

**ORIGINAL RESEARCH**

# Effects of Walking Exercise at a Pace With Versus Without Ischemic Leg Symptoms on Functional Performance Measures in People With Lower Extremity Peripheral Artery Disease: The LITE Randomized Clinical Trial

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**BACKGROUND:** In people with peripheral artery disease, post hoc analyses of the LITE (Low Intensity Exercise Intervention in Peripheral Artery Disease) randomized trial were conducted to evaluate the effects of walking exercise at a pace inducing ischemic leg symptoms on walking velocity and the Short Physical Performance Battery, compared with walking exercise without ischemic leg symptoms and compared with a nonexercising control group.

**METHODS AND RESULTS:** Participants with peripheral artery disease were randomized to: home-based walking exercise that induced ischemic leg symptoms; home-based walking exercise conducted without ischemic leg symptoms; or a nonexercising control group for 12 months. Outcomes were change of walking velocity over 4 m and change of the Short Physical Performance Battery (0–12, with 12=best) at 6- and 12-month follow-up. A total of 264 participants (48% women, 61% Black race) were included. Compared with walking exercise without ischemic symptoms, walking exercise that induced ischemic symptoms improved change in usual-paced walking velocity over 4 m at 6-month (0.056 m/s [95% CI, 0.019–0.094 m/s];  $P<0.01$ ) and 12-month follow-up (0.084 m/s [95% CI, 0.049–0.120 m/s];  $P<0.01$ ), change in fast-paced walking velocity over 4 m at 6-month follow-up ( $P=0.03$ ), and change in the Short Physical Performance Battery at 12-month follow-up (0.821 [95% CI, 0.309–1.334];  $P<0.01$ ). Compared with control, walking exercise at a pace inducing ischemic symptoms improved change in usual-paced walking velocity over 4 m at 6-month follow-up (0.066 m/s [95% CI, 0.021–0.111 m/s];  $P<0.01$ ).

**CONCLUSIONS:** In people with peripheral artery disease, those who walked for exercise at a comfortable pace without ischemic leg symptoms slowed their walking speed during daily life and worsened the Short Physical Performance Battery score, a potentially harmful effect, compared with people who walked for exercise at a pace inducing ischemic leg symptoms. Compared with a control group who did not exercise, home-based walking exercise at a pace inducing ischemic leg symptoms significantly improved change of walking velocity over 4 m at 6-month follow-up, but this benefit did not persist at 12-month follow-up.

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**Key Words:** functional performance ■ peripheral artery disease ■ randomized clinical trial ■ walking exercise

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## CLINICAL PERSPECTIVE

### What Is New?

- In a randomized clinical trial of 264 people with lower extremity peripheral artery disease, compared with walking for exercise at a comfortable pace, walking for exercise at a pace that induced ischemic leg symptoms improved walking velocity over 4 m and the Short Physical Performance Battery score at 12-month follow-up.
- In this randomized trial of people with peripheral artery disease, compared with a control group who did not exercise, walking for exercise at a pace inducing ischemic leg symptoms improved usual-paced walking velocity over 4 m at 6-month follow-up, but did not significantly improve walking velocity or the Short Physical Performance Battery at 12-month follow-up.

### What Are the Clinical Implications?

- Walking for exercise at a pace inducing ischemic leg symptoms is better than walking for exercise at a pace without ischemic leg symptoms for improving walking velocity and the Short Physical Performance Battery in peripheral artery disease.
- However, when compared with a control group who did not exercise, walking for exercise at a pace inducing ischemic leg symptoms did not improve walking velocity over 4 m or the Short Physical Performance Battery at 12-month follow-up.

### Nonstandard Abbreviations and Acronyms

<b>LITE</b>	Low Intensity Exercise Intervention in Peripheral Artery Disease
<b>SPPB</b>	Short Physical Performance Battery

**W**alking exercise is first-line therapy for people disabled by lower extremity peripheral artery disease (PAD).<sup>1,2</sup> However, ischemic leg symptoms are a major barrier to walking exercise in people with PAD. Some recent studies have evaluated whether walking for exercise at a pace without ischemic leg symptoms is effective for people with PAD.<sup>3,4</sup> However, the effects of walking exercise at a pace inducing ischemic leg symptoms on measures of lower extremity functional performance other than walking endurance, compared with walking exercise at a comfortable pace without ischemic leg symptoms, remain unclear.

The LITE (Low Intensity Exercise Intervention in Peripheral Artery Disease) randomized clinical trial demonstrated that a home-based walking exercise

intervention, in which exercise was performed at a pace without ischemic leg symptoms, did not improve 6-minute walk distance compared with a control group who did not exercise.<sup>5</sup> In contrast, walking exercise at a pace inducing ischemic leg symptoms improved 6-minute walk distance significantly and meaningfully, compared with walking exercise at a pace that did not induce ischemic leg symptoms and compared with a control group who did not exercise.<sup>5</sup> However, the effects of walking exercise at a pace inducing ischemic symptoms on other lower extremity functional outcomes, such as 4-m walking speed and Short Physical Performance Battery (SPPB), remain unclear. The 4-m walking velocity test and SPPB (consisting of 3 components: 4-m walking speed, strength for the chair rise, and balance tests) assess walking speed and standing balance, respectively, and lower scores are associated with higher rates of mobility loss and mortality in people with PAD.<sup>6,7</sup>

Therefore, in post hoc, exploratory analyses of the LITE randomized trial, we studied the effects of walking exercise at a pace inducing ischemic leg symptoms on the outcomes of 4-meter walking velocity, the SPPB, and participant-reported walking speed, compared with walking exercise at a pace without ischemic leg symptoms and compared with a control group who did not exercise. On the basis of results for the primary outcome,<sup>5</sup> investigators hypothesized that home-based walking exercise at a pace that induced ischemic leg symptoms would improve 4-meter walking velocity, the SPPB, and participant-reported walking speed more than walking exercise at a comfortable pace without ischemic leg symptoms and more than a control group who did not exercise. We also examined the effects of walking exercise at a pace without ischemic leg symptoms on these outcomes, compared with the control group who did not exercise.

