

Step-Monitored Home Exercise Improves Ambulation, Vascular Function, and Inflammation in Symptomatic Patients With Peripheral Artery Disease: A Randomized Controlled Trial

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Background—This prospective, randomized, controlled clinical trial compared changes in primary outcome measures of claudication onset time (COT) and peak walking time (PWT), and secondary outcomes of submaximal exercise performance, daily ambulatory activity, vascular function, inflammation, and calf muscle hemoglobin oxygen saturation (StO₂) in patients with symptomatic peripheral artery disease (PAD) following new exercise training using a step watch (NEXT Step) home-exercise program, a supervised exercise program, and an attention-control group.

Methods and Results—One hundred eighty patients were randomized. The NEXT Step program and the supervised exercise program consisted of intermittent walking to mild-to-moderate claudication pain for 12 weeks, whereas the controls performed light resistance training. Change scores for COT ($P<0.001$), PWT ($P<0.001$), 6-minute walk distance ($P=0.028$), daily average cadence ($P=0.011$), time to minimum calf muscle StO₂ during exercise ($P=0.025$), large-artery elasticity index (LAEI) ($P=0.012$), and high-sensitivity C-reactive protein (hsCRP) ($P=0.041$) were significantly different among the 3 groups. Both the NEXT Step home program and the supervised exercise program demonstrated a significant increase from baseline in COT, PWT, 6-minute walk distance, daily average cadence, and time to minimum calf StO₂. Only the NEXT Step home group had improvements from baseline in LAEI, and hsCRP ($P<0.05$).

Conclusions—NEXT Step home exercise utilizing minimal staff supervision has low attrition, high adherence, and is efficacious in improving COT and PWT, as well as secondary outcomes of submaximal exercise performance, daily ambulatory activity, vascular function, inflammation, and calf muscle StO₂ in symptomatic patients with PAD.

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Peripheral artery disease (PAD) is a highly prevalent,¹ costly,² and deadly condition.³ PAD is prevalent in 202 million people worldwide, and affects 15% to 20% of

individuals over 70 years of age.¹ The medical significance of PAD is rapidly growing, as the global prevalence of PAD increased by 23.5% from 2000 to 2010,¹ and is associated with elevated risk of cardiovascular mortality. Furthermore, the annual costs paid by Medicare related to PAD is \$3.9 billion in the United States alone,² and this cost is expected to increase dramatically in the future. Development of leg symptoms further complicates the clinical course of PAD, resulting in ambulatory dysfunction.^{4,5}

Supervised exercise therapy is a primary treatment for symptomatic PAD,⁶ but is limited because few programs exist, only a small percentage of patients can feasibly attend, and reimbursement is not provided by Medicare. We were the first to demonstrate that an approach for new exercise training using a step watch (NEXT Step) in a home-based setting was efficacious for improving claudication onset time (COT), peak walking time (PWT), and daily ambulatory activity.⁷ The NEXT Step exercise program performed in the community setting

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has numerous advantages from the perspective of both the patients and the clinical staff, as less time, effort, and resources are required to conduct home-based exercise. This study was designed to build upon our previous work⁷ by examining the efficacy of the NEXT Step home-exercise program that was less frequently monitored.

This prospective, randomized, controlled clinical trial compared changes in the primary outcome measures of COT and PWT, as well as secondary outcomes of submaximal exercise performance, daily ambulatory activity, vascular function, inflammation, and calf muscle hemoglobin oxygen saturation (StO₂) in symptomatic patients with PAD following the NEXT Step home-exercise program, a supervised exercise program, and an attention-control group who performed light resistance training exercise.

Methods

Patients

Approval and informed consent

The institutional review board at the University of Oklahoma Health Sciences Center, and the Research and Development committee at the Oklahoma City VA Medical Center approved the procedures of this study. Written informed consent was obtained from each patient at the beginning of investigation.

Recruitment

Patients participated in the study from October 2006 to July 2012. Patients were recruited from vascular labs and vascular clinics from the University of Oklahoma Health Sciences Center and the Oklahoma City VA Medical Center.

Medical Screening Through History and Physical Examination

Patients were evaluated in the morning at the Clinical Research Center, at the University of Oklahoma Health Sciences Center. Patients arrived fasted, but were permitted to take their usual medications. To begin the study visit, patients were evaluated with a medical history and physical examination in which demographic information, height, weight, waist circumference, cardiovascular risk factors, comorbid conditions, claudication history, ankle/brachial index (ABI), blood samples, and a list of current medications were obtained.

