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ORIGINAL RESEARCH

Perceived Versus Objective Change in Walking Ability in Peripheral Artery Disease: Results from 3 Randomized Clinical Trials of Exercise Therapy

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BACKGROUND: In people with lower-extremity peripheral artery disease, the effects of exercise on patient-reported outcomes remain unclear.

METHODS AND RESULTS: Four hundred four people with peripheral artery disease in 3 clinical trials were randomized to exercise (N=205) or a control group (N=199) and completed the 6-minute walk and the Walking Impairment Questionnaire distance score (score 0–100, 100=best) at baseline and 6-month follow-up. Compared with the control group, exercise improved 6-minute walk distance by +39.8 m (95% CI, 26.8–52.8, $P<0.001$) and the Walking Impairment Questionnaire distance score by +7.3 (95% CI, 2.4–12.1, $P=0.003$). In all, 2828 individual Walking Impairment Questionnaire distance score questions were completed at baseline and follow-up. Among participants who perceived no change in ability to walk 1 or more distances between baseline and follow-up, 6-minute walk improved in the exercise group and declined in the control group (+26.8 versus −6.5 m, $P<0.001$). Among participants who perceived that their walking ability worsened for 1 or more distances between baseline and follow-up, the 6-minute walk improved in the exercise group and declined in the control group (+18.4 versus −27.3 m, $P<0.001$). Among participants who reported worsening calf symptoms at follow-up, the exercise group improved and the control group declined (+28.9 versus −12.5 m, $P<0.01$).

CONCLUSIONS: In 3 randomized trials, exercise significantly improved the 6-minute walk distance in people with peripheral artery disease, but many participants randomized to exercise reported no change or decline in walking ability. These findings suggest a significant discrepancy in objectively measured walking improvement relative to perceived walking improvement in people with peripheral artery disease.

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Key Words: exercise ■ intermittent claudication ■ patient-reported outcome measures ■ peripheral artery disease

While exercise interventions significantly improve objective measures of walking performance in people with lower extremity peripheral artery disease (PAD), the effects of exercise on patient-reported outcomes in PAD remain unclear.[1–5] For example, among 111 people with PAD and aortoiliac stenosis in the CLEVER (Claudication: Exercise Versus Endoluminal Revascularization) Trial randomized to lower-extremity revascularization, supervised exercise, or a control group, supervised exercise improved treadmill walking time significantly more than revascularization, but revascularization improved

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CLINICAL PERSPECTIVE

What Is New?

- In data from 3 randomized trials of exercise in people with lower-extremity peripheral artery disease (PAD), those randomized to an exercise intervention substantially improved 6-minute walk distance, but many of those randomized to exercise reported no change or even decline in walking ability at 6-month follow-up.
- In contrast, people with PAD randomized to a control group without exercise who reported no change in walking ability experienced simultaneous declines in 6-minute walk distance.

What Are the Clinical Implications?

- These results demonstrate a significant discrepancy in objectively measured walking improvement relative to perceived walking improvement following an exercise intervention in people with PAD.
- Many people with PAD who meaningfully improved 6-minute walk distance after an exercise intervention perceived no change or even a decline in walking ability.
- The gradual improvement in 6-minute walk associated with exercise therapy in people with PAD may explain the failure to perceive improved walking ability for some people with PAD.

Nonstandard Abbreviations and Acronyms

CLEVER	Claudication: Exercise Versus Endoluminal Revascularization Trial
GOALS	Group-Oriented Arterial Leg Study
PROPEL	Progenitor Cell Release Plus Exercise to Improve Functional Performance in PAD
SILC	Study in Leg Circulation
WIQ	Walking Impairment Questionnaire

patient-reported outcome measures significantly more than supervised exercise.[1] In CLEVER, this discordance regarding the effects of revascularization versus exercise on change in objectively measured walking versus patient-reported outcome measures persisted at 18-month follow-up.[2]

To study the effects of exercise on patient-reported outcome measures in PAD, this study combined data from 3 randomized trials of exercise and compared the effects of an exercise intervention versus a control group on patient-reported walking ability and on objectively assessed walking ability in people with PAD. We hypothesized that compared with a control group, the exercise intervention would have a greater effect on improvement in objective measures of walking than on patient-reported measures of walking in people with PAD.

METHODS

Data were combined from 3 randomized clinical trials of exercise in participants with PAD that included both change in 6-minute walk distance and change in participant-reported walking ability, measured by the Walking Impairment Questionnaire (WIQ), at baseline and 6-month follow-up.[6–8] Institutional Review Boards at each participating site approved the study and participants provided written informed consent. The 3 randomized trials were the SILC (Study in Leg Circulation), the GOALS (Group-Oriented Arterial Leg Study), and the PROPEL (Progenitor Cell Release Plus Exercise to Improve Functional Performance in PAD).[6–8] Data supporting the findings of this article are available from the corresponding author upon reasonable request.

Summary of Included Trials

Methods for each trial have been reported.[6–8] In SILC, 156 participants with PAD were randomized to supervised treadmill exercise, supervised lower-extremity resistance training, or attention control for 6 months.[6] In GOALS, 194 participants with PAD were randomized to either a home-based walking exercise or an attention control group.[8] In PROPEL, 210 participants with PAD were randomized to 1 of 4 groups: Supervised treadmill exercise+granulocyte-macrophage colony-stimulating factor, supervised exercise+placebo, granulocyte-macrophage colony-stimulating factor+attention control, or placebo+attention control.[8] All 3 randomized trials demonstrated significant benefit of walking exercise on change in 6-minute walk distance at 6-month follow-up.[6–8] Because granulocyte-macrophage colony-stimulating factor did not significantly improve 6-minute walk distance with or without exercise, participants randomized to granulocyte-macrophage colony-stimulating factor were included in these analyses. Since this study focused on walking exercise, participants randomized to the resistance-trained group in the SILC Trial were not included in these analyses.

