Title

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Journal
Journal of Vascular Surgery, 71(3)

ISSN
0741-5214

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Publication Date
2020-03-01

DOI
10.1016/j.jvs.2019.05.058

Peer reviewed

HHS Public Access
Author manuscript
J Vasc Surg. Author manuscript; available in PMC 2021 March 01.

Published in final edited form as:
J Vasc Surg. 2020 March ; 71(3): 988–1001. doi:10.1016/j.jvs.2019.05.058.

COMPARING SIX-MINUTE WALK VS. TREADMILL WALKING DISTANCE AS OUTCOMES IN RANDOMIZED TRIALS OF PERIPHERAL ARTERY DISEASE

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Abstract

INTRODUCTION.—Randomized trials of people with peripheral artery disease (PAD) and intermittent claudication have traditionally used maximal treadmill walking distance as the primary outcome, but the six-minute walk test is increasingly used as a primary outcome in randomized trials of PAD. This study compared relative changes in maximal treadmill walking distance vs. six-minute walk distance in response to a therapeutic intervention or control in randomized trials of PAD participants.

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Disclosures:
There are no conflicts of interest.

METHODS.—Data from four randomized trials of therapeutic interventions in participants with PAD that measured both six-minute walk and treadmill walking performance at baseline and 6-month follow-up were combined. Two trials studied supervised treadmill exercise, one studied home-based walking exercise, and one studied resveratrol.

RESULTS.—Of 467 participants (mean age: 69.8 (standard deviation (SD)=9.7)), mean ankle brachial index was 0.66 (SD= 0.17)). At six-month follow-up, PAD participants randomized to control or placebo significantly declined in six-minute walk distance (−10.2 meters, 95% CI: −18.2,−2.2, p=0.013) but improved maximal treadmill walking distance (+25.7 meters, 95% CI: +6.0,+45.3 meters, P=0.010) (difference between change in six-minute walk vs. maximal treadmill walking distance: −37.3 meters (95% CI: −56.4, −18.2, P<0.001)). Home-based exercise improved six-minute walk distance by 43.2 meters, (95% CI:+28.4,+57.9), while supervised treadmill exercise improved six-minute walk distance by 25.0 meters (95% CI: +14.7,+35.2) (mean difference +18.2 meters favoring home-based exercise (95% CI: +0.2,+36.2 meters, P=0.048)). Among all participants, the presence (vs. absence) of treadmill exercise training was associated with a 141.3 meter greater improvement in maximal treadmill walking distance than in six-minute walk distance ((95% CI: 88.2–194.4, P<0.001), suggesting a benefit from treadmill training on the treadmill outcome.

CONCLUSIONS.—Maximal treadmill walking distance and six-minute walk distance are not interchangeable outcomes in PAD participants. PAD participants randomized to control groups improved treadmill walking distance but simultaneously meaningfully declined in six-minute walk distance. Supervised treadmill exercise training amplified improvement in treadmill walking distance because of a training to the outcome measure phenomenon.

Clinical Trials Registration.—NCT00693940; NCT02246660; NCT01408901; NCT00106327

Table of Contents Summary

In this meta-analysis of randomized trials of interventions for peripheral artery disease (PAD), participants randomized to the control group (no therapeutic interventions) declined in six-minute walk distance over 6-month follow-up, but simultaneously improved their treadmill walking performance. Treadmill walking outcome does not seem to detect the natural history of functional decline over time that is measured by the six-minute walk test, limiting the utility of treadmill testing as a meaningful outcome measure for people with PAD.

INTRODUCTION

Longitudinal observational studies demonstrate that people with lower extremity peripheral artery disease (PAD) have faster decline in six-minute walk and higher rates of mobility loss than people without PAD (1–3). Randomized trials are necessary to identify novel therapies for improving walking performance and preventing functional decline and mobility loss in PAD.

Treadmill walking is commonly used to measure change in walking endurance in therapeutic trials of PAD (4,5). However, six-minute walk distance is increasingly an outcome in randomized trials of participants with PAD (6–13). Since both treadmill testing and the six-minute walk measure walking endurance, they may be expected to improve similarly following therapeutic interventions and to decline similarly among PAD participants randomized to control. However, improved treadmill walking distance has been consistently documented in participants with PAD randomized to the placebo group of randomized trials (4,5). Relative changes in treadmill walking vs. six-minute walk distance in people with PAD randomized to the placebo or control group in randomized trials of people with PAD have not been described to our knowledge.

A disadvantage of treadmill testing, compared to the six-minute walk, is that walking on a moving belt does not reflect walking in daily life, while the six-minute walk is performed in a hall corridor and simulates walking in daily life (14–16). Understanding differences in responsiveness of treadmill vs. six-minute walk testing following therapeutic interventions in people with PAD has important implications for design and interpretation of clinical trials in PAD. This study analyzed data from four randomized trials that collected both six-minute walk and treadmill data at baseline and six-month follow-up to address three objectives: First, to compare the magnitude of change in maximal treadmill walking distance vs. six-minute walk distance in PAD participants randomized to six months of a) control (no intervention); b) supervised treadmill exercise; or c) home-based walking exercise. Second, to compare the degree to which a supervised treadmill exercise intervention vs. a home-based walking exercise intervention improved six-minute walk and maximal treadmill walking distances in PAD. Third, to compare correlations of six-month changes in maximal treadmill walking distance and six-minute walk distance with six-month changes in physical activity and six-month changes in participant perceived walking ability, measured by the walking impairment questionnaire (WIQ) distance score. We hypothesized that: a) among PAD participants randomized to a control group, six-minute walk distance would decline, while treadmill walking distance would improve; b) because of the ‘train to the outcome’ phenomenon, participants randomized to treadmill exercise would improve treadmill walking distance more than six-minute walk distance, relative to the control group; and that c) change in physical activity and change in the WIQ distance score would correlate more closely with change in six-minute walk than change in maximal treadmill distance.

METHODS

Data from four randomized trials of participants with PAD that included both six-minute walk and treadmill testing at baseline and six-month follow-up were combined (10–13). Participants provided written informed consent. The four randomized trials were the Study in Leg Circulation (SILC), the Group Oriented Arterial Leg Study (GOALS), the RESveratrol To Improve Outcomes in older pEople with PAD (RESTORE Trial), and the PROgenitor cell release Plus Exercise to improve functional performance in PAD: (PROPEL Trial) (10–13).

