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# Effect of Low-Intensity vs High-Intensity Home-Based Walking Exercise on Walk Distance in Patients With Peripheral Artery Disease
## The LITE Randomized Clinical Trial

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**IMPORTANCE** Supervised high-intensity walking exercise that induces ischemic leg symptoms is the first-line therapy for people with lower-extremity peripheral artery disease (PAD), but adherence is poor.

**OBJECTIVE** To determine whether low-intensity home-based walking exercise at a comfortable pace significantly improves walking ability in people with PAD vs high-intensity home-based walking exercise that induces ischemic leg symptoms and vs a nonexercise control.

**DESIGN, SETTING, AND PARTICIPANTS** Multicenter randomized clinical trial conducted at 4 US centers and including 305 participants. Enrollment occurred between September 25, 2015, and December 11, 2019; final follow-up was October 7, 2020.

**INTERVENTIONS** Participants with PAD were randomized to low-intensity walking exercise (n = 116), high-intensity walking exercise (n = 124), or nonexercise control (n = 65) for 12 months. Both exercise groups were asked to walk for exercise in an unsupervised setting 5 times per week for up to 50 minutes per session wearing an accelerometer to document exercise intensity and time. The low-intensity group walked at a pace without ischemic leg symptoms. The high-intensity group walked at a pace eliciting moderate to severe ischemic leg symptoms. Accelerometer data were viewable to a coach who telephoned participants weekly for 12 months and helped them adhere to their prescribed exercise. The nonexercise control group received weekly educational telephone calls for 12 months.

**MAIN OUTCOMES AND MEASURES** The primary outcome was mean change in 6-minute walk distance at 12 months (minimum clinically important difference, 8-20 m).

**RESULTS** Among 305 randomized patients (mean age, 69.3 [SD, 9.5] years, 146 [47.9%] women, 181 [59.3%] Black patients), 250 (82%) completed 12-month follow-up. The 6-minute walk distance changed from 332.1 m at baseline to 327.5 m at 12-month follow-up in the low-intensity exercise group (within-group mean change, −6.4 m [95% CI, −21.5 to 8.8 m]; $P = .34$) and from 338.1 m to 371.2 m in the high-intensity exercise group (within-group mean change, 34.5 m [95% CI, 20.1 to 48.9 m]; $P < .001$) and the mean change for the between-group comparison was −40.9 m (97.5% CI, −61.7 to −20.0 m; $P < .001$). The 6-minute walk distance changed from 328.1 m at baseline to 317.5 m at 12-month follow-up in the nonexercise control group (within-group mean change, −15.1 m [95% CI, −35.8 to 5.7 m]; $P = .10$), which was not significantly different from the change in the low-intensity exercise group (between-group mean change, 8.7 m [97.5% CI, −17.0 to 34.4 m]; $P = .44$). Of 184 serious adverse events, the event rate per participant was 0.64 in the low-intensity group, 0.65 in the high-intensity group, and 0.46 in the nonexercise control group. One serious adverse event in each exercise group was related to study participation.

**CONCLUSIONS AND RELEVANCE** Among patients with PAD, low-intensity home-based exercise was significantly less effective than high-intensity home-based exercise and was not significantly different from the nonexercise control for improving 6-minute walk distance. These results do not support the use of low-intensity home-based walking exercise for improving objectively measured walking performance in patients with PAD.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: NCT02538900

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Visual Abstract

Supplemental content

CME Quiz at jamacmelookup.com

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Current guidelines recommend supervised high-intensity walking exercise to improve walking ability for people with peripheral artery disease (PAD). However, few people with PAD participate.[1-5] High-intensity walking exercise induces ischemic leg symptoms in people with PAD, which may reduce adherence to walking exercise. Evidence also suggests that lower-extremity ischemia induced by high-intensity walking exercise in people with PAD may damage calf skeletal muscle.[6,7]

Low-intensity walking exercise, conducted at a comfortable pace without inducing ischemic leg symptoms, may improve exercise adherence in people with PAD. However, the benefits from low-intensity walking exercise in people with PAD are unclear.[8,9]

The Low-Intensity Exercise Intervention in PAD (LITE) randomized clinical trial (RCT) was conducted to determine whether a low-intensity home-based walking exercise intervention (consisting of walking exercise that does not induce ischemic leg symptoms) significantly improves walking distance in people with PAD compared with a high-intensity home-based walking exercise intervention (consisting of walking exercise that induces ischemic leg symptoms) and compared with a nonexercise control group.

### Key Points

**Question** Does a low-intensity (does not induce ischemic leg symptoms) home-based walking exercise intervention improve 6-minute walk distance more than a high-intensity (induces ischemic leg symptoms) home-based walking exercise intervention and does the low-intensity intervention improve 6-minute walk distance more than a nonexercise control (weekly health educational sessions only) among patients with lower-extremity peripheral artery disease (PAD)?

**Findings** In this multicenter randomized clinical trial that included 305 participants with PAD, low-intensity exercise, high-intensity exercise, and nonexercise control resulted in a mean 12-month change in 6-minute walk distance of −6.4 m, 34.5 m, and −15.1 m, respectively. Low-intensity exercise was significantly less effective than high-intensity exercise and was not significantly different from the nonexercise control.

**Meaning** These findings do not support the use of low-intensity walking exercise for patients with PAD.

## Methods

The institutional review board at each participating site (Northwestern University, Tulane University, University of Minnesota, and University of Pittsburgh) approved the trial protocol (appears in Supplement 1). Participants gave written informed consent. The study was an RCT with 3 parallel groups: a low-intensity home-based walking exercise intervention, a high-intensity home-based walking exercise intervention, and a nonexercise control. Enrollment occurred between September 25, 2015, and December 11, 2019; final follow-up occurred on October 7, 2020.

