Treadmill Exercise and Resistance Training in Patients With Peripheral Arterial Disease With and Without Intermittent Claudication

A Randomized Controlled Trial

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Context Neither supervised treadmill exercise nor strength training for patients with peripheral arterial disease (PAD) without intermittent claudication have been established as beneficial.

Objective To determine whether supervised treadmill exercise or lower extremity resistance training improve functional performance of patients with PAD with or without claudication.

Design, Setting, and Participants Randomized controlled clinical trial performed at an urban academic medical center between April 1, 2004, and August 8, 2008, involving 156 patients with PAD who were randomly assigned to supervised treadmill exercise, to lower extremity resistance training, or to a control group.

Main Outcome Measures Six-minute walk performance and the short physical performance battery. Secondary outcomes were brachial artery flow-mediated dilation, treadmill walking performance, the Walking Impairment Questionnaire, and the 36-Item Short Form Health Survey physical functioning (SF-36 PF) score.

Results For the 6-minute walk, those in the supervised treadmill exercise group increased their distance walked by 35.9 m (95% confidence interval [CI], 15.3-56.5 m; $P<.001$) compared with the control group, whereas those in the resistance training group increased their distance walked by 12.4 m (95% CI, −8.42 to 33.3 m; $P=.24$) compared with the control group. Neither exercise group improved its short physical performance battery scores. For brachial artery flow-mediated dilation, those in the treadmill group had a mean improvement of 1.53% (95% CI, 0.35%-2.70%; $P=.02$) compared with the control group. The treadmill group had greater increases in maximal treadmill walking time (3.44 minutes; 95% CI, 2.05-4.84 minutes; $P<.001$); walking impairment distance score (10.7; 95% CI, 1.56-19.9; $P=.02$); and SF-36 PF score (7.5; 95% CI, 0.00-15.0; $P=.02$) than the control group. The resistance training group had greater increases in maximal treadmill walking time (1.90 minutes; 95% CI, 0.49-3.31 minutes; $P=.009$); walking impairment scores for distance (6.92; 95% CI, 1.07-12.8; $P=.02$) and stair climbing (10.4; 95% CI, 0.00-20.8; $P=.03$); and SF-36 PF score (7.5; 95% CI, 0.0-15.0; $P=.04$) than the control group.

Conclusions Supervised treadmill training improved 6-minute walk performance, treadmill walking performance, brachial artery flow-mediated dilation, and quality of life but did not improve the short physical performance battery scores of PAD participants with and without intermittent claudication. Lower extremity resistance training improved functional performance measured by treadmill walking, quality of life, and stair climbing ability.

Trial Registration clinicaltrials.gov Identifier: NCT00106327

JAMA. 2009;301(2):165-174 www.jama.com

LOWER EXTREMITY PERIPHERAL ARterial disease (PAD) affects 1 in 16 US adults 40 years or older.[1] Men and women with PAD have greater functional impairment and more rapid rates of functional decline than those who do not have PAD.[2-4]

See also Patient Page.

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Supervised treadmill exercise improves treadmill walking performance in people with PAD who have symptoms of intermittent claudication.[5] However, to what extent such training improves the physical capabilities of those with PAD without symptoms of intermittent claudication remains unanswered. Most patients with PAD do not have classic symptoms of intermittent claudication, either because they are asymptomatic or because they have exertional leg symptoms other than intermittent claudication.[2,6-9] Individuals with PAD who do not have classic intermittent claudication symptoms have comparable or greater functional impairment and functional decline than those without PAD.[2,3,6,9] However, no prior exercise interventions have been tested on PAD participants with and without classic symptoms of intermittent claudication.

Additionally, benefits of lower extremity resistance (strength) training in PAD are unclear. Adults with PAD have smaller calf muscle area and poorer leg strength than those without PAD, and these muscle characteristics are associated with greater functional impairment among people with PAD.[10,11] However, clinical trials of lower extremity resistance training in persons with PAD have been small, have yielded mixed results, and have excluded PAD participants without classic symptoms of intermittent claudication.[12,13]

We performed a randomized controlled clinical trial involving men and women with PAD to address 2 clinical questions. First, we determined whether supervised treadmill exercise improves functional performance and other outcomes among participants with PAD with and without classic intermittent claudication symptoms. Second, we determined whether lower extremity-resistance training improves functional performance and other outcomes in participants with PAD with and without classic intermittent claudication symptoms. Each intervention group was compared with a control group.

METHODS

The institutional review boards of the participating hospitals and medical centers approved the protocol. Participants provided written informed consent.

In this randomized controlled clinical trial, participants were assigned to 1 of 3 groups: a supervised treadmill exercise, supervised lower extremity resistance training, or control group. The resistance training intervention included only lower extremity exercises. Data collection and study interventions were performed at Northwestern University Feinberg School of Medicine between April 1, 2004, and August 19, 2008.

Participant Identification

Eighty-five participants were recruited from newspaper and radio advertisements and 37 from among consecutive patients diagnosed with PAD in the noninvasive vascular laboratories and relevant clinics at Northwestern Memorial Hospital and other Chicago-area hospitals. Previous studies demonstrate that most patients diagnosed with PAD in noninvasive vascular laboratories do not have classic intermittent claudication symptoms.[3,6] Remaining participants were recruited from mailings to Chicago residents 60 years and older, posted flyers, recruitment mailings to people identified with PAD in the Lifeline of Screening program, and community outreach methods.[14]

Inclusion and Exclusion Criteria

The inclusion criterion was an ankle brachial index (ABI) of 0.95 or lower.[15-17] Exclusion criteria were dementia, critical limb ischemia, foot ulcers, major amputation, nursing home residence, inability to walk on a treadmill, inability to exercise at the medical center 3 times weekly, failure to complete exercise run-in sessions, major surgery or a myocardial infarction within the past 3 months, major surgery planned in the next year, current participation in other clinical trials, baseline exercise comparable with that offered in either exercise group, abnormal baseline exercise stress test, walking limitation from a cause other than PAD, poorly controlled hypertension, and a baseline short physical performance battery score of 12 (ie, maximal possible score).