Summary of included trials

Methods for each trial were published (10–13). In SILC, 156 PAD participants were randomized to supervised treadmill exercise, supervised lower extremity resistance training, or attention control for six months. In GOALS, 194 PAD participants were randomized to either an intervention to increase home-based walking exercise or control. In PROPEL, 210

PAD participants were randomized to one of four groups: Supervised treadmill exercise + granulocyte macrophage colony stimulating factor (GM-CSF), supervised treadmill exercise + placebo, GM-CSF + attention control, or placebo + attention control. In RESTORE, 66 PAD participants were randomized to resveratrol-500 mgs, resveratrol-125 mgs, or placebo. Participants randomized to a therapeutic intervention without exercise (i.e. GM-CSF+ attention control or resveratrol) were excluded. Participants in the placebo or control groups from all four studies were included. For therapeutic interventions, only participants randomized to a walking exercise intervention were included.

Participant Identification

In all trials, participants were identified from Chicago-area medical centers, through newspaper or radio advertisements, or from mailings to older people living in the Chicago area (10–13).

Inclusion criteria

All studies had an inclusion criterion of ankle brachial index (ABI) ≤ 0.90 or ABI ≤ 0.95 (10–13,17). In GOALS and PROPEL, potential participants with ABI >0.90 at baseline were eligible, if a hospital-affiliated vascular laboratory report or angiogram demonstrated PAD (11,13). For example, individuals with vascular laboratory evidence of a reduced toe pressure or toe brachial index consistent with PAD were eligible for GOALS or PROPEL. Participants with 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 fifty heel rises at a rate of one per second followed by repeat ABI (18). In RESTORE, potential participants with ABI >0.90 at baseline were eligible if they had documented lower extremity revascularization.

Exclusion criteria

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. SILC, GOALS, and PROPEL excluded potential participants using a walking aid other than a cane. RESTORE excluded potential participants using any walking aid. 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. In the exercise trials, potential participants for whom exercise may be unsafe, including those with an abnormal exercise stress test at baseline, were excluded.

MEASURES

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 as previously described (17,19,20).

Six-Minute Walk Test

Following a standardized protocol (1,6,21), participants walked up and down a 100-foot hallway for 6 minutes. A script was used for instructions to participants. All participants were advised that the goal of the test was to walk as far as possible in the six minutes. The distance completed after 6 minutes was recorded. Among participants with PAD, a small clinically meaningful change was defined as 12 meters and a large clinically meaningful change was defined as 34 meters (22).

Treadmill walking performance

Maximal treadmill walking distance was measured using the Gardner-Skinner protocol (5–8,23). Participants began walking at 2.0 miles per hour at zero percent grade. Grade was increased two percent every two minutes. Participants unable to walk at 2.0 miles/hour began at 0.50 miles per hour (5,10–13,23). Treadmill speed was increased by 0.50 miles/hour every two minutes until 2.0 miles per hour was achieved. Subsequently, grade was increased two percent every two minutes. All participants were advised to walk as far as possible on the treadmill. The same stress test (i.e. Gardner or modified Gardner) was performed at baseline and follow-up.

Physical activity

Physical activity was measured continuously for seven days using a vertical accelerometer (Caltrac, Muscle Dynamics Fitness Network, Inc., Torrance, CA) at baseline and six-month follow-up, according to established methods, yielding “activity units”(24–26).

Leg Symptoms

The presence and characteristics of exertional leg symptoms were measured using the San Diego Claudication Questionnaire (27). Intermittent claudication was defined as exertional calf pain that did not begin at rest and resolved within ten minutes of rest (1,27). Atypical exertional leg symptoms were defined as exertional leg symptoms that did not meet criteria for intermittent claudication (1,27). Participants reporting no exertional leg symptoms were classified as ‘asymptomatic’ (1,27).

Walking Impairment Questionnaire (WIQ) distance score

The WIQ distance score is a PAD-specific measure of patient reported difficulty walking long distances (28). The WIQ distance score is scored on a 0–100 scale (100=best), in which 0 represents the inability to walk even a short distance (across a small room) and 100 represents no difficulty walking long distances up to a mile.

INTERVENTIONS

Supervised treadmill exercise

Participants attended exercise sessions three times weekly with an exercise physiologist (10,13). Participants were encouraged to walk up to 50 minutes/session, not including rest.

Home based walking exercise

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 (11). Participants were helped to exercise five days per week, up to 50 minutes/session.

Supervised Lower Extremity Resistance Training

Participants randomized to resistance training attended three exercise sessions per week. They performed three sets of eight repetitions of knee extension, leg press, leg curls, and squat and toe rise exercises, supervised by a trainer (10).

Attention control sessions and placebo

Attention control groups attended one-hour educational sessions led by faculty members and staff. Topics included nutrition and cancer screening. RESTORE participants randomized to placebo took one placebo pill daily in a double blinded fashion for six months.

Other Measures

Medical history, race, and demographics were obtained using patient report (10,13). Height and weight were measured. Body mass index (BMI) was calculated as weight (kg)/(height (meters))^2.

Statistical analyses

Intention to treat analyses were used. Participants who dropped out of the intervention but returned for follow-up testing were included in analyses.

Correlations between six-minute walk distance and maximal treadmill walking distance were calculated at baseline and six-month follow-up. Correlations in six month change in six-minute walk distance and maximal treadmill walking distance were calculated for participants randomized to home-based exercise, supervised treadmill exercise, or a control group and for these combined groups. Physical activity was correlated with six-minute walk distance and with maximal treadmill walking distance at each time point. Six-month change in physical activity and the WIQ distance score were each correlated with six-month change in six-minute walk distance and maximal treadmill walking distance, respectively. The bootstrap method was used to compare the magnitude of correlations of change in physical activity and WIQ distance score with change in six-minute walk distance vs. change in maximal treadmill walking distance.

