for the 6-minute walk test in some other disease states has not been established in PAD. Thus, the physiological foundations, demonstrated ability to detect changes in performance with a variety of interventions, excellent test characteristics, strong clinical correlates, and wide acceptance suggest that treadmill testing should continue to be the testing modality of choice in clinical trials for interventions in PAD.
Six-Minute Walk Is a Better Outcome Measure Than Treadmill Walking Tests in Therapeutic Trials of Patients With Peripheral Artery Disease
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