Participant Identification

Participants were identified from Chicago-area medical centers, using newspaper or radio advertisements, study advertisements mailed to older people living in

the Chicago area, or Chicago Transit Authority bus and train advertisements.[6–8]

Inclusion Criteria

The SILC Trial included people with ankle–brachial index (ABI) <0.95.[6] GOALS and PROPEL included people with ABI ≤0.90.[7,8] In GOALS and PROPEL, potential participants with ABI >0.90 at the baseline visit were eligible if a hospital-affiliated vascular laboratory report or angiogram demonstrated PAD.[7,8] In the GOALS and PROPEL Trials, participants with an ABI of 0.90–1.00 at baseline and those with a normal ABI and prior lower-extremity revascularization were eligible if their ABI dropped by 20% after a heel-rise test, consisting of 50 heel rises at a rate of 1 per second followed by repeat ABI.[7–9]

Exclusion Criteria

For all 3 trials,[6–8] potential participants with a below or above-knee amputation, wheelchair confinement, walking impairment for a reason other than PAD, foot ulcer or critical limb ischemia, or significant visual or hearing impairment were excluded. Potential participants using a walking aid other than a cane were excluded. Potential participants with major surgery, revascularization, or cardiac rehabilitation participation during the previous 3 months or planned during the next 6 months were excluded. People requiring oxygen with activity were excluded. Potential participants for whom exercise may be unsafe, including those with an abnormal exercise stress test at baseline, were excluded. In the SILC Trial, participants with a baseline Short Physical Performance Battery Score >10 were excluded.[6]

Ankle–Brachial Index

A handheld Doppler probe (Nicolet Vascular Pocket Dop II, Golden, CO) was used to measure systolic blood pressures in the right brachial, dorsalis pedis, and posterior tibial arteries and left dorsalis pedis, posterior tibial, and brachial arteries as previously described.[10]

Six-Minute Walk Test

In each trial, change in 6-minute walk distance was the primary outcome and was used to objectively assess change in walking ability between baseline and 6-month follow-up.[6–8,11] The 6-minute walk test was administered by study coordinators unaware of participants' group assignment at baseline and 6-month follow-up. Following a standardized protocol, participants walked up and down a 100-foot hallway for 6 minutes.[11] All participants were advised that the goal of the test was to walk as far as possible in the 6 minutes. The distance completed within 6 minutes was recorded.

Leg Symptoms

The presence and characteristics of exertional leg symptoms were measured using the San Diego Claudication Questionnaire.[12,13] Intermittent claudication was defined as exertional calf pain that was not present at rest and resolved within 10 minutes of rest. Atypical exertional leg symptoms were defined as exertional leg symptoms that did not meet criteria for intermittent claudication. Participants reporting no exertional leg symptoms were classified as "asymptomatic."

WIQ Distance Score

The WIQ was developed specifically for people with PAD, to measure perceived difficulty walking distances in the community. The WIQ includes 3 domains: walking distance, walking speed, and stair climbing.[14] These analyses focused on the WIQ distance domain because it measures the participant's perception of difficulty walking long distances and therefore is most directly related to the 6-minute walk test, an objective assessment of walking endurance, than the other WIQ domains (stair climbing and walking speed). The WIQ distance questionnaire consists of 7 questions measuring participants' perceived difficulty walking 7 specified distances, ranging from walking indoors around the home to walking 5 blocks, without stopping to rest. For each question, participants indicated their perception of difficulty walking the distance on level ground without stopping to rest on a 0–4 scale, where 0 represents inability to walk the distance and 4 represents no difficulty walking the distance. A total WIQ distance score was calculated, ranging from 0 to 100 (100=best and indicates no difficulty walking any of the distances) as previously described.[14]

The WIQ also includes Likert scale questions about the degree to which pain, aching, or cramps in calves or buttocks cause difficulty walking and the degree to which pain or aching in the thighs cause difficulty walking. Responses to each question are rated on a 5-point scale, ranging from "none" to "very difficult". For these analyses, participants were classified according to whether their response at 6-month follow-up represented improvement, no change, or decline, compared with their baseline response.

INTERVENTIONS

Supervised Exercise Interventions

The SILC and PROPEL clinical trials tested the ability of 6-month supervised treadmill exercise to improve

6-minute walk distance at 6-month follow-up.[6,8] Participants randomized to supervised treadmill exercise in each trial attended treadmill walking exercise sessions 3 times weekly in the presence of an exercise physiologist. Participants were encouraged to walk up to 50 minutes/session, not including rest.

Home-Based Walking Exercise

In the GOALS home-based walking exercise intervention, participants were taught to set goals, self-monitor walking exercise activity, and implement other behavioral change methods to help them adhere to home-based walking exercise.[7] Participants met weekly with a small group of participants with PAD and a coach to discuss methods to help with adherence to home-based exercise. Participants randomized to exercise were helped to exercise 5 days per week at home, up to 50 minutes/session.

