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Supervised Exercise, Stent Revascularization, or Medical Therapy for Claudication Due to Aortoiliac Peripheral Artery Disease

The CLEVER Study

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ABSTRACT

BACKGROUND Treatment for claudication that is due to aortoiliac peripheral artery disease (PAD) often relies on stent revascularization (ST). However, supervised exercise (SE) is known to provide comparable short-term (6-month) improvements in functional status and quality of life. Longer-term outcomes are not known.

OBJECTIVES The goal of this study was to report the longer-term (18-month) efficacy of SE compared with ST and optimal medical care (OMC).

METHODS Of 111 patients with aortoiliac PAD randomly assigned to receive OMC, OMC plus SE, or OMC plus ST, 79 completed the 18-month clinical and treadmill follow-up assessment. SE consisted of 6 months of SE and an additional year of telephone-based exercise counseling. Primary clinical outcomes included objective treadmill-based walking performance and subjective quality of life.

RESULTS Peak walking time improved from baseline to 18 months for both SE (5.0 ± 5.4 min) and ST (3.2 ± 4.7 min) significantly more than for OMC (0.2 ± 2.1 min; $p < 0.001$ and $p = 0.04$, respectively). The difference between SE and ST was not significant ($p = 0.16$). Improvement in claudication onset time was greater for SE compared with OMC, but not for ST compared with OMC. Many disease-specific quality-of-life scales demonstrated durable improvements that were greater for ST compared with SE or OMC.

CONCLUSIONS Both SE and ST had better 18-month outcomes than OMC. SE and ST provided comparable durable improvement in functional status and in quality of life up to 18 months. The durability of claudication exercise interventions merits its consideration as a primary PAD claudication treatment. (Claudication: Exercise Versus Endoluminal Revascularization [CLEVER]; NCT00132743) (J Am Coll Cardiol 2015;65:999–1009) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ABI = ankle-brachial index

ANCOVA = analysis of covariance

COT = claudication onset time

OMC = optimal medical care

OMT = optimal medial therapy

PAD = peripheral artery disease

PAQ = Peripheral Artery Questionnaire

PWT = peak walking time

SE = supervised exercise

ST = stent revascularization

WIQ = Walking Impairment Questionnaire

Peripheral artery disease (PAD) is 1 of the most prevalent cardiovascular diseases (1), affecting up to 5% of individuals over 55 years of age (2–6). Claudication is the most frequent symptom of PAD and is associated with significant disability and substantial reductions in patient-reported health status and quality of life (7). Multiple clinical trials have demonstrated that supervised exercise (SE) is an effective treatment because it significantly improves walking performance (8) and quality of life (9,10). Despite this, access to SE is limited, because clinicians do not actively prescribe this claudication treatment, and it is usually not reimbursed by Medicare or by third-party payers.

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Lower-extremity endovascular revascularization is 1 of the most frequent peripheral vascular procedures (11). Over the last decade, the number of such procedures has increased 3-fold (12). Although outcomes of aortoiliac artery stent placement for claudication in uncontrolled studies are excellent (13,14), it is also known that patients with PAD appreciate the benefits of low-risk interventions when available (15). The CLEVER (Claudication: Exercise Versus Endoluminal Revascularization) study is a comparative effectiveness study that compared outcomes for aortoiliac stenting (ST) or SE with optimal medical therapy (OMT) at 6 and 18 months. The study, designed to measure a primary peak walking treadmill time outcome at 6 months, demonstrated that SE achieved a greater early functional status improvement compared with ST (16). This paper describes the results of the CLEVER study at 18 months.

METHODS

STUDY DESIGN AND OVERSIGHT. The CLEVER study was a randomized, multicenter clinical trial conducted at 29 centers in the United States and Canada. The study was designed to test the hypothesis that ST plus optimal medical care (OMC) and SE plus OMT would be associated with a greater improvement in peak walking time (PWT) on a graded treadmill test than with OMT alone. The CLEVER study secondarily tested whether ST plus OMT resulted in more improvement in PWT than SE plus OMC. The study was approved by the U.S. Food and Drug Administration, the Canadian Therapeutic Products Directorate, and institutional review boards at all participating centers, and was supported by the National Institutes of Health National Heart, Lung, and Blood Institute. The study has been registered as NCT00132743 since August 19, 2005, and was overseen by an independent data safety and monitoring committee. Details of the study design, methods, and early results were published previously (16,17). The lead author wrote the first draft of the manuscript, and all coauthors participated in and approved subsequent revisions.

POPULATION. Study participants were adults over 40 years of age with moderate-to-severe claudication that was due to aortoiliac PAD, who were enrolled between April 24, 2007, and January 11, 2011. A total of 999 patients were screened, 119 were enrolled, and 79 completed the 18-month follow-up clinical and treadmill assessment (**Figure 1**). Eight of the 119 enrolled patients were enrolled in a treatment group that included both ST and SE therapy. Because of slow enrollment, this group was terminated early in the recruitment phase, and their results are not included in this report.

Moderate-to-severe claudication was defined as the ability to walk at least 2 min on a treadmill at 2 miles per hour at no grade, but <11 min on a graded treadmill test using the Gardner-Skinner protocol (18). Walking 11 min on the Gardner-Skinner protocol is consistent with an approximately 5.5-MET workload, which is considered moderate-intensity physical activity (19). All subjects were enrolled on the basis of the presence of at least a 50% diameter

