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MEANINGFUL CHANGE IN SIX-MINUTE WALK IN PEOPLE WITH PERIPHERAL ARTERY DISEASE

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Abstract

OBJECTIVE.—Six-minute walk is a common outcome in clinical trials of people with lower extremity peripheral artery disease (PAD). However, meaningful change in six-minute walk distance is not well defined in people with PAD. This study related change in six-minute walk distance corresponding to the degree of participant reported improvement or decline in six-minute walk distance, in order to define meaningful change in 6-minute walk distance in people with PAD.

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DISCLOSURES

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METHODS.—PAD participants from three observational longitudinal studies completed the walking impairment questionnaire (WIQ) distance score and six-minute walk at baseline and one year later. The WIQ distance score measures participants' perceived difficulty walking seven different distances without stopping (ranging from walking around the home to five blocks) on a to 4 Likert scale, where 0 represents inability to walk the distance and 4 represents no difficulty. Mean changes in six-minute walk distance corresponding to participant report of no change, one unit change, or two unit change, respectively, in the 0–4 Likert scale between baseline and one-year follow-up were calculated for each WIQ distance.

RESULTS.—777 participants with PAD (mean age: 71.2 years (standard deviation (SD)=8.8) mean baseline six-minute walk: 350.1 meters (SD=118.1) completed 5,439 questions about difficulty walking each WIQ distance at baseline and follow-up. Participants with PAD who reported no change in difficulty walking each WIQ distance between baseline and follow-up declined by 7.2 meters (95% CI: −11.6, −2.8) in the six-minute walk test. Relative to people reporting no change in difficulty walking, people reporting one and two point improvements in walking ability (0–4 scale) had six-minute walk distance improvements of 7.8 meters (95% CI:−3, +15.9) and 20.1 meters (95% CI: +1.1, +39.2), respectively. Relative to people reporting no change in walking difficulty, those reporting one and two point declines in perceived walking difficulty corresponded to −11.2 meter (−95% CI:−19.0, −3.4) and −23.8 meter (95% CI:−37.4, −10.3) declines in six-minute walk distance.

CONCLUSIONS.—Among people with PAD, approximately 8 and 20 meter improvements in six-minute walk distance, respectively, represent small and large improvements in walking ability, respectively. People with PAD who reported no change in their ability to walk distances over one year simultaneously declined by a mean of seven meters in the six-minute walk test. These findings are useful for interpreting results of randomized trials of interventions to improve walking performance in people with PAD.

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At baseline and at one-year follow-up, this prospective observational study of 777 people with lower extremity peripheral artery disease (PAD) measured participant perceived difficulty walking and also measured six-minute walk distance. Increases of 8 and 20 meters represented small and large improvements in six-minute walk distance among people with PAD.

Increasingly, the six-minute walk test is an outcome measure in randomized trials of interventions to improve walking performance in PAD.[1–8] A meaningful change in an outcome is defined as a change that is noticeable and important to patients. While a meaningful change in the six-minute walk distance has been defined for older people without PAD,[9] people with PAD have significantly poorer six-minute walk distance than those without PAD.[10,11] Meaningful change in six-minute walk distance may not be the same for people with PAD compared to those without PAD. Defining meaningful change in six-minute walk distance for people with PAD is important for designing and interpreting results of randomized trials that test therapies for people with PAD.

This study combined data from three observational longitudinal studies that measured both six-minute walk distance and participant reported walking ability, in order to define a meaningful change in six-minute walk distance for people with PAD. The 'anchor based'

method was used to determine meaningful change.[12,13] The anchor based method links change in the outcome of interest (i.e. six-minute walk distance) to the patient's perspective on perceived degree of change.[12] In this report, a meaningful change for six-minute walk distance was defined by anchoring actual changes in six-minute walk distance to PAD participants' perceived ability to walk distance, measured during the same time period as the six-minute walk test. We also determined whether meaningful change in six-minute distance differed among people with more mild vs. severe PAD and according to higher vs. lower six-minute walk distance at baseline.

