Endovascular Revascularization and Supervised Exercise for Peripheral Artery Disease and Intermittent Claudication

A Randomized Clinical Trial

Farzin Fakhry, MD; Sandra Spronk, PhD; Lijckle van der Laan, MD, PhD; Jan J. Wever, MD, PhD; Joep A. W. Teijink, MD, PhD; Wolter H. Hoffmann, MD, PhD; Taco M. Smits, MD, PhD; Jerome P. van Brussel, MD, PhD; Guido N. M. Stultiens, MD; Alex Derom, MSc; Andre van Petersen, MD; Kristel Woltman, MD; Ingrid Hulst, MA, ANP; Marc R. H. M. van Sambeek, MD, PhD; Dimitris Rizopoulos, PhD; Ellen V. Rouwet, MD, PhD; M. G. Myriam Hunink, MD, PhD

Importance
Supervised exercise is recommended as a first-line treatment for intermittent claudication. Combination therapy of endovascular revascularization plus supervised exercise may be more promising but few data comparing the 2 therapies are available.

Objective
To assess the effectiveness of endovascular revascularization plus supervised exercise for intermittent claudication compared with supervised exercise only.

Design, Setting, and Participants
Randomized clinical trial of 212 patients allocated to either endovascular revascularization plus supervised exercise or supervised exercise only. Data were collected between May 17, 2010, and February 16, 2013, in the Netherlands at 10 sites. Patients were followed up for 12 months and the data were analyzed according to the intention-to-treat principle.

Interventions
A combination of endovascular revascularization (selective stenting) plus supervised exercise (n = 106) or supervised exercise only (n = 106).

Main Outcomes and Measures
The primary end point was the difference in maximum treadmill walking distance at 12 months between the groups. Secondary end points included treadmill pain-free walking distance, vascular quality of life (VascuQol) score (1 [worst outcome] to 7 [best outcome]), and 36-item Short-Form Health Survey (SF-36) domain scores for physical functioning, physical role functioning, bodily pain, and general health perceptions (0 [severe limitation] to 100 [no limitation]).

Results
Endovascular revascularization plus supervised exercise (combination therapy) was associated with significantly greater improvement in maximum walking distance (from 264 m to 1501 m for an improvement of 1237 m) compared with the supervised exercise only group (from 285 m to 1240 m for improvement of 955 m) (mean difference between groups, 282 m; 99% CI, 60-505 m) and in pain-free walking distance (from 117 m to 1237 m for improvement of 1120 m vs from 135 m to 847 m for improvement of 712 m, respectively) (mean difference, 408 m; 99% CI, 195-622 m). Similarly, the combination therapy group demonstrated significantly greater improvement in the disease-specific VascuQol score (1.34 [99% CI, 1.04-1.64] in the combination therapy group vs 0.73 [99% CI, 0.43-1.03] in the exercise group; mean difference, 0.62 [99% CI, 0.20-1.03]) and in the score for the SF-36 physical functioning (22.4 [99% CI, 16.3-28.5] vs 12.6 [99% CI, 6.3-18.9], respectively; mean difference, 9.8 [99% CI, 1.4-18.2]). No significant differences were found for the SF-36 domains of physical role functioning, bodily pain, and general health perceptions.

Conclusions and Relevance
Among patients with intermittent claudication after 1 year of follow-up, a combination therapy of endovascular revascularization followed by supervised exercise resulted in significantly greater improvement in walking distances and health-related quality-of-life scores compared with supervised exercise only.

Trial Registration
Netherlands Trial Registry Identifier: NTR2249

Intermittent claudication is the classic symptomatic form of peripheral artery disease, affecting approximately 20 to 40 million people worldwide and is increasing rapidly with the aging world population. Patients with claudication experience significant functional disability resulting in a sedentary lifestyle and reduced quality of life.