ABI Measurement

A handheld Doppler probe (Nicolet Vascular Pocket Dop II; Nicolet Biomedical Inc, Golden, Colorado) was used to obtain systolic pressures in the right and left brachial, dorsalis pedis, and posterior tibial arteries.[2,3,18] Each pressure was measured twice. The ABI was calculated by dividing the mean of the dorsalis pedis and posterior tibial pressures in each leg by the mean of the 4 brachial pressures.[18] Average pressures in the arm with the highest pressure were used when 1 brachial pressure was higher than the opposite brachial pressure in both measurement sets and the 2 brachial pressures differed by 10 mm Hg or higher in 1 measurement set.[19]

Medical History

Medical history, race, and demographics were obtained using patient report.[20] Race data were obtained to determine whether black participants were equally distributed across the 3 study groups. Prior study indicates that among persons with PAD, blacks have poorer functional performance than whites.[21]

Leg Symptoms

Leg symptoms were characterized using the San Diego claudication questionnaire.[22] Intermittent claudication was defined as exertional calf pain that does not begin at rest, causes the participant to stop walking, and resolves within 10 minutes of rest.[21] Participants without intermittent claudication were either asymptomatic (ie, no exertional leg symptoms) or had exertional leg symptoms not consistent with intermittent claudication.[22]

Outcomes

Outcomes were measured before randomization and at the 6-month follow-

up. Examiners were blinded to participant group assignment. The 2 prespecified primary outcomes were the 6-minute walk test and the short physical performance battery. The 6-minute walk was a primary outcome because persons with PAD are primarily limited in walking endurance.[2,3,6] Treadmill walking performance was not a primary outcome because treadmill performance is susceptible to a learning effect[23] and participants randomized to treadmill exercise practiced treadmill walking during exercise sessions. Furthermore, corridor walking such as that measured in the 6-minute walk may better represent community walking performance than treadmill walking.[19,24-26] The short physical performance battery is a functional performance measure that depends on leg strength and balance,[27,28] which were targets of the lower extremity resistance training intervention. Lower short physical performance battery scores are associated with increased mobility loss among persons with PAD.[4]

Secondary outcomes were brachial artery flow mediated dilation and physical activity. Exploratory outcomes were treadmill walking performance, quality of life, and leg strength.

Six-Minute Walk. Following a standardized protocol,[2-4,6,29] participants walk up and down a 100-foot hallway for 6 minutes after instructions to cover as much distance as possible. The distance completed after 6 minutes was recorded. The intraclass correlation coefficient for test retest reliability of the 6-minute walk was 0.90 ($P < .001$) among 155 PAD participants in our laboratory who completed 2 tests 1 to 2 weeks apart.

Short Physical Performance Battery. The short physical performance battery combines data from usual paced 4-m walking velocity, time to rise and stand from a seated position 5 times, and standing balance.[4,27,28] Individuals receive a score of 0 for each task they are unable to complete. Scores of 1 to 4 are assigned for remaining tasks, according to established methods.[4,27,28] Scores are summed to obtain the short physical performance battery, ranging from 0 to 12.[22,23] Test retest reliability of the short physical performance battery was 0.77 ($P < .001$) among 151 PAD participants in our laboratory who completed 2 tests 1 to 2 weeks apart.

Repeated Chair Rises. Participants sit in a straight-backed chair with arms folded across their chest and stand 5 times consecutively as quickly as possible. Time to complete 5 chair rises is measured.[27,28]

Standing Balance. Participants are asked to hold 3 increasingly difficult standing positions for 10 seconds each: the side-by-side stand, semi-tandem stand (standing with feet parallel and the heel of 1 foot touching the base of the first toe of the opposite foot), and the full-tandem stand (standing with 1 foot directly in front of the other).[27,28] Scores range from 0 (unable to hold the side-by-side stand for 10 seconds) to 4 (able to hold the full-tandem stand for 10 seconds).[27,28]

Four-Meter Walking Velocity. Walking velocity was measured with a 4-meter walk performed at usual pace, according to previously described methods.[2-4,22,23] To account for possible learning effects, we measured the short physical performance battery and 6-minute walk at 2 separate baseline visits, approximately 1 to 2 weeks apart. Performance at the second visit was used as the baseline value. However, 5 participants had the short physical performance battery measured at only 1 baseline visit and their first (only) score was used as their baseline value.

Brachial Artery Flow-Mediated Dilation. Brachial artery flow-mediated dilation was measured after a 12-hour fast by trained registered diagnostic cardiac sonographers, using standard procedures.[30,31] Participants were instructed to hold medications and not exercise or smoke prior to testing. Participants whose brachial systolic pressure differed by more than15 mm Hg between the right and left arms, those with a radical mastectomy, and those with a history of Raynaud phenomenon were excluded from flow-mediated dilation testing. The proximal brachial artery was imaged (B-mode and Doppler) using a linear array vascular ultrasound transducer (Sequoia Model 256, Siemens Medical Solutions, Hoffman Estates, Illinois; frequency, 8 MHz; range, 5-8 MHz). A blood pressure cuff proximal to the visualized brachial artery segment was inflated for 4 minutes at 50 mm Hg above systolic pressure. Longitudinal images of the brachial artery and Doppler blood flow were obtained 60 seconds after cuff deflation.[30] Images were interpreted by a single reader at the University of Wisconsin Atherosclerosis Imaging Research Program Core Laboratory, using established standards.[31] Measurement reproducibility in the core laboratory has a median flow-mediated dilation difference of 0.02% (interquartile range, –0.03 to 0.04) on blinded repeated readings.

Physical Activity. Habitual physical activity was measured objectively over 7 days using a vertical accelerometer (Caltrac, Muscle Dynamics Fitness Network, Inc, Torrance, California) according to established methods, yielding activity units.[32-34]

Treadmill Walking Performance. Maximal treadmill walking time and time to onset of ischemic leg symptoms were measured using the Gardner-Skinner protocol.[23,35] This protocol has a coefficient of variation of approximately 12% in persons with PAD.[23,35]

Quality of Life. The Walking Impairment Questionnaire is a PAD-specific measure of self-reported walking limitations with 3 domains: walking distance, walking speed, and stair climbing.[36] Each domain is scored on a 0 to 100 scale, for which 0 represents the most extreme limitation and 100 represents no difficulty walking long distances, walking rapidly, or climbing 3 stair flights, respectively.[36] We used the Medical Outcomes Study Short-Form 36 (SF-36) to assess functional status in the physical functioning domain.[37]

Strength Measures. Maximum isometric knee extension and plantar

flexion strength were measured in newtons over 6 seconds with a computerized strength chair (Good Strength Chair, Metitur Oy, Jyvasklya, Finland).[11,38] Two trials were performed, and the maximum was used in analyses.[11] The Good Strength Chair has high test retest reliability (Pearson product moment correlations, 0.88-0.96).[38] Knee extension power was measured in watts using the Nottingham power rig.[11,39]

Other Measures. Height and weight were measured at baseline. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.[2]

Randomization and Study Interventions

After baseline testing, eligible participants were randomized by computer using a randomly permuted block method. Randomization was stratified by the presence vs absence of intermittent claudication.