### Participant Identification

Participants were recruited using lists of patients with PAD and physician referrals at each medical center. Postcards advertising the study were mailed to people aged 50 years or older residing in Chicago, Illinois; Minneapolis, Minnesota; and New Orleans, Louisiana. Other methods were used to recruit people from Pittsburgh, Pennsylvania. In Chicago, advertisements also were placed on buses and trains. Individuals with PAD who completed prior studies and expressed interest in future research were invited to participate.

### Inclusion and Exclusion Criteria

The inclusion criterion was an ankle-brachial index (ABI) of 0.90 or less in either leg.[10] Individuals with a resting ABI between 0.91 and 1.00 at baseline were eligible if their ABI dropped by 20% or greater following a heel-rise test.[11] Individuals with a resting ABI greater than 0.90 were eligible if there was evidence of PAD from a vascular laboratory result or an angiogram. Most people with PAD do not have classic intermittent claudication symptoms.[12] Therefore, people with ischemic leg symptoms during walking that were not consistent with classic claudication symptoms, such as ischemic leg symptoms affecting the buttocks or thighs but not the calves, were included.

Exclusion criteria included major amputation, wheelchair confinement, use of a walking aid other than a cane, having a walking limitation for a reason other than PAD, having a foot ulcer or critical limb ischemia, having a Mini-Mental State Examination score of less than 23,[13] having a significant visual or hearing impairment, having a major surgery planned to occur within the next 12 months, and having undergone a lower-extremity revascularization or orthopedic surgery during the previous 3 months. Potential participants with major medical illness, those for whom exercise may be unsafe, those exercising at a level similar to that targeted in the exercise interventions, those unable to walk sufficiently slowly to avoid ischemic leg symptoms, and those without ischemic leg symptoms during walking were excluded.

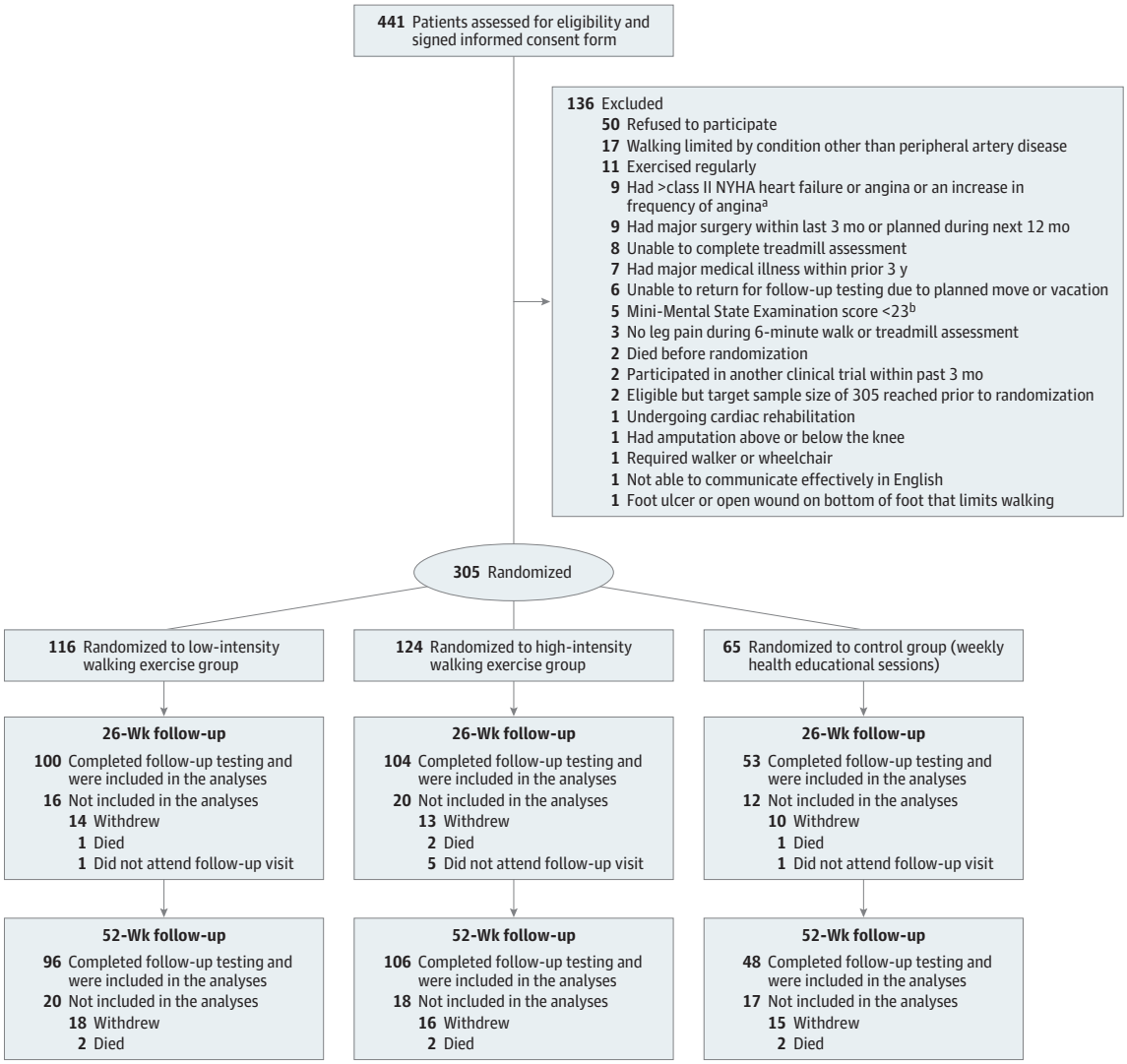
### Measurement of ABI

A handheld Doppler probe (Pocket Dop II; Nicolet Biomedical Inc) was used to measure systolic pressures twice in the right and left brachial, dorsalis pedis, and posterior tibial arteries.[10] 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.[14]

### Medical History, Race, and Demographics

Information regarding medical history, race, and demographics was obtained by questionnaire. Information on race was based on patient self-report that was collected by research coordinators using an open-ended question and was classified with fixed categories. This information was collected to assess the generalizability of the results and to comply with funding agency reporting requirements.