METHODS

Overview

Data from three longitudinal observational studies of participants with PAD were combined for these analyses.[2,3,14–16] These studies measured the natural history of functional performance in participants with PAD using both the six-minute walk test and the Walking Impairment Questionnaire (WIQ) at baseline and at one-year follow-up. No study interventions were administered by investigators between baseline and one-year follow-up testing. Methods for all three studies have been published and consisted of the Walking and Leg Circulation Study (WALCS), WALCS II, and WALCS III cohort studies.[14–16] The study aims, sample size, years of data collection, and study design for each study are shown in Table I. All participants provided written informed consent.

Participant Identification

Participants were identified from non-invasive vascular laboratories and from vascular surgery, cardiology, endocrinology, geriatric, and general medical practices at multiple medical centers in the Chicago area.[14–16]

Inclusion criteria

All included participants had PAD, defined as an ankle brachial index ≤0.90 at their baseline visit. The WALCS and WALCS II cohorts included participants age 55 and 59 and older, respectively.[14,15] The WALCS III cohort had no inclusion criterion for age.[16]

Exclusion criteria

Exclusion criteria for each study have been described and are summarized briefly here.[14–16] In all studies, potential participants with a below or above-knee amputation, wheelchair confinement, or foot ulcer or critical limb ischemia were excluded. Potential participants with major surgery or revascularization either during the 3 months prior to enrollment or planned at the time of enrollment were excluded. Potential participants with significant cognitive impairment were excluded. In addition, individuals who underwent lower extremity revascularization between baseline and one-year follow-up were excluded.

Ankle-brachial index (ABI)

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. Each measure was repeated. The ABI was calculated by dividing average pressures in each leg by the average of the four brachial pressures.[14–16] Average brachial pressures in the arm with highest pressure were used when one brachial pressure was higher than the opposite brachial pressure in both measurement sets, and the two brachial pressures differed by 10 or more mm Hg in at least one measurement set, since in such cases subclavian stenosis was possible.[17]

Six-Minute Walk Test

The six-minute walk was measured at baseline and follow-up using a standardized protocol.[14–16,18] the six-minute walk was conducted in a 100 foot course in a hallway.Participants received standardized instructions prior to the test, which included that the goal of the test was to cover as much ground as possible during the six minutes. The distance completed after 6 minutes was recorded. The test was repeated at 12 month follow-up.

Walking Impairment Questionnaire

The Walking Impairment Questionnaire (WIQ) was developed specifically for people with PAD to measure participants' perception of difficulty walking distances in the community. The WIQ includes three domains: walking distance, walking speed, and stair climbing.[19] Analyses reported here focused on the WIQ distance domain because it measures participants' perception of difficulty walking distances, analogous to the six-minute walk test's objective assessment of difficulty walking distance. The WIQ distance questionnaire consists of seven questions measuring participants' perceived difficulty walking seven specific distances without stopping to rest. The seven distances range from walking indoors around the home to walking five blocks. For each distance, participants are asked to rank on a 0 to 4 Likert scale their perceived degree of physical difficulty walking the distance on a level ground without stopping to rest, where 0 represents inability to walk the distance and 4 represents no difficulty walking the distance. In addition, a total distance score can be calculated for the WIQ distance questionnaire by multiplying the participant's Likert scale response by a constant value, part of the original derivation of the WIQ questionnaire, [19] that is weighted according to the length of the distance for the corresponding question. The resulting seven products are summed and divided by the maximum possible score to obtain a percent score ranging from 0 to 100 (100=best).

Other Measures

Race and demographics were obtained using patient report.[14–16] Height and weight were measured. Body mass index (BMI) was calculated as weight (kg)/ (height (meters))^2. Comorbidities were ascertained and verified at baseline using medical record review, prescribed medications, participant self-report, and results of a primary care physician questionnaire.[20] Data from these information sources were combined using algorithms from the Women's Health and Aging Study to adjudicate comorbid diseases.[20]

Statistical analyses

Characteristics of participants and the baseline total WIQ distance score were compared across baseline quintiles of six-minute walk distance using analyses of variance and statistical tests for trend. Tests for were performed using linear regression analyses, including a continuous independent variable with values of ‘x, y, z, ,etc. to represent x, y, z groups, respectively. Mean six-minute walk distances were compared across each Likert scale response (0–4) for each of the seven WIQ distance questions using analyses of variance and statistical tests for trend. Change in six-minute walk distance followed a normal distribution. Therefore, data transformation was not performed.