Inclusion and exclusion criteria

Patients with symptomatic PAD were included in this study if they met the following criteria: (1) a history of ambulatory leg pain; (2) ambulatory leg pain confirmed by treadmill exercise⁴;

and (3) an ABI \leq 0.90⁸ at rest or \leq 0.73 after exercise.⁹ Patients were excluded for the following conditions: (1) absence of PAD (ABI $>$ 0.90 at rest and ABI $>$ 0.73 after exercise); (2) noncompressible vessels (ABI \geq 1.40); (3) asymptomatic PAD; (4) use of medications indicated for the treatment of claudication (cilostazol or pentoxifylline) initiated within 3 months prior to investigation; (5) exercise limited by other diseases or conditions; (6) active cancer; (7) end-stage renal disease defined as stage 5 chronic kidney disease; (8) abnormal liver function; and (9) failure to complete the baseline run-in phase within 3 weeks. Patient flow in the study is shown in Figure.

Interventions

NEXT Step Home-Exercise Rehabilitation Program

We used a step activity monitor (StepWatch3™; OrthoInnovations, Inc, Oklahoma City, OK) to accurately record the duration and cadence of ambulation.⁷ This program consisted of 3 months of intermittent walking to mild-to-moderate claudication pain 3 days per week at a self-selected pace, in which exercise duration was progressively increased from 20 to 45 minutes per session. Intensity of walking, expressed as metabolic equivalents, was determined by first converting cadence of each home-based exercise session to an average speed of walking, and then estimating oxygen uptake from walking speed to calculate metabolic equivalents minutes, a measure of exercise volume, as previously described.⁷ Patients wore the step activity monitor during each exercise session, and returned the monitor and a logbook to the research staff at the end of week 1, 4, 8, and 12. During these brief 15-minute meetings, monitor data were downloaded, results were reviewed, and feedback was provided for the upcoming month of training. These meetings were less frequent than the biweekly meetings in our previous study to see whether the program could be successfully performed with even less intervention from the research staff. The total contact time that staff spent with each patient during the 4 study visits in the NEXT Step home exercise program was \approx 1 hour, with only several additional minutes being required at the end of the final baseline test visit prior to beginning the program to instruct patients how to properly use and wear the step activity monitor.

Supervised Exercise Rehabilitation Program

Exercise sessions in our supervised exercise program were performed while wearing a step activity monitor, as previously described.⁷ Briefly, the supervised program consisted of 3 months of intermittent treadmill walking to mild-to-moderate claudication pain 3 days per week at a speed of \approx 2 mph and at a grade equal to 40% of the highest work load achieved during the baseline maximal treadmill test. Exercise sessions