Supervised exercise is an effective first-line treatment for claudication and is recommended by international guidelines as the standard of care. Yet, in clinical practice, its value remains uncertain because supervised exercise programs are underused due to limited access in most countries, reimbursement issues, and poor patient compliance. As a consequence, endovascular revascularization is an increasingly attractive first-line alternative due to its immediate effect and potential to prevent disability. Studies have suggested that endovascular revascularization is not significantly different from supervised exercise for improving functional performance and quality of life. Hence, to date, the optimal first-line treatment in clinical practice for the increasing population of patients with claudication remains uncertain.

A combination therapy of early endovascular revascularization followed by supervised exercise seems promising because it combines the immediate improvement in claudication symptoms after revascularization with the added long-term benefits of exercise therapy. Two systematic reviews on this topic concluded that combination therapy might be superior to supervised exercise or endovascular revascularization alone. However, this conclusion was based on limited data and needed to be confirmed in a larger randomized clinical trial (RCT). To address this question, the Endovascular Revascularization And Supervised Exercise (ERASE) RCT was designed to compare both the effectiveness and cost-effectiveness of endovascular revascularization plus supervised exercise in patients with intermittent claudication with supervised exercise only. The outcomes on effectiveness are reported in this article. The cost-effectiveness analysis will be presented in the future.

Methods

Study Design
The ERASE study was a parallel-design RCT conducted in the Netherlands at 10 sites between May 17, 2010, and February 16, 2013, comparing endovascular revascularization plus supervised exercise for intermittent claudication with supervised exercise only. The institutional review board at each participating center approved the trial protocol (Supplement) and written informed consent was obtained from all patients.

Participants
Patients with peripheral artery disease and stable claudication (≥3 months) referred to the outpatient clinic in the participating centers were potentially eligible. Patients were included if they had a resting ankle brachial index (ABI) of 0.90 or less or if their ABI decreased by more than 0.15 after treadmill testing regardless of their ABI at rest. All participants also had 1 or more vascular stenoses at the aortoiliac level, the femoro-popliteal level, or both, as established by noninvasive vascular imaging. Furthermore, their maximum walking distance had to be between 100 m and 500 m as assessed on a graded treadmill using the protocol by Gardner et al. Patients were excluded if their target lesions were unsuitable for revascularization or if they had received prior treatment for the target lesions. Patients with limited life expectancy or ambulation due to a condition other than peripheral artery disease also were excluded.

Randomization
Eligible patients were assigned in a 1:1 ratio to either endovascular revascularization plus supervised exercise or supervised exercise only. Randomization and allocation was performed using web-based randomization software (TenALEA, Amsterdam, the Netherlands) based on the Pocock and Simon minimization method.

Intervention
Supervised Exercise
Exercise was provided to the patients by trained physiotherapists in a network of physiotherapy clinics in each patient’s neighborhood or at the physiotherapy center of the participating site. All physiotherapists were required to have completed a 2-day course on supervised exercise for claudication certified by the Royal Dutch Society for Physical Therapy and follow the society’s guideline on treatment of claudication. Most of the selected physiotherapists (82%) also participated in ClaudicioNet, a national network of integrated care to improve the quality and accessibility of supervised exercise for patients with claudication in which the participating physiotherapists receive regular training and monitoring.

The exercise program consisted primarily of treadmill walking to near-maximum claudication pain. The physiotherapists were advised to start with a frequency of 2 to 3 sessions every week and approximately 30 to 45 minutes per session during the first 3 months. After this phase, the frequency was reduced to at least 1 session per week between months 3 and 6 and then to a frequency of 1 session per 4 weeks at 12 months, depending on patients’ progress and preference.

Endovascular Revascularization Plus Supervised Exercise
Endovascular revascularization was performed by an experienced interventional radiologist or vascular surgeon following the latest standards in accordance with the normal practice of the participating site. For iliac and femoral revascularizations, a stent was used only if the initial balloon angioplasty was not successful (selective stenting). In addition, within 2 to 4 weeks after the procedure, patients were enrolled in the supervised exercise program described above.