For each participant, responses to each of the seven WIQ distance questions were compared between baseline and one-year follow-up. Each question was categorized according to whether the participant’s reported difficulty walking was unchanged, improved by one point, improved by two points, declined by one point, or declined by two points between baseline and one-year follow-up on the 0–4 point scale. We considered that a one-point change in participant reported difficulty walking each distance on the 0–4 scale represented a noticeable and important change. Due to small numbers of responses consisting of three or more point increases or decreases in WIQ questions, six-minute walk changes corresponding to three point improvements or declines were not included in analyses. Since WIQ questions in which the baseline response was at a ‘four’ could not improve at all, individual questions with this response at baseline were excluded from analyses of question improvements. Similarly, because WIQ questions for which the baseline response was at a ‘three’ could not improve by two points, these question responses at baseline were excluded from analyses of two point improvements. Similarly, questions for which the baseline response was either “zero” or “one” were not included in analyses of two-point decline, respectively. Mean change in six-minute walk distance was calculated for all individual question responses that were unchanged, improved by one point, improved by two points, declined by one point, or declined by two points between baseline and 12-month follow-up. For example, a participant who reported ‘no change’ in each of the WIQ distance questions would contribute their six-minute walk change value seven times (one for each of the seven WIQ distance questions) to the analysis of the six-minute walk change anchored to participants’ perception of no change in walking distance ability. A participant who reported a one point decline in their ability to walk five blocks, but no change in their ability to walk the distances less than five blocks would contribute their six-minute walk change value one time to the analysis of one-point decline in perceived walking ability and would contribute their change in six-minute walk distance six times to the mean change in six-minute walk distance that corresponded to no change in walking ability. Mean changes in six-minute walk distance for patient reported improvement, no change, or decline (i.e. − 2.0 points, - 1.0 point, no change, + 1.0 point, +2.0 points) consisted of weighted means of the change in six minute walk distance corresponding to each category across the seven questions. The mean changes in six-minute walk distance were weighted according to the total number of questionnaire responses for each change category across all seven questions. Mean changes in six minute walk distance for each category of improvement or decline in participant reported walking (i.e. −2.0 points, −1.0 point, +1.0 point, +2.0 points) were calculated relative to the mean

change in six-minute walk distance for participants who reported no change in ability to walk between baseline and one-year follow-up.

To account for the fact that one individual may contribute changes in six-minute walk distance multiple times across different questions in the WIQ distance score, a patient-based bootstrap method was used to calculate the 95% confidence interval (CI) for the average change in six-minute walk distance in each WIQ category (e.g. no change in reported difficulty, one-point improvement in reported difficulty, two-point improvement in reported difficulty, and so on) and the average change in six-minute walk distance corresponding to two different changes in WIQ response (e.g, the average change in six-minute walk corresponding to a one-point improvement in walking difficulty and the average change in 6-minute walk corresponding to no change in walking difficulty). Specifically, if a patient selected b time in a bootstrap sample, the corresponding change in six-minute walk distance also contributes b times to all relevant categories to preserve the correlations under the general assumption that all patients are independent.

Analyses were repeated separately among men and women, among blacks and whites, among younger and older participants (i.e. age≥65 vs. <65), among participants above vs. below the median of the six-minute walk distance at baseline, and among participants with severe PAD (ABI < 0.60) vs. mild or moderate PAD (ABI 0.60 to 0.90). A statistical test for interaction was performed to assess whether the meaningful change in six-minute walk distance was statistically significantly different for participants in each of these comparisons (i.e. men vs. women, blacks vs. whites etc.). The statistical analyses were conducted using SAS 9.4 (SAS Institute Inc.) and the statistical significance level was set at 0.05.

