Intermittent claudication : results of exercise therapy and endovascular interventions in perspective

INTERMITTENT CLAUDICATION

Results of exercise therapy and endovascular interventions in perspective

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INTERMITTENT CLAUDICATION

Results of exercise therapy and
endovascular interventions in perspective

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The studies presented in this thesis were performed at the Atrium medical centre Parkstad located in Heerlen, The Netherlands, in collaboration with the School for Public Health and Primary Care (Caphri) of the University of Maastricht and the Dutch Platform of Peripheral Arterial Disease (NPPAV).

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Voor Pap & Mam

Thuis

Alsof je een plek bereikt.
Om je heen kijkt en weet
dat je thuis bent.

Een weiland, vergeten
langs duinen en bosrand,
iemand buigt tussen jou
en een feest - op zoek
naar de wijn, een gezicht
wordt zijn eerste woorden,
wat geschreven werd voor jou
door een nooit gevoelde hand.

Alsof je dit al kende
voor je het zag. Er geweest was
voor je er zou komen.

Zo thuis.

(Kees Spiering)

PART ONE **SUPERVISED EXERCISE THERAPY IN PRACTICE**

PART TWO **TREATMENT OF INTERMITTENT CLAUDICATION COMPARED AND IMPROVED**

CHAPTER 1

INTRODUCTION AND OUTLINE OF THE THESIS

BACKGROUND

Atherosclerosis is a systemic disease that can affect every artery of the human body, however it mainly affects the coronary, cerebral and lower extremity arteries. Within the intima of the vascular wall, lipids, inflammatory cells, and smooth muscle cells accumulate, forming an atherosclerotic plaque. Clinical manifestations of atherosclerosis can be acute or chronic. Acute manifestations, like a heart attack or acute critical ischemia of the leg, are thought to occur when an atherosclerotic plaque ruptures, and/or the thrombogenic content of the plaque comes in contact with coagulation factors and causes the formation of a thrombus, that instantly can occlude the artery.[1-3] More chronic manifestations like angina pectoris or peripheral arterial disease (PAD) of the lower extremities, are probably caused by slow, but progressively narrowing of the affected artery by an atherosclerotic plaque.[3]

PAD of the lower extremities is a common condition in the elderly with a prevalence of 18 to 20 percent in the general population of the Netherlands aged 55 years or older.[4] However, the majority of these patients has asymptomatic or atypical disease.[5] Intermittent claudication, that is muscular leg pain that occurs with walking and is relieved in rest, is only reported by approximately 6% of the patients with PAD.[4] Furthermore, only 1 – 3% of the patients with PAD present with critical limb ischemia, and have pain when resting, or tissue loss.[5] The studies described in this thesis will focus on patients with symptoms of intermittent claudication. For most patients with intermittent claudication, amputation is their major fear. However, the fate of the leg is favourable with an amputation rate of less than 2% in patients with symptoms of intermittent claudication.[5] In contrast, patients have an increased risk on cardio- and cerebrovascular morbidity and mortality, as PAD is a marker of generalised atherosclerotic disease. Based on data in the absence of widespread use of vascular risk management the 10-year mortality rate of men with PAD is 62%, compared to 17% in the population of men without PAD. For women with PAD 10-year mortality is 33% compared to 12% in the population without PAD. This difference in total mortality was due to a sharp increase in cardiovascular death for patients with PAD.[6] Indeed, all patients with PAD, according to current guidelines should be treated with a platelet inhibitor and a statin (cholesterol lowering medication) to lower the risk of cardiovascular death. Furthermore, all patients with PAD should receive advice on smoking cessation and be treated for existing vascular risk factors like hypertension and diabetes mellitus.[7]

Although the prognosis for the affected limb in terms of amputation is favourable, patients with intermittent claudication score considerably worse for many measures of quality

of life and functional capacity as assessed by treadmill walking distance compared to individuals without PAD.[8,9] Treatments used to improve functional capacity and quality of life are (supervised) exercise therapy, percutaneous and surgical vascular interventions.