Figure 1. Participants Evaluated, Excluded, Randomized, and Analyzed in the LITE Randomized Clinical Trial




LITE indicates Low-Intensity Exercise Intervention in PAD (peripheral artery disease).

[a] New York Heart Association (NYHA) class I indicates no symptoms with normal physical activity (asymptomatic); class II, mild symptoms with normal physical activity; class III, moderate symptoms with activities of daily living; class IV, symptoms at rest.

[b] The score range is 0 to 30 (a score of 30 is the best).

## Randomization

Eligible participants were randomized to low-intensity exercise, high-intensity exercise, or nonexercise control (**Figure 1**) in a ratio of 120:120:65 using a SAS computer program (SAS Institute Inc) and a randomly permuted block method using block sizes of 61, stratified by study site and by consent for muscle biopsy. The randomization scheme was designed with a smaller sample size for the nonexercise control group because fewer participants were needed than in the high-intensity exercise group for adequate statistical power for the comparisons with the low-intensity exercise group.

## Interventions

The interventions were 12 months in duration. During weeks 1 through 4, participants in all 3 groups visited the medical center weekly. During weeks 5 through 52, interventions to each of the 3 groups were delivered by telephone. Two exercise coaches delivered the exercise interventions to participants in either exercise group. A separate staff member delivered the nonexercise control.

### Exercise Interventions

During weeks 1 through 4, participants randomized to the exercise groups met with a coach and were taught to use an accelerometer (worn at the hip) to monitor their walking exercise intensity. For each participant, accelerometer counts corresponding to low- and high-intensity walking exercise were determined. Low-intensity accelerometer counts were determined by having the participant wear the accelerometer while walking for 5 minutes comfortably without ischemic

leg discomfort. High-intensity accelerometer counts were determined by having the participant wear the accelerometer while walking for 5 minutes at a pace inducing maximal ischemic leg symptoms. These individualized intensity accelerometer counts were benchmarks for low- and high-intensity exercise for each participant that guided exercise intensity monitoring.

Both exercise groups were asked to walk for exercise in an unsupervised setting 5 times per week for up to 50 minutes per session wearing an accelerometer to document exercise intensity and time. The low-intensity exercise group walked at a pace without ischemic leg symptoms. The high-intensity exercise group walked at a pace eliciting moderate to severe ischemic leg symptoms.

Participants randomized to the exercise interventions wore their accelerometer during exercise activity and uploaded accelerometer data on exercise frequency, time, and intensity onto the study website using a home computer or tablet provided by the study. Accelerometer data were viewable to a coach who telephoned participants weekly for 12 months and helped them adhere to their prescribed exercise. Uploaded accelerometer data on exercise minutes and intensity were discussed during the weekly telephone calls. Accelerometer intensity benchmarks corresponding to low- and high-intensity exercise were remeasured at 1, 3, 6, and 9 months after randomization and after significant changes in participant health status. The coach administered instructions to obtain the low- and high-intensity exercise benchmarks by telephone.

### Nonexercise Control Group

During weeks 1 through 4, participants randomized to the control group attended weekly 1-hour educational sessions at the medical center. Topics included cancer screening and Medicare Part D. During weeks 5 through 52, participants received weekly educational telephone calls. Health topics were selected from National Institutes of Health materials.

## Outcomes

The outcomes were collected by staff members who were unaware of randomization group. The primary outcome was 12-month change in 6-minute walk distance. The secondary outcomes were 6-month change in 6-minute walk distance, 12-month change in maximal treadmill walking time, 6- and 12-month change in the Walking Impairment Questionnaire (WIQ) distance and speed scores, 6 and 12-month change in the 36-Item Short Form Health Survey (SF-36) physical functioning score, 6- and 12-month change in physical activity, adherence to exercise goals during the final month of the intervention (defined as attaining >80% of the participant's individualized goal for the number of minutes exercised per week), and change in calf muscle biopsy measures of nitrotyrosine, cyclooxygenase enzyme activity, citrate synthase, and mitochondrial DNA. Physical activity and calf muscle biopsy mitochondrial DNA data were not yet available for analysis.

Two clinical trials that were completed while this trial was ongoing reported that home-based high-intensity exercise with minimal in-person contact was not effective for PAD.[15,16] Therefore, prior to reviewing the results, comparisons of outcomes between the high-intensity exercise group and the nonexercise control group were specified in the protocol and statistical analysis plan (Supplement 1).

### 6-Minute Walk Test

Participants walked up and down a 100-foot hallway after receiving instructions to cover as much distance as possible in 6 minutes.[12,17-19] All participants received identical instructions from a script read by a research coordinator who was unaware of the participant's group assignment. The distance completed after 6 minutes was recorded. The minimum clinically important difference (MCID) in people with PAD ranges from 8 m to 20 m.[18,19]

### Treadmill Walking Performance

Maximal treadmill walking time was measured using the Gardner-Skinner protocol.[20] The MCID was defined as 121 seconds for patients with PAD.[18]

### Walking Impairment Questionnaire

The WIQ is a PAD-specific measure of self-reported walking limitations (score range, 0-100; 100 indicates the best score). The WIQ distance score measures difficulty walking distances up to 1500 feet. The WIQ speed score measures difficulty walking varying speeds for 1 block, ranging from slowly to jogging.[21] An MCID for the WIQ has not been defined.