RESULTS

Of 989 unique participants who completed both the six-minute walk and WIQ distance questions at baseline, 813 (82.2%) completed both the six-minute walk and the WIQ distance score at one year follow-up. Of these, 36 underwent lower extremity revascularization between baseline and one-year follow-up, leaving 777 participants for analyses. A total of 5,439 WIQ distance score questions were responded to at both baseline and one year follow-up and included in analyses. Of the 5,439 WIQ distance score questions responded to at baseline and follow-up, 2,963 (54.5%) of responses were the same at baseline and one-year follow-up (indicating no change in perceived difficulty walking that distance). After excluding questions in which the response increased to the best or declined to the worst score, 564 (10.4%) of responses were one- point better, 136 (2.5%) of responses were two points better, 704 (12.9%) were one point worse, and 236 (4.3%) were two points worse at follow-up, compared to baseline.

Shorter six-minute walk distance at baseline was associated with significantly older age, lower ABI, higher proportions of women and African Americans, higher BMI values, a higher prevalence of diabetes, and lower total WIQ distance score at baseline (Table II). Greater perceived difficulty walking each of the seven distances on the WIQ distance questionnaire was associated with shorter six-minute walk distance at baseline (Table III).

For the questions in which difficulty in walking ability did not change between baseline and one-year follow-up, corresponding mean change in six-minute walk distance declined by 7.2 meters between baseline and 1-year follow-up (Table IV). For questionnaire responses indicating a one-point improvement in walking the corresponding distance, mean six-minute walk distance improved by 7.8 meters, relative to the group reporting no change (Table IV). For questionnaire responses indicating a two-point improvement in walking a specific distance, mean change in six minute walk distance was a 20.1 meter improvement, relative to the group reporting no change (Table IV). For questionnaire responses indicating a one-point and two-point decline in participant reported walking difficulty, corresponding changes in six-minute walk distance were −11.2 meters and −23.8 meters, respectively (Table IV).

There were no significant differences in the magnitude of change in six-minute walk distance corresponding to participant perceived change in walking difficulty based on age, sex, race, whether participants had a shorter vs. longer six minute walk distance at baseline or among participants with more vs. less severe PAD at baseline (Table V).

DISCUSSION

Among 777 people with PAD who completed 5,439 WIQ distance score questions at baseline and one-year follow-up, participants who reported no difference in perceived difficulty walking between baseline and follow-up declined in six-minute walk distance by a mean of 7.2 meters during the same time period. Relative to perceived “no change” in difficulty walking distances, a one-point improvement in participant perceived walking ability on the five point Likert scale corresponded to a 7.8 meter improvement in six-minute walk distance, while a two- point improvement in perceived walking ability corresponded to a 20.1 meter improvement in six-minute walk distance. Relative to perceived “no change”, a one-point decline in perceived walking ability corresponded to a 11.2 meter decline in six-minute walk distance. A two-point decline in perceived walking ability corresponded to a 23.8 meter decline in six-minute walk distance. These results did not substantially differ between PAD participants with higher vs. lower six-minute walk distance at baseline or between PAD participants with mild vs. severe PAD at baseline. Together these findings suggest that six-minute walk changes corresponding to participants’ perception of small and larger improvements in their ability to walk long distances were approximately 8 meter and 20 meter gains in six-minute walk distance, respectively. Six- minute walk changes corresponding to participants’ perception of small and larger declines in their ability to walk long distances were approximately 11 and 24 meter declines, respectively.

Improving walking performance and functional status are primary goals in clinical practice guidelines for management of people with PAD.[21,22] In addition to defining meaningful change in six-minute walk distance, results reported here show that patients with PAD declined a mean of 7.2 meters per year, even when they perceived that their ability to walk long distances had not changed. These results suggest that functional decline in some people with PAD may be an insidious process, marked by gradual decline that patients with PAD may not be aware of until mobility loss is substantial. Prior work showed that decline in six-minute walk distance predicted mobility loss and mortality in people with PAD, underscoring the significance of decline in six-minute walk distance in PAD.[23] Results

reported here also show that the magnitude of the corresponding decline in six-minute walk for a one point decline in the 0–4 WIQ distance scale was greater than the magnitude of corresponding improvement in six-minute walk distance for a one point improvement in the 0–4 WIQ distance scale. A similar phenomenon was observed for a two point declines vs. two point improvement in the 0–4 WIQ distance scale. These findings further underscore that people with PAD are not fully aware of their declining ability to walk, most likely because the decline is gradual over shorter periods of time. Results reported here also demonstrate the importance of measuring both change in six- minute walk distance and change in participant-perceived walking ability, since the two measures are somewhat discordant.