EXERCISE THERAPY

The earliest suggested therapy for patients with intermittent claudication was exercise therapy. In 1898, Wilhelm Erb first described the results of a patient with intermittent claudication that was successfully treated with exercise.[10] The results of the first randomised clinical trial were reported in 1966 by Larsen et al.[11] In this study 7 patients were instructed to take a daily walk of at least one hour, besides their normal activities. Patients had to walk until claudication pain forced cessation of exercise and, after a period of rest until the pain disappeared, patients had to repeat the exercise. The 7 patients in the control group were given "medical treatment" in the form of lactose tablets. For the group treated with exercise, a significant increase in maximum walking time was seen, whereas the patients in the control group did not improve their walking distance.
Nowadays, exercise therapy is extensively studied, and according to several guidelines the therapy of first choice for patients with complaints of intermittent claudication.[5,7,12] The optimal training program for patients with intermittent claudication should be based on repeated walking until near-maximal pain followed by a short period of rest in a frequency of at least 3 times a week for 30 minutes during a period of at least 6 months.[13] However, the adherence of patients given an oral exercise advice is low. Co-morbidity, lack of (specific) advice, and lack of supervision are barriers to actually perform walking exercise.[14] Supervised exercise therapy (SET) performs better in increasing walking distance compared to an oral exercise advice.[15] The Trans-Atlantic Inter-Society Consensus Document on the management of PAD (TASC-II) recommends with 'level A evidence' that supervised exercise should be made available as part of the initial treatment for all patients with PAD.[5] However, in routine clinical practice most patients only receive an oral advice to increase their walking activities, since supervised exercise programs are not universally available and implemented in daily care for patients with PAD.

INVASIVE INTERVENTIONS

From a surgical point of view, treatment for PAD aims at bypassing or removing the arterial obstruction to create a patent blood flow to the lower extremities. The first endarterectomy of the arteria femoralis communis was performed by Cid Dos Santos in 1946.[16] Two years later, Jean Kunlin performed the first bypass procedure with a venous graft to overcome a obstruction in the arteria femoralis communis.[17] The first percutaneous vascular intervention (PVI) was a balloon dilatation and performed by Charles Dotter in 1964 in a patient with advanced gangrene who refused an amputation.[18] Since then, this technique was further developed. Intravascular stents have been increasingly used to support the vascular wall after angioplasty, as there is a tendency for the plaque to return to the original configuration after deflating the balloon.[2]

Nowadays, the general consensus is that patients with critical limb ischemia should be treated with invasive techniques to restore blood flow and prevent amputation.[5, 7] The treatment of intermittent claudication however, is heavily debated. Since the prognosis of the leg is favourable, intermittent claudication was mainly treated conservatively, as this is a safe and effective treatment. However, with the rise of the relatively safe PVIs (in comparison with surgery), PVI's are increasingly used for the treatment of intermittent claudication. Benefit of a PVI is the immediate result following treatment, in contrast with the results of conservative treatment that occur slowly.

Effectiveness of a PVI is usually described with initial success and patency rates. Although these are interesting outcome measurements for a physician, patients are more concerned about walking distance and quality of life. However, in literature mainly hemodynamic outcome measurements are reported. The initial success rate of an aorto-iliac procedure is approximately 90%, ranging from 80-85% for iliac occlusions to 98% for iliac stenoses.[19] The primary patency of aorto-iliac PVIs for intermittent claudication ranges from 60% for an iliac occlusion without stent placement to 75% for an iliac stenosis with stent placement after 3 years of follow up.[19]

The initial success rate for a femoro-popliteal procedure is corresponding with iliac procedures and approximately 90%, ranging from 81% (long femoral occlusions)[20] to 98% (femoral stenoses).[19] However, the patency rates are considerably worse with percentages of 50% to 60% after 3 years of follow up.[19] Therefore, in the TASC-II guideline,[5] it is recommended that aorto-iliac atherosclerotic disease should be considered for primary treatment with PVI.