## METHODS

### Study Population

Participants were part of the LITE randomized trial, a multicentered randomized clinical trial with 3 parallel groups that was originally designed to determine whether home-based walking exercise at a pace that did not induce ischemic leg symptoms significantly increased 6-minute walk distance in people with PAD, compared with home-based walking exercise at a pace inducing ischemic leg symptoms, and compared with a control group who did not exercise.<sup>5</sup> The details of the LITE trial have been described.<sup>5</sup> Briefly, participants were randomized at Northwestern University, Tulane University, University of Minnesota, and University of Pittsburgh, to home-based walking exercise at a pace that did not induce ischemic leg

symptoms, home-based walking exercise at a pace that induced ischemic leg symptoms, or a control group who did not exercise, and followed up for 12 months. Participants were recruited between September 2015 and December 2019. Final follow-up occurred in October 2020.<sup>5</sup> The institutional review boards at all participating institutions approved the protocol, and all participants provided written informed consent. Data from the trial may be available from the principal investigator (M.M.M.) on reasonable request.

### Participant Identification

Eligible patients with PAD were identified from among patients with PAD at each participating medical center. Recruitment methods included mailed postcards (advertising the study) to people aged  $\geq 50$  years in Chicago, IL, Minneapolis, MN, and New Orleans, LA. Participants were also recruited through advertisements on buses and trains in Chicago. People with PAD who had participated in previous studies and were interested in future studies were invited to participate.<sup>5</sup>

### Inclusion and Exclusion Criteria

Participants were included if they had an ankle-brachial index (ABI)  $\leq 0.90$ .<sup>8</sup> Individuals with ABI between 0.91 and 1.00 at baseline were eligible if their ABI decreased by  $\geq 20\%$  after a heel-rise test.<sup>9</sup> Individuals with ABI  $> 0.90$  were eligible if there was confirmation of PAD from a vascular laboratory or an angiogram.

Potential participants were excluded if they had severe functional impairment, as indicated by major amputation, or by requirement of a wheelchair or walking aid other than a cane. Potential participants were excluded if they had walking limitations for reasons other than PAD, or had a foot ulcer or critical limb ischemia. Potential participants with Mini-Mental State Examination score  $< 23$ ,<sup>10</sup> significant visual or hearing impairment, planned major surgery within 12 months, or lower extremity revascularization or orthopedic surgery during the previous 3 months were excluded. Those with major medical illness, those for whom exercise was unsafe, those who were exercising at a level similar to that targeted in the exercise interventions, those who were unable to walk slowly enough to avoid ischemic leg symptoms, and those without ischemic leg symptoms during walking exercise activity were excluded.<sup>5</sup>

### Ankle-Brachial Index

A hand-held Doppler probe (Nicolet Vascular Pocket Dop II; Nicolet Biomedical Inc, Golden, CO) was used to measure systolic blood pressures in the right brachial, posterior tibial, and dorsalis pedis arteries and left posterior tibial, dorsalis pedis, and brachial arteries. These measurements were repeated in reverse

order.<sup>8</sup> The ABI was calculated by dividing the mean of the dorsalis pedis and posterior tibial pressures in each leg by the mean of the 4 brachial pressures, based on prior study demonstrating that this method of ABI calculation correlated more closely with walking impairment in people with PAD than alternative methods of ABI calculation.<sup>11</sup>

### Randomization

Participants were randomized to 1 of 3 parallel groups: home-based walking exercise at a pace without ischemic leg symptoms, home-based walking exercise at a pace that induced ischemic leg symptoms, or an attention control group that did not exercise in a ratio of 120:120:65 using randomized permuted block sizes of 61, consisting of 24, 24, and 13 participants into 3 groups. Randomization was stratified by study site and consent to muscle biopsy.<sup>5</sup>

### Exercise Interventions

The exercise interventions lasted 12 months (ie, 52 weeks). Participants were asked to walk for exercise at home for 5 days per week, working up to 50 minutes of exercise per session. Between weeks 1 and 4, participants in the exercise intervention groups visited the medical center once weekly to meet with the coach, who oriented the participant to the exercise intervention and helped the participant adopt behaviors to help him/her adhere to walking exercise at home. Between weeks 5 and 52, participants were contacted via telephone by study coaches. During each coach contact (in person during weeks 1–4 and by telephone during weeks 5–52), behavioral methods were incorporated to assist those randomized to exercise with walking exercise at home 5 days per week. During the on-site visits, participants were taught to use the ActiGraph to collect data on their walking exercise activity and upload the data on a personal computer or a tablet provided by the study. Before beginning the exercise intervention, the coach worked with each participant randomized to an exercise group to identify the ActiGraph activity counts corresponding to walking exercise without ischemic leg symptoms (Likert ischemic claudication pain scale score,  $\leq 2$ ) and the ActiGraph activity counts corresponding to walking exercise that induced maximal ischemic leg symptoms (Likert ischemic claudication pain scale score, 4–5) for each individual. These personalized thresholds for each intensity of exercise were defined for each individual during the initial on-site visit by having him/her wear the ActiGraph to collect activity counts per minute while walking for exercise for  $\approx 5$  minutes at a pace inducing maximal ischemic leg symptoms and separately at a comfortable pace without leg symptoms. These ActiGraph benchmarks established for each participant were uploaded