The supervised treadmill exercise intervention consisted of treadmill exercise 3 times a week for 24 weeks, supervised by an exercise physiologist. Participants began with 15 minutes of exercise and increased to 40 minutes by week 8. Initial treadmill walking speed was 2.0 mph per hour or lower if the participant was unable to keep that pace. Between weeks 8 and 24, attempts to increase exercise intensity were made at least weekly either by increasing treadmill speed or by increasing the treadmill grade. Participants with leg symptoms were encouraged to exercise to near maximal leg symptoms. Asymptomatic participants were encouraged to exercise to a level of 12 to 14 (moderately hard) on the Borg rating of perceived exertion scale.[40]

Supervised Lower Extremity Resistance Training. Participants in the lower extremity resistance training group exercised 3 times a week for 24 weeks with a certified trainer. Participants performed 3 sets of 8 repetitions of knee extension, leg press, and leg curl exercises using standard equipment. For each exercise, the 1 repetition maximum (1 rm) was measured at baseline and subsequently every 4 weeks. Participants began exercising at 50% of their 1 rm. Weights were increased over the first 5 weeks until participants were lifting 80% of their 1 rm. Weights were adjusted after each monthly 1 rm and as needed to achieve an exercise intensity of a rating of perceived exertion of 12 to 14. Participants also performed 3 sets of 8 repetitions of squat and toe rise exercises. The toe rise exercises were plantar extension exercises, in which participants assumed a tip-toe position and lowered themselves 8 times consecutively.

Control. Those in the control group participated in 11 nutritional information sessions over 6 months. The 1-hour sessions were intended to provide regular contact with participants in the control group. Session topics included nutritional supplements, healthful restaurant eating, and increasing fruit and vegetable consumption. Sessions were led by registered dieticians but were not designed to change behavior.

Sample-Size Calculations

Power calculations assumed that 50 participants in each group would complete 6-month follow-up and that 2 separate 2-sample *t* tests using a 2-sided α of .05 would be conducted. The study was designed to have 80% power to detect a difference of 30 m change in the 6-minute walk distance and a difference of 0.97 change in the short physical performance battery between baseline and 6-month follow-up between each exercise and control group. These differences represent clinically meaningful change in study outcomes.[41] Power analyses assumed pooled standard deviations of 54 m and 1.74 units, respectively. Because the number of participants who actually completed 6-month follow-up testing was slightly lower, power was reduced to 0.76 to 0.79 for comparisons of each exercise group with the control group.

Statistical Analyses

χ^2 Tests and 1-way analyses of variance were used to compare characteristics of participants across the 3 groups at baseline. Two sample, 2-sided *t* tests were used to compare changes in outcomes between baseline and 6-month follow-up between each exercise group and the control group, respectively, without adjustments for multiple comparisons. A priori, the *P* value considered statistically significant was $P < .05$. Because of skewed distributions for quality-of-life measures and brachial artery flow-mediated dilation, differences in median values for these outcomes were compared using Kruskal-Wallis analysis of variance and Wilcoxon rank sum tests, with Hodges-Lehman 95% confidence intervals (CIs) computed for between-group differences.[42]

Intention-to-treat analyses were performed.[43] Analyses were repeated using multiple imputation for persons who died or dropped out before completing 6-month follow-up testing.[44,45] The multiple imputation for missing 6-month data was performed using SAS Proc MI (SAS Institute Inc, Cary, North Carolina) to obtain 5 imputed data sets. Results were combined using Proc Combine. Variables used to impute data sets included age, ABI, BMI, sex, race, smoking status, baseline outcome values, leg symptoms, and comorbidities. Imputations were performed with and without 4 participants: 2 who died, 1 diagnosed with end-stage renal disease, and 1 diagnosed with lung cancer. Analyses were performed using SAS computer software version 9.2.

RESULTS

Of 1009 potential participants who scheduled a baseline visit, 263 failed to show for their appointment and 261 had an ABI higher than 0.95. Of the remaining 485, there were 329 who met an exclusion criterion, leaving 156 eligible participants (FIGURE). Among those who scheduled a baseline visit, the average age of randomized vs nonrandomized participants was

73.73 vs 70.62 ($P=.002$). Randomized vs nonrandomized participants included 52% vs 46% women ($P=.17$) and 39.7% vs 36.0% blacks ($P=.37$). There were no differences in baseline characteristics across the 3 groups (TABLE 1).

Among participants in the treadmill exercise, resistance training, and control groups, median session attendance rates were 85%, 92%, and 100%, and 6-month follow-up data were obtained in 98%, 89%, and 91%, respectively. Two participants (1 in the resistance training group and 1 in the control group) died from cancer before the 6-month follow-up.

Primary Outcomes

For the 6-minute walk, those in the supervised treadmill exercise group increased their distance from baseline by a mean of 20.9 m vs those in the control group whose distance decreased from baseline by a mean of –15.0 m, for a mean increase of 35.9 m between groups (95% CI, 15.32-56.54 m; $P<.001$). Participants in the lower extremity resistance training group did not experience change in their 6-minute walk performance compared with the control group (12.4 m, 95% CI, –8.42 to 33.25 m; $P=.24$)(TABLE 2).

There were no differences in change in short physical performance battery score between the treadmill exercise and control groups or between the resistance training and the control groups at the 6-month follow-up (Table 2). Results for primary outcomes were not substantially changed when analyses were repeated using multiple imputation methods with and without the 4 participants with extreme outcomes (death or serious illness). Similarly, results were not substantially changed when analyses were repeated substituting baseline values for the 6-month follow-up time point for participants who did not return for follow-up, with and without exclusion of the 4 participants with extreme outcomes. Findings would be unchanged with multiple comparison adjustment ($P<.025$).