AIMS AND OUTLINE OF THE THESIS

The general purpose of this thesis is to describe the most frequently used treatments for intermittent claudication (exercise and endovascular therapy) from different perspectives. From a patient perspective we focus on walking distance and quality of life as outcome measurements. From a research perspective we focus on effectiveness of treatments and exploring variables that influence effectiveness. Finally, from a health care perspective we focus on implementation of exercise therapy in daily care.
The first part (supervised exercise therapy in practice) focuses on the functioning of SET in a community-based setting as primary treatment for patients with intermittent claudication. Furthermore, patient related variables that could influence the effectiveness of SET are explored. In the second part of the thesis (treatment of intermittent claudication: compared and improved) the effectiveness of different treatments were compared using meta-analysis. Furthermore, patient and treatment related variables influencing results of PVI are described.

PART ONE: SUPERVISED EXERCISE THERAPY IN PRACTICE
The importance of supervised exercise programs for patients with intermittent claudication is increasingly acknowledged. However, only small and local initiatives for SET are currently known, and the main exercise prescription is still "go home and walk". Therefore, in 2003, our research group implemented a community-based network for SET to be able to treat all patients with intermittent claudication.[21] Nowadays, patients in our centre are primarily treated with community-based SET for their complaints of intermittent claudication.
In chapter 2 an overview is given of recent studies conducted by our research group about implementing SET in clinical practice and the first results of this community-based approach. In chapter 3 the reproducibility and validity of a new outcome measurement is tested; the functional claudication distance (FCD), defined as the distance after which a patient prefers to stop exercise because of claudication pain. This outcome measurement is used in the majority of the studies described in this thesis, besides more commonly used outcome measurements. Chapter 4 describes the results at 1 year follow up of community-based SET as a part of clinical practice. Walking distances, loss to follow up, comparison with literature, and the clinical course of patients are discussed. Based on results from chapter 4, indicating that community based SET is effective, but not to all patients, we decided to search for patient related variables that could explain the dif-

ference between patients. In chapter 5 the potential difference in effectiveness of SET between patients with and without diabetes mellitus is addressed. Chapter 6 explores the possibility to predict results of SET with the help of patient related variables that exist at baseline.

PART TWO: TREATMENT OF INTERMITTENT CLAUDICATION COMPARED AND IMPROVED

Treatments, other than exercise training are increasingly used for symptomatic relief of intermittent claudication, especially endovascular treatments. According to guidelines certain subgroups of patients (e.g. aorto-iliac disease, higher success rate) can be considered for primary revascularisation.[5,7] In line with these recommendations, in our centre, we tend to treat patients with aorto-iliac disease primarily with a PVI. However, there is an ongoing discussion about the effectiveness. De Vries and collegues[22] concluded, based on a Markov decision model that endovascular treatment is more effective than exercise and, moreover, cost-effective. However, in a well designed randomised clinical trial comparing SET with PVI, the two treatments were equally effective in increasing walking distance and quality of life.[23] The cost-effectiveness of this trial concluded that endovascular treatment in general was more expensive than SET, favouring SET as primary treatment for intermittent claudication.[24] The debate is well illustrated in a critical article of Cao and De Rango[25] stating "Endovascular treatment of PAD: So old yet so far from evidence."

In chapter 7 we provide an overview of the most used treatments for intermittent claudication and their effectiveness in improving walking distance and quality of life. To use all available evidence, both direct as indirect evidence was used in a so-called network meta-analysis. Chapter 8 explores patient related variables that could possibly influence walking distance and persisting claudication complaints post-PVI. With the results of this study we hope to identify subgroups of patients who are likely to benefit more from a PVI. Little is known about the additional value of SET following a PVI. Chapter 9 describes the results of a randomised clinical trial that examines the effectiveness of SET following PVI compared to PVI alone.