to the study website and used to guide home walking exercise activity, helping participants to monitor the intensity of their walking exercise at home to help them adhere to walking exercise at the intensity corresponding to the participant's group assignment (ie, walking for exercise either with or without ischemic leg symptoms). Individualized benchmarks of ActiGraph activity counts were remeasured at months 1, 3, 6, and 9, and after significant medical illness to reflect change in these exercise intensity benchmarks as each participant progressed through the trial. These benchmarks were referred to when evaluating whether participants were adhering to the intensity of walking exercise assigned by the randomization process. Participants randomized to exercise wore their ActiGraph device during walking exercise activity and uploaded data on exercise frequency, intensity, and duration to the study website using their home computer or tablet provided by the study.<sup>5</sup> These data, viewable to the participant and study coach, were used by the coaches to provide feedback to participants during weekly telephone calls.

### Attention Control Group

The attention control group lasted 52 weeks and controlled for the time that participants randomized to an exercise group spent with the coaches in their exercise intervention. Between weeks 1 and 4, participants randomized to the attention control group attended weekly 1-hour group educational sessions at the medical center that covered topics of interest other than exercise, such as cancer screening and Medicare Part D. Between weeks 5 and 52, participants also were contacted individually via telephone to discuss health-related topics other than exercise.<sup>5</sup>

### Functional Performance Measures

All outcome measures were obtained at baseline, 6-month follow-up, and 12-month follow-up.

### The 4-m Walking Velocity

The 4-m walking velocity test is a test of walking speed and predicts mobility loss and mortality in people with PAD.<sup>6,7</sup> Walking velocity over a 4-m distance was measured at a usual and fastest pace. For usual-paced walking velocity, participants were instructed to walk at their usual pace, "as if going down the street to the store." For the fast paced walk, participants were instructed to walk at their "fastest pace." Each 4-m walk was performed twice, and the faster walking velocity in each pair was used in analyses.<sup>6,12</sup> The minimum clinically important difference for usual-paced 4-m walking velocity in people with mild to moderate mobility impairment ranges from 0.04 to 0.06 m/s.<sup>13</sup> The minimum clinically important difference for fast-paced 4-m walking velocity has not been defined.

### Short Physical Performance Battery

The SPPB is a global assessment of lower extremity functioning and predicts mobility loss and mortality in people with and without PAD.<sup>6,7,12</sup> The SPPB consists of 3 components: usual-paced 4-m walking velocity, time for 5 repeated chair rises, and standing balance in 3 increasingly challenging positions. Each component was scored on a Likert scale, ranging from 0 to 4, where 0 indicated the inability to perform the task and 4 indicated the best performance.<sup>12,14</sup> Scores of 1 to 4 were assigned on the basis of quartiles of performance for each measure from >6000 participants in the EPESE (Established Populations for Epidemiologic Study of the Elderly).<sup>12,14</sup> The total SPPB score was derived by summing the 0 to 4 scores from each of the 3 components (usual-paced 4-m walking velocity, repeated chair rises, and standing balance). Total SPPB scores ranged from 0 to 12 (12=best).<sup>12,14</sup> The minimum clinically important difference in people with mild to moderate mobility impairment ranges from 0.27 to 0.55 points.<sup>13</sup>

### Participant-Reported Walking Velocity

Self-reported walking velocity was measured using a physical activity questionnaire derived from the Harvard Alumni Activity Survey.<sup>15-17</sup> To measure participant-reported walking speed outside the home, participants were asked "When you walk outside your home, what is your usual pace?" Response options ranged from 1 to 5 (5=best). Score values were as follows: no walking at all (1), casual strolling (0-2 miles per hour) (2), average or normal (2-3 miles per hour) (3), fairly briskly (3-4 miles per hour) (4), and brisk or striding (>4 miles per hour) (5).

### Medical History, Race, and Demographics

Information on medical history, race, and demographics was obtained through self-report at the baseline visit.<sup>5</sup> The medical history included information on the following comorbidities: hypertension, diabetes, cancer, myocardial infarction, pulmonary disease, and stroke. Age, sex, race and ethnicity, and smoking status, based on self-report, were recorded. Weight was measured in kilograms and height in meters. Body mass index was calculated as weight in kilograms divided by the square of height in meters.

### Statistical Analysis

Baseline characteristics (summarized as mean [SD] for continuous variables and count [proportion] for categorical variables) were compared between the 3 groups to assess whether there were differences in baseline characteristics between the 3 groups.