Outcomes and Assessment
Outcome assessment was performed at baseline and at the 1-, 6-, and 12-month follow-up visits. Baseline medical history and demographic data, including sex and race, were obtained by patient report to allow external generalizability of the study results. In addition, lipid profile, weight, height, and waist circumference were measured at the study visit and patient...
The primary outcome was maximum walking distance at 12 months assessed during a graded treadmill test (maximum duration, 30 minutes). To ensure blinded outcome assessment, the treadmill test was overseen by an independent person, who was unaware of the specific treatment assigned, and patients were advised not to discuss their assigned treatment.

Secondary outcomes included pain-free walking distance, ABI (at rest and after exercise), and additional interventions (defined as any surgical or endovascular revascularization procedure, or both) offered to the patient during follow-up as a result of primary randomized treatment failure, number of leg amputations, and recurrent stenosis detected at 12 months by duplex ultrasonography in the endovascular revascularization plus supervised exercise group. Patient-reported generic quality of life was obtained using the Rating score, which is based on a single question in which patients rate their health state on a scale from 0 (worst imaginable) to 100 (best imaginable), and the 36-item Short-Form Health Survey domain scores for physical functioning, physical role function (ie, limitations due to physical problems), bodily pain, and general health perceptions on a scale from 0 (severe limitation) to 100 (no limitation)22; these are the most relevant health domains to describe the health status of patients with peripheral artery disease.21 In addition, disease-specific quality of life was measured using the VascuQol questionnaire, which consists of the following 5 domains of activities, symptoms, pain, emotional, and social scored on a scale from 1 (worst outcome) to 7 (best outcome).22

Statistical Analysis
Based on previous studies, a mean difference of 30% to 35% in treadmill maximum walking distance (corresponding to an approximately 150 m difference after 12 months) between the 2 groups was considered as a relevant effect size.23-25 The power calculations proposed that 210 patients would be needed to achieve a 90% power to detect a 30% difference in maximum walking distance between the groups, with a 2-sided type I error rate of 0.01 and anticipating a 10% loss to follow-up.

The main analyses were conducted according to the intention-to-treat principle. Completeness of follow-up in each group was calculated as the ratio of total observed person-time of follow-up to the potential maximum person-time of follow-up.26 Continuous variables at baseline are presented as means and standard deviations and categorical variables as proportions. Multiple imputation to replace the missing baseline variables (5.2% [range, 0%-13%] of the baseline values were missing) was performed by combining the results from 5 imputed data sets in which regression modeling was used to predict the missing values based on the existing baseline variables.27 Between-group differences for the continuous outcome measures were compared using mixed models for repeated measures with random-effects adjustment for center effects.

A significant number of patients reached the maximum of 30 minutes of walking on the treadmill during follow-up, causing a nonnormal distribution for walking distances. To address this ceiling effect and account for the correlations in the repeated measurements for each patient, we used the Tobit mixed-effects model.28 The computations were performed in SAS procedure NL MIXED using the general likelihood option. Between-group differences for additional interventions during follow-up were compared using Kaplan-Meier methods and Cox proportional hazards models. The proportional hazards assumptions were evaluated and met to estimate hazard ratios with corresponding 99% confidence intervals.

To account for multiple testing, we used a stringent significance level of .01 (2-sided) as statistically significant for all analyses. The statistical analyses were performed using SPSS version 21 (SPSS Inc) and SAS version 9.3 (SAS Institute Inc).

Results
A total of 666 patients were screened for inclusion. Of these, 212 patients were randomly assigned to supervised exercise (n = 106) or endovascular revascularization plus supervised exercise (n = 106; combination therapy group) (Figure 1).

The 2 groups were well matched at baseline (Table 1). The mean (SD) age was 65 (10) years, 132 patients (62%) were men, and noninvasive imaging identified 112 (53%) patients with predominant aortoiliac disease and 100 (47%) patients with predominant femoropopliteal disease. The types of noninvasive imaging used were duplex ultrasonography (n = 155), magnetic resonance angiography (n = 8), and computed tomography angiography (n = 49).

