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

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Background—Claudication is a common and disabling symptom of peripheral artery disease that can be treated with medication, supervised exercise (SE), or stent revascularization (ST).

Methods and Results—We randomly assigned 111 patients with aortoiliac peripheral artery disease to receive 1 of 3 treatments: optimal medical care (OMC), OMC plus SE, or OMC plus ST. The primary end point was the change in peak walking time on a graded treadmill test at 6 months compared with baseline. Secondary end points included free-living step activity, quality of life with the Walking Impairment Questionnaire, Peripheral Artery Questionnaire, Medical Outcomes Study 12-Item Short Form, and cardiovascular risk factors. At the 6-month follow-up, change in peak walking time (the primary end point) was greatest for SE, intermediate for ST, and least with OMC (mean change versus baseline, 5.8±4.6, 3.7±4.9, and 1.2±2.6 minutes, respectively; P<0.001 for the comparison of SE versus OMC, P=0.02 for ST versus OMC, and P=0.04 for SE versus ST). Although disease-specific quality of life as assessed by the Walking Impairment Questionnaire and Peripheral Artery Questionnaire also improved with both SE and ST compared with OMC, for most scales, the extent of improvement was greater with ST than SE. Free-living step activity increased more with ST than with either SE or OMC alone (114±274 versus 73±139 versus −6±109 steps per hour), but these differences were not statistically significant.

Conclusions—SE results in superior treadmill walking performance than ST, even for those with aortoiliac peripheral artery disease. The contrast between better walking performance for SE and better patient-reported quality of life for ST warrants further study.


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Key Words: claudication ■ comparative effectiveness research ■ peripheral artery disease ■ vascular diseases

Claudication, the most frequent symptom of peripheral artery disease (PAD),1 is experienced by an estimated 2 million Americans. Claudication profoundly limits physical functioning2,3 and results in a sedentary lifestyle,4 self-perceived ambulatory dysfunction,5 and poor health-related quality of life (QOL).6 Prior prospective randomized clinical trials have demonstrated the efficacy of cilostazol pharmacotherapy,7 supervised exercise rehabilitation,7,8 and endovascular revascularization9,10 to improve objective measures of walking performance and QOL in patients with claudication resulting from PAD. Although current guidelines suggest that pharmacotherapy, supervised exercise rehabilitation, and lower-extremity revas-
cularization are effective therapies for patients with claudication, the relative benefits of these distinct strategies of care are not known because no multicenter clinical trials have directly compared these 3 strategies. In this context, the Institute of Medicine ranked study of the comparative effectiveness of claudication treatment strategies in the top 50 of all American health challenges. Although studies comparing supervised exercise with endovascular revascularization have been performed, they have not included an optimal medical therapy group, have combined patients with aortoiliac and femoropopliteal artery PAD, and have shown either similar exercise performance between treatment groups or supervised exercise to be superior to revascularization. Nonetheless, there are important differences between patients with aortoiliac (ie, proximal) arterial stenoses and more distal disease that may limit the value of these comparisons. For example, individuals with aortoiliac PAD have more ischemic muscle mass with walking, are often more symptomatic than those with more distal obstruction, and might experience less improvement with exercise training. Moreover, there is considerably more experience with stent revascularization in the aortoiliac segment, and the results are more predictable and durable than those observed in the femoropopliteal arterial segment. Therefore, we designed a randomized clinical trial to compare the benefits of optimal medical care (OMC), supervised exercise (SE), and stent revascularization (ST) on both walking outcomes and measures of QOL in patients with claudication due to aortoiliac PAD.

Methods

Patient Selection

The study population consisted of individuals with symptoms of moderate to severe intermittent claudication (defined as ability to walk at least 2 but not more than 11 minutes on a graded treadmill test) involving the most symptomatic limb was established by noninvasive vascular testing (ankle-brachial index [ABI] <0.9, thigh-brachial index <1.1, common femoral artery systolic acceleration time >140 milliseconds, n = 41); duplex ultrasound (doubling of peak systolic velocity in the aortoiliac segment combined with an ABI <0.9; n = 26); computed tomographic angiography (n = 28) or magnetic resonance angiography (n = 5) confirming at least 60% stenosis by cross-sectional imaging test, combined with Doppler ultrasound waveform analysis (showing biphasic common femoral artery waveform); or catheter angiography (n = 19). Individuals meeting symptom and testing criteria were allowed in the study without regard to extent of aortoiliac obstruction or the presence of femoropopliteal PAD, except that patients with total aortoiliac occlusion from the level of the renal arteries to the inguinal ligaments were excluded.

Baseline Evaluation

Participants were evaluated at baseline and 6 months. Demographic data were collected, and anthropomorphic and physiological variables (body mass index, waist circumference, blood pressure, atherosclerosis risk factors [lipid profile, hemoglobin A1c], and inflammatory biomarkers [plasma fibrinogen, C-reactive protein] were also assessed. Participants were asked to wear pedometers during all waking hours for a 7-day period between the 2 baseline treadmill tests and to log compliance. Participants completed generic (ie, not disease specific) and disease-specific QOL surveys (Medical Outcomes Study 12-Item Short Form [SF-12], Walking Impairment Questionnaire [WIQ], and Peripheral Artery Questionnaire [PAQ]).