Mixed models for repeated measures analyses were used to compare changes in usual-paced 4-m walking velocity, fast-paced 4-m walking velocity, and the SPPB from baseline to month 6 and from baseline to month 12 between 3 groups (participants who walked for exercise at a comfortable pace without ischemic leg symptoms, participants who walked for exercise at a pace inducing ischemic leg symptoms, and participants in the attention control group who did not exercise). These analyses included all participants with follow-up data, regardless of adherence to their assigned intervention. The 6- and 12-month changes in usual-paced 4-m walking velocity, fast-paced 4-m walking velocity, and the SPPB were treated as dependent outcomes, whose covariance was modeled via an unstructured variance–covariance matrix. The regression analyses were additionally adjusted for each outcome measure at baseline. If either 6- or 12-month measurement was missing, the corresponding change was also missing and excluded from the analyses. Participants without baseline measures for study outcomes were excluded from analyses. The results from mixed models for repeated measures analyses are valid under the missing at random assumption. In additional analyses to examine the missingness mechanism, baseline characteristics between participants with PAD who completed all follow-up tests, those who completed some follow-up tests, and those who were excluded because they did not complete any follow-up tests reported herein were compared. In sensitivity analyses, statistical analyses were repeated using an alternative mixed models for repeated measures method that included participants with missing data at baseline for the outcome measures and adjusting for baseline characteristics that differed between the 3 groups at  $P \leq 0.20$ .

Self-reported walking speed was assessed at baseline, 6-month follow-up, and 12-month follow-up. Each participant's self-reported walking speed was classified as "improved" or "not improved" at 6- and 12-month follow-up, by comparing his/her responses to the question about his/her perceived walking speed at these follow-up visits to that reported at baseline. For each follow-up visit (ie, 6- and 12-month follow-up), participants who reported a lower or the same score for walking speed compared with baseline were classified as "not improved" for that follow-up visit; those who reported a higher score for walking speed at follow-up compared with baseline were classified as "improved." Logistic regression was used to examine the association between each randomized group (walking exercise at a comfortable pace without ischemic leg symptoms, walking exercise at a pace inducing ischemic leg symptoms, and no exercise) and the probability of "improvement" in perceived walking speed at 6- and 12-month follow-up. Odds ratios and 95% CIs were reported.

Statistical analyses were performed using SAS version 9.4, and  $P < 0.05$  was considered statistically significant.

## RESULTS

Of 305 participants randomized in the LITE trial, 264 (87%) (mean age,  $69 \pm 9$  years; 48% women; 61% Black race) completed  $\geq 1$  of the outcomes reported herein and were included. Of these participants, 236 (89%) completed 6-month follow-up and 205 (78%) completed 12-month follow-up. Of the 264 participants included, 101 (38%) were randomized to home-based walking exercise at a pace without ischemic leg symptoms, 109 (41%) were randomized to home-based walking exercise at a pace that induced ischemic leg symptoms, and 54 (20%) were randomized to the non-exercising control group (Figure S1). Baseline characteristics were similar between trial assignment groups (Table 1). Characteristics were similar between participants who completed all follow-up measures, those who completed some but not all follow-up measures, and those who were excluded because they did not complete any follow-up measures reported herein (Table S1).

### Walking Exercise Behavior

Participants randomized to home-based walking for exercise at a pace that induced ischemic leg symptoms walked a mean of  $2.9 \pm 1.3$  days per week, compared with  $3.7 \pm 1.3$  days per week for those randomized to walking exercise at a comfortable pace ( $P < 0.01$ ). Participants randomized to home-based walking exercise at a pace inducing ischemic leg symptoms walked for exercise for a mean of  $82.2 \pm 59.7$  minutes per week, compared with  $154.0 \pm 84.3$  minutes per week for participants randomized to exercise at a comfortable pace without ischemic leg symptoms ( $P < 0.01$ ).

### Effects of Walking Exercise at a Pace Inducing Ischemic Leg Symptoms on Change in Usual-Paced 4-m Walking Velocity

Compared with walking exercise at a comfortable pace without ischemic leg symptoms, walking exercise at a pace inducing ischemic leg symptoms significantly improved usual-paced 4-m walking velocity at 6-month follow-up (0.056 m/s [95% CI, 0.019–0.094 m/s];  $P < 0.01$ ) and at 12-month follow-up (0.084 m/s [95% CI, 0.049–0.120 m/s];  $P < 0.01$ ) (Figure 1). Compared with the nonexercising control group, walking exercise at a pace that induced ischemic leg symptoms significantly improved usual-paced 4-m walking velocity at 6-month follow-up (0.066 m/s [95% CI, 0.021–0.111 m/s];  $P < 0.01$ ) but had no statistically significant effect at 12-month follow-up (0.03 m/s [95% CI,  $-0.013$  to 0.073 m/s];  $P = 0.17$ ) (Figure 1).

**Table 1. Baseline Characteristics of Participants With PAD, According to Group Assignment**

Characteristic	Walking exercise at a pace inducing ischemic leg symptoms (N=109)	Walking exercise at a pace conducted without ischemic leg symptoms (N=101)	Attention control group (N=54)
Age, mean (SD), y	69 (9)	70 (10)	69 (10)
Sex, n (%)			
Men	56 (51)	55 (54)	27 (50)
Women	53 (49)	46 (46)	27 (50)
Race, n (%)			
Black	74 (68)	56 (55)	32 (59)
White	34 (31)	39 (39)	20 (37)
Other races*	1 (1)	6 (6)	2 (4)
Body mass index, mean (SD), kg/m <sup>2</sup>	31.2 (7.0)	29.4 (5.5)	30.8 (7.7)
Ankle-brachial index, mean (SD)	0.67 (0.15)	0.65 (0.18)	0.68 (0.14)
Current smoker, n (%)	26 (24)	35 (35)	13 (24)
Hypertension, n (%)	98 (90)	88 (87)	43 (80)
Diabetes, n (%)	48 (44)	40 (40)	29 (54)
Cancer, n (%)	18 (17)	21 (21)	11 (20)
Myocardial infarction, n (%)	28 (26)	17 (17)	4 (7)
Pulmonary disease, n (%)	17 (16)	13 (13)	10 (19)
Stroke, n (%)	25 (23)	15 (15)	13 (24)

PAD indicates peripheral artery disease.