Finally in chapter 10, the main findings of this thesis are summarised and discussed. Methodological aspects of the different studies, implications for clinical practice, and implications for future research are described.

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PART ONE **SUPERVISED EXERCISE THERAPY IN PRACTICE**

CHAPTER 2

SUPERVISED EXERCISE THERAPY FOR INTERMITTENT CLAUDICATION IN A COMMUNITY-BASED SETTING

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ABSTRACT

- Supervised exercise therapy programmes have significant benefits compared with non-supervised programmes.
- Community-based supervised exercise therapy has both economic and logistic advantages over clinic-based supervised exercise therapy.
- Community-based supervised exercise therapy programmes seem to be as effective as supervised exercise therapy provided in a clinic-based setting and are a promising approach to providing conservative treatment for patients with intermittent claudication.
- Supervised exercise therapy in a community-based setting should ideally be the initial standard of care for patients with intermittent claudication, but a study of cost-effectiveness should be awaited.

INTRODUCTION

The primary and most effective treatment for patients with intermittent claudication is exercise therapy.[1] An overall improvement in maximal walking ability of approximately 150% has been described, whereas significant improvements in walking time have been shown when comparing exercise with angioplasty or antiplatelet therapy.[2] In regular care, exercise therapy is usually prescribed in the form of advice to 'go home and walk', without supervision or follow-up.[3,4] Yet, there is no evidence to support the efficacy of this advice, and compliance is known to be low.[3,5] Factors such as fear of pain, inadequate knowledge and poor general condition contribute to the difficulty of starting, sustaining and maintaining exercise therapy.[3] Supervised exercise therapy entails adequate coaching to increase the maximal walking distance as well as coaching in the necessary changes in lifestyle, such as smoking cessation, weight control and an increase in overall exercise. Unfortunately, supervised programmes are available only sporadically.[6] The supervised programmes described in the literature so far have been provided in a clinic-based setting. In our hospital, however, we have observed that supervised exercise therapy in a clinic-based setting has several disadvantages:

- Limited capacity. Three half-hour sessions weekly per patient proved overly time-consuming for an already busy physiotherapy and rehabilitation department. Consequently, only a limited number of patients can be offered clinic-based supervised exercise therapy.
- High transport costs. Journeys to and from the hospital, especially using public transport, are costly for many patients.
- Time-consuming. The need to visit the hospital two or three times a week in the initial phase can be problematic for a majority of patients, especially for those who do not live near the hospital.

In this paper, supervised exercise therapy will be compared with non-supervised exercise therapy programmes, and the superiority of supervised therapy will be demonstrated. Based on this knowledge as well as our experience with clinic-based supervised exercise therapy, a new community-based concept of supervised exercise therapy was developed and implemented; its development and implementation will be addressed. Furthermore, the first results of this community-based therapy programme will be presented and compared with the results of supervised exercise therapy programmes provided in clinical settings, as described in literature.

SUPERVISED VERSUS NON-SUPERVISED EXERCISE THERAPY

Eight clinical trials, all involving a small number of patients (20–59), have compared supervised with non-supervised exercise therapy.[5,7–13] A meta-analysis of their data on walking distance has consistently demonstrated statistically significant and clinically relevant differences in improvement of walking distances in favour of supervised exercise therapy.[14] The reported data for walking time and distance were standardized so that the difference in increase between the two treatment groups could be calculated. Translating the standardized data back to walking distances, the summary estimates of the maximal treadmill walking distance showed an approximately 150 m difference in increase in favour of the supervised over the non-supervised exercise regimen after 3 months of therapy. This difference was maintained at 6 months (table 1).

In order to determine the clinical relevance of the ability to walk 150 m further, one should realize that a mean maximal walking distance at baseline is approximately 300 m, with an even shorter pain-free walking distance of approximately 200 m. Hence, these mostly elderly patients with symptomatic peripheral arterial disease become more independent after increasing their walking distance. However, differences in quality of life, measured in 4 out of 8, trials were not striking.

