Measures and determinants of outcome in conservative intermittent claudication treatment

Measures and Determinants of Outcome in Conservative Intermittent Claudication Treatment

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Voor Coen en Dineke

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PERIPHERAL ARTERIAL DISEASE

Peripheral arterial disease (PAD) is a chronic condition caused by progressive atherosclerotic narrowing and blocking of the arteries supplying the lower extremities. Over 200 million individuals globally are diagnosed with PAD.[1] It is a manifestation of systemic atherosclerosis and thus associated with high rates of cardiovascular morbidity and mortality. In fact, some 20% of patients die within 5 years after the diagnosis, mainly due to atherosclerotic ischemic events.[2]

In PAD, the impaired blood supply to the lower extremities leads to diminished oxygenation of distal tissue beds. Most PAD patients are asymptomatic, but progressive narrowing of the arteries may eventually lead to symptoms. Initially, leg pain or discomfort is provoked during exercise, when inadequate blood flow is unable to meet the increased locoregional muscular demand. At rest, blood flow still suffices and limb ischemic symptoms disappear. This phenomenon is termed intermittent claudication (IC): the most common manifestation of PAD and focus of this thesis. If disease progresses, critical limb ischemia (CLI) may develop. CLI is defined as the presence of ischemic rest pain, ischemic lesions or gangrene, objectively attributable to arterial occlusive disease. CLI patients are at considerable risk of losing (part of) their limbs. In contrast, claudication symptoms usually remain stable and seldomly worsen at rapid rates. Indeed, the prognosis of patients with IC is marked by an increased risk of cardiovascular ischemic events rather than loss of the affected limb.[2]

Treatment of IC aims to reduce the significant cardiovascular risk burden and improve symptoms. Cardiovascular risk management consists of medical therapy (antiplatelets and statins, optimal hypertension and diabetes control) and lifestyle modification. Modifiable risk factors include smoking cessation, adoption of a balanced diet, and stimulating daily physical activity. Symptomatic treatment focusses on augmenting the distance at which lower-extremity discomfort occurs and a patient is forced to stop walking. Improvement of this so-called 'walking capacity' aims to improve (health-related) quality of life (QoL). To achieve these goals, several treatment modalities exist.

TREATMENT MODALITIES IN INTERMITTENT CLAUDICATION

Exercise therapy

IC pain limits ambulation leading to a sedentary lifestyle, which leads to further functional decline.[3] Patients need to breach this vicious circle and exercise therapy has long been a mainstay in doing so. In 1898, the German neurologist Wilhelm Erb first described success after exercise therapy in an IC patient.[4] The first

randomized controlled trial (RCT) demonstrating the efficacy of exercise was performed by Larsen and Lassen in 1966[5], followed by many case series, RCTs and meta-analyses. Consequently, the effectiveness of exercise therapy in improving walking capacity and health-related QoL in IC is beyond discussion.[6]

The most basic exercise therapy prescription consists of a single advice to 'walk more', usually without supervision or follow-up. Unfortunately, compliance appears to be low in the PAD population. Patients often cite a lack of a detailed instruction and no supervision as important barriers.[7] Acknowledgment of the role of supervision by trained medical personnel has resulted in structured supervised exercise therapy (SET) programmes entailing detailed exercise prescription with adequate coaching and guidance on lifestyle modification by a physical therapist or other exercise specialist. SET appeared more effective than non-supervised exercise in patients with IC regarding walking capacity measures.[6] In addition to the benefits on limb ischemic symptoms, SET is associated with improvements in markers of cardiovascular risk, including blood pressure, serum lipid profile and glycemic control.[8]

A typical SET program, as studied in this thesis, entails 30 to 60 minutes of treadmill- or track-based exercises that are performed at least three times a week, for a minimum of 12 weeks. The initial workload of the treadmill is set to a speed and grade that elicits claudication symptoms within three to five minutes. Patients are asked to continue to walk at this workload until they experience claudication of moderate severity. A brief period of rest permits symptoms to resolve. This exercise-rest-exercise cycle is repeated several times during the (half-)hour of supervision.[9]

SET likely offers symptomatic improvement due to a combination of cardiovascular and systemic mechanisms. Reported biological mechanisms include (a combination of) enlargement of existing collateral vessels, exercise induced angiogenesis, enhanced nitric oxide endothelium-dependent vasodilatation of the microcirculation, improved bioenergetics of skeletal muscle and improved physical properties of blood flow.[2] In addition, an adapted pain tolerance enables patients to endure a greater intensity of IC pain. Interestingly, there is no strong relation between improved walking performance after SET and measures of hemodynamic improvement such as the ankle-brachial index.[10] Moreover, alternative modes of exercise (i.e. cycling, strength training and upper-arm ergometry) have been described, yielding significant results.[11,12] Exercise apparently exerts its effects through mechanisms other than improvement of limb vascular resistance.

Open and endovascular revascularization

When conservative management does not suffice, the stenotic vessel may be opened or bypassed to improve vascularization. Several ways with varying degrees of invasiveness can be explored. Traditionally, open vascular surgery offers the "gold standard" with respect to durability and efficacy. Such open revascularization (OR) is conducted either by removing the atherosclerotic plaque (endarterectomy), or by constructing a 'bypass' parallel to the obstruction. Minimally invasive endovascular techniques have been developed since the sixties of the previous century (dr. Charles Dotter, 1963), and were continuously refined in order to avoid complications associated with open surgery and general anaesthesia, as well as enhance patency. Percutaneous intraluminal angioplasty (PTA) can be used to open blocked vessels, with possible stenting to prevent recoil or restenosis.[13] The durability of PTA has improved markedly over the past decades, making it first-line invasive treatment option in most arterial lesion types.[14] Nonetheless, reinterventions may be necessary to maintain vessel patency and prevent recurrent symptoms. Major determinants for procedural success and the need for reintervention are the extent and location of atherosclerotic disease. Proximal aortoiliac endovascular revascularization (ER) shows better procedural results and patency rates when compared to endovascular treatment of more distal disease.

As stipulated previously, only a small portion of claudication patients will progress to limb-threatening symptoms. In this light, a major concern with intervention in IC patients is the risk that patients may suffer complications that worsen their symptoms. In these unfortunate cases, the 'cure was worse than the disease'. Therefore, clinicians should carefully weigh the burden of symptoms against the risks of an intervention in each individual patient. To do so, objective assessment of functional limitations due to IC is necessary.

ASSESMENT OF WALKING PERFORMANCE IN INTERMITTENT CLAUDICATION

The severity of claudication symptoms, as well as their response to treatment, may be estimated using objective measures of walking performance. Maximal performance is expressed as the walking distance at which intolerable claudication pain forces a patient to stop. This so-called maximal walking distance can either be estimated by the patient or measured using standardized tests. Most commonly, treadmill tests are used, functioning as primary outcome measure in both clinical trials and daily practice in PAD treatment programmes. A variety of test protocols, with different durations, speeds and slopes exist. These tests are reliable, reproducible, and detect changes following treatment.[15] However, despite their wide use, several important issues hinder their applicability.

The relation between treadmill measurements, daily life performance and a patient's perception of treatment effect is poorly understood. Treadmill testing has been criticized for being an artificial form of walking that poorly reflects walking outdoors.[16] In addition, in daily clinical practice often a patient's own estimation is used. How does walking using different treadmill protocols compare to walking outdoors, or to a patient's own estimation? **Chapter 2** aims to investigate this matter. Furthermore, when using treadmill measurements, it is unknown what numerical difference constitutes a meaningful change to patients. The concept of the 'minimally important difference' (MID) allows the estimation of the smallest change in an outcome measure that patients consider as important.[17] Hiatt et al.[15] underlined the importance of establishing these MIDs for treadmill testing in PAD. The study presented in **Chapter 3** estimates the MIDs for treadmill test outcomes after 3 months of SET in an IC population.

A measure of walking capacity is a useful objective assessment of symptom severity. Yet, it may be but a proxy for what actually matters to the patient's perceived QoL and general prognosis: improving daily activity. Patients with PAD are sedentary, and increasing their physical activity level likely improves functional and cardiovascular outcomes.[3] Consequently, daily physical activity is increasingly recognized as an important treatment goal and outcome measure in IC management. Unfortunately, treadmill-measured walking distance and daily physical activity show minimal correlation in patients with IC.[18] Merely defining successful treatment using improvements of walking capacity may thus fail to address inactive behaviour. Despite extensive research on the clinical effectiveness of treatment modalities in IC regarding walking ability, it remains unclear whether they have a meaningful impact on physical activity. In **Chapter 4** this problem is investigated by aggregating all previous randomized trials on IC treatments that included physical activity as outcome measure in a network meta-analysis.

STEPPED CARE MANAGEMENT OF THE CLAUDICATION PATIENT

Over the past decade, SET and ER have been shown to be equally effective with regard to improving walking performance and quality of life.[19] However, SET is non-invasive, safer[20], and less expensive compared to an intervention[21]. Therefore, current guidelines recommend SET as primary treatment in the management of patients with IC.[2] Invasive treatment is indicated if patients are unresponsive to SET. This approach is termed 'stepped care'. Using a stepped care approach, an intervention can be prevented in approximately 80% of patients, up to 7 years after first presentation.[22,23] Despite this strong evidence indicating SET's efficacy and

safety, several issues have hindered world-wide implementation of this stepped care approach.

SET places a substantial burden on patients in terms of effort and responsibility. Exercise therapy involves frequent exposure to the ischemic limb pain, whereas ER offers a rather painless "quick fix". As a consequence, patients need convincing by their physician to attempt SET before interventional therapy. Therefore, easy access to SET programs is a prerequisite. If patients cannot find a qualified SET practitioner close to their home, and treatment costs are not reimbursed, they are (even more) attracted to the 'quick fix' of an invasive procedure. Global availability of SET is utopian at present.[24,25] Health care policy makers should be informed on the potential long-term benefits of providing access to SET for all IC patients, considering a health care payers perspective. To do so, **Chapter 5** presents an investigation on the impact of a SET-first strategy (with ER in the event of SET failure) on both costs and effectiveness.

In the Netherlands, community-based SET is nationally available through *ClaudicatioNet* as of 2011 and fully covered by the basic health insurance since 2017. These developments went hand-in-hand with a paradigm shift among clinicians, reflected by an increasing adherence to the SET-first guidelines nationally.[22,23] Even so, some vascular specialists remain reluctant to first try SET in each IC patient. Self-interest of doctors performing interventions that involve fee-for-service is undoubtedly a contributor. Moreover, offering quick relief of symptoms using ER to an IC patient who is unmotivated for SET is attractive. Some recent studies indeed indicate greater short-term improvements when patients first undergo ER combined with SET afterwards, compared to SET alone.[26,27] Longer-term reports show that the effect differences disappear over time and over half of the individuals who were initially treated with SET do not require any intervention at all.[28,29] At present therefore, the current stepped care guideline recommendation remains the most efficient strategy for the IC population as a whole. Nonetheless, these trials open the debate for a more patient-tailored approach, perhaps offering early revascularization with SET afterwards in a selected patient population.

Improving efficiency in stepped-care

Early identification of a subset of patients who do not successfully respond to SET but require an intervention can lead to a more individualized stepped care approach. In theory, this subset of patients may undergo a more intensive exercise programme, or may receive early revascularization. By providing the proper treatment to the right patient at the right time, patients may either be protected against unnecessary interventions or redundant exercise therapy. At present, an evidence base favouring such approach is lacking. Arguably, only very

strong predictors could preclude an attempt to avoid invasive treatment and its associated risks.

Previous research identified several patient characteristics associated with fewer improvements in walking performance after SET, albeit with low predictive value. These include advanced age, female sex, BMI, cardiac and pulmonary comorbidity, smoking behaviour, and lower walking capacity at baseline.[30-32] Both the need for revascularization and location of stenosis were not evaluated previously, nor were functional outcomes other than treadmill walking. The location and extent of the atherosclerotic lesion play a crucial role in the decision to perform ER, being important determinants of the risk-benefit ratio of the intervention.[33] The impact of this parameter on functional and clinical outcomes of SET however, is unknown. In **Chapter 6**, a prospective cohort study is outlined, aimed to link anatomical characteristics of atherosclerotic disease to the functional and clinical outcomes of a SET-first management strategy in IC. **Chapter 7** presents its 6-months results.

AIM AND OUTLINE OF THESIS

The general aim of this dissertation is to contribute to various aspects of the management of IC. In the first part, a number of parameters reflecting walking performance in an IC patient are studied. In **Chapter 2**, the agreement between walking capacity as estimated by the patient, as measured using different treadmill protocols, and as measured during outside walking, is determined. **Chapter 3** aims to identify what improvement or deterioration in walking performance on a treadmill is perceived as a meaningful, clinically relevant, change by the IC patient. Merely improving the ability to walk longer distances does not necessarily translate into walking more frequently in a sedentary PAD patient. It remains unclear whether treatment in IC has a meaningful impact on physical activity. In **Chapter 4**, all existing evidence on the effect of the various treatment modalities in IC on physical activity are summarized in a network meta-analysis.

In the second part of the thesis, the efficiency of the stepped care treatment strategy in IC is investigated. To this end, **Chapter 5** compares costs and effects of SET versus ER as primary treatment in the general IC population. In daily practice, clinicians tailor treatment decisions to the individual patient. **Chapter 6** describes the protocol of a study assessing the potential impact of patient characteristics on SET outcomes. An important practice-based reason for early revascularization rather than await the efficacy of SET is location and extent of the atherosclerotic lesions. In **Chapter 7,** the effect of arterial disease level on the outcomes of SET is investigated.

Findings of this thesis including methodological considerations, implications for clinical practice, and suggestions for future research are discussed in **Chapter 8**. Its impact on science and society is presented in **Chapter 9**. Finally, in **Chapter 10** a summary of this thesis is presented in Dutch.

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PART I

Improving assessment of walking performance

CHAPTER 2

Agreements and discrepancies between the estimated walking distance, non-graded and graded treadmill testing and outside walking in patients with intermittent claudication

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ABSTRACT

Objective: Disease severity in patients with intermittent claudication (IC) is often assessed using walking distances and treadmill tests. The aim of this study was to determine the agreement between walking distance as estimated by the patient, as measured during outside walking and as determined using a non- (NGTP) and an incremental graded (Gardner Skinner) treadmill protocol (GSP).

Methods: In this prospective observational study, 30 patients with IC estimated their maximum walking distance (MWD) and completed a 'Walking Impairment Questionnaire' (WIQ). Outside walking was determined using a measuring wheel and a GPS controlled device. Primary outcomes were differences in MWD and variability (coefficient of variation, COV). Secondary outcomes were results of WIQ and differences in walking speed.

Results: Estimated walking distance was significantly higher than MWD as objectively measured during outside walking (400m vs 309m, respectively P=.02). A substantial variability (COV=55%) was found between both parameters. A small 35m MWD difference between outside walking and GSP was found with a substantial scatter (COV=42%). In contrast, a much larger 122m MWD difference was present between outside walking and NGTP (COV: 89%). Patients walked significantly faster in the open air than on treadmills (median outside walking speed=3.8 km/h, GSP=3.2 km/h, NGTP=2.8 km/h; P<.001).

Conclusions: An incremental graded (Gardner Skinner) treadmill protocol demonstrated the best agreement to outside walking. Discrepancies between treadmill tests and outside walking may be explained by a difference in walking speed. A single determination of a walking distance is a poor reflection of true walking capacity.

INTRODUCTION

Intermittent claudication (IC) is a classical symptom reflecting peripheral arterial disease (PAD). IC limits walking capacity and daily functioning [1]. Overall treatment strategies are well described in international guidelines [2-4]. Limitations in walking distance play an important role in the assessment of disease severity. However, the value of various walking distance assessments is disputed. For instance, patients' estimations of walking distances do not properly reflect objectively measured daily life walking distances [5-7]. A disease specific questionnaire such as the Walking Impairment Questionnaire (WIQ) may quantify walking impairments in IC patients better but correlations with walking distances appeared weak [6].

Standardized treadmill tests are widely used for the objective assessment of walking distances [2-4]. However, there is a substantial variability in treadmill protocols [8]. In previous studies, fixed inclination was compared with flat off-treadmill walking (in- and outdoors) [5,6,9,10]. Interestingly, none of these comparing studies used a graded incremental treadmill test, while such type of testing is recommended in the guidelines for physical therapy because of its high reliability [11,12]. Furthermore, previous studies used corridor walking as an imitation of daily life walking [5,6,10]. IC patients are mostly limited during outside walking with variations in speed, weather condition and surface. Compared to corridor walking, outside walking might be a more reliable reflection of daily life walking.

This study aims to compare the results in walking distances in a group of IC patients using four different tools that are frequently used by physical therapists in the assessment of IC severity. Results of a graded and a non-graded treadmill protocol, patient estimations and outside walking were compared in a single model.

METHODS

Subjects

This study was approved by the Medical Ethics Committee of the Catharina Hospital, Eindhoven, The Netherlands. Thirty consecutive patients with complaints of IC, confirmed by non-invasive testing (<0.9 Ankle-Brachial Index (ABI) at rest or a fall in systolic ankle pressure by more than 20% after exercise), were recruited from the vascular outpatient clinic. Patients with comorbidity possibly limiting walking apart from IC (i.e. neurological disorders, severe COPD, congestive heart failure, orthopedic impairments) or with insufficient knowledge of the English or Dutch language were excluded. All participants provided verbal and written informed consent.

Study Protocol

Baseline characteristics, comorbidity, medical history and cardiovascular risk factors were recorded. All patients performed an open air distance measuring test and completed two treadmill protocols on one day. The order of the three tests was randomized using 'Randomizer' (Kwixo Designs, lite version) for Android smartphones. Three physiotherapy students were trained to standardize patients' encouragement. Pairing of patient and physiotherapy student was also randomized. To minimize a difference in grade of encouragement, these tests were all performed under supervision of the same student. Patients rested for 20 minutes (supine or seated) between tests as ABI values are known to recover within this time interval[13] Primary study outcomes were maximal walking distance (MWD) as determined by the patient's estimation, as obtained during outside walking and during the two treadmill tests. In addition, walking speed and the WIQ results were analyzed.

Self-reported MWD

Before testing, patients were asked to estimate their MWD, defined as 'the maximum distance (meters) you can walk before you are forced to stop by leg pain'.

Outside walking

To approximate a real 'daily life' maximal walking distance, patients were asked to walk a standardized outside walking course on the parking lot of our training facility. They walked mostly in straight lines on the sidewalk and and were not interrupted by traffic, traffic lights, cyclists or otherwise. The course is a big square that is paved with regular stones and has a few curbs. One of the team of three researchers always walked some 3-5 meters behind the patient. The degree of encouragement during outside walking or during treadmill testing were similar. Each patient was instructed to continue until they were forced to stop by leg pain. MWD was recorded using both a measuring wheel (Stanley Black & Decker Inc., New Britain USA) and a GPS controlled device (iPhone 4s; Apple, Silicon Valley, USA). Walking time was recorded using the iPhone.

Treadmill tests

Two different treadmill protocols were used. A graded incremental test (Gardner-Skinner Protocol, GSP) allows patients to walk at 3.2 kilometer per hour (km/h) with a 0% incline that increases by 2% every 2 minutes [14]. The maximum test duration is 20 minutes. The non-graded treadmill protocol (NGTP) has a fixed 0% incline and allows the patient to walk with a favorite walking speed which was set during the first 30 seconds of the treadmill testing. The use of handrails during treadmill walking was not permitted. Results are expressed as MWD.

Walking Impairment Questionnaire
Patients were asked to complete the WIQ evaluating several components of daily walking ability including an estimation of walking distance, speed and stair-climbing ability [15]. Patients were instructed to rank the degree of difficulty for each component using a 0 to 4 Likert scale. A validated Dutch version of the WIQ was used [16].

Walking Speed
Average walking speed of outside walking was calculated by dividing walking distance by time and was expressed in kilometer per hour (km/h).

Statistical analysis
It was assumed that outside walking reflected daily life walking most closely, and was therefore used as reference value. The distance in meters as obtained with the measuring wheel was used as reference value in all analyses. The Friedman two-way analysis of variance test determined differences between multiple assessments. A Wilcoxon Signed Rank test was used for comparison of two measurements. A Bonferroni method was used as post-hoc procedure for correction of multiple comparison testing.

Various methods were used to assess study outcomes. Overall reliability was assessed by means of an Intraclass Correlation Coefficients (ICC) with 95% confidence intervals (CI). Variability in measurements was assessed using coefficient of variation (COV). The COV was calculated as the standard deviation of the absolute difference between two assessments (outside walking vs. patient's estimation, outside walking vs. GSP, outside walking vs. NGTP) divided by the mean of the averages. Reproducibility was analyzed in Bland-Altman plots. These plots were used to visualize agreement between two measurements and were presented with 95% limits of agreement, calculated as the mean difference ± 1.96 standard deviation (SD). The mean of both measurements was depicted on the horizontal axis whereas the difference was illustrated on the vertical axis. Linear regression analysis was performed and mean difference (bias) was calculated. Spearman rank correlations were estimated to compare WIQ scores with walking distances and speed. A correlation coefficient was considered strong if ≥ 0.7, moderate if between 0.3 and 0.7, and weak if ≤ 0.3. P values less than 0.05 were considered statistically significant. Statistical analysis was performed using SPSS Statistics for Windows (version 20.0).

RESULTS

Demographics and baseline characteristics of the 30 patients are presented in table 1. Walking distances and walking speeds are listed in table 2.

Table 1. Baseline characteristics (n=30).

Characteristics	**Value**
Patient characteristics, median	
Age, years	67 (44-87)
Body mass index, kg/m^2	27 (18-37)
Male	63
Diabetes Mellitus	23
Hypercholesterolemia	17
Hypertension	17
Smoking	
Current	40
Former	47
Never	13
Cardiovascular history	
MI	20
CABG	3
Other	13
None	63
Chronic Obstructive Pulmonary Disease	17
Arthritis	23

Data are expressed as numbers (percent) or median (range).
CABG, Coronary artery bypass grafting; MI, Myocardial infarction;

Table 2. Walking distances and walking speed.

Outcomes	GSP, Median (IQR)	NGTP, Median (IQR)	OW, Median (IQR)	ED Median (IQR)	Overall P Value[a]	Per Comparison Difference	P Value[b]	ICC (95% CI), P Value
MWD, m	250 (178-463)	317 (190-546)	309 (178-478)	400 (188-740)	.05	OW-GSP:	.70	0.67 (0.42-0.83), P<.001
						OW-NGTP:	.20	0.46 (0.14-0.70), P=.004
						OW-ED:	.02	0.62 (0.34-0.80), P<.001
Walking Speed, km/h	3.16 (3.11-0.18)	2.76 (2.48-3.44)	3.81 (3.21-4.50)	n.a.	<.001	OW-GSP:	<.001	0.08 (-.12-0.34), P=.226
						OW-NGTP:	<.001	0.41 (-.10-0.75), P<.001
						GSP-NGTP:	0.08	0.10 (-.23-0.42), P=.287

CI, Confidence interval; ED, Estimated distance; GSP, Gardner-Skinner protocol; ICC, Intraclass correlation coefficient; IQR, Interquartile range; MWD, Maximum walking distance; NGTP, non-graded treadmill protocol; n.a., not available; OW, outside walking; PFWD, pain-free walking distance; VAS, Visual Analogue Scale.

[a] Considering a Friedman two-way analysis of variance test.

[b] Considering a Wilcoxon signed-rank test. A bonferroni-corrected significance level of P<0.02 indicates statistically significant difference.

Table 3. WIQ and estimated: correlations.

	WIQ distance score	WIQ total score	ED
ED	0.81	0.69	-
GSP MWD	0.80	0.66	0.86
NGTP MWD	0.73	0.64	0.76
OW MWD	0.77	0.70	0.74

ED, Estimated difference; GSP, Gardner-Skinner protocol; MWD, Maximum walking distance; NGTP, non-graded treadmill protocol ; OW, outside walking; VAS, Visual Analogue Scale; WIQ, Walking Impairment Questionnaire.
Values shown represent Spearman rank correlations.

Outside walking versus estimated walking distance

A moderate reliability was found between these outcomes (ICC=0.62). The median patients' estimated MWD was 400m, which is significantly higher than measured during outside walking (median=309m, P=.02) (table 2). The mean difference found in the Bland-Altman plot in MWD between both outcomes was 122m (95% limits of agreement: -677.4m – 433.6m). A substantial and significant divergent scatter was reflected by the Bland-Altman plot (figure 1) indicating that the agreement between outside walking and estimated distances decreased when patients judged that their walking distance was longer than it actually was. This variability between outcomes was confirmed by a 55% COV value.

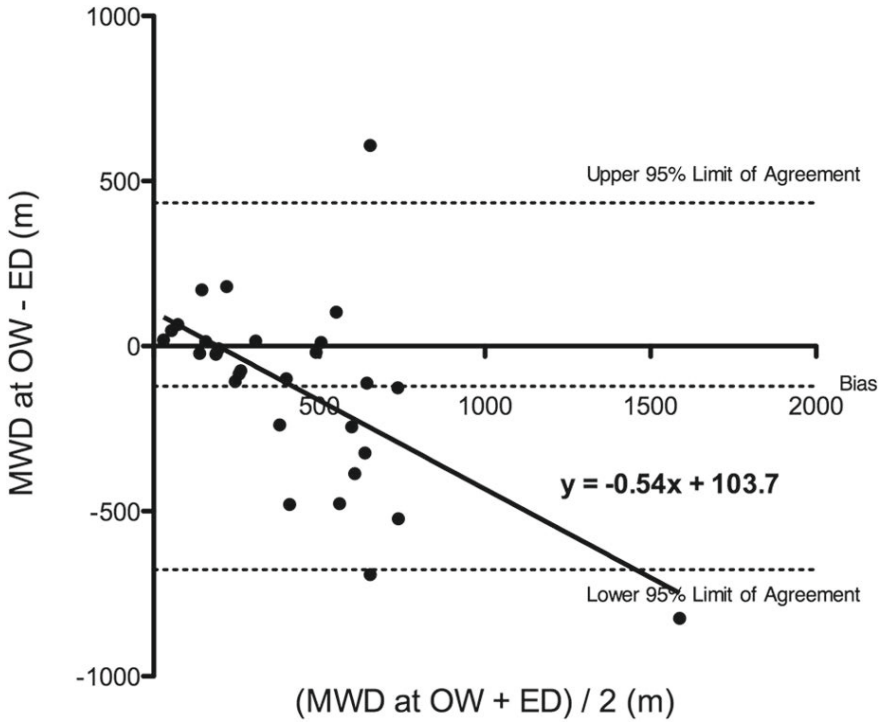

Figure 1. Bland-Altman plot with linear regression analysis of MWD either after outside walking (OW) or estimated distance (ED)

Outside walking versus Gardner Skinner Treadmill Protocol (GSP)
Again a moderate reliability was found between these outcomes (ICC=0.67). No significant differences were found in median MWD as measured during outside walking (309m) and GSP (250m, P=.70, table 2). The mean difference in MWD as shown in the Bland Altman plot between outside walking and the GSP was 35m (95% limits of agreement: -328.5m – 399.0m) (figure 2). A 42% COV was found, dropping to 19% after removing two extremes (figure 2).

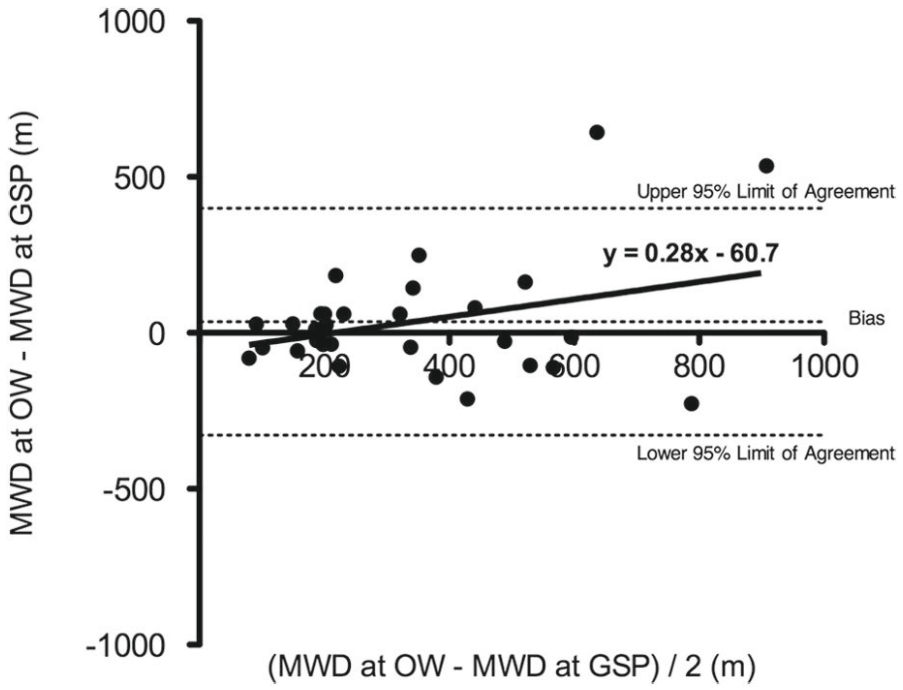

Figure 2. Bland-Altman plot with linear regression analysis of MWD either after outside walking (OW) or Gardner-Skinner protocol (GSP).

Outside walking versus Non Graded Treadmill Protocol (NGTP)

A moderate reliability was found between these outcomes (ICC=0.46). No significant differences in median MWD were found comparing outside walking (309m) with NGTP (317m, P=.20, table 2). A -122m mean difference (95% limits of agreement: -920.5 – 676.4) was calculated and depicted in the Bland Altman plot (figure 3). A significant negative scatter trend was seen (figure 3) indicating that the agreement between outside walking and the NGTP outcomes was lower in patients with larger walking distances. An 89% COV variability was found, which dropped to 32% after removing two extreme outliers.

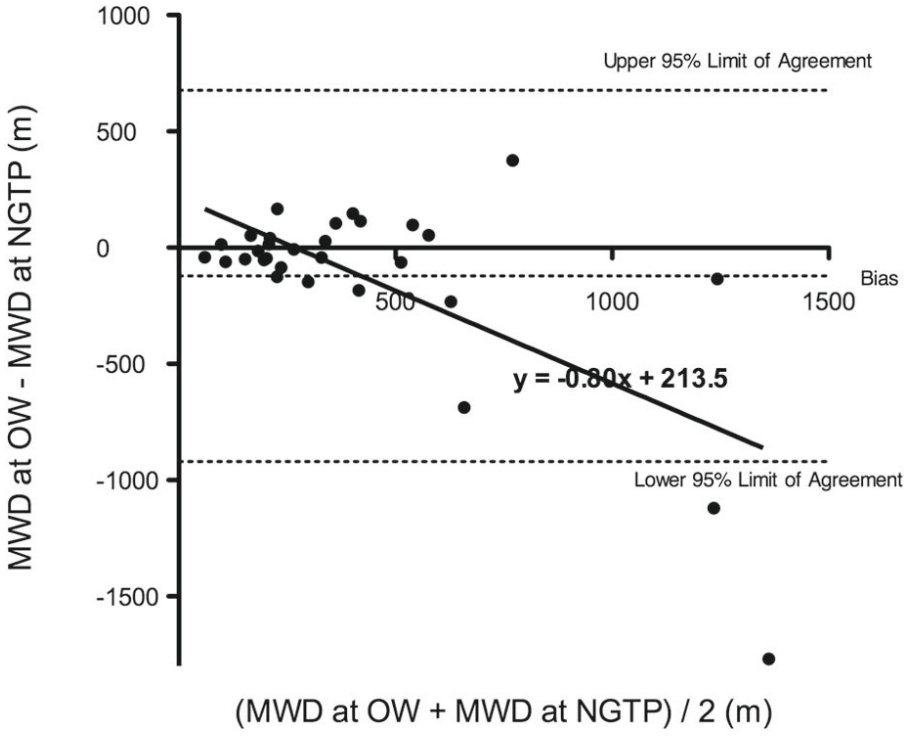

Figure 3. Bland-Altman plot with linear regression analysis of MWD either after outside walking (OW) or non-graded treadmill protocol (NGTP).

WIQ scores and correlations

The WIQ distance score correlated well with values of MWD as estimated by the patient or as measured during outside walking or following GSP or NGTP testing (table 3). In contrast, the WIQ total score correlated moderately with these distances (table 3).

Walking speed

Walking speed during outside walking was significantly faster than during the GSP and NGTP (medians: outside walking=3.8 km/h, GSP=3.2 km/h, NGTP=2.8 km/h; P<.001, table 2). Outside walking speed correlated moderately with the WIQ speed score (r = 0.62, p<.001).

Outside walking measuring methods

Median MWD as measured with the iPhone (309m) were not different compared to values obtained with a measuring wheel (290m, P=.064). A strong correlation was observed between these values (ICC=0.997)

DISCUSSION

The efficacy of treatment strategies for clinical decision-making and research purposes in patients with IC is often evaluated on the basis of changes in walking distances [2-4]. Such distances may be estimated by the patient or measured using a treadmill. The value of both assessments is debatable as these parameters merely provide insight into walking capacity, which not necessarily reflects the patient's perceived disability [6,11]. Self-reported walking capacity appeared a poor reflection of objectively measured MWD [5-7,10]. The present study confirms these findings.

