# Gender differences following supervised exercise therapy in patients with intermittent claudication

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***Objective:*** **Prevalence of peripheral arterial disease is equal in men and women. However, women seem to suffer more from the burden of disease. Current studies on gender-related outcomes following supervised exercise therapy (SET) for intermittent claudication (IC) yield conflicting results.**

***Methods:*** **A follow-up analysis was performed on data from the 2010 Exercise Therapy in Peripheral Arterial Disease (EXITPAD) study, a multicenter randomized controlled trial including IC patients receiving SET or a walking advice. The SET program was supervised by physiotherapists and included interval-based treadmill walking approximating maximal pain combined with activities such as cycling and rowing. Patients usually started with three 30-minute sessions a week. Training frequency was adapted during the following year on the basis of individual needs. The primary outcome was gender differences regarding the change in absolute claudication distance (ACD) after SET. ACD was defined as the number of meters that a patient had covered just before he or she was forced to stop walking because of intolerable pain. Secondary outcomes were gender differences in change of functional walking distance, quality of life, and walking (dis) ability after SET. Walking distances were obtained by standardized treadmill testing according to the Gardner-Skinner protocol. Quality of life was measured by the 36-Item Short Form Health Survey, and walking (dis)ability was determined by the Walking Impairment Questionnaire (WIQ). Measurements were performed at baseline and after 3, 6, 9, and 12 months. Only patients who met the 12-month follow-up measure were included in the analysis.**

***Results:*** **A total of 113 men and 56 women were available for analysis. At baseline, groups were similar in terms of clinical characteristics and ACD walking distances (men, 250 meters; women, 270 meters; $P = .45$). ACD improved for both sexes. However, ACD increase was significantly lower for women than for men during the first 3 months of SET (Δ 280 meters for men vs Δ 220 meters for women; $P = .04$). Moreover, absolute walking distance was significantly shorter for women compared with men after 1 year (565 meters vs 660 meters; $P = .032$). Women also reported less on several WIQ subdomains, although total WIQ score was similar (0.69 for men vs 0.61 for women; $P = .592$). No differences in quality of life after SET were observed.**

***Conclusions:*** **Women with IC benefit less during the first 3 months of SET and have lower absolute walking distances after 12 months of follow-up compared with men. More research is needed to determine whether gender-based IC treatment strategies are required. (J Vasc Surg 2015;62:681-8.)**

Peripheral arterial disease (PAD) affects >12% of the aging population[1] and was initially thought to be more prevalent in men than in women.[2] However, recent population-based studies demonstrated an almost equal sex distribution (13.4% in men vs 15.6% in women).[3] Interestingly, women may suffer more from the consequences of PAD. For instance, they were found to perceive a lower physical function, to experience greater impact on hampered daily activities and mood state, and to report greater body pain compared with men with PAD.[4] Moreover, a faster functional decline with greater mobility loss,[5] poorer outcomes after lower extremity revascularization procedures,[6] and a twofold higher mortality rate with symptomatic disease were found in women with PAD compared with their male counterparts.[7] Conversely, no gender-related differences were observed regarding self-reported community-based walking ability.[4]

Intermittent claudication (IC) is the most common manifestation of PAD. A growing number of reports consistently demonstrate beneficial effects of supervised exercise therapy (SET) on overall walking ability in patients with IC.[8,9] Most studies compared the efficacy of various types of SET to controls receiving pharmacologic therapy or a revascularization procedure.[8,10-13] However, gender-specific outcomes after SET for patients with IC are seldom reported, and results are conflicting.[14-16] Two studies suggested that gender did not influence walking performance[14] and that both sexes equally benefited from SET.[15] In contrast, a third study found that women responded less favorably to a program of exercise rehabilitation compared with men.[16] No study addressed a possible gender-specific response to SET in terms of

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absolute walking distances or perceived walking (dis)ability. The paucity of data so far is likely due to a consistent female under-representation in randomized controlled trials. In a recent scientific statement, the American Heart Association released a call to action for more research into gender-based differences of patients with PAD.[17]

The present study evaluated whether men and women with IC responded differently to SET with respect to walking distance, walking (dis)ability, and quality of life. It was hypothesized that women have inferior outcomes after SET associated with an accelerated functional decline.[5]

## METHODS

This study consists of a follow-up analysis of data that were generated by the 2010 Exercise Therapy in Peripheral Arterial Disease (EXITPAD) study. This multicenter randomized clinical trial, approved by the Institutional Review Board of the Atrium Medical Center and at each of the participating sites, was undertaken to study the effect of either SET or walking advice in IC patients. Methods and results in terms of walking distance and quality of life were previously published.[18] The EXITPAD study included patients with Fontaine stage II PAD (eg, IC), defined as having an ankle-brachial index (ABI) <0.9, who were considered for conservative therapy. Exclusion criteria were an absolute claudication distance (ACD) >500 meters, prior exercise therapy or vascular interventions, insufficient command of the Dutch language, serious cardiopulmonary limitations (New York Heart Association class III-IV), leg amputation, psychiatric instability, and other serious comorbidities prohibiting physical exercise therapy.