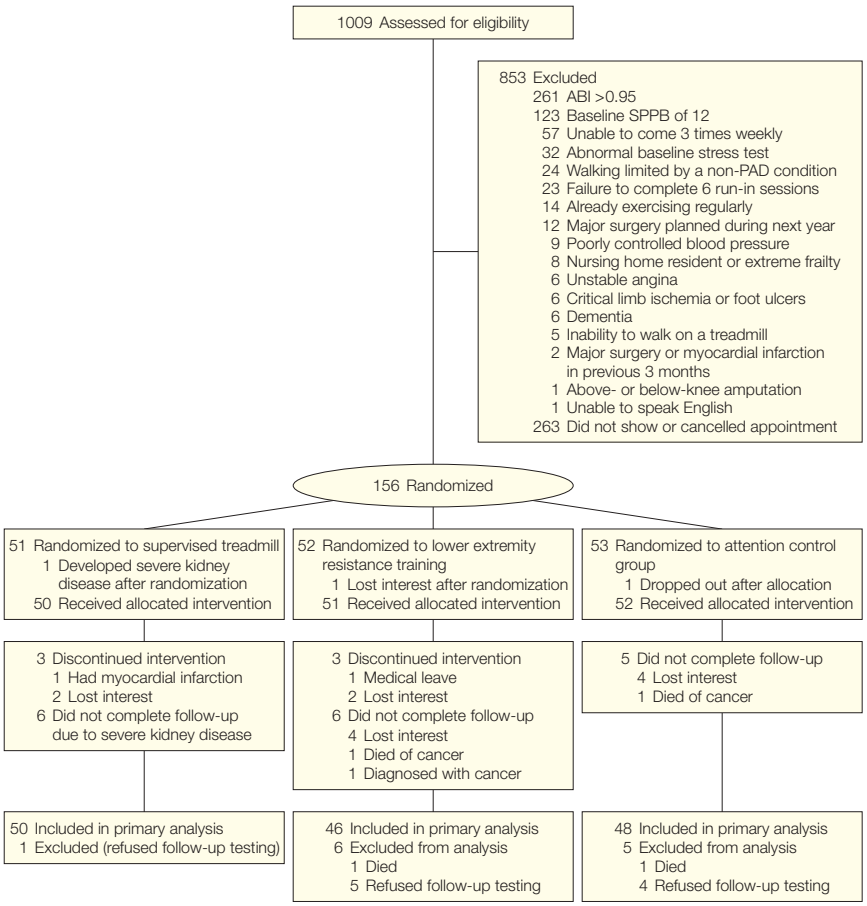
Secondary Outcomes

One hundred-one participants met inclusion criteria for brachial artery flow-mediated dilation testing and adhered to requirements for testing. At the 6-month follow-up, participants in the treadmill exercise group had more favorable changes in brachial arterial flow-mediated dilation than the control group (1.53%; 95% CI, 0.35%-2.70%; $P=.02$ and 0.06 mm; 95% CI, 0.00-0.11 mm; $P=.04$). Changes in brachial artery flow-mediated dilation among participants in the resistance training group were not different from the control group (Table 2). At the 6-month follow-up, there were no differences in changes in accelerometer-measured physical activity in either exercise group compared with the control group (Table 2).

Exploratory Outcomes

Participants in the treadmill exercise and in the resistance training groups each had significantly greater increases in mean maximum treadmill walking time at the 6-month follow-up, than the control group (3.44 minutes, 95% CI, 2.05-4.84 minutes; $P<.001$ for the treadmill group and 1.90 minutes, 95% CI, 0.49-3.31 minutes, $P=.009$ for the resistance training group; TABLE 3). Participants in the

Figure. Study Participation and Follow-up Rates Among Participants in the Study to Improve Leg Circulation



Fifty-two individuals either attended the control sessions or received a make-up packet in the mail and a telephone call. Eleven individuals did not attend any control sessions but did receive a make-up packet and telephone call; 4 of these individuals did not complete the follow-up. ABI indicates ankle-brachial index, SPPB, short physical performance battery.

treadmill exercise group had greater mean increases in treadmill time to onset of ischemic leg symptoms than the control group (1.65 minutes; 95% CI, 0.34-2.95; $P=.01$; Table 3). Similarly, the treadmill exercise group had significantly greater mean improvement in their SF-36 physical functioning score (7.50; 95% CI, 0.00-15.0; $P=.02$) and in their walking impairment distance score (10.7; 95% CI, 1.56-19.9; $P=.02$) than the control group (Table 3). The resistance training group had greater mean improvement in their SF-36 physical functioning score (7.50; 95% CI, 0.00-15.0; $P=.04$) and in their walking impairment distance (6.92; 95% CI, 1.07-12.8; $P=.02$) and stair climbing scores (10.4; 95% CI, 0.00-20.8; $P=.03$) than the control group (Table 3).

Participants in the treadmill group did not have greater improvement in any leg strength measure at 6 months than the control group (Table 3). The resistance training group improved isometric knee extension strength compared with the control group (mean, 80.2 N; 95% CI, 36.8-124 N, $P<.001$; Table 3).

Associations of treadmill exercise with greater absolute change in brachial artery flow-mediated dilation and associations of lower extremity resistance training with improved SF-36 physical functioning score compared with the control group would not be statistically significant after multiple comparison adjustment at $P<.025$.

The study was not designed to have statistical power for comparing differences in outcomes between the 2 exercise groups. However, the treadmill exercise group had greater increases in the 6-minute walk distance (23.5 m; 95% CI, 2.8-44.2 m; $P=.03$) and in the maximum treadmill walking time (1.54 minutes; 95% CI, 0.17-2.92 minutes; $P=.03$) compared with the resistance group. Participants in the resistance group experienced greater increases in knee extension isometric strength (83.5 N; 95% CI, 39.4-127.6 N; $P<.001$) and in knee extension power (14.4 W; 95% CI, 1.43-27.4 W; $P=.03$) compared with the treadmill exercise group.

The study also was not designed to have statistical power for comparing differences in outcomes between different leg symptom groups. The magnitude of change for our primary outcomes was reasonably similar between participants with vs without intermittent claudication and between asymptomatic participants vs symptomatic participants (data not shown).

Several adverse events occurred related to study participation. One participant had a cardiac arrest during treadmill exercise, 4 months after randomization. The participant was successfully resuscitated and hospitalized. The patient did not have a myocardial infarction but was found to have nonobstructive coronary disease and did not

Table 1. Baseline Characteristics of Study Participants in the Study to Improve Leg Circulation