Our results may indicate that treadmill testing provides a reliable reflection of the outside walking distance in IC patients. Differences between MWD after either a treadmill or outside walking were not significant. However, only moderate ICCs and substantial COVs were found regarding these parameters. Others found MWD variation in a single patient, when repeatedly measured, which probably contributes to these large COV values[17]. Some judged that differences in MWD following treadmill walking and off treadmill corridor were due to the inclination in treadmill protocols [6]. Although this explanation may seem adequate, the present study challenges this assumption as worse results regarding variability, reproducibility and reliability of a NGTP compared to a GSP with regard to outside walking were found. Another possible explanation for this discrepancy is the difference in walking speed. Walking at a faster pace might give a patient the impression of longer distance coverage, while a higher walking speed causes a higher metabolic demand leading to lower walking distances. In other words, the incremental inclination in the GSP may compensate for the increased outside walking speed. Surprisingly, patients did not walk faster during NGTP testing, possibly causing the poor results in variability, reproducibility and reliability values. Although precautions were made to ensure that patient encouragement did not differ during testing, the influence of a researcher (one of a team of three) who was escorting the patient during the outside walking test could not be excluded. In conclusion, a single MWD assessment is not a proper reflection of walking impairment in IC patients and may not necessarily correspond with daily life walking.

The findings of our study have implications for the evaluation of outcomes in clinical practice and future research. Researchers should realize that the frequently used MWD outcome shows substantial variability. Additionally, our study confirms results of other studies indicating that a functional impairment questionnaire such as the WIQ may be an adequate instrument for monitoring walking capacity in IC [6,18]. However, one should realize that the Spearman rank correlation coefficients to analyze WIQ data may have been overestimated when compared to our ICC values. Spearman's coefficients do not correct a systematic

measurement error. Nevertheless, future research should focus more on patient-reported outcomes of health related quality of life, perceived disability and burden of disease. These parameters can be of more importance than the determination of a patients' walking capacity alone as is currently obtained by a WIQ. In addition, walking (exercise) behavior should be monitored over prolonged periods of time to provide a more reliable reflection of a patients' walking impairment (outside walking). A 6-minute walking test, a shuttle walking-test or GPS-based accelerometers (physical activity monitors) may be alternatives to treadmill testing. The present data also indicate that a dedicated application on a smartphone is a valid alternative for a measuring wheel. Future novel applications for measuring walking behavior in combination with an assessment of disease burden in daily life could contribute to a better understanding of the impact of walking limitations in IC patients.

Study Limitations

The present study harbors methodological shortcomings. Although the test order was randomized, a potential 'training effect' could have biased our results. Furthermore, walking distances and speed were assessed as a one-time measurement whereas a multiple assessment might have strengthened our conclusion. Patients were not blinded to distance and time while walking the treadmill tests. In addition, a relatively small population was studied although its size is similar or even larger compared to most previous studies [7,10,14,19].

Conclusion

An incremental graded treadmill protocol in IC patients reflects outside walking best compared to a patient's estimated walking distance or a non-graded protocol. A single MWD assessment is not a proper reflection of the walking impairment in IC patients, probably due to the wide intra-variability in walking distances. Treadmill walking may not necessarily correspond with daily life walking. Future research should focus on walking behaviour over prolonged periods of time and patient-reported outcomes of health related quality of life and burden of disease.

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CHAPTER 3

The minimally important difference of the absolute and functional claudication distance in patients with intermittent claudication

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ABSTRACT

Objectives: Disease severity and treatment outcomes in patients with intermittent claudication (IC) are commonly assessed using walking distance measured with a standardized treadmill test. It is unclear what improvement or deterioration in walking distance constitutes a meaningful, clinically relevant, change from the patients' perspective. The purpose of our study was to estimate the minimally important difference (MID) for the absolute claudication distance (ACD) and functional claudication distance (FCD) in patients with IC.

Method: The MIDs were estimated using an anchor-based approach with a previously defined clinical anchor derived from scores of the walking impairment questionnaire (WIQ) in a similar IC population. We used baseline and three-month follow-up data on WIQ scores and walking distances (ACD and FCD) from 202 patients receiving supervised exercise therapy from the 2010 EXITPAD randomized controlled trial. The external WIQ anchor was used to form three distinct categories: patients with 'clinically relevant improvement', 'clinically relevant deterioration' and 'no clinically relevant change'. The MIDs for improvement and deterioration were defined by the upper and lower limits of the 95% confidence interval of the mean change in ACD and FCD, for the group of IC patients that remained unchanged according to the WIQ anchor.

Results: For the estimation of the MID of the ACD and FCD 102 and 101 patients were included, respectively. The MID for the ACD was 305m for improvement, and 147m for deterioration. The MID for the FCD was 250m for improvement, and 120m for deterioration.

Conclusions: The MIDs for the treadmill-measured ACD and FCD can be used to interpret the clinical relevance of changes in walking distances after supervised exercise therapy and may be used in both research and individual care.

INTRODUCTION

Intermittent claudication (IC) is the most common symptom of peripheral arterial disease (PAD). Atherosclerosis in the major vessels supplying the lower extremities causes muscle discomfort provoked by exercise in IC patients. Exertional limitations of walking ability lead to functional disability in daily life.[1] Treatment of IC aims at reducing symptoms and thereby improving walking capacity and health related quality of life (HRQoL).[1, 2] Disease severity and treatment outcomes are commonly assessed by walking distance with standardized treadmill tests, and patient-reported outcome measures reflecting HRQoL.[1, 3]

However, the clinical value of different outcome parameters in IC is currently under debate. Treadmill-measured walking distances have been disputed for being an inadequate reflection of walking capacity in daily life[4, 5], and for failing to address actual physical activity limitations[6]. Additionally, walking distances correlate moderately with HRQoL measures.[5] Notwithstanding these concerns, changes in walking distance remain an important indicator of treatment effect in clinical decision-making.[1, 2] Moreover, it functions as primary end point in most trials assessing IC.[1, 3] Despite this important role, it is unclear what improvement or deterioration in walking performance constitutes a meaningful, clinically relevant, change from a patient's perspective.

The concept of the minimally important difference (MID) represents the smallest change on an outcome measure which patients value as important.[7] It was first described by Jaeschke et al.[8] in an attempt to elucidate what change in an asthma QoL questionnaire score would be meaningful. Recently, Conijn et al.[9] introduced the MID for an IC population. In their study, the MID was calculated for the Walking Impairment Questionnaire (WIQ); a patient reported assessment of walking impairment. The MID can be used to estimate clinically relevant improvement and deterioration, thus giving meaning to outcome measures such as walking distance. Hiatt et al[10] postulated an established MID as a requirement for an optimal functional test in PAD. Determination of the MID of walking distance could facilitate clinicians and researchers in their interpretation of this widely used outcome measure.

The purpose of the present study was to estimate the MID for the absolute claudication distance (ACD) and functional claudication distance (FCD) in patients with IC.

MATERIALS AND METHODS

Study population

We used data from the 2010 'Exercise Therapy in Peripheral Arterial Disease' (EXITPAD) trial. The EXITPAD study was a multicenter, randomized controlled trial of supervised exercise therapy (SET) versus a verbal walking advice. Patients with Fontaine stage II peripheral arterial disease (PAD), an ankle brachial index (ABI) <0.9 and an ACD of <500 meters were included from eleven outpatient vascular surgery clinics in the Netherlands. Their respective institutional review boards approved the trial and all patients gave written informed consent. Details on methodology were previously published[11]; below we will briefly describe aspects relevant to the current study.

In the present study, we used the baseline and three-month follow-up data on WIQ scores and walking distances from the 202 patients receiving SET in the former EXITPAD study. Patients were referred to a local physical therapist and received a SET programme according to recommendations in the guidelines of the Royal Dutch Society for Physical Therapy.[12] Prior to SET, all patients received cardiovascular risk management including cholesterol lowering medication, antiplatelet therapy, a 'stop smoking' advice and modification of other atherosclerotic present risk factors.

Walking distances

The ACD is defined as the walking distance where intolerable claudication pain forces a patient to stop. An alternative term for ACD is maximal walking distance. The FCD is defined as the distance at which the patient preferred to stop walking due to pain.[13] Walking distances were determined by a standardized progressive treadmill test (i.e. Gardner_Skinner protocol) with a constant speed of 3.2 km/h starting with 0% inclination, increasing every 2 minutes by 2%.[14] The maximum inclination was 10%, maximum duration of the test 30 minutes (1600 meters).[11]

The walking impairment questionnaire

The WIQ is a patient-reported outcome measure designed to assess the functional capacity of IC patients. It asks patients to rate their perceived difficulty regarding walking speed, distance and stair climbing. The total WIQ score constitutes a value ranging from 0 to 1. Lower scores represent more impairment. The validated Dutch version of the WIQ was used.[15, 16]

Determination of the MID

As per current recommendations we used an anchor-based approach, as opposed to a distribution-based approach, in estimating the MID, using longitudinal prospective data.[17] An anchor is an external criterion for a meaningful change, and

can be based on patient reported outcome measures that have demonstrated MID in the target population.[18] We used a previously defined MID for the WIQ as an anchor. A study by Conijn et al.[9] reported a MID of -0.03 for deterioration and 0.11 for improvement. Meaning a decrease in WIQ score of ≥0.03 is clinically relevant, as is an improvement of ≥0.11. Based on this anchor the current study population was divided into three categories: patients with 'clinically relevant improvement', 'clinically relevant deterioration' and 'no clinically relevant change'. Analogous to Conijn et al.[9] the MID for improvement was determined using the upper limit of the 95% confidence interval (CI) of the mean change in walking distance of patients who experienced 'no clinically relevant change' according to the WIQ-anchor. The MID for deterioration was defined by the lower limit of the 95% CI in this 'unchanged' category.

Statistical analysis

It is advised that the anchor and the outcome measure should correlate ≥0.3 to ensure that an association between the two exists.[18] So, the Pearson correlation coefficient was calculated between the change in walking distance (between baseline and after 3 months of SET) and the anchor. Categorical variables were presented as numbers with percentages. Continuous variables were reported as means ± standard deviations if normally distributed, or as medians with interquartile ranges (IQR) in case of a skewed distribution. Our methodology required the calculation of 95% CIs in the 'no clinically relevant change' category. Thus, when changes in ACD or FCD for the 'unchanged' patients demonstrated a distribution that was not normal, these variables were assessed for outliers. One patient, who deviated approximately 4 standard deviations from the mean change in ACD, was excluded for this reason. Baseline characteristics were compared using a Pearson's Chi-square test for categorical variables and a student's *t*-test for continuous variables. A statistical significance level of $p<0.05$ was applied. All analyses were performed with SPSS version 22.0 (SPSS Inc, Chicago, Ill).

RESULTS

Out of a total of 202 patients, data on WIQ scores as well as ACD and FCD were available for 103 and 102 patients, respectively. After removal of the one outlier, estimation of the MID for the ACD was based on 102 patients, and for the FCD on 101 patients. Baseline characteristics of in- and excluded patients are reported in Table 1. There were no statistically significant differences between baseline characteristics of patient included and excluded from analysis, except for chronic obstructive pulmonary disease (COPD) prevalence and baseline FCD values. Based on the WIQ-anchor, 56.9% of the included patients had a clinically relevant improvement after 3 months of SET, 23.5% remained unchanged, and 19.6% of the patients deteriorated.

Table 1. Baseline characteristics.

Variable	Included patients (n=102)	Excluded patients (n=99)	pb
Age, y	66.3 ±10	65.3 ±9.3 (n=98)	0.471
Body mass index, kg/m²	28.0 (5.3) (n=99)	27.0 (5.7) (n=93)	0.374
Ankle brachial index	0.70 (0.23) (n=100)	0.66 (0.22) (n=95)	0.229
Baseline WIQ score	0.46 ±0.21	0.44 ±0.22 (n=51)	0.427
Baseline ACD, m	280 (210)	249 (190) (n=97)	0.176
Baseline FCD, m	164 (150)	130 (110) (n=97)	0.006
Male sex	73 (71.6)	62 (62.2)	0.177
Arterial hypertension	63 (61.8)	57 (57.6) (n=96)	0.731
Diabetes mellitus	25 (24.5)	19 (19.2)	0.362
Hyperlipidemia	69 (67.6) (n=101)	64 (64.6) (n=94)	0.972
Orthopedic disease	15 (14.7)	17 (17.2) (n=95)	0.544
History of cerebrovascular disease	13 (12.7)	12 (12.1) (n=96)	0.959
History of cardiac disease	26 (25.5) (n=99)	22 (22.2) (n=95)	0.616
COPD	27 (26.5)	9 (9.1) (n=96)	0.002
Smoking			
Current	41 (40.2) (n=101)	40 (40.4)(n=94)	0.781
Former	54 (52.9) (n=101)	43 (43.3)(n=94)	0.501
Never	6 (5.9) (n=101)	11 (11.1)(n=94)	0.154

ACD, absolute claudication distance; COPD, chronic obstructive pulmonary disease; FCD, functional claudication distance; IQR, interquartile range; SD, standard deviation; WIQ, walking impairment questionnaire;

[a] Normally distributed continuous values are presented as mean ±SD, and as median (IQR) in case of a skewed distribution. Categorical values are presented as number (percentages).

[b] By student's t-test for parametric continuous variables, by Mann-Whitney U test for non-parametric continuous variables, and by Pearson's Chi-square test for categorical variables.

MID of the ACD

Three-month change in ACD was significantly correlated to the anchor (r Pearson=0.31, P=0.001), thus complying with the criterion of Revicki.[18] Table 2 presents the distribution of the ACD over the three categories (i.e. improved, unchanged, deteriorated) defined by the WIQ-anchor. The MID for the ACD was 305m for improvement, and 147m for deterioration. The MID for deterioration is a positive value and implicates that a small numerical improvement in ACD (<147m) is still perceived as clinical deterioration by the patient.

Table 2. Distribution and MID of the ACD (meters) after 3 months of SET.

Baseline (IQR)	Follow up	Median change	Correlation with anchor
280 (210)	507 (340)	210 (253)	0.31a
Compared with anchor	**Patients, n**	**Mean change in ACD**	
Improved	58	245b	IQR: 456
Unchanged	24	226	95% CI: 147 to 305
Deteriorated	20	125	95% CI: 39 to 212
MID of the ACD			
Improvement		305	
Deterioration		147	

ACD, absolute claudication distance; CI, confidence interval; IQR, interquartile range; MID, minimally important difference; SET, supervised exercise therapy.
[a] Pearson correlation coefficient.
[b] Value represents a median.

MID of the FCD

Three-month change in FCD was significantly correlated to the anchor as well (r Pearson=0.30, P=0.001). Table 3 presents the distribution of the FCD over the three categories defined by the WIQ-anchor. The MID for the FCD was 250m for improvement, and 120m for deterioration. Thus, a numerical improvement in FCD of <120m is considered as a clinical deterioration by the patient. Figure 1 shows a visual representation of the MIDs for both the ACD and FCD.

Table 3. Distribution and MID of the FCD (meters) after 3 months of SET.

Baseline (IQR)	Follow up	Median Change	Correlation with anchor
167 (145)	370 (315)	200 (240)	0.30[a]
Compared with anchor	**Patients, n**	**Mean change in FCD**	
Improved	58	200[b]	IQR: 238
Unchanged	24	185	95% CI: 120 to 250
Deteriorated	19	107	95% CI: 37 to 178
MID of the FCD			
Improvement		250	
Deterioration		120	

CI, confidence interval; FCD, functional claudication distance; IQR, interquartile range; MID, minimally important difference; SET, supervised exercise therapy.
[a] Pearson correlation coefficient.
[b] Value represents a median.

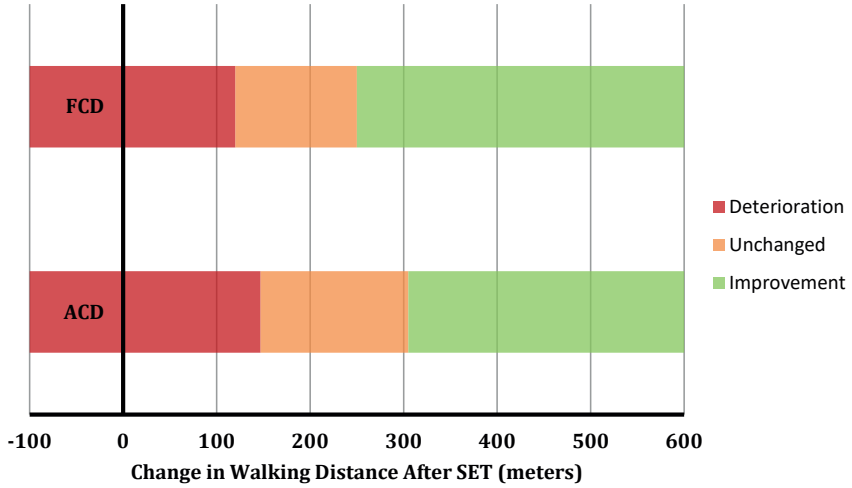

Figure 1. The MID of walking distance.
Threshold values at which the change in absolute claudication distance (ACD) and functional claudication distance (FCD) after three months of supervised exercise therapy (SET) is perceived as a clinically relevant improvement or deterioration by the patient.

DISCUSSION

This study was the first to estimate MIDs for the ACD and FCD in patients with IC. Our results can facilitate clinicians and researchers in appointing what numerical changes in walking distance indicate a clinically meaningful change. Recently, Hiatt et al[10] underlined the importance of assessing the MID for treadmill walking performance in the PAD population. Namely, a change in performance on a test should be related to a patient's perception of his or her limitations. Based on our estimations a change in ACD of more than 305m, and FCD of more than 250m, is viewed as clinically relevant by the patient. Interestingly, the MIDs for deterioration were positive values. This indicates that small improvements in walking distance are apparently not satisfactory in the patients' eyes. This may not be surprising as SET demands a considerable investment of time and effort, therefore patients' expectations of treatment effect are not readily met. On the other hand, patients might also have unrealistic expectations. In general, a 50-200% improvement of ACD has been reported.[19] Besides, as walking on the ground requires higher ground reaction forces and movement power compared with treadmill walking,[20] it may also be possible that an increase in treadmill based walking distance of approximately 100 m is insufficient to reveal any effect on walking distance in daily life. These findings might suggest that SET should not

only be focused on treadmill walking, but should additionally include outdoor walking and strength training.

The MID is population specific[18], and users should consider several factors before applying our MID values to their own patient population. There is a plethora of ways of measuring walking capacity in IC. Notably, walking capacity can be objectified using a treadmill test[10], the corridor-based 6-minute walking test[3], or by tracking outside walking via global positioning system (GPS) devices[22, 22]. Walking distance values measured for the same patient with different tests generally do not correspond well.[4, 23] Likely, the MID values found in this study are only transferable to walking distances measured using a graded treadmill protocol. Treadmill training has been criticized for being an artificial form of walking that does not necessarily translate to improved ambulatory function in daily life.[24] However, others found excellent agreement with values measured during outside walking, implying agreement with daily life impairment.[23] The use of a standardized treadmill protocol with a graded inclination, such as the one used in the present study[14], is well established[10] and advised in current guidelines[1]. It is the most reliable treadmill test[25] and demonstrates the best agreement to outside walking when compared with a non-graded treadmill protocol[26]. Accordingly, it is widely used to assess the effect of SET.[12] Thus, the MIDs found in this study are likely applicable to the majority of the IC patients, in both research and daily clinical practice, after three months of SET.

Limitations in walking distance are, irrespective of measuring method, not necessarily a true reflection of disease severity in patients with IC. Other authors reported important discrepancies between treadmill measurements and walking impairment as perceived by the patient.[4, 26] Moreover, an improvement of walking distance does not necessarily equal increased physical activity levels in patients with IC[6], and it lacks correlation with IC-specific HRQoL[5]. Evidently, walking distance is an imperfect outcome parameter. Nonetheless, it is widely used in clinical trials, as its value in assessing treatment effect has been well established.[13, 25] Indeed, assessment of walking distance provides the means to directly measure the primary treatment goal in IC: improvement of ambulatory (dis)function. The MIDs found in the current study strengthen the connection between this widely used outcome measure and patients' perception of treatment effect.

Our study had some important limitations. First, a single MID may be insufficient for all study applications as multiple approaches to estimating the MID will produce a range of different values. Besides, MIDs may vary by context and values will therefore differ for various treatment strategies (i.e. endovascular intervention).[18] So, final selection of MID values for a specific outcome measure should be based on several methods. Second, the MID is preferably determined

using an anchor that has been established in the target population. Preferably, the anchor provides a direct measurement of the patient's perspective on the results of treatment. A "global rating of change" question seems best suited for this purpose in IC. Unfortunately, the present data did not include such a question, thus an external anchor was used as established in a separate study.[9] Patient populations were similar, thereby approving the current external anchor strategy. Third, to ensure the greatest agreement between the external anchor's population and the present study subjects, outcome data after 3 months of SET were used. Yet, most IC patients are treated over prolonged periods in clinical practice. Preferably, future studies should incorporate a longer follow up duration to ensure optimal translation to the real world population. Fourth, almost half of the study population had to be excluded for failing to complete the WIQ at both baseline and after 3 months of SET. Although few differences in baseline characteristics between the included and excluded population were found, MID values may have been influenced by unknown confounders. Notably, a similar number of exclusions were found in the study by Conijn et al.,[9] highlighting the problem of early drop-out in this specific population. Finally, the correlation between the WIQ-anchor and ACD or FCD just barely fulfilled Revicki's criterion (a correlation of 0.3).[18] Future research is needed to validate the present findings by directly relating data on ACD and FCD to an anchor in the same population. Ideally, this anchor should incorporate aspects beyond walking capacity, like disease specific quality of life (i.e. VascuQol 6 or 25), to include a broader perceived health status. As various methods for estimating MIDs often converge, repetition is supported for the generalizability of MID estimates in similar applications.

Conclusion

The MID of treadmill-measured ACD in patients with IC was 305m for improvement and 147m for deterioration. The MID for FCD was 250m for improvement and 120m for deterioration. The MIDs as found may be helpful in the interpretation of the clinical relevance of changes in walking distances, which may be used in both research and the individual care setting.

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CHAPTER 4

Effect of supervised exercise, home-based exercise and endovascular revascularization on physical activity in patients with intermittent claudication: A network meta-analysis

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ABSTRACT

Background: It is unclear whether supervised exercise therapy (SET), home-based exercise therapy (HBET) and endovascular revascularization (ER) for intermittent claudication (IC) have a meaningful impact on physical activity, despite extensive research on their effect on walking performance.

Methods: Multiple databases were searched systematically up to May 2018 for RCTs harbouring objective measurements of physical activity in IC patients. A Bayesian network meta-analysis was performed comparing the change in physical activity between baseline and follow-up between treatments (SET, HBET or ER) and control (usual care). The standardized mean difference (SMD) with 95% credible interval (CI) was calculated as a summary statistic and converted into steps per day to aid interpretation.

Results: Eight trials involving 656 IC patients investigating the short-term effect of treatment on daily physical activity were included. Both SET (SMD 0.41, 95% CI 0.10 – 0.72: this corresponds to a difference of +803 steps/day on a pedometer) and HBET (SMD 0.50, 95% CI 0.18 – 0.88: +980 steps/day) displayed a benefit over control, based on evidence of moderate and low quality, respectively. The benefit of ER compared to control was SMD 0.36 (95% CI -0.22 – 0.99: +705 steps/day), but only one trial supplied the direct evidence resulting in a low rating of the quality of evidence. Comparisons between treatments yielded no statistically significant differences. The results were robust to several sensitivity analyses.

Conclusions: SET improves daily physical activity levels in patients with IC over control. HBET may have a similar benefit, while invasive treatment failed to lead to a statistically significant improvement of physical activity compared to control. However, the underlying quality of evidence for comparisons with ER and HBET is low, impeding definite conclusions.

INTRODUCTION

Lower-extremity peripheral arterial disease (PAD) is a manifestation of systemic atherosclerosis and thus associated with high rates of cardiovascular morbidity and mortality.[1,2] Among PAD patients, greater physical activity levels are associated with reduced functional decline[3], mortality, and cardiovascular events[4]. Owing to these potential benefits, there is a growing clinical interest in battling inactivity in this population.[5] Unfortunately, intermittent claudication (IC), the most common symptom of PAD, renders patients sedentary, evidenced by diminished daily physical activity levels compared to healthy individuals.[6,7]

Current guidelines recommend supervised exercise therapy (SET) as preferred initial treatment for patients with IC, reserving endovascular revascularization (ER) for patients unresponsive to SET.[1] Home-based exercise therapy (HBET) is a feasible alternative to SET when the latter is unavailable, as remains the case in most countries.[8] SET, HBET, and ER all primarily aim to increase the distance patients are able to walk at the maximum of their capacity, thereby improving functional status and quality of life (QoL).[1] However, walking capacity and daily physical activity are different concepts, evidenced by their minimal correlation in patients with IC.[9] Consequently, successful treatment of claudication symptoms (i.e. improvement of walking capacity) may fail to influence inactive behaviour. Notwithstanding extensive research on their respective clinical effectiveness regarding walking ability, it remains unclear whether SET, HBET, and ER have a meaningful impact on physical activity. Observational studies revealed no statistically significant improvement of daily activity after invasive treatment[10] and SET[11] in IC patients, despite substantial increases in walking capacity measures. Likewise, improvements after HBET failed to reach statistical significance in recent trials, despite the inherent focus of HBET on increasing ambulatory activity in the home environment.[12,13]

Objectively measured physical activity is only sparsely used as outcome in clinical trials[5], and to our knowledge HBET, SET and ER have never been compared in one trial. Thus, a standard meta-analysis does not suffice for simultaneous comparison of all three treatment modalities. A network meta-analysis combines direct evidence from head-to-head trials with 'indirect' evidence derived from multiple trials with a common reference treatment. As a consequence, the precision of the inferred treatment effects is increased and inferences regarding the relative effectiveness of several interventions can be made despite the absence of trials comparing all of them directly.[14] The aim of this study was to compare the effects of SET, HBET and ER on physical activity in IC patients.

MATERIALS AND METHODS

Study Design

A systematic review with network meta-analysis of randomized controlled trials was conducted to evaluate the comparative effects of different treatment modalities on daily ambulatory physical activity in IC patients. The study was performed according to standards as described in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).[15] The study protocol has been registered at PROSPERO (http://www.crd.york.uc/PROSPERO) with registration number CRD42017056355 prior to data synthesis.

Eligibility criteria

A study was eligible for inclusion if it was a parallel-group randomised controlled trial with IC patients (PAD Fontaine stage 2, Rutherford I-III) and reported both baseline as well as follow-up assessments of an objective measure of free-living physical activity (i.e. using an accelerometer or pedometer). Furthermore, a comparison of at least two of the following treatment regimens had to be considered: SET, HBET, ER, or control as common reference treatment.

A study reporting on treatment modalities was considered eligible for inclusion if the following conditions were met: (1) SET, treadmill walking performed under the supervision of trained medical personnel (e.g. physical therapists), either hospital or community-based, with a minimum of two supervised sessions per week for at least six weeks; (2) HBET, the advice to increase walking in the home-setting, quantified by keeping a walking diary or using a physical activity tracker (pedometer or accelerometer), prompted by follow-up telephone calls or visits by a healthcare professional (at least one follow-up contact, with a maximum of twice a week); (3) invasive treatment, comprised of either endovascular or open revascularization. Reference treatment was considered 'control' in this meta-analysis if no known effective- or (oral) placebo treatment was given. No limitations for inclusion on the (non-)use of additional cardiovascular risk modification methods, including the use or non-use of an explicit walking advice, were formulated.

Search strategy, study selection and data extraction

Multiple databases were searched (EMBASE, MEDLINE and Cochrane Central Register of Controlled Trials) from inception to May 23th, 2018. Additionally, clinical trial registries (http://www.clinicaltrials.gov and http://www.clinicaltrialsregister.eu) and reference lists of published reviews and meta-analyses were checked for potentially eligible studies. The search terms included variations on: PAD and IC, the treatment modalities of interest, and physical activity outcomes (See **Appendix S1** in the supplementary material for

the detailed search strategy). Two investigators (M.v.d.H., D.H.) independently screened titles and abstracts and subsequently retrieved and reviewed the full-texts of RCTs evaluating the treatments of interest. Conflicts were solved by consensus. Studies meeting the eligibility criteria were selected, in consultation with a third investigator (L.G.). All relevant data on study, patient, and treatment characteristics, co-interventions, and outcome assessment were extracted and independently checked by the two investigators (M.v.d.H., D.H.).

Outcomes

The primary outcome of interest was the comparative change in objectively measured physical activity between baseline and follow-up. Ambulatory physical activity is a complex health behaviour that is difficult to accurately measure.[16] Self-report methods, being subject to recall bias, have proven to be of limited use for the assessment of physical activity in PAD populations.[6] Therefore, only objective measurements (i.e. pedometers or accelerometers) were included into the primary analysis. The inclusion of trials in which physical activity was assessed through self-report was evaluated in a sensitivity analysis.

Quality Assessment

Two investigators (M.v.d.H., D.H.) independently assessed the included studies' risks of bias using the Cochrane's Collaboration tool.[17] Characteristics of the included trials were evaluated to assess whether sufficient similarity existed regarding potential effect modifiers to allow network meta-analysis. It was postulated that this so-called transitivity would be violated by differences across comparisons regarding the content and duration of the exercise program, median age of the study population, proportion of male participants, baseline ankle brachial index, co-morbidities, duration of follow-up, and method of outcome measurement.

The GRADE working group approach was used to rate the quality of the evidence underlying the estimates from the network meta-analysis. The GRADE tool considers the quality of evidence underlying a direct or indirect treatment comparison to be high; if all trials are at low risk of bias; if no important differences between populations, treatments, outcomes and other potential effect modifiers exist among studies (indirectness); if trials show similar estimates of treatment effect (consistency, low heterogeneity); and if effect estimates are precise (narrow confidence intervals).[18,19]

Statistical Analysis

A traditional pairwise meta-analysis was performed for treatment comparisons where direct RCT evidence was available. We used a random-effects models according to DerSimonian and Laird for pooling of the continuous outcomes

to account for between-study variance.[20] Indirect comparisons were calculated using the method described by Bucher.[21] Network meta-analysis was performed to incorporate direct and indirect treatment comparisons in a single analytical framework. A range of measurement tools for physical activity were used amongst trials, with various units (kcal, steps, metabolic equivalents) and time denominators (per day, per hours) reported. Therefore, the standardized mean difference (SMD, Hedges *g*) was calculated as a summary statistic. The SMD expresses the size of the intervention effect in each study relative to the variability observed. Generally, an SMD of <0.4 is considered small, 0.4 to 0.7 moderate, and >0.7 large.[22] SMDs were calculated by dividing reported change-from-baseline scores by their SDs. Considerable differences between baseline values existed. Change scores from baseline to follow-up take such baseline variability into account, as opposed to the sole use of follow-up scores. Furthermore, some studies only reported change scores. To re-express the SMDs as steps per day the outcomes of network meta-analysis were multiplied by the pooled SD of the baseline daily steps in the control groups of included trials where this was reported, as recommended by the Cochrane Handbook.[22]

A Bayesian Markov Chain Monte Carlo (MCMC) model was computed using the gemtc package in R.[23] The gemtc package implements the models recommended by NICE in their technical support document 2[24] using JAGS to provide the underlying MCMC simulations. JAGS (Just Another Gibbs Sampler) is a software program for analysis of Bayesian hierarchical models. A burn-in of 40,000 simulations was used, followed by a further run of 40,000 simulations, which were used for obtaining parameter estimates. Model convergence was assessed using graphical assessment of the MCMC trace, autocorrelation plots and posterior distributions of the model parameters. If there were any doubts about convergence of the estimates then more simulations were conducted. The analysis used the SMD with corresponding standard error (SE) for each treatment comparison within each trial in a random effects model. In trials with more than 2 arms, the variance of the control arm was assumed to be the same as the SE for the first treatment comparison. The uncertainty around the effect estimate is expressed with 95% credible intervals (CIs), the Bayesian statistics equivalent of confidence intervals.

All analyses were performed using intention to treat data. Statistical heterogeneity was assessed with the I^2 statistic. A formal assessment of potential publication bias was omitted due to limited amount of studies included. To validate the assumption of consistency in the network, the disagreement between direct and indirect evidence was assessed. To this end, the inconsistency factor was calculated between the direct and indirect estimates for closed evidence loops, and expressed as the Z-statistic with its p-value. Paucity of data decreases the power to detect inconsistency in network meta-analysis.

Sensitivity Analysis

Several sensitivity analyses were performed to assess whether the results of the primary analysis were robust to changes regarding important assumptions. Several parameters where adjusted to determine whether this induced a meaningful change in the results. Including applying a fixed-effect model and the inclusion of a trial that assessed physical activity using a self-report tool.