Randomization and Interventions

This study evaluated distinct strategies of care in 3 treatment groups: OMC, SE, and ST. A fourth treatment group that combined ST and SE was dropped after 8 participants were enrolled on the recommendation of the Data Safety and Monitoring Board to enhance enrollment in treatment groups that were part of the primary end point. Randomization was performed with a real-time web-based randomization system in a 2:2:1 ratio (ST:SE:OMC). Half as many enrolled in OMC because the treatment effect between the other groups and OMC was assumed to be much larger than between SE and ST. Randomization was stratified by geographic region and cilostazol use at baseline.

OMC was established via active promotion of the standards established by the intersocietal 2005 American College of Cardiology/American Heart Association guidelines for the management of patients with peripheral artery disease to promote best practices for risk factor management, use of antiplatelet therapy, and use of claudication pharmacotherapy. All study participants received cilostazol (Pletal; Otsuka America, Inc, San Francisco, CA) 100 mg by mouth twice daily as tolerated. In addition, OMC included advice about the use of home exercise and diet in the form of standardized verbal instructions and printed material (Krames Staywell, San Bruno, CA). Cardiovascular risk factor data were collected and feedback was provided to the sites by a central risk factor committee. Risk factors were then managed directly by the local study site.

SE consisted of 26 weeks of exercise, 3 times a week, for 1 hour at a time. Sites were trained to provide SE using a common protocol, and the progress of each participant was monitored by an oversight committee.

ST was done to relieve all hemodynamically significant stenoses (>50% by diameter) in the aorta and iliac arteries with Food and Drug Administration–approved self-expanding or balloon-expandable stents. The protocol allowed femoropopliteal endovascular revascularization to treat any additional focal lesions, but this was not done for any study participant. Intraprocedural or postprocedural oral antiplatelet medication use was at the discretion of the operator.

Follow-Up

Participants were called monthly to inquire about adverse events, at 3 months to refill their cilostazol medication, and at 6 months to undergo the same testing as at baseline, except that the treadmill test was performed only once at the 6-month outcome evaluation. Any recurrence of claudication symptoms would initiate an evaluation for significant restenosis. Pedometers were worn for 7 consecutive days immediately before the 6-month treadmill test.

End Points

The study primary end point was the change from baseline to 6 months in the peak walking time (PWT) on a graded treadmill test (Gardner protocol). PWT has been considered the most objective and
reliable end point to evaluate improvements in functional status for patients with claudication evaluated in clinical trials. Secondary end points included changes in the following parameters: claudication onset time (COT), change in community-based walking as assessed by pedometer measurements over 7 consecutive days, self-reported walking and QOL, and biomarkers of cardiovascular disease risk.

**Definitions**

COT was defined as the treadmill time when calf muscle discomfort was first noticed by a study participant on the graded treadmill test. For those individuals who did not experience any claudication symptoms during follow-up testing, COT was considered to be the same as the PWT. Community-based step activity was measured with pedometers (Omron Healthcare Inc, Lake Forest, IL). Pedometers cumulatively recorded 7 days of step activity and required no interaction from study participants. Because the purpose was to measure unstructured walking, participants in the SE group were instructed not to wear their pedometers during SE training sessions, and steps were normalized per hour of free-living daily activity as recorded by participants. Body mass and height were measured with medical stadiometers and converted to body mass index (mass in kilograms divided by height in square meters). Waist circumference was measured with a flexible tape measure under clothing on a horizontal plane at the level of the upper iliac crest. Biochemistry tests were done by the core laboratory at the University of Minnesota. Cilostazol compliance was assessed by pill counts performed at quarterly visits.

**Symptoms and QOL**

Patient-reported symptoms, functional status, and health-related QOL were assessed with 3 validated questionnaires, each administered at baseline and 6 months.

The SF-12 was used to assess generic QOL. Physical and mental summary scores from the SF-12 correlate highly with those obtained with other well-established health surveys.27 The minimum clinically important difference has not been established for the WIQ.

**Statistical Methods**

Baseline characteristics were compared by use of the χ² test for categorical variables and 1-way ANOVA for continuous variables. The primary end point was assessed by use of sequential pairwise ANCOVA with adjustment for clinical site, baseline PWT, and cilostazol use (adjustments done to increase precision of the statistical comparison). The second baseline treadmill test was used for the comparison. Separate pairwise models were fit by use of the given 2 groups being compared. First, SE and ST were each compared with OMC with a 1-sided level of significance of 0.025. Given the significance of both comparisons, SE and ST were then compared with a 2-sided level of significance of 0.05.