The following meta-analyses were performed. First, Gaussian random effects model was used to compare 6-month changes in six-minute walk and maximal treadmill walking distance in PAD participants randomized to the placebo or attention control group from all four trials. Sidik-Jonkman estimators for average change in six-minute walk, treadmill walking distance and their difference were used due to small number of studies in the meta-analysis. Second, 6-month changes in six-minute walk distance and maximal treadmill walking distance were compared between participants randomized to home-based vs. supervised treadmill exercise. Third, six-month changes in maximal treadmill walking distance vs. six-minute walk distance were compared among participants randomized to supervised treadmill exercise and home-based walking exercise, respectively. Fourth, meta regression was conducted to compare the statistical significance of the difference between the 6-month change in six-minute walking distance and 6-month change in treadmill walking distance among participants randomized to supervised treadmill exercise, placebo or attention control, and home-based walking exercise. Within study correlations were accounted for by study-specific random effects in the Meta regression model. All tests were two-sided. A p value < 0.05 was considered statistically significant.

RESULTS

Six hundred and twenty-six participants with PAD were randomized in the four trials and 558 (89%) completed both six-minute walk and treadmill testing at baseline and six-month follow-up (Figure 1). Forty-two participants randomized to resveratrol in RESTORE and 49 randomized to GM-CSF alone in PROPEL were excluded, leaving 467 for analyses. Mean age was 69.8 years (standard deviation (SD) = 9.7). Mean ABI was 0.66 (SD=0.17). Two hundred forty-two (51.8%) participants were men and 238 (51.0%) were African-American (Table 1).

Correlations of six-minute walk distance and maximal treadmill walking distance

Among all participants, correlations between the six-minute walk and treadmill walking distances were 0.616 at baseline and 0.698 at 6-month follow-up (Table 2). The correlation between six-month change in six-minute walk and maximal treadmill walking distance was 0.297.

Six month changes in six-minute walk and maximal treadmill walking distance in the control group

Between baseline and six-month follow-up, participants randomized to a control group, who received no therapeutic interventions, declined by 10.2 meters in six-minute walk distance (P=0.013), but simultaneously improved maximal treadmill walking distance by 25.7 meters despite completing only two treadmill tests (one at baseline and one at follow-up) (Figure 2). These participants increased their treadmill walking distance even though they did not receive any therapeutic interventions between the first and the second treadmill tests. In random effects analysis of participants randomized to a control group, six-minute walk distance declined significantly relative to change in maximal treadmill walking distance (−37.3 meters, 95% CI: − 56.4, −18.2, P<0.001) (Figure 3).

Effects of a home-based walking exercise vs. a supervised treadmill exercise on six-minute walk distance

Between baseline and six-month follow-up, PAD participants randomized to home-based exercise improved their six-minute walk distance by 43.2 meters, compared to 25.0 meters for those randomized to supervised treadmill exercise (Figure 4a). The difference in change in six-minute walk distance in those randomized to home-based vs. supervised treadmill exercise was +18.2 meters favoring home-based exercise (95% CI: +0.2 to +36.2 meters) (P=0.0478).

Effects of a home-based walking exercise vs. supervised treadmill exercise on maximal treadmill walking distance

Between baseline and six-month follow-up, PAD participants randomized to supervised treadmill exercise improved their maximal treadmill walking distance by 234.4 meters compared to 82.4 meters for those randomized to home-based exercise (Figure 4a). (Difference:+152 meters (95% CI: 98.4, 205.6, P<0.001)).

Changes in treadmill vs. six-minute walk distance following supervised and home-based exercise

Following the home-based exercise intervention, maximal treadmill walking distance improved by 39.2 meters more than six minute walk distance (Figure 4b). Following a supervised treadmill exercise, maximal treadmill walking distance improved by 209 meters more than six-minute walk distance.

Effects of treadmill exercise training on change in treadmill walking distance vs. six-minute walk distance

In meta regression analyses including all 467 participants, the presence (vs. absence) of treadmill exercise training was associated with a 141.3 meter greater improvement in maximal treadmill walking distance than six-minute walk distance (95% CI: 88.2–194.4, P<0.001), demonstrating that treadmill training preferentially improved the treadmill walking outcome, relative to six-minute walk distance.

Correlations of change in six-minute walk and treadmill walking distance with change in physical activity and WIQ distance score

In the two randomized trials measuring physical activity, change in six-minute walk was significantly correlated with change in physical activity (correlation=0.306 (P<0.001) and 0.325 (P=0.003) respectively (Table 3)). Change in maximal treadmill walking distance was not correlated with change in physical activity (correlations= 0.100 (P=0.193) and 0.121 (P=0.277), respectively (Table 3)). The correlation of change in physical activity with change in six-minute walk distance was significantly higher than the correlation of change in physical activity with change in maximal treadmill walking distance (P=0.015).

Among participants randomized to an exercise intervention, the WIQ distance score increased from 33.0 (SD-26.2) to 43.9 (SD-29.4) (mean change:+10.9, 95% CI: +7.3,+14.6). Among all participants randomized to a control group, the WIQ distance score increased from 31.9 (SD-24.3) to 35.3 (SD-28.0), (mean change:+3.4, 95% CI:+0.3,+6.4. Correlations of change in WIQ distance score with change in six-minute walk distance were 0.254 (P<0.001) for those randomized to exercise and 0.206 (P<0.01) for those randomized to the control group. Corresponding correlations of change in WIQ distance score with change in maximal treadmill walking distance were 0.122 (P=0.072) and 0.117 (P=0.114), respectively.

Results in participants with and without classical symptoms of intermittent claudication

When results were repeated separately in the participants with vs. without classical symptoms of intermittent claudication at baseline, results were not substantially changed from results for the entire sample (Tables IV and V).

DISCUSSION

In four randomized trials including 467 participants with PAD who completed the six-minute walk and treadmill testing at both baseline and six-month follow-up, there were several important findings. First, PAD participants randomized to a control group declined in six-minute walk distance by 10.2 meters over six-month follow-up, but simultaneously improved maximal treadmill walking distance by 25.7 meters. Results were consistent across the four trials. The 10 meter decline in six-minute walk distance at 6-month follow-up in the control group is only slightly less than the 12 meter decline in six-minute walk distance defined as clinically meaningful for PAD patients (22) and underscores the ability of the six-minute walk test to measure meaningful decline in walking endurance over a short (six month) time period in PAD participants not receiving therapeutic interventions. Second, a home-based walking exercise intervention was associated with significantly greater improvement in six-minute walk distance compared to supervised treadmill exercise. Third, supervised treadmill exercise was associated with significantly greater improvement in maximal treadmill walking distance compared to home-based walking exercise. Fourth, in meta-regression, supervised treadmill exercise was associated with a 141.3 meter greater improvement in maximal treadmill walking distance, compared to six-minute walk, suggesting that treadmill training preferentially improves treadmill walking, likely in part because participants become comfortable with treadmill walking. Fifth, change in physical activity during daily life and change in the WIQ distance score were more closely correlated with change in six-minute walk distance than change in treadmill walking distance. These results demonstrate important differences in the responsiveness of six-minute walk and treadmill walking outcomes in randomized trials involving people with PAD. Six-minute walk test and treadmill testing should not be considered interchangeable measures of walking endurance.