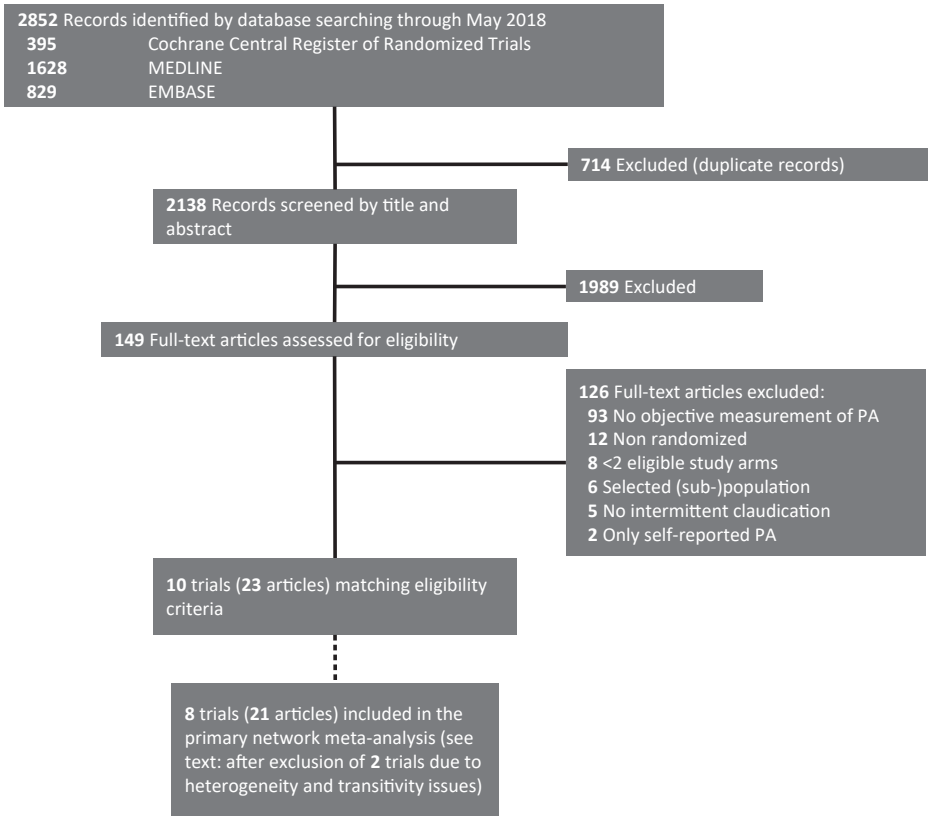


Figure 1. Flow diagram of study identification and selection for network meta-analysis.

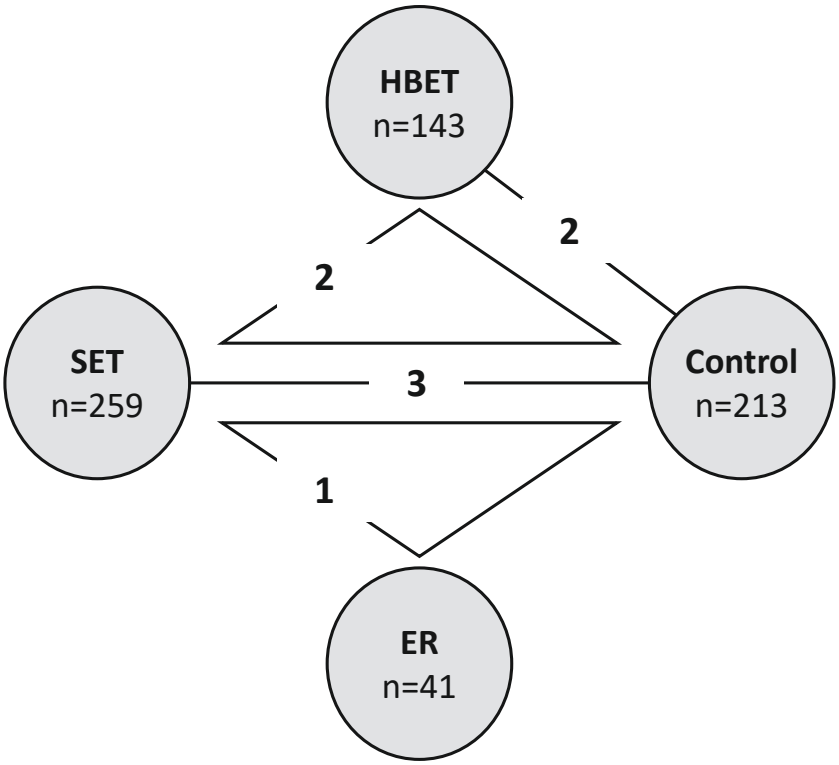


Figure 2. Graphical representation of the distribution of the primary network meta-analysis.

Nodes represent treatment modalities. Connecting lines between nodes represent head-to-head comparisons in randomized trials (RCTs), triangles represent three-arm RCTs. The number of trials are presented within the lines, the number of included patients are presented within the nodes. Abbreviations: ER, endovascular revascularization; HBET, home-based exercise therapy; SET, supervised exercise therapy.

RESULTS

Electronic searching through May 23rd, 2018, retrieved 2852 citations, 2138 after removal of duplicates (**Figure 1**). A total of 23 citations on 10 trials fulfilled the eligibility criteria. However, significant statistical heterogeneity for the treatment outcome of trials investigating SET versus control was found (I^2 of 93%, p<0.00001, supplementary material **Table S1**). This reduced to 0% (p=0.82) upon exclusion of a single study[25], without obvious reasons for these extreme outlying results. Thus, primary analysis was presented after omission of this study. Sensitivity analysis revealed that inclusion of this trial indeed led to grossly imprecise outcomes across all comparisons (**Appendix S2**). Furthermore, a trial by Crowther et al.[26] presented the outcomes of a SET programme at 12 months follow-up. Other >12 months

results were sparse precluding meta-analysis. For the transitivity assumption to hold, these longer-term results were not included in the primary meta-analysis but qualitatively described.

Thus, a total of 8 trials involving 656 IC patients were included in the primary meta-analysis. Three trials evaluated SET versus control, two trials compared HBET with control, two trials evaluated HBET versus SET versus control, and one trial compared ER to SET and control. **Table 1** summarizes key characteristics of studies included in the primary analysis. The risk of bias assessment is presented in **Table 2**. Blinding of participants is not possible for exercise interventions and was therefore not considered in the overall risk of bias assessment. The clinical trials were deemed sufficiently similar regarding study-level intervention characteristics, population characteristics (Supplementary material, **Table S2**), and trial methodology (follow-up duration), ensuring that a network meta-analysis was appropriate. Control treatment was defined differently among trials, consisting of: non-exercise usual care (either including advice to walk more[27-30] or excluding such walking advice[25,31]), attention-control with light-resistance training[13] and health education sessions[32,33].

Table 1. Characteristics of trials included for the primary analysis.

Trial	Patients per treatment arm				Follow-up	Physical activity outcome	Number of monitoring days	Risk of bias
First author, year	SET	HBET	ER	Control	Months[b]	Measure (Device)[b]		
Regensteiner, 1996[a]	10	-	-	10	3	% time active (accelerometer)	1	Moderate
McDermott, 2009[a]	12	-	-	6	6	Units/7d (accelerometer)	7	Moderate
Gardner, 2011	33	29	-	30	3	Steps/d (pedometer)	7	Moderate
Gardner, 2012	106	-	-	36	4	Kcal/d (accelerometer)	2	Moderate
Murphy, 2012	38	-	41	20	6	Steps/h (pedometer)	7	Moderate
Cunningham, 2012	-	28	-	30	4	Steps/d (pedometer)	6	High
McDermott, 2013	-	26	-	21	6	Units/7d (accelerometer)	7	Low
Gardner, 2014	60	60	-	60	3	Steps/d (pedometer)	7	Moderate

Abbreviations: ER, endovascular revascularization; HBET, home-based exercise therapy; SET, supervised exercise therapy.

[a] Three arm trial, third arm not relevant to current meta-analysis.

[b] Used for the primary meta-analysis.

Direct meta-analysis
Conventional pairwise meta-analyses using direct evidence (supplementary material, **Table S3**) indicated that HBET and SET were both more efficacious than control, with SMDs of 0.53 (95% CI 0.09 – 0.97) and 0.29 (95% CI 0.09 – 0.49) respectively. Significant heterogeneity was found for the HBET versus control estimate (I^2 = 69%). ER showed no statistically significant benefit over control (SMD 0.51 95% CI -0.04 – 1.05) based on the results of a single trial. There was no significant difference found between SET and HBET (SMD 0.01 95% CI -0.28 – 0.30), or SET and ER (SMD -0.19 95% CI -0.63 – 0.25).

Network meta-analysis
Table 3 shows the results of the network meta-analyses for the effect of SET, HBET, and ER on daily physical activity in patients with IC considering a follow-up of three to six months. Compared to control both SET (SMD 0.41, 95% CI 0.10 – 0.72) and HBET (SMD 0.50, 95% CI 0.18 – 0.88) displayed a statistically significant benefit, based on moderate and low quality of evidence, respectively. The benefit of ER on daily physical activity over control was not statistically significant (SMD 0.36, 95% CI -0.22 – 0.99), but only one trial supplied the evidence resulting in a low rating of the quality of evidence. Network meta-analysis revealed no important differences among the various treatments (SET versus HBET, SET versus ER, and HBET versus ER, see **Table 3**).

The pooled SD of the baseline mean steps per day of the control groups of Gardner et al. 2011[13], Gardner et al. 2014[13], Cunningham et al. 2011[27], and Murphy et al. 2012[30] amounted to 1959 steps/day. Thus, re-expressing the SMDs resulted in a benefit of SET over control of 803 steps/day (95% CI 196 – 1410), of HBET versus control 980 steps/day (95% CI 352 – 1724), and ER versus control 705 steps/day (95% CI -429 – 1939).

Network Consistency
A graphical representation of the networks of direct comparisons is shown in **Figure 2**. No inconsistencies between direct and indirect evidence were detected by visual inspection of the forest plots (**Figure 3**). The inconsistency factor was calculated for the closed loops of control vs SET vs HBET (Z=0.293; p=0.77) and control vs SET vs ER (Z=0.198; p=0.84), and revealed no evidence of statistical inconsistency between direct and indirect estimates.

Sensitivity Analyses
The results of the primary analysis were robust to variations in several parameters assessed through sensitivity analysis. The details of these analyses and the forest plots are presented in the supporting information (**Appendix S2**). Notably, the results of ER versus control were more precise when applying a fixed-effect

network meta-analysis compared to the primary analysis. Thereby, ER showed a statistical significant benefit of SMD 0.35 (95% CI 0.08 – 0.61) over control treatment.

Review of longer-term treatment results

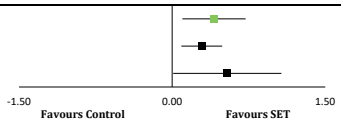
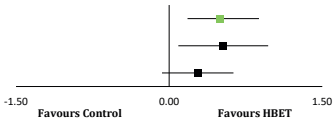
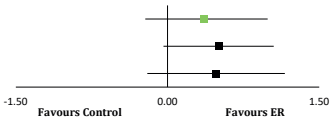
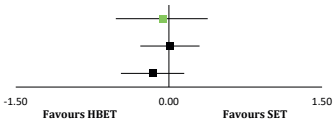
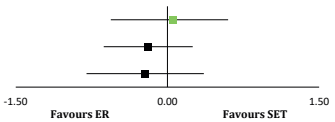
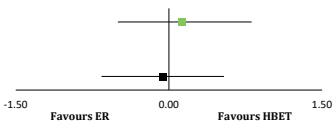
The late effects of a HBET programme, from the trial by Cunningham et al.[34], showed an adjusted difference in daily steps of 1374 (95% CI 528 – 2220) at 12 months, and 1630 (95% CI 495 - 2765) at 24 months, compared to control. Similarly, Gardner et al.[35] reported a maintained benefit for SET over control at 18 months follow-up (560±87 versus 408±58 kcal/d, $p<0.05$). In contrast, Crowther et al. [26] found no statistically significant effect for SET versus usual care after 12 months on daily steps.

Table 2. Risk of bias assessment.

Study	**Selection bias**		**Performance bias**	**Detection bias**	**Attrition bias**	**Reporting bias**
First author, y	Random Sequence generation	Allocation concealment	Blinding of participants and personnel[a]	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Regensteiner, 1996	?	?	-	?	+	+
McDermott, 2009	?	?	-	+	-	+
Gardner, 2011	+	+	-	?	+	+
Murphy, 2012	+	?	-	?	+	+
Cunningham, 2012	+	+	-	-	+	+
Gardner, 2012	+	+	-	?	+	+
McDermott, 2013	+	+	-	+	+	+
Gardner, 2014	?	?	-	?	+	+

+ indicates low risk of bias; - indicates high risk of bias; ? indicates unclear risk of bias.
a Participants and direct personnel cannot be blinded to exercise interventions, thus this was not factored in the overall assessment of risk of bias.

Table 3. Standardized mean differences produced by random-effects network meta-analysis of physical activity using direct and indirect comparisons.

Comparison	Estimate		SMD (95% CI)	Quality of evidence
SET vs Control	Network meta-analysis		0.41 (0.10 – 0.72)	⊕⊕⊖⊖
	Direct evidence		0.29 (0.09 – 0.49)	⊕⊕⊖⊖[a]
	Indirect evidence		0.54 (0.01 – 1.07)	⊕⊕⊖⊖[a]
HBET vs Control	Network meta-analysis		0.50 (0.18 – 0.88)	⊕⊕⊖⊖
	Direct evidence		0.53 (0.09 – 0.97)	⊕⊕⊖⊖[a, c]
	Indirect evidence		0.28 (-0.07 – 0.63)	⊕⊕⊖⊖[a, d]
ER vs Control	Network meta-analysis		0.36 (-0.22 – 0.99)	⊕⊕⊖⊖
	Direct evidence		0.51 (-0.04 – 1.05)	⊕⊕⊖⊖[a, d]
	Indirect evidence		0.48 (-0.20 – 1.16)	⊕⊕⊖⊖[a, d]
SET vs HBET	Network meta-analysis		-0.06 (-0.52 – 0.38)	⊕⊕⊖⊖
	Direct evidence		0.01 (-0.28 – 0.30)	⊕⊕⊖⊖[a, d]
	Indirect evidence		-0.16 (-0.47 – 0.15)	⊕⊕⊖⊖[a, d]
SET vs ER	Network meta-analysis		0.05 (-0.56 – 0.60)	⊕⊕⊖⊖
	Direct evidence		-0.19 (-0.63 – 0.25)	⊕⊕⊖⊖[a, d]
	Indirect evidence		-0.22 (-0.80 – 0.36)	⊕⊕⊖⊖[a, d]
HBET vs ER	Network meta-analysis		0.13 (-0.50 – 0.81)	⊕⊕⊖⊖
	Direct evidence		N/A	N/A
	Indirect evidence		-0.06 (-0.66 – 0.54)	⊕⊕⊖⊖[a, b, d]

Abbreviations: SET, supervised exercise therapy; HBET, home-based exercise therapy; ER, endovascular revascularization; SMD, standardized mean difference; CI, credible interval; N/A, not applicable.

Forest plots showing the relative effect of each treatment strategy on objective measurements of free-living physical activity among patients with intermittent claudication. Direct estimates and indirect estimates are shown and combined in the results of the network meta-analyses. Quality of evidence was established using the GRADE tool for network meta-analysis.[18] Quality can be downgraded one point each due to;

[a] Study limitations (contributing evidence of moderate quality);

[b] Indirectness;

[c] Inconsistency and/or heterogeneity;

[d] imprecision.

⊕⊕⊕⊕=High quality; ⊕⊕⊕⊖=Moderate quality; ⊕⊕⊖⊖=Low quality; ⊕⊖⊖⊖=Very low quality.

DISCUSSION

This network meta-analysis represents a comprehensive synthesis of the effect of various treatment modalities on objectively measured daily physical activity in patients with IC. SET showed a moderate effect over usual care control treatments. Potential benefits of HBET appeared similar, but quality of evidence was graded 'low' due to heterogeneity and risk of bias in the underlying trials. No significant differences between the efficacy of ER, SET and HBET were found. The effect size of ER compared to control based on this study is similar to that of SET and HBET, but not statistically significant. However, only one trial reported objectively measured daily physical activity after ER, which was detrimental for the reliability. In general, the paucity of randomized trials investigating the effect of IC treatment on physical activity undermined the quality of evidence across comparisons. Therefore, cautious interpretation of the results is warranted and facilitated by the reported GRADE scores.

Daily physical activity is increasingly recognized as an important treatment goal and outcome measure in IC management.[5] Nonetheless, it has been sparsely investigated in randomized trials where treatment effects generally failed to reach statistical significance due to inadequate sample size. Aggregation of all available evidence in this network meta-analysis revealed a statistically significant benefit of SET and HBET compared to control treatments. The current study thus provides novel evidence to indicate that SET and HBET lead to substantial increases equating some 800 and 1000 steps per day over control treatment, respectively. This may already be a clinically meaningful improvement, as the baseline mean daily steps among the included studies' populations was approximately 3000. Few studies investigated the dose-response effect of increases in daily steps on (cardiovascular) mortality and morbidity, but the available evidence supports a graded inverse relationship.[36,37] To further increase the benefits confirmed by this meta-analysis, the aims of IC treatment need to extend beyond merely improving walking distance limitations. Interestingly, HBET has an inherent larger focus on increasing physical activity in the home environment than SET, but failed to show more benefit in this meta-analysis. Home-based programs stimulate patients to quantify home-exercise using techniques such as walking diaries and pedometers.[12,13,28] Modern ambulatory devices, such as wearable accelerometers and smartphone apps, make monitoring of daily life behaviour increasingly accessible. These devices can function as potentiators of health behaviour change, but probably only when incorporated into larger engagement strategies.[38,39] Indeed, such technology adjunctive to SET has recently shown promising results[40], but failed to improve physical activity in a HBET programme with limited in-person guidance[41]. The benefits of exercise therapy on daily activity found in the current

study may be potentiated by incorporating the supervised use of new wearable devices.

The effects of percutaneous revascularization on daily physical activity in claudication patients are poorly studied. Despite a thorough systematic search with a wide scope, only one randomized trial was identified by the current study.[30] Subsequent network meta-analysis revealed no statistically significant difference between ER compared to SET, HBET, or control treatment. Even so, the lack of direct evidence was detrimental for the reliability of the inferred summary effect. This is indicative of the general tendency in research on invasive treatment in vascular disease to focus on anatomic and hemodynamic endpoints rather than functional measures. Indeed, clinical trials investigating new percutaneous therapies mainly report on arterial patency and the consequent need for repeat revascularization, all important indicators of technical success. Unfortunately, the degree of lumen narrowing (i.e. patency) is poorly related to function and symptomatology, thus repeat revascularization is often not truly 'clinically driven'.[42] Even the ankle-brachial index, a parameter that integrates the hemodynamic impact of all stenoses in the limb into a single measure, shows poor correlation with walking function.[42,43] Arguably, the most used functional outcomes - exercise capacity on standardized treadmill tests or during corridor walking - are a poor reflection of patients' actual daily disability as well.[9,44] Future studies should incorporate an assessment of physical activity as it is an important modifiable risk factor and treatment goal in IC and objective measurements are readily available.

Based on this network meta-analysis, SET and HBET are probably preferred treatments when attempting to increase ambulatory physical activity in IC patients. ER failed to show a statistically significant benefit over control treatment, as opposed to SET and HBET, although with similar effect size. While no differences between ER and SET or HBET were found, the underlying quality of evidence for these comparisons was low to very low, indicating that the true effects may be substantially different from the estimates.[18] One can argue that the impact of ER on lifestyle factors such as physical activity is minimal as there is little time for in-person guidance, apart from the short clinical consultations with the interventionalist. In contrast, exercise programs permit a trained healthcare professional to influence patients through multiple face-to-face contacts over an extended period, using several behavioural-change techniques.[45] The current study cannot definitively add weight to this argument due to the lacking quality of evidence for comparisons among treatments. Moreover, the actual impact of supervised- or home-based exercise programs on cardiovascular mortality and morbidity remains unknown. Exercise programs provide the opportunity to induce meaningful changes in a patient's cardiovascular health, arguably more

so than a vascular intervention, but these benefits need to be substantiated beyond the current study.

Several limitations need to be considered. First, many treatment comparisons were assessed as low or very low quality of evidence in the GRADE framework. This is mainly caused by the moderate-to-high risk of bias of the included trials and the fact that physical activity is not commonly measured in randomized controlled trials. To ameliorate this drawback, authors were contacted for additional data and network meta-analysis was used to allow the inclusion of indirect comparisons thereby improving the preciseness of the estimates. Nonetheless, this is a limitation and the reported GRADE scores are added for transparency, aiding the reader with interpreting the results. Second, follow-up durations differed from three to six months, which may be a cause for bias. However, improvements in walking function with SET are mostly obtained in the first months.[29] Still, six months is a short timeframe: longer-term adherence to the gained activity level is probably a greater challenge. While some longer-term results were reported, such data is largely unavailable, warranting more research. Third, the common reference 'control' group of this meta-analysis consisted of various usual care variants. Notably, the current meta-analysis combined study arms where an explicit verbal walking advice was given, with usual care treatments where this was not the case. This may be deemed controversial[46], but a mere walking advice (without quantification as in HBET) has a marginal effect and cannot be really seen as an active intervention distinct from best medical treatment or usual care. Furthermore, whether clinicians indeed refrained from such advise in trials where it was not explicitly mentioned in the article text cannot be established.

Conclusion

This study shows that SET leads to a moderate short-term improvement of physical activity in patients with IC compared to control therapies. HBET demonstrated similar effects, but the confidence in this evidence was graded low. The effects of ER on physical activity are not well studied and statistical insignificance and low-quality evidence barred definite conclusions for this treatment modality.

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PART II

Efficient management of intermittent claudication

CHAPTER 5

Cost-effectiveness of supervised exercise therapy compared with endovascular revascularization for intermittent claudication

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ABSTRACT

Background: Current guidelines recommend supervised exercise therapy (SET) as the preferred initial treatment for patients with intermittent claudication (IC). The availability of SET programs is however limited and such programs are usually not reimbursed. Evidence on the long-term cost-effectiveness of SET compared to endovascular revascularization (ER) as primary treatment for IC is required for successful implementation in clinical practice.

Methods: A Markov model was constructed to determine the incremental costs, incremental quality-adjusted-life years (QALYs) and incremental cost-effectiveness ratio of SET versus ER for a hypothetical cohort of patients with newly diagnosed IC, from the Dutch healthcare payer's perspective. In case of primary treatment failure possible secondary interventions were repeat ER, open revascularization, or major amputation. Data sources for model parameters included original data from two randomized controlled trials, as well as evidence from the medical literature. The robustness of the results was tested with probabilistic- and one-way sensitivity analysis.

Results: Considering a 5-year time horizon, probabilistic sensitivity analysis revealed that SET was associated with cost-savings (-€6412, 95% credibility interval; -€11 874 to -€1939) compared to ER. The mean difference in effectiveness was -0.07 QALY (95% CI; -0.27 to 0.16). ER was associated with an additional €91 600 per QALY gained as compared with SET. One-way sensitivity analysis indicated more favourable cost-effectiveness for ER in subsets of patients with low quality of life scores at baseline.

Conclusions: SET is a more cost-effective primary treatment for IC compared to ER. These results support implementation of supervised exercise programs in clinical practice.

INTRODUCTION

Intermittent claudication (IC) is the most common manifestation of peripheral arterial occlusive disease (PAD). It is prevalent in around 2% of the population aged 40-44, increasing to 8% at 70-74 years.[1] With the aging population in Western societies the prevalence of IC is increasing.[2] Consequently, IC will place a growing burden on health care resources.

Treatment of IC aims to improve quality of life (QoL) and walking distance. Over the past decade, several studies have compared supervised exercise therapy (SET), endovascular revascularization (ER) or a combination of these treatments. In general, most studies found no difference between SET and ER with respect to walking distance or QoL, even after 7 years of follow-up.[3-8] SET is a relatively safe, non-invasive treatment.[9] Accordingly, current international guidelines recommend SET as the primary treatment in the management of IC.[1,10-12] However, access to adequate SET programs worldwide is limited.[13,14] Furthermore, in contrast to ER they are often not, or only partially, reimbursed by insurance plans.[15,16] As a result, SET remains underutilized in the treatment of IC.

Considering the equal effectiveness of SET and ER, other aspects like costs, mortality and morbidity of the intervention can play a decisive role in choosing the initial treatment strategy. Previous cost-effectiveness studies found a SET-first approach to be less expensive and equally effective compared to ER.[17-19] Implementation of a SET-first approach in the treatment of IC could lead to significant savings of health care resources.[16] However, these studies either considered a limited time-horizon of 12-15 months[18,19], or did not include effectiveness[16,17].

A clinical decision model, such as a Markov model, incorporates existing scientific evidence to analyse the clinical outcome of a disease.[20] It can be used to evaluate the cost-effectiveness of different treatment strategies over an extended period of time. A comprehensive Markov model, using contemporary evidence from multiple sources, is necessary to facilitate the optimal allocation of available health care resources.

The purpose of the present study was to incorporate current evidence on the costs and effectiveness of SET and ER into a clinical decision model and to evaluate the cost-effectiveness of a SET-first strategy (with ER in case of SET failure) compared to an ER-first strategy for the management of IC.

METHODS

Study Design

A Markov model was developed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA) to assess the cost-effectiveness, from the perspective of the Dutch healthcare payer, of SET and ER for patients with newly diagnosed IC (PAD Fontaine II, Rutherford 1-3). The model was designed to simulate the effect of both treatment strategies on the clinical course of a hypothetical cohort of patients. It consisted of 7 health states: asymptomatic PAD, mild claudication, moderate claudication, severe claudication, CLI, post major amputation and death (Figure 1). All patients started with an intervention, either SET or ER. With each cycle, representing 3 months, transition probabilities determined whether patients would relocate to a different health state or remain in the same state. The decision model kept track of costs, time spent in each health state and impact on QoL. Subsequent analysis over a 5-year time horizon (20 cycles) provided results on the cost-effectiveness of SET and ER. Outcomes of interest were total quality adjusted life years (QALYs), total costs (reported in euros), and the incremental cost-effectiveness ratio (ICER).

Treatment strategies

Two primary treatment strategies were analysed. (1) One year of SET, performed by a physical therapist trained in SET according to the guidelines of the Royal Dutch Society for Physical Therapy.[21] A typical SET-session includes interval training to near-maximal pain, as well as strength and endurance training, and focuses on risk factor modification and improving self-management. (2) ER, specifically a percutaneous transluminal angioplasty (PTA) followed by a stent when balloon dilatation was inadequate.

All patients received cardiovascular risk factor management according to present guidelines, including cholesterol lowering medication and antiplatelet therapy.[1,10-12] In the event of failure of primary treatment (SET or ER) secondary interventions were either open revascularization (OR), (repeated) ER or major amputation.

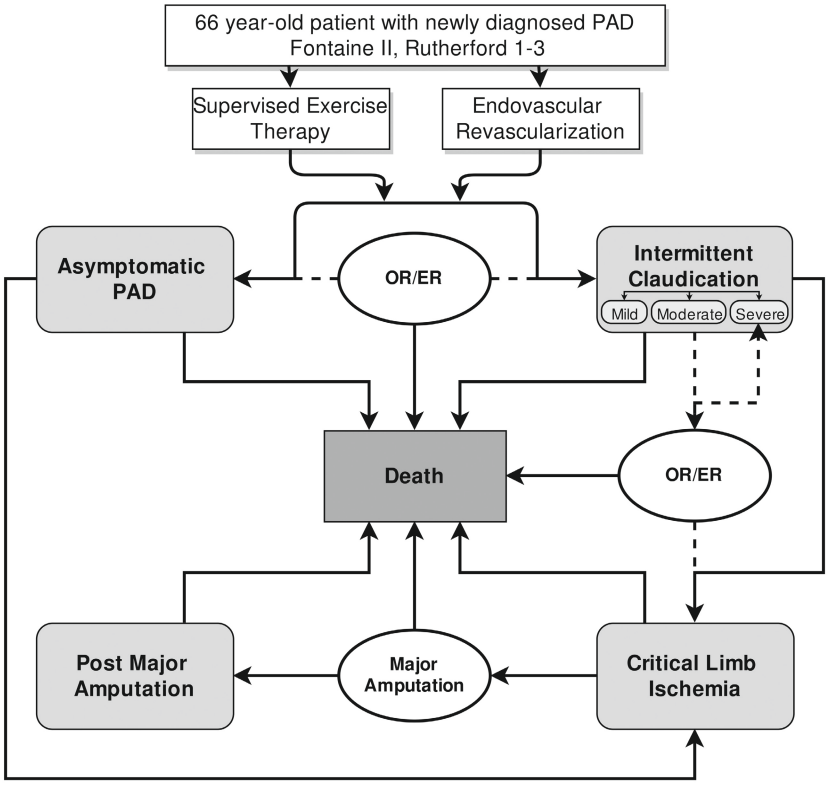

Figure 1. Simplified Diagram of the Markov Model Structure.

Patients start the cycle in one of the 'Intermittent claudication'(IC) health states and will primarily get either supervised exercise therapy or endovascular revascularization. Every grey box represents a health state, the oval boxes represent a possible secondary intervention: major amputation, open- or endovascular revascularization (OR/ER). The arrows indicate the possible transitions between health states. Transition probabilities define how patients may move during a cycle. Both the SET and ER group have distinct transition probabilities. NB: To keep the figure clear simplifications were made. The IC health states are represented in a single box. In the model intermittent claudication was split in 3 groups (mild/moderate/severe) based on symptom severity as defined by quality of life. Also, all health states had possible transitions to itself not shown in the figure.

Model input sources

Costs, utilities and transition probabilities were derived from existing medical literature[18,19,22-36] and original patient data from two sources: the Exercise Therapy in Peripheral Arterial Disease (EXITPAD) study[37] and the Comparing Exercise Training with Angioplasty for Claudication (CETAC) study[3].

The EXITPAD study was a multicentre randomized controlled trial (RCT) that included 304 patients from eleven outpatient vascular surgery clinics throughout the Netherlands. Patients were randomized to either a verbal walking advice or SET performed by a local physical therapist. The CETAC study was a single centre RCT. 151 consecutive patients who presented with symptoms of IC due to iliac or femoro-popliteal arterial stenosis were included. Patients with lesions unsuitable for revascularization were excluded. Patients were randomly assigned to either hospital based SET or ER. Further details on methodology were previously published.[3,37]

The baseline and 12-month follow-up data from the SET treatment arms of the EXITPAD study (169 patients) and both the ER and SET arms of the CETAC study (151 patients) were used. A comparison of baseline characteristics can be found in the supplemental material (Table S3, supporting information). Their respective institutional review boards approved both trials and all patients gave written informed consent. For the current study, authors of both studies approved their data usage.

Health states

The starting health state was either *mild claudication*, *moderate claudication* or *severe claudication*. In the cycles after the initial intervention patients could either; recover completely (*asymptomatic PAD*); stay in the same health state; transit to any of the other IC states; develop *CLI* (PAD Fontaine III and IV, Rutherford 4-6) and possibly require an amputation (*post major amputation)*, or die (*death*). Patients requiring secondary revascularization had the same possible health state transitions afterwards, however with different transition probabilities (Table S2, supporting information).

The health states mild, moderate and severe claudication were defined using the tertile values for the EuroQol 5 Dimension score (EQ-5D) in the combined EXITPAD and CETAC data as thresholds to form the three distinct health states. At the start of the simulation, the virtual cohort was divided over these health states based on the initial distribution in the combined database (the ratio mild:moderate:severe was 34:44:22).

Input parameters

Transition probabilities

Table S1 and S2 (supporting information) show the input transition probabilities with their corresponding sources and ranges used for probabilistic sensitivity analysis. Some assumptions had to be made where data sources were insufficient, as described below.

Both mortality and progression to CLI were rare events in the EXITPAD and CETAC trials. Therefore, annual mortality[23] and CLI incidence[22] for health states mild, moderate and severe claudication were derived from the literature.

The model-structure only allowed for one type of secondary intervention. To be able to incorporate outcome and costs for both ER and OR, we calculated weighted averages of cost and effectiveness outcomes combining the results based on observed ratios of OR:ER (10:293[16] for IC and 10:27[29] for CLI).

Transitions for a patient in the CLI health state differed depending on type of treatment received. A study by Frans et al.[29] found that in 150 consecutive CLI patients, 7.3% were treated conservatively, 3.3% required a major amputation, 24.1% were treated with OR, and 65.3% with ER. Accordingly, different transition probabilities, from different sources, were used for CLI patients treated conservatively (with wound care and pharmacotherapy alone)[25], after ER or OR[26] and after amputation[28] (Table S1 and S2, supporting information).

Costs

All costs (Table 1) were established from a Dutch health care payer's perspective. The costs of SET were calculated assuming a physical therapists fee of €30.00 per half-hour training session and 48 training sessions in 12 months.[16] Costs for the initial ER treatment strategy were taken from the CETAC database considering the procedure, follow-up and overhead costs.[19] The costs for the initial outpatient consultation and diagnostic work-up were considered equal for SET and ER, and were thereby not included in the analysis. Costs for secondary interventions were determined for ER[19], OR[31] and major amputation[35] separately. The costs of being in the health state 'CLI' were derived from Stockl et al.[33], considering wound care for patients with diabetic ulcers. The cost of being in the mild, moderate or severe claudication health state was calculated considering one yearly outpatient follow-up visit[38] and medication costs[39]. The cost of asymptomatic PAD was based on medication costs only.