In the EXITPAD study, all eligible patients standardly received cardiovascular risk management including cholesterol-lowering medication and antiplatelet therapy. They were also counseled about management of additional atherosclerotic risk factors (eg, smoking, body weight). Patients were randomized into three groups after written informed consent was obtained. A first group received walking advice ("go home and walk"); a second group underwent SET "with feedback"; and the third group received SET "without feedback." Patients of the walking advice group were advised by a vascular surgeon to walk as often as possible. Patients of the two SET study groups were referred to regional physiotherapists who were previously selected and had undergone training to participate in the EXITPAD study. These physiotherapists were educated according to the guideline on IC of the Royal Dutch Society for Physical Therapy and were asked to administer SET according to this guideline.[19] The main goal of SET was to increase maximum walking distance. Additional goals were improvement of aerobic endurance, pain tolerance, gait pattern, and specific activities (eg, stair climbing). Last, information on lifestyle changes was provided by these physiotherapists to stimulate healthy behaviour.[20] The training program predominantly consisted of interval-based treadmill walking approximating (sub)maximal pain. An example of the training protocol is provided in Table I. Patients assigned to the SET group with feedback received a similar SET program and also carried a personal activity monitor accelerometer (PAM B.V., Doorwerth, The Netherlands) to monitor physical activity during daily life.

**Table I.** Example of the supervised exercise therapy (SET) training protocol for intermittent claudication (IC)

| | |
|---|---|
| Frequency | Started at three times a week. Frequency is then adapted to the individual need, meaning that patients who perform well and comply with the exercise recommendations can phase down the therapy frequency sooner than other patients. |
| Duration | 20-40 minutes per training session |
| Intensity | 40%-70% of $Vo_2$max or Borg RPE score 11-15 |
| Content | Interval training: regimen included 2 to 5 minutes of walking (near to ACSM Claudication Pain Rating Scale score 2-3) and a subsequent 2 to 5 minutes of passive rest. Three to five cycles per training session<br>Aerobic endurance training |
| Activities | Primarily walking (on a treadmill, with slope of 2 to 8 degrees)<br>Combined with cycling, rowing, stepping, and sports activities in general |
| Progression | Duration (ie, amount of interval cycles) and intensity (ie, duration of interval cycles) of training are increased as based on individual progression. In general, first intensification takes place when a patient is able to exercise for 20 minutes (eg, five cycles of 4 minutes). |
| Home work | Moderate exercising for 30 minutes (in bouts of at least 10 minutes): 5 days per week |
| Evaluation | Continuous evaluation. Treadmill testing at least after 6 and 12 weeks |
| Termination | Program ends when patient is satisfied and the physiotherapist expects no further progression. |

*ACSM,* American College of Sports Medicine (claudication pain scores range from 1 to 4: respectively, minimal discomfort to unbearable pain); *Borg RPE,* Borg Rating of Perceived Exertion (score ranges from 6 to 20: respectively, no exertion at all to maximal exertion); *$Vo_2max$,* maximal oxygen consumption (reflects the aerobic physical fitness).

Detailed therapy evaluation and documentation sheets determining frequency, duration, and content of the therapy were completed by the physiotherapists after 6, 12, 26, and 52 weeks of SET.

**Outcome measurements of the present study.** Because the EXITPAD trial found no additional improvement in patients receiving extra feedback,[18] it was allowed to combine data of both SET groups for the purpose of the present study. Data of patients receiving walking advice were not used. Evaluation of data generated at baseline and after 3, 6, 9, and 12 months of SET was performed by a blinded observer (L.N.M.G.). The primary outcome was a gender difference in ACD. Secondary outcomes were gender differences regarding functional claudication distance (FCD) and scores obtained by the Walking Impairment Questionnaire (WIQ) and the 36-Item Short Form Health Survey (SF-36).

The ACD was defined as the number of meters that a patient had covered just before he or she was forced to stop walking because of intolerable pain. FCD was defined as