Pharmaceuticals. Dr. Cutlip has received either a research contract or grant support paid to his institution from Medtronic, Boston Scientific, and Abbott Vascular. Dr. Cohen has received research grant support from Medtronic, Boston Scientific, Abbott Vascular, and Cardiovascular Systems, Inc.; and has served as a consultant to Medtronic, Abbott Vascular, and Cardiovascular Systems, Inc. Dr. Reynolds has served as a consultant to Medtronic, Inc. Dr. Jaff has equity in Micell, Inc. and PQ Bypass; has served on the board of VIVA Physicians, Inc.; and has served as a consultant to Becker Venture Services Group, Abbott Vascular, Boston Scientific, Cordis Corporation, Covidien/eV3, and Medtronic Vascular. Dr. Hirsch has received research grants from Abbott Vascular, Aastrom Biosciences, Viromed, and AstraZeneca; and served as a consultant to Novartis and Merck & Co. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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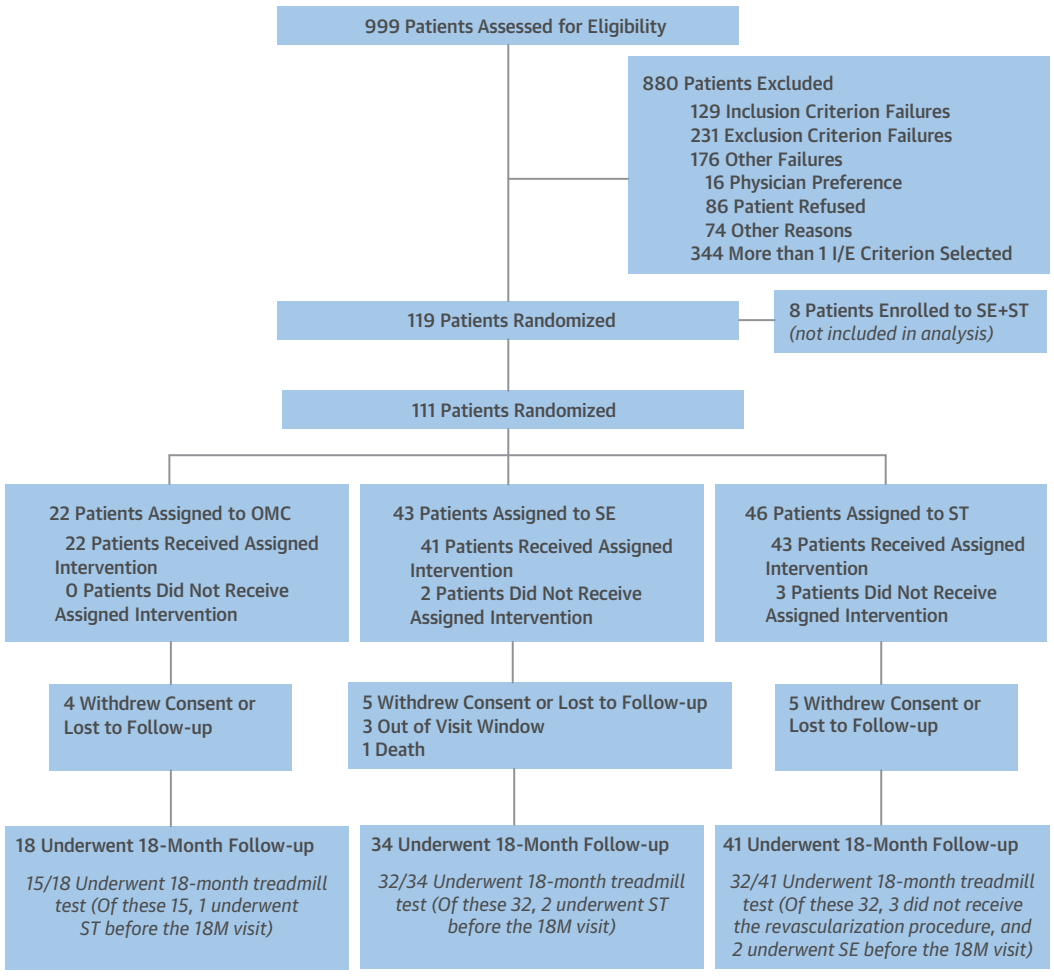
FIGURE 1 CONSORT Diagram



Participants were randomized after consenting for study participation and undergoing eligibility testing. Potentially eligible study participants were screened at the discretion of the study site. The proportion that did not expire, withdraw consent, exit the study, or were not lost to follow-up before completion of the 18-month follow-up was 93 of 111 (84%). Of the 93 who remained in the study for the entire 18 months of follow-up, treadmill test data were available for 79 of 111 (71%) at 18 months. Of the 14 who remained in the study for the duration of follow-up but did not undergo the treadmill test at 18 months, there were 9 in ST, 2 in SE, and 3 in OMC. The reasons for 9 ST participants missing PWT were: 1) could not be contacted (1); 2) comorbid condition (recent laminectomy) (1); 3) out of 2-week window (2); and 4) refused (5, 3 of whom had crossed over to structured exercise). The reasons for 3 OMC participants missing PWT were: 1) comorbid condition (unknown) (1); and 2) no show (2). The reasons for 2 SE participants missing PWT were: 1) refused (1); and 2) unknown (1). Of the 14 patients who did not have the 18-month PWT, 7 had other 18-month endpoints collected, and 13 had QOL data collected by telephone. All study participants were confirmed to be alive at the 18-month follow-up interval, except for 1 person in SE who expired before the 6-month follow-up. 18M = 18-month; I/E = inclusion/exclusion; OMC = optimal medical care; PWT = peak walking time; QOL = quality of life; SE = supervised exercise treatment; ST = stenting treatment.

stenosis of the distal aorta or iliac arteries involving the more symptomatic leg, which was confirmed by either noninvasive vascular laboratory testing (n = 92) or catheter angiography (n = 19), as previously described (16). Distal angiographic anatomy was not evaluated because individuals with claudication as a result of aortoiliac PAD are known to achieve substantial functional (treadmill) and quality-of-life benefit from aortoiliac ST, regardless of the presence of distal arterial stenosis (7). Additionally, baseline angiographic study is invasive and was not considered necessary or appropriate for a study in which 2 of 3 treatment strategies were noninvasive.

RANDOMIZATION AND INTERVENTIONS. Randomization was designed to be unbalanced in order to achieve twice as many participants in the ST and SE

cohorts compared with OMC. OMC was consistent with published evidence-based PAD care guidelines (20) and included use of atherosclerosis risk factor management; the claudication medication, cilostazol (Pletal, Otsuka America, Rockville, Maryland); and home exercise counseling, as described previously (16). Other details of the OMC intervention, including risk factor management, have been reported previously (16).

ST participants received OMC in addition to ST of hemodynamically significant stenoses in the aorta and iliac arteries in the symptomatic leg(s), as indicated (16).

SE participants received OMC plus SE, which was designed on the basis of a meta-analysis that described optimal features of such therapy (8) and was consistent with current guidelines (20). It consisted of treadmill walking for up to 78 scheduled exercise sessions that were 1 h long, 3 days a week, for 6 months, as previously described (21). Patients in the SE group received quarterly contact by research coordinators during the supervised phase, and then participated in a telephone-based maintenance program designed to promote exercise adherence during the unsupervised phase of the study. This telephone support system was provided to SE patients from the beginning of month 7 to the end of month 18. This program consisted of initial contact with a trained health educator in month 5; biweekly telephone consultation between months 7 and 12; and then monthly telephone contact between months 13 and 18. Participants received log books to monitor their exercise, exercise tip sheets, and a pedometer. Telephone-based counseling utilized several behavioral strategies based on social cognitive theory that included goal setting, relapse prevention, time management, increasing social support, self-efficacy for exercise, enjoyment of exercise, and motivation (22). At each session, the participant set goals and reported on the attainment of those goals in the following session.