Cost input derived from American sources was converted to the Dutch healthcare system using the healthcare-specific purchasing power parity of the United States relative to the average of a group of developed countries.[40] All costs were updated to September 2014 euros with the Dutch and United States' inflation indices (http://www.statline.cbs.nl and http://www.bls.gov/data/inflation_calculator.htm).

Quality of life

To assess the effect of treatment on QoL, utility scores were assigned to each health state (Table 1). A utility is the valuation of a person's health ranging from 0

(worst possible health) to 1 (perfect health). Utility scores for mild, moderate and severe claudication as well as asymptomatic PAD were derived from the EXITPAD and CETAC data by calculating median EQ-5D values for these respective states. Utilities for post-major amputation[41] and CLI[26] were drawn from literature.

Table 1. Utilities and Costs with Distribution Used in Probabilistic Sensitivity Analysis.

Model parameters	Value* (standard error)	Distribution	Source
Health state utilities			
Asymptomatic PAD	0.81 (0.002)	Beta	exitpad/cetac
Mild claudication	0.78 (0.006)	Beta	exitpad/cetac
Moderate claudication	0.65 (0.002)	Beta	exitpad/cetac
Severe claudication	0.54 (0.020)	Beta	exitpad/cetac
Critical limb ischemia	0.42 (0.144)†	Beta	[26]
Post major amputation	0.54 (0.076)†	Beta	[26]
Health state costs (2014 €)			
Asymptomatic PAD	16 (4)‡	Gamma	[39]
Mild claudication	93 (20)‡	Gamma	[38, 39]
Moderate claudication	93 (20)‡	Gamma	[38, 39]
Severe claudication	93 (20)‡	Gamma	[38, 39]
Critical limb ischemia	13 881 (6000)‡	Gamma	[26,33]
Post major amputation	2777 (437)	Gamma	[34]
Costs of interventions (2014 €)			
Primary treatment:			
SET	1440 (1260)	Gamma	See text
ER	7530 (1530)	Gamma	[19]
Secondary interventions:			
ER/OR for IC	7552§ (1534)	Gamma	[19,31]
ER/OR for CLI	12 559§ (3000)‡	Gamma	[31]
Major amputation	14 917 (1817)	Gamma	[35]

Abbreviations: PAD, peripheral arterial disease; ER, endovascular revascularization; IC, intermittent claudication; OR, open revascularization.

*All values are presented yearly. They were converted into 3-monthly values to fit the cycle length of the model.

†Based on a range of values from different studies reported by Barshes et al.[26]

‡Estimated standard error due to lack of published data in the literature.

§Costs of secondary intervention 'ER/OR' was calculated combining separate costs assuming an OR:ER ratio of 10:293[16] for IC and 10:27[29] for CLI.

Analysis

Validation

The internal validity of the model was tested by comparing the health state distribution after one simulated year with the distribution in the observed data from the EXITPAD and CETAC study. The external validity was verified by comparing important simulated outcome parameters to values as described in the practice guidelines from the Society for Vascular Surgery.[12]

Base case analysis

All probabilities, costs and utilities were calculated to 3-month-values, the cycle length of this Markov model. The age at the start of the simulation was set at 66 years (mean age in the combined EXITPAD and CETAC database). Future costs and outcomes were discounted at the rates of 4% and 1.5% respectively, following the Dutch Guidelines for Pharmaco-Economic Research.[42] Total QALYs were calculated by multiplying the time a patient remained in a certain health state by the associated utility and the results were summed across health states. Incremental costs and QALYs were determined by subtracting total costs and QALYs for the ER-first arm from their respective SET-first counterparts. A strategy was considered dominant if both effectiveness increased and costs decreased compared to the other strategy. To calculate the ICER for non-dominant situations, incremental costs were divided by incremental effectiveness (as measured by QALYs).

Uncertainty

To account for the uncertainty of the model outcome, we performed a probabilistic sensitivity analysis using Monte Carlo simulation. A probability distribution was derived for each parameter, either from reported standard errors, confidence intervals, alternative probabilities found in the literature or expert opinion (as presented in Table 1, and Table S1 and S2 in the supporting information). The simulation ran 1000 times for a hypothetical cohort of 100 000 patients for each treatment strategy. Each time the value for each parameter differed based on random selection from their respective distributions. The mean costs and QALYs from the 1000 simulations were reported, along with their 95% credibility interval (CI). CIs are the Bayesian statistics equivalent of a confidence interval.

The probability of SET or ER being cost-effective at different willingness to pay (WTP) thresholds was presented in cost-effectiveness acceptability curves (CEACs). There is no consensus on an appropriate threshold for the costs society is willing to pay per QALY gained. In the Netherlands a WTP threshold range of €20 000-€80 000/QALY has been suggested.[43] A threshold WTP for a QALY of €40 000 was considered since this is close to the commonly used threshold of 50 000/QALY.[44] Various one-way sensitivity analyses were performed to evaluate

the effect of alternate inputs and assumptions on the outcomes of the model. In particular, sensitivity analyses varying the time horizon, using alternative discount rates, varying the age of the patients, alternating the frequency of SET-sessions (according to NICE guideline recommendations[11]), using different costs or secondary intervention rates, applying cardiovascular health benefits after SET[45], and isolating patients with mild, moderate or severe disease (as defined by EQ-5D scores).

RESULTS

The outcome of 1000 Monte Carlo Markov model simulations of a hypothetical cohort of 100 000 IC patients is presented in Figure 2. Over a 5-year time horizon, the mean total costs of SET and ER were €10 219 and €16 631, respectively. Mean total QALYs were 2.78 for SET, and 2.85 for ER. The distribution of virtual patients across health states after 5 years are presented in the supplement (Table S3, supporting information). Probabilistic sensitivity analysis showed that SET saved costs (-€6412, 95% CI -€11 874 to -€1939) compared with ER. There was no statistically significant difference in effectiveness (-0.07 QALY, 95% CI -0.27 to 0.16). ER was associated with an additional €91 600 (US $118 164) per QALY gained as compared with SET. This exceeds the Dutch WTP threshold of €20 000 - €80 000/QALY. There were no statistically significant differences regarding the number of secondary interventions (ER/OR and major amputations) between SET and ER.

Figure 3 shows the CEACs for the SET-first and ER-first treatment strategies. The probability of ER being cost-effective increased with a rising WTP threshold. Even so, using WTP thresholds of up to €100 000, the probability that ER was the optimal primary treatment choice did not exceed 53%.

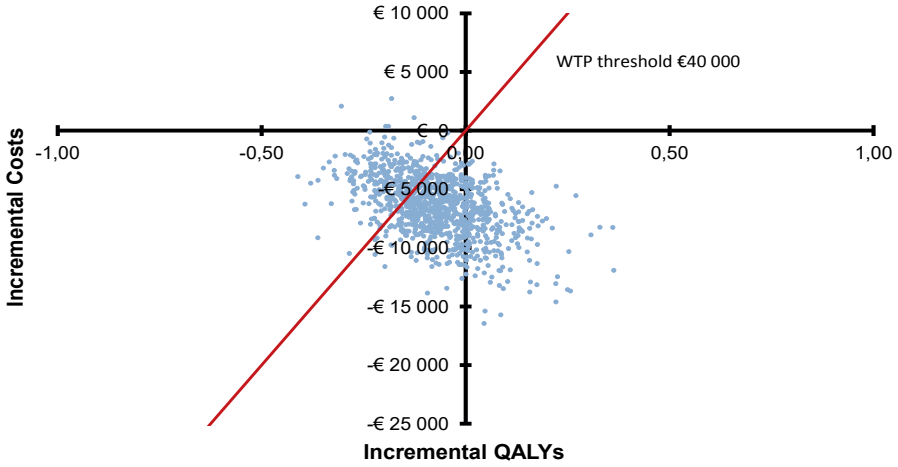

Figure 2. Incremental Cost-Effectiveness Plane.

Incremental Cost-effectiveness plane for supervised exercise therapy (SET) vs. endovascular revascularization (ER). On the x-axis the incremental quality-adjusted life years (QALYs) for SET compared with ER. On the y-axis the incremental costs for SET compared with ER. The differences in costs (incremental costs) and QALYs (incremental QALYS) are calculated for each of the 100 000 hypothetical patients and represented as a dot. The red line represents a €40 000 willingness-to-pay (WTP) threshold. SET was the preferable treatment in all samples south of this line, constituting 73% of the 1000 simulations.

One-way sensitivity analysis

The SET-first approach would remain the most cost-effective option, given a hypothetical WTP threshold of €40 000, in all one-way sensitivity analyses except one alternative scenario where all patients started in the severe claudication health state (Table 2). Alternate input values regarding cost estimations for ER and secondary intervention rates, as well as applying cardiovascular health benefits to the SET-first treatment arm, markedly improved cost-effectiveness of SET. Changing the time horizon to lifetime decreased the probability that SET was cost-effective compared to the base case (as demonstrated by the CEACs in the supplemental material: Figure S1). However, this would assume a continued treatment effect of the initial intervention well beyond the follow-up time span of available trial data, inducing a greater amount of uncertainty concerning incremental QALYs. This is shown by the wide spread of simulation results on the incremental cost-effectiveness plane of lifetime analysis in the supplement (Figure S2).

Validation

The model adequately predicted the health state distributions after one simulated year as observed in the EXITPAD and CETAC study, and after five simulated

years compared to outcomes as presented by Conte et al.[12] (Table S4, supporting information).

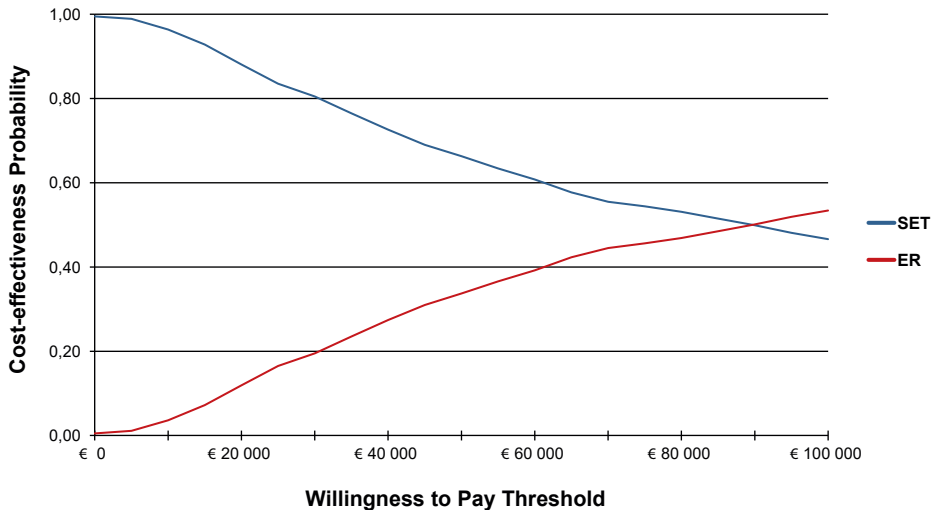

Figure 3. Cost-Effectiveness Acceptability Curves.

Acceptability curves for a range of willingness-to-pay (WTP) thresholds for the treatment of intermittent claudication. The x-axis shows different WTP thresholds that society may be willing to pay to gain one quality-adjusted life year (QALY). The y-axis shows the percentage of samples that demonstrated cost-effectiveness for supervised exercise therapy (SET) and endovascular revascularization (ER).

Table 2. Input and Outcomes of One-Way Sensitivity Analyses.

Parameters	Incremental costs (€)*	Incremental QALYs*	CEP†
Base case analysis	-6412 (-11 874;-1939)	-0.07 (-0.27;0.16)	73%
Cost of ER			
€12 512[31]	-11 353 (-16 098;-6624)	-0.07 (-0.27;0.14)	93%
Cost of SET			
24 sessions (2/wk for 3mo)[48]	-6832 (-12 058;-1848)	-0.07 (-0.27;0.14)	76%
2 hourly sessions/wk for 3mo (NICE guidelines)[11]	-6084 (-14 522;2572)	-0.07 (-0.53;0.36)	72%
Discount rates (%)			
Costs 3, outcome 3	-6619 (-11 744;-1827)	-0.06 (-0.26;0.15)	77%
Costs 5, outcome 5	-6462 (-11 606;-1963)	-0.07 (-0.26;0.12)	75%
Age			
55 years	-6445 (-12 166;-1387)	-0.07 (-0.31;0.17)	72%
75 years	-6637 (-11 662;-2334)	-0.06 (-0.23;0.10)	81%
Time horizon			
Lifetime horizon	-6341 (-13 707;424)	-0.09 (-0.54;0.35)	61%
10 years	-6220 (-12 570;62)	-0.10(-0.44;0.26)	59%
Secondary intervention rate			
SET 6.4%, ER 35.2%[16]	-8207 (-14 371;-2848)	-0.09 (-0.30;0.14)	78%
Cardiovascular health benefits SET			
52% mortality reduction[48]	-6036 (-11 029;-1649)	0.01 (-0.19;0.23)	87%
Starting health state			
Mild Claudication	-8051 (-13 219;-2380)	0.04(-0.18;0.26)	93%
Moderate Claudication	-6193 (-12 603;-735)	-0.08 (-0.30;0.17)	63%
Severe Claudication	-4618 (-10 319;1250)	-0.23 (-0.55;0.14)	29%

Abbreviations: CEP, cost-effectiveness probability; ER, endovascular revascularization; PAD, peripheral arterial disease; QALY, quality-adjusted life year; SET, supervised exercise therapy;
*SET minus ER. Value in parentheses are 95% credibility intervals.
†Probability that SET is cost-effective compared to ER considering a willingness-to-pay threshold of €40 000.

DISCUSSION

This cost-effectiveness analysis, comparing SET and ER as primary treatment in patients with newly diagnosed IC, showed that SET is more cost-effective than ER. The mean costs of a SET-first treatment strategy over a 5-year period were lower per patient, but there was no statistically significant difference in effectiveness. Submitting a new IC patient to ER as opposed to SET would cost an additional €91 600 per QALY gained. This exceeds most international WTP thresholds. These results, therefore, support a SET-first approach in the treatment of IC.

The outcome of our model-based cost-effectiveness analysis is in line with previous economic evaluations. Reynolds et al.[46] used a Markov model to extrapolate the results of a recent trial comparing SET, stenting, and optimal medical care for IC patients. Data from one trial, containing a small sample of patients, was used. Consequently, comparisons between SET and endovascular stenting lacked statistical power to detect small differences. Furthermore, their model did not include PAD progression to critical limb ischemia (CLI) and secondary interventions such as repeated ER, open revascularization or amputation. In their analysis stenting demonstrated an ICER of $122 600 per QALY gained, compared to SET. These results are analogous to the ICER of ER versus SET found in the current study (US $118 164), despite differences in setting and scope between both studies. Likewise, a previous study used invoice data from a large Dutch health insurance company and demonstrated that implementation of SET as initial treatment would amount to yearly cost savings of up to €6677 per patient.[16] Two trial-based economic analyses found SET to be equally effective and less costly compared to ER.[18,19] A retrospective analysis of costs by O'brien-irr et al.[17] showed that a trial of SET was cost-effective, even if 80% of patients still required ER afterwards. Thus, the present study confirms the findings of previous cost-effectiveness research on SET versus ER. Moreover, it adds that the potential cost savings can be achieved considering an extended time horizon and without a detrimental effect on QoL, secondary intervention rate or mortality.

An advantage of Markov modelling is the possibility to test the effect of separate clinical scenarios on cost-effectiveness. Indeed, several one-way sensitivity analyses yielded interesting results. Notably, the cost-effectiveness of ER became more favourable when all virtual patients started in the severe claudication health state, which was defined based on QoL scores assessed by the EQ-5D questionnaire. In daily practice these patients may be difficult to identify, as objective variables such as ankle-brachial index and lesion characteristics on imaging correlate poorly with QoL.[12] Nonetheless, these results warrant further research on the relation between a patient's perception of impairment and the threshold for invasive treatment.

Four international guidelines recommend SET as primary treatment for IC patients.[1,10-12] However, in practice there are several important impediments to routine implementation of SET. Firstly, availability of SET programs is lacking.[13] This study again supports the relevancy of implementation of a network of trained SET providers to improve accessibility. Moreover, it indicates that the initial investment required to develop the necessary infrastructure for a SET program will be compensated by the economic benefits SET yields. Secondly, insurance coverage of SET is poor, as opposed to ER.[15,16] Our results, in accordance with previous analyses[16-19,46], advocate the allocation of health care resources to support reimbursement by health insurers. Finally, it has been postulated that IC patients generally favour ER, as it provides a 'quick fix'.[15] However, others found that SET improves patients' walking capacity rapidly in the first two months[47], achieving maximal effectiveness at three months[48]. Emphasizing these short-term benefits could help motivate patients for SET. In addition, the costs of SET decrease when less training sessions are required to achieve the same effectiveness.

As it is inherent for a model to make simplifying assumptions about clinical reality, our study had several limitations. First, this study was conducted from the perspective of the Dutch population and health care setting and both costs and health effects are influenced by such situational factors. Second, we used EQ-5D QoL scores to quantify effectiveness instead of more conventional outcome measurements such as walking distance or the Walking Impairment Questionnaire (WIQ). Dividing the study population over 3 distinct health states using these traditional outcome measurements provided no distinct QoL values for each state. Notably, the appropriate outcome measurement in IC is still under debate.

Third, we compared both treatment arms using combined data from two different studies. While baseline characteristics were generally analogous, significant differences between baseline walking distances and smoking status were found. This could be a cause for heterogeneity. Fourth, most input parameters were based on data spanning a one-year period. In our model, we assumed a continued effect from both ER and SET up to 5 years, as opposed to lifetime analysis. Sensitivity analysis using a lifetime horizon, assuming continuous effect of treatment, showed this assumption had moderate effect on the outcome. Fifth, a recent trial showed a greater improvement in walking distances and health-related QoL after ER followed by SET compared with SET only.[49] These results raise the question whether the observed improved effectiveness of combined treatment is associated with an acceptable increase in costs. The current analysis does not comment on this matter. Finally, due to lack of sound evidence, we did not model the benefits of exercise on cardiovascular health and quality of life in the base case. We examined the effect of a 52% reduction in cardiovascular mortality after 12 weeks of SET[45]

on outcome in one-way sensitivity analysis. This provided an expected dramatic increase of relative cost effectiveness for SET. Future research should further clarify the potentially beneficial effect SET provides on general cardiovascular health in this patient population.

Conclusion

This study has shown that SET is a more cost-effective primary treatment for IC compared to ER. These results add to an impressive body of evidence and consequent guideline recommendations advocating a SET-first approach in the treatment of IC. Policymakers' efforts and further research should focus on realizing implementation of SET in clinical practice.

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CHAPTER 6

Protocol for a prospective, longitudinal cohort study on the effect of arterial disease level on the outcomes of supervised exercise in intermittent claudication: The ELECT Registry

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ABSTRACT

Introduction: Despite guideline recommendations advocating conservative management before invasive treatment in intermittent claudication, early revascularisation remains widespread in patients with favourable anatomy. The aim of the ELECT Registry is to determine the effect of the location of stenosis on the outcomes of supervised exercise in patients with intermittent claudication due to peripheral arterial disease.

Methods and analysis: This multicentre prospective cohort study aims to enrol 320 patients in ten vascular centres across the Netherlands. All patients diagnosed with intermittent claudication (peripheral arterial disease: Fontaine II/Rutherford 1-3), who are considered candidates for supervised exercise therapy by their own physicians are appropriate to participate. Participants will receive standard care, meaning supervised exercise therapy first, with endovascular or open revascularization in case of insufficient effect (at the discretion of patient and vascular surgeon). For the primary objectives, patients are grouped according to anatomical characteristics of disease (aortoiliac, femoropopliteal, or multilevel disease) as apparent on the preferred imaging modality in the participating centre (either duplex, computed tomography angiography, or magnetic resonance angiography). Changes in walking performance (treadmill tests, 6-minute walk test) and quality of life (QoL; Vascular QoL Questionnaire-6, World Health Organization QoL Questionnaire-Bref) will be compared between groups, after multivariate adjustment for possible confounders. Freedom from revascularization and major adverse cardiovascular disease events, and attainment of the treatment goal between anatomical groups will be compared using Kaplan-Meier survival curves.

Ethics and dissemination: This study has been exempted from formal medical ethical approval by the Medical Research Ethics Committees United 'MEC-U' (W17.071). Results are intended for publication in peer-reviewed journals and for presentation to stake-holders nationally and internationally.

Trial registration: NTR7332; Pre-results.

INTRODUCTION

Peripheral arterial disease (PAD) is a chronic condition caused by atherosclerotic narrowing and blocking of the peripheral arteries. Intermittent claudication (IC) is the most common manifestation of PAD and is marked by exertional discomfort in the leg muscles. These symptoms limit walking ability leading to functional disability in daily life. Treatment of IC symptoms aims at improving walking capacity and thereby health-related quality of life (QoL).[1] Over the past decade, supervised exercise therapy (SET) and endovascular revascularization (ER) have been shown to be equally effective in this regard.[2-8] As SET is the non-invasive[9] and less costly[10] option, current guidelines recommend SET as primary treatment in the management of patients with IC.[1] Ideally, invasive treatment is saved for patients unresponsive to SET, which is the case in approximately 20% of patients after 2 years.[11]

Clinical practice often deviates from the guidelines, as world-wide reimbursement issues and lacking availability of adequate SET programmes hamper widespread adoption.[12-14] In the Dutch healthcare system SET is both available and reimbursed.[15] Nevertheless, a significant proportion of patients receive early ER in the Netherlands.[11] Some vascular professionals argue that in certain subsets of patients SET will probably fail and a lower threshold to initiate invasive treatment is warranted. Divergent reasons, oftentimes contradictory, are cited considering factors such as; age, comorbidity, (vascular) medical history, or personality traits. However, these claims are mostly practice-based as the current literature provides no grounds to discern a subset of patients who will be unresponsive to SET.

One of the main arguments for early revascularization is the location and extent of the atherosclerotic lesion. Excellent patency rates and procedural results of aortoiliac ER in clinical trials prompt some clinicians to employ more liberal indications to intervene first in these patients.[16] However, three randomized controlled trials (RCTs) compared SET with ER for patients with IC due to an iliac artery obstruction and found no important differences regarding walking distance or QoL.[3,5,17] Nonetheless, the idea that in a real-world setting individuals with proximal disease might experience less improvement after exercise training compared to patients with distal lesions remains widespread. Most studies examining the functional outcomes of patients after following a SET programme do not specify the anatomic distribution of disease. Greenhalgh et al.[18] reported the outcome of SET for aortoiliac and femoropopliteal disease separately, from a trial comparing SET with ER. No formal comparison between outcomes in both anatomic groups was made and the sample size was small, but no apparent difference in effectiveness can be noted. The premise that the outcomes of SET

depend on anatomic location and extent of disease is not based on empirical evidence.

Based on the available evidence an inferior effect of SET due to lesion location cannot be assumed. Therefore, the primary aim of this study is to determine the effect of the location of stenosis (femoropopliteal versus aortoiliac versus multilevel disease) on the outcomes of SET in patients with IC. To this end the functional and clinical outcomes from 'real world' subjects treated with SET will be recorded, applying a minimal amount of subject selection criteria.

RESEARCH OBJECTIVES

Primary objective
The aim of the ELECT Registry (Effect of Disease Level on Outcomes of Supervised Exercise in Intermittent Claudication) is to determine the effect of the location of stenosis on the outcomes of SET in patients with IC (PAD Fontaine 2, Rutherford I-III), by recording the clinical outcomes from consecutive 'real world' subjects treated with SET. The primary objective is to determine the outcomes of SET in patients with aortoiliac disease compared with femoropopliteal disease with regards to the following measures.

1. The primary endpoint is change in maximum and functional walking distance on a standardized treadmill test after 3, 6 and 12 months of SET.
2. Change in Six-Minute Walk Test (6MWT) performance after 3, 6 and 12 months of SET.
3. Change in Vascular Quality of Life Questionnaire-6 (VascuQoL-6) and World Health Organization Quality of Life questionnaire (WHOQOL-BREF) outcomes at 3 and 6 months, and 1, 2, and 5 years, follow-up.
4. Freedom from vascular interventions for the lower-extremities, at 6 months and 1, 2, and 5 years, follow-up.
5. Achievement of the main treatment goal, as drafted by the physical therapist and patient at the start of the SET program, and indicated in the feedback letter after 3, 6 and 12 months of SET.
6. Freedom from major adverse cardiovascular events at 1, 2 and 5 years, follow-up.

Secondary objectives
This study will also determine the outcomes of SET in patients with aortoiliac disease compared with femoropopliteal disease, multilevel disease, and patients without aortoiliac and femoropopliteal disease, with regards to the above-mentioned measures.

The ELECT Registry dataset will furthermore be used to investigate the effect of SET on the overall IC population regarding the following objectives.

- To determine whether several baseline clinical characteristics and functional measures are predictive of changes in walking performance and clinical outcomes of SET.
- To determine whether specific personality traits (extraversion, neuroticism, conscientiousness, self-control, barrier self-efficacy, anxiety, depression, and optimism) measured at baseline are predictive of the clinical outcomes of SET.
- To determine the change in barrier self-efficacy after 3, 6 and 12 months of SET.

METHODS

Study design and setting

The ELECT Registry is a multicentre prospective cohort study initiated from the vascular surgery department of the Catharina Hospital in Eindhoven, the Netherlands. All patients diagnosed with IC (PAD; Fontaine II/Rutherford 1-3), who are considered candidates for SET by their own physicians, and meet the inclusion criteria (**Table 1**), are eligible. Recruitment will take place in ten vascular surgery departments throughout the Netherlands: the Catharina Hospital, Amphia Hospital, Elisabeth Twee Steden Hospital, Albert Schweitzer Hospital, Rijnstate Hospital, Medical Spectrum Twente, University Medical Centre Utrecht, Amsterdam University Medical Centre, Máxima Medical Centre, and VieCuri Medical Centre. In these centres, the treating vascular surgeon will seek verbal consent from eligible patients to be approached by a research coordinator. Candidates will subsequently receive written information on the study, inviting them to participate, with two consent forms and a self-addressed envelope. These patients will be contacted by telephone by the coordinating investigator within one week after their visit to the vascular surgeon to establish formal agreement to participate in the study. If the patient agrees to participate, he/she will sign the consent forms and will send both forms in the self-addressed envelope to the coordinating investigator. After receiving the two consent forms, the coordinating investigator will sign both forms and return one version to the patient. To ensure adequate data collection, the participating centres are recommended to schedule the subjects' follow-up visit(s) based on the current standard of care as prescribed by the Dutch guidelines, which is at 3 to 6 months. At this moment, the decision to either continue conservative management, or treat invasively (endovascular or open revascularization) is generally made.

Treatment of subjects

All patients will receive standard cardiovascular risk management (CVRM) by their physician; including smoking cessation advice, statin therapy and platelet inhibitors, as explicated in the multidisciplinary guidelines.[1] Furthermore, patients will receive a standard regimen of SET, which entails exercise and lifestyle coaching. SET is provided by qualified physical therapists according to usual practice (specified in the physical therapy guidelines).[19] All therapists are affiliated with ClaudicatioNet, a Dutch network of physical therapists specialized in SET with lifestyle guidance. This guarantees uniform quality of care through mandatory training courses in practice guidelines, motivational interviewing skills, and other IC-relevant topics.[15] A typical SET program contains up to 37 individual sessions, spanning 3 to 12 months. A session consists of 30 minutes of treadmill-based or track-based exercise. The initial workload of the treadmill is set to a speed and grade that elicits claudication symptoms within three to five minutes. Patients are asked to continue to walk at this workload until they experience claudication of moderate severity. A brief period of rest permits symptoms to resolve. An exercise-rest-exercise cycle is repeated several times. Such a program requires intense monitoring of patients aimed at increasing workload by adjusting treadmill grade or speed (or both).[15, 19] This will generally be performed at least three times a week in the first four weeks and one to two times a week for the next eight weeks.[15] After that, there is a maintenance phase during which SET will be given for one to two times a month. As stated in their guidelines, the physical therapist records several outcome measurements at 3, 6, 9 and 12-months follow-up.[19] To investigate the study's objectives, data obtained in this standard follow-up routine will be recorded prospectively.

Table 1. Eligibility criteria.

Inclusion criteria:
IC due to unilateral or bilateral PAD (Fontaine II, Rutherford 1-3).
Resting ABI <0.9 (or TBI <0.7) or drop in ABI > 0.15 after exercise.
Candidate for SET as a primary treatment, at the discretion of the treating vascular surgeon.
Recent or planned imaging of at least the aortoiliac and femoropopliteal tract (within 6 months of SET initiation, but prior to possible vascular intervention): either colour Duplex Scanning or CTA or MRA.
Signed informed consent form.
Exclusion criteria:
Advanced PAD beyond IC (i.e. ischemic rest pain and/or ulcers, Fontaine >II, Rutherford 4-6).
High probability of non-adherence to physician's, or physical therapist's follow-up requirements (e.g. due to lacking motivation or past compliance issues).
Current participation in a concurrent trial that may confound study results.
Vascular intervention as primary treatment, at the discretion of the treating vascular surgeon.
Prior SET, performed in accordance with the guidelines of the Dutch Society for Physical Therapists, in the previous 12 months.
Prior revascularization in the lower-extremities in the previous 12 months.
Neurogenic/venous/orthopedic claudication more dominant than arterial claudication complaints.

Abbreviations: ABI, ankle-brachial index; CTA, computed tomographic angiography; IC, intermittent claudication; MRA, magnetic resonance angiography; PAD, peripheral arterial disease; SET, supervised exercise therapy; TBI, toe-brachial index.

Table 2. Study timeline and assessments.

	Baseline T_0	*3mo* t_1	*6mo* t_2	*12mo* t_3	*2y* t_4	*5y* t_5
Baseline characteristics						
Sociodemographic data	X					
Cardiovascular risk factors	X					
Comorbidity	X					
Medical History	X					
Prior vascular interventions	X					
Vascular laboratory assessment	X					
Vascular imaging (DUS/CTA/MRA)	X*	X*				
Outcome measures						
Treadmill test°	X	X	X	X		
6MWT°	X	X	X	X		
WHOQOL-BREF	X	X	X	X		
Barrier self-efficacy scale	X	X	X	X		
Vascuqol-6	X	X	X	X	X	X
Smoking status	X	X	X	X	X	X
Attainment of treatment goal		X	X	X	X	X
Freedom from vascular intervention		X	X	X	X	X
Major adverse cardiovascular events		X	X	X	X	X
Personality traits						
Big Five Inventory	X					
HADS	X					
Brief Self-Control Score	X					
Life Orientation Test-Revised	X					
Barrier Self-Efficacy Scale	X	X	X	X		

Abbreviations: 6MWT, six-minute walk test; CTA, computed tomographic angiography; DUS, duplex ultrasound scanning; HADS, hospital anxiety and depression scale; IC, intermittent claudication; MRA, magnetic resonance angiography; Vascuqol-6, Vascular Quality of Life Questionnaire-6; WHOQOL-BREF, World Health Organization Quality of Life Questionnaire-Bref.

*Imaging is eligible when performed ≤3 months before or after inclusion.

°The treadmill test and 6MWT are performed on different days, thus two visits are necessary per time point to collect all outcome measures.

ASSESSMENTS

This study will use diagnostic- and outcome measures that are recorded as part of the usual clinical practice, supplemented by several questionnaires, all specified below. Outcomes are collected from the standardized feedback letter sent by physical therapists (see supplementary file) and the patient's hospital electronic health record. Table 2 provides an overview of all study assessments.

Baseline patient characteristics
Participants' sociodemographic data (age, sex), medical history and comorbidity (chronic obstructive pulmonary disease, lower-extremity musculoskeletal disease, diabetes mellitus, dyslipidaemia, hypertension, kidney disease, cerebrovascular disease, ischemic heart disease, heart failure), cardiovascular risk factors (body mass index, smoking status), prior (cardio-)vascular interventions (coronary artery bypass grafting, percutaneous coronary intervention, open or endovascular abdominal aortic aneurysm repair, lower-extremity revascularization), and prior SET, will be extracted from the electronic health records of the hospital and/or physical therapist.

Vascular imaging and laboratory assessment
Resting and post-exercise ankle-brachial index (ABI) determinations in both legs are performed by trained vascular technicians in all participating centres using handheld Doppler instruments, as part of the routine work-up. The ABI is defined as the ratio between the highest systolic pressure of the dorsal pedal or posterior tibial artery, and the highest of the left or right brachial pressure. To determine the anatomic location and extent of atherosclerotic disease the ELECT Registry utilizes the preferred vascular imaging modality of the treating vascular surgeon, performed ≤3 months before or after inclusion.