In the combination therapy group, endovascular revascularization at baseline was technically successful in 102 patients (96%). Procedure-related minor complications occurred in 7 patients (7%), including groin hematoma (n = 5) and localized arterial dissection (n = 2); however, no major complications were recorded. Of the 4 patients in whom endovascular revascularization technically failed, 3 underwent an open surgical procedure, including endarterectomy (n = 2) and bypass (n = 1) procedures, and 1 received only supervised exercise.

Among the 102 patients with technically successful endovascular revascularization, balloon angioplasty was followed by selective stent placement in 63 patients (62%). The average number of completed exercise sessions in the combination therapy group was 30 sessions compared with the recommended 46 to 59 sessions during the 1-year follow-up. In the supervised exercise group, the average number of completed exercise sessions was 43 sessions compared with the recommended 46 to 59 sessions during the 1-year follow-up. The completeness of 1-year follow up was 96% (5211/5438 person-weeks) in the exercise group and 97% (5329/5518 person-weeks) in the combination therapy group (Figure 1).
Primary Outcome
During follow-up, the maximum treadmill walking distance improved significantly in both the supervised exercise only group and in the endovascular revascularization plus supervised exercise group. Compared with the supervised exercise only group, the improvement was significantly greater in the combination therapy group with a mean difference of 566 m (99% CI, 358-774 m) at 1 month, 409 m (99% CI, 183-636 m) at 6 months, and 282 m (99% CI, 60-505 m) at 12 months (Table 2).

Secondary Outcomes
One year after randomization, endovascular revascularization plus supervised exercise led to greater improvement in pain-free walking distance compared with supervised exercise only with a mean between-group difference of 408 m (99% CI, 195-622 m). Similarly, ABI at rest and after exercise showed significantly greater improvement in the combination therapy group (Table 2).

During the 1-year follow up, 2 patients (2%) in the supervised exercise group and none in the combination therapy group underwent a minor amputation due to deterioration of claudication to progressive lower limb ischemia. Twenty-three patients (22%) in the supervised exercise group needed an intervention during follow-up due to deterioration of symptoms or persisting disabling symptoms, including 21 patients who required an endovascular revascularization procedure and 2 patients who required an open revascularization procedure. In the combination therapy group, 8 patients (8%) required a secondary intervention, including 3 patients who underwent an endovascular revascularization procedure and 5 patients who underwent an open revascularization procedure. This resulted in a significantly higher proportion of patients without an additional intervention after 1 year of follow-up in the combination therapy group (92%) compared with the supervised exercise group (77%) (hazard ratio, 3.2 [99% CI, 1.1-9.2]; P = .005; Figure 2).

At 1 year, 73 of the 100 patients available for follow-up in the endovascular revascularization plus supervised exercise group received duplex ultrasonography to assess restenosis of the revascularized dominant lesion. In this group, significant restenosis was identified in 23 patients (32%), including 17 (74%) with significant restenosis in the femoropopliteal seg-
ment and 6 (26%) with significant restenosis in the aortoiliac segment. In the group with a significant restenosis, 4 patients (17%) required a secondary revascularization procedure due to deterioration of claudication during the 1-year follow-up.

One year after randomization, the disease-specific VascuQol score significantly improved in both groups. The improvement was significantly greater for the combination therapy group with a mean between-group difference of 0.62 (99% CI, 0.20–1.03). Similarly, at 1-year follow-up, the Rating
score was significantly greater in the combination therapy group (Table 3). For the 36-item Short-Form Health Survey domains, only physical functioning was significantly greater at 12 months in the combination therapy group (Table 3).

**Discussion**

The ERASE trial was designed to examine whether endovascular revascularization plus supervised exercise compared with supervised exercise only would further improve functional and quality-of-life outcomes in patients with intermittent claudication. After 1 year, patients in both groups improved significantly; however, patients receiving the combination therapy had more rapid and significantly greater improvements in their walking performance and disease-specific quality of life.