ENDPOINTS. All endpoints were assessed at 6 months and at 18 months. The 6-month outcomes were reported previously (16). Functional status was measured by treadmill performance measurements that included the PWT and claudication onset time (COT).

Observers blinded to the treatment group administered treadmill tests. Three quality-of-life health status measures were used: the Medical Outcomes Study Short Form-12 (23), the Walking Impairment Questionnaire (WIQ) (10), and the Peripheral Artery Questionnaire (PAQ) (24). To determine the adequacy of revascularization procedures in the ST group, as well as changes in lower-extremity perfusion among all participants throughout the study, ankle-brachial index (ABI) values were obtained at baseline and both follow-up intervals.

Adverse events were monitored throughout the study. Restenosis was monitored long term at scheduled visit intervals or prompted by recurrent symptoms between those scheduled visits on the basis of clinical symptoms and ABI values, indicated by a decrease in the ABI by $\geq$0.10 compared with the first post-procedure ABI. Cost-effectiveness data were collected prospectively and will be reported in a subsequent paper.

DEFINITIONS. PWT was defined as the maximal time a participant could walk during the graded treadmill test, and COT was defined as the time when claudication was first noticed by a participant. COT was assumed to equal PWT if no claudication was experienced (16). Major complications were defined as death, amputation of the target limb, critical limb ischemia, target limb revascularization, or myocardial infarction and were adjudicated by a blinded clinical events committee.

STATISTICAL ANALYSIS. All endpoints were analyzed according to the intention-to-treat principle. Secondary analyses were performed on a per-protocol population, which excluded those patients who did not receive their assigned treatment. Baseline characteristics were compared using 1-way analysis-of-variance for continuous variables and the Fisher exact test for binary characteristics.

The sample size was determined by the anticipated treatment effect on the primary endpoint, the change in PWT at 6 months, as previously reported (16). All 3 pairwise comparisons of change in PWT between baseline and 18 months among the 3 treatment groups (OMC, ST, and SE) were of interest and were carried out using analysis of covariance (ANCOVA) adjusted for baseline PWT, baseline cilostazol use, and study region, as previously reported (16). Sequential testing was performed so as to allow a 2-sided 0.05 level of significance for each pairwise comparison (16). Nonparametric tests using rank ANCOVA adjusted for study region, baseline cilostazol use, and baseline value of PWT were also done. Interaction tests were done to compare the effect of enrollment volume on outcomes for PWT, COT, and ABI. All p values are 2-sided, and p values of 0.05 were considered statistically significant, without adjustments for multiple comparisons. Statistical analyses were performed using SAS for Windows (version 9.1.3, SAS, Cary, North Carolina).

RESULTS

POPULATION. Study design and patient flow from enrollment through the 18-month endpoint assessment,

TABLE 1 Demographic and Background Characteristics

	All Patients (N = 111)	Patients With 18-Month PWT (n = 79)	Optimal Medical Care With 18-Month PWT (n = 15)	Supervised Exercise With 18-Month PWT (n = 32)	Stent With 18-Month PWT (n = 32)
Age, yrs	64.4 ± 9.5 (111)	65.0 ± 9.5 (79)	62.3 ± 8.5 (15)	65.9 ± 8.8 (32)	65.2 ± 10.5 (32)
Male	62.2 (69/111)	62.0 (49/79)	60.0 (9/15)	56.3 (18/32)	68.8 (22/32)
Risk factor history					
Diabetes	23.9 (26/109)	24.7 (19/77)	21.4 (3/14)	18.8 (6/32)	32.3 (10/31)
Hypertension	84.7 (94/111)	87.3 (69/79)	93.3 (14/15)	90.6 (29/32)	81.3 (26/32)
Current smoking	54.1 (60/111)	53.2 (42/79)	53.3 (8/15)	53.1 (17/32)	53.1 (17/32)
Former smoking	37.8 (42/111)	38.0 (30/79)	40.0 (6/15)	37.5 (12/32)	37.5 (12/32)
Hypercholesterolemia	80.2 (89/111)	77.2 (61/79)	73.3 (11/15)	78.1 (25/32)	78.1 (25/32)
Statin use	75.7 (84/111)	74.7 (59/79)	73.3 (11/15)	78.1 (25/32)	71.9 (23/32)
Antiplatelet agent use*	78.4 (87/111)	81.0 (64/79)	86.7 (13/15)	78.1 (25/32)	81.3 (26/32)
Comorbid cardiovascular diseases					
Prior TIA	5.4 (6/111)	5.1 (4/79)	6.7 (1/15)	3.1 (1/32)	6.3 (2/32)
Prior stroke	8.1 (9/111)	7.6 (6/79)	0.0 (0/15)	18.8 (6/32)	0.0 (0/32)
Prior angina	2.7 (3/111)	3.8 (3/79)	6.7 (1/15)	0.0 (0/32)	6.3 (2/32)
Prior myocardial infarction	21.5 (23/107)	21.8 (17/78)	33.3 (5/15)	16.1 (5/31)	21.9 (7/32)
Prior percutaneous coronary revascularization	18.0 (20/111)	17.7 (14/79)	26.7 (4/15)	9.4 (3/32)	21.9 (7/32)
Prior coronary artery bypass graft	18.0 (20/111)	19.0 (15/79)	13.3 (2/15)	15.6 (5/32)	25.0 (8/32)
Peripheral artery disease history					
Prior lower extremity endovascular procedure	4.5 (5/111)	3.8 (3/79)	6.7 (1/15)	0.0 (0/32)	6.3 (2/32)
Prior lower extremity open surgical revascularization procedure	3.6 (4/111)	2.5 (2/79)	6.7 (1/15)	0.0 (0/32)	3.1 (1/32)
Cilostazol use prior to randomization	18.0 (20/111)	19.0 (15/79)	13.3 (2/15)	18.8 (6/32)	21.9 (7/32)
Risk factors					
Blood pressure					
SBP, mm Hg	135.6 ± 19.0 (111)	135.7 ± 19.6 (79)	136.7 ± 13.4 (15)	135.9 ± 22.6 (32)	134.8 ± 19.3 (32)
DBP, mm Hg	74.4 ± 11.4 (110)	74.0 ± 11.0 (78)	77.8 ± 10.2 (14)	74.0 ± 13.0 (32)	72.3 ± 8.9 (32)
Lipid profile					
LDL, mg/dl	103.2 ± 36.4 (107)	103.6 ± 35.5 (77)	104.6 ± 40.6 (15)	97.9 ± 36.3 (31)	108.8 ± 32.4 (31)
HDL, mg/dl	48.6 ± 14.4 (109)	49.3 ± 14.9 (79)	48.5 ± 13.5 (15)	51.9 ± 16.0 (32)	47.0 ± 14.4 (32)
Triglycerides, mg/dl	144.7 ± 108.1 (109)	149.1 ± 119.1 (79)	139.8 ± 72.8 (15)	141.5 ± 83.0 (32)	161.0 ± 161.8 (32)
HbA_{1c}, %	6.2 ± 1.2 (108)	6.2 ± 1.2 (79)	6.1 ± 0.7 (15)	6.0 ± 1.2 (32)	6.4 ± 1.3 (32)
C-reactive protein, mg/dl	0.99 ± 0.28 (109)	0.97 ± 0.27 (79)	0.98 ± 0.27 (15)	0.96 ± 0.22 (32)	0.99 ± 0.31 (32)
Fibrinogen, mg/dl	408.0 ± 94.0 (107)	419.6 ± 90.1 (77)	428.7 ± 63.3 (15)	423.1 ± 100.5 (30)	409.6 ± 92.4 (32)
Anthropometric characteristics					
BMI	28.5 ± 5.7 (111)	28.4 ± 5.7 (79)	29.0 ± 5.9 (15)	27.5 ± 5.0 (32)	28.9 ± 6.4 (32)
Waist circumference, cm	99.9 ± 14.3 (109)	99.4 ± 14.7 (79)	100.0 ± 15.4 (15)	96.5 ± 13.3 (32)	102.0 ± 15.6 (32)
PAD characteristics					
Prior lower extremity endovascular procedure	4.5 (5/111)	3.8 (3/79)	6.7 (1/15)	0.0 (0/32)	6.3 (2/32)
Prior lower extremity open surgical revascularization procedure	3.6 (4/111)	2.5 (2/79)	6.7 (1/15)	0.0 (0/32)	3.1 (1/32)
Prior to randomization use of cilostazol	18.0 (20/111)	19.0 (15/79)	13.3 (2/15)	18.8 (6/32)	21.9 (7/32)
Baseline performance					
PWT, min	5.3 ± 2.2 (111)	5.5 ± 2.3 (79)	5.7 ± 2.6 (15)	5.6 ± 2.4 (32)	5.2 ± 2.1 (32)
COT, min	1.7 ± 0.8 (111)	1.8 ± 0.9 (79)	1.8 ± 0.7 (15)	1.8 ± 0.9 (32)	1.8 ± 1.0 (32)
7-day free-living steps	19,294.6 ± 1,2853.0 (81)	18,517.1 ± 12,731.1 (60)	18,671.1 ± 15,990.2 (13)	18,287.6 ± 11,060.1 (25)	18,687.0 ± 13,013.8 (22)
Hourly free-living steps	286.8 ± 253.0 (93)	298.2 ± 285.9 (65)	333.5 ± 461.7 (14)	301.5 ± 230.3 (27)	273.9 ± 213.6 (24)