Control Groups

In all included trials, participants randomized to the nonexercise control group attended 1-hour educational sessions led by faculty members and staff. Educational topics included nutrition, cancer screening, diabetes mellitus management, vaccines, and other topics of interest to older individuals. Walking exercise was not discussed.[6–8]

Other Measures

Medical history, race, and demographics were obtained using patient report. Height and weight were measured. Body mass index was calculated as weight (kg)/(height [meters])^2.[6–8]

Statistical Analysis

Participant characteristics, baseline 6-minute walk distance, and baseline total WIQ distance score were compared between participants randomized to exercise versus the control group. Analyses of variance and statistical tests for trend were used to compare change in 6-minute walk distances between baseline and follow-up across the degree of change in Likert scale responses for each of the 7 distances evaluated in the WIQ distance questionnaire.

For each participant, responses to each of the 7 WIQ distance questions at follow-up were categorized according to whether the response represented no change, improvement by 1 point, improvement by 2 points, decline by 1 point, or decline by 2 points compared with baseline on the 0–4-point scale. Mean change in 6-minute walk distance was calculated for question responses that were unchanged, improved by 1 point, improved by 2 points, declined by 1 point, or declined by 2 points between baseline and follow-up. For example, a participant who reported no change in their ability to walk the distances listed in the first 3 questions and a 1-point improvement in their ability to walk the distances in the final 4 questions, contributed their 6-minute walk change value 3 times to analyses of no change in perceived walking ability and 4 times to analyses of 1-point improvement in perceived walking ability (Figure S1).

To account for the fact that 1 individual could contribute changes in 6-minute walk distance multiple times across different questions in the WIQ distance score, a patient-based bootstrap method was used to calculate the 95% CI for the average change in 6-minute walk distance in each WIQ category (eg, no change in reported difficulty, 1-point improvement in reported difficulty, 2-point improvement in reported difficulty, and so on) and the average change in 6-minute walk distance corresponding to 2 different changes in WIQ response (eg, the average change in 6-minute walk distance corresponding to a 1-point improvement in walking difficulty and the average change in 6-minute walk corresponding to no change in walking difficulty). Change in 6-minute walk distance corresponding to change in WIQ response (eg, no change, 1- and 2-point improvement, and 1- and 2-point decline) were compared between participants randomized to exercise versus the control group. In sensitivity analyses, 2 additional analyses were performed. First, analyses were repeated among participants who did not use a cane at baseline or follow-up (N=10 excluded, 2%). Second, analyses were repeated, excluding participants who were asymptomatic at baseline (N=25, 6.1%).

In addition, mean change in 6-minute walk distance and mean change in total WIQ distance score were calculated according to whether participants reported worsening, no change, or improvement in the degree to which leg symptoms in the calf or buttock and in the thigh made walking difficult. Statistical analyses were conducted using SAS 9.4 (SAS Institute Inc.) and the statistical significance level was set at 0.05.

RESULTS

Of 464 unique participants randomized into the 3 randomized clinical trials, 404 (87%) completed both the 6-minute walk and WIQ distance questions at baseline and 6-month follow-up and were included in the analyses. Of the 404 participants, 205 were randomized to an exercise group and 199 were randomized to a control group. There were no meaningful differences in clinical characteristics, 6-minute walk distance, or total WIQ distance score at baseline between those randomized to exercise versus control (Table 1).

At 6-month follow-up, the exercise group improved 6-minute walk distance by 33.8 m, while the control group declined by 6.0 m (mean difference: +39.8 m

Table 1. Characteristics of Participants With Peripheral Artery Disease From 3 Randomized Trials of Exercise

Clinical Characteristic	Total N=404	Control n=199	Exercise n=205
Age, y	68.7 (9.3)	68.4 (9.5)	69.0 (9.2)
Women, n (%)	184 (45.5)	90 (45.2)	94 (45.9)
ABI*	0.64 (0.15)	0.65 (0.15)	0.63 (0.15)
Black patients, n (%)	229 (56.7)	111 (55.8)	118 (57.6)
Body mass index, kg/m^2	30.0 (6.7)	30.3 (6.9)	29.7 (6.4)
Diabetes mellitus, n (%)	146 (36.1)	77 (38.7)	69 (33.7)
Angina, n (%)†	64 (15.9)	29 (14.6)	35 (17.1)
Current or former smoking, n (%)	349 (86.4)	171 (85.9)	178 (86.8)
Six-min walking distance, m	343.1 (94.8)	343.2 (91.4)	343.1 (98.3)
Walking Impairment Questionnaire distance score (range 0–100, 100=best)	32.1 (25.3)	31.8 (24.3)	32.4 (26.4)

ABI indicates ankle–brachial index.
*People with baseline ABI>0.9 were excluded. The sample size for control was 177, and for exercise it was 190.
†1 person in control groups had missing data in baseline angina.

favoring exercise [95% CI, 26.8–52.8, *P*<0.001]) (Table 2). At 6-month follow-up, the exercise group improved the total WIQ distance score by 11.0 points and the control group improved the WIQ distance score by 3.7 points (mean difference: +7.3 favoring exercise [95% CI, 2.4–12.1, *P*=0.003]) (Table 2).