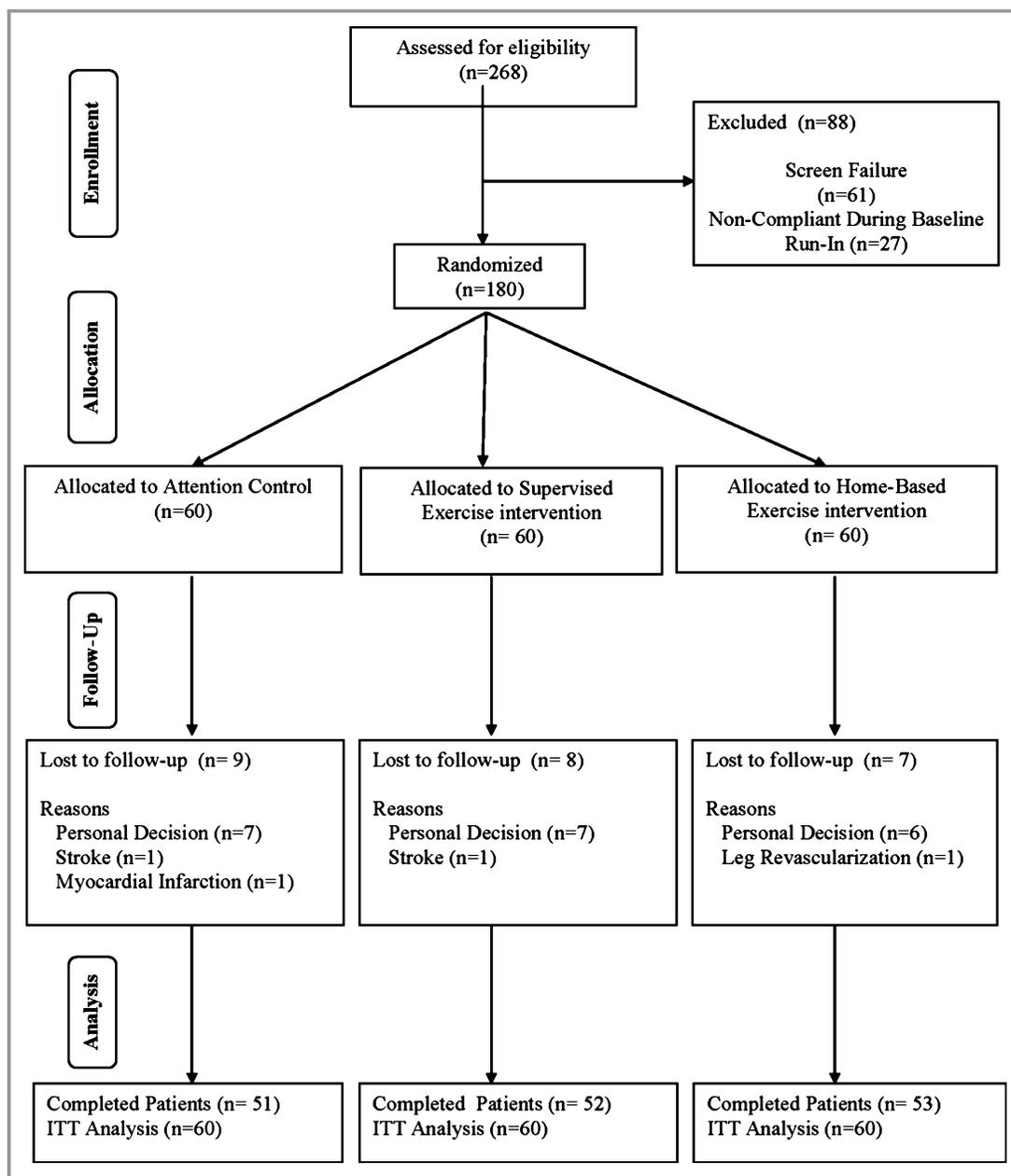


Figure. Consolidated standards of reporting trials (CONSORT) flow diagram of patients through the trial. ITT indicates intent-to-treat.

progressively increased during the program from 15 to 40 minutes. To quantify volume of exercise performed, expressed as metabolic equivalents minutes, the intensity of each exercise training session was determined by using the oxygen uptake value obtained during the baseline maximal treadmill test that corresponded to the exercise training grade, as previously described.⁷

Attention-Control, Light Resistance Program

Light resistance training was performed 3 times per week, without any walking exercise, using a Pro-Form Fusion 6.0 LX

weight system. On entry, the resistance that caused fatigue in various muscle groups after 15 repetitions (15-rep maximum) was established, and was reassessed each month. The resistance training phase consisted of performing upper extremity exercises that included the bench press, military press, butterfly, biceps curl, triceps press-down, and lat pull-down. Lower extremity exercises included the leg press, leg curl, and leg extension. One set of 15 repetitions was performed for each exercise. If the resistance from the exercise machine could not be lifted, resistance bands were used instead. During each exercise session, patients wore a

step-activity monitor to quantify the total time of their visit, which served as a measure of the amount of exposure they had with the research staff.

Primary Outcome Measures

Graded maximal treadmill test: COT and PWT

Patients performed a graded treadmill test to determine study eligibility, and then repeated the test on a following visit within 1 week to obtain the primary outcome measures of COT and PWT as previously described. The measurement of COT and PWT during our graded treadmill test is highly stable and reliable with repeat testing.⁴

Secondary Outcome Measures

Graded maximal treadmill test: ischemic window, and calf muscle StO₂

Ankle systolic blood pressure was obtained from the more severely diseased lower extremity before and after the treadmill test^{4,10} to determine the ischemic window.¹¹ Calf muscle StO₂ was measured using a continuous-wave, NIRS unit (InSpectra model 325; Hutchinson Technology, Inc, Hutchinson, MN), an optical cable attached to a 25-mm probe, InSpectra software (version 2.0), and a dedicated laptop computer.¹²

Submaximal walking economy test

Oxygen uptake was measured during a constant, submaximal work rate at a treadmill speed of 2 mph and a grade of 0% until maximal claudication pain, or for a maximum of 20 minutes at baseline.¹³ The walking economy test at follow-up was performed for the same duration as at baseline. Walking economy was measured as oxygen uptake during the final minute of exercise. Fractional utilization was calculated as walking economy oxygen uptake/peak oxygen uptake.

6-minute walk test

Patients performed a 6-minute walk test and the total walking distances was recorded, as previously described.¹⁴

Ambulatory activity monitoring

Daily ambulatory activity was assessed during 7 consecutive days using a step-activity monitor (StepWatch3™, Orthoinnovations, Inc, Oklahoma City, OK) as previously described.¹⁵ The step-activity monitor is accurate and reliable.¹⁵ None of the exercise interventions was included in the monitoring period.