Values are mean ± SD (n) or % (n/N). *Antiplatelet use means use either of aspirin, clopidogrel, or both.

BMI = body mass index; COT = claudication onset time on the graded treadmill test; DBP = diastolic blood pressure; HbA_{1c} = glycosylated hemoglobin; HDL = plasma high-density lipoproteins; LDL = plasma low-density lipoproteins; PAD = peripheral artery disease; PWT = peak walking time on the graded treadmill test; SBP = systolic blood pressure; TIA = transient ischemic attack.

TABLE 2 Primary and Secondary Endpoints–Patients With 18-Month Visit

	OMC (min)	Supervised Exercise (min)	Stent (min)	Supervised Exercise vs. OMC*	Stent vs. OMC*	Supervised Exercise vs. Stent*
PWT						
Baseline	5.7 ± 2.6 (15)	5.6 ± 2.4 (32)	5.2 ± 2.1 (32)			
18 months	5.9 ± 2.9 (15)	10.6 ± 5.7 (32)	8.4 ± 5.6 (32)			
Baseline to 18-month change	0.2 ± 2.1 (15)	5.0 ± 5.4 (32)	3.2 ± 4.7 (32)	4.7 (2.6 to 6.9), p < 0.001	3.0 (1.1 to 5.0), p = 0.04	1.7 (−0.8 to 4.2), p = 0.16
COT						
Baseline	1.8 ± 0.7 (15)	1.8 ± 0.9 (32)	1.8 ± 0.9 (32)			
18 months	2.6 ± 1.7 (15)	5.1 ± 4.0 (32)	4.8 ± 4.7 (32)			
Baseline to 18-month change	0.9 ± 1.3 (15)	3.4 ± 3.9 (32)	3.0 ± 4.5 (32)	2.5 (1.0 to 4.0), p = 0.03	2.2 (0.5 to 3.9), p = 0.12	0.3 (−1.7 to 2.4), p = 0.77
ABI						
Baseline	0.7 ± 0.2 (15)	0.7 ± 0.2 (32)	0.6 ± 0.2 (32)			
18 months	0.8 ± 0.1 (15)	0.7 ± 0.2 (32)	0.9 ± 0.2 (31)			
Baseline to 18-month change	0.0 ± 0.1 (15)	0.0 ± 0.1 (32)	0.2 ± 0.2 (31)	−0.0 (−0.1 to 0.1), p = 0.82	0.2 (0.1 to 0.3), p = 0.002	−0.2 (−0.3 to −0.1), p < 0.001

Values are mean ± SD (n) or difference (95% CI). *The p values were calculated using change scores, and are on the basis of analysis of covariance, adjusting for study region, baseline cilostazol use, and baseline value of the endpoint.

ABI = ankle-brachial index in the most symptomatic leg; CI = confidence interval; OMC = optimal medical care; other abbreviations as in Table 1.

as well as reasons for missing follow-up, are shown in Figure 1. Baseline characteristics of the 3 study groups were similar (Table 1). There were more participants with a history of stroke in the SE group compared with other groups, but subjects with residual neurological deficits that might affect walking performance were excluded from study participation. The baseline PWT demonstrated severe ambulatory limitation at slightly over 5 min, which was similar across treatment groups. The population that completed the 18-month follow-up was similar to the baseline population (Table 1); there were no significant differences in baseline characteristics between the 79 patients who completed the 18-month treadmill test and the 32 patients who did not (Table 1).

ADHERENCE TO ASSIGNED TREATMENT AND MISSING DATA. Compliance with the therapeutic assignment was high and crossovers were minimal. There were 8 of 111 (7%) participants in the original randomized population who did not receive their assigned treatment or crossed over to 1 of the alternative treatments during study follow-up, but did not withdraw from the study (Figure 1). This included 1 participant in the OMC group and 2 participants in the SE group who underwent ST between the 6-month and 18-month visits. Two participants in the ST group, who were incorrectly identified as having aortoiliac disease, did not undergo their assigned stent treatment. One additional participant in the ST group refused their assigned treatment after being diagnosed with colon cancer after randomization, but before stent placement. Two patients in the ST group self-enrolled in structured exercise programs and are therefore defined as crossovers. To clarify the treatment-specific benefits, a per-protocol analysis was done that excluded these 8 participants. Endpoints such as quality of life and medication compliance were collected within the same time windows, but by telephone, and therefore have better data compliance than treadmill test data.