Prior study of older people without PAD concluded that a small minimal clinically important change in six-minute walk distance was approximately 20 meters and that a large minimal clinically important change was approximately 50 meters.[9] However, people with PAD have significantly shorter six-minute walk distance and decline in six-minute walk distance at a fast rate than people without PAD.[10,11] Thus, smaller changes in six-minute walk may be more meaningful to people with PAD. Consistent with this possibility, our results suggest that meaningful changes in six-minute walk distance among people with PAD are substantially shorter than for people without PAD.

Gardner et al recently reported that a small minimal clinically important change in six-minute walk distance was 12 meters and that moderate and large minimal clinically important changes were 32 and 34 meters, respectively.[24] This prior study included 156 participants with PAD randomized to a supervised treadmill exercise intervention, a home-based exercise intervention, or control group for 12 weeks.[24] At 12-week follow-up, participants randomized to supervised treadmill exercise improved their six-minute walk distance by 11 meters relative to the control group and those randomized to a home-based walking exercise program improved their six-minute walk distance by 41 meters, relative to control.[2] Gardner et al defined a small meaningful change as the change in six-minute walk distance corresponding to a five percent improvement in the total WIQ distance score. Moderate and large meaningful changes were defined as changes in six-minute walk distance corresponding to 25% and 40% improvements in the total WIQ distance score, respectively.[24] In contrast to the study by Gardner et al, the present study anchored change in six-minute walk distance to individual question responses, rather than percent changes in the total score. In the present study, improvements of one and two points in individual distance questions corresponded to 20% and 40% improvements on the five point Likert scale and to 7.8 and 20.1 meter improvements in six-minute walk distance, respectively. The larger meaningful changes in six-minute walk distance reported by Gardner et al may have been observed because the participants with PAD were enrolled in a randomized trial of exercise and therefore achieved greater improvement in six-minute walk distance for a given perceived improvement in the WIQ score. In contrast, PAD participants in the current study were enrolled in observational longitudinal cohorts and received no therapeutic interventions that may have biased their perception of improvement. Other differences in this report compared to the prior report by Gardner et al include the larger sample size and longer duration of follow-up in the current study.

This result illustrates that without therapy, average six-minute walk declines over time in people with PAD, even while participants with PAD perceived no difference in their walking ability over the same time period. For this reason, definitions of meaningful change in six-minute walk that corresponded to a one or two point improvement or decline in walking ability were reported relative to participants reporting no change in their walking ability over time. The mean decline in six-minute walk distance observed here is consistent with the decline in six- minute walk distance observed in the control (untreated) groups of randomized trials of people with PAD.[25]

This study has limitations. First, change in six-minute walk distance was measured at 12 month follow-up. Results may not apply to different periods of time. Second, participants were recruited from Chicago-area hospitals. Results may not be generalizable to individuals who did not meet eligibility criteria for these studies. However, three cohorts, including 777 participants with PAD, were included in these analyses. There is no reason to believe that associations reported here would not exist in other populations of people with PAD. Third, participants who underwent lower extremity revascularization were excluded from analyses. Results may not apply to individuals undergoing lower extremity revascularization. Fourth, interpretation of a meaningful change may vary between individuals. However, we assumed that a minimum of a one point change in participants' report of their ability to walk a specific distance, on a 0–4 point scale, represented a noticeable difference. Fifth, meaningful change has not been defined for the WIQ score. Sixth, for some point estimates of meaningful change, the 95% Confidence Interval values were relatively wide.