	Treadmill Walking Exercise (n = 51)	Lower Extremity Resistance Training (n = 52)	Control Group (n = 53)	*P* Value[a]
Age, mean (SD), y	71.7 (8.7)	71.7 (8.7)	68.5 (11.9)	.19
Female sex, No. (%)	27 (52.9)	26 (50.0)	28 (52.8)	.94
Black, No. (%)	21 (41.2)	15 (28.9)	26 (49.1)	.10
Intermittent claudication, No. (%)	12 (23.5)	9 (17.3)	8 (15.1)	.52
Ankle brachial index, mean (SD)	0.60 (0.18)	0.62 (0.15)	0.60 (0.18)	.89
Diabetes mellitus, No. (%)	20 (39.2)	24 (46.2)	25 (48.1)	.64
Current smoker, No. (%)	11 (21.6)	9 (17.3)	17 (32.1)	.19
BMI	30.4 (6.2)	30.4 (7.0)	29.9 (7.1)	.92
Statin use, No. (%)	34 (66.7)	33 (63.5)	31 (58.5)	.68
Baseline performance on study outcomes, mean (SD)				
6-Minute walk performance, m	327.8 (87.0)	304.5 (92.9)	316.6 (83.2)	.40
Short physical performance battery	9.2 (2.1)	8.4 (2.3)	8.5 (2.7)	.24
Treadmill performance, mean (SD)				
Maximum walking distance, min	7.68 (4.64)	7.15 (3.57)	6.69 (4.02)	.43
Distance to onset of leg symptoms, m	160 (135)	152 (111)	144 (114)	.82
Walking impairment score, mean (SD)				
Distance	26.0 (19.1)	27.7 (27.9)	30.5 (24.0)	.66
Speed	32.1 (22.9)	23.7 (21.1)	27.9 (18.0)	.14
Stair climbing	41.0 (24.7)	35.9 (25.5)	42.2 (24.9)	.41
Short-form 36 physical functioning score	40.5 (19.4)	37.2 (19.0)	42.6 (18.9)	.37
Brachial artery				
Baseline diameter, mm	4.5 (0.8)	4.4 (0.7)	4.4 (0.7)	.95
Relative FMD-60 s, %	5.4 (4.2)	6.0 (4.8)	6.1 (4.0)	.71
Absolute FMD-60 s, mm	0.23 (0.16)	0.25 (0.20)	0.26 (0.17)	.69

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; FMD, flow-mediated dilation.
[a] *P* value represents the overall comparison between the 3 study groups.

have an inducible arrhythmia on electrophysiological testing. He was discharged home on medical therapy but experienced persistent memory loss. Another participant randomized to the treadmill exercise group developed chest pain during an exercise session. A subsequent coronary catheterization revealed coronary atherosclerosis without a flow-limiting lesion. The participant was treated medically and returned to exercise. A third participant fell during the follow-up 6-minute walk test and fractured her arm. A fourth participant with a history of prior ankle injury developed severe ankle pain after a run-in resistance training session. The participant could not exercise for several weeks, until the ankle pain resolved. He was ultimately randomized to treadmill exercise and completed the trial uneventfully.

COMMENT

This randomized controlled clinical trial demonstrates that a 6-month supervised treadmill exercise intervention increases walking endurance, measured by the 6-minute walk and treadmill walking performance, in patients with PAD both with and without classic intermittent claudication symptoms. Supervised treadmill exercise also increased brachial arterial flow-

Table 2. Associations of Supervised Treadmill Exercise and Lower Extremity Resistance Training With Primary and Secondary Study Outcomes in Peripheral Arterial Disease Participants With and Without Intermittent Claudication

Outcome Measures	No. of Participants	Baseline Value	Six-Month, Value	Within-Group Changes, Mean (95% CI)	Between-Group Comparison vs Control Group, Mean (95% CI)	Pair-Wise *P* Value	*P* Value
Primary Outcome Measures							
6-Minute walk, mean (SD), m							
Control	47	320 (87)	305 (93)	−15.02 (−29.7 to −0.37)	NA	NA	<.001
Strength	46	311 (90)	309 (89)	−2.60 (−17.42 to 12.21)	12.42 (−8.42 to 33.25)	.24	
Treadmill	48	327 (89)	348 (80)	20.9 (6.41 to 35.4)	35.93 (15.32 to 56.54)	<.001	
SPPB[a]							
Control	48	8.44 (2.77)	8.98 (2.98)	0.54 (0.02 to 1.06)	NA	NA	.82
Strength	46	8.54 (2.25)	9.09 (2.73)	0.54 (0.02 to 1.07)	0 (−0.74 to 0.74)	>.99	
Treadmill	50	9.12 (2.06)	9.46 (2.00)	0.34 (−0.17 to 0.85)	−0.20 (−0.93 to 0.52)	.58	
6-Minute walk change, mean (SE), m							
Control	53	317 (12.1)	300 (12.3)	−16.46 (−31.00 to −1.93)	15.00 (−5.46 to 35.45)[b]	.15	.01
Strength	52	304 (12.2)	303 (12.3)	−1.47 (−15.70 to 12.76)	36.20 (15.32 to 57.09)[c]	<.001	
Treadmill	51	328 (12.3)	348 (12.4)	19.74 (5.44 to 34.04)	21.21 (0.81 to 41.61)[d]	.04	
SPPB change, mean (SE)							
Control	53	8.53 (0.33)	8.94 (0.36)	0.41 (−0.09 to 0.91)	0.13 (−0.59 to 0.85)[b]	.72	.07
Strength	52	8.42 (0.33)	8.97 (0.37)	0.54 (0.03 to 1.05)	−0.14 (−0.85 to 0.58)[c]	.71	
Treadmill	51	9.16 (0.33)	9.43 (0.37)	0.27 (−0.23 to 0.78)	−0.27 (−0.98 to 0.45)[d]	.46	
Secondary Outcome Measures							
Relative change in brachial artery FMD 60 s after cuff release, median (IQR),%[e]							
Control	28	5.97 (3.80 to 8.91)	5.28 (3.60 to 7.44)	−0.86 (−2.86 to 0.60)	NA	NA	.07
Strength	36	4.89 (2.59 to 9.24)	6.13 (2.20 to 8.37)	0.11 (−2.03 to 1.33)	0.90 (−0.58 to 2.37)	.23	
Treadmill	37	5.54 (3.09 to 6.87)	5.39 (3.27 to 8.16)	0.70 (−0.77 to 1.82)	1.53 (0.35 to 2.70)	.02	
Absolute change in brachial artery FMD 60 s after cuff release, median (IQR), mm[e]							
Control	28	0.29 (0.16 to 0.40)	0.24 (0.17 to 0.34)	−0.04 (−0.11 to 0.03)	NA	NA	.14
Strength	36	0.22 (0.11 to 0.37)	0.27 (0.10 to 0.35)	0.02 (−0.09 to 0.06)	0.04 (−0.03 to 0.10)	.22	
Treadmill	37	0.24 (0.17 to 0.29)	0.23 (0.15 to 0.32)	0.02 (−0.05 to 0.07)	0.06 (0.00 to 0.11)	.04	
Physical activity, mean (SD), units							
Control	41	702 (530)	689 (441)	−12.85 (−226 to 200)	NA	NA	.49
Strength	37	578 (391)	529 (353)	−49.03 (−274 to 175)	−36.17 (−346 to 273)	.82	
Treadmill	46	658 (317)	780 (869)	122 (−79.55 to 323)	135 (−159 to 428)	.37	