### Health-Related Quality of Life

The SF-36 physical functioning score measures health-related quality of life (score range, 0-100; 100 indicates the best score). The MCID for the SF-36 physical functioning score is 5 to 7 points.[22,23]

### Calf Muscle Biopsy

An open muscle biopsy was performed in the medial head of the gastrocnemius muscle at baseline and 12-month follow-up in participants providing written informed consent. Anesthesia was achieved with subcutaneous lidocaine. Muscle was frozen at −80 °C. Baseline and 12-month follow-up muscle specimens were analyzed together using mitochondrial enzyme activity assays (citrate synthase and cyclooxygenase enzyme) or immunoblotting for nitrotyrosine.[24]

## Power Calculation

The 2 primary comparisons were the difference in change in 6-minute walk distance at 12-month follow-up between the low- and high-intensity exercise groups and between the low-intensity exercise group and the nonexercise control group. Power calculations assumed a follow-up rate of 85%. The planned sample size of 305 participants provided 80% power to detect a minimum difference in change in 6-minute walk distance at 12-month follow-up of 0.43 SD (26 m) between the low- and high-intensity exercise groups and a difference of 0.52 SD (31 m) between the low-intensity exercise group and the nonexercise control group using 2-sided 2-sample *t* tests with a significance level of .025 to adjust for

2 comparisons. When the study was designed, small and large MCIDs in 6-minute walk distance were considered 20 m and 50 m, respectively.[25] More recently, small and large MCIDs in participants with PAD were defined as 8 m and 20 m, respectively.[18,19]

### Statistical Analyses

The baseline characteristics were summarized using mean (SD) and counts (proportion) for continuous and categorical variables, respectively. All participants were asked to return for follow-up measurements and were included in the analyses regardless of adherence to their intervention. The original plan to use 2-sample 2-tailed *t* tests was changed to mixed-model repeated-measures analyses on August 27, 2020, prior to analyzing any data. This change was made because as of August 27, 2020, investigators projected a lost to follow-up rate of approximately 16% at 12 months. The mixed-model repeated-measures analyses were used to compare changes in 6-minute walk distance at 12-month follow-up between the low- and high-intensity exercise groups and between the low-intensity exercise group and the nonexercise control group with an accounting for missing data under the assumption that missing data were missing at random. The study was considered positive if either primary comparison was statistically significant with $P < .025$. Other comparisons were considered statistically significant if $P < .05$.

The 6-month and 12-month changes in 6-minute walk distance from baseline were treated as correlated outcomes. The independent variables included visit (at 6 and 12 months), treatment (low-intensity exercise, high-intensity exercise, nonexercise control), baseline 6-minute walk distance, and visit or treatment interactions. An unstructured variance-covariance matrix was used to model the within-person correlations. Similar mixed-model repeated-measures regression analyses (without adjustment for baseline outcome measures) were used for the secondary comparisons.

In post hoc analyses, subgroup analyses were performed by participant characteristics. The primary and secondary analyses were repeated including site as a random effect in the mixed-model repeated-measures regression analyses. Because of the potential for type I error inflation due to multiple comparisons, the findings for the analyses of the secondary end points should be interpreted as exploratory.

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc).

## Results

Of 441 individuals with PAD who provided written informed consent, 305 were randomized, including 146 (48%) women and 181 (59%) Black adults (**Table 1**). Among these patients, 257 (84%) completed 6-month follow-up and 250 (82%) completed 12-month follow-up, including 96 (82.8%) in the low-intensity exercise group, 106 (85.5%) in the high-intensity exercise group, and 48 (73.8%) in the nonexercise control group (Figure 1).

### Intervention Adherence

During weeks 1 through 4, the adherence rate for the 4 onsite visits was 88.8% (103/116) in the low-intensity exercise group, 91.9% (114/124) in the high-intensity exercise group, and 60.0% (39/65) in the nonexercise control group and scheduled intervention calls were completed between weeks 5 and 52 for 84.6%, 85.1%, and 61.8% of participants, respectively.

The low-intensity exercise group exercised at a lower intensity (median intensity, 728 [range, 139-2757] activity units) compared with the high-intensity exercise group (median intensity, 1584 [range, 229-4710] activity units) ($P < .001$; eFigure 1 in Supplement 2) and exercised on more days per week (mean, 3.5 [SD, 1.5] days [range, 0.1-6.4 days] vs 2.8 [SD, 1.3] days [range, 0.2-5.6 days], respectively, $P < .001$) and for more minutes per week (mean, 145 [SD, 89] minutes/week [range, 0.7-454 minutes/week] vs 77 [SD, 58] minutes/week [range, 2.6-327 minutes/week], $P < .001$). The low-intensity exercise group attained their target exercise intensity more frequently than the high-intensity exercise group (92% vs 63%, respectively, $P < .001$).

### Primary Outcome

At 12-month follow-up, low-intensity exercise was significantly less effective in improving 6-minute walk distance compared with high-intensity exercise (−6.4 m vs 34.5 m, respectively; between-group change, −40.9 m [97.5% CI, −61.7 to −20.0 m], $P < .001$) (**Table 2**, **Figures 2** and **3**, and eFigure 2 in Supplement 2). At 12-month follow-up, there was no significant difference in change in 6-minute walk distance between the low-intensity exercise group and the nonexercise control group (−6.4 m vs −15.1 m, respectively; between-group change, 8.7 m [97.5% CI, −17.0 to 34.4 m], $P = .44$) (Table 2, Figures 2 and 3, and eFigure 2 in Supplement 2).

### Secondary Outcomes

#### Low-Intensity Exercise vs Nonexercise Control

At 12-month follow-up, low-intensity exercise significantly improved the WIQ distance score compared with the nonexercise control (14.6 vs 1.1, respectively; between-group change, 13.5 [95% CI, 4.4 to 22.6], $P = .004$) and the WIQ speed score (7.2 vs −5.0; between-group change, 12.2 [95% CI, 4.1 to 20.3], $P = .003$) (Table 2 and eFigures 3-4 in Supplement 2). At 6-month follow-up, low-intensity exercise significantly improved the WIQ distance score compared with the nonexercise control (17.6 vs −1.3, respectively; between-group change, 18.9 [95% CI, 10.2 to 27.7], $P < .001$), the WIQ speed score (7.4 vs −5.6; between-group change, 13.1 [95% CI, 6.1 to 20.0], $P < .001$), and the SF-36 physical functioning score (9.0 vs 1.0; between-group change, 8.1 [95% CI, 1.2 to 15.0], $P = .02$) (eFigures 3-5 and eTable 1 in Supplement 2). Low-intensity exercise did not significantly improve 6-minute walk distance at 6-month follow-up compared with the nonexercise control and did not significantly improve maximal treadmill walking time at 12-month follow-up (eFigure 2 and eTable 1 in Supplement 2).