To our knowledge, the ERASE trial is the first adequately powered RCT assessing the effectiveness of a combination therapy of endovascular revascularization plus supervised exercise vs supervised exercise only in patients with aortoiliac and femoropopliteal peripheral artery disease. In the Claudication: Exercise vs Endoluminal Revascularization trial, which was funded by the National Institutes of Health and assessed the effectiveness of treatment strategies for aortoiliac disease, the fourth treatment group combining endovascular revascularization plus supervised exercise was prematurely stopped and removed from the analysis due to slow enrollment. Similarly, in the Mild to Moderate Intermittent Claudication trial that assessed the adjuvant benefit of endovascular revascularization above supervised exercise, recruitment was stopped prematurely due to slow enrollment. The authors included 67 patients in the combination therapy group and demonstrated that after 24 months of follow-up, patients in the endovascular revascularization plus supervised exercise group had significantly higher maximum walking distance compared with the patients in the exercise only group. A more recent trial by Mazari et al that assessed the effectiveness of a combination therapy of endovascular revascularization plus supervised exercise compared with a monotherapy of endovascular revascularization...
or supervised exercise in patients with femoropopliteal disease showed that the combination therapy was not different after 1 year regarding improvement in walking distance and quality of life. The lack of a statistically significant difference in walking distance between the groups might have been due to a ceiling effect because the treadmill test duration was limited to only 5 minutes (215 m).

The present study reopens the debate for revascularization in patients with claudication, in particular in terms of an approach using endovascular revascularization first. By improving lower extremity blood flow, early percutaneous revascularization of the target lesion gives an impulse to patient mobility and quality of life in the short-term. This, in turn, facilitates subsequent exercising and allows the patient to profit from the long-term benefits of an additional supervised exercise program. Even though almost one-third of the patients in the combination therapy group showed a restenosis of their initially revascularized lesion at 1-year follow-up, only 4% required a secondary intervention because of recurrent claudication symptoms. This suggests that the addition of a supervised exercise program may prevent deterioration despite restenosis or progression of atherosclerotic lesions. Similarly, Mazari et al.32 found a sustained clinical improvement after combination therapy with none of the patients reporting deterioration or requiring reintervention by 1 year. An important condition to achieve this synergetic effect is to have a well-established standardized and accessible supervised exercise program for patients to follow after the endovascular revascularization procedure, as was the case in the ERASE trial.

In addition to demonstrating benefits of a combination therapy, this study also confirmed the beneficial effects of exercise in the management of claudication with significant improvements in walking distances and quality of life in patients receiving supervised exercise only with the majority of patients reporting symptom improvements in walking distance and quality of life.