There are several plausible mechanisms that might explain the beneficial results of supervised over non-supervised exercise therapy regimens. A first explanation could be the fact that the regimen of the supervised exercise therapy group mainly consisted of treadmill-walking, which has a higher workload than the level-ground walking at 'normal' speed used by the non-supervised group.[8]

It is difficult to measure the intensity of training, but it is generally assumed that home training cannot be considered to be performed with the same energy as training under supervision.[10]

Second, a higher workload will lead to a larger positive effect on the patient's general physical condition, possibly due to increased cardiovascular stress, providing a better stimulus for exercise-induced adaptation. A small study was able to show a relationship between general physical condition and walking distance in the current population by using upper-limb exercise to increase maximal walking distance.[15] Furthermore, a supervised programme could offer patients additional encouragement and motivation, with a higher adherence rate.

Nevertheless, in terms of compliance, nothing can be suggested from the contrasting results of the two trials[7,8] about the influence of a supervised exercise regimen. However, compliance in a supervised exercise setting is easily measurable during the session, unlike that during home-based intervals or in home-based settings. A possible solution to difficulties in measuring compliance during home-based exercise is a personal activity monitor, a small device that patients should wear all day. By means of a storage function, the amount of activity can thus be measured. The usefulness of a personal activity monitor in patients with intermittent claudication for increasing compliance is currently being determined.

Table 1. Estimates of effect on maximal treadmill walking distance / time

Outcome	Trial	Reported value Mean (SD)		Estimate of effect
		SET	nonSET	Effect (95%-CI)
3 months	Nielsen[10]	N = 25	N = 26	–0.39
		2.3 min (1.4 min)	2.9 min (1.6 min)	(–0.95 – 0.16)
	Patterson[5]	N = 25	N = 23	0.73
		9.9 min (4.9 min)	8.5 min (4.9 min)	(0.15 – 1.32)
	Regensteiner[12]	N = 10	N = 10	0.96
		10.9 min (4.5 min)	6.5 min (4.2 min)	(0.02 – 1.89)
	Savage[13]	N = 11	N = 10	0.27
		833.3 m (376.3 m)	736.5 m (290.3 m)	(–0.59 – 1.13)
	Degischer[8]	N = 19	N = 21	0.91
		905.6 m (439.8 m)	588.5 m (212.9 m)	(0.25 – 1.56)
	Cheetham[7]	N = 28	N = 28	1.21
		220.0 m (80.9 m)	119.0 m (80.9 m)	(0.64 – 1.79)
Overall effect: 0.58 (0.31, 0.85) (P<0.0001), 150 m difference in increase				
6 months	Patterson[5]	N = 19	N = 19	1.21
		14.6 min (6.1 min)	8.5 min (3.1 min)	(0.51 – 1.91)
	Savage[13]	N = 11	N = 10	0.07
		741.9 m (365.6 m)	715.0 m (394.4 m)	(–0.78 – 0.93)
	Degischer[8]	N = 19	N = 21	0.88
		846.0 m (397.2 m)	551.6 m (241.9 m)	(0.23 – 1.53)
	Cheetham[7]	N = 28	N = 28	1.24
		302.0 m (102.4 m)	174.0 m (102.4 m)	(0.66 – 1.81)
	Kakkos[9]	N = 12	N = 9	0.38
		220.0 m (282.5 m)	140.0 m (60 m)	(–0.58 – 1.35)
Overall effect: 0.89 (0.57, 1.21) (P<0.0001), 225 m difference in increase				

SUPERVISED EXERCISE THERAPY PROVIDED IN A COMMUNITY-BASED SETTING

Based on the knowledge that supervised exercise therapy is more effective than non-supervised exercise therapy, as well as the abovementioned disadvantages of supervised exercise therapy in a clinic-based setting, a new community-based concept of supervised exercise therapy was developed and implemented – the so-called Network for Exercise Therapy, Parkstad (NETP).[16]
We hypothesized that the community-based network of well-distributed physiotherapy practices would offer supervised exercise therapy closer to patients' homes and consequently lower transport costs and time.