Abbreviations: CI, confidence interval; FMD, flow-mediated dilation; IQR, interquartile range; NA, not applicable; SPPB, Short Physical Performance Battery.
[a]The score ranges from 0 to 12 with 12 indicating the best score.
[b]Compares strength with control.
[c]Compares treadmill with control.
[d]Compares treadmill with strength.
[e]Within group changes for brachial artery flow mediated diameter are median changes (Hodges-Lehmann CI).

mediated dilation and improved quality of life. A 6-month lower extremity resistance training intervention did not improve 6-minute walk distance in PAD participants. However, resistance training improved maximal treadmill walking time and quality-of-life measures, particularly stair climbing ability. Supervised treadmill exercise was associated with greater increases in 6-minute walk performance than the resistance-training group.

To our knowledge, this is the first randomized controlled clinical trial of exercise in PAD to include participants with and without classic symptoms of intermittent claudication. Most patients with PAD do not have classic intermittent claudication symptoms.[6-9] Results reported herein indicate that clinicians should recommend supervised treadmill exercise to PAD patients, with or without classic symptoms of intermittent claudication. To our knowledge, this is also the first randomized controlled clinical trial to demonstrate that supervised tread-

Table 3. Associations of Supervised Treadmill Exercise and Lower Extremity Resistance Training With Exploratory Outcome Measures in Peripheral Arterial Disease Participants With and Without Intermittent Claudication

Outcome Measures, by Group	No. of Participants	Baseline[a]	6 Months[a]	Within-Group Changes (95% CI)[a]	Between-Group Changes vs Control Group (95% CI)[a]	Pair-Wise *P* Value	*P* Value
Maximal treadmill walking time, mean (SD), min							
Control	44	6.69 (4.02)	7.20 (4.01)	0.51 (–0.49 to 1.52)	NA	NA	<.001
Strength	46	7.15 (3.57)	9.56 (4.06)	2.41 (1.43 to 3.40)	1.90 (0.49 to 3.31)	.009	
Treadmill	48	7.68 (4.64)	11.6 (5.57)	3.96 (2.99 to 4.92)	3.44 (2.05 to 4.84)	<.001	
Treadmill time to onset of leg symptom, mean (SD), min							
Control	33	2.42 (1.68)	3.67 (3.21)	1.25 (0.31 to 2.19)	NA	NA	.05
Strength	37	3.19 (1.98)	5.10 (2.62)	1.91 (1.03 to 2.80)	0.66 (–0.63 to 1.95)	.31	
Treadmill	35	2.64 (2.07)	5.53 (3.22)	2.90 (1.99 to 3.81)	1.65 (0.34 to 2.95)	.01	
Short-form 36 physical functioning score, mean (IQR)							
Control	40	42.5 (30.0 to 55.0)	45.0 (32.5 to 55.0)	5.00 (–5.00 to 15.0)	NA	NA	.04
Strength	40	35.0 (22.5 to 52.5)	50.0 (25.0 to 65.0)	10.0 (0.00 to 17.5)	7.50 (0.00 to 15.0)	.04	
Treadmill	46	35.0 (25.0 to 50.0)	52.5 (40.0 to 70.0)	10.0 (0.00 to 30.0)	7.50 (0.00 to 15.0)	.02	
Walking impairment questionnaire, mean (IQR)							
Distance score							
Control	34	26.6 (11.6 to 43.5)	28.1 (12.1 to 46.7)	0.25 (–6.39 to 9.16)	NA	NA	.02
Strength	43	18.5 (3.98 to 46.8)	26.5 (10.5 to 62.8)	8.52 (0.00 to 17.0)	6.92 (1.07 to 12.8)	.03	
Treadmill	41	20.1 (10.2 to 36.1)	37.1 (16.9 to 65.9)	9.94 (–0.21 to 25.0)	10.7 (1.56 to 19.9)	.02	
Speed							
Control	36	25.0 (10.9 to 35.9)	27.7 (15.8 to 46.7)	0.00 (–5.43 to 17.9)	NA	NA	.66
Strength	42	19.6 (6.52 to 37.0)	27.2 (10.9 to 43.5)	4.34 (–3.26 to 18.5)	1.63 (–5.43 to 8.70)	.55	
Treadmill	44	25.0 (15.8 to 45.1)	40.8 (25.4 to 54.3)	10.3 (–3.80 to 21.7)	3.80 (–4.35 to 12.0)	.39	
Stair climbing							
Control	37	41.7 (16.7 to 66.7)	41.7 (16.7 to 66.7)	0.00 (–12.5 to 8.33)	NA	NA	.04
Strength	42	29.2 (16.7 to 45.8)	43.8 (25.0 to 66.7)	12.5 (0.00 to 25.0)	10.4 (0.00 to 20.8)	.02	
Treadmill	42	39.6 (20.8 to 50.0)	43.8 (29.2 to 66.7)	4.17 (0.00 to 25.0)	8.33 (0.00 to 16.7)	.06	
Knee extension isometric strength, mean (SD), N							
Control	30	296 (141)	310 (114)	14.7 (–15.1 to 44.6)	NA	NA	<.001
Strength	27	232 (104)	326 (142)	94.9 (63.4 to 126)	80.2 (36.8 to 124)	<.001	
Treadmill	28	274 (100)	286 (114)	11.4 (–19.5 to 42.3)	–3.32 (–46.3 to 39.7)	.88	
Knee extension power, mean (SD), W							
Control	41	92.9 (59.0)	98.5 (62.0)	5.63 (–4.13 to 15.4)	NA	NA	.09
Strength	45	84.4 (51.4)	100.2 (58.5)	15.8 (6.50 to 25.1)	10.2 (–3.32 to 23.7)	.14	
Treadmill	48	101.8 (48.3)	103.2 (49.4)	1.42 (–7.61 to 10.4)	–4.22 (–17.5 to 9.09)	.53	
Plantarflexion isometric strength, mean (SD), N							
Control	30	301 (116)	379 (151)	78.2 (15.9 to 140)	NA	NA	.69
Strength	29	318 (176)	435 (202)	117 (53.7 to 180)	38.8 (–50.0 to 128)	.39	
Treadmill	29	336 (167)	435 (161)	98.7 (35.4 to 162)	20.6 (–68.2 to 110)	.65	

Abbreviations: CI, confidence interval; IQR, interquartile range; NA, not applicable.
[a]Within-group changes for the short-form 36 physical functioning score and the walking impairment questionnaire scores are median changes (Hodges-Lehmann CI).

mill exercise improves brachial artery flow-mediated dilation in persons with PAD. Patients with PAD typically have severe systemic atherosclerosis and poorer endothelial function than patients without PAD.[46] Among persons with PAD, poorer brachial arterial flow-mediated dilation is associated with higher cardiovascular event rates.[47,48] Our findings suggest that supervised treadmill exercise confers a favorable systemic vascular effect that may reduce cardiovascular events in persons with PAD.