\*\*Other" category includes total 9 participants (6 Asian + 3 Unknown).

### Effects of Walking Exercise at a Pace Inducing Ischemic Leg Symptoms on Change in Fast-Paced 4-m Walking Velocity

Compared with walking exercise at a comfortable pace without ischemic leg symptoms, walking exercise at a pace that induced ischemic leg symptoms significantly improved fast-paced 4-m walking velocity at 6-month follow-up (0.05 m/s [95% CI, 0.006–0.094 m/s];  $P=0.03$ ), but had no significant effect on fast-paced 4-m walking velocity at 12-month follow-up (0.043 m/s [95% CI, –0.014 to 0.099 m/s];  $P=0.14$ ) (Figure 2). Compared with the nonexercising control group, walking exercise at a pace that induced ischemic leg symptoms had no effect on fast-paced 4-m walking velocity at 6- or at 12-month follow-up (Figure 2).

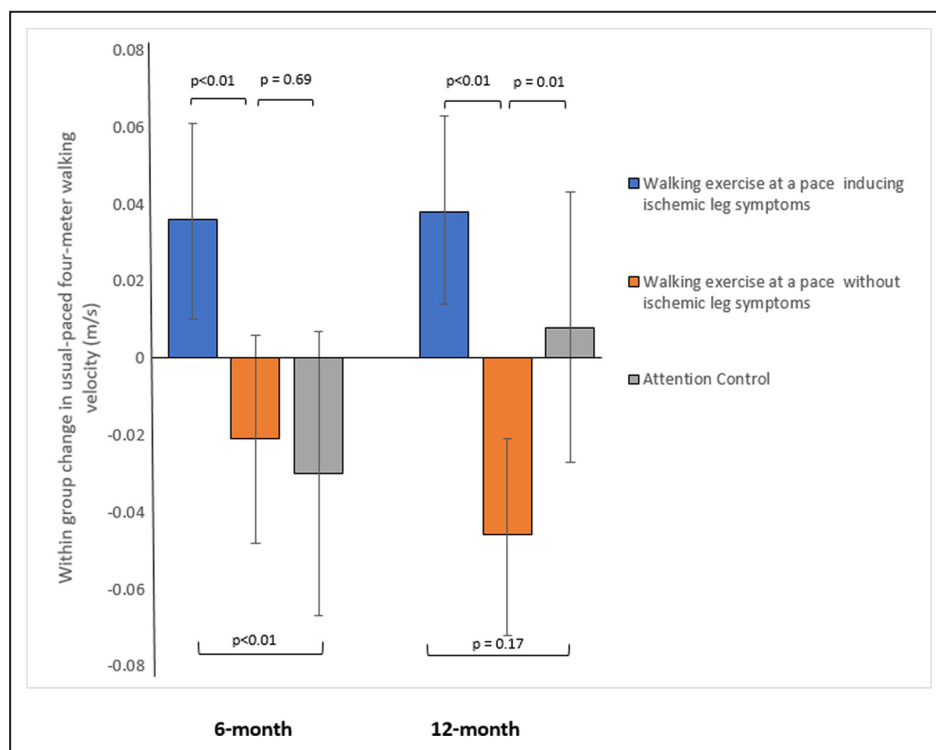
### Effects of Walking Exercise at a Pace Inducing Ischemic Leg Symptoms on Change in the SPPB

Compared with walking exercise at a comfortable pace without ischemic leg symptoms, walking exercise at a pace that induced ischemic leg symptoms had no significant effect on the SPPB at 6-month follow-up (0.426 [95% CI, –0.087 to 0.939];  $P=0.10$ ) but significantly improved the SPPB at 12-month follow-up (0.821 [95% CI, 0.309–1.334];  $P<0.01$ ) (Figure 3).

Compared with the nonexercising control group, walking exercise at a pace that induced ischemic leg symptoms had no significant effect on the SPPB at 6-month follow-up (0.332 [95% CI, –0.299 to 0.963];  $P=0.30$ ) or at 12-month follow-up (0.333 [95% CI, –0.290 to 0.957];  $P=0.29$ ) (Figure 3).

### Effects of Walking Exercise at a Pace Inducing Ischemic Leg Symptoms on Change in Participant-Reported Walking Velocity

Compared with participants who walked for exercise at a comfortable pace without ischemic pain, participants who walked for exercise at a pace that induced ischemic leg symptoms were significantly more likely to report walking speed that was improved at 6-month follow-up (45/101 [45%] versus 25/97 [26%]; odds ratio [OR], 2.31 [95% CI, 1.27–4.22];  $P<0.01$ ) and 12-month follow-up (33/98 [34%] versus 17/92 [18%]; OR, 2.24 [95% CI, 1.14–4.39];  $P=0.02$ ) (Table 2). Compared with the nonexercising control, participants who walked at a pace that induced ischemic leg symptoms were significantly more likely to report a walking speed that was improved at 6-month follow-up (45/101 [45%] versus 10/52 [19%]; OR, 3.38 [95% CI, 1.53–7.46];  $P<0.01$ ) but not at 12-month follow-up (33/98 [34%] versus 14/47 [30%]; OR, 1.20 [95% CI, 0.56–2.54];  $P=0.64$ ) (Table 2).



**Figure 1.** Effects of walking exercise at a pace inducing ischemic leg symptoms on usual-paced 4-m walking velocity at 6- and 12-month follow-up in people with lower extremity peripheral artery disease.