Walking impairment questionnaire

Self-reported ambulatory ability was obtained using a validated questionnaire for PAD patients that assesses ability

to walk at various speeds and distances, and to climb stairs.¹⁶

Health-related quality of life

Self-reported physical function was assessed with the Medical Outcomes Study Short-Form 36 General Health Survey.¹⁷

Diastolic pulse contour analysis

Large artery elasticity index (LAEI) and small artery elasticity index (SAEI) were obtained by an HDI/Pulsewave™ CR-2000 Cardiovascular Profiling System (Hypertension Diagnostic, Inc) following 5 to 10 minutes of rest in the supine position.¹⁸ Measurements were averaged over 3 continuous 30-second trials. LAEI and SAEI are reliable in patients with PAD.¹⁸

Statistical Analyses

Patients were randomized to 3 groups using off-site Number Cruncher Statistical System (NCSS) random number program with blocking to assure that group sizes never differed by more than 2 at any time during allocation. Study personnel were allowed access to the allocation list only after patient eligibility was determined and baseline data were completed. Measurement variables at baseline were summarized within each group as means and standard deviations. Dichotomous variables were summarized as percent with attribute present. An intent-to-treat analysis was made for all outcome variables. Missing data were imputed using the NCSS missing data program, which utilizes a regression equation based on baseline demographic variables and observed responses to predict missing responses. Exercise intervention measures were compared using independent *t* tests. Note that by the nature of the exercise intervention variables related to ambulation, data were available for only 2 of the groups for some variables. The change from baseline was the metric used for measuring impact of the exercise program on each performance variable. Within each group, the mean of changes for each performance variable from baseline was examined for difference from zero using a paired *t* test. Comparison among the change means for groups utilized a 1-way ANOVA followed by a Tukey-Kramer test for pairwise comparison with α set at 0.05. The paired *t* test achieved 80% power for differences in means of 0.37 SDs of the changes. The ANOVA achieved at least 80% power to detect a difference in any set of 3 means where the largest and smallest mean differed by 0.56 SDs of the pooled SD of the changes. Vascular and calf muscle StO₂ measures were examined for associations with primary outcome measures using Pearson Correlation Coefficients. All computations were made with the NCSS computer package. Statistical significance was defined as $P < 0.05$.

Results

Baseline Clinical Characteristics and Patient Flow Through the Trial

The clinical characteristics of the groups are shown in Table 1. The groups consisted of a mix of older, overweight white and African American men and women with a high prevalence of cardiovascular risk factors. One hundred fifty-six patients completed the study, whereas 24 did not (Figure). Missing data in the trial consisted of the missing post-test observations from the 24 patients who did not complete the study. Baseline characteristics remained not significantly different among groups after only including the 156 patients who completed the trial (data not shown). Of the 24 patients who did not complete the study, the number of dropouts was not significantly different among the 3 groups. Overall, there were only 14 adverse events during the trial, of which only 4 patients were discontinued due to an adverse event (Figure).

Exercise Intervention Measures

The number of exercise sessions completed in the 3 groups was not different (Table 2). By design, the average time of each visit to the exercise lab for the attention-control group (39.5 ± 10.0 min/visit) and the supervised exercise group (41.1 ± 6.7 min/visit) was not different ($P=0.404$). These measures were not applicable for the NEXT Step home-exercise group because they did not attend the lab for their exercise sessions. Total time spent exercising throughout intervention, average time spent exercising per session, and average number of strides taken during each exercise session were all greater in the NEXT Step home-exercise group than compared to supervised exercise. However, average ambulatory cadence during each session was slower in the NEXT Step home-exercise group.

Primary Outcome Measures

The change scores for the primary outcomes of COT and PWT (Table 3) were different among the 3 groups ($P<0.001$). Both COT and PWT increased significantly from baseline in the NEXT Step and supervised exercise programs ($P<0.001$), and the change scores were greater than in the control group ($P<0.05$). Additionally, the change score for PWT in the supervised exercise group was significantly greater than in the NEXT Step home-exercise group ($P<0.05$).

Secondary Outcome Measures

The change scores for 6-minute walk distance ($P=0.028$), walking economy ($P<0.001$), and fractional utilization ($P<0.001$) were different among the 3 groups (Table 3).