The secondary end point of change in free-living daily step activity measured by pedometer use, biomarkers, and QOL indicators was assessed by pairwise ANCOVA with adjustment for baseline cilostazol use and study center but with a 2-sided significance level of 0.05 for each comparison without adjustment for multiple comparisons. Pedometer activity was normalized to steps per hour to account for differences in hours of pedometer use during the assessment period. All analyses were conducted according to the intention-to-treat principle. Results were based on available data. Multiple imputation of missing primary end point data was also performed.

From published data,7,9,10 we estimated that the PWT would improve by 60% with OMC, 125% with SE, and 164% with ST. Given a baseline mean PWT estimate of 5.0 minutes (SD, 3.8 minutes), with 63 evaluable participants in both the ST and SE groups or 158 participants total between ST, SE, and OMC; the study had 80% power to detect the difference between SE and ST, >99% power for the ST versus OMC comparison, and 98% power for SE versus OMC. Allowing for 30% premature withdrawal and inclusion of an exploratory arm of ST plus SE, we planned a sample size of 252. The sample size was adjusted to 217 after removal of the ST plus SE arm owing to slow enrollment. Although the study did not meet conservative prespecified stopping rules, recruitment was stopped early on the recommendations of the Data Safety and Monitoring Board as a result of slow enrollment after review of the interim results.

**Results**

**Study Population**

Between April 2007 and January 2011, 119 study participants were randomized (the Figure). The final population of 119
reflects the sample size after enrollment was terminated by the Data Safety and Monitoring Board. At baseline, the study population age was 64.0 ± 9.5 years; 61.3% were male; 53.8% were current smokers, and 23.1% had diabetes mellitus. All 3 groups were well matched in terms of baseline demographics and performance variables, except for a higher prevalence of male sex and prior stroke in the SE group (Table 1). Baseline anthropomorphic, physiological, and biochemical characteristics were also similar at baseline across the treatment groups (Table 2).

Treatment Delivery
There were no crossovers during the 6-month follow-up period. Of the 43 patients assigned to the SE group, 2 withdrew before beginning treatment, and 29 of the remaining 41 (71%) attended at least 70% of their 78 scheduled SE sessions.

For patients assigned to the ST group, all ST procedures were technically successful. There were 19 right common iliac arteries, 8 right external iliac arteries, 20 left common iliac arteries, and 7 left external iliac arteries treated. One patient underwent aortic stenting, and no patients underwent a concomitant femoropopliteal artery endovascular procedure. The mean lesion length was 3.9 ± 3.4 cm, and the mean preprocedural stenosis was 83 ± 19%. The population was similar in terms of disease severity to other uncontrolled case series that have been published,17 with 14 of 37 of ST patients (38%) who received the ST treatment having total occlusions. The mean postprocedural stenosis was 5 ± 8%. The mean ABI was 0.66 ± 0.2 at baseline and improved by 0.29 ± 0.33 at 6 months. The average number of stents used per participant was 1.8 ± 1.2. An evaluation for restenosis was not indicated by recurrent leg symptoms during follow-up in any study participant.

Adherence to cilostazol was 90% and similar across all 3 treatment groups. Similarly, there were no differences in the use of statin medications or rates of current smoking across treatment groups (see Table 1).

Primary End Point
Compared with baseline, the primary end point (PWT) improved by 1.2 ± 2.6 minutes with OMC alone, 5.8 ± 4.6 minutes with SE, and 3.7 ± 4.9 minutes with ST. Compared with OMC alone, SE led to a greater mean improvement in PWT by 4.6 minutes (95% confidence interval, 2.7–6.5; P < 0.001), whereas ST had a somewhat smaller relative
Atherosclerosis risk factors demonstrated a greater improvement in high-density lipoprotein cholesterol among individuals in the SE group compared with ST participants. There was also a statistically significant greater decrease in plasma fibrinogen levels in the SE group compared with the OMC group (Table 3).

**Improvement in PWT**

In PWT of 2.5 minutes (95% confidence interval, 0.6-4.4; P=0.022), a direct comparison of SE and ST demonstrated a greater improvement in PWT with SE by a mean of 2.1 minutes (95% confidence interval, 0.0-4.2; P=0.04). Similar results were observed with nonparametric analyses (Table 3). Analyses were repeated without inclusion of individuals with a stroke history in the SE group and were similar to those for the entire cohort.

**Secondary End Points**

At the 6-month follow-up, there were no statistically significant changes in ABI measurements compared with baseline in either the OMC and SE treatment group, whereas the resting ABI improved by 0.29±0.33 in the ST group (P<0.0001; Table 3). For COT, both SE and ST demonstrated significantly greater improvement compared with OMC, but no significant difference was observed between ST and SE participants. Patients assigned to both SE and ST had greater increases in community-based step activity than OMC participants, but this was not statistically significant (Table 3).

Atherosclerosis risk factors demonstrated a greater improvement in high-density lipoprotein cholesterol among individuals in the SE group compared with the ST group and a trend for high-density lipoprotein cholesterol improvement in the OMC group compared with ST patients. There was also a statistically significant greater decrease in plasma fibrinogen levels in the SE group compared with the OMC group (Table 3).

