

# Promoting cardiovascular health through personalized supervised exercise therapy in intermittent claudication

Citation for published version (APA):

Jansen, S. C. P. (2022). *Promoting cardiovascular health through personalized supervised exercise therapy in intermittent claudication*. [Doctoral Thesis, Maastricht University]. Proefschriftenprinten.nl. <https://doi.org/10.26481/dis.20220211sj>

## Document status and date:

Published: 01/01/2022

## DOI:

[10.26481/dis.20220211sj](https://doi.org/10.26481/dis.20220211sj)

## Document Version:

Publisher's PDF, also known as Version of record

## Please check the document version of this publication:

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In this thesis, several studies are presented that may aid in optimising supervised exercise therapy (SET) with emphasis on personalisation of treatment and cardiovascular risk management in patients with intermittent claudication (IC). The first part covers introductory remarks that set the stage for the studies that are presented in the second and third parts of the thesis. The second part contains two chapters that are dedicated to the effects of SET on cardiovascular risk, secondary interventions and mortality. Finally, the third part contains four studies that primarily cover the suitability of SET in IC patients.

## **PART I Introduction**

Peripheral artery disease (PAD) is caused by systemic atherosclerosis affecting the infrarenal aorta and lower limb arteries and usually occurs after the age of 50.<sup>1</sup> The classical presentation of PAD is intermittent claudication (IC) defined as leg pain during walking that is relieved upon a short period of rest. The 5-year mortality risk is 10-15%, mostly due to fatal cardiovascular events, whereas an additional 30% of patients are confronted with a non-fatal cardiovascular event.<sup>1-4</sup> Therefore, the main goals of IC treatment are symptom relief and cardiovascular risk management (CVRM). Current guidelines recommend SET as initial treatment for IC and support a stepped care approach in which revascularization is reserved when SET is not successful.<sup>1,5</sup> The general aim of this thesis was to explore if SET could be optimised as a lifestyle intervention with emphasis on personalisation of treatment and CVRM.

## **PART II Studies on the potential influence of supervised exercise therapy on cardiovascular risk, secondary interventions and mortality**

PAD is associated with an increased risk of cardiovascular and all-cause mortality, even after adjustment for other cardiovascular risk factors.<sup>6,7</sup> This finding underscores the importance of CVRM in IC treatment. Next to medication and lifestyle advice, exercise has been demonstrated to exert positive effects on cardiovascular disease and associated risk factors.<sup>8-11</sup> As a consequence, exercise training is recommended as a central component of rehabilitation and preventive interventions.<sup>1,5,11-13</sup> **Chapter 2** reports on a systematic review and meta-analysis of prospective studies including 27 studies (n= 808 patients) that evaluates the effects of SET on cardiovascular risk factors in IC patients. This . Pooled mean differences between follow-up and baseline were analysed using a random-effects model for the following risk factors: blood pressure (systolic or diastolic), heart rate, lipid profile (total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol), glucose, glycated haemoglobin, body weight, body mass index, and cigarette smoking. After 6 weeks to 3 months of SET, systolic blood pressure decreased with 4 mm Hg and diastolic blood pressure with 2 mm Hg. After

6 to 12 months of SET, low-density lipoprotein cholesterol and total cholesterol both decreased by 0.2 mmol / L. These findings support the prescription of SET programs not only to increase walking distances but also for their associated beneficial effects on a number of cardiovascular risk factors.

Although SET is recommended as primary treatment, guideline adherence is not yet self-evident in daily practice.<sup>14-16</sup> In the Netherlands, availability and accessibility of SET are optimized through a nationwide community-based organization. Furthermore, SET is fully reimbursed and increased awareness of referring physicians probably improved SET referral rates.<sup>17,18</sup> These factors have most likely contributed to the considerable increase of SET as primary treatment (from 63% in 2013 to 87% in 2017), as shown in a nationwide retrospective data analysis of health insurance claims of 54504 newly diagnosed IC patients (**Chapter 3**). Multiple regression analysis demonstrated that patients who underwent endovascular revascularisation (ER) or open surgery as a primary treatment had a higher risk of secondary revascularizations (hazard ratio (HR) 1.44 and HR 1.45, respectively) and demonstrated a higher mortality risk compared to SET as a primary treatment (HR 1.38 and HR 1.49, respectively). Although this analysis had its restrictions, it provides a unique insight into real-world data and illustrates the potential beneficial long-term effects of the 'exercise-first strategy'.