A total of 2828 individual WIQ distance score questions were completed at baseline and 6-month follow-up (total of 5656 question responses). Of these, 1435 questions were completed by participants randomized to exercise and 1393 were completed by participants randomized to the control group. At 6-month follow-up, 620 (43.2%) of question responses from 188 participants randomized to exercise indicated no change in ability to walk 1 or more distances, compared with 688 (49.4%) from 185 randomized to the control group (*P*=0.019). Among these participants who reported no change in ability to walk 1 or more distances between baseline and follow-up, those randomized to exercise improved their 6-minute walk distance by 26.8 m while those randomized to the control group declined by 6.5 m (*P*<0.001) (Figure 1). Among all participants who reported a 1-point improvement in walking 1 or more distances at 6-month follow-up (0–4 scale), those randomized to exercise simultaneously improved their 6-minute walk distance by 42.5 m while those randomized to control improved the 6-minute walk distance by only 10.1 m (*P*<0.001 for difference between exercise and control) (Figure 1). Among participants reporting a 1-point decline (0–4 scale) in ability to walk 1 or more distances, participants randomized to exercise improved their 6-minute walk distance by 18.2 m while those randomized to control declined by 14.4 m (*P*=0.001 for difference between exercise and control) (Figure 1). Among all participants reporting a 2-point decline (0–4 scale) in ability to walk 1 or more distances, participants randomized to exercise improved 6-minute walk distance compared with those randomized to the control group at 6-month follow-up (Figure 1).

Of 159 participants who reported no change between baseline and follow-up in the degree to which pain, aching, or cramps in the calf or buttock made walking difficult, those randomized to exercise had

Table 2. Change in 6-Minute Walk Distance and the Walking Impairment Questionnaire Distance Score Among Participants With Peripheral Artery Disease Randomized to Exercise Versus Control

	Baseline	6-mo Follow-Up	Within-Group Change	*P* Value for Within-Group Comparison	Between-Group Difference in Change	*P* Value for Between-Group Comparison
6-min walk distance, m						
Exercise group (n=205)	343.1	376.9	+33.8	<0.001	+39.8	<0.001
Control group (n=199)	343.2	337.3	−6.0	0.21	Ref.	Ref.
Walking Impairment Questionnaire Distance score (0–100 scale, 100=best)						
Exercise group (n=205)	32.4	43.4	+11.0	<0.001	+7.3	0.003
Control group (n=199)	31.8	35.5	+3.7	0.022	Ref.	Ref.

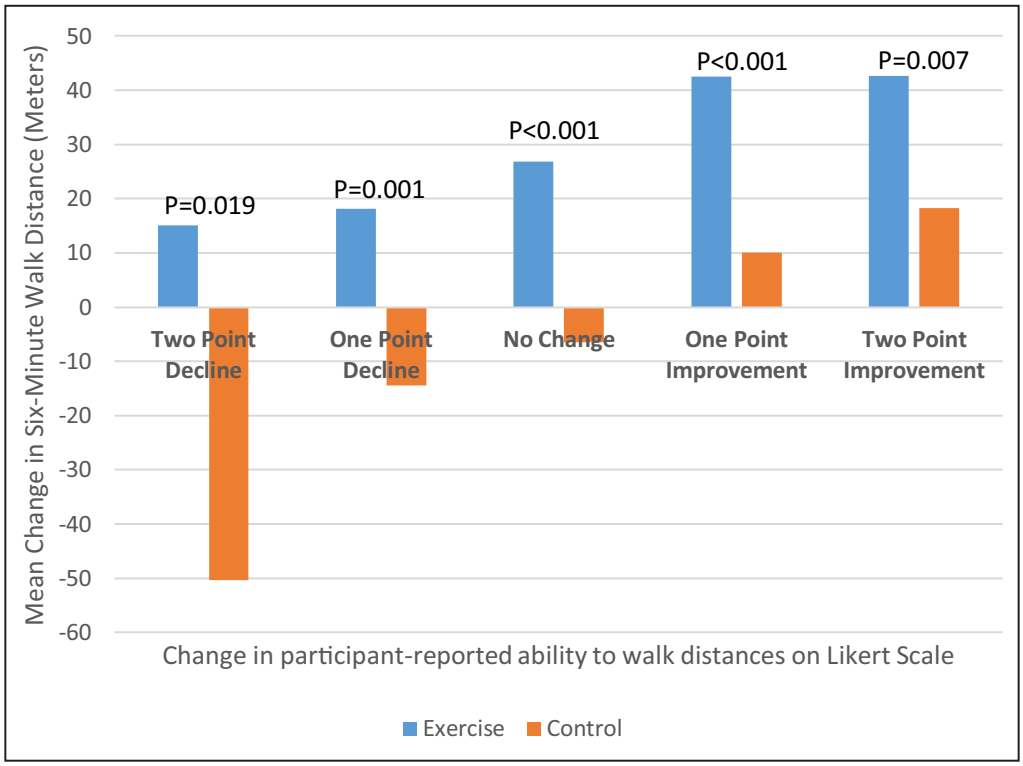

Figure 1. Mean change in 6-minute walk distance corresponding to participant-perceived change in walking ability.
The number of participants in the exercise and control groups reporting specific changes in walking ability (scale:-2 to +2, +2=best) is as follows: Exercise group: –2: n=24, –1: n=81, no change: n=188, +1: n=144; +2: n=89; Control group: –2: n=33; –1: n=107; no change: n=185; +1: n=121; +2: n=54.

significantly greater improvement in 6-minute walk distance compared with those randomized to control (+33.9 versus –7.5 m, *P*<0.001) (Figure 2). Among the 87 participants who reported worsening in pain, aching, or cramps in the calf or buttock during walking, those randomized to exercise had significantly greater improvement in 6-minute walk distance compared with those randomized to control (+28.9 versus –12.5 m, *P*=0.003) (Figure 2). Similarly, those randomized to exercise significantly improved 6-minute walk distance compared with control, even while reporting no change or worsening in the degree to which thigh symptoms worsened walking ability (Figure 2).