Table 1. Baseline Clinical Characteristics

Variables	Attention-Control Group (n=60)	Supervised-Exercise Group (n=60)	Home-Exercise Group (n=60)
Age, y	65 (9)	65 (11)	67 (10)
Weight, kg	82.9 (17.0)	81.9 (19.9)	82.7 (18.5)
Body mass index, kg/m ²	29.0 (6.1)	29.3 (6.7)	29.0 (5.7)
Ankle/brachial index	0.74 (0.21)	0.68 (0.25)	0.68 (0.24)
Sex (% men)	60	48	52
Race (% white)	58	52	62
Current smoking (% yes)	42	37	35
Hypertension (% yes)	83	90	88
Medication use (% yes)	80	85	82
Number of medications (n)	1.9 (1.3)	1.9 (1.2)	1.9 (1.3)
Dyslipidemia (% yes)	87	88	93
Medication use (%)	65	77	72
Number of medications (n)	0.8 (0.7)	0.9 (0.7)	1.0 (0.8)
Diabetes (% yes)	37	48	40
Medication use (%)	33	45	32
Number of medications (n)	0.6 (0.9)	0.8 (1.2)	0.6 (1.0)
Abdominal obesity (% yes)	48	55	55
Metabolic syndrome (% yes)	75	82	85
Metabolic syndrome components (n)	3.3 (1.3)	3.6 (1.4)	3.6 (1.2)
Obesity (% yes)	40	42	43
Lower extremity revascularization (% yes)	27	32	37
Coronary artery disease (% yes)	28	30	35
Myocardial infarction (% yes)	18	22	17
Cerebrovascular disease (% yes)	10	12	25
Chronic kidney disease (% yes)	24	18	36
Chronic obstructive pulmonary disease (% yes)	23	37	23
Dyspnea (% yes)	58	65	57
Arthritis (% yes)	63	63	55

Values are means (SD) or percentage of patients.

Table 2. Exercise Intervention Measures

Variables	Supervised-Exercise Group (n=60)	Home-Exercise Group (n=60)	P Value
Exercise sessions completed, %*	81.7 (20.5)	80.6 (27.4)	0.181
Total exercise time, minutes	762 (314)	1011 (649)	0.009
Total exercise strides, strides	34 189 (14 736)	39 172 (28 244)	0.229
Total volume of exercise, MET-minutes*	2131 (937)	2472 (1564)	0.158
Average exercise time, min/exercise session	24.7 (4.5)	38.3 (18.8)	<0.001
Average exercise strides, strides/exercise session	1112 (263)	1427 (655)	<0.001
Average exercise cadence, strides/min	45.0 (7.1)	37.7 (9.0)	<0.001

Values are means (SD). MET indicates metabolic equivalents.

*Percentage of exercise sessions completed by the attention-control group was 79.2±23.1% (mean±SD).

The 6-minute walk distance increased significantly from baseline in the NEXT Step home-exercise group ($P<0.001$) and within the supervised-exercise group ($P<0.05$), and the change score in the NEXT Step group was greater than the change scores in the other 2 groups ($P<0.05$). Walking economy ($P<0.001$) and fractional utilization ($P<0.001$) increased significantly from baseline in the supervised exercise group, and both change scores were greater than the change scores in the control group ($P<0.05$). Finally, the change scores for physical function ($P=0.012$) and walking impairment questionnaire distance ($P=0.025$), speed ($P=0.038$), and stair-climbing ($P=0.046$) were significantly different among the 3 groups (data not shown). All of these measures increased significantly from baseline in the NEXT Step and supervised-exercise groups ($P<0.05$), and these changes scores were greater than the change scores in the control group ($P<0.05$).

The change scores for maximal cadences of 20 minutes ($P=0.011$), 30 minutes ($P=0.002$), and 60 minutes ($P=0.002$) of ambulation, and average cadence ($P=0.031$) were significantly different among the 3 groups (Table 4). These variables increased significantly from baseline values in the NEXT Step exercise group ($P<0.001$), and these change scores were greater than the change scores in the control group ($P<0.05$).

The change scores for ischemic window, high-sensitivity C-reactive protein (hsCRP) ($P=0.041$), and LAEI ($P=0.012$) were

significantly different among the groups, and these measures changed significantly from baseline in the NEXT Step exercise group ($P<0.05$) (Table 5). Furthermore, the change scores for the time to minimum calf StO_2 ($P=0.025$) and the recovery half-time ($P=0.020$) were significantly different among the 3 groups. The time to minimum calf StO_2 increased significantly from baseline in both the NEXT Step exercise group and in the supervised-exercise group ($P<0.001$), and these change scores were greater than the change score in the control group ($P<0.01$). The recovery half-time of calf StO_2 decreased significantly from baseline in both exercise groups ($P<0.001$), and these change scores were greater than the change score in the control group ($P<0.01$).

In the NEXT Step group, the change in the ischemic window and the change in hsCRP were correlated with the change in PWT ($r=0.38$, $P=0.002$, and $r=-0.31$, $P=0.015$, respectively), the change in LAEI was correlated with the change in 6-minute walk total distance ($r=0.035$, $P=0.006$), and the change in time to minimum calf StO_2 was correlated with the change in COT ($r=0.59$, $P<0.001$) and the change in PWT ($r=0.52$, $P<0.001$). In the supervised-exercise program, the change in time to minimum calf StO_2 was correlated with the change in COT ($r=0.32$, $P=0.047$) and the change in PWT ($r=0.43$, $P=0.006$).