Advantages of treadmill testing include that it takes place in a highly controlled setting and measures maximal capacity and cardiorespiratory fitness in addition to walking endurance (7). However, walking on the treadmill moving belt does not represent walking in daily life, which requires walking on a motionless but often uneven surface and navigating turns. Furthermore, most patients with PAD do not reach maximum cardiorespiratory fitness in their daily walking activity. Compared to treadmill walking, change in six-minute walk distance was more closely associated with participant perception of change in walking ability, measured by change in the WIQ walking distance score. However, correlations of six-minute walk testing with the WIQ distance score were modest. Future study may focus on measures of walking performance that combine participant report and objective measures of walking performance.

Results showing decline in six-minute walk over time and improvement in treadmill walking distance over time in the placebo/control group are consistent with prior study (4,5,13).

However, to our knowledge, no prior studies have analyzed combined results from multiple randomized trials of PAD participants that measured both change in treadmill and six-minute walk distance in the same cohort. Among PAD participants randomized to control/placebo, the 25.7 meter improvement in maximal treadmill walking distance over six-month follow-up contrasted significantly with the 10.2 meter decline in six-minute walk distance in the same participants over the same time period. This difference demonstrates an adaptability to treadmill testing that is not observed for the six-minute walk. It is possible that weak but effective therapeutic interventions may not have sufficient effect on treadmill walking performance to demonstrate efficacy compared to placebo, since even participants with PAD randomized to placebo demonstrated improved treadmill walking performance over time. Consistent with this possibility, a recent randomized trial of 125 mgs of resveratrol demonstrated a 17 meter improvement in six-minute walk distance compared to the control group, but simultaneously demonstrated no improvement in treadmill walking distance relative to the control group (12).

The finding that a home-based walking exercise intervention improved six-minute walk distance more than a treadmill exercise intervention is important, since clinical practice guidelines currently recommend supervised treadmill exercise as first-line therapy for symptomatic PAD patients (Class I), while home based exercise is considered a reasonable alternative to supervised treadmill exercise (Class IIa) (29). Recent conclusions that supervised treadmill exercise is superior to home-based exercise in PAD were based on randomized trials using treadmill testing as the primary outcome (30). The apparent superiority of treadmill exercise over home-based exercise could be explained by the phenomenon of training on the outcome measure that provides greater familiarity with treadmill walking. Findings reported here suggest that home-based walking exercise interventions preferentially improved six-minute walk distance, while supervised treadmill exercise interventions preferentially improve maximal treadmill walking distance.

This study has limitations. First, all included randomized trials were six months in duration. Results may not be generalizable to longer or shorter randomized trials in PAD. Second, results may not be generalizable to PAD patients not eligible to participate in randomized trials included in these analyses. Third, the number of studies included in the meta-analysis was small. Fourth, only one prior study has defined a minimum clinically important change for six-minute walk distance in people with PAD (22).

Conclusions

In conclusion, treadmill testing and six-minute walk results are not interchangeable measures of walking endurance in randomized trials of patients with PAD. Participants randomized to placebo/control, who received no study interventions, declined in six-minute walk distance during six-month follow-up, but simultaneously significantly improved their treadmill walking performance, demonstrating an adaptability to treadmill testing in control groups that may obscure the ability to detect benefits from therapeutic interventions that are not as effective as walking exercise.

Acknowledgments

Sources of Funding:

Funded by the National Heart Lung and Blood Institute (R01HL107510, R01-HL083064, R01-HL73351) and by the National Institute on Aging (R21 AG046510). Also funded by the Jesse Brown VA Medical Center, the Office of Dietary Supplements and by the intramural program at the National Institute on Aging.

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ARTICLE HIGHLIGHTS

TYPE OF RESEARCH.

Meta-analysis of four single-center randomized trials

KEY FINDINGS.

Among 195 patients with peripheral artery disease (PAD), randomized to a control group (no therapy), six-minute walk distance declined by 10.2 meters over the six-month follow-up period, while maximal treadmill walking distance simultaneously improved by 25.7 meters, despite lack of therapy.

TAKE HOME MESSAGE.

Among people with PAD, the treadmill walking outcome does not detect the natural history of functional decline over time that is measured by the six-minute walk test, and this phenomenon limits the utility of treadmill testing as a meaningful outcome measure for people with PAD.