**Symptoms and QOL**

The SF-12 physical summary score and disease-specific measures of symptoms, physical limitation, and walking ability were low at baseline, with a lower baseline WIQ distance score in the SE group, but no other differences between treatment groups (Table 4). In particular, the SF-12 physical summary scores were nearly 2 SDs below the US population average.

At 6 months, the ST group improved more than the OMC group for every QOL measure except the SF-12 mental summary scale, which was normal at baseline, and the WIQ distance score in the SE group, but no other differences between treatment groups (Table 4). In particular, the SF-12 physical summary scores were nearly 2 SDs below the US population average.
Table 3. Six-Month End Points and Risk Factors

<table>
<thead>
<tr>
<th>Primary end point</th>
<th>OMC (n=20)</th>
<th>SE + OMC (n=38)</th>
<th>ST + OMC (n=41)</th>
<th>SE vs OMC [95% CI] (P)</th>
<th>ST vs OMC [95% CI] (P)</th>
<th>SE vs ST [95% CI] (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change of PWT from baseline to 6 mo, mins</td>
<td>1.2 ± 2.6</td>
<td>5.8 ± 4.6</td>
<td>3.7 ± 4.9</td>
<td>4.6 [2.7–6.5] (&lt;0.0001)*</td>
<td>2.5 [0.6–4.4] (0.021)*</td>
<td>2.1 [0.0–4.2] (0.042)</td>
</tr>
<tr>
<td>P, nonparametric analysis</td>
<td></td>
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</tr>
<tr>
<td>Multiple imputation analysis</td>
<td>1.0 ± 2.8</td>
<td>6.1 ± 4.6</td>
<td>3.6 ± 4.9</td>
<td>5.1 [4.5–5.7] (&lt;0.0001)*</td>
<td>2.6 [2.0–3.2] (0.017)*</td>
<td>2.5 [1.9–3.1] (0.028)</td>
</tr>
<tr>
<td>Secondary end points</td>
<td></td>
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<tr>
<td>Change in COT from baseline to 6 mo, min</td>
<td>0.7 ± 1.1</td>
<td>3.0 ± 2.9</td>
<td>3.6 ± 4.2</td>
<td>2.2 [1.2–3.3] (0.003)</td>
<td>2.9 [1.5–4.3] (0.006)</td>
<td>0.7 [0.9–2.3] (0.425)</td>
</tr>
<tr>
<td>Change in hourly free-living steps from baseline to 6 mo, rt</td>
<td>-5.6 ± 109.4 (268.2, 168.9)</td>
<td>72.6 ± 138.7 (-185.2, 425.7)</td>
<td>114.3 ± 273.9 (-192.6, 976.4)</td>
<td>78.3 [0.7–157.2] (0.0625)</td>
<td>120.0 [3.5–236.5] (0.1024)</td>
<td>41.7 [73.4–156.8] (0.4661)</td>
</tr>
<tr>
<td>Change in ABI from baseline to 6 mo</td>
<td>0.01 ± 0.10 (0.24, 0.12)</td>
<td>0.03 ± 0.11 (0.23, 0.37)</td>
<td>0.29 ± 0.33 (0.12, 1.59)</td>
<td>0.0 [0.0–0.1] (0.578)</td>
<td>0.3 [0.2–0.4] (&lt;0.001)</td>
<td>0.3 [0.2–0.4] (&lt;0.001)</td>
</tr>
<tr>
<td>Risk factors (change from baseline)</td>
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<tr>
<td>LDL cholesterol, mg/dL</td>
<td>-4.4 ± 42.3</td>
<td>-3.6 ± 17.4</td>
<td>-9.3 ± 24.7</td>
<td>P=0.813</td>
<td>P=0.686</td>
<td>P=0.474</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>7.9 ± 15.4</td>
<td>5.6 ± 8.4</td>
<td>0.4 ± 8.5</td>
<td>P=0.551</td>
<td>P=0.061</td>
<td>P=0.013</td>
</tr>
<tr>
<td>Hemoglobin A(_{1c}), %</td>
<td>-0.09 ± 0.27</td>
<td>0.01 ± 0.50</td>
<td>0.01 ± 0.35</td>
<td>P=0.344</td>
<td>P=0.303</td>
<td>P=0.977</td>
</tr>
<tr>
<td>Fibrinogen, g/dL</td>
<td>31.7 ± 64.1</td>
<td>-15.0 ± 84.5</td>
<td>-2.0 ± 89.1</td>
<td>P=0.043</td>
<td>P=0.151</td>
<td>P=0.541</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>-5.8 ± 20.7</td>
<td>-0.95 ± 19.1</td>
<td>-5.6 ± 21.9</td>
<td>P=0.381</td>
<td>P=0.974</td>
<td>P=0.323</td>
</tr>
</tbody>
</table>

OMC indicates optimal medical care; SE, supervised exercise; ST, stent revascularization; CI, confidence interval; PWT, peak walking time; COT, claudication onset time; ABI, ankle-brachial index; LDL, low-density lipoprotein; and HDL, high-density lipoprotein. Values are mean ± SD (minimum, maximum) when appropriate. P values are based on ANCOVA with adjustment for study center, baseline cilostazol use, and baseline value of the end point.