Discussion

A primary novel finding was that the NEXT Step home-exercise program was superior to the other groups for improving 6-minute walk distance, whereas the supervised-exercise program was superior for improving PWT. Furthermore, both exercise programs improved the microcirculation of the calf muscle during and after treadmill exercise. Finally, the NEXT Step home-exercise program was the only intervention to lower hsCRP, and to increase LAEI and daily cadence. Thus, this study extends the literature by demonstrating that NEXT Step home exercise not only improves 6-minute walk distance and daily ambulatory activity, but it also improves calf muscle StO_2 , vascular function, and inflammation.

Adherence, Exercise Volume, and Attrition

The adherence rate in the NEXT Step home-exercise program was 81%, which was similar to that found for the supervised-exercise program. The high adherence rate to NEXT Step home exercise agrees with previous randomized controlled trials using a step activity monitor,^{7,19} and a group-mediated cognitive behavioral intervention.²⁰ Importantly, adherence rate in the NEXT Step home-exercise program of the current study was similar to that found with our previous trial,⁷ even though there were 3 fewer meetings with staff to review

Table 3. Exercise Performance Measures in Patients in the Attention-Control Group (n=60), Supervised-Exercise Group (n=60), and Home-Exercise Group (n=60)

Variables/Group	Pretest	Post-Test	Change Score	ITT ANOVA for Change Scores (<i>P</i> Values)
Claudication onset time, seconds				
Control	205 (167)	222 (180)	17 (138)	<0.001
Supervised	193 (150)	363 (292)	170 (182) ^{‡§}	
Home	195 (171)	300 (242)	104 (162) ^{‡§}	
Peak walking time, seconds				
Control	464 (237)	486 (260)	22 (159)	<0.001
Supervised	356 (222)	547 (299)	192 (190) ^{‡§}	
Home	380 (274)	490 (350)	110 (193) ^{‡§}	
Walking economy, mL·kg⁻¹·min⁻¹				
Control	10.5 (1.9)	10.7 (2.1)	0.2 (1.7)	<0.001
Supervised	10.4 (2.1)	9.4 (1.8)	−0.9 (1.6) ^{‡§}	
Home	9.9 (2.3)	9.6 (2.0)	−0.3 (1.3)	
Fractional utilization, %				
Control	82 (19)	85 (21)	3 (22)	<0.001
Supervised	91 (17)	75 (24)	−17 (27) ^{‡§}	
Home	86 (17)	80 (16)	−6 (13) [†]	
6MWT total distance, m				
Control	376 (73)	380 (81)	4 (40)	0.028
Supervised	326 (94)	341 (87)	15 (52) [*]	
Home	328 (108)	372 (119)	45 (53) ^{‡§}	

Values are means (SD). 6MWT indicates 6-minute walk test; ITT, intent-to-treat.

Change from pretest ^{*}*P*<0.05; [†]*P*<0.01; [‡]*P*<0.001.

[§]Different from control group (*P*<0.05).

^{||}Different from supervised-exercise group (*P*<0.05).

progress. Our results suggest that individualized monthly feedback is adequate for patients to adhere to NEXT Step home-exercise training.

Patients in the NEXT Step home-exercise program walked for an average of 9 minutes per session beyond that recommended in their exercise prescription, and for 14 minutes more per session than the supervised-exercise group. Greater ambulatory time with NEXT Step home exercise resulted in 300 more strides taken per session than supervised exercise, although ambulation was done at a slower cadence. Compared to supervised exercise, greater ambulation accomplished per session in the NEXT Step home-exercise program, coupled with the possibility of performing ambulatory sessions more frequently (eg, daily), underscores the unique advantage of exercise in the home setting. Consequently, much greater ambulatory activity can be completed with NEXT Step home exercise than compared to a standard supervised exercise program, which typically consists of 31-hour sessions per week.

The 13% attrition rate in this study was nearly half of the 23% rate from our previous randomized controlled trial.⁷ One reason was that we utilized a run-in phase at baseline in which patients needed to complete testing within 3 weeks to be randomized into the study. In our previous study we did not use a run-in phase, and patients who took longest to complete baseline testing were more likely to drop out soon after randomization.

Exercise Performance and Daily Ambulatory Activity

A particular strength of the current study was that the change in exercise performance following interventions was quantified from multiple perspectives. During maximal exercise, both the NEXT Step home program and the supervised program elicited improvements in the primary outcomes of COT and PWT during a maximal treadmill test with progressive increments in work load. We⁷ and others^{19,20} have reported

Table 4. Daily Ambulatory Activity Measures in Patients in the Attention-Control Group (n=60), Supervised-Exercise Group (n=60), and Home-Exercise Group (n=60)