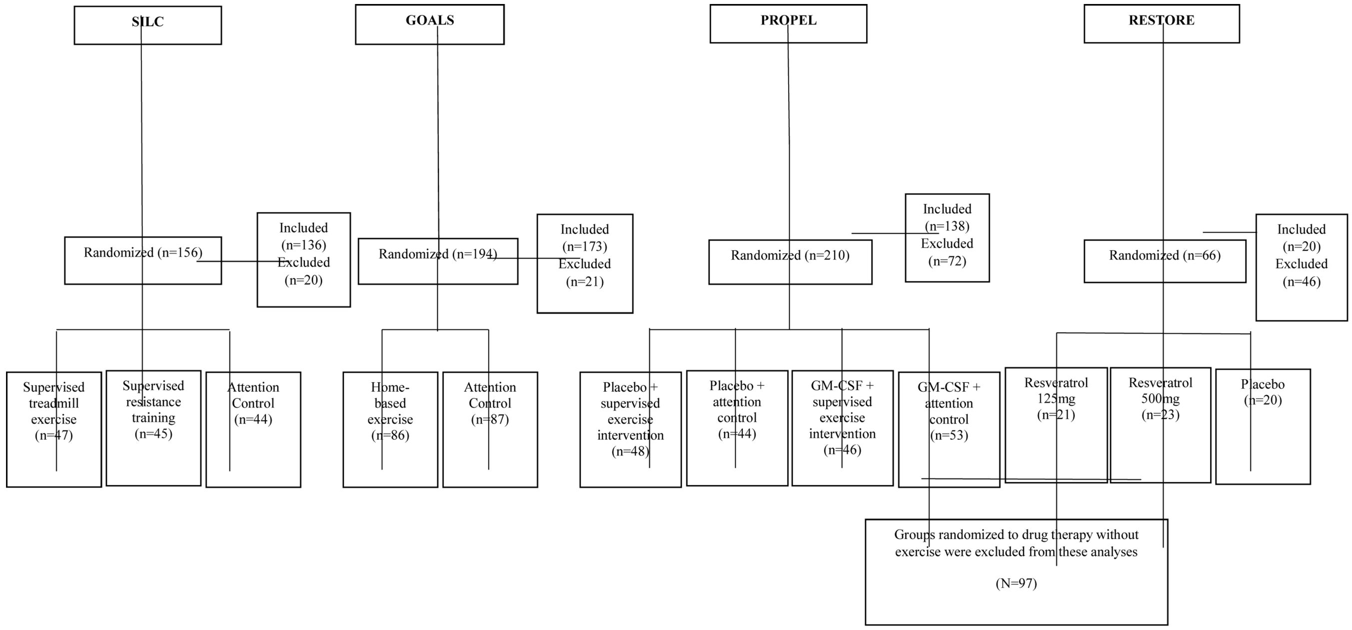


Figure 1.
Overview of included studies and number of participants

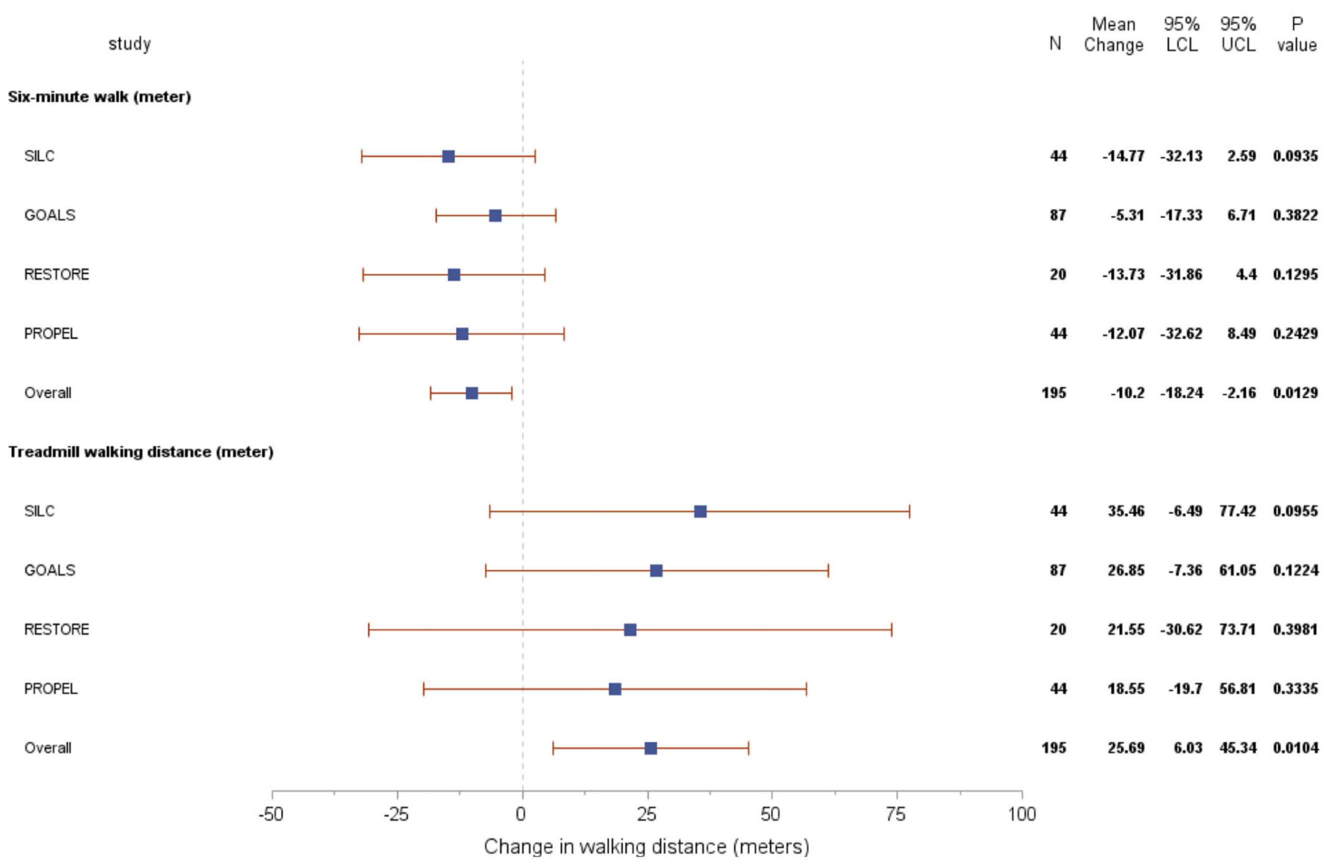


Figure 2A.

Six month absolute changes in six-minute walk distance and treadmill walking performance at six-month follow-up among peripheral artery disease patients randomized to a control group in four randomized clinical trials.