In case of magnetic resonance angiography (MRA) or computed tomography angiography (CTA), the scan is evaluated and interpreted by experienced radiologists in the participating centres as per usual care. A stenosis of >50% on MRA or CTA is considered significant. The reported accuracy of CTA and MRA to detect significant arterial stenosis in PAD is >90%.[1] Duplex ultrasound scanning (DUS) is carried out by accredited vascular technicians to determine the location, extent, and severity of the atherosclerotic lesions. A lesion is considered significant if either a peak systolic velocity (PSV) ratio of ≥ 2.5, or an end diastolic velocity (EDV) of ≥0.6 m/s is observed, or if an occlusion is visualized (no flow). The reported sensitivity and specificity of DUS in patients with PAD to detect significant arterial stenoses is over 80% and 90%, respectively.[1]

To categorize all participants according to anatomic location a team of three physicians (1 vascular surgeon, 2 PhD Candidates) will independently assess the DUS reports and readings and/or MRA or CTA scans and radiologist reports. Participants will be divided into four groups:

1. Aortoiliac lesions, containing patients with significant stenoses or occlusions in the common iliac artery, external iliac artery, and/or internal iliac artery.
2. Femoropopliteal lesions, containing patients with significant stenoses or occlusions in the common femoral artery, superficial femoral artery, and/or popliteal artery.
3. Multilevel disease, containing patients with significant stenoses at both the aortoiliac and femoropopliteal level.
4. Rest group, containing patients with no significant stenoses in the aortoiliac and femoropopliteal tract. Notably, undetected infrageniculate disease distally from the area scanned with DUS may exist in this group. This category is expected to contain some 5% of patients meeting the eligibility criteria based on a retrospective exploratory analysis of a consecutive cohort of patients from the vascular surgery outpatient clinic in the initiating center.

The same three physicians will also assign a TASC classification for each arterial trajectory with a significant lesion. Notably, the inter-observer agreement for rating TASC classifications is poor.[20,21] Thus, disagreement is solved by discussion and consultation of a fourth observer (vascular surgeon).

Walking performance

Treadmill-measured walking distance

The maximum walking distance (MWD) and functional walking distance (FWD) will be recorded for each patient at baseline, 3, 6 and 12 months follow-up, using a standardized treadmill test. The MWD is defined as the walking distance where intolerable claudication pain forces a patient to stop. An alternative term for MWD is 'absolute claudication distance'. The FWD is defined as the distance at which the patient prefers to stop walking because of pain. Notably, this is a different measure from the 'pain-free walking distance' or 'initial claudication distance' commonly used in PAD literature. The FWD was previously found to be reliable (intraclass correlation coefficient 0.959) and probably a better reflection of functional impairment compared to the initial claudication distance.[22] Walking distances are determined by a standardized progressive treadmill test (i.e. Gardner_Skinner protocol[23]) with a constant speed of 3.2 km/h starting with 0% incline, increasing every 2 minutes by 2%. The maximum incline is 10%, and the maximum duration of the test is 30 minutes, resulting in a maximum distance of 1600m. The test protocol is advised by the Dutch physical therapy guidelines.[19] ClaudicatioNet

therapists are taught to offer verbal encouragement and coaching during testing, but this was not standardized in this study.

Six-Minute Walk Test (6MWT)
To assess walking performance in a setting more resembling daily life, participants will perform the Six-Minute Walk Test (6MWT) at baseline, 3, 6 and 12 months follow-up. Physical therapists are instructed to perform the treadmill test and 6MWT on different days. The 6MWT records the total distance an individual is able to walk over a total of six minutes on a hard, flat surface. Participants traverse back and forth along a marked walkway. They are allowed to self-pace and rest as needed, while timing continues up to 6 minutes. The 6MWT has been validated, shown to be responsive to treatment, and is predictive of mortality and mobility loss in a PAD population.[24]

Quality of Life
Two questionnaires are used in the ELECT Registry to investigate the effect of treatment on quality of life. The Vascular Quality of Life Questionnaire-6 (Vascuqol-6) is a valid and responsive instrument for the assessment of health-related quality of life in PAD.[25] It is a shortened version of the Vascuqol-25 and contains questions relating to the patient's activities, symptoms, pain, and emotional and social well-being. Answers are recorded on a four-point scale and added up, resulting in a total score between 6 and 24. Higher scores indicate better health-related quality of life. The ELECT Registry utilizes the Dutch version of the Vascuqol-6.

The WHOQOL questionnaire provides a generic assessment of QoL.[26,27] The abbreviated version of this tool (WHOQOL-BREF) is used in this registry and was previously found to be valid and reliable.[27] It contains questions on four domains, each scored on a 5-point Likert scale: physical health, psychological health, social relationships, and environment. Two additional questions assess the subject's overall QoL and general health. Domain scores are obtained by averaging the scores from the individual questions and subsequent rescaling to a 0-100 scale, where higher scores represent a better QoL.

Success of conservative management
Arguably, a successful conservative treatment eliminates the need for invasive therapies. Thus, success of SET is objectified by freedom from vascular interventions, defined as either PTA (with or without stent), bypass, endarterectomy, or major amputation of the lower-extremities at 6 months, and 1, 2, and 5 years, follow-up.

The decision to intervene is influenced by the risk-benefit ratio of the patient's lesion and general health status, as well as the preferences of the treating vascular surgeon and patient. Thus, freedom from intervention is only a partial reflection of treatment success. To better capture patient satisfaction with treatment the attainment of the main treatment goal is recorded. At the start of each SET programme each patient determines the main treatment goal in conjunction with his or her physical therapist. This is recorded in an open text field at the start of treatment, with no restrictions with regards to the domain or measure it applies to. Satisfactory achievement of this goal ('yes' or 'no') and the (im)probability of further improvement with SET ('yes' or 'no') are followed-up at 3, 6 and 12 months and indicated in the standard feedback letter to the vascular surgeon (see Supplementary file 1).

Cardiovascular mortality and morbidity
The incidence of major adverse cardiovascular events (MACE) at 1, 2, and 5 years follow-up. Events considered are atherosclerotic cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (three-component MACE), recorded from hospital records.

Psychological assessments
The five self-report questionnaires described below assess personality traits, emotional symptoms, and barrier self-efficacy. Missing data, if not completely at random, will be imputed by means of multiple imputation methodology to minimize bias.[28]

Big Five Inventory (BFI)
The BFI[29] consists of 44 items regarding statements of characteristics associated with five personality traits, which are openness to experiences, agreeableness, extraversion, neuroticism, and conscientiousness. This study will focus on the last three traits. Every item starts with 'I see myself as someone who…' and items are rated on a five-point Likert scale (1 = disagree strongly, 5 = agree strongly). The BFI has a high test-retest reliability with intraclass correlation coefficients ranging from .93 to 0.96.[30] A validated Dutch translation[31] is used in this study, with satisfactory reliability for measuring the individual traits, with Cronbach's alpha ranging among traits from 0.73 to 0.86 ($\alpha > 0.7$ is a sign of good reliability). The scores will be analysed as continuous and as categorical variables. Because there are no official cut-off scores available, the median scores from the current sample will be used as cut-off points to translate scores into low and high on a specific trait ('low' < median ≥ 'high').

Hospital Anxiety and Depression Scale (HADS)
The HADS is a 14-item self-report screening scale which is used to indicate the possible presence of anxiety and/or depressive symptoms.[32] The scale includes 7 items on anxiety and 7 items on depression, both with a score ranging from 0 to 21. The total score is classified into no anxiety or depression disorder (≤7), possible disorder (8-10), and probable disorder (≥11). The Dutch translation of the HADS[33] used in the ELECT Registry is validated in multiple populations. The internal consistency (Cronbachs' alpha ranged from 0.71 to 0.90) and the test-retest stability (Pearson correlation coefficient 0.91) are high.

Brief self-control score (BSCS)
The BSCS[34] is used to determine self-control in which a higher score is associated with higher self-control. It consists of 13 items rated on a five-point Likert scale (1 = disagree strongly, 5 = agree strongly) with a maximum score of 54. This brief scale has a good test-retest reliability with a coefficient of 0.87. A validated Dutch translation[35] with high internal consistency (Cronbachs' alpha 0.80) will be used.

Life Orientation Test-Revised (LOT-R)
The LOT-R[36] measures optimism by means of 10 items, including four 'filler' items which do not contribute to the total score. The items are rated on a five-point Likert scale (0 = disagree strongly, 4 = agree strongly). The total score ranges between 0 and 24 and a higher total score is associated with a higher level of optimism. This revised test has a satisfactory test-retest reliability of 0.60 to 0.68. The validated Dutch translation[37], with moderate to high internal consistency (Cronbachs' alpha ranging from 0.58 to 0.80), is used.

Barrier self-efficacy scale (BSES)
The BSES[38] consists of 13 items describing the possibility that one would exercise despite the presence of possible barriers, such as bad weather or lack of interest. The inventors of the BSES determined the barriers by attributive analysis of participants' arguments for discontinuing exercise programs. Participants indicate their degree of confidence for each item on a 0% (no confidence at all) to 100% (complete confidence) scale. The mean percentage of all items comprises the total score, in which a higher score is associated with higher barrier self-efficacy. This study uses a validated Dutch translation[39] in which one question ('My work schedule conflicted with my exercise session') is left out because this would not be relevant to the majority of our study population. The internal consistency of the Dutch scale is high (Cronbachs' alpha 0.84) and has a satisfactory test-retest stability with an intraclass correlation coefficient of 0.63.

ANALYSIS

Sample size

We hypothesize that there will be no clinically relevant difference in changes in maximum walking distance between subjects with aortoiliac and femoropopliteal disease after 6 months. Analogous to previous trials in this population, we would consider a mean difference of 150 m change in walking distance between groups to be clinically relevant (standard deviation of 300 m).[40,41] To exclude a difference in means of 150 m with an alpha of 0.01, a power of 0.80 (beta of 0.2), 96 patients are needed per arterial disease level group. The ELECT Registry primarily aims to compare patients with single-level disease (aortoiliac versus femoropopliteal). Based on a retrospective analysis of consecutive patients with IC in our hospital, this will be the case in some 75% of the patients. Thus, for the primary analysis the required sample size amounts to a total of 256 patients ((1/0.75)*(96+96)). Assuming a conservative drop-out rate of 20%, 320 subjects are required to investigate the primary objective.

Statistical analysis

Categorical variables at baseline will be presented as numbers with percentages. Continuous variables as means ± standard deviations if normally distributed, or as medians with interquartile ranges in case of a skewed distribution. Participants will be divided into four groups based on anatomical characteristics of disease, as apparent on the preferential imaging modality of the participating centre (either DUS, CTA or MRA). Groups are defined as follows: aortoiliac disease, femoropopliteal disease, multilevel disease, or rest group. The primary comparison of interest is aortoiliac versus femoropopliteal disease.

Changes in walking distances (treadmill tests, 6MWT) and quality of life (Vascuqol-6, WHOQOL-Bref) will be compared between groups, after multivariate adjustment. Adjustment of these measures for possible confounding variables will be performed using a general linear model with anatomical group as the independent variable. Covariates used for this adjustment are selected using univariate analysis (inclusion criteria $p<0.2$). A stringent significance level of 0.01 will be used to account for multiple comparisons. Freedom from revascularization, freedom from adverse cardiovascular disease events, and attainment of the main treatment goal between groups will be compared using Kaplan-Meier survival curves and log rank tests. Cox proportional hazard analysis will be performed to adjust for the abovementioned possible confounders.

Analysis for the remainder of secondary objectives is performed on the overall population (regardless of lesion location). Multivariable logistic regression will be used to determine the impact of several patient characteristics (e.g. age, sex, extent

of atherosclerotic disease, comorbidity, history of cardiovascular disease and previous lower-extremity interventions) on success of conservative management. Associations between baseline personality traits and SET-related outcomes (walking distance, 6MWT, QoL, and freedom from interventions), defined as change-from-baseline scores at follow-up, will be determined. For categorized BFI traits this will be analyzed with unpaired t-tests (or Mann-Whitney U-test in case of non-normal distribution) for continuous outcomes and Chi-square or Fisher's exact tests for categorical outcomes. Multiple linear regression is performed with personality traits as independent variables and the SET-related outcomes as dependent variables. A hierarchical series of three models with increasing covariate adjustment will be used. In model I, age and sex are included as covariates. In model II, secondary invasive treatment (if applicable) is added. Finally, in model III, the HADS score is added in order to correct for possible symptoms of anxiety and/or depression. To analyse the change in self-efficacy at 3, 6, and 12 months follow-up, a linear mixed model will be used.

Data storage and retention

All data will be handled in accordance with local regulations and privacy laws in an anonymised dataset. Physical data will be anonymised and stored accessible only by the research team, digital data will be secured using dedicated data management software 'Research Manager' (de Research Manager, Deventer, the Netherlands). After the last participant's final follow-up moment, all data will be stored for a minimum of 15 years.

Ethics and dissemination

This trial does not hamper routine vascular surgery or physical therapy treatment for the participants. Furthermore, it mainly records diagnostic and outcome measures that are performed as part of the usual clinical routine, supplemented by several short, non-intrusive questionnaires. Therefore, the ELECT Registry has been exempted from formal medical ethical approval by the Medical Research Ethics Committees United 'MEC-U' (reference number W17.071). Nonetheless, privacy laws require that each subject must authorize the treating physician(s), therapists and institutions to release their medical information. Each subject must therefore sign a Patient Informed Consent (PIC) form before any data can be sent to the coordinating centre. The results are intended for publication in peer-reviewed journals and for presentation to stake-holders nationally and internationally.

Patients and public involvement

Patients and public were not explicitly involved in the design or conduct of this study. All participants will be informed of the results of the ELECT Registry through post or email.

DISCUSSION

The ELECT Registry will link anatomical characteristics of atherosclerotic disease to the functional and clinical outcomes of a SET-first management strategy in IC. This prospective observational study will thus primarily offer insight in the effect of lesion location on the outcomes of SET. It will produce novel results as most previously published research on SET as primary treatment either does not specify the location of the stenosis, does not include all lesions in its study design, or does not include functional outcome measures. By including a diverse range of vascular surgery centres throughout the Netherlands, the study will feature a heterogenous patient population closely resembling real-world practice.

The dataset from this study will secondarily be used to identify predictors of treatment outcome from various functional and clinical variables. Previously published research aimed to investigate the effect of various patient characteristics on outcomes of conservative management in IC.[42-44] However, this is the first study to include information on extent and location of PAD in such analysis. Moreover, the ELECT Registry will include a multitude of functional and clinical outcomes at both baseline and follow-up. The results will facilitate the development of a management strategy more tailored to the individual IC patient.

The ELECT Registry is an observational study and thus prone to several validity issues. Mainly, included patients in the different lesion location groups are expected to differ regarding several clinical characteristics. Indeed, van Zitteren et al.[45] and Aboyans et al.[46] previously found differences in smoking status, diabetes mellitus, BMI and ABI between proximal and distal disease. The influence of these potential confounders is addressed in the study protocol by applying multivariate regression analysis. Despite this covariate adjustment, unmeasured confounding could influence the results. For instance, intensity of exercise during SET sessions is not recorded, nor daily life physical activity levels of patients. Furthermore, DUS is a non-invasive and valid tool to assess location and extent of stenosis in PAD, but has its limitations. Namely, visualization of the iliac vessels can be limited due to body habitus and/or bowel gas, possibly introducing bias in the study design.

Conclusion

The ELECT Registry, a multicentre prospective cohort study, will produce a dataset linking the functional and clinical outcomes of SET in IC to the location and extent of the atherosclerotic lesions. The results from this real-world cohort will inform clinical practice, working towards a more tailored management of IC patients.

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CHAPTER 7

The effect of arterial disease level on outcomes of supervised exercise therapy in intermittent claudication: A prospective cohort study

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ABSTRACT

Objective: To assess whether level of arterial obstruction determines the effectiveness of supervised exercise therapy (SET) in patients with intermittent claudication (IC).

Background Data: Guidelines advocate SET before invasive treatment for IC, but early revascularization remains widespread, especially in patients with aortoiliac disease.

Methods: Patients were recruited from ten Dutch centers between October 2017 and October 2018. Participants received SET first, followed by endovascular or open revascularization in case of insufficient effect. They were grouped according to level of stenosis (aortoiliac, femoropopliteal, multilevel, or rest group with no significant stenosis). Changes from baseline walking performance (maximal and functional walking distance on a treadmill test, 6-minute walk test) and Vascular Quality of Life Questionnaire-6 (Vascuqol-6) at 3 and 6 months were compared, after multivariate adjustment for possible confounders. Freedom from revascularization was estimated with Kaplan-Meier analysis.

Results: Some 267 patients were eligible for analysis (aortoiliac n=70, 26%; femoropopliteal n=115, 43%; multilevel n=69, 26%; no disease n=13,5%). No between group differences in walking performance or Vascuqol-6 were found. Mean improvement in maximal walking distance after 6 months was 439m (99% CI 297-581), 466m (99% CI 359-574), 353m (99% CI 210-496), and 403m (99% CI 58-749), respectively (p=0.40). Freedom from intervention was 73.9% for aortoiliac disease and 88.6% for femoropopliteal disease (hazard ratio 2.46, 99% CI 0.96 – 6.30, p=0.013).

Conclusions: Short-term effectiveness of SET for IC is not determined by the location of stenosis. Although aortoiliac disease patients improved walking performance and health-related quality of life similarly compared to other arterial disease level groups, they underwent revascularization more often.

INTRODUCTION

Patients with intermittent claudication (IC) due to peripheral arterial disease (PAD) are first treated with supervised exercise therapy (SET). Invasive open or endovascular revascularization (OR, ER) is considered if SET fails to satisfactorily relieve symptoms.[1] With this approach the majority of patients do not require any intervention at all[2], even after 7 years of follow-up[3]. Revascularization as initial treatment, thus unnecessary in most, leads to higher costs[4], considerable re-intervention rates[5] and more amputations[6].

ER of aortoiliac stenoses is associated with more favorable procedural results and patency rates compared to revascularization in more distal disease.[1] Nonetheless, SET remains the guideline-advocated treatment of choice in all IC patients. Three randomized controlled trials (RCTs) compared SET with ER for aortoiliac stenoses and reported no important differences regarding walking performance or health-related quality of life).[7-9] Even so, IC patients with aortoiliac disease are four times more often referred for early revascularization.[10] This discrepancy is probably related to optimal safety and efficacy of ER in aortoiliac disease compared to femoropopliteal disease, but may also suggest that some vascular surgeons consider these patients less responsive to SET. Proximal and distal PAD indeed are different entities, associated with distinct risk factor profiles[11,12] and general prognosis[13,14]. Nevertheless, the effect of arterial disease level on outcomes of SET is unknown.

The current study compared the effectiveness of SET in patients with IC according to the location of stenosis (aortoiliac, femoropopliteal, or multilevel disease) regarding walking performance, health-related quality of life, and clinical outcome.

METHODS

Study design

The ELECT Registry is a multi-center prospective observational study ('Nederlands Trial Register' registration number: NTR732). Participants were included between October 2017 and October 2018 in ten vascular surgery centers across the Netherlands. A detailed account of the study methods is found in a previously published study protocol.[15] In summary, all patients diagnosed with IC (PAD Fontaine II/Rutherford 1-3) who were considered candidates for SET as primary treatment by their physicians were eligible. Patients were excluded in case of advanced stage of PAD (ischemic rest pain and/or ulcers: Fontaine >II, Rutherford 4-6), vascular intervention as primary treatment, prior PAD treatment

(SET or revascularization) <12 months before inclusion, or co-morbidity limiting proper ambulation.

This study used diagnostic and outcome measures that were recorded as part of the standard of care, supplemented by a set of questionnaires and imaging of the aortoiliac and femoropopliteal tract (color duplex ultrasound scanning (DUS), magnetic resonance angiography (MRA), or computed tomography angiography (CTA)). Functional outcomes regarding walking performance and health-related quality of life were collected by the physical therapist responsible for SET and were extracted from the standardized feedback letter that is sent to the referring vascular surgeon. The participant's hospital electronic health record was used to document baseline characteristics, vascular laboratory and imaging data. The ELECT Registry was exempted from formal medical ethical approval by the Medical Research Ethics Committees United 'MEC-U' (reference number W17.071). All participants provided formal written informed consent.

Treatment of subjects

All participants were treated according to current guideline recommendations.[1] In short, they received a standard regimen of SET, which entails treadmill-based or track-based exercise and lifestyle coaching. SET was provided by qualified physical therapists participating in the nationwide network ClaudicatioNet[16] and following usual practice as specified in the physical therapy guidelines[17]. After 3 to 6 months, a follow-up evaluation by the vascular surgeon was scheduled. During these visits, the decision to either continue conservative management or treat invasively (endovascular or open revascularization) was made in a shared decision-making environment.

Determination of arterial disease level

The choice of vascular imaging modality was left to the discretion of the treating vascular surgeon. Execution of imaging, mandatorily as part of the ELECT Registry, occurred ≤3 months before or after inclusion. MRA and CTA were interpreted by experienced radiologists in the participating centers, as per usual care. A >50% stenosis on MRA or CTA was considered significant. In some centers DUS was performed, by accredited vascular technicians. A lesion was considered significant if either a peak systolic velocity (PSV) ratio of ≥ 2.5 or an end diastolic velocity (EDV) of ≥0.6 m/s was observed, or if flow was absent (occlusion).

A team of physicians including one vascular surgeon (JT) and two MDs (PhD candidates; MH, SJ) independently assessed all DUS and MRA or CTA scans readings and radiologist reports. Based on these assessments, participants were divided into four groups:

1. Aortoiliac disease: significant stenoses or occlusions in the common iliac artery, external iliac artery, and/or internal iliac artery.
2. Femoropopliteal disease: significant stenoses or occlusions in the common femoral artery, superficial femoral artery, and/or popliteal artery.
3. Multilevel disease: significant stenoses at both the aortoiliac and femoropopliteal level.
4. No disease: no significant stenoses in the aortoiliac and femoropopliteal tract. Notably, this does not rule out undetected infrageniculate disease distally from the area scanned with DUS.

Each significant lesion was classified according to TASC.[18] It must be appreciated that the inter-observer agreement of this classification is poor.[19,20] If required, disagreement was solved by discussion and consultation of a fourth observer (vascular surgeon, MS).

Study end points

The primary objective was to compare outcomes of SET in patients with aortoiliac disease compared with femoropopliteal disease with respect to change in maximal and functional walking distance (MWD, FWD) on a standardized treadmill test. The standardized Gardner Skinner protocol[21], set at a walking speed of 3.2 km/h, was advocated in the study protocol. Nevertheless, a small portion of physical therapists deviated from this suggested protocol and adjusted the speed to the comfort of the patient (either 2 km/u or 4.2 km/u). As no significant difference in set speed was identified between groups (Supplemental Table 1, Supplemental Digital Content), this factor was not considered in the primary analysis.

Secondary endpoints were changes in Six-Minute Walk Test (6MWT) performance and Vascular Quality of Life Questionnaire-6 (VascuQoL-6), freedom from vascular interventions for the lower extremities, and achievement of the main treatment goal as drafted by the physical therapist and patient at the start of the SET program. All outcomes were also compared for patients with aortoiliac disease, femoropopliteal disease, multilevel disease, and the no disease group.

Sample size

We hypothesized that there is no clinically relevant difference in change in MWD between subjects with aortoiliac and femoropopliteal disease after 6 months. In an equivalence study design, to exclude a mean difference between groups of >150 m change with a standard deviation (SD) of 300m, an α of 0.01, and a power of 80%, enrollment of 96 patients per arterial disease level group was projected.

Statistical analysis

Statistical analysis was performed with SPSS version 22 (IBM Corporation, Armonk, NY). Categorical variables were presented as numbers with percentages and compared using χ^2 or Fisher's Exact test. Continuous variables were reported as means ± SD or as medians with interquartile range (IQR). They were compared using one-way ANOVA or Kruskall-Wallis rank sum tests for the four groups, and Tukey's HSD test or Man Whitney U Test for the comparison between aortoiliac and femoropopliteal disease, as appropriate. To account for multiple comparisons, only the two *a priori* formulated comparisons were conducted throughout the study (between the four groups overall and between aortoiliac and femoropopliteal disease specifically). Furthermore, a strict significance level of 0.01 was used. Missing continuous outcome and predictor data were imputed using multivariate imputation by chained equation.

Changes from baseline walking performance (FWD, MWD, 6MWT) and Vascuqol-6 sum scores at 3- and 6-months follow-up were compared between groups after multivariate adjustment. To this end, a general linear model was used with disease level as the independent variable. Covariates used for this adjustment were selected in univariable and multivariable methods. Effects with a p-value of less than 0.2 were considered significant. First, baseline variables displaying a significant difference between aortoiliac and femoropopliteal groups were entered in the multivariable model. Then, covariates were selected using backwards elimination in the multivariable analysis to keep only factors significantly affecting change in MWD in the model. Sex, age and body-mass index (BMI) were included regardless of p-value, as the literature considers these parameters as predictors of walking performance.[22-24] Walking performance data are generally non-normally distributed, thus for the general linear model the assumption of normality of the residuals was confirmed. A detailed account on the effect of various baseline measures on the different outcome measures in the ELECT Registry will be published separately.

Freedom from intervention between groups was estimated using Kaplan-Meier survival analysis and compared with log rank tests. Cox proportional hazard analysis was used to correct for the effect of several unevenly distributed potential confounders ($p<0.05$, and $p<0.2$) between disease level groups at baseline. The time to attainment of the main treatment goal was not exactly measured, but rather determined at fixed intervals (3 and 6 months). Thus, instead of the pre-planned Kaplan-Meier survival analysis for this outcome, rates for attainment of the treatment goal were compared between groups using χ^2 at 3 months and 6 months follow-up.

Sensitivity analysis
Several sensitivity analyses assessed the impact of methodological decisions on the conclusions. First, we conducted an analysis without imputation (complete-case analysis). Second, we performed a 'per protocol' analysis were all patients who underwent an intervention were excluded. Third, a supplemental analysis redefining disease level to 'inflow' lesions (aortoiliac and multilevel disease) versus 'outflow' lesions (no evidence of aortoiliac disease).

RESULTS

During the 1-year inclusion period, 439 patients were evaluated and 343 patients were willing to participate in the ELECT Registry. As 46 were excluded for reasons listed in Figure 1, a total of 297 patients participated in the study. Data were missing or incomplete in 30, therefore 267 patients were eligible for the primary analysis (aortoiliac disease n=70, 26%; femoropopliteal disease n=115, 43%; multilevel disease n=69, 26%; no significant stenosis in either tract n=13, 5%).

Baseline characteristics per group are compared in Table 1. In general, participants with aortoiliac disease were on average seven years younger, had diabetes mellitus over three times less often, and had higher ABI values and less severe TASC scores compared to participants with femoropopliteal disease. Participants had completed a mean number of 17 ± 5 (n=204) SET sessions after 3 months, and 26 ± 6 (n=171) after 6 months. The mean number of SET sessions were not different between the aortoiliac, femoropopliteal, multilevel, and no disease group at 3 months (17±5, 17±5, 20±4, 17±5, respectively; p=0.27) and 6 months follow-up (26±6, 26±6, 26±7, 29±6, respectively; p=0.64).

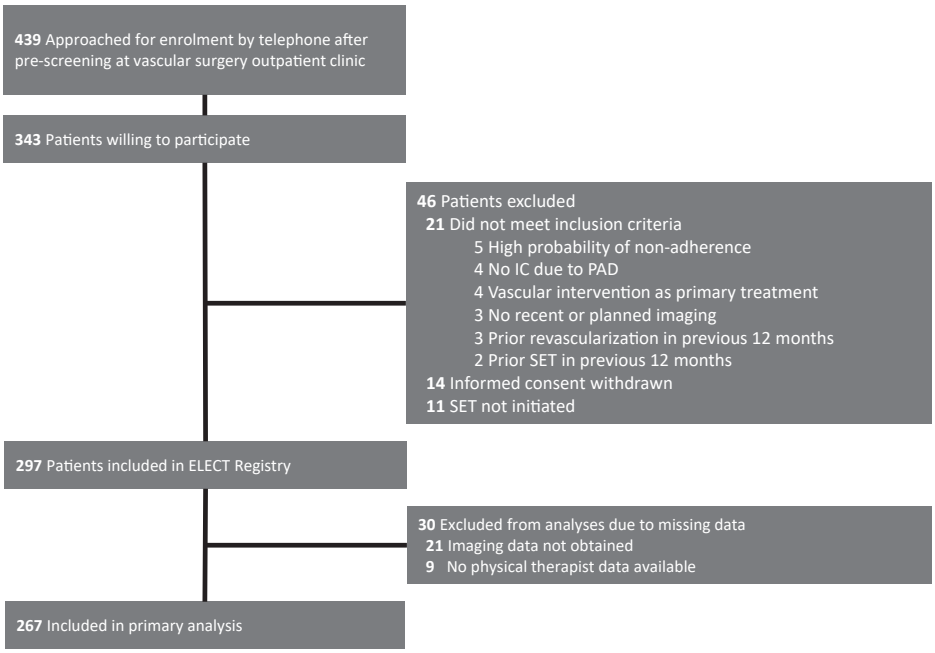

Figure 1. Flow chart of the inclusion process.

Table 1. Baseline population characteristics by disease level (n=267).

	Aortoiliac disease (n=70)	Femoro-popliteal disease (n=115)	Multilevel disease (n=69)	No disease (n=13)	Overall *P* Value	AoI vs FP *P* Value
Age, y	63.7 ± 8.9	70.6 ± 8.8	68.8 ± 8.2	67.5 ± 10.8	**<0.001**	**<0.001**
Female sex, n (%)	36 (51.4)	43 (37.4)	20 (29)	4 (30.8)	0.045	0.068
BMI	26.4 (6)	25.9 (4)	26.8 (5)	28 (6)	0.105	-
Smoking						
Current, n (%)	37 (52.9)	40 (34.8)	34 (49.3)	4 (30.8)	0.039	0.011
Former, n (%)	28 (38.6)	48 (41.7)	28 (40.6)	6 (46.2)		
Comorbidity, n (%)						
Diabetes	8 (11.4)	40 (34.8)	17 (24.6)	4 (30.8)	**0.003**	**<0.001**
Dyslipidemia	32 (45.7)	54 (47)	46 (66.7)	10 (76.9)	**0.009**	0.88
Hypertension	36 (51.4)	70 (60.9)	47 (68.1)	10 (76.9)	0.138	-
Kidney disease	3 (4.3)	10 (8.7)	16 (23.2)	0	**0.002**	0.376
Cerebrovascular disease	3 (4.3)	13 (11.3)	15 (21.7)	1 (7.7)	0.015	0.114
Ischemic heart disease	15 (21.4)	26 (22.6)	15 (21.7)	3 (23.1)	1.0	-
Heart failure	1 (1.4)	6 (5.2)	7 (10.1)	1 (7.7)	0.11	-
COPD	17 (24.3)	16 (13.9)	17 (24.6)	0	0.045	0.079
Musculoskeletal disease legs	8 (11.4)	16 (13.9)	14 (20.3)	2 (15.4)	0.515	-
Prior CVD intervention, n (%)						
CABG	4 (5.7)	10 (8.7)	7 (10.1)	1 (7.7)	0.769	-
PCI	9 (12.9)	13 (11.3)	7 (10.1)	2 (15.4)	0.887	-
EVAR or open AAA repair	2 (2.8)	1 (0.9)	3 (4.3)	0	0.395	-
Previous IC treatment, n (%)						
ER	12 (17.1)	13 (11.3)	18 (26.1)	4 (30.8)	0.034	0.275
OR	0	7 (6.1)	5 (7.2)	1 (7.7)	0.074	-
SET	6 (7.1)	13 (11.3)	6 (8.7)	2 (15.4)	0.584	-
Symptomatic leg, n (%)						
Left	16 (22.9)	33 (28.7)	13 (18.8)	1 (7.7)		
Right	22 (31.4)	32 (27.8)	8 (11.6)	7 (53.8)	**0.002**	0.665
Both	32 (45.7)	50 (43.5)	48 (69.6)	5 (38.5)		
ABI in rest	0.72 (0.21)	0.58 (0.23)	0.55 (0.24)	0.79 (0.33)	**<0.001**	**<0.001**
ABI after exercise	0.39 (0.31)	0.3 (0.23)	0.22 (0.15)	0.5 (0.25)	**<0.001**	0.031
FWD, m	280 (258)	284 (304)	195 (214)	220 (450)	0.026	0.407

Table 1. *Continued.*

	Aortoiliac disease (n=70)	Femoro-popliteal disease (n=115)	Multilevel disease (n=69)	No disease (n=13)	Overall *P* Value	AoI vs FP *P* Value
MWD, m	443 (378)	450 (432)	335 (250)	377 (422)	**0.007**	0.901
6-minute walking test, m	396 ± 114	383 ± 86	327 ± 117	412 ± 126	**<0.001**	0.863
Vascuqol-6 sumscore	16 (6)	16 (6)	14 (7)	15 (7)	0.353	-
TASC Score, n (%)						
TASC A	47 (67.1)	44 (38.3)	15 (21.7)*	n/a		
TASC B	17 (24.3)	46 (40)	27 (39.1)*	n/a		
TASC C	1 (1.4)	16 (13.9)	16 (23.2)*	n/a	**<0.001**	**<0.001**
TASC D	4 (5.7)	7 (6.1)	10 (14.5)*	n/a		
Unknown	1 (1.4)	2 (1.7)	1 (1.4)	n/a		

Presented are numbers with percentages, means ± standard deviations, and median (interquartile range)

P values are added for comparison between groups overall and between aortoiliac and femoropopliteal disease specifically in case of p<0.05 for the overall comparison. Significant p values (<0.01) are displayed in bold.