DEVELOPMENT AND IMPLEMENTATION OF THE NETP

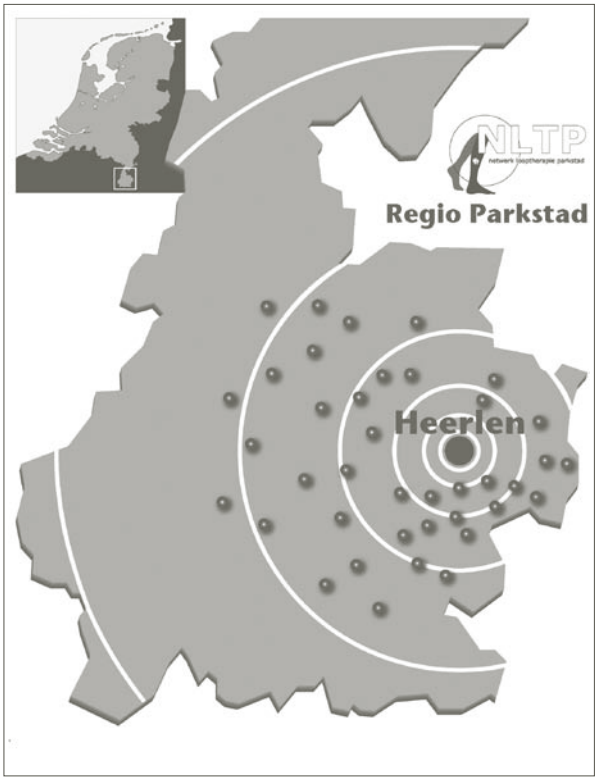
In October 2003, all 59 regional physiotherapy practices (including over 100 physiotherapists) were invited to attend a mini-symposium on supervised exercise therapy in a physiotherapy setting. Physiotherapists interested in providing exercise therapy were asked to register, and five physiotherapists were invited to join a steering committee. Within the steering committee, four task groups were formed:

1. exercise therapy education;
2. exercise therapy implementation;
3. inter-professional communication;
4. exercise therapy prolongation.

In June 2004, an accredited 2-day in-hospital educational programme on supervised exercise therapy was provided by the Royal Dutch Society for Physiotherapy and the Dutch Paramedic Institute. Twenty-nine practices were selected, equally dispersed over the south-east part of Limburg as well as the department of physiotherapy and rehabilitation in our own hospital (figure 1). In total, 30 practices are participating in the NETP, this number addressing the previously mentioned problem of the capacity of clinic-based supervised exercise therapy.
To facilitate inter-professional communication, as well as for research purposes, a web-based database was developed. As supervised exercise therapy is reimbursed for a period of only 1 year, three walking groups were set up (once a week each) based on volunteers (former NETP patients) as well as physiotherapy students from the Hogeschool Zuyd (Physiotherapy Academy) in Heerlen acting as coaches. After 1 year of supervised exercise therapy (or even during that year), patients could join the nearest walking group

for a once-a-week training session. Smoking is strictly prohibited at these sessions.
After implementing the NETP, patients with peripheral arterial disease who are eligible for supervised exercise therapy are referred to a nearby physiotherapist participating in the network. Over a period of 1 year, each patient receives approximately 30 physiotherapy sessions. Reimbursement from the tenth session for the remainder of the 12 months is financed by National Insurance of Health Care (AWBZ). Reimbursement for the initial nine sessions depends on the patient's insurance policy.