### Effects of Walking Exercise at a Comfortable Pace on Change in Walking Performance Measures

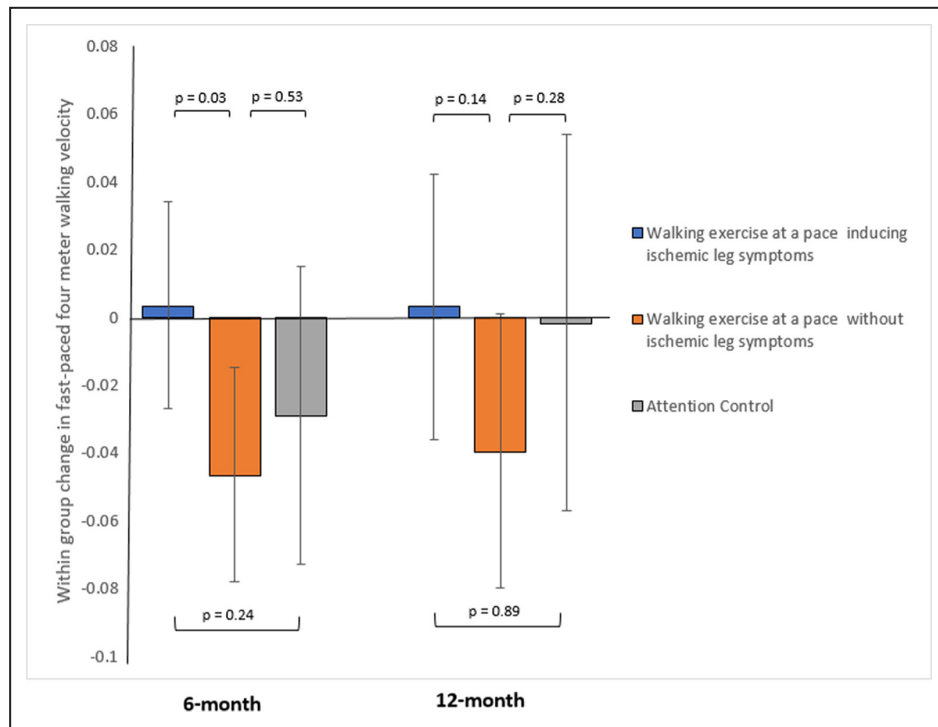
Compared with the nonexercising control group, walking exercise at a comfortable pace without ischemic leg symptoms did not improve usual-paced 4-m walking velocity, fast-paced 4-m walking velocity, or SPPB at 6-month follow-up (Figures 1–3). Compared with the nonexercising control group, walking exercise at a comfortable pace without ischemic leg symptoms significantly worsened usual-paced 4-m walking velocity at 12-month follow-up ( $-0.054$  m/s [95% CI,  $-0.098$  to  $-0.011$  m/s];  $P=0.01$ ) but did not have any effects on fast-paced 4-m walking velocity or SPPB at 12-month follow-up (Figure 1). Compared with the nonexercising control group, walking exercise at a comfortable pace did not have any significant effect on participant-reported walking speed at 6- or 12-month follow-up (Table 2).

Results for the objective outcome measures were not significantly different when analyses were repeated using the mixed model for repeated measures method, in which participants who had missing data at the baseline visit were included (data not shown). Results for the objective outcome measures were not significantly different when analyses were repeated,

adjusting for baseline characteristics that differed between the 3 groups at  $P \leq 0.20$  (cigarette smoking, race, body mass index, hypertension, and history of myocardial infarction).

## DISCUSSION

In this multicentered randomized clinical trial of people with PAD, compared with home-based walking exercise conducted at a comfortable pace without ischemic leg symptoms, home-based walking exercise conducted at a pace that induced ischemic leg symptoms significantly improved performance on 4 of 6 functional outcomes not related to walking endurance, including usual-paced 4-m walking velocity at 6- and 12-month follow-up, fast-paced walking velocity at 6-month follow-up, and the SPPB at 12-month follow-up. Compared with home-based walking exercise at a comfortable pace, home-based walking exercise at a pace that induced ischemic leg symptoms also significantly increased participant-reported walking speed at 6- and at 12-month follow-up. The statistically significant effects of home-based walking exercise at a pace inducing ischemic leg symptoms on usual-paced 4-m walking velocity at 6- and 12-month follow-up and on the SPPB at 12-month follow-up met the criteria for a



**Figure 2.** Effects of walking exercise at a pace inducing ischemic leg symptoms on fast-paced 4-m walking velocity at 6- and 12-month follow-up in people with lower extremity peripheral artery disease.

clinically meaningful change, compared with walking exercise at a pace without ischemic leg symptoms.<sup>13</sup> Similarly, the statistically significant effects of home-based walking exercise conducted at a pace inducing ischemic leg symptoms on usual-paced 4-m walking velocity at 6-month follow-up met the criterion for a clinically meaningful change, compared with the attention control group.<sup>13</sup> Together, these results showed that home-based walking exercise at a pace that does not induce ischemic leg symptoms was significantly worse than walking exercise that induces ischemic leg symptoms for outcomes of walking speed and the SPPB. Results also showed that walking for exercise at a pace without ischemic leg symptoms was significantly worse than the control group for the outcome of usual-paced walking velocity at 12-month follow-up.