In sensitivity analyses, results did not substantially change when the 10 participants (2%) who used a cane for the 6-minute walk at baseline or follow-up were excluded from analyses (Table S1). Results did not substantially change when the 25 participants (6%) who were asymptomatic at baseline were excluded from analyses (Table S2).

DISCUSSION

Among 404 people with PAD in 3 randomized clinical trials, exercise significantly improved 6-minute walk distance compared with the control group by 39.8 m, consistent with a large clinically meaningful change.[15] However, exercise had a less potent effect on patient-reported walking ability. Of 205 participants with PAD randomized to exercise, 149 (73%) improved their 6-minute walk distance at 6-month follow-up, but only 602 (42%) of questionnaire responses indicated improved walking ability over the same period, only 92 participants (45%) perceived improvement in difficulty walking because of calf or buttock pain or aching, and only 78 participants (38%) perceived improvement in difficulty walking because of thigh discomfort. Furthermore, among all participants in the exercise and control groups who reported no change in ability to walk at 6-month follow-up for 1 or more distances, those randomized to exercise actually improved their 6-minute walk by a mean of 26.8 m while those randomized to control simultaneously declined by 6.5 m. Among those who reported greater walking difficulty at 6-month follow-up than at baseline because of calf or buttock pain or aching, those randomized to exercise nonetheless improved 6-minute walk by 28.9 m while those randomized to the control group declined by 12.5 m. A previous study showed that a small meaningful change in 6-minute walk distance was 8 m and a large meaningful change was 20 m.[15]

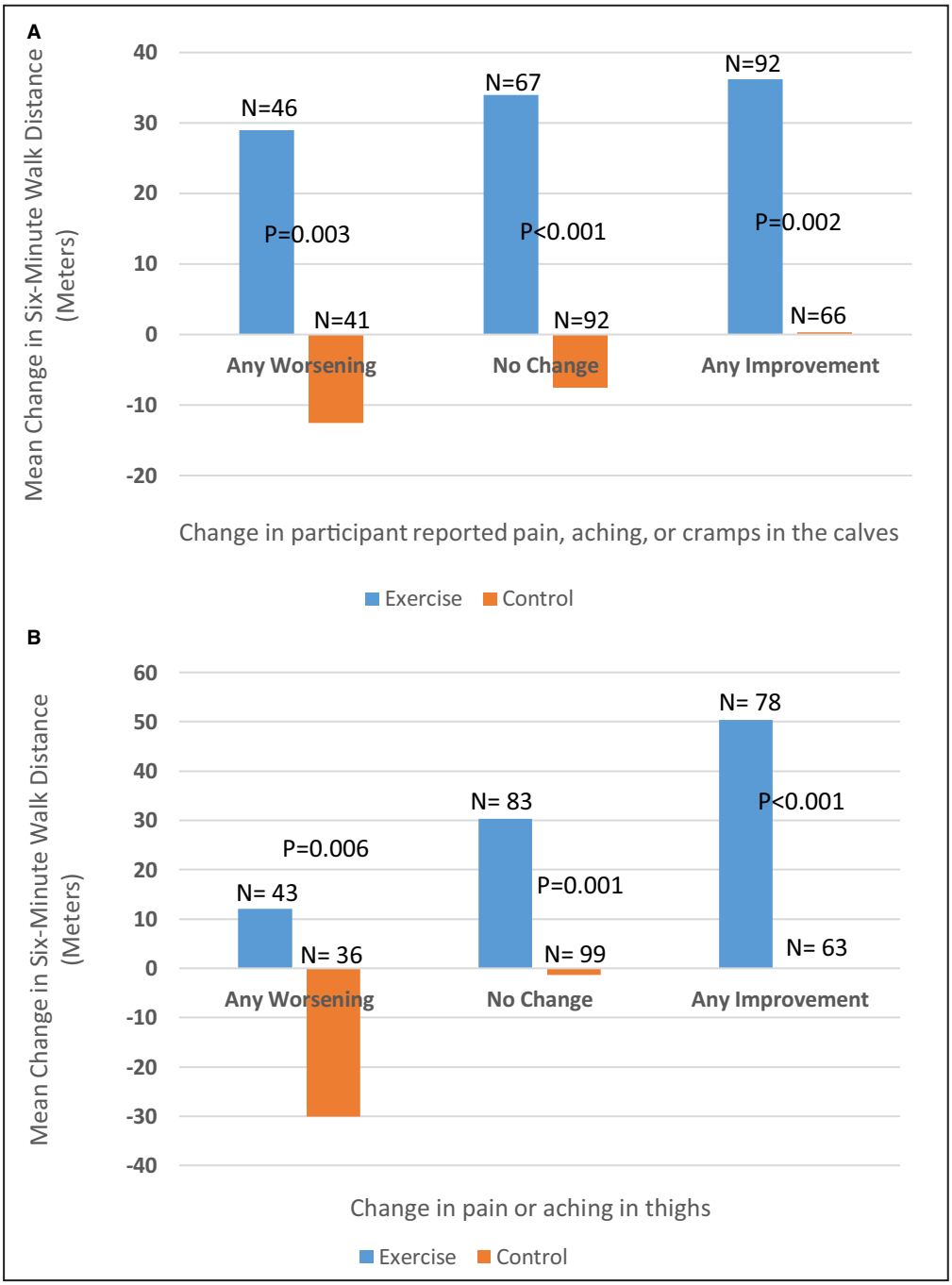

Figure 2. Mean change in 6-minute walk distance according to participant-reported change in (A) calf symptoms and (B) pain or aching in thighs.