### Table 3. Quality-of-Life Measures

<table>
<thead>
<tr>
<th>Quality-of-Life Measures</th>
<th>Mean (99% CI)</th>
<th>Endovascular Revascularization Plus Supervised Exercise (n = 106)</th>
<th>Between-Group Difference</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>VascuQol score&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>At baseline</td>
<td>4.51 (4.25 to 4.77)</td>
<td>4.48 (4.25 to 4.71)</td>
<td>1.25 (0.94 to 1.56)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1 mo</td>
<td>0.27 (0.04 to 0.50)</td>
<td>1.52 (1.29 to 1.76)</td>
<td>8.7 (2.4 to 15.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>6 mo</td>
<td>0.62 (0.37 to 0.88)</td>
<td>1.41 (1.16 to 1.66)</td>
<td>10.6 (4.3 to 17.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>12 mo</td>
<td>0.73 (0.43 to 1.03)</td>
<td>1.34 (1.04 to 1.64)</td>
<td>6.5 (0.2 to 12.7)</td>
<td>&lt;.001</td>
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<tr>
<td>Rating score&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>At baseline</td>
<td>64.9 (60.4 to 69.4)</td>
<td>67.9 (63.4 to 72.4)</td>
<td>-2.4 (−7.3 to 2.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1 mo</td>
<td>1.1 (~3.9 to 6.2)</td>
<td>9.9 (5.1 to 14.7)</td>
<td>8.7 (2.4 to 15.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>6 mo</td>
<td>-0.5 (~5.5 to 4.5)</td>
<td>10.1 (5.2 to 15.0)</td>
<td>10.6 (4.3 to 17.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>12 mo</td>
<td>1.4 (~3.5 to 6.3)</td>
<td>7.9 (3.0 to 12.8)</td>
<td>6.5 (0.2 to 12.7)</td>
<td>&lt;.001</td>
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<tr>
<td>SF-36 physical functioning&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>At baseline</td>
<td>52.7 (47.4 to 58.0)</td>
<td>51.4 (47.3 to 55.5)</td>
<td>-1.3 (~3.6 to 0.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1 mo</td>
<td>4.0 (~0.7 to 8.6)</td>
<td>27.3 (22.7 to 31.8)</td>
<td>23.3 (17.3 to 29.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>6 mo</td>
<td>12.7 (7.7 to 17.7)</td>
<td>27.2 (22.3 to 32.2)</td>
<td>14.6 (7.9 to 21.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>12 mo</td>
<td>12.6 (6.3 to 18.9)</td>
<td>22.4 (16.3 to 28.5)</td>
<td>9.8 (1.4 to 18.2)</td>
<td>&lt;.001</td>
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<tr>
<td>SF-36 physical role functioning score&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>At baseline</td>
<td>53.4 (43.2 to 63.7)</td>
<td>59.2 (49.1 to 69.3)</td>
<td>-5.8 (~11.3 to 0.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1 mo</td>
<td>2.6 (~7.2 to 12.3)</td>
<td>19.7 (10.0 to 29.4)</td>
<td>17.1 (4.5 to 29.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>6 mo</td>
<td>5.9 (~4.4 to 16.1)</td>
<td>18.9 (8.8 to 28.9)</td>
<td>13.0 (~0.1 to 26.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>12 mo</td>
<td>5.0 (~6.4 to 16.5)</td>
<td>19.0 (7.8 to 30.2)</td>
<td>14.0 (~0.8 to 28.7)</td>
<td>&lt;.001</td>
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<tr>
<td>SF-36 bodily pain, mo&lt;sup&gt;e&lt;/sup&gt;</td>
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<tr>
<td>At baseline</td>
<td>53.1 (47.9 to 58.3)</td>
<td>52.7 (48.3 to 57.1)</td>
<td>-0.4 (~6.9 to 6.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1 mo</td>
<td>-3.1 (~8.1 to 2.0)</td>
<td>22.7 (17.7 to 27.8)</td>
<td>25.8 (19.2 to 32.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>6 mo</td>
<td>6.6 (1.2 to 11.9)</td>
<td>21.0 (15.7 to 26.3)</td>
<td>14.4 (7.4 to 21.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>12 mo</td>
<td>10.4 (4.3 to 16.5)</td>
<td>17.9 (12.0 to 23.9)</td>
<td>7.6 (~0.6 to 15.7)</td>
<td>&lt;.001</td>
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<tr>
<td>SF-36 general health perceptions, mo&lt;sup&gt;e&lt;/sup&gt;</td>
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</tr>
<tr>
<td>At baseline</td>
<td>53.9 (48.9 to 59.0)</td>
<td>59.3 (55.4 to 63.2)</td>
<td>-5.4 (~11.8 to 0.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1 mo</td>
<td>-0.6 (~4.7 to 3.5)</td>
<td>5.0 (0.8 to 9.1)</td>
<td>5.6 (0.1 to 11.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>6 mo</td>
<td>1.6 (~2.8 to 5.9)</td>
<td>5.8 (1.5 to 10.1)</td>
<td>4.2 (~1.6 to 9.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>12 mo</td>
<td>-2.4 (~7.3 to 2.5)</td>
<td>1.7 (~3.1 to 6.5)</td>
<td>4.1 (~2.4 to 10.6)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: SF-36, 36-item Short-Form Health Survey; VascuQol, Vascular Quality of Life Questionnaire.