#### Low-Intensity vs High-Intensity Exercise

At 6-month follow-up, low-intensity exercise was significantly less effective for improving 6-minute walk distance

Table 1. Baseline Characteristics of Participants With Peripheral Artery Disease

| | Low-intensity walking exercise (n = 116) | High-intensity walking exercise (n = 124) | Nonexercise control (n = 65) |
|---|---|---|---|
| Age, mean (SD), y | 69.8 (10.1) | 68.8 (8.7) | 69.5 (10.1) |
| Sex, No. (%) | | | |
| Male | 62 (53.5) | 64 (51.6) | 33 (50.8) |
| Female | 54 (46.6) | 60 (48.4) | 32 (49.2) |
| Race, No. (%) | | | |
| White | 45 (38.8) | 41 (33.1) | 28 (43.1) |
| Black | 65 (56.0) | 81 (65.3) | 35 (53.9) |
| Asian | 4 (3.4) | 0 | 2 (3.1) |
| Other, unknown, or not reported[a] | 2 (1.7) | 2 (1.6) | 0 |
| Hispanic ethnicity, No. (%) | 1 (0.9) | 3 (2.4) | 3 (4.6) |
| Ankle-brachial index, mean (SD) | 0.66 (0.17) | 0.67 (0.15) | 0.67 (0.15) |
| Body mass index, mean (SD)[b] | 30.3 (6.7) | 31.1 (7.3) | 30.8 (7.3) |
| Comorbidities, No. (%) | | | |
| Hypertension | 102 (87.9) | 111 (89.5) | 52 (80.0) |
| Diabetes | 46 (39.7) | 53 (42.7) | 35 (53.9) |
| Cancer | 24 (20.7) | 21 (16.9) | 16 (24.6) |
| Myocardial infarction | 17 (14.7) | 32 (25.8) | 7 (10.8) |
| Angina | 17 (14.7) | 24 (19.4) | 10 (15.4) |
| Pulmonary disease | 16 (13.8) | 19 (15.3) | 10 (15.4) |
| Former smoker | 59 (50.9) | 71 (57.3) | 38 (58.5) |
| Current smoker | 40 (34.5) | 29 (23.4) | 14 (21.5) |
| Frequency of walking for exercise, mean (SD), times/wk | 1.3 (2.2) | 1.5 (2.2) | 1.0 (1.7) |
| Time spent walking for exercise, mean (SD), min/wk | 29.6 (67.4) | 31.5 (54.0) | 23.4 (38.5) |
| 6-min walk distance, m[c,d] | | | |
| Mean (SD) | 326 (99) | 329 (101) | 328 (87) |
| Median (IQR) | 337 (254-395) | 335 (248-396) | 333 (261-378) |
| Walking Impairment Questionnaire distance score[d,e] | | | |
| Mean (SD) | 35.0 (25.4) | 33.6 (26.5) | 37.4 (26.8) |
| Median (IQR) | 31.2 (14.4-49.4) | 27.6 (11.9-48.8) | 35.0 (14.8-55.3) |
| Walking Impairment Questionnaire speed score[d,f] | | | |
| Mean (SD) | 35.0 (23.8) | 35.5 (22.2) | 40.4 (24.9) |
| Median (IQR) | 32.6 (17.4-50.0) | 32.6 (15.2-50.0) | 39.1 (25.0-56.5) |
| Maximal treadmill walking time, min[d,g] | | | |
| Mean (SD) | 7.1 (4.6) | 7.5 (4.4) | 8.0 (4.2) |
| Median (IQR) | 6.0 (4.0-9.3) | 6.5 (4.1-10.9) | 7.3 (5.0-11.1) |

Abbreviation: IQR, interquartile range.

[a] American Indian and Alaska Native participants were included in the category of other.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Represents the maximal distance a participant can walk in 6 minutes and potentially ranges from a small number of meters to farther than 500 m. Small and large minimum clinically important difference values for 6-minute walk distance have been defined as 8 m to approximately 20 m.[18,19]

[d] Baseline values were comparable with other randomized trials of exercise in participants with peripheral artery disease.[15,26-28]

[e] Measures the participant's reported difficulty in walking distances that range from across a small room to 1500 feet, with higher scores indicating greater ease when walking long distances (score range, 0-100; 100 indicates the best). These data were collected using a self-administered questionnaire. A minimum clinically important difference has not been defined.

[f] Measures the participant's reported difficulty walking at different speeds ranging from slow to fast, with higher scores indicating greater ease when walking at faster speeds (score range, 0-100; 100 indicates the best). These data were collected using a self-administered questionnaire. A minimum clinically important difference has not been defined.

[g] Measures the participant's time that he or she can walk on the treadmill (range, <2 to >25 minutes). For most participants, the speed of the treadmill was 2 miles per hour and the treadmill grade was increased by 2% every 2 minutes. However, individuals unable to walk at 2 miles per hour were started at a treadmill speed of 0.50 miles per hour and the speed was increased by 0.50 miles per hour every 2 minutes until the speed reached 2 miles per hour, at which point the grade was increased by 2% every 2 minutes. The minimum clinically important difference for maximal treadmill walking time has been defined as 2 minutes.[18]

compared with high-intensity exercise (−3.7 m vs 27.7 m, respectively; between-group change, −31.4 m [95% CI, −49.1 to −13.8, $P < .001$) (eFigure 2 and eTable 1 in Supplement 2). At 12-month follow-up, low-intensity exercise was significantly less effective for improving maximal treadmill walking time compared with high-intensity exercise (0.7 vs 1.8 minutes,