TREATMENT COMPLIANCE AND RESULTS. The initial revascularization was technically successful for all ST group participants for whom it was attempted (16). One ST patient underwent a revascularization procedure for restenosis, which occurred between 6 and 18 months.

Among SE participants, 29 of 41 (71%) attended at least 70% of their scheduled SE training sessions. Most subjects (36 of 41; 88%) randomized to the SE treatment arm sustained participation in the home-based telephone support exercise adherence program after the SE component ended in month 6.

At 18 months, 91% of all study participants were taking cilostazol, with no statistically significant differences in compliance among treatment groups.

TREADMILL WALKING AND HEMODYNAMIC ENDPOINTS. PWT at 18 months improved least for OMC patients (0.2 ± 2.1 min), more for ST (3.2 ± 4.7 min), and most for SE patients (5.0 ± 5.4 min) between baseline and 18 months (Table 2, Central Illustration).

The extent of the PWT improvement was greater for ST and SE compared with OMC, but the groups did not differ statistically (95% confidence limits −0.8, 4.2; p = 0.16). COT increased from baseline to 18 months by 0.9 ± 1.3 min for OMC patients, 3.0 ± 4.5 min for ST, and 3.4 ± 3.9 min for SE (Table 2). The difference between OMC and SE was statistically significant, but no other COT comparisons achieved significance. For both PWT and COT, the nonparametric analysis produced results similar to those of the ANCOVA. Rank ANCOVA p values for PWT comparisons were SE versus OMC p < 0.001; ST versus OMC p = 0.06; and ST versus SE p = 0.04. Rank ANCOVA p values for COT comparisons were SE versus OMC p < 0.0001; ST versus OMC p = 0.19; and ST versus SE p = 0.26. The per-protocol analysis at 18 months also showed statistical superiority for SE and ST for the PWT endpoint compared with OMC (5.0 ± 5.4 vs. 3.2 ± 4.7, vs. 0.2 ± 2.1; p = 0.001 and 0.04, respectively), and no statistically significant difference was observed between ST and SE (p = 0.16). For COT, the per-protocol improvements were similar for ST and SE compared with OMC (3.0 ± 4.5 and 3.4 ± 4.0, respectively, vs. 0.9 ± 1.3; p = 0.12 and 0.02, respectively), and the COT difference between ST and SE at 18 months by the per-protocol analysis was not significant (p = 0.77).

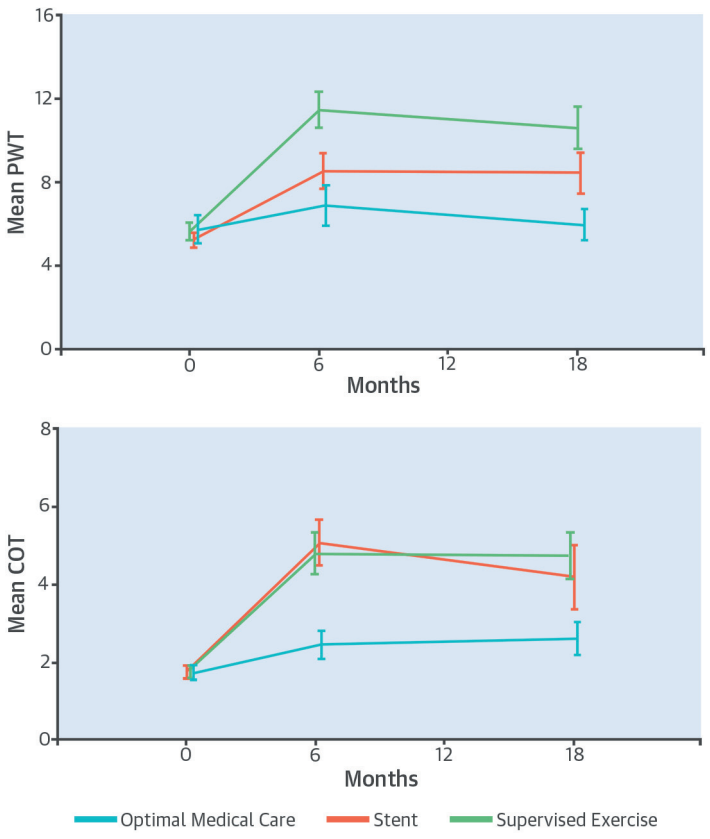
Mean ABI values were normalized in the stented patients and changed by 0.00 ± 0.1 for OMC, 0.2 ± 0.2 for ST, and 0.00 ± 0.1 for SE (p = 0.002 for ST vs. OMC and p < 0.001 for ST vs. SE) (Table 2, Central Illustration). The per-protocol analysis of ABI also showed statistically significant differences for the comparison of ST versus OMC (p = 0.001) and ST versus SE (p < 0.0001).

Interaction tests did not show any significant difference in outcomes for PWT, COT, or ABI on the basis of enrollment volume when comparing high-enrolling (>10 participants) versus low-enrolling centers (all p values >0.4). Considering the number of participants who did not have treadmill test data obtained at 18 months, 6-month PWT and COT results were compared among participants who lacked 18-month follow-up data (Online Table 1). Although participants who missed the 18-month treadmill test in all 3 treatment groups tended to have better outcomes at 6 months than those who complied, this analysis is flawed because more than one-half of those who missed the 18-month treadmill test also missed the 6-month treadmill test.

QUALITY OF LIFE. There were no baseline differences in quality of life among the treatment groups. At 18 months, improvement in disease-specific scales (WIQ, PAQ) was statistically superior for ST and SE compared with OMC, but ST and SE differed significantly from each other (favoring ST) only for PAQ symptoms, PAQ treatment satisfaction, PAQ quality of life, and PAQ summary (Table 3, Figure 2).

SAFETY. There were 3 pre-specified major adverse events, all of which occurred in the first 6 months (16). These included a myocardial infarction in the OMC group, a death in the SE group, and a target limb revascularization in the ST group. Four stent procedure-related adverse events occurred in 3 of the 46 ST participants and were previously reported (16).

CENTRAL ILLUSTRATION Exercise or Intervention for Claudication Due to Aortoiliac PAD: PWT and COT



Murphy, T.P. et al. J Am Coll Cardiol. 2015; 65(10):999-1009.