Variables/Groups	Pretest	Post-Test	Change Score	ITT ANOVA for Change Scores (P Values)
Total strides, strides/day				
Control	3763 (1746)	3670 (1417)	-93 (1531)	0.305
Supervised	2983 (1533)	3241 (1816)	258 (1162)	
Home	2971 (1674)	3137 (1615)	166 (1134)	
Total activity time, min/day				
Control	306 (106)	299 (85)	-7 (98)	0.260
Supervised	256 (107)	272 (120)	16 (70)	
Home	256 (108)	253 (96)	-3 (73)	
Maximum 5-minute cadence, strides/min				
Control	31.5 (9.1)	31.2 (7.7)	-0.3 (8.1)	0.124
Supervised	26.8 (5.6)	28.7 (7.3)	1.9 (5.7)*	
Home	27.2 (8.0)	28.9 (9.0)	1.7 (5.2)*	
Maximum 20-min cadence (strides/min)				
Control	19.6 (7.9)	19.0 (8.2)	-0.6 (7.0)	0.011
Supervised	15.5 (5.2)	16.6 (6.5)	1.1 (5.3)	
Home	15.9 (6.9)	18.6 (9.1)	2.7 (5.5) ^{‡§}	
Maximum 30-min cadence, strides/min				
Control	16.6 (7.0)	16.1 (7.3)	-0.5 (5.9)	0.002
Supervised	13.0 (4.7)	14.1 (5.8)	1.1 (4.5)	
Home	13.4 (6.1)	16.2 (8.7)	2.8 (5.1) ^{‡§}	
Maximum 60-min cadence, strides/min				
Control	12.3 (5.2)	11.7 (4.8)	-0.6 (4.7)	0.002
Supervised	9.6 (3.8)	10.3 (4.5)	0.8 (3.2)	
Home	9.8 (4.7)	11.9 (6.6)	2.1 (4.1) ^{‡§}	
Average cadence, strides/min				
Control	11.9 (3.2)	12.2 (3.0)	0.2 (2.3)	0.031
Supervised	11.5 (2.6)	11.7 (2.6)	0.2 (1.8)	
Home	11.1 (2.7)	11.8 (3.0)	0.7 (1.7) [†]	

Values are means (SD). ITT indicates intent-to-treat.

Change from pretest * $P < 0.05$; [†] $P < 0.01$; [‡] $P < 0.001$.

[§]Different from control group ($P < 0.05$).

improvements in COT and PWT following a home-based exercise program. The current study is the first study to show that the change in PWT with supervised treadmill exercise is greater than with monitored NEXT Step home exercise.

This is the first study to directly compare changes in self-paced and standardized submaximal exercise following the NEXT Step home program and the supervised-exercise program. The 6-minute walk distance increased following NEXT Step home exercise, which agrees with previous reports.^{7,20} Additionally, the increase in 6-minute walk distance was greater with NEXT Step home exercise,

indicating that exercise adaptations are specific to the type of training performed, as a program of overground walking was more efficacious than a program of treadmill walking. Specificity of training was also noted for walking economy, as it improved only in the supervised-exercise group, and fractional utilization improved the most in the supervised group, supporting our previous work.¹³ This suggests that the higher training intensity of supervised-exercise sessions, due to walking up inclines on a treadmill, improves metabolic economy of walking at a given submaximal exercise intensity. Thus, daily ambulation performed at a given pace can be done

Table 5. Vascular and Calf Muscle StO₂ Measures in Patients in the Attention-Control Group (n=60), Supervised-Exercise Group (n=60), and Home-Exercise Group (n=60)

Variables/Groups	Pretest	Post-Test	Change Score	ITT ANOVA for Change Scores (P Values)
Ischemic window max (AUC/meter)				
Control	-0.63 (1.54)	-0.52 (0.65)	0.11 (1.00)	0.008
Supervised	-0.59 (0.74)	-0.51 (0.94)	0.09 (0.94)	
Home	-0.72 (0.97)	-0.47 (0.78)	0.26 (0.79)*	
Large artery elasticity index (mL×mm Hg⁻¹)×10				
Control	13.1 (4.0)	13.5 (4.4)	0.4 (4.3)	0.012
Supervised	12.2 (5.5)	12.9 (7.2)	0.7 (4.9)	
Home	14.0 (6.4)	16.2 (8.7)	2.2 (7.7)*	
Small artery elasticity index (mL×mm Hg⁻¹)×100				
Control	3.4 (1.7)	3.6 (2.1)	0.2 (1.6)	0.952
Supervised	2.9 (1.3)	3.0 (1.1)	0.1 (1.2)	
Home	3.6 (2.0)	3.7 (2.2)	0.1 (1.4)	
High-sensitivity C-reactive protein, mg/L				
Control	5.91 (5.96)	5.32 (3.87)	-0.59 (5.14)	0.041
Supervised	5.70 (6.39)	5.38 (5.78)	-0.32 (4.96)	
Home	7.68 (19.72)	5.86 (11.60)	-1.82 (9.77)*	
Time to minimum calf StO₂, seconds				
Control	245 (283)	272 (236)	27 (318)	0.025
Supervised	166 (196)	308 (275)	142 (269) ^{†‡}	
Home	195 (247)	341 (259)	146 (232) ^{†‡}	
Recovery half-time of calf StO₂, seconds				
Control	145 (149)	141 (145)	-4 (156)	0.020
Supervised	165 (147)	94 (76)	-71 (125) ^{†‡}	
Home	168 (184)	92 (94)	-76 (141) ^{†‡}	

Values are means (SD). ITT indicates intent-to-treat, StO₂, hemoglobin oxygen saturation. Change from pretest *P<0.05; †P<0.001.