Table 2. Effects of Low-Intensity and High-Intensity Home-Based Exercise on Primary and Secondary Outcomes at 12-Month Follow-up

| | Low-intensity walking exercise | | | High-intensity walking exercise | | | Nonexercise control | | | Between-group change[a] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean (SD)[b] | | Within-group change, mean (95% CI) | Mean (SD)[b] | | Within-group change, mean (95% CI) | Mean (SD)[b] | | Within-group change, mean (95% CI) | Low-intensity vs high-intensity walking exercise | Low-intensity walking exercise vs nonexercise control | High-intensity walking exercise vs nonexercise control |
| | Baseline | 12-mo follow-up | | Baseline | 12-mo Follow-up | | Baseline | 12-mo follow-up | | | | |
| **Primary outcome** | | | | | | | | | | | | |
| 6-min walk distance, m[c] | 332.1 (95.8) | 327.5 (109.3) | −6.4 (−21.5 to 8.8) | 338.1 (102.6) | 371.2 (116.8) | 34.5 (20.1 to 48.9) | 328.1 (91.0) | 317.5 (98.9) | −15.1 (−35.8 to 5.7) | −40.9 (−61.7 to −20.0) | 8.7 (−17.0 to 34.4) | 49.6 (24.3 to 74.9)[d] |
| No. | 116 | 93 | | 124 | 104 | | 65 | 48 | | | | |
| *P* value | | | .34 | | | <.001 | | | .10 | <.001 | .44 | <.001 |
| **Secondary outcomes** | | | | | | | | | | | | |
| WIQ distance score[e] | 37.2 (25.8) | 51.3 (34.1) | 14.6 (9.3 to 19.9) | 36.2 (26.8) | 49.8 (32.6) | 13.7 (8.6 to 18.7) | 35.3 (25.8) | 37.5 (26.8) | 1.1 (−6.3 to 8.5) | 0.9 (−6.4 to 8.2) | 13.5 (4.4 to 22.6) | 12.6 (3.7 to 21.6) |
| No. | 116 | 95 | | 124 | 105 | | 65 | 48 | | | | |
| *P* value | | | | | | | | | | .81 | .004 | .006 |
| WIQ speed score[f] | 37.3 (24.5) | 44.3 (23.9) | 7.2 (2.5 to 11.9) | 36.7 (22.2) | 48.2 (24.5) | 11.7 (7.2 to 16.2) | 40.9 (23.9) | 35.4 (24.0) | −5.0 (−11.6 to 1.6) | −4.5 (−11.0 to 2.0) | 12.2 (4.1 to 20.3) | 16.7 (8.7 to 24.7) |
| No. | 115 | 95 | | 123 | 105 | | 65 | 47 | | | | |
| *P* value | | | | | | | | | | .17 | .003 | <.001 |
| Maximal treadmill walking time, min[g] | 7.4 (4.8) | 8.1 (6.1) | 0.7 (0.1 to 1.4) | 8.3 (4.7) | 10.0 (5.3) | 1.8 (1.2 to 2.5) | 7.2 (4.1) | 7.7 (4.9) | 0.4 (−0.5 to 1.3) | −1.1 (−2.0 to −0.2) | 0.3 (−0.8 to 1.4) | 1.4 (0.3 to 2.5) |
| No. | 116 | 74 | | 124 | 74 | | 65 | 37 | | | | |
| *P* value | | | | | | | | | | .02 | .61 | .01 |
| SF-36 physical functioning score[h] | 52.7 (19.9) | 58.2 (25.4) | 5.9 (1.7 to 10.0) | 51.0 (22.5) | 58.3 (23.1) | 7.5 (3.5 to 11.4) | 46.6 (22.4) | 49.7 (22.8) | 4.0 (−1.8 to 9.8) | −1.6 (−7.3 to 4.2) | 1.9 (−5.2 to 9.0) | 3.5 (−3.6 to 10.5) |
| No. | 116 | 95 | | 124 | 105 | | 65 | 48 | | | | |
| *P* value | | | | | | | | | | .59 | .60 | .33 |

Abbreviations: SF-36, 36-Item Short Form Health Survey; WIQ, Walking Impairment Questionnaire.

[a] For the primary outcome, data are expressed as mean (97.5% CI) and the secondary outcomes are expressed as mean (95% CI).

[b] Unless otherwise indicated.

[c] Represents the maximal distance a participant can walk in 6 minutes and potentially ranges from a small number of meters to farther than 500 m. Small and large minimum clinically important difference values for 6-minute walk distance have been defined as 8 m to approximately 20 m.[18,19]

[d] This is a secondary outcome.

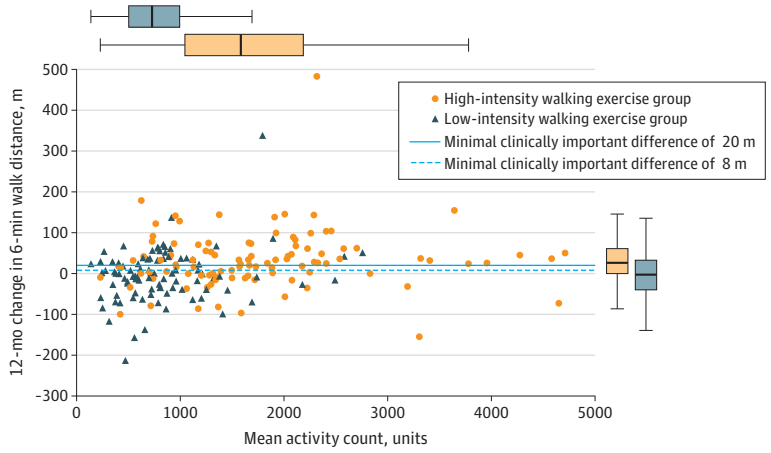
[e] Measures the participant's reported difficulty in walking distances that range from across a small room to 1500 feet, with higher scores indicating greater ease when walking long distances (score range, 0-100; 100 indicates the best). These data were collected using a self-administered questionnaire. A minimum clinically important difference has not been defined.