(Upper panel) PWT. Patients with 18-month follow-up visit only. **(Lower panel)** COT. COT = claudication onset time on a graded treadmill test; PAD = peripheral artery disease; PWT = peak walking time on a graded treadmill test.

DISCUSSION

The 18-month follow-up results of the CLEVER study demonstrate a comparable, clinically important, and durable benefit in functional status, as measured by the PWT, for both ST and SE compared with OMC. The

TABLE 3 Quality-of-Life Endpoints: Patients With 18-Month Visit

	OMC (n = 15)	Supervised Exercise (n = 32)	Stent (n = 32)	Supervised Exercise vs. OMC*	Stent vs. OMC*	Supervised Exercise vs. Stent*
SF-12 Physical						
Baseline	32.3 ± 9.8 (15)	33.6 ± 9.3 (32)	34.6 ± 9.1 (32)			
18 months	31.0 ± 7.6 (14)	38.0 ± 10.0 (31)	37.9 ± 9.4 (32)			
Baseline to 18-month change†	−1.0 ± 7.6 (14)	4.3 ± 8.6 (31)	3.3 ± 11.1 (32)	5.4 (0.4 to 10.4), p = 0.03	4.3 (−1.2 to 9.9), p = 0.05	1.0 (−3.9 to 5.9), p = 0.61
WIQ pain severity						
Baseline	28.3 ± 20.8 (15)	32.8 ± 26.5 (32)	34.4 ± 28.2 (32)			
18 months	38.3 ± 24.8 (15)	63.3 ± 26.2 (32)	75.0 ± 29.1 (32)			
Baseline to 18-month change†	10.0 ± 24.6 (15)	30.5 ± 35.8 (32)	40.6 ± 43.0 (32)	20.5 (2.9 to 38.0), p = 0.02	30.6 (11.2 to 50.0), p = 0.002	−10.2 (−29.5 to 9.2), p = 0.17
WIQ walking distance						
Baseline	23.3 ± 30.9 (15)	13.6 ± 12.2 (32)	15.8 ± 15.6 (32)			
18 months	19.6 ± 20.7 (15)	43.0 ± 32.7 (31)	56.8 ± 37.8 (32)			
Baseline to 18-month change†	−3.7 ± 27.6 (15)	29.9 ± 30.6 (31)	41.0 ± 34.7 (32)	33.6 (16.0 to 51.2), p < 0.001	44.8 (26.4 to 63.2), p < 0.001	−11.2 (−27.3 to 4.9), p = 0.16
PAQ physical limitation						
Baseline	33.6 ± 30.4 (14)	32.4 ± 18.6 (30)	29.7 ± 20.3 (30)			
18 months	28.2 ± 17.0 (13)	44.2 ± 24.0 (30)	56.8 ± 32.7 (32)			
Baseline to 18-month change†	0.0 ± 24.4 (12)	9.4 ± 24.4 (28)	24.4 ± 31.0 (30)	9.4 (−7.1 to 25.8), p = 0.22	24.4 (6.7 to 42.1), p = 0.01	−15.1 (−29.4 to −0.8), p = 0.04
PAQ symptoms						
Baseline	43.7 ± 17.8 (15)	42.6 ± 19.2 (32)	50.4 ± 20.7 (32)			
18 months	53.0 ± 20.7 (14)	58.8 ± 24.3 (30)	74.3 ± 27.7 (32)			
Baseline to 18-month change†	8.1 ± 17.2 (14)	17.3 ± 22.9 (30)	23.8 ± 25.6 (32)	9.2 (−3.0 to 21.4), p = 0.19	15.7 (3.1 to 28.3), p = 0.05	−6.5 (−18.6 to 5.6), p = 0.26
PAQ quality of life						
Baseline	43.9 ± 25.9 (15)	46.4 ± 19.0 (32)	43.5 ± 18.3 (32)			
18 months	49.4 ± 25.3 (13)	60.3 ± 23.1 (30)	70.2 ± 27.4 (32)			
Baseline to 18-month change†	5.8 ± 25.5 (13)	13.3 ± 25.9 (30)	26.7 ± 28.5 (32)	7.6 (−9.1 to 24.3), p = 0.33	20.9 (3.9 to 38.0), p = 0.02	−13.4 (−26.9 to 0.2), p = 0.04
PAQ summary						
Baseline	46.3 ± 23.6 (15)	45.8 ± 16.3 (32)	44.8 ± 18.1 (32)			
18 months	45.1 ± 21.3 (14)	58.0 ± 21.6 (31)	69.1 ± 26.7 (32)			
Baseline to 18-month change†	−2.3 ± 19.8 (14)	12.2 ± 21.5 (31)	24.3 ± 27.4 (32)	14.5 (1.6 to 27.3), p = 0.03	26.5 (12.5 to 40.6), p = 0.002	−12.0 (−24.2 to 0.1), p = 0.04