*One-sided P value.
†Adjusted with pedometer logs.
This distinction was less apparent for COT, which correlated 0.24, 0.025 with the PAQ physical limitation score (0.33, PWT leads to an average improvement in WIQ of 2.0; both 0.69 for WIQ; both P<0.001) with no significant interaction with treatment group (P=0.26).

Safety
Overall, there were 4 serious adverse events within 30 days of the stent procedure. They were seen in 1 patient with arterial perforation managed with a stent graft without sequelae, 1 participant who required a transfusion (the same patient who had the perforation), and 2 patients with localized dissections. On follow-up, there were no serious adverse events associated with the use of SE, and cilostazol was well tolerated.

Table 4. Six-Month Leg Symptoms and Quality of Life

<table>
<thead>
<tr>
<th>Measure</th>
<th>OMC (n=20)</th>
<th>SE+OMC (n=38)</th>
<th>ST+OMC (n=41)</th>
<th>P, SE vs OMC</th>
<th>P, ST vs OMC</th>
<th>P, SE vs ST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline scores</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SF-12 physical</td>
<td>31.6±10.5</td>
<td>32.3±8.8</td>
<td>34.3±9.3</td>
<td>0.901</td>
<td>0.366</td>
<td>0.463</td>
</tr>
<tr>
<td>SF-12 mental</td>
<td>52.4±8.3</td>
<td>54.2±9.3</td>
<td>53.1±11.4</td>
<td>0.441</td>
<td>0.834</td>
<td>0.711</td>
</tr>
<tr>
<td>WIQ pain severity</td>
<td>28.4±20.8</td>
<td>30.2±25.9</td>
<td>33.7±27.5</td>
<td>0.842</td>
<td>0.423</td>
<td>0.292</td>
</tr>
<tr>
<td>WIQ walking distance</td>
<td>22.9±26.8</td>
<td>12.7±11.6</td>
<td>17.9±15.5</td>
<td>0.023</td>
<td>0.359</td>
<td>0.061</td>
</tr>
<tr>
<td>WIQ walking speed</td>
<td>26.5±20.8</td>
<td>21.4±16.9</td>
<td>26.3±18.3</td>
<td>0.252</td>
<td>0.930</td>
<td>0.190</td>
</tr>
<tr>
<td>WIQ stair climbing</td>
<td>33.5±30.0</td>
<td>30.3±22.1</td>
<td>33.2±23.7</td>
<td>0.542</td>
<td>0.889</td>
<td>0.561</td>
</tr>
<tr>
<td>PAQ physical limitation</td>
<td>32.9±27.0</td>
<td>28.9±18.0</td>
<td>30.5±19.5</td>
<td>0.566</td>
<td>0.621</td>
<td>0.897</td>
</tr>
<tr>
<td>PAQ symptoms</td>
<td>43.3±19.7</td>
<td>41.0±19.0</td>
<td>48.2±21.1</td>
<td>0.585</td>
<td>0.434</td>
<td>0.114</td>
</tr>
<tr>
<td>PAQ social limitation</td>
<td>59.7±32.3</td>
<td>55.6±25.5</td>
<td>55.0±26.5</td>
<td>0.636</td>
<td>0.438</td>
<td>0.718</td>
</tr>
<tr>
<td>PAQ treatment satisfaction</td>
<td>75.0±26.5</td>
<td>74.0±20.2</td>
<td>79.3±22.0</td>
<td>0.876</td>
<td>0.495</td>
<td>0.253</td>
</tr>
<tr>
<td>PAQ quality of life</td>
<td>44.4±25.5</td>
<td>44.0±18.4</td>
<td>46.1±19.4</td>
<td>0.915</td>
<td>0.853</td>
<td>0.664</td>
</tr>
<tr>
<td>PAQ summary</td>
<td>45.6±23.3</td>
<td>42.8±16.2</td>
<td>45.3±18.3</td>
<td>0.560</td>
<td>0.840</td>
<td>0.587</td>
</tr>
</tbody>
</table>