## **PART III Suitability of supervised exercise therapy in patients with intermittent claudication**

SET is generally regarded as an effective treatment for IC, but the question arises whether it is the most suitable therapy for each IC patient. Although three randomized controlled trials comparing SET to ER for aortoiliac stenoses found similar results regarding walking performance and quality of life<sup>19-21</sup>, location of stenosis is a commonly used argument for a revascularisation-first strategy. The ELECT Registry aimed to provide insight into the discussion questioning the effectiveness of SET for aortoiliac disease. **Chapter 4** covers the rationale and protocol for this multicentre prospective observational study. **Chapter 5** depicts the results of this unique effort. A total of 267 patients were studied, of which 26% suffered from aortoiliac disease and 43% of femoropopliteal disease. Patients were primarily treated with SET according to current guidelines. All patients demonstrated equal improvements in walking performance and health related quality of life after 3 and 6 months of SET, regardless of stenosis/occlusion location. This study confirms that, ideally, all IC patients should receive a trial of SET before possibly considering invasive treatment, regardless of location or extent of the stenosis/occlusion.

Other potentially moderating influences on the effectiveness of SET are psychological constructs. In other words, does the psychological make-up of an IC patient determine outcomes of SET? A substudy of the ELECT Registry that is presented in **Chapter 6** analysed possible associations between SET-related

outcomes (walking distances, Six-Minute Walk Test, and VascuQol-6) and a set of psychological factors (extraversion, neuroticism, conscientiousness, anxiety, depression, self-control, optimism, and self-efficacy). Multiple linear regression analyses demonstrated a limited number of small overall effects of questionable clinical relevance. Interestingly however, these investigated factors did not affect (in either direction) the clinical course after 6 months of follow-up. Furthermore, self-efficacy did not improve during 12 months of follow-up. Consequently, it is concluded that the beneficial effects of SET occur regardless of the psychological constructs of an IC patient.

In addition to studying the spectrum of indications of SET, the mode of exercise may also be relevant. SET often consists of treadmill or track walking. However, not all patients with IC are able to complete such exercise protocols because of concomitant comorbidity (e.g. osteoarthritis, pulmonary disease, cardiac disease). Alternative modes of supervised exercise training do exist and are also associated with improved walking capacity. A Cochrane review in **Chapter 7** included 10 studies with a total of 527 randomised IC participants. The investigated alternative modes of exercise were cycling, lower-extremity resistance training, upper-arm ergometry, Nordic walking, and combinations of exercise modes. No clear differences were detected between alternative exercise modes and supervised walking exercise with respect to improving maximum and pain-free walking distance. These findings indicate that alternative exercise modes may also be useful when walking is not a suitable option. Because the certainty of evidence was judged to be low, mainly due to small sample size and risk of bias concerns, it was not possible to conclude that the alternative modes are equally effective to walking for all IC patients.

## CONCLUSIONS OF THIS THESIS

1. Supervised exercise therapy (SET) has favourable effects on modifiable cardiovascular risk factors, specifically blood pressure and cholesterol levels.
2. The exercise-first approach is successfully implemented in the Netherlands, as 87% of patients with intermittent claudication (IC) received a primary course of SET in 2017.
3. Patients receiving primary SET had fewer lower limb revascularisations and demonstrated better survival than patients undergoing primary endovascular revascularisation or open surgery.
4. Location of stenosis/occlusion does not affect short-term effectiveness of SET.
5. The beneficial effects of SET occur regardless of certain psychological constructs, including depression and anxiety.
6. Alternative exercise modes may be useful when supervised walking exercise is not a suitable option, e.g. due to common comorbidities.