[f] Measures the participant's reported difficulty walking at different speeds ranging from slow to fast, with higher scores indicating greater ease when walking at faster speeds (score range, 0-100; 100 indicates the best). These data were collected using a self-administered questionnaire. A minimum clinically important difference has not been defined.

[g] Measures the participant's time that he or she can walk on the treadmill (range, <2 to >25 minutes). For most participants, the speed of the treadmill was 2 miles per hour and the treadmill grade was increased by 2% every 2 minutes. However, individuals unable to walk at 2 miles per hour were started at a treadmill speed of 0.50 miles per hour and the speed was increased by 0.50 miles per hour every 2 minutes until the speed reached 2 miles per hour, at which point the grade was increased by 2% every 2 minutes. The minimum clinically important difference for maximal treadmill walking time has been defined as 2 minutes.[18]

[h] Measures the participants perceived state of health and ability to function physically using a self-administered questionnaire (score range, 0-100; higher scores are better). The minimum clinically important difference ranges from 5 to 7.[22,23]

Figure 2. Association of Mean Change in 6-Minute Walk Distance With Mean Exercise Intensity Among Participants With Peripheral Artery Disease




respectively; between-group change, −1.1 minutes [95% CI, −2.0 to −0.2 minutes], $P = .02$; Table 2). At 6-month follow-up, low-intensity exercise significantly improved the WIQ distance score compared with high-intensity exercise (17.6 vs 8.0, respectively; between-group change, 9.6 [95% CI, 2.4 to 16.9], $P = .009$) (eFigure 3 and eTable 1 in Supplement 2). There were no other statistically significant differences between low-intensity and high-intensity exercise for the secondary outcomes at 6-month or 12-month follow-up (eFigures 3-5 and eTable 1 in Supplement 2). During the final month of the intervention, 64 (67.4%) of those randomized to low-intensity exercise attained at least 80% of their goal for exercise minutes per week compared with 59 (55.7%) of those randomized to high-intensity exercise ($P = .09$).

### High-Intensity Exercise vs Nonexercise Control

At 12-month follow-up, high-intensity exercise significantly improved 6-minute walk distance compared with the nonexercise control (34.5 m vs −15.1 m, respectively; between-group change, 49.6 m [95% CI, 24.3 to 74.9 m], $P < .001$), maximal treadmill walking time (1.8 vs 0.4 minutes; between-group change, 1.40 minutes [95% CI, 0.30 to 2.50 minutes], $P = .01$), the WIQ distance score (13.7 vs 1.1; between-group change, 12.6 [95% CI, 3.7 to 21.6], $P = .006$), and the WIQ speed score (11.7 vs −5.0; between-group change, 16.7 [95% CI, 8.7 to 24.7], $P < .001$; Table 2 and eFigures 2-5 in Supplement 2).

At 6-month follow-up, high-intensity exercise significantly improved 6-minute walk distance compared with the nonexercise control (27.7 vs −14.2 m, respectively; between-group change, 41.9 m [95% CI, 20.6 to 63.1 m], $P < .001$), the WIQ distance score (8.0 vs −1.3; between-group change, 9.3 [95% CI, 0.6 to 17.9], $P = .04$), and the WIQ speed score (6.2 vs −5.6; between-group change, 11.8 [95% CI, 4.9 to 18.7], $P < .001$; eFigures 2-4 and eTable 1 in Supplement 2).

## Post Hoc Analyses

In post hoc analyses, there were no significant interactions among the baseline characteristics for the effects of low- or high-intensity exercise on change in 6-minute walk distance at 12-month follow-up (eFigures 6-8 in Supplement 2). In post hoc analyses, the results for the primary and secondary comparisons did not meaningfully change when the analyses were repeated including site as a random effect (eTable 2 in Supplement 2).

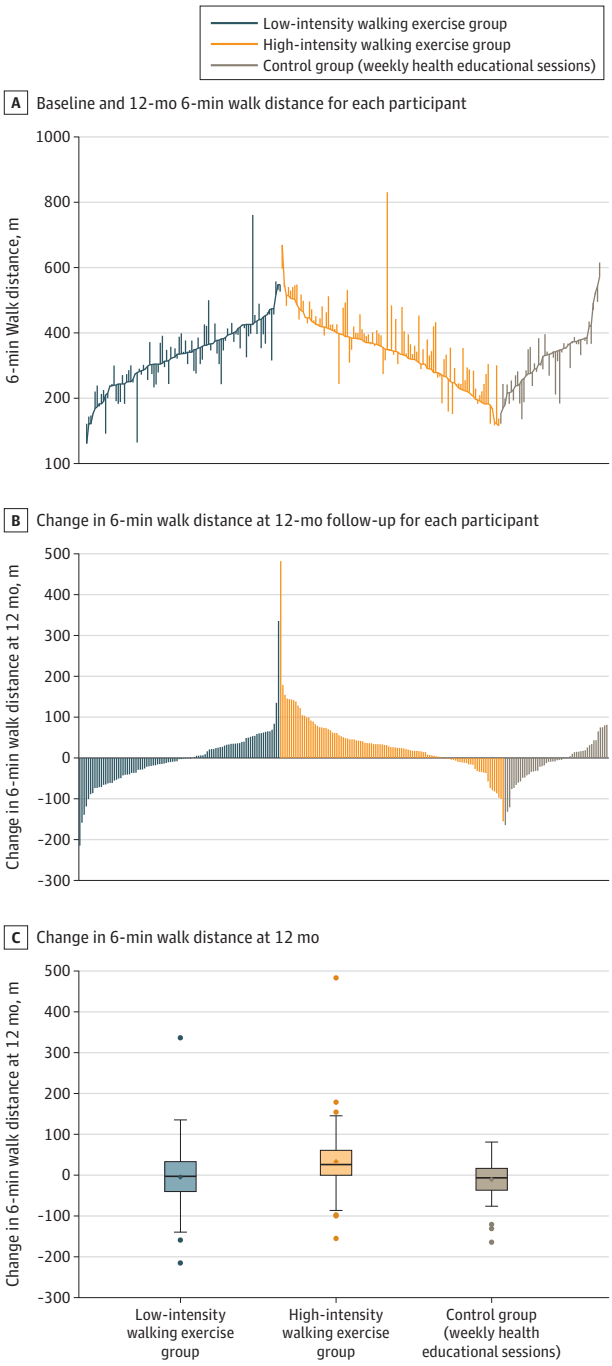
Among 47 participants who underwent calf muscle biopsies at baseline and follow-up, there were no significant effects of either exercise group on calf muscle biopsy outcomes (eTable 3 in Supplement 2).