In the CLEVER Trial of 111 participants with PAD and aorto-iliac atherosclerosis who were randomized to either revascularization with stenting, supervised treadmill exercise for 6 months, or a control group, the effects of exercise were greater on change in treadmill walking time than on patient-reported outcome measures.[1] In the CLEVER Trial, supervised treadmill exercise improved maximal treadmill walking time by 2.1 minutes more than revascularization (95% CI, 0–4.2 minutes, *P*=0.002 in nonparametric testing), but revascularization improved the WIQ distance score by 18.7 points more than supervised exercise (*P*=0.029).[1] Furthermore, in CLEVER, changes in the WIQ distance score significantly correlated with changes in peak treadmill walking time in participants randomized to stenting, but not in patients randomized to supervised exercise.[3] In 2 meta-analyses of clinical trials that

compared outcomes between participants with PAD randomized to supervised treadmill exercise versus home-based walking exercise, supervised treadmill exercise was associated with significantly greater gains in treadmill walking time compared with home-based exercise, but there were no differences in patient-reported outcome measures between those randomized to supervised exercise versus home-based exercise.[4,5] While these prior results suggested a discordance between the degree of objective improvement in walking performance and patient-reported change in walking ability, to our knowledge, no randomized trials have simultaneously compared changes in 6-minute walk distance with changes in participant-reported walking ability among people with PAD randomized to exercise versus control.

There are several potential reasons why patient-reported measures suggest less benefit from an exercise intervention, compared with objective measurements. First, exercise interventions improve walking ability gradually in people with PAD.[7,16] In the PROPEL randomized trial, the exercise intervention improved 6-minute walk distance by 11.6 m at 6-week follow-up, 30.3 m at 12-week follow-up, and 32.1 m at 6-month follow-up.[7] These gradual improvements in 6-minute walk distance may make it difficult for people with PAD to detect objectively measured improvement. The abrupt change in improved walking ability after revascularization may be more immediately potent, resulting in an immediate positive perception in people with PAD. Second, it is possible that people with PAD randomized to exercise have higher expectations than those randomized to a control group, and therefore those randomized to exercise may be less likely to report improvement. Third, greater increases in walking distances and exercise activity may increase ischemic leg symptoms in people randomized to an exercise intervention, thereby reducing appreciation of improved walking distances. If participants experienced more ischemic pain after the exercise intervention in the process of walking longer distances, this may explain the discordance in change in 6-minute walk distance versus participant-reported measures. Fourth, it is possible that improvement in 6-minute walk distance does not translate into the same amount of improvement in walking distances in daily life for participants with PAD. Fifth, it is possible that the WIQ distance score is not sufficiently sensitive to detect participants' perceptions of improved walking ability, reflected by improved 6-minute walk distance. However, 1 recent randomized trial in people with PAD demonstrated that low-intensity walking exercise significantly improved the WIQ distance score but did not improve 6-minute walk distance, relative to a control group.[17] Further study is needed to determine whether providing feedback on measured objective improvement helps people with PAD better appreciate their improved walking performance in response to exercise.

This study has limitations. First, data were collected over a 6-month period. Results may not apply to longer interventions. Second, results may not be generalizable to people with PAD who were not eligible for these exercise trials. Third, the number of people who reported 2-point improvement or decline in 1 or more WIQ distances was relatively small. Fourth, investigators did not collect data on change in blood pressure, pulse, or perceived exertion before or after the 6-minute walk test.

In summary, people with PAD randomized to an exercise intervention substantially improved 6-minute walk distance, but many perceived no change or even decline in walking ability at 6-month follow-up, measured by WIQ questions. These data suggest the possibility that significant improvements in objectively measured walking measures after exercise interventions are underappreciated by people with PAD.

ARTICLE INFORMATION

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Supplementary Material

Tables S1-S2
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Sensitivity analyses excluding participants with walking aid use at either baseline or follow-up.