Change from baseline to 6 mo

<table>
<thead>
<tr>
<th>Measure</th>
<th>OMC (n=20)</th>
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<th>P, ST vs OMC</th>
<th>P, SE vs ST</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-12 physical</td>
<td>1.2±11.0</td>
<td>5.9±10.1</td>
<td>6.6±8.5</td>
<td>0.047</td>
<td>0.023</td>
<td>0.958</td>
</tr>
<tr>
<td>SF-12 mental</td>
<td>−2.4±8.0</td>
<td>−2.2±11.5</td>
<td>−1.7±9.9</td>
<td>0.810</td>
<td>0.713</td>
<td>0.862</td>
</tr>
<tr>
<td>WIQ pain severity</td>
<td>16.3±34.7</td>
<td>26.3±36.3</td>
<td>40.4±43.9</td>
<td>0.251</td>
<td>&lt;0.001</td>
<td>0.014</td>
</tr>
<tr>
<td>WIQ walking distance</td>
<td>−0.5±26.0</td>
<td>25.1±27.6</td>
<td>43.8±42.2</td>
<td>0.007</td>
<td>&lt;0.001</td>
<td>0.029</td>
</tr>
<tr>
<td>WIQ walking speed</td>
<td>1.47±15.69</td>
<td>16.5±19.7</td>
<td>30.8±31.0</td>
<td>0.007</td>
<td>&lt;0.001</td>
<td>0.007</td>
</tr>
<tr>
<td>WIQ stair climbing</td>
<td>10.2±29.3</td>
<td>24.0±20.9</td>
<td>29.3±39.1</td>
<td>0.071</td>
<td>0.051</td>
<td>0.539</td>
</tr>
<tr>
<td>PAQ physical limitation</td>
<td>0.6±22.5</td>
<td>16.2±19.2</td>
<td>28.1±30.9</td>
<td>0.012</td>
<td>&lt;0.001</td>
<td>0.043</td>
</tr>
<tr>
<td>PAQ symptoms</td>
<td>1.0±17.2</td>
<td>16.3±21.4</td>
<td>29.2±27.4</td>
<td>0.008</td>
<td>&lt;0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>PAQ social limitation</td>
<td>−10.6±29.6</td>
<td>8.8±30.0</td>
<td>17.6±30.2</td>
<td>0.016</td>
<td>&lt;0.001</td>
<td>0.156</td>
</tr>
<tr>
<td>PAQ treatment satisfaction</td>
<td>−8.1±19.1</td>
<td>4.6±20.7</td>
<td>4.0±25.9</td>
<td>0.013</td>
<td>0.010</td>
<td>0.323</td>
</tr>
<tr>
<td>PAQ quality of life</td>
<td>0.8±26.7</td>
<td>17.3±20.8</td>
<td>30.4±28.3</td>
<td>0.010</td>
<td>&lt;0.001</td>
<td>0.006</td>
</tr>
<tr>
<td>PAQ summary</td>
<td>−3.1±18.6</td>
<td>13.8±17.0</td>
<td>28.0±26.4</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>0.002</td>
</tr>
</tbody>
</table>

OMC indicates optimal medical care; SE, supervised exercise; ST, stent revascularization; SF-12, Short Form-12; WIQ, Walking Impairment Questionnaire; and PAQ, Peripheral Artery Questionnaire. Values are mean±SD. P values for baseline scores are based on ANCOVA with adjustment for study center and baseline cilostazol use. P values for change from baseline to 6 months are based on ANCOVA with adjustment for study center, baseline cilostazol use, and baseline score. P values for change from baseline to 6 months for PAQ symptom stability score are based on ANCOVA with adjustment for study center and baseline cilostazol use only. The physical and mental summary scores from the SF-12 correlate highly with those obtained from the SF-36 and are scaled to a US population mean of 50 and SD of 10 (higher scores are better). Multiple groups have suggested minimal clinically important changes in SF-12 summary scores to be ≥2 to 2.5 points and moderate changes to be ≥5 points.6 The WIQ grades symptom severity and patient ratings of their walking distance, walking speed, and ability to climb stairs on scales of 0 to 100, with higher scores indicating lesser symptoms and greater functional capacity. The PAQ assesses PAD-related physical limitation, symptoms, quality of life, social function, and treatment satisfaction, also on scales of 0 to 100; higher scores are better. For the PAQ summary scale, a difference of 8 points has been proposed as clinically important.7 The minimum clinically important difference has not been established for the WIQ.

association with QOL measures (PAQ physical limitation, P=0.025; WIQ distance, P=0.01). For the ST group, the degree of improvement in PWT was highly correlated with improvement in both the PAQ physical limitation score and the WIQ distance domain (a 1-minute improvement in PWT leads to an average improvement in PAQ of 4.1 and in WIQ of 5.9; Pearson correlation r versus PWT is 0.65 for PAQ and 0.69 for WIQ; both P<0.001). On the other hand, for the SE group, the PWT improvement was more weakly correlated with the WIQ distance domain (a 1-minute improvement in PWT leads to an average improvement in WIQ of 2.0; r=0.33, P=0.05), and there was no significant correlation with the PAQ physical limitation score (r=0.24, P=0.19). This distinction was less apparent for COT, which correlated strongly with both the PAQ physical limitation and WIQ distance scores (1-minute improvement in COT leads to an average improvement in PAQ of 3.9 and in WIQ of 5.6; r versus COT is 0.62 for PAQ and 0.66 for WIQ; both P<0.001) with no significant interaction with treatment group (P=0.26).
Discussion

This study represents the first multicenter randomized controlled trial to examine the relative benefit of SE, ST, and OMC and the first trial conducted exclusively in patients with aortoiliac PAD, long considered ideal for stent revascularization. The population had relatively severe PAD, with 38% of the ST group having total occlusions in the aortoiliac segment, with low ABIs, poor treadmill test performance, and poor QOL throughout all treatment groups at baseline.