Conclusion

An eight meter improvement in six-minute walk distance corresponds to a small meaningful improvement in six-minute walk distance and a 20 meter improvement in six-minute walk distance corresponds to a large meaningful change in people with PAD, based on participant report of their perceived walking ability. People with PAD who reported no changein perceived walking ability actually declined in six-minute walk distance by a mean of seven meters per year. These results should inform randomized trials in participants with PAD that include six-minute walk testing as an outcome measure.

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Appendix

APPENDIX.

Walking Impairment Questionnaire Distance Score

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

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Article Highlights.

Type of research. Prospective observational study.

Key findings. In 777 people with peripheral artery disease (PAD), participants reporting no change in walking ability declined by seven meters in the six-minute walk test in one year.

Small and large patient reported improvements in walking ability were associated with six-minute walk distance changes of +7.8 meters and +20.1 meters, respectively, compared to those reporting no improvement.

Take home message. Among people with PAD, approximately 8 and 20 meter improvements in six-minute walk distance, respectively, represent small and large clinically important improvements, respectively. Participants reporting no change in walking ability declined in six- minute walk, suggesting an insidious decline in some people with PAD.

Table 1.

Overview of randomized trials and observational studies included in analyses

Study name	Sample size of PAD participants included in these analyses*	Years conducted	Study design	Study primary aim	Randomized groups (if applicable)
WALCS	339	1998–2004	Observational longitudinal	To define the association of the ankle brachial index with decline in 6-minute walk distance over time	Not applicable
WALCS II	177	2002–2009	Observational longitudinal	To define the association of calf skeletal muscle characteristics with decline in 6-minute walk distance	Not applicable
WALCS III	261	2007–2014	Observational longitudinal	To define the association of MRI measured plaque characteristics in the superficial femoral artery with change in six-minute walk distance.	Not applicable

* Excludes participants who were part of more than one study, individuals who did not complete the six-minute walk distance and the WIQ distance score at baseline and one year follow-up, and participants who had lower extremity revascularization between baseline and follow-up.

TABLE 2.

Clinical characteristics of peripheral artery disease participants, according to quintiles of six-minute walk distance at baseline

	Quintiles of six-minute walk distance at baseline					
Clinical Characteristic	**Quintile 1 N=155 14.6–248 Meters**	**Quintile 2 N=151 249–335 Meters**	**Quintile 3 N=161 335–392 Meters**	**Quintile 4 N=155 393–447 Meters**	**Quintile 5 N=155 447–727 Meters**	**P trend**
Age (years)	73.4 (9.6)	72.3 (8.6)	70.8 (8.5)	70.6 (8.6)	69.1 (7.9)	<0.001
Females, N (%)	77 (49.7)	85 (56.3)	68 (42.2)	41 (26.5)	41 (26.5)	<0.001
Ankle brachial index	0.60 (0.17)	0.60 (0.15)	0.65 (0.15)	0.68 (0.13)	0.71 (0.12)	<0.001
Black, N (%)	47 (30.3)	42 (27.8)	33 (20.5)	36 (23.2)	21 (13.5)	<0.001
Body mass index (kg/M^2)	30.7 (7.0)	28.1 (6.5)	28.0 (5.2)	27.5 (4.2)	26.4 (4.5)	<0.001
Diabetes mellitus, N (%)	76 (49.0)	52 (34.4)	53 (32.9)	54 (34.8)	33 (21.3)	<0.001
Angina, N (%)	48 (31.2)	48 (31.8)	53 (33.1)	40 (26.0)	36 (23.4)	0.065
Current or former smoking, N (%)	118 (76.1)	125 (82.8)	144 (89.4)	128 (82.6)	133 (85.8)	0.043
Total WIQ distance score (range 0–100, 100=best)	15.8 (19.2)	30.0 (25.3)	40.2 (26.1)	52.5 (29.0)	69.1 (26.7)	<0.001
Statins, N (%)	93 (60.0)	80 (53.0)	90 (55.9)	83 (53.5)	83 (53.5)	0.33
Anti-platelet therapy, N (%)	95 (61.3)	106 (70.2)	111 (68.9)	107 (69.0)	94 (60.6)	0.85
Cilostazol, N (%)	14 (9.0)	11 (7.3)	8 (5.0)	5 (3.2)	12 (7.7)	0.29
ACE inhibitors, N (%)	61 (39.4)	53 (35.1)	57 (35.4)	54 (34.8)	39 (25.2)	0.017

Table 3.