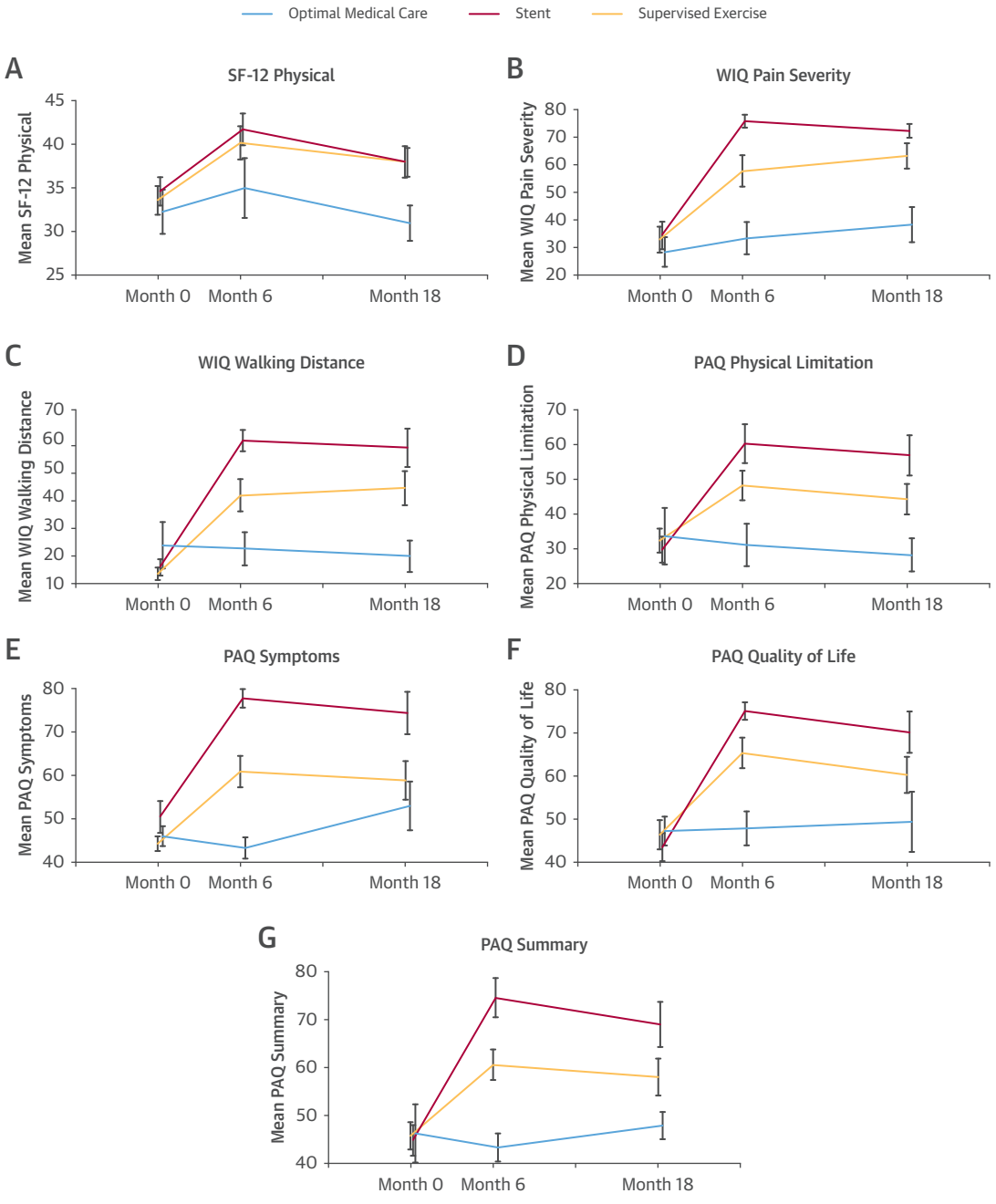
Values are mean ± SD (n) or difference (95% CI). The WIQ includes sections to ascertain PAD specificity and differential diagnosis, as well as 14 questions about walking distance, walking speed, and stair climbing. The PAQ consists of 14 questions designed to elicit information about disease-specific quality of life across a range of PAD-specific domains. *The p values are calculated using change scores, and are based on analysis of covariance adjusting for study center, baseline cilostazol use, and baseline value of the endpoint. †Baseline to 18-month change values were calculated only for participants for whom both baseline and 18-month data were collected.

PAQ = Peripheral Artery Questionnaire; SF-12 = Medical Outcomes Study Short Form-12; WIQ = Walking Impairment Questionnaire; other abbreviations as in Tables 1 and 2.

robustness of this result is reinforced by the improvement in COT that was greater in subjects assigned to the SE strategy of care compared with OMC, and comparable to that seen in ST participants. The durability of the functional status and quality-of-life improvements in response to provision of an SE strategy of care should be of particular interest, because this study provides the first data to demonstrate the preservation of this benefit for a full year after formal SE ended.

Exercise therapy for claudication, first described in 1966 (25), is known to substantially improve functional status, as defined by treadmill walking performance (26). Home exercise for claudication has been compared with SE in previous randomized trials. Notably, when the home regimen is composed solely of informal clinician advice about exercise, PAD home exercise results have been consistently inferior to those achieved with SE, which provides a more consistent therapeutic environment and workload progression (9,27–29). Further, patients with claudication treated with SE in previous randomized studies have enjoyed at least as much or greater functional improvement as those treated with angioplasty (30–32). The biological adaptive response of SE is well established (26). Evidence from pre-clinical and multiple human investigations suggests several mechanisms for such clinical benefits, including

FIGURE 2 **Mean (±1 Standard Error) Quality of Life by Treatment Group**



Patients with 18-month follow-up visit only. **(A)** SF-12 Physical. **(B)** WIQ Pain Severity. **(C)** WIQ Walking Distance. **(D)** PAQ Physical Limitation. **(E)** PAQ Symptoms. **(F)** PAQ Quality of Life. **(G)** PAQ Summary. PAQ = Peripheral Artery Questionnaire; SF-12 = Medical Outcomes Study Short Form-12; WIQ = Walking Impairment Questionnaire.

improved endothelial function, angiogenesis, and capillary density, oxidative metabolism and oxygen extraction, decreased blood viscosity, muscle innervation, and improved walking economy. The durability of the treatment effect of SE up to a year after termination of SE provides evidence that the benefits in treadmill walking are not solely due to a treadmill-specific training effect.

Individuals treated by primary iliac artery stenting also demonstrated an improved PWT compared with OMC, and this benefit is gained with a low risk of adverse events or clinical evidence of restenosis.

Patients assigned to SE, which required regular walking until symptomatic throughout the study, reported higher claudication symptom levels as assessed by the PAQ instrument at 18 months compared with those treated with SE or OMC. This subjective finding was present despite no significant difference in COT between the groups, and therefore may be attributable to an anomaly related to the questionnaire and the SE treatment. That is, patients in the exercise group who were instructed to walk regularly to claudication may be expected to report more frequent claudication symptoms. Subjective symptom improvement in the ST group may be attributable in part to a placebo effect, because there was no sham treatment, and all participants were aware that they were revascularized. Such subjective symptom improvements are often reported in that context even when no objective improvement can be measured (33). Alternatively, the closer association of quality of life with claudication pain versus peak walking distance may relate to better ability to achieve activities of daily living when pain is minimized.

STUDY LIMITATIONS. Randomized comparative effectiveness strategy-of-care studies, especially those that compare invasive and noninvasive treatments, are difficult to conduct. Although screening criteria were broadly defined, this study had an almost 10:1 ratio of those screened to those enrolled (**Figure 1**). This enrollment fraction is common and is similar to rates reported from most other randomized trials of similar populations (34,35). Another limitation is that of the 93 participants with 18 months of follow-up, treadmill test data at that interval were only available for 79 (**Figure 1**). Although the patients with and those without the treadmill test were similar (**Table 1**), it is impossible to be certain that the reasons for their missing data are random.

CONCLUSIONS

Patients with aortoiliac artery PAD and moderate-to-severe claudication, a population widely regarded as optimal for ST, achieve significant improvements in clinical outcomes when treated with either SE or ST compared with OMC alone, and this benefit is durable for at least 18 months. The benefit of SE, a strategy of care that provides several proven biological benefits that improve limb muscle strength, efficiency, and performance, was equal to the invasive stent strategy and was maintained for a full year after completion of the supervised training phase with use of a telephone-based counseling program. These data provide strong support in favor of comparable access to both SE and ST to improve the primary ischemic symptom of PAD, claudication.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: Treatment options for patients with claudication attributed to aortoiliac artery disease include revascularization and supervised exercise rehabilitation.