Prior randomized trials comparing supervised exercise and percutaneous revascularization pooled patients with aortoiliac and femoropopliteal PAD and have shown SE to provide superior treadmill test walking at 6 months. It has been questioned whether such studies that showed the benefits of supervised exercise vis-à-vis endovascular revascularization were generalizable to patients with aortoiliac PAD. This study shows that for a population with advanced aortoiliac PAD, changes in PWT over 6 months were greater among those who received SE than those revascularized with ST.

It is noted that improvements in treadmill measures of functional status were not observed in the pedometer-derived measurements of community walking. This has been observed in other clinical trials of exercise for PAD; use of SE has been shown to increase 6-minute walk and treadmill walking outcomes but not pedometer-based measures of community walking. It is possible that improved leg function may, even with an associated improvement in claudication symptoms, not consistently lead to an increase in a patient’s ambulatory behavior.

Both SE and ST demonstrated improvements in PWT and QOL. Although SE showed more improvement in PWT, considered the standard end point for claudication research, the greatest improvements in self-reported QOL were observed in the ST cohort. This study was not designed to determine the cause of differential objective PWT, and subjective QOL outcomes from patients provided these distinct strategies of care. Superior treadmill-defined benefits from the SE group could be derived from the “specificity-of-training” effect or from improved cardiorespiratory fitness because the use of SE is known to be associated with physiological improvement in systemic and limb function. This study also did not evaluate the exact mechanism(s) by which SE improved exercise performance, which can include multiple physiological adaptive effects and treadmill use familiarity. Eighteen-month results, obtained a year after completion of treadmill training, should provide valuable additional information.

This study demonstrated adequate adherence to SE in a community treatment setting using a centrally administered program, risk factor control achieved via use of a structured patient informational program, SE and ST benefit in the context of an active claudication medication, the safety of both SE and ST interventions, and the finding that SE is an efficacious intervention for patients with PAD in the aortoiliac segment.

In summary, these results indicate that both treatments are superior to OMC and provide widened choices for all patients. The selection of the ideal treatment will depend on the patient’s preference. At the very least, the CLEVER 6-month results suggest that SE is a reasonable strategy compared with ST and that efforts should be made to develop SE programs that are available and affordable to patients.

Limitations

These 6-month results are relatively short term, and the 6-month end point coincided with the completion of SE when exercise benefits are expected to be their greatest. The longer-term 18-month benefit and harm of exercise and stenting and the health economic impact of these approaches to claudication treatment are under evaluation in this study. However, in a study of a chronic disease for which treatments are directed at symptom relief, near-term outcomes are clinically relevant. The efficacy of these strategies of care for individuals with claudication caused by femoropopliteal PAD anatomy is not known. However, there is much controversy surrounding methods of revascularization for the femoropopliteal segment, in contrast to the aortoiliac segment, for which stent revascularization has a proven track record. Indeed, the results of this study are generalizable to patients with aortoiliac PAD, a large population, with or without concomitant femoropopliteal artery PAD. Finally, the study has a smaller sample size than originally planned, partly because of slow enrollment. Slow enrollment has been a hallmark of most comparative effectiveness clinical trials, in which recruitment is typically hampered by clinician bias in favor of 1 treatment strategy or a reimbursement bias that is not comparable across the tested interventions.

Conclusions

This study demonstrates that for patients with claudication, SE provides a superior improvement in treadmill walking performance compared to both primary aortoiliac ST and OMC (home walking and cilostazol) over 6 months. This benefit is associated with an improvement in self-reported walking distance, an increase in high-density lipoprotein, and a decrease of fibrinogen. Secondary measures of treatment efficacy favored primary stenting, with greater improvements in self-reported physical function.

Appendix

The CLEVER investigators, coauthors, and committee members were as follows. Principal investigators (in order of decreasing number of patients who were randomly assigned to a treatment group): T. Murphy, Rhode Island Hospital, Providence; J. Ehrman, Henry Ford Hospital, Detroit, MI; V. Krishnamurthy, VA Ann Arbor, Ann Arbor, MI; J. Nadarajah, Aiyan Diabetes Center, Augusta, GA; A.T. Hirsch, University of Minnesota and Minneapolis Heart Institute Foundation, Minneapolis; A. Comerota, Johns Hopkins Hospital, Baltimore, MD; A. Tassiopoulos, Hahnemann University, Philadelphia; W. Abernethy, Asheville Cardiology, Asheville, NC; J. Matsura, Iowa Clinic, Des Moines; J. Kaufman, Oregon Health Science University, Portland; J. Martinez, Peripheral Vascular Associates, San Antonio, TX; M. Moursi, VA Central Arkansas, Little Rock; and F. Bech, VA Palo Alto, Palo Alto,