* Based on disease level with highest score

AAA indicates abdominal aortic aneurysm; ABI, ankle brachial index; BMI, body mass index; AoI, aortoiliac; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; ER, endovascular revascularization; EVAR, endovascular aneurysm repair; FP, femoropopliteal; FWD, functional walking distance; IC, intermittent claudication; MWD, maximal walking distance; OR, open revascularization; PCI, percutaneous coronary intervention; SET, supervised exercise therapy.

Walking performance and health-related quality of life

Unadjusted changes from baseline after 3 and 6 months of SET are shown in Table 2. Patients with aortoiliac, femoropopliteal or multilevel stenoses all showed significant improvements in MWD, FWD, 6MWD and Vascuqol-6 sum scores. Participants in the 'no disease group' did not improve in Vascuqol-6 and 6MWT. No statistically significant differences in outcomes between overall disease level groups and between patients with femoropopliteal and aortoiliac disease were found.

Table 3 shows changes in outcome parameters following correction for age, sex, BMI, comorbid chronic obstructive pulmonary disease (COPD), prior ER, and TASC score. Selection of these covariates is summarized in Supplemental Table 2 in the Supplemental Digital Content. Again, between-group differences were absent. The adjusted difference between aortoiliac and femoropopliteal disease

patients regarding change in MWD after 3 months was -112m (99% CI -274 - 50, p=0.093), after 6 months -27m (99% CI -211 - 157, p=0.63). For change in FWD after 3 months this was -73m (99% CI -241 - 94, p=0.28), after 6 months -12m (99% CI -199 - 175, p=0.60). Regarding change in 6MWT after 3 months this was 10m (99% CI -27 - 46, p=0.52), after 6 months 29m (99% CI -28 - 86, p=0.23). For Vascuqol-6 sum scores after 3 months this was -1.4 (99% CI -3.2 – 0.5, p=0.072), after 6 months -0.6 (99% CI -2.4 – 1.3, p=0.46). The various sensitivity analyses (Supplemental tables 3 – 6, Supplemental Digital Content) did not lead to different conclusions.

Freedom from revascularization

After 6 months follow-up, 73.9% (51/69) of patients in the aortoiliac group remained free from intervention, compared to 88.6% (101/114) of femoropopliteal disease patients, 75.4% (52/69) of multilevel disease patients and all (100%) participants in the no disease group. Kaplan-Meier survival curves (figure 2) show that between-group differences start to appear after 3 months of follow-up (log rank test for overall comparison: χ^2=10.92, p=0.012; for aortoiliac versus femoropopliteal disease χ^2=6.559, p=0.0104). Subsequently, the association between aortoiliac disease versus femoropopliteal disease and freedom from revascularization was assessed while adjusting for potential confounding variables that were distributed differently between disease level groups at baseline, using Cox proportional hazard analysis (Table 4). Aortoiliac disease was associated with a statistically significant higher risk for early revascularization in the adjusted, but not the unadjusted, analysis. For the overall population, only resting ABI was identified as additional significant predictor of early revascularization (Supplemental table 7, Supplemental Digital Content).

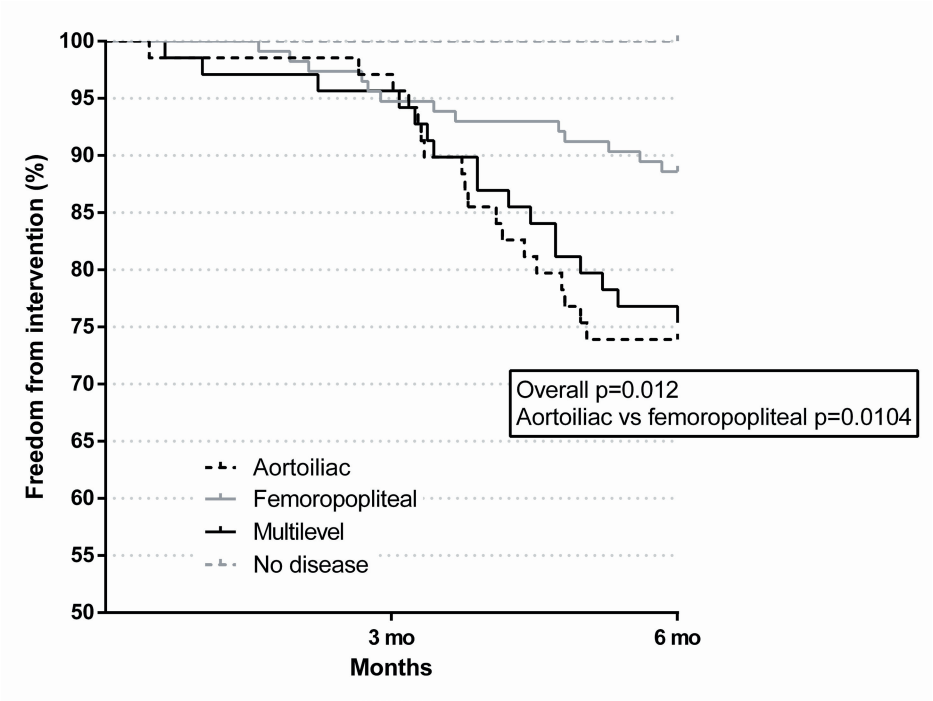

Figure 2. Freedom from intervention after 6 months of treatment.

Number at risk

Aortoiliac	69	66	51
Femoropopliteal	114	108	101
Multilevel	69	66	52
No disease	13	13	13

Table 2. Unadjusted mean changes from baseline after 3 and 6 months of SET in patients with IC, according to disease level.

	Aortoiliac (n=70)		Femoropopliteal (n=115)		Multilevel (n=69)		No disease (n=13)		*P* value overall		*P* value AoI vs FP	
Outcome Measures	3 Months change	6 Months change	3 Months change	6 Months change	3 Months change	6 Months change	3 Months change	6 Months change	3mo change	6mo change	3mo change	6mo change
MWD, m												
Mean	270	437	405	498	250	328	408	381	0.056	0.20	0.039	0.43
99% CI	151-388	289-586	300-509	381-614	155-344	221-435	80-737	86-675				
FWD, m												
Mean	312	512	397	503	248	341	427	325	0.097	0.081	0.26	0.50
99% CI	190-434	364-660	287-508	382-624	154-343	231-451	76-779	50-599				
6MWT, m												
Mean	44	78	36	38	50	54	-6	24	0.11	0.33	0.62	0.15
99% CI	13-76	24-131	17-55	12-64	25-76	11-96	-52-40	-60-108				
Vascuqol-6												
Mean	1.3	3.4	2.6	3.9	2.3	3.1	3.4	4.1	0.31	0.45	0.081	0.52
99% CI	0-2.7	2.0-4.9	1.7-3.5	2.9-4.9	0.8-3.7	1.6-4.5	-0.6-7.5	0.7-7.6				

P values are added for overall comparison between groups using Kruskal-Wallis rank sum test, and between aortoiliac and femoropopliteal disease using Mann Whitney U.
6MWT indicates 6-minute walking test; AoI, aortoiliac; CI, confidence interval; FP, femoral-popliteal. FWD, functional walking distance; MWD, maximal walking distance.

Table 3. Adjusted mean changes from baseline after 3 and 6 months of SET in patients with IC, according to disease level.

	Aortoiliac (n=69)		Femoropopliteal (n=113)		Multilevel (n=68)		No disease (n=13)		*P* value overall		*P* value AoI vs FP	
Outcome Measures	3 Months change	6 Months change	3 Months change	6 Months change	3 Months change	6 Months change	3 Months change	6 Months change	3 Months	6 Months	3 Months	6 Months
MWD, m												
Mean	273	439	385	466	274	353	370	403	0.20	0.40	0.093	0.63
99% CI	148-398	297-581	291-479	359-574	148-399	210-496	66-673	58-749				
FWD, m												
Mean	308	479	381	491	269	364	421	388	0.26	0.28	0.28	0.60
99% CI	178-437	334-623	283-479	381-600	139-399	219-510	106-736	37-740				
6MWT, m												
Mean	44	69	34	40	56	58	-12	16	0.11	0.40	0.52	0.23
99% CI	16-72	25-113	13-55	7-74	27-84	14-102	-81-56	-92-123				
Vascuqol-6												
Mean	1.3	3.3	2.6	3.9	2.2	2.8	3.8	5.8	0.16	0.18	0.072	0.46
99% CI	-0.1-2.7	1.9-4.8	1.6-3.7	2.8-5.0	0.8-3.6	1.4-4.2	0.4-7.2	2.3-9.2				

Covariates used for adjustment include age, sex, body-mass index, comorbid chronic obstructive pulmonary disease, prior endovascular revascularization, and TASC score (4 patients excluded due to missing TASC score).
P values are added for overall comparison between all four groups and between aortoiliac and femoropopliteal disease using one-way MANCOVA *F*-test.
6MWT indicates 6-minute walking test; AoI, aortoiliac; CI, confidence interval; FP, femoral-popliteal. FWD, functional walking distance; MWD, maximal walking distance.

Table 4. Cox proportional hazard analysis of association of aortoiliac disease versus femoropopliteal disease with need for revascularization after 6 months follow-up.

	Hazard ratio (99% CI)	*P*
Unadjusted	2.46 (0.96 – 6.30)	0.013
Model 1 (adjusted)*	2.99 (1.09 – 8.05)	0.005
Model 2 (adjusted)*	3.82 (1.11 – 13.11)	0.005
Model 3 (adjusted)*	3.68 (1.04 – 13.05)	0.008

*Models adjusted for: Model 1= TASC score (5 patients excluded because of missing data); Model 2 = Model 1 + age, smoking status, diabetes, ankle brachial index in rest and after exercise; Model 3 = Model 2 + sex, cerebrovascular accident, and chronic obstructive pulmonary disease. CI indicates confidence interval; HR, hazard ratio.

Attainment of the treatment goal

Data accrual for attainment of the main treatment goal was poor with 87/267 (32.6%) missing cases at 3 months, and 111/267 (41.6%) at 6 months. Nonetheless, of the participants with complete data sets, 7/46 (15.9%) patients with aortoiliac disease, 25/79 (31.6%) femoropopliteal disease patients, 11/45 (24.4%) of the multilevel group, and 1/10 (10%) of the no disease group had attained their treatment goal at the 3 months follow-up visit (p=0.14). After 6 months of therapy these percentages were 20/40 (50%), 33/70 (47.1%), 15/38 (39.5%), and 3/8 (37.5%), respectively (p=0.79).

DISCUSSION

This prospective observational study demonstrates that patients with IC achieve equal benefits after 3 and 6 months of SET, regardless of arterial disease location. Disease level groups showed similar improvements in walking performance and health-related quality of life, as well as rates of attainment of the treatment goal. Nonetheless, patients with aortoiliac disease appeared more likely to undergo a vascular intervention compared to femoropopliteal disease, especially after adjustment for baseline differences.

The results of the ELECT Registry justify guideline recommendations advocating exercise therapy first, prior to considering more invasive treatment options.[1] IC patients with aortoiliac, femoropopliteal, and multilevel stenoses showed meaningful improvements on all outcomes beyond previously established minimally important differences[25-27]. No between-group differences were present. These results are consistent with previous randomized trials on the effectiveness of SET[2,28], as well as the presumed working mechanisms of exercise therapy in PAD. With SET, improvement of claudication symptoms is established due to a

combination of (cardiovascular) systemic mechanisms and adaptations in pain tolerance, rather than improving measures of limb vascular resistance such as the ABI.[29] Moreover, alternative modes of exercise such as upper-extremity training appear to have similar effects on walking performance compared with walking exercise.[30] This study confirms that the distribution of atherosclerotic disease does not determine any functional outcomes of SET. As a consequence, it is not necessary to obtain imaging (CTA, MRA or duplex) of the lower extremity arteries prior to referral to a physical therapist contributing to the cost-effectiveness of SET. While this is already recommended in current guidelines[1], it is not widespread standard practice.

In this study, single-level aortoiliac disease appeared associated with a higher probability of undergoing vascular interventions. Likewise, multilevel disease patients showed similar intervention rates probably attesting to the practice of 'fixing the inflow first' among vascular professionals. An earlier study identified proximal disease as the strongest predictor of primary revascularization as opposed to conservative management.[10] Apart from any functional improvements after SET, the risk-benefit ratio of a possible intervention understandably plays a role in a shared decision to intervene. In aortoiliac disease, risks are less and benefits more durable, compared to ER in more distal lesions.[1] Moreover, in the current study, patients with aortoiliac disease had overall less severe TASC scores and were younger than femoropopliteal disease patients, factors possibly playing a role in the trend towards more interventions. When correcting for these and other factors, statistical certainty for the difference in freedom from revascularization increased.

In general, the need for revascularization in this study cohort (23%) was higher than reported in other Dutch population-based series with longer follow-up (6% - 19%).[5,31] This may be partly explained by bias introduced by the study design and setting. First, as dictated by the inclusion criteria, the location of disease was known for all patients in the analysis. This knowledge may have lowered the threshold to intervene. Second, all participants were recruited from outpatient vascular surgery clinics. Over the past years, a growing sample of patients in the Netherlands is referred to SET by a first-line general practitioner. As only the presence of symptoms of IC and a valid ABI reading suffice for an appropriate referral, a consultation of a vascular surgeon is generally not needed unless more invasive treatment is possibly indicated. In addition, a hospital patient population may be more inclined to a vascular intervention by default. Furthermore, the proportion of patients with prior vascular interventions was relatively high, as was having TASC A lesions. Interestingly however, only aortoiliac disease and resting ABI appeared significant predictors for early revascularization. More research is needed to elucidate the determinants of the need for intervention

relative to location of disease and functional outcomes. The longer-term results from the ELECT Registry will be used in this regard.

The ELECT Registry is the first study to couple the extent and location of atherosclerotic disease in IC patients treated with SET to a wide range of functional and clinical outcome measures. However, several limitations should be taken in consideration when interpreting the results. First, a relatively large number of patients declined participation, possibly introducing bias where only patients most motivated for the treatment are reflected in the results. Second, more participants were having multilevel disease than projected causing a smaller sample size in the aortoiliac group. Therefore, the current study lacked power for detecting small differences in outcomes between groups, especially with the stringent $p<0.01$ significance level. However, the sample size was sufficient to detect clinically relevant differences, especially in the inflow versus outflow disease sensitivity analysis. Moreover, the reported p-values exceed more conservative significance levels, especially after correction for confounders. Third, while a wide range of baseline characteristics were measured and accounted for in the analyses, unmeasured confounding may possibly have influenced the results. For instance, the intensity of exercise during SET sessions is not recorded, nor daily life physical activity levels. Fourth, DUS is a non-invasive and accurate tool to assess location and extent of stenosis in PAD, but has its limitations. For instance, visualization of the iliac vessels can be limited due to body habitus and/or bowel gas, possibly introducing bias in the study design. Finally, the current report shows short-term results but not any long-term data.

Conclusion

The efficacy of SET with regards to improving walking performance and health-related quality of life in IC patients in the short term is not influenced by arterial disease level. Despite equal improvements in functional measures, aortoiliac disease patients were prone to early revascularization compared with patients with femoropopliteal stenoses. This study confirms that all intermittent claudication patients should receive a trial of exercise therapy before invasive treatment is considered, regardless of the location or extent of the stenosis.

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SUMMARY, DISCUSSION AND IMPACT

CHAPTER 8

General discussion, summary and future perspectives

The general aim of this dissertation was to contribute to various aspects of the management of intermittent claudication (IC). In the following chapter, the findings are summarized and discussed, including methodological considerations, implications for clinical practice, and suggestions for future research.

PART I: IMPROVING ASSESSMENT OF WALKING PERFORMANCE

Walking capacity and treadmill testing

IC impedes walking ability. Exercise-induced limb symptoms diminish both walking endurance and peak performance. Successful treatment of symptoms may enhance the distance at which symptoms force a patient to stop walking and/or the total distance a patient can walk in a set time. Increasing this 'walking capacity' leads to improved (health-related) quality of life in IC patients.[1] Consequently, symptom severity and response to treatment are most commonly expressed through measures of walking capacity. Several validated test protocols exist, providing standardized and reproducible test conditions, allowing for comparisons between time points within one patient or between different individuals. Traditionally, treadmill tests have been most commonly used in peripheral arterial disease (PAD) research, attesting to their reproducibility, accessibility (no need for large test facilities), and extensively studied test characteristics.[1] Several limitations of treadmill walking hamper their use and were thus studied in this thesis.

Treadmill walking has been criticized for being an artificial form of walking.[2] To what extent do the walking limitations as measured on the treadmill correspond to limitations that are experienced in outside, real-world environments? This issue was investigated in **Chapter 2** of this thesis. The results show that a treadmill protocol using a gradually increasing inclination during the test optimally reflects outside walking, compared with a non-graded protocol or a patient's own estimation. However, the overall agreement between treadmill tests and outside walking was just moderate, and there was substantial variation between individual measurements. The findings suggest that treadmill-measured impairment of walking capacity does not necessarily correspond to the impairment patients experience during outside walking. A conclusion that is also supported by another study.[3] To more accurately assess a patient's daily life impairment (and monitor improvement or deterioration with treatment, perhaps even more relevant to the patient), alternative testing modalities should be explored.

Despite its shortcomings, treadmill testing remains widely used and useful when its limitations are heeded while interpreting their results. Changes in treadmill tests after various treatments in IC are well studied. Comparisons among treatment groups or among various trials and pooling of results in meta-

analyses are thus facilitated. However, what change after treatment do *patients* consider important? In **Chapter 3** the minimally important difference (MID) for walking distance that is measured on a treadmill is investigated to establish a first answer to this question. Changes in treadmill test outcomes were coupled with a clinical 'anchor' that is used to define improvement or deterioration as judged by the patient. Using this methodology, the MID of treadmill measured maximum walking distance in IC patients was approximately +300m for improvement and +150m for deterioration. An important takeaway from the study is that small improvements (i.e. <150m) are not satisfactory in the patient's eyes and may even be considered a deterioration. Of note, MIDs are population and context specific. In this instance, the results of three months of SET in a selected randomized trial population were used. The values that are presented in Chapter 3 should therefore be applied carefully in clinical care and research practice. The MIDs possibly only apply on similar patient populations and treatment circumstances, and should be validated in larger cohorts of patients. Nevertheless, the MIDS as found are helpful in the interpretation of the clinical relevance of numerical changes in walking distances.

Towards physical activity

Walking capacity, such as measured on a treadmill and studied in the first two chapters, provides information on a patient's (sub)maximal exercise limitations. However, an important part of a patient's performance is the way they actually use their capacity. In other words, how does improving walking capacity in a PAD patient translate to physical activity in daily life? This is particularly relevant when considering that inactivity is one of the main risk factors and determinants of prognosis for atherosclerosis and thus PAD.[4]

IC symptoms render patients sedentary.[5] Successful treatment of claudication symptoms (i.e. improvement of walking capacity) may facilitate improvement of inactive behaviour by removing the barriers to walking for prolonged distances. However, as shown in Chapter 2, only moderate correlation and substantial variation between measurements of walking capacity on the treadmill and during outside walking exist. Others found only a minimal correlation between walking capacity and physical activity in patients with IC.[6] The ability to walk further without claudication pain does not necessarily lead to the behavioural change of becoming more active in daily life. By extension, measuring improved walking capacity on a treadmill after treatment may only provide a proxy for improved physical functioning in daily life.

The benefits of supervised exercise therapy (SET), home-based exercise therapy (HBET), and endovascular revascularization (ER) regarding improving walking capacity have been studied extensively. By contrast, objectively measured

physical activity has only sparsely been used as outcome measure in clinical trials in IC. Some observational studies even reported no significant changes in physical activity after SET[7] or ER[8]. In **Chapter 4** all available evidence from randomized trials was aggregated in a network meta-analysis to get an inferred treatment effect. The study showed that SET leads to a moderate short-term improvement of physical activity, translating into some 800 steps/day, compared to control treatments. Mean daily steps at baseline was approximately 3000. This improvement may thus be substantial in the PAD population. HBET showed a similar benefit, but with low quality underlying evidence, thus the confidence in this outcome was less. Furthermore, the paucity of trials on the effect of ER on physical activity barred definite conclusions on this treatment modality.

Future perspectives on assessment of walking performance

One of the main criticisms regarding treadmill testing that was not investigated in this thesis is a possible learning effect associated with SET. As most or all training during therapy is performed on a treadmill, some authors are concerned with a 'training to the outcome' phenomenon. Alternatively, the 6-minute walk test (6MWT) is coined as test of walking performance. The 6MWT records the total distance an individual can walk over a total of 6 minutes on a hard, flat surface. Participants traverse back and forth along a marked walkway. They are allowed to self-pace and rest as needed, while timing continues up to 6min. The 6MWT has been validated, shown to be responsive to treatment, and is predictive of mortality and mobility loss in PAD populations.[2] Furthermore, a change in physical activity during daily life was more closely correlated with change in six-minute walk distance compared to change in treadmill walking distance.[9] Including this outcome parameter in future studies on PAD, next to treadmill testing is important, as they likely cover different domains of walking performance. In part 2 of this thesis this was considered as part of the ELECT Registry. Future analyses from this or other studies may shed more light on the relative value of treadmill testing and the 6MWT in the PAD population.

New wearable technology permits ambulatory measurement of walking capacity in the patient's own environment. Modern smartphones provide internet access, video, audio, social media, and can utilize built-in or wearable measurement devices such as accelerometers or global positioning systems (GPS), aggregating data on a patient's health behavior, including daily physical activity. Collection and subsequent incorporation of these data permits the provision of interactive interventions, individualized to the specific patient's individual characteristics and context. Furthermore, with objective information on patients' daily health behavior, physical therapists can better tailor lifestyle counseling and SET sessions. Future studies in PAD patients using this technology may provide

researchers and clinicians with novel outcome measures to more accurately reflect the limitations that patients experience in daily life.

PART II: EFFICIENT MANAGEMENT OF INTERMITTENT CLAUDICATION

International guidelines recommend SET as primary treatment for IC. Invasive open revascularization (OR) or ER is considered if SET fails to satisfactorily relieve symptoms.[10] However, worldwide access to exercise programs remains limited, also in the Western society, partly prompted by lacking reimbursement by insurance plans. This situation was at hand in the Netherlands prior to 2017, as SET was widely available by then, but not reimbursed. In **Chapter 5**, a study is presented using existing evidence on the effectiveness and costs of PAD treatment that were incorporated into a clinical decision model. With the use of this mathematical model, cost-effectiveness of a SET-first strategy (with ER in the event of SET failure) was compared with an ER-first strategy in a virtual cohort of IC patients. These virtual patients were subjected to a simulated course of disease, changing disease states and undergoing (re-)interventions based on probabilistic chances derived from data from a randomized trial as well as the literature. The accumulated costs and impact on quality of life, secondary interventions, and mortality were calculated. Analyses showed that over the 5 years after start of treatment, a mean of €6500 could be saved per patient if SET would be employed as first treatment as opposed to ER. These savings could be achieved over an extended time horizon and without detrimental effect on quality of life, secondary intervention rate (ER/OR or amputations) or mortality.

The conclusions of Chapter 5 are in line with previous economic evaluations[11,12] and cost-effectiveness analyses[13–15] that were previously used to inform policymakers in the Dutch government. Consequently, SET was reimbursed for all IC patients per 2017. A decision that has shown great impact on PAD care and outcomes nationally. Guideline compliance (i.e. referral to SET as primary treatment) increased to 87%, with freedom from intervention rates of up to 80% for the first five years after SET.[16] Evidently, in a healthcare system where SET is available and reimbursed IC patients can be spared unnecessary interventions. These findings become even more important in light of emerging evidence indicating that early revascularization in IC leads to higher rates of disease progression to chronic limb ischemia and consequent major amputation.[17,18]

Despite these benefits, some clinicians advocate a more personalized treatment plan where early revascularization is offered to those patients believed to be(come) unresponsive to SET. Their arguments are fueled by studies indicating greater short-term improvements when patients first undergo ER combined with SET

afterwards.[19,20] In theory, opening up the vessels of these patients provides short term relief of symptoms, with exercise afterwards to sustain results. An evidence-base for selecting these SET non-responders is lacking. One of the main arguments for early revascularization is the location and extent of the atherosclerotic lesion. Aortoiliac lesions are often considered appropriate for an endovascular approach, with more favorable procedural results and patency rates compared to revascularization in distal disease. IC patients with aortoiliac disease are four times more often referred for early revascularization, foregoing an attempt at SET.[21] However, the influence of arterial disease level on SET outcomes was never investigated. Consequently, the ELECT Registry was designed to study the influence of various potential determinants of outcome - including the location and extent of atherosclerotic disease - on treatment outcomes in IC. The study protocol is outlined in **Chapter 6**. It is the first study in an IC population that couples relevant anatomical and clinical patient characteristics with diverse outcomes reflecting walking performance, health-related quality of life, and clinical outcomes.

The ELECT Registry was conducted in 10 hospitals (both teaching and non-teaching) throughout the Netherlands, so Dutch vascular surgery practice was properly reflected. In **Chapter 7**, the short-term results are presented. This prospective observational study demonstrated that patients with IC achieve equal benefits after 3 and 6 months of SET, regardless of arterial disease location. Patients with aortoiliac, femoropopliteal, and multilevel disease showed meaningful improvements in walking performance and health-related quality of life, as well as rates of attainment of the treatment goal. No between-group differences were present. Nonetheless, patients with aortoiliac disease more often underwent a vascular intervention, compared to patients with femoropopliteal disease (26.1% vs. 11.4%). Apart from any functional improvements after SET, the risk-benefit ratio of a possible intervention understandably plays a role in a shared decision to intervene. The lower rates of freedom from interventions in patients with aortoiliac disease are thus probably attesting to the practice of 'fixing the inflow first' among vascular professionals. The ELECT Registry showed that all IC patients should receive a trial of exercise therapy before such invasive treatment is considered, regardless of the location or extent of the stenosis.

Future perspectives towards more efficient stepped care management

The studies in this thesis add to an already overwhelming body of evidence favoring SET as primary treatment in IC. Implementation of this strategy nationally reduced the number of patients needing invasive treatment.[16] Unfortunately, these benefits are withheld from most PAD patients over the Dutch border as worldwide implementation continues to lack. In several developed countries SET costs are still not reimbursed despite the evidence as presented

in this thesis. Even when reimbursement issues are solved, as has been the case in the United States since 2017, referral rates are poor.[22] One of the important reasons cited from the patient's perspective is discouragement by the large travel distance to the therapy facilities, as SET is mainly *hospital-based* in the United States. Efforts should be made to make *community-based* SET available, as in the Netherlands. Alternatively, HBET alternatives have been propagated as a solution.[10] However, HBET is possibly less effective than SET when reviewing all available evidence.[23,24] This is probably due to heterogeneity in the intensity and prescription of exercise in the various included trials. Moreover, some studies lacked elements that appeared successful in others. For instance, some included (remote) monitoring of exercise using wearable devices, goal setting, and regular feedback on performance.[24] These issues have thus hindered the implementation of efficient home-based alternatives to SET.

Apart from offering symptomatic relief, the main treatment goal in IC is improvement of cardiovascular prognosis. Nonetheless, the effect of IC treatment on cardiovascular outcomes, or even determinants of cardiovascular disease, remains largely unknown. One small prospective study showed a decrease in overall cardiovascular mortality by 52% and morbidity by 30% after a 12-week SET program[25], but these results have not been confirmed by other authors yet. Our study group conducted a systematic review and meta-analysis on the effect of SET on well-known modifiable risk factors for cardiovascular disease (i.e. hypertension, dyslipidemia, obesity, hyperglycemia, tobacco smoking, and physical inactivity). A total of 29 prospective studies were included. Our analysis provided some evidence that SET contributes to a reduction of systolic and diastolic blood pressure in the short term and a lowering of LDL cholesterol and total cholesterol in the midterm. However, the validity of these conclusions is unclear, as the available studies were of small sample size, moderate quality, and with heterogeneous populations and methodology. Furthermore, the influence of medical treatment of hypertension or dyslipidemia was unclear.[26] Evidently, cardiovascular mortality and morbidity in PAD patients remains under-reported and under-examined. Future research is needed to evaluate the current cardiovascular health benefit of exercise therapy in IC.

The implementation of eHealth solutions in IC treatment has been advocated to improve cardiovascular health outcomes, as well as support HBET alternatives to SET. As stated in Chapter 4 of this thesis, modern ambulatory devices, such as wearable accelerometers and smartphone apps, make monitoring and adjustment of daily life behavior increasingly accessible. An assessment among PAD patients and therapists showed that a smartphone app aimed at improving health behavior has the potential to reach a substantial proportion of PAD patients.[27] These devices can function as potentiators of health behavior change, but probably

only when incorporated into larger engagement strategies.[28,29] Indeed, such technology adjunctive to SET has recently shown promising results[30], but failed to improve physical activity in HBET programs with limited in-person guidance[31,32]. Furthermore, smartphone ownership in the PAD population is associated with younger age and higher attained educational level, both characteristics that carry a relatively favorable cardiovascular risk.[27] Care must be taken to design a solution that can be incorporated in the current supervised setting. By doing so, results may be optimized whereas patient subgroups who need it most are also included.

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CHAPTER 9

Impact

RESEARCH AIMS

This dissertation aimed to contribute to various aspects of the management of intermittent claudication (IC). In the two-part thesis it was investigated how treatment outcomes are measured and how various patient characteristics determine the outcome of conservative treatment.

In the first part, measures of outcome were investigated to improve their use in both clinical and research practice. It was shown what improvement or deterioration in walking performance on a treadmill after supervised exercise therapy (SET) is perceived as a meaningful change by the IC patient. Furthermore, a study revealed that patients generally overestimate their maximal walking ability. Treadmill-measured impairment of walking capacity does not necessarily correspond to the impairment patients experience during outside walking. Then does the ability to walk further without claudication pain on a treadmill, leads to the behavioural change of becoming more active in daily life? This was assessed by aggregating all available evidence from randomized trials on the benefits of SET, home-based exercise therapy (HBET) and endovascular revascularization (ER). Results showed that SET, and probably HBET, lead to substantial increases in daily physical activity levels in patients with IC in the short term.

In the second part, the efficiency of the stepped care treatment strategy in IC was investigated by assessing the cost-effectiveness of SET as primary treatment, and determinants of its outcomes. First, the impact on costs and quality of life of a SET-first strategy (with ER in the event of SET failure) was compared with an ER-first strategy. Analyses showed that over the 5 years after start of treatment, a mean of €6500 could be saved per patient if SET would be employed as first treatment. These savings could be achieved without detrimental effects on quality of life, secondary intervention rate (ER, open revascularization or amputations) or mortality. Thus, for the general IC population, SET should be employed first. In daily practice however, clinicians tailor treatment decisions to the individual patient. For instance, an important practice-based reason for early revascularization rather than await the efficacy of SET is location and extent of the atherosclerotic lesions. The results of the ELECT Registry revealed that patients with aortoiliac, femoropopliteal, and multilevel disease show meaningful improvements in walking performance and health-related quality of life, with no between-group differences. All IC patients should receive a trial of SET before invasive treatment is considered, regardless of the location or extent of the stenosis.

IMPACT

The main beneficiaries of all research performed as part of this thesis are patients with IC (peripheral arterial disease Fontaine stage 2, Rutherford I-III). The principal conclusions have likely resulted in a more efficient management of the IC population in the Netherlands. For instance, SET was universally reimbursed for all IC patients per 2017. In addition, referral to SET as primary treatment increased to 87%, with freedom from intervention rates of up to 80% for the first five years after SET. Extrapolating these referral rates to the worldwide population, where SET is largely unavailable, carries great potential. Especially given the high prevalence of IC combined with the mean cost savings per patient referred to SET as exhibited in this thesis. To realize this potential, further dissemination of the Dutch real-world results and their underlying evidence (to which this thesis contributed) to policy makers in other healthcare systems is required. This dissertation has shown that the initial investment required to develop the necessary infrastructure for a SET program will be compensated for by the economic benefits SET yields. More importantly, IC patients can be spared unnecessary vascular interventions and its complications, and substantially increase their daily physical activity, which is an important prognostic factor in cardiovascular health. Expanding the knowledge of vascular specialists and general practitioners on these important benefits should increase referral rates, thus greatly impacting the prognosis of the global IC population.

On a smaller scale, the results of the ELECT Registry have confirmed it is not necessary to obtain imaging (computed tomography angiography, magnetic resonance angiography or duplex) of the lower extremity arteries prior to referral to SET. While this is already recommended in current guidelines, it is not widespread standard practice. Omitting these diagnostics from the standard work-up saves patients time and harmful radiation (in case of computed tomography angiography), as well as avoids costs.

Finally, the results of this thesis are of interest to healthcare professionals responsible for administering exercise therapy in their community. They have regular in-person contact with the patient, thus have the ability to directly impact treatment. In the Netherlands, these mainly consists of physical therapist affiliated with ClaudicatioNet, a Dutch network of physical therapists specialized in SET with lifestyle guidance. ClaudicatioNet's conditions for participation mandate regular schooling and attendance to a yearly symposium, allowing up-to-date research insights to be incorporated on the short-term. This way, most of the presented research in this thesis was disseminated quickly after its conception, directly changing the way outcome is measured in all Dutch IC patients. For instance, the choice of treadmill test (graded instead of non-graded), or the increased use of measures of physical activity.