Figure 1. Network of Exercise Therapy, Parkstad



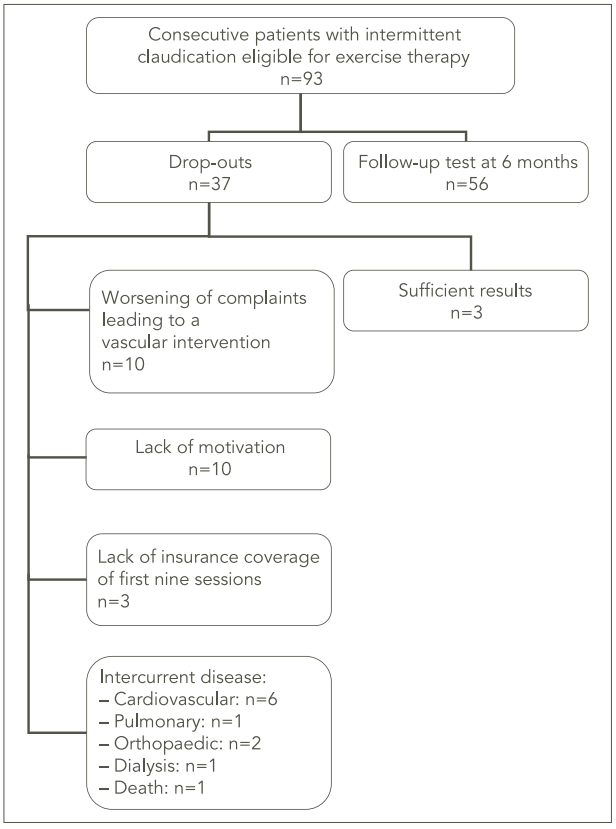
SUPERVISED EXERCISE THERAPY PROGRAMME

Supervised exercise therapy was administered according to the guidelines of the Royal Dutch Society for Physiotherapy.[17] The mode of exercise was mainly treadmill walking up to maximal pain, alternating with other cardiovascular training and strength training. During the training sessions, walking patterns were corrected to ameliorate the quality of walking. In general, patients received two to three sessions a week of approximately

30 minutes each in the initial phase, phasing down to once every 2 weeks and then once every month. Additionally, patients were encouraged to exercise daily by walking as much as possible to near-maximal pain.

To evaluate supervised exercise therapy in time, walking distances were measured by a progressive treadmill exercise test with a constant walking speed of 3.2 km per hour beginning at 0% incline with an increasing gradient of 2% every 2 minutes. The outcomes for walking distance were the initial and absolute claudication distances. The initial claudication distance was defined as the moment at which the patient preferred to stop because of pain when no supervision was provided. The absolute claudication distance was defined as the maximal possible walking distance.

Figure 2. Flowchart of analyzed population



FIRST RESULTS OF THE NETP PROGRAMME

From January to October 2005, 93 consecutive patients with intermittent claudication were eligible for community-based supervised exercise therapy and were included in the study cohort. During the 6-month study period, 37 patients (39.8%) discontinued the programme (figure 2). Of these, 10 experienced insufficient symptom relief and eventually underwent vascular intervention. Three patients left the programme at 3, 4 and 5 months of supervised exercise therapy, respectively, stating that they were satisfied with the regained walking distance and did not require further therapy. Ten patients were not sufficiently motivated to continue the programme, and none of these sought medical attention for intermittent claudication elsewhere. In three patients, a lack of adequate insurance cover was the reason for dropping out. A total of 11 patients quit the programme because of emerging disease (6 cardiovascular, 1 pulmonary, 2 orthopaedic, 1 renal insufficiency) or death (one patient with a ruptured abdominal aortic aneurysm). Data for the remaining 56 patients were used to analyse the change in walking distance over the 6-month study period. The baseline characteristics are shown in table 2. Of the 56 patients, two (3.6%) had severe chronic heart failure. Based on this cardiac co-morbidity, both patients were referred for supervised exercise therapy to the hospital department of physiotherapy and rehabilitation instead of to a community-based physiotherapist.

WALKING DISTANCE

At baseline, the mean initial claudication distance was 395 m (range 55–1600 m), with a mean absolute claudication distance of 563 m (range 60–1700 m). After 3 months of supervised exercise therapy, these values improved significantly to a mean initial claudication distance of 840 m (range 180–2260 m) and a mean absolute claudication distance of 1154 m (range 290–3740 m). The means for both distances increased further after 6 months, with a mean initial claudication distance of 1005 m (range 210–3810) and a mean absolute claudication distance of 1312 m (range 270–3980 m).