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Disclosures
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References
Claudication is the most common ischemic symptom of peripheral artery disease (PAD), affecting approximately 30% of these patients and limiting pain-free walking in over 2 million Americans. There are 3 treatments available for these symptoms, including claudication pharmacotherapy (cilostazol), supervised exercise, and endovascular revascularization, but little data comparing their relative efficacy, harm, and cost-effectiveness. There has been a marked rise in use of invasive (percutaneous) angioplasty and stenting, while PAD exercise programs remain mostly unavailable. The Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) study is an NHLBI-sponsored comparative effectiveness clinical investigation that randomly assigned 111 patients with aortoiliac PAD (the optimal anatomic site for stenting) to receive 1 of 3 treatments: optimal medical care (OMC, using home exercise and cilostazol), OMC plus supervised exercise (SE), or OMC plus stent revascularization (ST). At 6 months of follow-up (the primary end point), the improvement in peak walking time was greatest for SE, intermediate for ST, and least with OMC (mean change versus baseline 5.8±4.6, 3.7±4.9, and 1.2±2.6 minutes, respectively; \( P=0.02 \) for ST versus OMC, and \( P=0.04 \) for SE versus ST). Disease-specific quality of life improved with both SE and ST compared with OMC, but the improvement was greater with ST than SE. This study demonstrates that supervised exercise treatment results in superior treadmill walking performance than stent placement for patients with aortoiliac PAD. The longer-term impact of SE and ST on functional status and health economic outcomes in individuals with aortoiliac PAD will be assessed at 18 months.
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


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Comparaison entre l'entraînement à la marche supervisé et la pose de stent primaire dans le traitement de la claudication intermittente secondaire à une artériopathie périphérique aorto-iliaque

Résultats à six mois de l'étude Claudication: Exercise Versus Endoluminal Revascularization (CLEVER)

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Contexte—La claudication intermittente est un symptôme fréquemment associé à l'existence d'une artériopathie des membres inférieurs, qu'il est possible de prendre en charge par un traitement médicamenteux, un entraînement à la marche supervisé (EMS) ou une revascularisation avec pose de stent (RPS).

Méthodes et résultats—Nous avons randomisé 111 patients présentant une artériopathie périphérique aorto-iliaque en leur assignant l'un des trois traitements ci-après : traitement médical optimal (TMO), TMO plus EMS ou TMO plus RPS. Le critère de jugement principal a été l'évolution à 6 mois du temps de marché maximal réalisé lors d'une épreuve sur tapis roulant comparativement à celui enregistré à l'entrée dans l'étude. Les critères de jugement secondaires ont été le périmètre de marche, la qualité de vie évaluée par les scores du Walking Impairment Questionnaire, du Peripheral Artery Questionnaire et du questionnaires à 12 items de la Medical Outcomes Study ainsi que les facteurs de risque cardiovasculaire. Au terme des 6 mois de suivi, la plus forte amélioration du temps de marché maximal (le critère de jugement principal) a été observée dans le groupe ayant bénéficié d'un EMS, l'amélioration ayant été de 230 mètres après RPS et maximale chez les patients qui avaient uniquement fait l'objet d'un TMO. Les modifications moyennes (apportées par rapport aux temps initialement mesurés avant l'étude) étaient respectivement de 3,6 ± 6,6, 3,7 ± 4,9 et 1,2 ± 2,6 minutes ; p < 0,001 pour la comparaison entre EMS et TMO, p = 0,64 pour la comparaison entre EMS et RPS. Bien que l'évaluation de la qualité de vie spécifique des patients ait été différente sur les scores du Walking Impairment Questionnaire et du Peripheral Artery Questionnaire, l'effet apparaît se confirmer ainsi bien dès les patients ayant bénéficié d'un EMS que chez ceux pris en charge par RPS, comparativement au groupe uniquement soumis au TMO, pour la plupart des échelles, l'amélioration a été plus marquée après RPS que sous EMS. Le périmètre de marche a davantage augmenté après RPS que sous EMS ou sous TMO seul (114 ± 274 mètres contre 73 ± 130 et -6 ± 109), mais les différences n'ont pas été statistiquement significatives.

Conclusions—Le EMS contribue à améliorer le temps de marché sur tapis roulant comparativement à la RPS, y compris chez les individus atteints d'une artériopathie périphérique aorto-iliaque. Toutefois, l'effet que le temps de marché atteint supérieur dans le groupe ayant bénéficié d'un EMS alors que la qualité de vie ressentie par les patients a été meilleure après RPS justifie une étude plus approfondie.

Mots-clés : claudication intermittente, recherche sur l'efficacité comparative, artériopathie périphérique des membres inférieurs, maladies vasculaires