Reasons for lack of improvement in the short physical performance battery in either exercise group are unclear. Balance and leg strength are important determinants of the short physical performance battery score. Our results suggest that treadmill exercise does not improve balance and leg strength significantly. One potential explanation for the lack of improvement in the short physical performance battery in the resistance-training group is that baseline leg strength was relatively high in our cohort.[49] Resistance training may more effectively improve components of the short physical performance battery in persons with poorer baseline strength. The poorer test retest reliability of the short physical performance battery compared with the 6-minute walk may also make meaningful change in the short physical performance battery more difficult to achieve.

Despite their associations with improved walking performance, the exercise interventions did not increase accelerometer-measured physical activity during daily life. Interventions specifically targeted to physical activity behavior may be necessary to increase daily physical activity in persons with PAD.

This study has several limitations. First, our exclusion criterion of the maximum short physical performance battery score of 12 and the relatively large proportion of potential participants who were unwilling to attend on-site exercise sessions 3 times a week reduces the generalizability of our findings. Second, missing data at follow-up were more common in more frail participants. However, sensitivity analyses demonstrated that these missing data are not likely to have significantly altered our findings. Third, median session attendance rates varied from 85% for the treadmill exercise group to 100% for the control sessions. This difference may have influenced results. Fourth, because of additional exclusion criteria for flow-mediated dilation and patient refusal to adhere to test requirements, the sample size for the flow-mediated dilation measurement was lower than that for the entire cohort. Sample sizes for secondary and exploratory outcomes were smaller than for the primary outcomes. Finally, the sample size was not large enough to allow meaningful comparisons in outcomes between categories of leg symptoms.

Based on findings reported in this trial, physicians should recommend supervised treadmill exercise programs for PAD patients, regardless of whether they have classic symptoms of intermittent claudication. Our findings regarding brachial artery flow-mediated dilation suggest that supervised treadmill exercise improves global vascular health in patients with PAD. Lower extremity resistance training improves treadmill walking performance and quality of life, particularly stair climbing, in patients with PAD with and without intermittent claudication.

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Obtained funding: McDermott, Liu, Criqui.
Administrative, technical, or material support: Ades, Van Horn, Garside, Domanchuk, Stein, Green.
Study supervision: McDermott, Garside, McPherson, Laing, McCarthy, Criqui.
Financial Disclosures: Dr McDermott reports having received consulting fees and honoraria from educational activities from Sanofi-Avantis and Bristol-Myers Squibb; otherwise, no other financial conflicts were reported.
Funding/Support: Supported by grants R01-HL073551 from the National Heart, Lung, and Blood Institute and by RR-00048 from the National Center for Research Resources, National Institutes of Health. This was also supported in part by the Intramural Research Program, National Institutes on Aging.
Role of the Sponsor: The funding agency played no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.
Disclaimer: Dr McDermott, a *JAMA* contributing editor, was not involved in the review of or decision to publish this article.

REFERENCES

1. Allison MA, Ho E, Denenberg JO, et al. Ethnic-specific prevalence of peripheral arterial disease in the United States. *Am J Prev Med*. 2007;32(4):328-333.
2. McDermott MM, Greenland P, Liu K, et al. The ankle brachial index is associated with leg function and physical activity: the Walking and Leg Circulation Study. *Ann Intern Med*. 2002;136(12):873-883.
3. McDermott MM, Liu K, Greenland P, et al. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. *JAMA*. 2004;292(4):453-461.
4. McDermott MM, Guralnik J, Ferrucci L, Liu K, Liao Y, Criqui M. Baseline functional performance predicts the rate of mobility loss in persons with peripheral arterial disease. *J Am Coll Cardiol*. 2007;50(10):974-982.
5. Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain: a meta-analysis. *JAMA*. 1995;274(12):975-980.
6. McDermott MM, Greenland P, Liu K, et al. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. *JAMA*. 2001;286(13):1599-1606.
7. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA*. 2001;286(11):1317-1324.
8. Wang JC, Criqui MH, Denenberg JO, McDermott MM, Golomb BA, Fronek A. Exertional leg pain in pa-