CHAPTER 10

Nederlandse samenvatting

DEEL I: HET METEN EN INTERPRETEREN VAN BEPERKINGEN IN LOPEN

Loopcapaciteit en loopband tests

Claudicatio Intermittens (CI) is het meest voorkomende symptoom van perifeer arterieel vaatlijden (PAV). Tijdens inspanning treedt pijn of ongemak van de benen op, dit beperkt het vermogen van de patiënt om te lopen. Zowel de prestaties tijdens rustig wandelen als bij maximale inspanning verminderen. Succesvolle behandeling van deze symptomen kan worden gemeten aan de hand van de afstand waarop de pijn een patiënt dwingt tot stoppen met lopen, als de totale afstand die een patiënt in een bepaald aantal minuten kan lopen. Toename van deze zogenaamde 'loopcapaciteit' leidt tot een verbetering van de (gezondheids-gerelateerde) kwaliteit van leven bij patiënten met CI.[1] Zodoende worden de ernst van de symptomen en respons na behandeling gewoonlijk uitgedrukt in maten van loopcapaciteit. Er bestaan meerdere gevalideerde tests waarmee vergelijkingen tussen verschillende punten in de tijd binnen één patiënt, of tussen verschillende individuen, gemaakt kunnen worden. Loopbandtests worden het meest gebruikt in de praktijk, vanwege hun uitstekende reproduceerbaarheid en toegankelijkheid, en omdat de diagnostische waarde uitgebreid bestudeerd is.[1] Desondanks zijn er verschillende belangrijke gebreken die de bruikbaarheid van loopbandtests beperken en daarom in dit proefschrift werden onderzocht.

Lopen op een loopband wordt bekritiseerd omdat het een kunstmatige manier van wandelen is.[2] Hoe verhouden beperkingen in lopen gemeten op de loopband zich tot de beperkingen die de patiënt ervaart tijdens het buiten lopen in het dagelijkse leven? Dit werd onderzocht in **Hoofdstuk 2** van dit proefschrift. De resultaten laten zien dat een loopbandtest-protocol waarbij de hellingshoek geleidelijk stijgt beter overeenkomt met buiten lopen dan een 'plat' loopbandtest-protocol, of een schatting van de patiënt. Echter, de loopcapaciteit gemeten op de loopband en tijdens het buiten lopen kwam slechts matig overeen. Bovendien was er sprake van substantiële variatie tussen individuele metingen binnen dezelfde patiënt. Deze bevindingen suggereren dat de beperking in loopcapaciteit op de loopband niet noodzakelijk goed overeenkomt met de loopbeperking die een patiënt ervaart in het dagelijks leven. Deze conclusie sloot aan op een eerdere studie met gelijke opzet.[3] Alternatieve testmodaliteiten moeten worden onderzocht om een betere inschatting van de beperkingen van CI patiënten in het dagelijkse leven te krijgen.

Desalniettemin blijft de loopband een van de meest gebruikte testmodaliteiten bij CI. Wanneer bij de interpretatie rekening gehouden wordt met de tekortkomingen uit Hoofdstuk 2 blijft het toch een bruikbaar instrument. Het resultaat van behandeling voor CI op loopbandtest uitkomsten is namelijk uitgebreid onderzocht. Derhalve kunnen de resultaten van verschillende behandelingen

goed onderling worden vergeleken aan de hand van deze tests. Het is echter onduidelijk wat patiënten een belangrijke verandering vinden. In **Hoofdstuk 3** werd daarom de '*minimally important difference*' (MID, minimaal belangrijke verschil) voor loopcapaciteit gemeten op de loopband onderzocht. De MID is een maat voor het kleinste effect dat waardevol is voor de patiënt. Verandering in de maximale loopafstand die de patiënt op de loopband kan afleggen voor en na 3 maanden gesuperviseerde looptherapie (GLT) werden gekoppeld aan een vraag aan de patiënt over de daadwerkelijk ervaren verbetering. Met deze methode bleek de MID voor maximale loopafstand ongeveer +300m voor verbetering, en +150m voor verslechtering. Een belangrijke boodschap van deze studie is dat een kleine numerieke verbetering in loopcapaciteit (<150m) in de ogen van de patiënt wordt gezien als een achteruitgang van de functie. Het is belangrijk te benadrukken dat MIDs sterk afhangen van de context van de data waarop ze zijn gebaseerd. Ze zijn dus niet zomaar overdraagbaar naar andere CI populaties of andere behandelingen.

Fysieke activiteit

Loopcapaciteit, zoals gemeten op de loopband en onderzocht in de eerste twee hoofdstukken, geeft informatie over de (sub)maximale inspanningsbeperking. Echter, een belangrijk onderdeel van de prestaties van een CI patiënt is hoe ze deze capaciteit daadwerkelijk gebruikt. Met andere woorden, hoe vertaalt een verbeterde loopcapaciteit zich in meer fysieke activiteit in het dagelijks leven? Een belangrijke vraag, aangezien fysieke activiteit een van de belangrijkste risicofactoren voor atherosclerose - en dus PAV - vormt én een belangrijke determinant is voor de prognose en levensverwachting van de patiënt.[4]

Patiënten met CI leiden veelal een zittend bestaan.[5] Succesvolle behandeling van de symptomen (met andere woorden: verbetering van de loopcapaciteit) kan een belangrijke barrière voor het lopen van langere afstanden wegnemen. In theorie faciliteert een verbeterde loopcapaciteit zo dus een actiever bestaan. Echter, zoals in Hoofdstuk 2 werd aangetoond, bestaat er slechts een matige correlatie en een substantiële variatie tussen loopcapaciteit gemeten op de loopband en tijdens buiten lopen. Anderen vonden slechts een minimale correlatie tussen loopcapaciteit en fysieke activiteit in patiënten met CI.[6] Het vermogen om verder te lopen zonder de pijn van CI leidt dus niet noodzakelijk tot een gedragsverandering van actiever worden in het dagelijks leven. In het verlengde daarvan, het meten van een verbeterde loopafstand op een loopband na behandeling vormt wellicht een slechte afgeleide van wat daadwerkelijk bereikt moet worden: een verbeterde fysieke functie in het dagelijks leven.

Het effect van GLT, '*home-based*' looptraining (HBLT, thuis trainingen ondersteund door regelmatige monitoring op afstand) en endovasculaire revascularisatie

(ER, 'dotteren') op het verbeteren van loopcapaciteit is uitgebreid onderzocht. Daarentegen bestaat er maar weinig onderzoek waar objectief gemeten fysieke activiteit als uitkomstmaat werd gebruikt. Enkele observationele studies suggereerden zelfs dat met GLT[7] of ER[8] geen significante verbetering van fysieke activiteit wordt bewerkstelligd. In **Hoofdstuk 4** werd al het beschikbare bewijs uit gerandomiseerde studies samengevoegd in een zogeheten 'netwerk meta-analyse' om mogelijk alsnog een behandeleffect te kunnen afleiden. Dit onderzoek liet zien dat GLT wel degelijk leidt tot een matige verbetering van fysieke activiteit op de korte termijn, gelijkstaand aan ongeveer 800 stappen extra per dag. Het gemiddeld aantal dagelijks gelopen stappen in de populatie bedroeg ongeveer 3000. Het gevonden effect kan dus een substantiële verbetering zijn in de PAV-populatie. HBLT liet een soortgelijk effect zien, maar met onderliggend bewijs van lage kwaliteit. Derhalve is het vertrouwen in de juistheid van deze uitkomst laag. Er zijn te weinig beschikbare studies naar het effect van ER op fysieke activiteit. Om een zinvolle uitspraak te kunnen doen over het effect van ER op fysieke activiteit is dus meer onderzoek nodig.

DEEL II: EFFICIENTE BEHANDELING VAN CLAUDICATIO INTERMITTENS

Nederlandse en internationale richtlijnen bevelen GLT als eerste behandeling voor CI aan. Invasieve open revascularisatie (OR) of ER kan worden overwogen als er met GLT alleen niet in wordt geslaagd de symptomen naar tevredenheid te behandelen.[9] Wereldwijde toegang tot GLT blijft tot op heden beperkt, ook in Westerse landen, deels veroorzaakt door uitblijvende vergoeding door zorgverzekeraars. In Nederland was er een soortgelijke situatie voor 2017. GLT was destijds beschikbaar via ClaudicatioNet voor iedere patiënt, maar werd niet vergoed. In het onderzoek beschreven in **Hoofdstuk 5** werd bestaand bewijs over de effectiviteit en kosten van de behandeling van CI in een klinisch beslismodel gevoegd. Met behulp van dit rekenmodel kon zo de kosteneffectiviteit van een behandelstrategie met 'eerst GLT' (en ER wanneer dit faalde; '*stepped care*') worden vergeleken met een 'eerst ER' strategie in een virtueel cohort van CI patiënten. Deze virtuele patiënten doorliepen vervolgens een gesimuleerd verloop van hun ziekte, waar symptomen toe- en afnamen, er (re-) interventies werden gedaan, gebaseerd op probabilistische kansenverhoudingen uit data van gerandomiseerde studies en de medische literatuur. De geaccumuleerde kosten en impact op kwaliteit van leven, secundaire interventies en mortaliteit werden berekend. Deze analyses lieten zien dat 5 jaar na start van de behandeling gemiddeld €6500 per patiënt kon worden bespaard als GLT de behandeling van eerste keus zou zijn. Deze besparingen waren mogelijk over een langere tijd dan in eerder onderzoek was gevonden, en zonder negatief effect op de kwaliteit van leven, het aantal benodigde interventies (ER/OR of amputaties), of de mortaliteit.

De conclusies uit Hoofdstuk 5 kwamen overeen met eerdere economische evaluaties[10, 11] en kosteneffectiviteit analyses[12, 13] die werden gebruikt om Nederlandse beleidsmakers te informeren. Als gevolg hiervan werd per 1 januari 2017 GLT opgenomen in het basispakket. Hiermee werd een belangrijke drempel weggenomen voor patiënt en verwijzer. GLT wordt nu, volgens de meest recente cijfers van Nederlandse zorgverzekeraars, in 87% van de nieuwe gevallen van CI voorgeschreven als eerste behandeling. Van deze patiënten blijft in 83% van de gevallen een vasculaire interventie uiteindelijk 5 jaar lang achterwege.[15] Dit is een forse vermindering in het aantal (klaarblijkelijk onnodige) interventies met bijbehorende complicaties voor de patiënt. Bovendien blijkt uit recent onderzoek dat zulke vroege interventies bij patiënten met CI kunnen leiden tot een hogere kans op progressie van ziekte naar kritieke ischemie en meer amputaties.[16, 17]

Desondanks blijft voor sommige vaatchirurgen een meer gepersonaliseerd behandelplan nog altijd aantrekkelijk. In plaats van 'eerst GLT voor iedere patiënt' propageren zij vroege revascularisatie voor die patiënten waarvan *a priori* de kans van slagen van GLT laag wordt ingeschat. Dit argument lijkt ondersteund door onderzoek waarin een kortdurend voordeel op de kwaliteit van leven werd gezien voor een behandelstrategie met eerst een dotter en nadien GLT (hoewel dit voordeel verdween gedurende follow-up).[18, 19] Een van de meest gebruikte argumenten voor zo'n vroege revascularisatie is de locatie en uitgebreidheid van de atherosclerotische laesie. Zo zijn de meeste aortoiliacale vernauwingen endovasculair ('van binnen uit', met een Dotter) te benaderen, met gunstigere procedurele resultaten en '*patency*' (duurzaamheid van doorgankelijkheid) in vergelijking met revascularisatie van meer distale ziekte (in het femoropopliteale traject). Het blijkt dan ook dat CI patiënten met een aortoiliacale stenose of occlusie vier keer vaker worden verwezen voor vroege revascularisatie, zonder voorafgaande GLT.[20] Het is echter niet duidelijk of de locatie van het vaatletsel invloed heeft op de uitkomst en succeskans na GLT. Is het wel terecht om patiënten met een aortoiliacale laesie GLT te onthouden en daarmee de kans om invasieve behandeling te vermijden? Om die reden werd de ELECT Registry ontworpen, waarvan het onderzoeksprotocol in **Hoofdstuk 6** uiteen werd gezet.

Het doel van de ELECT Registry was het bestuderen van de invloed van verschillende potentiële anatomische en klinische determinanten op de uitkomst van conservatieve behandeling van CI. Het was de allereerste studie ooit waarin de locatie en uitgebreidheid van de atherosclerotische ziekte werd gekoppeld aan de uitkomst van GLT. De ELECT Registry werd in 10 Nederlandse (academische en perifere) ziekenhuizen uitgevoerd. Het geeft daarmee een goede weergave van de doorsnee Nederlandse vaatchirurgische praktijk. In **Hoofdstuk 7** werden de korte-termijn resultaten gepresenteerd. Dit prospectieve observationele onderzoek liet zien dat alle patiënten met CI een gelijk voordeel behalen na 3 en 6 maanden GLT,

ongeacht de locatie van arteriële stenose of occlusie. Patiënten met aortoiliacaal, femoropopliteaal, en '*multilevel*' laesies lieten betekenisvolle verbeteringen zien in loopcapaciteit en ziekte-gerelateerde kwaliteit van leven. Bovendien bereikten ze in dezelfde mate hun vooropgestelde behandeldoel. Er werden geen verschillen tussen de groepen onderling gevonden. Desalniettemin ondergingen patiënten met een aortoiliacale stenose of occlusie wel vaker een vasculaire interventie in vergelijking met patiënten met femoropopliteale ziekte (26.1% vs. 11.4%). Drie tot 6 maanden na de start van de behandeling neemt normalerwijze de patiënt samen met de vaatchirurg de beslissing om wel of niet over te gaan op een interventie. Het is invoelbaar dat hierin niet alleen de functionele verbetering na GLT meeweegt, maar ook de risico-baten verhouding van een eventuele interventie. De hogere kans op het ondergaan van een ER bij aortoiliacale ziekte in de studiepopulatie reflecteert dientengevolge waarschijnlijk het adagium in de vaatchirurgie om eerst de '*inflow*' te behandelen. De ELECT Registry heeft aangetoond dat alle patiënten met CI in ieder geval eerst een gedegen conservatief traject moeten doorlopen alvorens invasieve behandeling wordt overwogen, ongeacht de locatie of uitgebreidheid van de stenose of occlusie.

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APPENDICES

SUPPLEMENTAL CONTENT

SUPPLEMENTAL CONTENT CHAPTER 4

Effect of supervised exercise, home-based exercise and endovascular revascularization on physical activity in patients with intermittent claudication: a network meta-analysis

Contents

Appendix S1 Search terms and results

Search results from MEDLINE (PubMed), cut-off date May 23rd 2018.

PICO	Search #	Search Terms	#results
P	#1	("Peripheral arterial disease"[MeSH Terms] OR peripheral arter* disease[tiab] OR "intermittent claudication"[MeSH Terms] OR claudication[tiab])	25862
I	#2	(Exercise therapy[Mesh] OR (exercise AND therapy) OR exercise therapy OR Exerc* OR "exercise"[Mesh] OR Treadmill OR Home-training OR home training OR Home-based OR home based OR supervised exercise OR non-supervised exercise OR community based OR community-based OR rehabilitation OR Community walking program OR walking therapy OR "walking"[Mesh] OR Angioplasty[Mesh] OR Angioplasty OR (Percutaneous OR transluminal AND angioplasty) OR Percutaneous transluminal angioplasty OR pta OR Percutaneous endoluminal angioplasty OR balloon dilation OR (Stents[Mesh] OR Stents OR stent) OR (Percutaneous AND revascularization) OR Endovascular procedures[Mesh] OR (endovascular AND procedures) OR Endovascular procedures OR (endoluminal AND revascularization) OR endoluminal revascularization OR Femoral Artery/Surgery[Mesh] OR Popliteal Artery/Surgery[Mesh] OR Tibial arteries/surgery[Mesh] OR Arteries/Surgery[Mesh] OR Graft OR Grafts OR Grafting OR Bypass OR Conduit OR Femoropopliteal OR Femorotibial OR Aortobifemoral OR Atherectomy[Mesh] OR Atherectomy))	2195754
C	#3	((((((((((randomized controlled trial [pt]) OR controlled clinical trial [pt]) OR randomized [tiab]) OR placebo [tiab]) OR drug therapy [sh]) OR randomly [tiab]) OR trial [tiab]) OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))))	3686353
O	#4	(((Physical OR ambulatory OR walking OR daily) AND activity) OR "Accelerometry"[Mesh] OR Accelerometer OR Pedometer OR gps OR Global Positioning System OR "Geographic information systems"[Mesh] OR Ambulatory function OR Physical Function OR Physical functioning OR Physical activity OR "Activities of daily living"[Mesh] OR "Leisure activities"[Mesh] OR Daily activity OR Steps OR Activity time OR Activity count OR Kilocalories OR kcal OR "Metabolic Equivalent"[Mesh] OR metabolic equivalent OR met OR mets OR oxygen consumption OR Energy expenditure OR sedentary OR "Monitoring, ambulatory"[MeSH Terms] OR "physical exertion"[MeSH Terms]))	2835963
PI	#5	#1 AND #2	12002
PIC	#6	#3 AND #5	3514
PICO	#7	#4 AND #6	1628

Search results from EMBASE (Ovid) database, cut-off date May 23rd 2018.

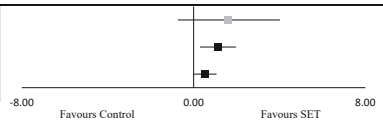
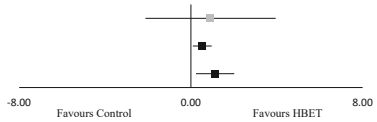
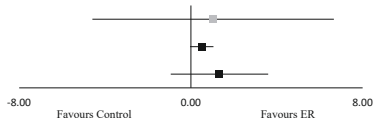
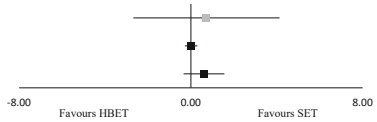
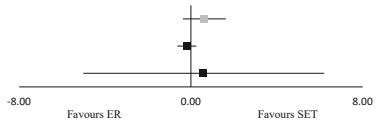
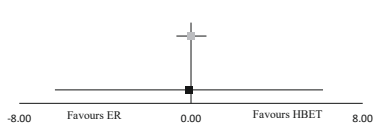
PICO	Search #	Search Terms	#results
P	#1	peripheral arterial disease.mp. or peripheral occlusive artery disease/ or intermittent claudication.mp. or intermittent claudication/ or peripheral vascular disease.mp. or peripheral vascular disease/	65876
I	#2	exercise therapy mp or exp kinesiotherapy/ or exp walking/ or exp treadmill exercise/ or exp exercise/ or exp rehabilitation/ or exercise rehabilitation mp or percutaneous transluminal angioplasty mp or exp percutaneous transluminal angioplasty/ or patch angioplasty or exp angioplasty/ or exp percutaneous transluminal angioplasty balloon/ or angioplasty mp or stents mp or exp stent/ or exp blood vessel shunt/	994927
C	#3	Randomized controlled trial or double-blind procedure or single-blind procedure or random* or factorial* or placebo* or (singl* adj blind*) or (double* adj blind*) or assign* or allocate*	1993507
O	#4	physical activity.mp. or exp physical activity/ or leisure activities.mp. or exp leisure/ or accelerometer.mp. or exp accelerometer/ or pedometer.mp. or exp pedometer/ or global positioning system.mp. or exp global positioning system/ or steps.mp. or exp energy expenditure/ or kcal.mp. or kilocalories.mp. or metabolic equivalent.mp. or exp metabolic equivalent/	397374
PI	#5	#1 AND #2	15271
PIC	#6	#3 AND #5	2694
PICO	#7	#4 AND #6	829

Search results from CENTRAL (Cochrane) database, cut-off date May 23rd 2018.

PICO	Search #	Search Terms	#results
P	#1	(Peripheral arterial disease(MeSH Terms) OR peripheral arter* disease OR intermittent claudication(MeSH Terms) OR claudication)	4791
I	#2	exercise(Mesh) OR Treadmill OR Home-training OR home training OR Home-based OR home based OR supervised exercise OR non-supervised exercise OR community based OR community-based OR rehabilitation OR Community walking program OR walking therapy OR walking(Mesh) OR Angioplasty(Mesh) OR Angioplasty OR (Percutaneous OR transluminal AND angioplasty) OR Percutaneous transluminal angioplasty OR pta OR Percutaneous endoluminal angioplasty OR balloon dilation OR (Stents(Mesh) OR Stents OR stent) OR (Percutaneous AND revascularization) OR Endovascular procedures(Mesh) OR (endovascular AND procedures) OR Endovascular procedures OR (endoluminal AND revascularization) OR endoluminal revascularization OR Surgery OR Graft OR Grafts OR Grafting OR Bypass OR Conduit OR Femoropopliteal OR Femorotibial OR Aortobifemoral OR Atherectomy(Mesh) OR Atherectomy	241433
O	#3	((Physical OR ambulatory OR walking OR daily) AND activity) OR Accelerometry(Mesh) OR Accelerometer OR Pedometer OR gps OR Global Positioning System OR Geographic information systems(Mesh) OR Ambulatory function OR Physical Function OR Physical functioning OR Physical activity OR Activities of daily living(Mesh) OR Leisure activities(Mesh) OR Daily activity OR Steps OR Activity time OR Activity count OR Kilocalories OR kcal OR Metabolic Equivalent(Mesh) OR metabolic equivalent OR met OR mets OR oxygen consumption OR Energy expenditure OR sedentary OR Monitoring, ambulatory(MeSH Terms) OR physical exertion(MeSH Terms)	102909
PI	#4	#1 AND #2	2436
PICO	#6	#3 AND #4	395

Appendix S2. Results of sensitivity analysis.

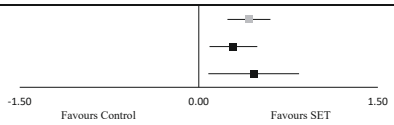
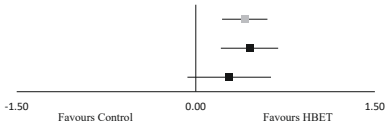
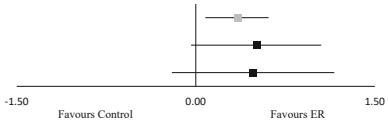
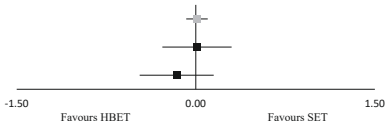
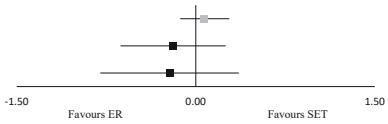
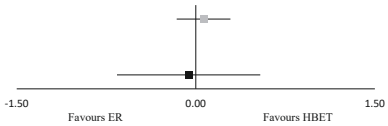
Standardized mean differences produced by random-effects network meta-analysis of physical activity **with inclusion of the outlying trial by Gardner et al.**(*J Am Geriatr Soc.* 2001).

Comparison	Estimate		SMD (95% CI)
SET vs Control	Network meta-analysis		1.60 (-0.73 -4.02)
	Direct evidence		1.14 (0.30 – 1.98)
	Indirect evidence		0.54 (0.01 – 1.07)
HBET vs Control	Network meta-analysis		0.90 (-2.12 -3.95)
	Direct evidence		0.53 (0.09 – 0.97)
	Indirect evidence		1.13 (0.24 – 2.02)
ER vs Control	Network meta-analysis		1.01 (-4.59 – 6.66)
	Direct evidence		0.51 (-0.04 – 1.05)
	Indirect evidence		1.33 (-0.94 – 3.60)
SET vs HBET	Network meta-analysis		0.68 (-2.68 – 4.13)
	Direct evidence		0.01 (-0.28 – 0.30)
	Indirect evidence		0.61 (-0.34 – 1.56)
SET vs ER	Network meta-analysis		0.58 (-5.01 – 6.21)
	Direct evidence		-0.19 (-0.63 – 0.25)
	Indirect evidence		0.63 (-0.37 – 1.63)
HBET vs ER	Network meta-analysis		-0.12 (-6.34 – 6.15)
	Direct evidence		N/A
	Indirect evidence		0.02 (-0.68 – 0.72)

Abbreviations: SET, supervised exercise therapy; HBET, home-based exercise therapy; ER, endovascular revascularization; SMD, standardized mean difference; CI, credible interval; N/A, not applicable.

Forest plots showing the relative effect of each treatment strategy on objective measurements of free-living physical activity among patients with intermittent claudication.

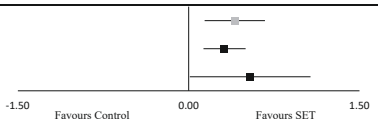
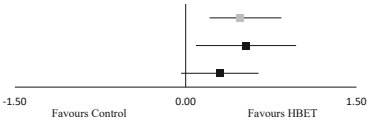
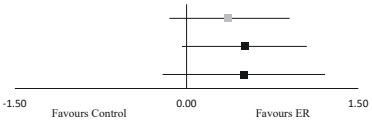
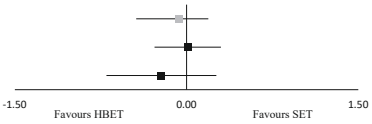
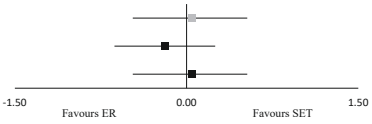
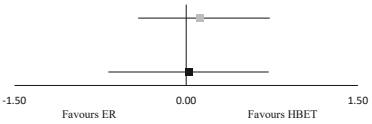
Standardized mean differences produced by **fixed-effects** network meta-analysis of physical activity.

Comparison	Estimate		SMD (95% CI)
SET vs Control	Network meta-analysis		0.42 (0.24– 0.60)
	Direct evidence		0.29 (0.09 – 0.49)
	Indirect evidence		0.46 (0.08 – 0.84)
HBET vs Control	Network meta-analysis		0.41 (0.22 – 0.60)
	Direct evidence		0.45 (0.21 – 0.69)
	Indirect evidence		0.28 (-0.07 – 0.63)
ER vs Control	Network meta-analysis		0.35 (0.08 – 0.61)
	Direct evidence		0.51 (-0.04 – 1.05)
	Indirect evidence		0.48 (-0.20 – 1.16)
SET vs HBET	Network meta-analysis		0.01 (-0.08 – 0.10)
	Direct evidence		0.01 (-0.28 – 0.30)
	Indirect evidence		-0.16 (-0.47 – 0.15)
SET vs ER	Network meta-analysis		0.07 (-0.13 – 0.28)
	Direct evidence		-0.19 (-0.63 – 0.25)
	Indirect evidence		-0.22 (-0.80 – 0.36)
HBET vs ER	Network meta-analysis		0.07 (-0.16 – 0.29)
	Direct evidence		N/A
	Indirect evidence		-0.06 (-0.66 – 0.54)

Abbreviations: SET, supervised exercise therapy; HBET, home-based exercise therapy; ER, endovascular revascularization; SMD, standardized mean difference; CI, credible interval; N/A, not applicable.

Forest plots showing the relative effect of each treatment strategy on objective measurements of free-living physical activity among patients with intermittent claudication.

Standardized mean differences produced by random-effects network meta-analysis of objectively measured and **self-reported** physical activity using objective.

Comparison	Estimate		SMD (95% CI)
SET vs Control	Network meta-analysis		0.41 (0.14 -0.67)
	Direct evidence		0.31 (0.13 – 0.50)
	Indirect evidence		0.54 (0.01 – 1.07)
HBET vs Control	Network meta-analysis		0.48 (0.21 -0.84)
	Direct evidence		0.53 (0.09 – 0.97)
	Indirect evidence		0.30 (-0.04 – 0.64)
ER vs Control	Network meta-analysis		0.36 (-0.15 – 0.90)
	Direct evidence		0.51 (-0.04 – 1.05)
	Indirect evidence		0.50 (-0.21 – 1.21)
SET vs HBET	Network meta-analysis		-0.07 (-0.44 – 0.19)
	Direct evidence		0.01 (-0.28 – 0.30)
	Indirect evidence		-0.22 (-0.70 – 0.26)
SET vs ER	Network meta-analysis		0.05 (-0.47 – 0.53)
	Direct evidence		-0.19 (-0.63 – 0.25)
	Indirect evidence		-0.20 (-0.78 – 0.38)
HBET vs ER	Network meta-analysis		0.12 (-0.42 – 0.73)
	Direct evidence		N/A
	Indirect evidence		0.02 (-0.68 – 0.72)

Abbreviations: SET, supervised exercise therapy; HBET, home-based exercise therapy; ER, endovascular revascularization; SMD, standardized mean difference; CI, credible interval; N/A, not applicable.

Forest plots showing the relative effect of each treatment strategy on objective measurements of free-living physical activity among patients with intermittent claudication.

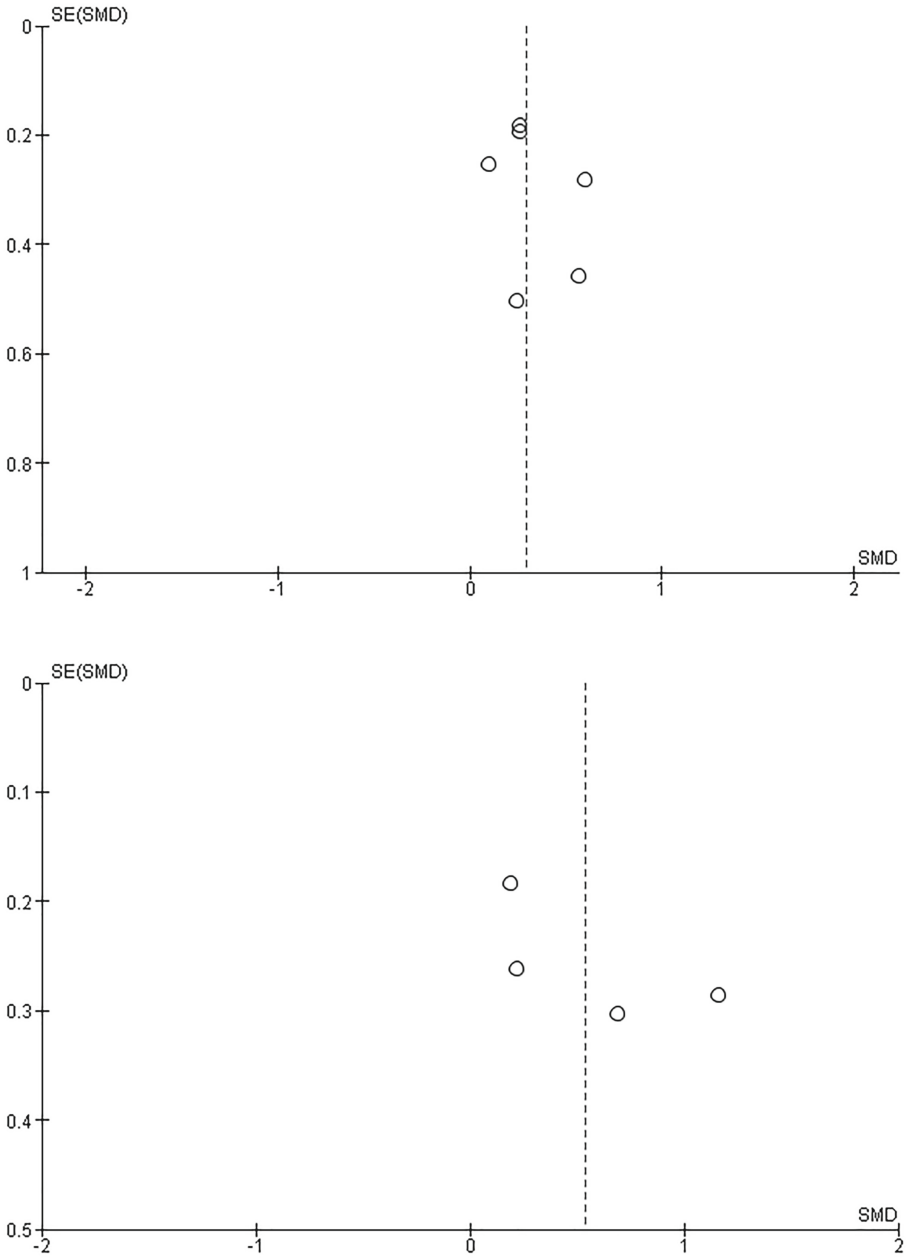
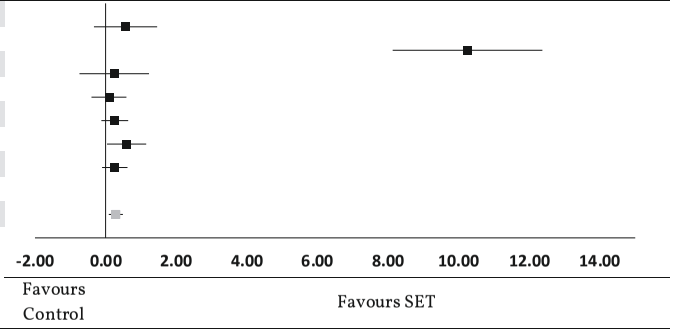


Fig. S1 Funnel plots for direct meta-analysis of the effect of intermittent claudication treatment on physical activity: supervised exercise therapy (SET) *versus* control (upper plot) and home-based exercise therapy (HBET) *versus* control (lower plot).