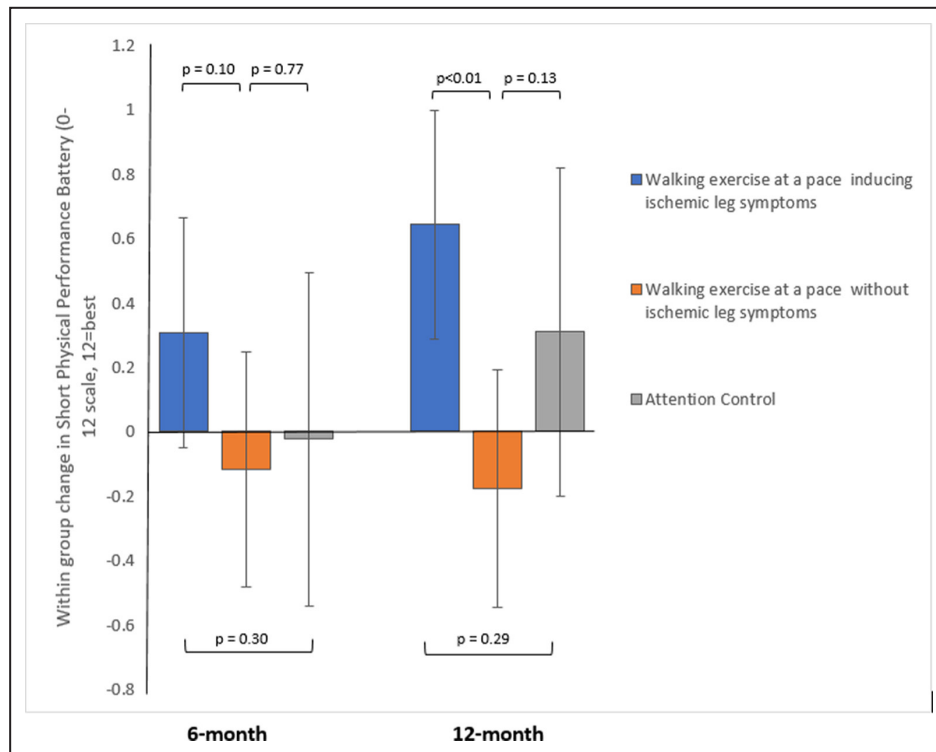
Previous small clinical trials suggested that supervised treadmill walking exercise at a comfortable pace improved walking performance measures in people with PAD and attained benefit that was not significantly different from supervised treadmill walking exercise at a pace that induced maximal ischemic leg symptoms.<sup>3,4,18</sup> However, these prior studies had small sample sizes and may have lacked statistical power to demonstrate significantly different effects of walking exercise at a pace that induced ischemic leg symptoms compared with walking exercise at a pace

without ischemic leg symptoms. In addition, these prior randomized trials used treadmill walking performance as the primary outcome measure. Prior work documented a learning effect of treadmill walking exercise on the outcome of treadmill walking performance in people with PAD.<sup>19,20</sup> Compared with these prior studies,<sup>3,4,18</sup> results reported herein included a larger sample size and studied functional outcome measures that have been previously shown to predict mobility loss, cardiovascular mortality, and all-cause mortality.<sup>6,7</sup>

Home-based walking exercise at a pace inducing ischemic leg symptoms significantly improved usual-paced 4-m walking velocity, compared with the non-exercising control group at 6-month follow-up, but had no effect on the usual-paced 4-m walking velocity at 12-month follow-up, compared with the control group. These results suggest diminished potency of the walking exercise intervention at high intensity over time for this outcome.

Although participants randomized to walking exercise at a comfortable pace without ischemic leg symptoms walked for exercise for a longer duration (more minutes and more days), compared with participants randomized to walking exercise at a pace that induced ischemic leg symptoms, walking exercise at a comfortable pace did not improve walking velocity or the SPPB at either 6- or 12-month follow-up, compared





**Figure 3.** Effects of walking exercise at a pace inducing ischemic leg symptoms on the Short Physical Performance Battery at 6- and 12-month follow-up in people with lower extremity peripheral artery disease.

with the control group who did not exercise. This observation is consistent with the hypothesis that walking for exercise at a pace inducing ischemic leg symptoms is more important than walking for exercise more frequently or for a longer duration. On the basis of data reported herein, participants with PAD should not be advised to walk for exercise at a pace without ischemic leg symptoms.

In this study, home-based walking exercise at a pace without ischemic leg symptoms was significantly worse than home-based walking exercise at a pace inducing ischemic leg symptoms for multiple functional outcomes. In comparison, the control group who did not exercise was significantly worse than home-based walking exercise at a pace inducing ischemic leg symptoms for only 2 outcomes (usual-paced walking velocity and participant-reported walking velocity at 6-month follow-up). Walking exercise at a comfortable pace could potentially have adverse effects on walking speed or the SPPB if participants slowed their walking speed during daily life in response to the exercise intervention, in which they were instructed to walk at a pace without ischemic leg symptoms. However, because the nonexercise control group was not asked to walk for exercise, the control group would not have voluntarily slowed its walking speed, which may explain

why the nonexercise control group was significantly worse for a smaller number of outcomes than the group who walked for exercise at a comfortable pace, and compared with the group who walked for exercise at a pace inducing ischemic leg symptoms. In addition, the control group had a smaller sample size than the 2 exercise groups, which reduced statistical power to demonstrate statistically significant differences in change in 4-m walking velocity or the SPPB between the participants randomized to walking exercise at a pace inducing ischemic leg symptoms and the control group who did not exercise.