tients with and without peripheral arterial disease. *Circulation*. 2005;112(22):3501-3508.
9. McDermott MM, Fried L, Simonsick E, Ling S, Guralnik JM. Asymptomatic peripheral arterial disease is independently associated with impaired lower extremity functioning: the Women's Health and Aging Study. *Circulation*. 2000;101(9):1007-1012.
10. McDermott MM, Hoff F, Ferrucci L, et al. Lower extremity ischemia, calf skeletal muscle characteristics, and functional impairment in peripheral arterial disease. *J Am Geriatr Soc*. 2007;55(3):400-406.
11. McDermott MM, Tian L, Ferrucci L, et al. Associations between lower extremity ischemia, upper and lower extremity strength, and functional impairment in peripheral arterial disease. *J Am Geriatr Soc*. 2008; 56(4):724-729.
12. McGuigan MRM, Bronks R, Newton RU, et al. Resistance training in patients with peripheral arterial disease: effects on myosin isoforms, fiber type distribution, and capillary supply to skeletal muscle. *J Gerontol A Biol Sci Med Sci*. 2001;56(7):B302-B310.
13. Hiatt WR, Wolfel EE, Meier RH, Regensteiner JG. Superiority of treadmill walking exercise versus strength training for patients with peripheral arterial disease. *Circulation*. 1994;90(4):1866-1874.
14. McDermott MM, Domanchuk K, Dyer A, Ades P, Kibbe M, Criqui MH. Recruiting participants with peripheral arterial disease for clinical trials: Experience from the Study to Improve Leg Circulation (SILC). *J Vasc Surg*. In Press.
15. Yao ST, Hobbs JT, Irvine WT. Ankle systolic pressure measurements in arterial disease affecting the lower extremities. *Br J Surg*. 1969;56(9):676-679.
16. Ouriel K, Zarins CK. Doppler ankle pressure: an evaluation of three methods of expression. *Arch Surg*. 1982;117(10):1297-1300.
17. Fowkes FGR, Murray GD, Butcher C, et al; Ankle Brachial Index Collaboration. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events. *JAMA*. 2008;300(2):197-198.
18. McDermott MM, Criqui MH, Liu K, et al. Lower ankle/brachial index, as calculated by averaging the dorsalis pedis and posterior tibial arterial pressures, and association with leg functioning in peripheral arterial disease. *J Vasc Surg*. 2000;32(6):1164-1171.
19. Shadman R, Criqui MH, Bundens WP, et al. Subclavian artery stenosis: prevalence, risk factors, and association with cardiovascular diseases. *J Am Coll Cardiol*. 2004;44(3):618-623.
20. McDermott MM, Ades P, Dyer A, et al. Corridor-based functional performance measures correlate better with physical activity during daily life than treadmill measures in persons with peripheral arterial disease. *J Vasc Surg*. 2008;48(1):1231-1237.
21. Rucker-Whitaker C, Greenland P, Liu K, et al. Peripheral arterial disease in African Americans: clinical characteristics, leg symptoms, and lower extremity functioning. *J Am Geriatr Soc*. 2004;52(6):922-930.
22. Criqui MH, Denenberg JO, Bird CE, Fronek A, Klauber MR, Langer RD. The correlation between symptoms and non-invasive test results in patients referred for peripheral arterial disease testing. *Vasc Med*. 1996;1(1):65-71.
23. Gardner AW, Skinner JS, Cantwell BW, Smith LK. Progressive vs single-stage treadmill tests for evaluation of claudication. *Med Sci Sports Exerc*. 1991; 23(4):402-408.
24. Greig C, Butler F, Skelton D, Mahmud S, Young A. Treadmill walking in old age may not reproduce the real life situation. *J Am Geriatr Soc*. 1993;41(1): 15-18.
25. Swerts PMJ, Mostert R, Wouters EFM. Comparison of corridor and treadmill walking in patients with severe chronic obstructive pulmonary disease. *Phys Ther*. 1990;70(7):439-442.
26. Peeters P, Mets T. The 6-minute walk as an appropriate exercise test in elderly patients with chronic heart failure. *J Gerontol A Biol Sci Med Sci*. 1996; 51(4):M147-M151.
27. Guralnik JM, Ferrucci L, Simonsick E, Salive ME, Wallace RB. Lower extremity function in persons over 70 years as a predictor of subsequent disability. *N Engl J Med*. 1995;332(9):556-561.
28. Guralnik JM, Ferrucci L, Pieper CF, et al. Lower extremity function and subsequent disability: Consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *J Gerontol A Biol Sci Med Sci*. 2000; 55(4):M221-M231.
29. Montgomery PS, Gardner AW. The clinical utility of a six-minute walk test in peripheral arterial occlusive disease patients. *J Am Geriatr Soc*. 1998; 46(6):706-711.
30. Corretti MC, Anderson TJ, Benjamin EJ, et al; International Brachial Artery Reactivity Task Force. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol*. 2002;39 (2):257-265.
31. Gottdiener JS, Bednarz J, Devereux RM, et al; American Society of Echocardiography. American Society of Echocardiography's recommendations for use of echocardiography. *J Am Soc Echocardiogr*. 2004; 17(10):1086-1119.
32. McDermott MM, Liu K, O'Brien E, et al. Measuring physical activity in peripheral arterial disease: a comparison of two physical activity questionnaires with an accelerometer. *Angiology*. 2000;51(2): 91-100.
33. McDermott MM, Ohlmiller SM, Liu K, et al. Gait alterations associated with walking impairment in people with peripheral arterial disease with and without intermittent claudication. *J Am Geriatr Soc*. 2001; 49(6):747-754.
34. Garg PK, Tian L, Criqui MH, et al. Physical activity during daily life and mortality in patients with peripheral arterial disease. *Circulation*. 2006;114 (3):242-248.
35. Hiatt WR, Regensteiner JG, Hargarten ME, Wolfel EE, Brass EP. Benefit of exercise conditioning for patients with peripheral arterial disease. *Circulation*. 1990; 81(2):602-609.
36. Regensteiner JG, Steiner JF, Panzer RJ, et al. Evaluation of walking impairment by questionnaire in patients with peripheral arterial disease. *J Vasc Med Biol*. 1990;2:142-152.
37. Ware JE, Snow KK, Kosinski M, et al. *SF-36 Health Survey: Manual and Interpretation Guide*. Boston, Mass: The Health Institute, New England Medical Center; 1993.
38. Curb JD, Ceria-Ulep CD, Rodriguez BL, et al. Performance-based measures of physical function for high-function populations. *J Am Geriatr Soc*. 2006; 54(5):737-742.
39. Bassey EJ, Short AH. A new method for measuring power output in a single leg extension: feasibility, reliability, and validity. *Eur J Appl Physiol Occup Physiol*. 1990;60(5):385-390.
40. Noble BJ. Clinical applications of perceived exertion. *Med Sci Sports Exerc*. 1982;14(5):406-411.
41. Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. *J Am Geriatr Soc*. 2006;54(5):743-749.
42. Hollander M, Wolfe DA. *Nonparametric Statistical Methods*. New York, NY: John Wiley & Sons Inc; 1973.
43. Altman DG, Schulz KF, Egger M, et al; CONSORT Group. The Revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med*. 2001;134(8):663-694.
44. Raghunathan TE. What do we do with missing data? some options for analysis of incomplete data. *Annu Rev Public Health*. 2004;25:99-117.
45. Harel O, Zhou XH. Multiple imputation: review of theory, implementation, and software. *Stat Med*. 2007;26(16):3057-3077.
46. Harris LM, Faggioli GL, Shah R, et al. Vascular reactivity in patients with peripheral vascular disease. *Am J Cardiol*. 1995;76(3):207-212.
47. Philpott A, Anderson TJ. Reactive hyperemia and cardiovascular risk. *Arterioscler Thromb Vasc Biol*. 2007;27(10):2065-2067.
48. Gokce N, Keaney JF Jr, Hunter LM, Watkins MT, Menzoian JO, Vita JA. Risk stratification for postoperative cardiovascular events via noninvasive assessment of endothelial function: a prospective study. *Circulation*. 2002;105(13):1567-1572.
49. Rantanen T, Guralnik JM, Ferrucci L, Leveille S, Fried LP. Coimpairments: strength and balance as predictors of severe walking disability. *J Gerontol A Biol Sci Med Sci*. 1999;54(4):M172-M176.