Table S1. Results of direct, random effects, meta-analysis of supervised exercise therapy versus control for intermittent claudication on objectively measured daily physical activity with with inclusion of the outlying trial by Gardner et al.(*J Am Geriatr Soc.* 2001).

Study	Year	SET			Control			SMD	Forest plot
		Mean	SD	n	Mean	SD	n	[95% CI]	SMD (95% CI)
Regensteiner	1996	2.8	5.2	10	0.4	2.5	10	0.56 [-0.33, 1.46]	
Gardner	2001	138	22	28	-161	35	24	10.25 [8.13, 12.37]	
McDermott	2009	33.6	496	12	-88.7	445	6	0.24 [-0.74, 1.23]	
Gardner	2011	169	1120	33	51	1265	30	0.10 [-0.40, 0.59]	
Gardner	2012	81	117	106	34	297	36	0.26 [-0.12, 0.64]	
Murphy	2012	72.6	138.7	38	-5.6	109.4	20	0.60 [0.04, 1.15]	
Gardner	2014	258	1162	60	-93	1531	60	0.26 [-0.10, 0.62]	
Total				287			186	1.14 [0.30, 1.98]	



Heterogeneity: $Tau^2 = 1.10$; $Chi^2 = 86.15$, df = 6 (P = <0.00001; $I^2 = 93\%$

Abbreviations: SET, supervised exercise therapy;; ER, endovascular revascularization; SD, standard deviation; SMD, standardized mean difference; CI, confidence interval.

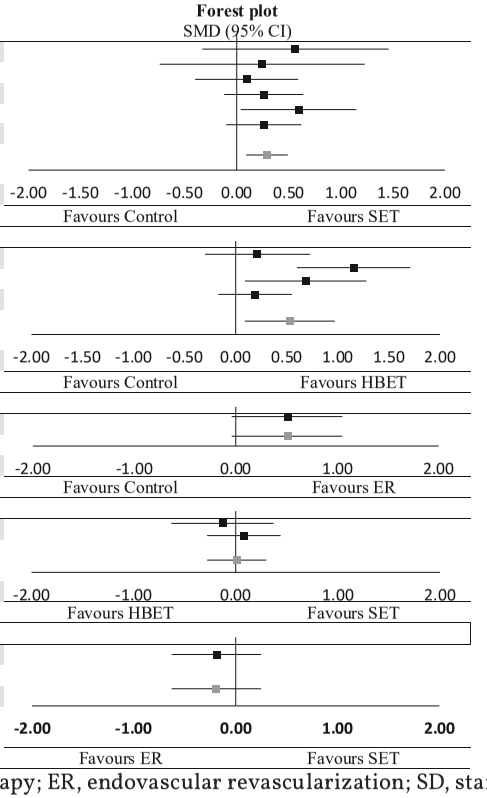
Table S2. Summary of mean study-level patient characteristics of all included trials for SET, HBET, ER and control.

Characteristic	SET	HBET	ER	Control
Age, y ±SD	66.3 ±9.6	66.7 ±9.6	64.9 ±10.2	65.7 ±9.1
ABI ±SD	0.66 ±0.22	0.68 ±0.21	0.66 ±0.2	0.71 ±0.20
Gender, % male	63.2	52	69.6	69.3
BMI ±SD	28.5 ±5.7	29.4 ±5.7	29.3 ±6	29.3 ±6
% Smokers	39.4	26.7	50	33.3
PWT, min ±SD	6.3 ±3.7	6.7 ±4.8	5.2 ±2	7.2 ±3.6
Daily steps ±SD	2788 ±1481	3230 ±1843	2926 ±1824	3688 ±1960

Abbreviations: ABI, ankle brachial index; BMI, body mass index; ER, endovascular revascularization; HBET, home-based exercise therapy; SD, standard deviation; SET, supervised exercise therapy; PWT, peak walking time.

Table S3. Results of direct, random effects, meta-analysis of supervised exercise therapy, home-based exercise therapy, and endovascular revascularization for intermittent claudication on objectively measured daily physical activity.

Study	Year	SET			Control			SMD
		Mean	SD	n	Mean	SD	n	[95% CI]
Regensteiner	1996	2.8	5.2	10	0.4	2.5	10	0.56 [-0.33, 1.46]
McDermott	2009	33.6	496	12	-88.7	445	6	0.24 [-0.74, 1.23]
Gardner	2011	169	1120	33	51	1265	30	0.10 [-0.40, 0.59]
Gardner	2012	81	117	106	34	297	36	0.26 [-0.12, 0.64]
Murphy	2012	72.6	138.7	38	-5.6	109.4	20	0.60 [0.04, 1.15]
Gardner	2014	258	1162	60	-93	1531	60	0.26 [-0.10, 0.62]
Total				259			162	0.29 [0.09, 0.49]
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 2.18$, df = 5 (P = 0.82); $I^2 = 0\%$								
Study	**Year**	**HBET**			**Control**			**SMD**
Gardner	2011	324	1256	29	51	1256	30	0.21 [-0.30, 0.73]
Cunningham	2012	1358	1437	28	-226	1268	30	1.16 [0.60, 1.71]
McDermott	2013	226	319	26	-37	437	21	0.69 [0.09, 1.28]
Gardner	2014	166	1134	60	-93	1531	60	0.19 [-0.17, 0.55]
Total				143			141	0.53 [0.09, 0.97]
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 9.55$, df = 3 (P = 0.02); $I^2 = 69\%$								
Study	**Year**	**ER**			**Control**			**SMD**
Murphy	2012	114.3	273.9	41	-5.6	109.4	20	0.51 [-0.04, 1.05]
Total				41			20	0.51 [-0.04, 1.05]
Heterogeneity: Not applicable								
Study	**Year**	**SET**			**HBET**			**SMD**
Gardner	2011	169.0	1120.0	33	324.0	1256.0	29	-0.13 [-0.63, 0.37]
Gardner	2014	258.0	1162.0	60	166.0	1134.0	60	0.08 [-0.28, 0.44]
Total				93			89	0.01 [-0.28, 0.30]
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.44$, df = 1 (P = 0.51); $I^2 = 0\%$								
Study	**Year**	**SET**			**ER**			**SMD**
Murphy	2012	72.6	138.7	38	114.3	273.9	41	-0.19 [-0.63, 0.25]
Total				38			41	-0.19 [-0.63, 0.25]
Heterogeneity: Not applicable								



Abbreviations: SET, supervised exercise therapy; HBET, home-based exercise therapy; ER, endovascular revascularization; SD, standard deviation; SMD, standardized mean difference; CI, confidence interval.

SUPPLEMENTAL CONTENT CHAPTER 5

Cost-effectiveness of supervised exercise therapy compared with endovascular revascularization for intermittent claudication

Contents

Table S1 Baseline characteristics and disease severity.

	SET (*n* = 234†)	**ER** (*n* = 75‡)	***P*§**
Age (years)*	66(9)	65(11)	0.429¶
Men (%)	62	59	0.564#
Arterial hypertension (%)	55	43	0.070#
Diabetes mellitus (%)	21	15	0.204#
Hyperlipidaemia (%)	61	53	0.260#
History of ischaemic heart disease (%)	22	19	0.513#
Osteoarthritis of limb (%)	10	9	0.817#
History of cerebrovascular disease (%)	12	11	0.760#
Smoking (%)			
Current	33	16	0.003#
Ever	50	53	0.686#
Never	17	31	0.009#
Body mass index (kg/m^2)*	27(4.6)	26(4.3)	0.097¶
Ankle : brachial pressure index*	0.66(0.18)	0.62(0.18)	0.095¶
Maximum pain-free walking distance (m)*	156(100)	82(50)	< 0.001¶
Maximum walking distance (m)*	251(127)	175(82)	<0.001¶
EQ-5D™ quality-of-life score*	0.67(0.13)	0.67(0.21)	0.84¶

*Values are mean(s.d.). SET, supervised exercise therapy; ER, endovascular revascularization. †Combined population of 75 patients from the CETAC study and 159 from the EXITPAD study; ‡patients from CETAC only. EQ-5D™, EuroQoL 5 Dimension. §P < 0.050 was considered statistically significant. ¶Student *t* test.; #Pearson's chi-square test.

Table S2 Secondary intervention rates and outcome.

	Value*		Range†		
	SET	ER	SET	ER	Source
Secondary intervention rates					
Probability of ER/OR					
For mild claudication	0.051	0.128	±0.069	±0.105	EXITPAD/CETAC
For moderate claudication	0.060	0.053	±0.051	±0.102	EXITPAD/CETAC
For severe claudication	0.139	0.059	±0.113	±0.151	EXITPAD/CETAC
For CLI	0.894		±0.049		29
Probability of major amputation					
For CLI	0.033		±0.029		29
Secondary intervention outcome					
After ER/OR from mild/moderate/severe claudication to					
Asymptomatic PAD	0.263		±0.198		EXITPAD/CETAC
Mild claudication	0.316		±0.209		EXITPAD/CETAC
Moderate claudication	0.158		±0.164		EXITPAD/CETAC
Severe claudication	0.263		±0.198		EXITPAD/CETAC
Death (within 30 days)	0.007		±0.005		36
After OR from CLI to‡					
Severe claudication	0.547		±0.026		26
CLI	0.206		±0.021		26
Amputation	0.091		±0.015		26
Death	0.156		±0.019		26
After ER from CLI to‡					
Severe claudication	0.552		±0.046		26
CLI	0.196		±0.037		26
Amputation	0.122		±0.053		26
Death	0.130		±0.031		26
After major amputation from CLI to					
Death (in hospital)	0.168		±0.005		32
Post major amputation	0.832		±0.005		32

*All values are presented per year; they were converted for the model into 3-monthly values to fit the cycle length. †All ranges presented here are 95 per cent confidence intervals. In the model a dirichlet (b) distribution determined the range of values used in probabilistic sensitivity analysis. ‡For the outcome endovascular revascularization (ER)/open revascularization (OR) for critical limb ischaemia (CLI) a composite probability was calculated, combining the presented transition probabilities, and assuming a 27 : 10 ratio of ER *versus* OR as reported by Frans *et al.*[29]. SET, supervised exercise therapy; PAD, peripheral arterial disease.

Table S3 Input transition probabilities.

	Value*		Range†		
	SET	ER	SET	ER	Source
From mild claudication to‡					
Asymptomatic PAD	0.359	0.308	±0.1089	±0.102	EXITPAD/CETAC
Mild claudication	0.385	0.436	±0.1121	±0.118	EXITPAD/CETAC
Moderate claudication	0.256	0.102	±0.0942	±0.062	EXITPAD/CETAC
Severe claudication	0.000	0.154	–	±0.075	EXITPAD/CETAC
From moderate claudication to‡					
Asymptomatic PAD	0.083	0.316	±0.0546	±0.107	EXITPAD/CETAC
Mild claudication	0.333	0.368	±0.0960	±0.115	EXITPAD/CETAC
Moderate claudication	0.393	0.211	±0.1006	±0.0881	EXITPAD/CETAC
Severe claudication	0.191	0.105	±0.0784	±0.063	EXITPAD/CETAC
From severe claudication to‡					
Asymptomatic PAD	0.111	0.471	±0.0640	±0.129	EXITPAD/CETAC
Mild claudication	0.361	0.294	±0.1099	±0.104	EXITPAD/CETAC
Moderate claudication	0.250	0.176	±0.0935	±0.081	EXITPAD/CETAC
Severe claudication	0.278	0.059	±0.0980	±0.047	EXITPAD/CETAC
From any claudication state to					
Critical limb ischaemia	0.064		±0.008		22
Death	0.053		±0.009		23
From asymptomatic PAD to					
Asymptomatic PAD	0.955		±0.051		24
Mild claudication	0.007§		±0.024		24
Moderate claudication	0.007§		±0.024		24
Severe claudication	0.007§		±0.024		24
Critical limb ischaemia	0.004		±0.019		24
Death	0.020		±0.037		24

Table S3 *Continued.*

	Value*		Range†		
	SET	ER	SET	ER	Source
From critical limb ischaemia to¶					
Critical limb ischemia	0.500		±0.106		25,26
Amputation	0.380		±0.101		25,26
Death	0.120		±0.024		26,27
From post major amputation to					
Post major amputation	0.775		±0.050		28
Death	0.225		±0.050		28

*All values are presented per year; they were converted for the model into 3-monthly values to fit the cycle length. †All ranges presented here are 95 per cent confidence intervals. In the model a dirichlet (b) distribution determined the range of values used in probabilistic sensitivity analysis. ‡Conditional on not transitioning to the critical limb ischaemia or death states. §Probabilities were divided by 3 to divide them over the three claudication states. ¶Considering conservative management: local wound care and pharmacotherapy alone. SET, supervised exercise therapy; ER, endovascular revascularization; PAD, peripheral arterial disease.

Table S4 Distribution across health states at 5 years.

	Distribution after 20 model cycles (%)	
	SET	ER
Asymptomatic PAD	49.9	51.8
Mild claudication	3.0	4.0
Moderate claudication	2.4	1.5
Severe claudication	3.7	1.9
Critical limb ischaemia	2.8	2.5
Post major amputation	0.3	0.3
Death due to PAD	16.9	17.0
Background death	21.0	21.0

SET, supervised exercise therapy; ER, endovascular revascularization; PAD, peripheral arterial disease.

Table S5 Model validation.

	Observed in source		Predicted in model	
	SET	ER	SET	ER
Internal validity				
Health state after 12 months (%)*				
Asymptomatic PAD†	31.8	38.6	32.8	37.7
Mild claudication	25.3	37.4	22.0	36.4
Moderate claudication	19.7	13.4	20.2	13.9
Severe claudication	23.2	10.7	25.0	12.0
External validity‡				
5-year outcomes (%)				
Critical limb ischaemia	1–3		2.8	2.5
Cardiovascular mortality	10–15		16.9	17
Major amputation	< 1		0.6	0.6
Repeat ER/OR	7–40		–	16.1
1-year outcomes (%)				
ER/OR after SET§	6.4		8.1	–

*Calculated after subtracting mortality and critical limb ischaemia incidence from the observed EXITPAD and CETAC data. Transitions from the asymptomatic peripheral arterial disease (PAD) health state were influenced by data input other than the combined EXITPAD and CETAC data in the Markov model; this is a probable explanation for discrepancies between the observed and predicted distribution. ‡Observed disease progression and intervention rates after 5 years were derived from the Society for Vascular Surgery practice guidelines, and compared with 5-year model outcomes. A wide spread for repeat endovascular revascularization (ER)/open revascularization (OR) is shown, as reported in the guidelines, as this is highly dependent on the technology used for revascularization and lesion characteristics. §Repeat revascularizations after 1 year of supervised exercise therapy (SET) were derived from invoice data from a large Dutch health insurance company, as reported by Fokkenrood *et al.*

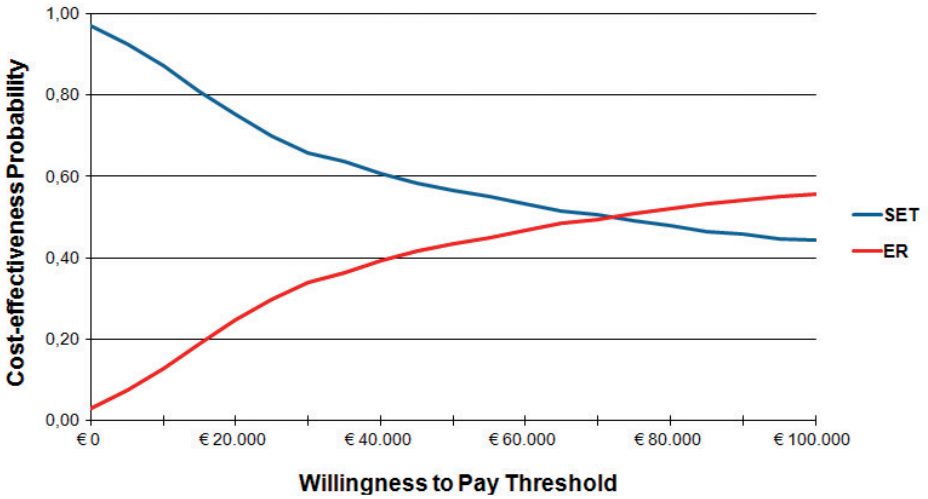


Fig. S1 Cost-effectiveness acceptability curves for lifetime horizon analysis showing the range of willingness-to-pay (WTP) thresholds for the treatment of intermittent claudication. The *x*-axis shows different WTP thresholds that society may be willing to pay to gain 1 quality-adjusted life-year considering a lifetime horizon. The *y*-axis shows the proportion of samples that demonstrated cost-effectiveness for supervised exercise therapy (SET) and endovascular revascularization (ER).

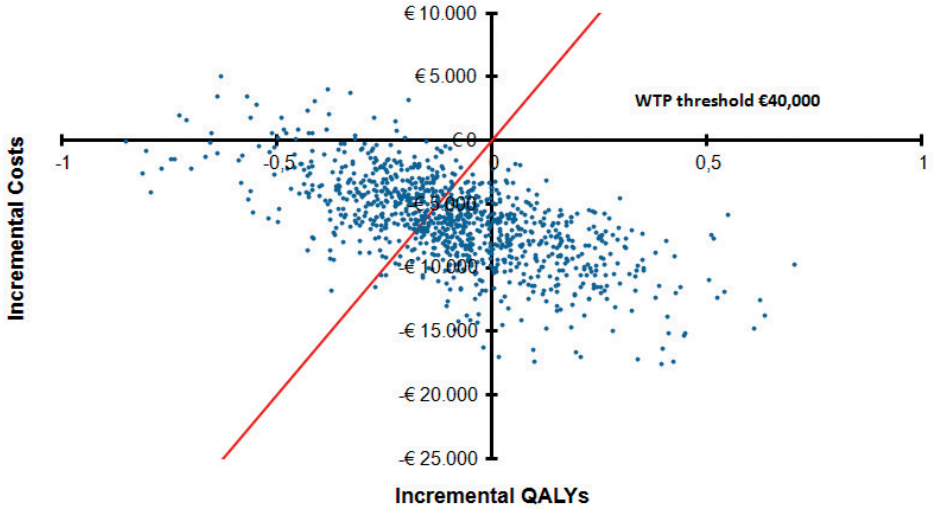


Fig. S2 Incremental cost-effectiveness plane for supervised exercise therapy (SET) *versus* endovascular revascularization (ER) in lifetime horizon analysis.The *x*-axis shows the incremental quality-adjusted life-years (QALYs), and the *y*-axis the incremental costs, for SET compared with ER. The differences in costs (incremental costs) and QALYs (incremental QALYS) are calculated for each of the 100 000 hypothetical patients over a lifetime and represented as a dot. The red line represents a €40 000 willingness-to-pay (WTP) threshold. SET was the preferable treatment in all samples below this line, constituting 61 per cent of the 1000 simulations.

SUPPLEMENTAL CONTENT CHAPTER 7

The effect of arterial disease level on outcomes of conservative management in intermittent claudication: A Prospective cohort study.

Contents

Supplemental Table 1. Walking speed used for treadmill testing per disease level group.

	Aortoiliac disease (n=59)	Femoral-popliteal disease (n=89)	Multilevel disease (n=59)	No disease (n=11)	*p*
Treadmill speed, no.					
2 km/h	1 (1.7%)	3 (3.4%)	7 (11.9%)	1 (9.1%)	
3.2 km/h	50 (84.%)	74 (83.1%)	49 (83.1%)	9 (81.8%)	0.19
4.4 km/h	8 (13.6%)	12 (10.4%)	4 (6.8%)	1 (9.1%)	

P values are added for overall comparison between groups using Pearson's χ^2

Supplemental Table 2. Multivariable linear regression analysis of factors independently correlated with change in maximal walking distance from baseline at 6 months.

	Multivariable model		Final model	
Variables	*P* value	Beta per unit	*P* value	Beta per unit
Female sex	0.65	15	0.61	21
Age, y	0.24	4	0.31	3
Body mass index, kg/m^2	0.18	-11	0.19	-10
ABI in rest	0.45	-149	-	-
ABI after exercise	0.30	-206	-	-
Smoking status			-	-
Never	0.47	-63		
Current smoker	0.74	17	-	-
Former smoker	Reference	Reference	-	-
Diabetes Mellitus	0.55	-38	-	-
Hypercholesterolemia	0.55	-31	-	-
Hypertension	0.48	53	-	-
Kidney disease	0.60	-52	-	-
Cerebrovascular disease	0.42	59	-	-
Heart failure	0.56	-86	-	-
COPD	0.28	-82	0.16	-112
Prior ER	0.25	-114	0.093	-143
Prior OR	0.42	-128	-	-
Symptomatic leg	0.42	-45	-	-
TASC score			0.61	-6
TASC A	0.61	2.6	-	-
TASC B	0.39	0.39	-	-
TASC C	0.18	0.18	-	-
TASC D	Reference	Reference	-	-

ABI indicates ankle brachial index; COPD, chronic obstructive pulmonary disease; ER, endovascular revascularization; OR, open revascularization.

Supplemental Table 3. Unadjusted mean changes from baseline after 3 and 6 months of SET in patients with IC, according to disease level, for the complete case.

	Aortoiliac (n=70)		Femoropopliteal (n=115)		Multilevel (n=69)		No disease (n=13)		*P* value overall		*P* value AoI vs FP	
Outcome Measures	3 Months change	6 Months change	3 Months change	6 Months change	3 Months change	6 Months change	3 Months change	6 Months change	3mo change	6mo change	3mo change	6mo change
MWD, m	*n=57*	*n=46*	*n=88*	*n=77*	*n=55*	*n=43*	*n=11*	*n=11*				
Mean	271	481	418	531	253	302	361	357	0.093	0.13	0.032	0.50
95% CI	173-370	340-623	326-511	422-640	175-331	209-396	106-616	137-577				
FWD, m	*n=56*	*n=45*	*n=87*	*n=77*	*n=54*	*n=42*	*n=11*	*n=11*				
Mean	308	537	407	514	244	307	384	276	0.19	0.037	0.23	0.96
95% CI	203-412	387-688	307-507	399-629	163-325	205-409	119-650	101-451				
6MWT, m	*n=51*	*n=41*	*n=83*	*n=73*	*n=49*	*n=41*	*n=11*	*n=10*				
Mean	42	80	34	46	43	52	0	6	0.28	0.36	0.81	0.40
95% CI	14-71	21-139	18-49	28-64	22-65	12-93	-29-29	-46-59				
Vascuqol-6	*n=55*	*n=45*	*n=86*	*n=78*	*n=54*	*n=45*	*n=11*	*n=10*				
Mean	1.4	3.6	2.4	3.7	2.4	2.8	2.6	3	0.65	0.46	0.20	0.88
95% CI	0.3-2.5	2.3-4.9	1.6-3.1	2.8-4.5	1.1-3.7	1.5-4.2	-0.5-5.8	0.3-5.7				

P values are added for overall comparison between groups using Kruskal-Wallis rank sum test, and between aortoiliac and femoropopliteal disease using Mann Whitney U.

6MWT indicates 6-minute walking test; AoI, aortoiliac; CI, confidence interval; FP, femoral-popliteal. FWD, functional walking distance; MWD, maximal walking distance.

Supplemental Table 4. Adjusted mean changes from baseline after 3 and 6 months of SET in patients with IC, according to disease level, for the complete case.

	Aortoiliac (n=70)		Femoropopliteal (n=115)		Multilevel (n=69)		No disease (n=13)		*P* value overall		*P* value AoI vs FP	
Outcome Measures	3 Months change	6 Months change	3 Months change	6 Months change	3 Months change	6 Months change	3 Months change	6 Months change	3 Months	6 Months	3 Months	6 Months
MWD, m	*n=35*	*n=26*	n=40	*n=36*	*n=28*	*n=25*	*n=10*	*n=9*				
Mean	265	395	305	406	279	292	306	423	0.97	0.65	0.64	0.91
95% CI	104-425	203-588	156-454	244-568	102-457	97-487	-40-651	43-805				
FWD, m	*n=35*	*n=26*	n=40	*n=36*	*n=28*	*n=25*	*n=10*	*n=9*				
Mean	300	487	334	350	273	291	404	357	0.83	0.27	0.70	0.15
95% CI	134-466	302-671	180-488	194-506	90-456	104-478	47-760	-8-723				
6MWT, m	*n=35*	*n=26*	n=40	*n=36*	*n=28*	*n=25*	*n=10*	*n=9*				
Mean	43	92	39	31	57	56	4	9	0.58	0.37	0.84	0.12
95% CI	2-85	16-168	1-77	-32-95	12-103	-21-132	-85-93	-141-159				
Vascuqol-6	*n=35*	*n=26*	n=40	*n=36*	*n=28*	*n=25*	*n=10*	*n=9*				
Mean	0.6	3.6	2.4	3.4	2.9	2.6	3.5	5.2	0.099	0.58	0.078	0.86
95% CI	-1.2-2.5	1.4-5.8	0.7-4.2	1.5-5.2	0.9-5.0	0.3-4.8	-0.5-7.5	0.8-9.5				

Covariates used for adjustment include age, sex, body-mass index, comorbid chronic obstructive pulmonary disease, prior endovascular revascularization, and TASC score (154 patients excluded due to missing values at 3 months, 171 excluded at 6 months).
P values are added for overall comparison between all four groups and between aortoiliac and femoropopliteal disease using one-way MANCOVA *F*-test.
6MWT indicates 6-minute walking test; AoI, aortoiliac; CI, confidence interval; FP, femoral-popliteal. FWD, functional walking distance; MWD, maximal walking distance.

Supplemental Table 5. Adjusted mean changes from baseline after 3 and 6 months of SET in patients with IC, according to disease level, excluding patients who underwent early revascularization.

	Aortoiliac (n=50)		Femoropopliteal (n=99)		Multilevel (n=51)		No disease (n=13)		*P* value overall		*P* value AoI vs FP	
Outcome Measures	3 Months change	6 Months change	3 Months change	6 Months change	3 Months change	6 Months change	3 Months change	6 Months change	3 Months	6 Months	3 Months	6 Months
MWD, m												
Mean	281	401	413	481	315	361	388	415	0.26	0.42	0.081	0.35
99% CI	132-431	233-568	309-517	365-597	166-465	194-528	69-708	57-772				
FWD, m												
Mean	326	461	407	511	300	394	453	425	0.37	0.46	0.30	0.50
99% CI	170-481	289-633	299-515	392-630	144-455	222-565	120-785	58-792				
6MWT, m												
Mean	37	61	34	40	55	61	-17	1	0.098	0.28	0.68	0.41
99% CI	7-67	18-104	13-55	10-70	24-85	17-104	-81-47	-92-104				
Vascuqol-6												
Mean	1.6	2.6	2.8	3.7	2.8	2.5	3.4	5.6	0.32	0.11	0.12	0.16
99% CI	0.1-3.2	1-4.1	1.8-3.9	2.6-4.8	0.7-3.8	0.9-4.1	0.1-6.7	2.2-9.0				

Covariates used for adjustment include age, sex, body-mass index, comorbid chronic obstructive pulmonary disease, prior endovascular revascularization, and TASC score (4 patients excluded due to missing TASC score).

P values are added for overall comparison between all four groups and between aortoiliac and femoropopliteal disease using one-way MANCOVA *F*-test.

6MWT indicates 6-minute walking test; AoI, aortoiliac; CI, confidence interval; FP, femoral-popliteal. FWD, functional walking distance; MWD, maximal walking distance.

Supplemental Table 6. Adjusted mean changes from baseline after 3 and 6 months of SET in patients with IC with inflow disease versus outflow disease.

	Inflow stenosis (n=137)		**Outflow stenosis (n=113)**		**P value**	
Outcome Measures	3 Months change	6 Months change	3 Months change	6 Months change	3 Months change	6 Months change
MWD, m						
Mean	271	397	383	468	0.044	0.28
95% CI	186-357	299-496	289-478	359-577		
FWD, m						
Mean	287	423	382	497	0.083	0.31
95% CI	198-375	322-523	284-480	386-609		
6MWT, m						
Mean	50	63	33	41	0.20	0.27
95% CI	30-69	32-93	12-55	7-74		
Vascuqol-6						
Mean	1.8	3.2	2.6	4	0.20	0.20
95% CI	0.8-2.7	2.2-4.1	1.6-3.7	2.9-5.1		

Covariates used for adjustment include age, sex, body-mass index, comorbid chronic obstructive pulmonary disease, prior endovascular revascularization, and TASC score (4 patients excluded due to missing TASC score).
P values are added for comparison using one-way MANCOVA *F*-test.
6MWT indicates 6-minute walking test; AoI, aortoiliac; CI, confidence interval; FP, femoral-popliteal. FWD, functional walking distance; MWD, maximal walking distance.

Supplemental Table 7. Multivariable analysis for predictors of early revascularization at 6-months clinical follow-up.

	Initial model			Final model		
Variables	*P* value	HR	99% CI	*P* value	HR	99% CI
Female sex	0.87	1.060	0.41 – 2.71	-	-	-
Age, y	0.077	0.96	0.91 – 1.02	0.18	0.98	0.94 – 1.02
Body mass index, kg/m²	0.22	0.94	0.83 – 1.07	-	-	-
ABI in rest	0.024	0.059	0.002 – 1.48	0.001	0.034	0.002 – 0.48
ABI after exercise	0.55	0.50	0.025 - 10	-	-	-
Smoking status						
Never		Reference				
Current smoker	0.69	0.81	0.22 – 3.06	-	-	-
Former smoker	0.33	0.60	0.15 – 2.33	-	-	-
Diabetes Mellitus	0.77	0.89	0.31 – 2.56	-	-	-
Hypercholesterolemia	0.22	1.59	0.60 – 4.19	-	-	-
Hypertension	0.99	1.00	0.39 – 2.56	-	-	-
Kidney disease	0.50	0.69	0.16 – 2.89	-	-	-
Cerebrovascular disease	0.54	0.72	0.18 – 2.88	-	-	-
Heart failure	0.52	0.56	0.053 – 5.83	-	-	-
COPD	0.49	1.35	0.45 – 4.04	-	-	-
Prior ER	0.15	1.83	0.61 – 5.48	0.11	1.78	0.71 – 4.45
Prior OR	0.48	0.55	0.060 – 4.95	-	-	-
Baseline MWD, m	0.23	1.0	0.997 – 1.001	-	-	-
Baseline 6-minute walking test, m	0.12	1.0	0.99 – 1.002	0.068	1.00	0.99 – 1.001
Bilateral symptoms	0.13	0.59	0.24 – 1.47	0.055	0.56	0.26 – 1.22
Location of stenosis*						
Aortoiliac	0.093	2.29	0.64 – 8.14	0.040	2.37	0.81 – 6.95
Femoropopliteal	0.40	0.67	0.20 – 2.27	0.13	0.54	0.19 – 1.54
Multilevel		Reference			Reference	
TASC score						
TASC A	0.19	1.68	0.61 – 4.65	0.81	1.16	0.24 – 5.52
TASC B	0.33	1.69	0.43 – 6.69	0.26	1.91	0.44 – 8.34
TASC C	0.89	1.10	0.20 – 6.11	0.34	1.84	0.36 – 9.31
TASC D		Reference			Reference	

* Excluding the 'no disease' group due to absence of lesions appropriate for intervention.
ABI indicates ankle brachial index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ER, endovascular revascularization; MWD, maximal walking distance; OR, open revascularization.

Appendices

LIST OF PUBLICATIONS

Publications in this thesis

van den Houten MML, Jansen S, van der Laan L, Vriens PWHE, Willigendael EM, Koelemay MJW, Scheltinga MRM, Teijink JAW; ELECT Study Group. *The Effect of Arterial Disease Level on Outcomes of Supervised Exercise Therapy for Intermittent Claudication: A Prospective Cohort Study.* Ann Surg. 2022 Mar 1;275(3):609-616.

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CURRICULUM VITAE

Marijn Marinus Leonardus van den Houten was born on February 24 1992 in Eindhoven, the Netherlands. In 2010 he graduated cum laude from secondary school at Pleincollege Eckart in Eindhoven. From 2010 he studied Medicine at the University of Maastricht from where he followed an elective internship at the Surgery department of the Akademisch Ziekenhuis Paramaribo, in Surinam. During his Master's degree he participated in a vascular research project in the Vascular Surgery department of the Catharina Hospital. This project resulted in a PhD Track under the supervision of prof. dr. Joep A.W. Teijink and dr. Marc R.M. Scheltinga. After obtaining his Medical Degree (cum laude) in 2016, he started working formally as a PhD Candidate at the Vascular Surgery department of the Catharina Hospital, affiliated to CAPHRI Research School (Maastricht University). He simultaneously worked as Medical Coordinator for ClaudicatioNet, where he was responsible for the schooling of physical therapists and various projects including the quality initiative and the development and testing of a smartphone application. In October 2018 he continued his medical career as a resident. First at the Intensive Care Department of the Catharina Hospital in Eindhoven, and from August 2019 at the General Surgery Department. He started his training as general surgeon as of July 2020 under supervision of dr. Simon W. Nienhuijs and dr. Grard A.P. Nieuwenhuijzen. Marijn lives together with his girlfriend Checca in Eindhoven.

Appendices

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