Associations of difficulty walking specific distances and six-minute walk distance at baseline in people with peripheral artery disease[1]

Participant reported degree of difficulty	Unable	Much	Some	Slight	None	Trend P value
	Difficulty walking indoors on the Walking Impairment Questionnaire					
	Unable (N=1)	**Much (N=30)**	**Some (N=120)**	**Slight (N=143)**	**None (N=483)**	**Trend P value**
Six-minute walk distance (meters)	61.0 (NA)	233.6 (109.9)	281.1 (120.2)	297.8 (104.2)	390.6 (101.6)	<0.001
	Difficulty walking 50 feet on the Walking Impairment Questionnaire					
	Unable (N=8)	**Much (N=50)**	**Some (N=97)**	**Slight (N=139)**	**None (N=483)**	**Trend P value**
Six-minute walk distance (meters)	141.6 (77.1)	264.9 (124.0)	262.1 (106.9)	304.5 (101.8)	393.2 (100.4)	<0.001
	Difficulty walking 150 feet on the Walking Impairment Questionnaire					
	Unable (N=35)	**Much (N=71)**	**Some (N=156)**	**Slight (N=147)**	**None (N=368)**	**Trend P value**
Six-minute walk distance (meters)	165.6 (92.4)	292.1 (114.8)	290.9 (95.3)	331.5 (98.2)	411.3 (96.2)	<0.001
	Difficulty walking 300 feet on the Walking Impairment Questionnaire					
	Unable (N=64)	**Much (N=136)**	**Some (N=168)**	**Slight (N=164)**	**None (N=245)**	**Trend P value**
Six-minute walk distance (meters)	195.8 (104.7)	292.7 (101.0)	323.2 (94.5)	375.2 (103.8)	423.9 (90.2)	<0.001
	Difficulty walking 600 feet on the Walking Impairment Questionnaire					
	Unable (N=153)	**Much (N=172)**	**Some (N=168)**	**Slight (N=120)**	**None (N=164)**	**Trend P value**
Six-minute walk distance (meters)	237.4 (103.8)	320.0 (95.5)	365.1 (95.6)	392.1 (96.2)	440.7 (89.7)	<0.001
	Difficulty walking 900 feet on the Walking Impairment Questionnaire					
	Unable (N=218)	**Much (N=203)**	**Some (N=155)**	**Slight (N=89)**	**None (N=112)**	**Trend P value**
Six-minute walk distance (meters)	254.3 (104.3)	347.2 (91.1)	381.4 (98.6)	412.6 (94.4)	448.9 (91.1)	<0.001
	Difficulty walking 1500 feet on the Walking Impairment Questionnaire					
	Unable (N=318)	**Much (N=187)**	**Some (N=128)**	**Slight (N=64)**	**None (N=80)**	**Trend P value**
Six-minute walk distance (meters)	279.7 (106.4)	357.0 (95.7)	408.4 (86.4)	426.8 (89.2)	459.2 (97.0)	<0.001

[1]Data shown are mean and standard deviations

Table 4.

Change in six-minute walk distance corresponding to participant perceived change in walking distance