			indoors	50 feet	150 feet	300 feet	600 feet	900 feet	1500 feet	Average	Weighted Average	P value
No change	Exercise	N	114	94	74	65	72	83	100			<0.001
		Average change in six-minute walk (meters)	29.7 (61.0)	31.3 (72.9)	25.0 (72.3)	22.3 (80.6)	21.3 (50.6)	28.0 (49.0)	32.3 (51.0)	27.1	27.8 (20.0, 35.5)	
	Control	N	107	110	92	73	78	99	112			
		Average change in six-minute walk (meters)	4.3 (59.5)	1.5 (56.8)	-11.1 (55.6)	-9.8 (58.6)	-17.4 (60.8)	-9.6 (57.7)	-4.0 (54.3)	-6.6	-5.8 (-13.3, 1.8)	
One-point Improvement	Exercise	N	46	54	54	65	55	48	38			<0.001
		Average change in six-minute walk (meters)	52.1 (75.8)	47.7 (57.9)	45.7 (66.2)	39.9 (50.8)	46.8 (67.9)	34.6 (56.0)	40.3 (81.0)	43.9	43.9 (34.5, 53.3)	
	Control	N	31	35	38	44	52	39	30			
		Average change in six-minute walk (meters)	11.1 (48.1)	11.2 (50.3)	6.8 (55.3)	7.5 (51.9)	11.1 (55.0)	11.5 (62.9)	11.3 (69.4)	10.1	10.0 (1.1, 18.9)	
Two-point Improvement	Exercise	N	19	21	31	25	30	25	17			0.006
		Average change in six-minute walk (meters)	40.5 (76.4)	33.3 (77.9)	46.1 (55.9)	39.0 (59.6)	36.3 (54.1)	58.3 (93.1)	51.1 (67.9)	43.5	43.4 (30.1, 56.7)	
	Control	N	16	8	12	18	10	11	9			
		Average change in six-minute walk (meters)	-12.2 (45.4)	-7.4 (47.5)	44.8 (61.1)	30.4 (49.4)	35.1 (47.1)	24.7 (38.0)	9.7 (34.5)	17.9	18.3 (6.7, 30.0)	
Any Improvement	Exercise	N	67	78	93	102	98	87	67			<0.001
		Average change in six-minute walk (meters)	47.8 (74.6)	44.3 (62.9)	48.2 (64.0)	46.4 (59.3)	49.5 (67.1)	47.9 (71.2)	48.2 (75.8)	47.5	47.5 (38.3, 56.7)	
	Control	N	48	50	57	68	71	56	45			
		Average change in six-minute walk (meters)	1.9 (48.2)	4.8 (53.2)	15.1 (56.7)	13.9 (51.5)	15.1 (53.3)	13.9 (57.2)	11.5 (60.8)	10.9	11.4 (3.3, 19.6)	
One-point Decline	Exercise	N	16	23	21	21	21	19	24			<0.001
		Average change in six-minute walk (meters)	11.9 (64.3)	19.2 (49.9)	7.7 (52.4)	18.5 (50.8)	29.9 (87.7)	23.1 (93.8)	18.5 (90.7)	18.4	18.6 (3.7, 33.4)	
	Control	N	24	26	37	36	37	31	33			
		Average change in six-minute walk (meters)	-35.0 (67.7)	-29.2 (73.9)	-3.5 (66.1)	-14.3 (59.0)	-3.7 (58.9)	-9.9 (64.8)	-23.2 (81.7)	-17.0	-15.4 (-27.5, -3.4)	

			indoors	50 feet	150 feet	300 feet	600 feet	900 feet	1500 feet	Average	Weighted Average	P value
Two-point Decline	Exercise	N	3	4	11	11	8	10	6			0.016
		Average change in six-minute walk (meters)	53.3 (15.5)	33.9 (31.2)	37.4 (46.2)	26.8 (44.1)	-20.8 (73.9)	1.5 (73.9)	-16.5 (41.0)	16.5	14.2 (-6.9, 35.3)	
	Control	N	9	3	5	13	7	8	3			
		Average change in six-minute walk (meters)	-14.3 (65.1)	-6.2 (48.2)	-19.2 (64.4)	-9.7 (84.7)	-42.5 (106.6)	-53.0 (110.7)	-67.2 (101.7)	-30.3	-26.9 (-52.7, -1.1)	
Any Decline	Exercise	N	19	28	33	33	30	30	33			<0.001
		Average change in six-minute walk (meters)	18.5 (60.9)	19.6 (47.5)	18.8 (51.1)	23.3 (48.6)	18.7 (85.9)	15.4 (85.2)	14.9 (81.2)	18.5	18.5 (5.1, 31.8)	
	Control	N	39	34	45	53	45	39	37			
		Average change in six-minute walk (meters)	-37.3 (76.4)	-38.3 (82.1)	-16.4 (77.7)	-21.4 (75.2)	-13.7 (72.5)	-18.7 (76.7)	-26.3 (81.6)	-24.6	-23.8 (-39.0, -8.6)	

Table S2. Results of sensitivity analyses in which the 25 participants who were asymptomatic at baseline were excluded.

			indoors	50 feet	150 feet	300 feet	600 feet	900 feet	1500 feet	Average	Weighted Average	P value
No change	Exercise	N	92	71	58	50	61	70	90			<0.001
		Average change in six-minute walk (meters)	31.8 (61.6)	38.9 (76.9)	28.5 (77.9)	23.8 (90.1)	25.7 (52.1)	31.1 (49.7)	32.3 (51.3)	30.3	30.9 (22.3, 39.4)	
	Control	N	90	95	81	62	65	91	102			
		Average change in six-minute walk (meters)	10.1 (52.0)	4.7 (49.1)	-6.7 (47.6)	-2.7 (48.4)	-13.0 (53.7)	-3.7 (50.3)	-1.3 (56.1)	-1.8	-1.2 (-7.5, 5.2)	
One-point Improvement	Exercise	N	42	49	47	57	47	40	33			<0.001
		Average change in six-minute walk (meters)	54.8 (76.9)	44.8 (58.5)	51.4 (62.2)	42.5 (48.5)	50.9 (68.8)	36.1 (53.8)	48.9 (79.0)	47.0	46.9 (37.1, 56.8)	
	Control	N	27	31	33	41	49	34	28			
		Average change in six-minute walk (meters)	13.7 (50.5)	16.8 (50.5)	10.2 (57.4)	11.0 (52.0)	14.2 (55.3)	14.3 (66.6)	11.0 (71.8)	13.0	13.0 (3.5, 22.6)	
Two-point Improvement	Exercise	N	16	19	27	21	21	19	10			0.007
		Average change in six-minute walk (meters)	45.3 (80.4)	34.7 (81.4)	41.7 (58.9)	44.7 (48.5)	43.7 (43.6)	75.3 (92.2)	74.4 (67.3)	51.4	49.2 (35.0, 63.4)	
	Control	N	14	6	11	15	9	9	7			
		Average change in six-minute walk (meters)	-12.7 (48.2)	-9.3 (53.8)	51.3 (59.6)	32.2 (53.4)	35.7 (49.9)	30.6 (36.5)	21.8 (28.6)	21.4	22.0 (8.5, 35.5)	
Any Improvement	Exercise	N	60	71	82	89	80	69	51			<0.001
		Average change in six-minute walk (meters)	51.1 (76.2)	42.8 (64.2)	50.3 (62.9)	50.3 (56.3)	55.6 (66.6)	55.2 (71.5)	60.1 (76.9)	52.2	51.8 (42.0, 61.6)	
	Control	N	41	43	49	59	63	46	37			
		Average change in six-minute walk (meters)	4.7 (50.7)	9.9 (54.7)	20.4 (58.0)	18.0 (52.5)	19.5 (54.2)	19.2 (60.5)	15.8 (64.8)	15.4	15.9 (6.9, 24.9)	
One-point Decline	Exercise	N	12	20	17	18	18	19	19			0.001
		Average change in six-minute walk (meters)	21.4 (74.6)	21.2 (52.7)	10.4 (57.3)	22.2 (49.5)	26.8 (93.5)	22.3 (94.1)	21.7 (98.8)	20.8	20.9 (3.0, 38.8)	
	Control	N	22	22	30	33	34	24	28			
		Average change in six-minute walk (meters)	-36.7 (69.4)	-29.4 (80.1)	-5.6 (68.9)	-12.7 (63.8)	-4.7 (59.8)	-14.7 (68.9)	-28.9 (84.5)	-19.0	-17.4 (-31.2, -3.7)	