This study has some limitations. First, results reported herein may not apply to supervised treadmill exercise interventions. Second, a small proportion of participants randomized into the LITE trial (41/305 [13%]) did not complete the 4-m walking velocity measures or the SPPB, or respond to the question on self-reported walking pace, and were not included in these analyses. Third, these results are post hoc and exploratory and require confirmation. Fourth, some comparisons likely lacked statistical power to attain a statistically significant difference because of the relatively small sample size. For example, the 2 comparisons between the 2 exercise groups that were not statistically significant had  $P < 0.15$ , favoring the exercise group who

**Table 2. Effects of Walking Exercise at a Pace Inducing Ischemic Leg Symptoms on Participant-Reported Walking Speed at 6- and 12-Month Follow-Up**

Trial assignment	Baseline score, mean (SD)	Follow-up score, mean (SD)	Within-group change, mean (SD)	Within-group proportion who improved, N (%)	Walking exercise with ischemic pain compared with walking exercise without ischemic pain*	Walking exercise with ischemic pain compared with attention control*	Walking exercise at a comfortable pace compared with attention control*
<b>12-mo Follow-up</b>							
Walking exercise at pace inducing ischemic symptoms (N=98)	2.53 (0.76)	2.70 (0.75)	0.17 (0.86)	33 (34)	2.24 (1.14–4.39) P=0.02	1.20 (0.56–2.54) P=0.64	0.53 (0.24–1.21) P=0.13
Walking exercise at a pace without ischemic symptoms (N=92)	2.40 (0.71)	2.42 (0.54)	0.02 (0.63)	17 (18)			
Attention control (N=47)	2.55 (0.72)	2.70 (0.78)	0.15 (0.86)	14 (30)			
<b>6-mo Follow-up</b>							
Walking exercise at pace inducing ischemic symptoms (N=101)	2.50 (0.73)	2.85 (0.87)	0.36 (1.09)	45 (45)	2.31 (1.27–4.22) P=0.006	3.38 (1.53–7.46) P=0.003	1.46 (0.64–3.33) P=0.37
Walking exercise at a pace without ischemic symptoms (N=97)	2.37 (0.74)	2.45 (0.68)	0.08 (0.81)	25 (26)			
Attention control (N=52)	2.54 (0.70)	2.46 (0.78)	-0.08 (0.84)	10 (19)			

\*Pairwise comparison odds ratios compare the proportion of participants who indicated walking speed improved between different groups. Comparisons presented as odds ratio (95% CI); P value.

induced ischemic leg symptoms. In addition, the control group included a smaller sample size than the 2 exercise groups. Fifth, the validity of the comparison based on mixed models for repeated measures analysis depends on the missing at random assumption, which was not empirically verifiable. However, there were no statistically significant differences in characteristics of people who completed all follow-up visits, those who completed some follow-up visits, and those excluded because they did not complete follow-up visits (Table S1). Sixth, in these post hoc analyses, outcomes were not prioritized and there was no formal adjustment for multiple testing. Therefore, some comparisons may have been statistically significant by chance. Seventh, some baseline characteristics were different between the 3 comparison groups. However, except for prevalence of myocardial infarction at baseline, none of the differences was statistically significant and additional adjustment for characteristics that differed at  $P \leq 0.2$  across the 3 groups at baseline did not meaningfully change the results.

## CONCLUSIONS

In people with PAD, those who walked for exercise at a comfortable pace without ischemic leg symptoms slowed their walking speed during daily life and worsened the SPPB score, a potentially harmful effect, compared with people who walked for exercise at a pace inducing ischemic leg symptoms. Compared with a control group who did not exercise, home-based walking exercise at a pace inducing ischemic leg symptoms significantly improved 4-m walking velocity at 6-month follow-up, but this benefit did not persist at 12-month follow-up.

## ARTICLE INFORMATION

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## Supplemental Material

Table S1  
Figure S1

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# **SUPPLEMENTAL MATERIAL**

**Table S1. Baseline characteristics of participants with peripheral artery disease according to follow-up test completion \***

	<b>Did not complete any follow-up test and excluded (N=41)</b>	<b>Completed some but not all follow- up measures (N=79)</b>	<b>Completed all follow up measures (N=185)</b>
Age mean (SD) ,years	70 (11)	70 (10)	69 (9)
Sex			
Male n(%)	21 (51)	40 (51)	98 (53)
Female n(%)	20 (49)	39 (49)	87 (47)
Race			
Black n(%)	19 (46)	49 (62)	113 (61)
White n(%)	21 (51)	29 (37)	64 (35)
Other races n(%)	1 (2)	1 (1)	8 (4)
Body mass index mean (SD), kilograms/meter <sup>2</sup>	32.5 (9.2)	29.9 (5.7)	30.7 (7.0)
Ankle brachial index mean (SD)	0.67 (0.14)	0.64 (0.16)	0.67 (0.16)
Current smoker n(%)	9 (22)	19 (24)	55 (30)
Hypertension n(%)	36 (88)	70 (89)	159 (86)
Diabetes n(%)	17 (41)	34 (43)	83 (45)
Cancer n(%)	11 (27)	16 (20)	34 (18)
Myocardial infarction n(%)	7 (17)	17 (22)	32 (17)
Pulmonary disease n(%)	5 (12)	9 (11)	31 (17)
Stroke n(%)	11 (27)	21 (27)	32 (17)

\*Follow up measures included for this table were usual-paced and fast-paced four meter walking velocity, and the Short physical performance battery.  
SD: standard deviation

**Figure S1. Study participant selection**