Participant report	Walking indoors around home	50 feet	150 feet	300 feet	600 feet	900 feet	1,500 feet	Overall weighted average (95% CI)
No change in difficulty walking between baseline and follow-up	−5.0 meters N=519	−4.7 meters N=471	−5.4 meters N=408	−7.6 meters N=376	−10.1 meters N=380	−8.9 meters N=391	−9.6 meters N=418	−7.2 meters (−11.6, −2.8)
One unit improvement in perceived walking difficulty, relative to “no change”.	−19.4 meters N=38	−2.2 meters N=50	−0.3 meters N=74	+8.5 meters N=89	+15.2 meters N=104	+16.6 meters N=106	+11.4 meters N=103	+7.8 meters (−0.3, +15.9)
Two unit improvement in perceived walking difficulty, relative to “no change”.	−32.9 meters N=2	+49.2 meters N=13	−2.4 meters N=15	+10.7 meters N=24	+24.4 meters N=24	+21.7 meters N=29	+25.2 meters N=29	+20.1 meters (+1.1, +39.2)
One unit decline in perceived walking difficulty, relative to “no change”	−25.1 meters N=92	−29.2 meters N=115	+0.4 meters N=125	−7.2 meters N=119	−5.1 meters N=102	−4.0 meters N=82	−8.2 meters N=69	−11.2 meters (−19.0, −3.4)
Two unit decline in perceived walking difficulty, relative to “no change”	−33.1 meters N=33	−28.9 meters N=40	−48.7 meters N=45	−24.7 meters N=40	−11.3 meters N=33	−2.1 meters N=27	+13.2 meters N=18	−23.8 meters (−37.4, −10.3)

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Table 5.

Change in six-minute walk distance associated with change in perceived walking ability according to baseline six- minute walk distance and disease severity among people with peripheral artery disease *

	Weighted mean six-minute walk change among participants reporting no change in difficulty walking between baseline and follow-up Mean (95% CI)	P value for interaction	Weighted mean six-minute walk change among participants reporting a one point improvement in difficulty walking distances* Mean (95% CI)	P value for interaction	Weighted mean six-minute walk change among participants reporting a two point improvement in difficulty walking distances* Mean 95% CI	P value for interaction
Participants with baseline six-minute walk distance < median (N=388)**	−5.3 meters (−13.6, +2.9)	0.49	+9.6 meters (−1.6, +20.8)	0.62	+19.8 meters (−8.1, +47.8)	0.97
Participants with baseline six-minute walk distance ≥ median (N=389)**	−8.8 meters (−14.2, −3.3)		+5.3 meters (−7.6, +18.1)		+20.6 meters (+1.7, +39.4)	
Baseline ABI < 0.60 (N=280)	−12.5 meters (−21.6, −3.5)	0.13	+12.7 meters (−1.0, +26.4)	0.43	+5.1 meters (−28.3, +38.5)	0.11
Baseline ABI 0.6–0.9 (N=497)	−4.4 meters (−9.8, +1.1)		+5.5 meters (−5.6, +16.6)		+35.8 meters (+17.9, +53.6)	
Age <= 65 years old (N=206)	−2.7 meters (−12.6, +7.2)	0.28	+14.2 meters (+1.5, +26.8)	0.27	+14.8 meters (−26.5, +56.1)	0.76
Age > 65 years old (N=571)	−8.9 meters (−14.2, −3.5)		+5.0 meters (−5.0, +15.1)		+22.2 meters (−0.001, +44.3)	
Female (N=312)	−12.3 meters (−19.9, −4.6)	0.088	+14.5 meters (+1.7, +27.2)	0.18	+28.9 meters (−4.1, +61.9)	0.48
Male (N=465)	−4.0 meters (−9.7, +1.8)		+2.9 meters (−8.5, +14.2)		+14.3 meters (−10.3, +38.9)	
AA race (N=179)	−6.2 meters (−15.2, +2.8)	0.82	+14.5 meters (−2.8, +31.8)	0.37	+11.8 meters (−25.9, +49.5)	0.52
Non-AA race (N=598)	−7.4 meters (−12.9, −2.0)		+5.5 meters (−4.5, +15.4)		+26.3 meters (+3.6, +49.0)	

* The tests for interaction included an interaction term for (baseline six-minute walk distance X meaningful change in six-minute walk distance) and for (baseline ABI value X meaningful change in six-minute walk distance). The p value for the interaction term indicates whether the change in six-minute walk was statistically significantly different for participants with a) six-minute walk distance below vs. above the mean and b) baseline ABI < 0.60 vs. 0.60 to 0.90. Mean change is reported relative to the participants without change in difficulty between baseline and follow-up. Median baseline six-minute walk among the 777 participants with PAD was 361 meters.