			indoors	50 feet	150 feet	300 feet	600 feet	900 feet	1500 feet	Average	Weighted Average	P value
Two-point Decline	Exercise	N	3	4	9	9	7	8	4			0.017
		Average change in six-minute walk (meters)	53.3 (15.5)	51.7 (17.2)	44.6 (48.1)	28.3 (49.1)	-27.0 (77.6)	-2.0 (83.3)	-32.3 (42.0)	16.7	15.7 (-9.8, 41.2)	
	Control	N	11	5	7	12	7	9	2			
		Average change in six-minute walk (meters)	-31.5 (112.7)	-47.4 (154.7)	-44.9 (133.3)	-43.4 (115.0)	-82.5 (145.4)	-81.2 (133.9)	-87.3 (135.1)	-59.8	-54.8 (-107.0, -2.6)	
Any Decline	Exercise	N	15	25	27	28	26	28	26			<0.001
		Average change in six-minute walk (meters)	27.8 (67.7)	24.1 (49.8)	23.2 (54.9)	26.4 (48.9)	15.2 (91.0)	14.8 (88.5)	16.5 (89.0)	21.1	20.7 (4.9, 36.5)	
	Control	N	39	32	40	49	42	33	31			
		Average change in six-minute walk (meters)	-42.1 (89.6)	-44.0 (99.6)	-24.8 (92.8)	-29.2 (87.0)	-21.9 (86.5)	-32.8 (93.8)	-31.9 (85.3)	-32.4	-31.8 (-50.4, -13.2)	

Figure S1. Example responses to the Walking Impairment Questionnaire Distance Component.

A participant completing the baseline and follow-up questionnaire in the manner below would have their change in six-minute walk distance included three times for the "no change" outcome and four times for the "improvement by one point" outcome.

Example baseline questionnaire responses

B. WALKING DISTANCE: Please report the degree of physical difficulty that best describes how hard it was for you to walk on level ground without stopping to rest for each of the following distances **during the last week**.

	Degree of Difficulty				
Distance	**None**	**Slight**	**Some**	**Much**	**Unable**
09. Walking indoors (i.e., around the home)?	☒ 4	☐ 3	☐ 2	☐ 1	☐ 0
10. Walking 50 feet?	☒ 4	☐ 3	☐ 2	☐ 1	☐ 0
11. Walking 150 feet (1/2 block)?	☐ 4	☒ 3	☐ 2	☐ 1	☐ 0
12. Walking 300 feet (1 block)?	☐ 4	☐ 3	☒ 2	☐ 1	☐ 0
13. Walking 600 feet (2 blocks)?	☐ 4	☐ 3	☒ 2	☐ 1	☐ 0
14. Walking 900 feet (3 blocks)?	☐ 4	☐ 3	☐ 2	☒ 1	☐ 0
15. Walking 1500 feet (5 blocks)?	☐ 4	☐ 3	☐ 2	☒ 1	☐ 0

Example follow-up questionnaire responses

B. WALKING DISTANCE: Please report the degree of physical difficulty that best describes how hard it was for you to walk on level ground without stopping to rest for each of the following distances **during the last week**.

	Degree of Difficulty				
Distance	**None**	**Slight**	**Some**	**Much**	**Unable**
09. Walking indoors (i.e., around the home)?	☒ 4	☐ 3	☐ 2	☐ 1	☐ 0
10. Walking 50 feet?	☒ 4	☐ 3	☐ 2	☐ 1	☐ 0
11. Walking 150 feet (1/2 block)?	☐ 4	☒ 3	☐ 2	☐ 1	☐ 0
12. Walking 300 feet (1 block)?	☐ 4	☒ 3	☐ 2	☐ 1	☐ 0
13. Walking 600 feet (2 blocks)?	☐ 4	☒ 3	☐ 2	☐ 1	☐ 0
14. Walking 900 feet (3 blocks)?	☐ 4	☐ 3	☒ 2	☐ 1	☐ 0
15. Walking 1500 feet (5 blocks)?	☐ 4	☐ 3	☒ 2	☐ 1	☐ 0