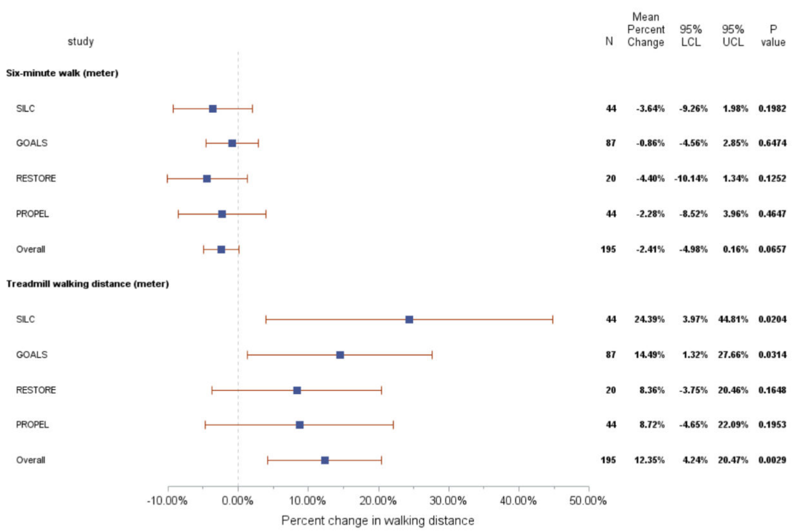
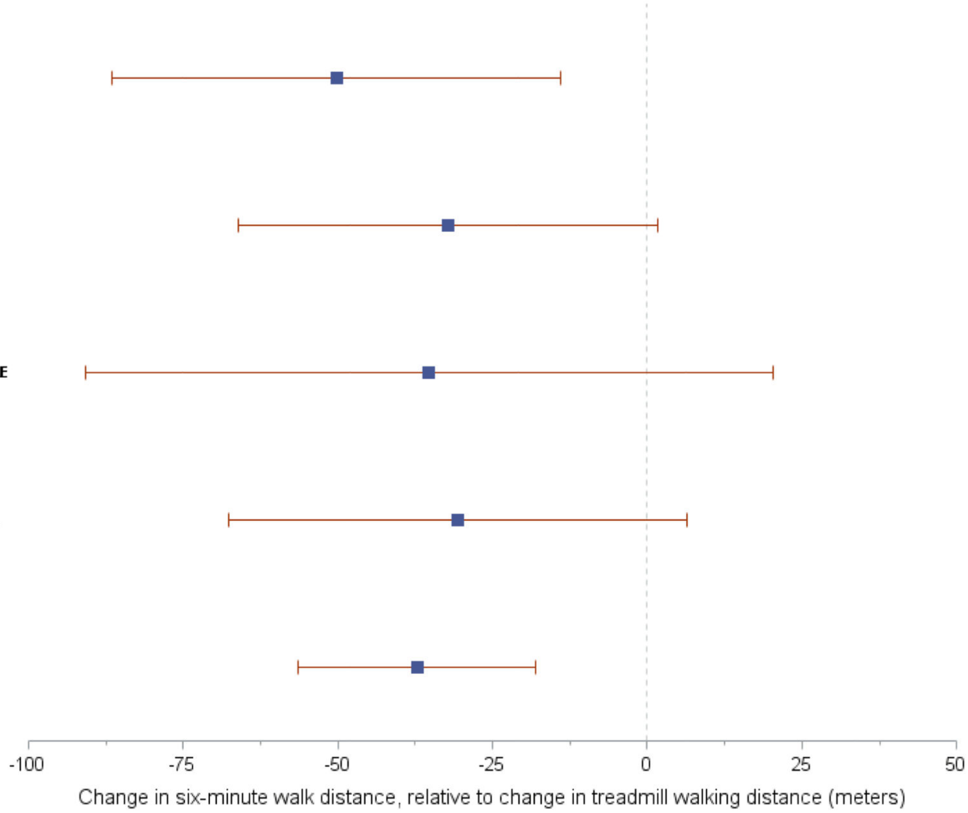


Figure 2B.

Six month percent changes in six-minute walk distance and treadmill walking performance at six-month follow-up among peripheral artery disease patients randomized to a control group in four randomized clinical trials.



study	N	Dif of Change	95% LCL	95% UCL	P value
SILC	44	-50.23	-86.54	-13.93	0.0078
GOALS	87	-32.16	-66.06	1.75	0.0627
RESTORE	20	-35.28	-90.86	20.3	0.1997
PROPEL	44	-30.62	-67.6	6.36	0.1022
Overall	195	-37.25	-56.36	-18.15	0.0001

Figure 3.

Difference in change in six-minute walk and maximal walking distance at 6-month follow-up among peripheral artery disease patients randomized to a control group

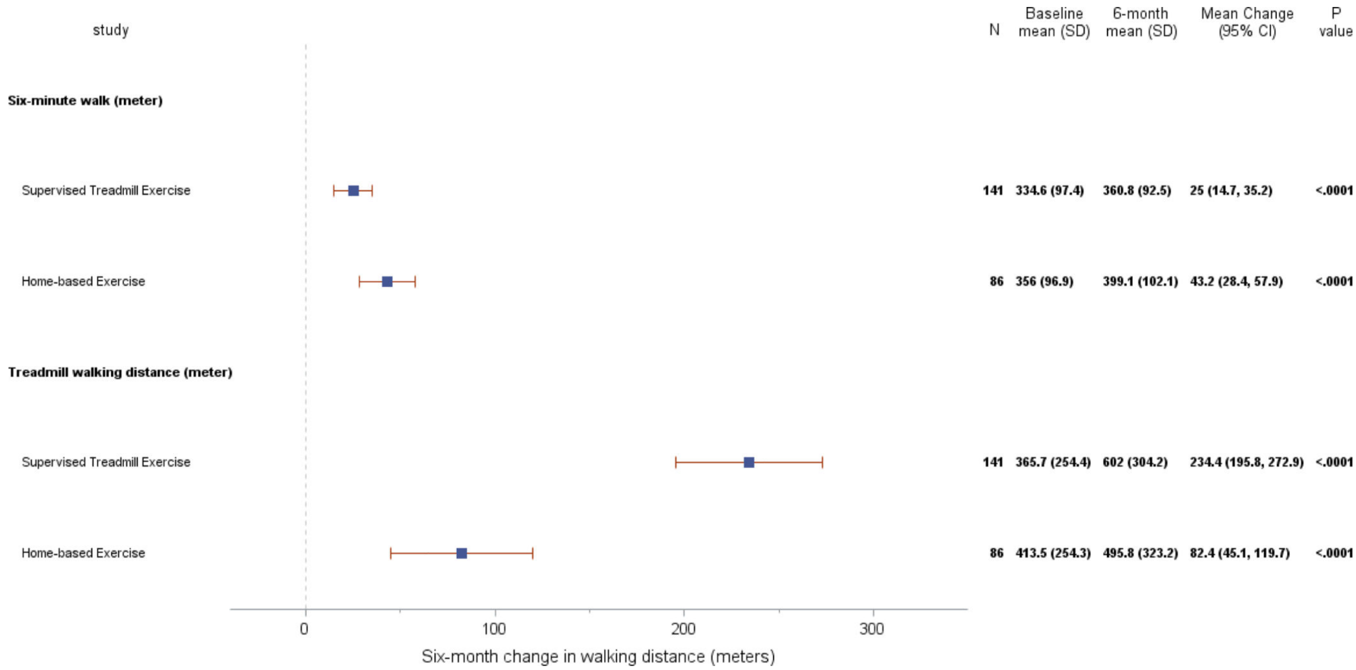


Figure 4a.