[‡]Different from control group (P<0.01).

with less exertion following a program of supervised exercise. It is unlikely that the change is due to a learning effect because we have found that treadmill exercise performance is highly reliable and stable over repeated tests, particularly if handrail support is not permitted.²¹

Daily ambulatory activity quantifying cadence ranging from 5- to 60-minute epochs, as well as the average cadence all increased following NEXT Step home exercise. The increase in daily ambulatory cadences supports our previous investigation,⁷ and a recent study that found home-based exercise increased daily activity measured with an accelerometer.²⁰ Interestingly, the total activity time and total number of strides taken each day did not change with NEXT Step home-exercise training, confirming previous work.^{7,19} This suggests that following training, patients may ambulate from 1 location to another more quickly by walking at faster cadence, but this

does not necessarily translate into ambulating to more locations. Thus, NEXT Step home exercise improves the quality of ambulation by enabling symptomatic patients to walk at faster paces throughout the day even though the number of strides taken each day is not increased.

Vascular Function and Inflammation

This is the first study to show that a NEXT Step home-exercise program is efficacious to improve microcirculation of the lower extremities, measured by calf muscle StO₂. Additionally, calf muscle StO₂ was improved following the supervised-exercise program, which agrees with a previous report.²² The improved microvascular function was observed during exercise, as measured by longer time to reach the minimum calf muscle StO₂, indicating that exercise-mediated oxygen

desaturation was less pronounced following both exercise programs. Furthermore, improved microcirculation was also evident during supine recovery after the treadmill test, measured by shorter recovery half-time of calf muscle StO₂ to baseline. The clinical significance of the improved microcirculation following the NEXT Step home program and the supervised-exercise program is that this is a possible physiologic mechanism for the improvements in maximal and submaximal exercise performance, and in the increases in daily ambulatory activity.

NEXT Step home exercise also improved LAEI by 16%. This is the first study to report an improvement in arterial elasticity in symptomatic patients with PAD following exercise rehabilitation, and suggests that exercise in the home setting is more efficacious than supervised exercise for this adaptation. This supports our previous investigation that found an improvement in endothelial function.²³ NEXT Step home exercise also reduced inflammation as hsCRP decreased by 24%, which supports our previous report that found baseline daily ambulatory activity was negatively associated with hsCRP in symptomatic patients with PAD,²⁴ and another report that found inflammation was associated with greater functional decline in patients with PAD.²⁵ Our current study extends our earlier baseline observation of beneficial effects of ambulatory activity on inflammation by demonstrating that a program of NEXT Step home exercise lowers hsCRP. This result agrees with other reports that found supervised exercise lower hsCRP,²⁶ interleukin-6,²⁷ and endothelium-derived inflammatory markers of E-selectin and intercellular adhesion molecule-1.²⁸

Limitations

Although this trial supports the efficacy of the NEXT Step home program and supervised exercise rehabilitation for PAD patients, several limitations exist. One limitation is that patients volunteered to participate in this study. Thus, a self-selection bias may exist because they may represent those who had greater interest participating, better access to transportation to the research center, and better health than PAD patients who did not volunteer. A second limitation is that the results of this study are only generalizable to patients with symptomatic PAD, and may not be applicable to patients with less severe or more severe PAD. Another limitation is that although patients were randomized into 1 of the groups prior to intervention, the possibility that those who participated in home exercise were more motivated than other patients cannot be ruled out.

Conclusions and Clinical Implications

NEXT Step home exercise utilizing minimal staff supervision has low attrition, high adherence, and is efficacious in

improving the primary outcome measures of COT and PWT, as well as secondary outcomes of submaximal exercise performance, daily ambulatory activity, vascular function, calf muscle StO₂, and inflammation. Furthermore, exercise-mediated changes are specific to the training program performed, as improvement in 6-minute walk distance is best accomplished with over-ground NEXT Step home exercise, whereas improvements in COT and PWT are best achieved by on-site supervised treadmill exercise. The clinical significance is that NEXT Step home exercise is a new model to improve not only claudication measures, 6-minute walk distance, and daily ambulatory activity, but also to improve vascular function, inflammation, and calf muscle StO₂.

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Disclosures

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