* Calculated using the likelihood ratio test.

Composed of 25 questions in 5 domains including activities, symptoms, pain, emotional, and social, which are scored on a scale from 1 (worst outcome) to 7 (best outcome). The minimal clinically important difference for VascuQol has been established as greater than 0.36 points to 0.48 points.

Data are expressed as mean improvement compared with baseline.

Composed of a single question in which patients score their health state on a scale from 0 (worst imaginable) to 100 (best imaginable). For patients with peripheral arterial disease, the minimum clinically important difference for this rating score has not been established.

In this study, the SF-36 questionnaire is composed of 4 separate domain scores, which are the weighted sums of the questions in each domain. Each domain score is expressed on a scale from 0 (severe limitation) to 100 (no limitation). The minimal clinically important difference for the SF-36 score is suggested to be greater than 2 points to 2.5 points.
and is under way to address the question of whether the incremental benefit of the combination therapy as demonstrated in this study will also be cost-effective given the substantially higher costs of endovascular revascularization compared with supervised exercise.33-35

In clinical practice, especially in the United States, endovascular revascularization alone is being performed more frequently than the recommended care of supervised exercise. This is mainly due to reimbursement issues and unavailability of supervised exercise. Previous studies have shown exercise alone to be no different than24,32 or even superior to endovascular revascularization alone.30,31 Thus, in the ERASE trial we chose to study the treatment strategy of combining supervised exercise and endovascular revascularization.

We believe this was the most relevant comparison from a scientific point of view and also the most relevant comparison in the context of recommended clinical practice as formulated in the guidelines.5-9

The ERASE study has several limitations. First, the results are only generalizable to patients with stable claudication meeting our eligibility criteria. Second, an adequate screening log for all eligible patients was only stored at the largest center. Due to an absence of screening logs at the other centers, some patients might have been eligible for inclusion but were not screened or might have been excluded based on the preference of physicians. Yet, no indication for such bias exists and the baseline characteristics of the population included in this study are comparable with previously published RCTs of patients with claudication.23,24,32,36

Third, due to an absence of a well-defined and validated value for a clinically relevant difference in treadmill walking distance,37 it remains uncertain to what extent the significant difference in treadmill walking distance will affect the patients daily mobility. Fourth, the study follow-up was limited to 1 year and, given the decreasing mean difference in maximum walking distance between the 2 groups, the long-term effects of the combination therapy beyond 1 year remains unanswered and warrants further research. The exact reason for the decreasing mean difference in walking distance between the groups over time is unknown. Table 2 shows that the improvement in walking distance is sustained between 6 and 12 months with combination therapy, whereas with supervised exercise alone walking distance continues to improve during this period. This suggests that improvement in walking distance may take longer to develop with exercise alone because collateral circulation needs to develop and muscle metabolism needs to change. Alternatively, this may be explained by the revascularization interventions in the supervised exercise group, which were performed for deterioration of symptoms.

Fifth, the number of supervised exercise sessions followed by the patients was lower compared with the number of sessions as recommended by the guideline,7 which might have resulted in a less effective supervised exercise. Nonetheless, significant improvement was demonstrated in walking distance and quality of life in the supervised exercise group, which was comparable or even superior to previously published RCTs assessing the effectiveness of supervised exercise.23,24,30,32,36,38

In addition, the optimal number of supervised exercise sessions to complete remains unknown.8 The supervised exercise program in the ERASE study was in accordance with the single RCT on this issue, which suggests an important role for intensive training offered during the first 2 months of supervised exercise.39

Conclusions

Among patients with intermittent claudication after 1 year of follow-up, a combination therapy of endovascular revascularization followed by supervised exercise resulted in significantly greater improvement in walking distances and health-related quality-of-life scores compared with supervised exercise only.
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REFERENCES