Simultaneous changes in six-minute walk distance and treadmill walking performance at 6-month follow-up among PAD participants randomized to either a home-based exercise intervention or a supervised treadmill exercise intervention

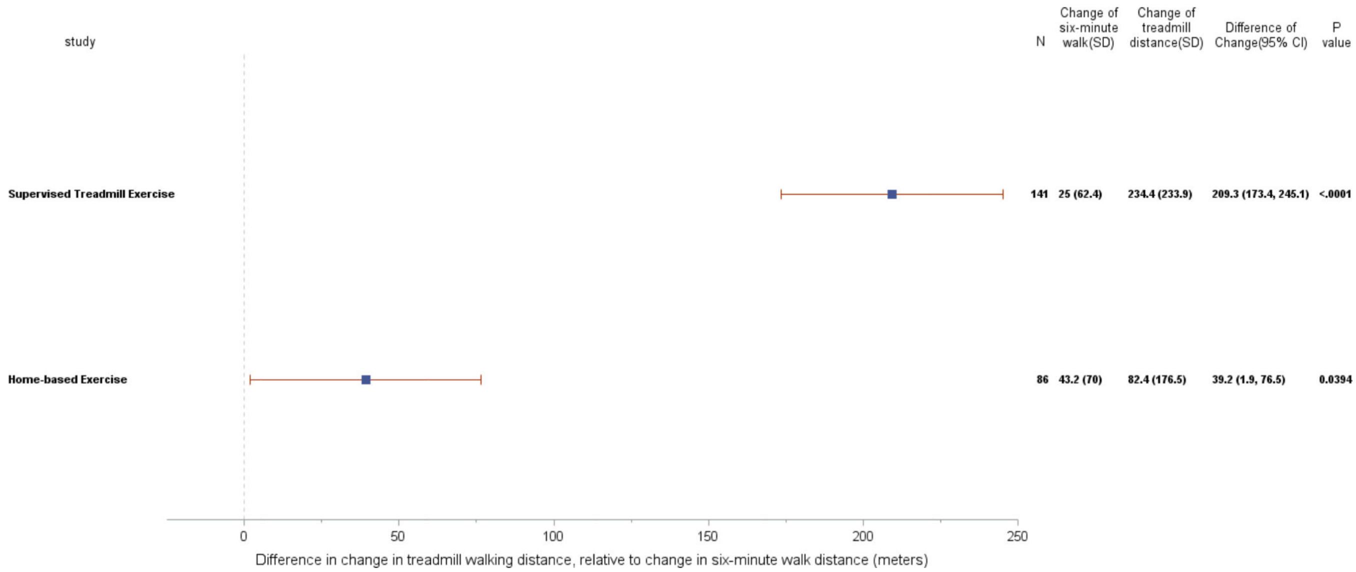


Figure 4b.

Difference in change of six-minute walk distance vs. change in maximal treadmill walking distance in PAD participants randomized to either a supervised treadmill exercise intervention or a home-based exercise intervention.

Table I.

Characteristics of Participants with Peripheral Artery Disease in Randomized Trials that included Six-minute walk and treadmill walking outcomes.

	Overall (N=467)	SILC (N=136)	GOALS (N=173)	RESTORE (N=20)	PROPEL (N=138)
Age	69.8 (9.7)	70.9 (10.3)	70.0 (9.5)	74.4 (6.3)	66.9 (8.9)
Male sex	242 (51.8)	64 (47.1)	87 (50.3)	13 (65.0)	78 (56.5)
Black race	238 (51.0)	56 (41.2)	83 (48.0)	9 (45.0)	90 (65.2)
ABI	0.66 (0.17)	0.60 (0.17)	0.67 (0.17)	0.65 (0.12)	0.68 (0.18)
BMI (Kg/M2)	29.8 (6.5)	29.9 (6.5)	28.9 (6.7)	31.5 (5.0)	30.7 (6.3)
Diabetes	182 (39.0)	56 (41.2)	59 (34.1)	13 (65.0)	54 (39.1)
Angina	73 (15.7)	16 (11.9)	27 (15.6)	4 (20.0)	26 (18.8)
Myocardial infarction	79 (17.0)	26 (19.4)	22 (12.7)	0 (0.0)	31 (22.5)
Heart failure	53 (11.4)	15 (11.2)	19 (11.0)	4 (20.0)	15 (10.9)
Current smoking	120 (25.7)	30 (22.1)	37 (21.4)	4 (20.0)	49 (35.5)
Classical claudication symptoms	152 (32.5)	48 (35.3)	48 (27.8)	6 (30.0)	50 (36.2)
Exertional leg symptoms other than claudication	279 (59.7)	77 (56.6)	110 (63.6)	10 (50.0)	82 (59.4)
No exertional leg symptoms (asymptomatic)	36 (7.7)	11 (8.1)	15 (8.7)	4 (20.0)	6 (4.4)
Baseline six-minute walk	340.0 (93.7)	318.7 (87.7)	355.2 (94.8)	352.8 (72.0)	340.1 (97.5)
Baseline maximal treadmill walking distance	376.9 (241.9)	350.2 (224.6)	403.1 (255.4)	457.4 (250.2)	358.5 (236.6)

Table II.