TRANSLATIONAL OUTLOOK: Longer-term studies are needed to compare the durability of revascularization and supervised exercise rehabilitation, alone and in combination, on the symptomatic and functional status of patients with aortoiliac arterial obstructive disease.

REFERENCES

1. Criqui MH, Denenberg JO, Langer RD, et al. The epidemiology of peripheral arterial disease: importance of identifying the population at risk. Vasc Med 1997;2:221–6.

2. Fowkes FG, Housley E, Cawood EH, et al. Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. Int J Epidemiol 1991;20:384–92.

3. Murabito JM, Evans JC, Nieto K, et al. Prevalence and clinical correlates of peripheral arterial disease in the Framingham Offspring Study. Am Heart J 2002;143:961–5.

4. Meijer WT, Hoes AW, Rutgers D, et al. Peripheral arterial disease in the elderly: the Rotterdam Study. Arterioscler Thromb Vasc Biol 1998;18:185–92.

5. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. Circulation 2004;110:738–43.

6. Fowkes FG, Rudan D, Rudan I, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet 2013;382:1329–40.

7. Murphy TP, Soares GM, Kim HM, et al. Quality of life and exercise performance after aortoiliac stent placement for claudication. J Vasc Interv Radiol 2005;16:947–53, quiz 954.

8. Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of

claudication pain. A meta-analysis. JAMA 1995; 274:975–80.

9. Patterson RB, Pinto B, Marcus B, et al. Value of a supervised exercise program for the therapy of arterial claudication. J Vasc Surg 1997;25:312–8. discussion 318–9.

10. Regensteiner JG, Steiner JF, Hiatt WR. Exercise training improves functional status in patients with peripheral arterial disease. J Vasc Surg 1996; 23:104–15.

11. Whyman MR, Fowkes FG, Kerracher EM, et al. Randomised controlled trial of percutaneous transluminal angioplasty for intermittent claudication. Eur J Vasc Endovasc Surg 1996;12:167–72.

12. Sachs T, Pomposelli F, Hamdan A, et al. Trends in the national outcomes and costs for claudication and limb threatening ischemia: angioplasty vs bypass graft. J Vasc Surg 2011;54:1021–31.e1.

13. Murphy TP, Ariaratnam NS, Carney WI Jr., et al. Aortoiliac insufficiency: long-term experience with stent placement for treatment. Radiology 2004; 231:243–9.

14. Maurel B, Lancelevee J, Jacobi D, et al. Endovascular treatment of external iliac artery stenoses for claudication with systematic stenting. Ann Vasc Surg 2009;23:722–8.

15. Zafar AM, Harris TJ, Murphy TP, et al. Patients' perspective about risks and benefits of treatment for peripheral arterial disease. J Vasc Interv Radiol 2011;22:1657–61.

16. Murphy TP, Cutlip DE, Regensteiner JG, et al., for the CLEVER Study Investigators. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: six-month outcomes from the claudication: exercise versus endoluminal revascularization (CLEVER) Study. Circulation 2012;125:130–9.

17. Murphy TP, Hirsch AT, Ricotta JJ, et al., for the CLEVER Steering Committee. The Claudication: Exercise Vs. Endoluminal Revascularization (CLEVER) study: rationale and methods. J Vasc Surg 2008;47:1356–63.

18. Gardner AW, Skinner JS, Cantwell BW, et al. Progressive vs single-stage treadmill tests for evaluation of claudication. Med Sci Sports Exerc 1991;23:402–8.

19. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000;32:S498–504.

20. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. J Am Coll Cardiol 2006;47:e1–192.

21. Bronas UG, Hirsch AT, Murphy T, et al., for the CLEVER Research Group. Design of the multicenter standardized supervised exercise training intervention for the claudication: exercise vs endoluminal revascularization (CLEVER) study. Vasc Med 2009;14:313–21.

22. Bandura A. Social Foundations of Thought and Action: A Social Cognitive Theory. Englewood Cliffs, NJ: Prentice-Hall, 1986.

23. Ware JJ, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220–33.

24. Spertus J, Jones P, Poler S, et al. The peripheral artery questionnaire: a new disease-specific health status measure for patients with peripheral arterial disease. Am Heart J 2004;147:301–8.

25. Larsen OA, Lassen NA. Effect of daily muscular exercise in patients with intermittent claudication. Lancet 1966;2:1093–6.

26. Stewart KJ, Hiatt WR, Regensteiner JG, et al. Exercise training for claudication. N Engl J Med 2002;347:1941–51.

27. Regensteiner JG, Meyer TJ, Krupski WC, et al. Hospital vs home-based exercise rehabilitation for patients with peripheral arterial occlusive disease. Angiology 1997;48:291–300.

28. Savage P, Ricci MA, Lynn M, et al. Effects of home versus supervised exercise for patients with intermittent claudication. J Cardiopulm Rehabil 2001;21:152–7.

29. Bendermacher BL, Willigendael EM, Teijink JA, et al. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. Cochrane Database Syst Rev 2006: CD005263.

30. Murphy TP, Spronk S, de Ridder M, et al. Primary end-point error. Radiology 2010;256: 1011, author reply 1011–2.

31. Perkins JM, Collin J, Creasy TS, et al. Exercise training versus angioplasty for stable claudication. Long and medium term results of a prospective, randomised trial. Eur J Vasc Endovasc Surg 1996; 11:409–13.

32. Mazari FA, Khan JA, Carradice D, et al. Randomized clinical trial of percutaneous transluminal angioplasty, supervised exercise and combined treatment for intermittent claudication due to femoropopliteal arterial disease. Br J Surg 2012; 99:39–48.

33. Sutherland ER. Sham procedure versus usual care as the control in clinical trials of devices: which is better? Proc Am Thorac Soc 2007;4: 574–6.

34. Nylaende M, Abdelnoor M, Stranden E, et al. The Oslo balloon angioplasty versus conservative treatment study (OBACT)—the 2-years results of a single centre, prospective, randomised study in patients with intermittent claudication. Eur J Vasc Endovasc Surg 2007;33:3–12.

35. Whyman MR, Fowkes FG, Kerracher EM, et al. Is intermittent claudication improved by percutaneous transluminal angioplasty? A randomized controlled trial. J Vasc Surg 1997;26: 551–7.

KEY WORDS angioplasty, ankle-brachial index, cilostazol, exercise rehabilitation, quality of life, walking

APPENDIX For an expanded list of the CLEVER investigators, coauthors, and committee members, as well as a supplemental table, please see the online version of this article.