There were 74 serious adverse events in the low-intensity exercise group, 80 in the high-intensity exercise group, and 30 in the nonexercise control group and the serious adverse event rates per participant were 0.64, 0.65, and 0.46, respectively. Two of the serious adverse events were considered related to study participation. In 1 participant, a transient supraventricular arrhythmia developed after the baseline exercise stress test. After randomization to the low-intensity exercise group, cardiac testing was performed by this participant's physician because of the arrhythmia, resulting in hospitalization to undergo coronary artery stent placement. In a participant who was randomized to the high-intensity exercise group, chest discomfort developed while exercising. This participant was hospitalized and underwent coronary artery stent placement.

## Discussion

In this multicenter RCT of 305 participants with PAD, low-intensity home-based walking exercise (performed at a comfortable pace without ischemic leg symptoms) was significantly less effective for improving 6-minute walk distance than high-intensity home-based walking exercise (performed at a pace eliciting moderate to severe ischemic leg symptoms). High-intensity exercise was significantly more effective than low-intensity exercise even though the high-intensity exercise group walked for exercise approximately 50% fewer

Figure 3. Baseline, 12-Month Follow-up, and Change in 6-Minute Walk Distance at 12 Months Among Participants With Peripheral Artery Disease




A, Each vertical line represents an individual participant, with participants ordered by baseline value and the vertical line extending up (improvement) or down (deterioration) to the 12-month value.

B, Vertical lines extending up denote the degree of improvement in 6-minute walk distance at 12-month follow-up. Vertical lines extending down denote the degree of decline in 6-minute walk distance.

C, Each box ranges from the 25th to 75th percentile of the distribution with the black horizontal line signifying the median. The whiskers extend to the furthest points that are within the 1.5 × interquartile range of the box (the upper and lower adjacent values). The solid circles beyond the whiskers are outliers.

minutes per week than the low-intensity exercise group. The 6-minute walk distance was not significantly improved among individuals in the low-intensity exercise group compared with individuals in the nonexercise control group.

Despite having no effect on objective walking performance measures, low-intensity exercise significantly improved the WIQ distance and speed scores at 6-month and 12-month follow-up compared with the nonexercise control group. This discordance regarding subjective and objective outcomes is important given recent emphasis on patient-reported outcomes.[29] There are at least 3 possible explanations for this discordance. First, participants were unblinded to their assigned group, which may have influenced their responses to the subjective questionnaire measures. Second, the low-intensity exercise intervention may have encouraged a slower habitual walking pace, potentially reducing 6-minute walk distance at follow-up. However, the low-intensity exercise group did not significantly improve treadmill walking time compared with the nonexercise control and had significantly less improvement in maximal treadmill walking time, a measure of maximal walking capacity, compared with the high-intensity exercise group. In the treadmill test, walking pace was set by the treadmill protocol. Third, participants randomized to low-intensity exercise walked for exercise a mean of 145 minutes during a mean of 3.5 days per week. This amount of walking exercise may have influenced their perceptions about their walking ability, despite lack of significant improvement in the objective walking measures compared with the high-intensity exercise group or the nonexercise control group.

This RCT demonstrated that high-intensity home-based exercise with telephone coaching meaningfully improved 6-minute walk distance in patients with PAD. Previously, the efficacy of home-based exercise for PAD has been unclear.[15,16,26,27,30] Even though the 2016 clinical practice guidelines indicated that home-based walking exercise was reasonable and useful for patients with PAD (class IIA recommendation),[1] 2 RCTs published since 2016 showed no benefits from home-based exercise in patients with PAD.[15,16]

Supervised exercise, but not home-based exercise, is currently reimbursed by the Centers for Medicare & Medicaid Services. Because home-based exercise requires fewer visits to the medical center than supervised exercise and is less burdensome for patients, the results presented in this article suggest that coverage of home-based exercise by the Centers for Medicare & Medicaid Services may be reasonable.

This study has several strengths. First, the trial was performed at multiple centers, which increases generalizability. Second, of all participants, 59% were Black adults and PAD is common among Black adults.[31] Third, walking exercise intensity was documented with an accelerometer and demonstrated excellent fidelity to the assigned exercise intensity group.

## Limitations

This study has several limitations. First, 18% of participants did not return for 12-month follow-up testing. Mixed-model repeated-measures analyses were used to adjust for missing data, but this method assumes the data were missing at random. Second, because of the COVID-19 pandemic,

treadmill stress tests at 12-month follow-up could not be performed after March 15, 2020, resulting in additional missing data for this outcome.

Third, the results may not be generalizable to supervised treadmill exercise interventions. Fourth, adherence to telephone calls was lower in the nonexercise control group than in the 2 exercise groups. This may have been because participants in the nonexercise control group were less enthusiastic about their study group assignment than those randomized to an exercise group.

## Conclusions

Among patients with PAD, low-intensity home-based exercise was significantly less effective than high-intensity home-based exercise and was not significantly different from the nonexercise control for improving 6-minute walk distance. These results do not support the use of low-intensity home-based walking exercise for improving objectively measured walking performance in patients with PAD.

## ARTICLE INFORMATION

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**Data Sharing Statement:** See Supplement 3.

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