Six-month changes in six-minute walk and treadmill walking distance among participants with peripheral artery disease in randomized trials

	Control Group			Intervention Group		
	Baseline	**6-month follow-up**	**6-month change**	**Baseline**	**6-month follow-up**	**6-month change**
SILC randomized trial of supervised treadmill exercise						
	N=44			N=47		
Six-minute walk distance (meters)	322.4 (87.1)	307.7 (93.1)	−14.8 (57.1)	326.1 (89.3)	347.3 (80.8)	+21.2 (47.7)
Maximal treadmill walking distance (meters)	328.2 (218.4)	363.6 (234.1)	+35.5 (138.0)	386.6 (250.0)	605.3 (304.4)	+218.7 (203.4)
Correlations between treadmill and 6-minute walk	0.483 P<0.001	0.746 P<0.001	0.510 P<0.001	0.566 P<0.001	0.659 P<0.001	0.145 P=0.3314
GOALS randomized trial of home-based exercise						
	N=87			N=86		
Six-minute walk distance (meters)	354.5 (93.2)	349.2 (102.0)	−5.3 (56.4)	356.0 (96.9)	399.1 (102.1)	+43.2 (69.0)
Maximal treadmill walking distance (meters)	392.9 (257.5)	419.8 (285.5)	+26.8 (160.5)	413.5 (254.3)	495.8 (323.2)	+82.4 (174.0)
Correlations between treadmill and 6-minute walk	0.677 P<0.001	0.730 P<0.001	0.201 P=0.062	0.595 P<0.001	0.669 P<0.001	0.201 P=0.064
RESTORE randomized trial						
	N=20					
Six-minute walk distance (meters)	352.8 (72.0)	339.0 (86.7)	−13.7 (38.7)			
Maximal treadmill walking distance (meters)	457.4 (250.2)	479.0 (262.2)	+21.5 (1115)			
Correlations between treadmill and 6-minute walk	0.684 P<0.001	0.858 P<0.001	−0.021 P=0.932			
PROPEL randomized trial						
	N=44			N=94		
Six-minute walk distance (meters)	342.9 (89.5)	330.8 (96.7)	−12.1 (67.6)	338.8 (101.4)	367.6 (97.5)	+28.8 (66.8)
Maximal treadmill walking distance (meters)	365.3 (187.7)	383.9 (208.1)	+18.6 (125.8)	355.3 (257.2)	600.4 (305.7)	+245.1 (234.3)
Correlations between treadmill and 6-minute walk	0.617 P<0.001	0.705 P<0.001	0.330 P=0.029	0.6500 P<0.001	0.7728 P<0.001	0.3422 P<0.001

All participants randomized**			
	N=467		
	Baseline	**6-month follow-up**	**6-month change**
Six-minute walk distance (meters)	340.0 (93.7)	351.5 (99.7)	11.5 (63.7)
Maximal treadmill walking distance (meters)	376.9 (241.9)	486.4 (293.7)	109.5 (200.3)

All participants randomized**			
	N=467		
	Baseline	**6-month follow-up**	**6-month change**
Correlations between treadmill and 6-minute walk	0.616 P<0.001	0.698 P<0.001	0.297 P<0.001

* Data shown are means (standard deviations).

** Includes participants in SILC randomized to strength training- therefore sample size is greater than the combined sample sizes from other cells in the table.

Table III.

Correlations of changes in six-minute walk vs. treadmill walking performance with physical activity level

	Six-minute walk				Treadmill walking performance		
	Baseline	**6-month follow-up**	**Change**		**Baseline**	**6-month follow-up**	**Change**
GOALS randomized trial (N=171)							
Six-minute walk	355.5 (94.8)	372.8 (104.8)	+17.4 (65.5)	**Treadmill walking performance**	400.5 (255.4)	451.2 (302.2)	+50.7 (166.6)
Physical activity	722.3 (371.5)	752.9 (383.5)	+30.7 (347.3)	**Physical activity**	722.3 (371.5)	752.9 (383.5)	+30.7 (347.3)
Correlations with physical activity	0.456 P<0.001	0.517 P<0.001	0.306 P<0.001	**Correlations with physical activity**	0.419 P<0.001	0.448 P<0.001	0.100 P=0.193
SILC randomized trial (N=83)							
Six-minute walk	329.9 (85.5)	332.1 (88.7)	+2.2 (57.1)	**Treadmill walking performance**	375.1 (238.3)	506.7 (300.5)	+131.6 (204.1)
Physical activity	692.6 (443.1)	762.0 (715.3)	+69.5 (797.7)	**Physical activity**	692.6 (443.1)	762.0 (715.3)	+69.5 (797.7)
Correlations with physical activity	0.200 P=0.070	0.232 P=0.035	0.325 P=0.003	**Correlations with physical activity**	0.187 P=0.090	0.164 P=0.138	0.121 P=0.277

Table IV.

Six-month changes in six-minute walk distance and maximal treadmill walking distance among PAD participants randomized to a control group, according to presence vs. absence of intermittent claudication symptoms

	Participants with intermittent claudication symptoms (N=58)	**Participants without intermittent claudication symptoms (N=137)**
Six month change in six-minute walk distance	−3.0 meters (95% CI: −19.0, +13.0)	−13.3 meters (95% CI: −23.1, −3.4)
Six-month change in maximal treadmill walking distance	+38.7 meters (95% CI: −3.0, +80)	+24.2 meters (95% CI: +1.3, +47.1)
Difference in six month change between six-minute walk distance and maximal treadmill walking distance	−35.9 meters (95% CI:−75, +3.6)	−40.0 meters (95% CI: −63.9, −16.2)

CI = Confidence interval

Table V.

Change in six-minute walk distance and maximal treadmill walking distance following home-based and supervised treadmill exercise interventions, according to presence vs. absence of intermittent claudication

	Classic intermittent claudication			Symptoms other than intermittent claudication		
	Baseline (Meters) Mean (SD)	**6-month follow-up Mean (SD)**	**Change between 6-month follow-up and baseline (meters) Mean (95% CI)**	**Baseline (meters) Mean (SD)**	**6-month follow-up Mean (SD)**	**Change between 6-month follow-up and baseline (meters) Mean (95% CI)**
6-month change in six-minute walk distance among participants randomized to home-based exercise.	341 (97)	395 (108)	+53.6 (+20.3, +86.9)	363 (SD: 97)	401 (100)	+38.4 (+22.5, +54.3)
6-month change in six-minute walk distance among participants randomized to supervised treadmill exercise.	335 (95)	357 (95)	+20.1 (+4.2, +36.1)	335 (SD: 99)	363 (92)	+27.7 (+15.2, +40.2)
6-month change in treadmill walking distance in participants randomized to home-based exercise.	401 (269)	501 (363)	+100 (+35.5, +165.1)	419 (SD: 249)	493 (307)	+74.1 (+27.4, +120.9)
6-month change in treadmill walking distance in participants randomized to supervised treadmill exercise	316 (228)	584 (306)	+246 (+132, +360)	394 (SD: 265)	613 (304)	+218.6 (+171.9, +265.4)

SD = Standard Deviation

CI = Confidence interval