Translating these results into percentage increases, the initial claudication distance increased by 187% and the absolute claudication distance by 142% after 3 months. After 6 months, the initial claudication distance increased by 240% and the absolute claudication distance by 191% (table 3).

Table 2. Demographic and clinical characteristics of patients referred for community-based supervised exercise therapy

Characteristic*	Analysed population (N = 56)	Drop-outs (N = 37)
Age (years)	64.0 ± 10.4	64.7 ± 10.8
Men, n (%)	35 (62.5 %)	25 (67.6 %)
Body mass index	26.3 ± 3.9	26.1 ± 3.9
Current smokers	24 (42.9 %)	11 (29.7 %)
Ever smoked	19 (33.9 %)	13 (35.1 %)
Never smoked	13 (23.2 %)	10 (27.0 %)
Hypertension	45 (80.4 %)	31 (83.8 %)
Diabetes mellitus	23 (41.1 %)	13 (35.1 %)
Hypercholesterolaemia	49 (87.5 %)	26 (70.3 %)
Coronary heart disease	16 (28.6 %)	9 (24.3 %)
Stroke or transient ischaemic attack	4 (7.1 %)	9 (2 4.3 %)
COPD	9 (16.1 %)	4 (10.8 %)
Ankle brachial index	0.73 ± 0.18	0.70 ± 0.14

* Nominal variables are presented as frequency (%) and interval variables as mean ± SD.

SD: Standard deviation, COPD: Chronic Obstructive Pulmonary Disease

Table 3. Mean percentage increase in walking distance of patients referred for community-based supervised exercise therapy (N= 56)

Follow-up	Initial claudication distance		Absolute claudication distance	
	Mean % (SD)	Range %	Mean % (SD)	Range %
1 month	80.9 (402.0)	–53.9 to 579.0	73.8 (105.5)	–32.1 to 515.4
	P<0.0001		P<0.0001	
3 months	187.3 (187.1)	–25.5 to 772.7	142.2 (150.0)	–24.8 to 728.3
	P<0.0001		P<0.0001	
6 months	240.2 (284.2)	–39.8 to 1282.5	190.6 (229.5)	–22.9 to 1187.6
	P<0.0001		P<0.0001	

SD: Standard deviation

COMMUNITY-BASED VERSUS CLINIC-BASED SUPERVISED EXERCISE THERAPY

Earlier studies have reported absolute claudication distances after supervised compared with non-supervised exercise therapy in patients with intermittent claudication,[5,7–10,12,13] but in these studies supervised exercise therapy was provided in a clinic-based setting and sample sizes were small (8–28 subjects).

To compare these results with those of our community-based supervised exercise therapy programme, we summarised the reported absolute claudication distance or absolute claudication time of the clinic-based supervised exercise therapy groups for each follow-

up time point. For each trial, the percentage increase in absolute claudication distance or absolute claudication time was calculated, as shown in table 4.
After 3 months of clinic-based supervised exercise therapy, increases of between 35% and 137% were found, with a mean increase of 76% compared with a mean increase of 142% in a community-based setting. After 6 months, an increase of 90% occurred (range 42–159%) in a clinic-based setting, compared with 191% for community-based supervised exercise therapy.

Table 4. Increase in absolute claudication distance in previous studies using supervised exercise therapy in primary claudicants

Trial	Number of patients	Duration of SET (months)	Increase in absolute claudication distance	
			3 months	6 months
Cheetham[7]	28	6	66.6	128.8
Degischer[8]	19	3	82.4	70.4
Kakkos[9]	12	6	–	51.7
Savage[13]	11	6	59.8	42.3
Nielsen[10]	25	3	35.3	–
Patterson[5]	25	3	75.5	158.9
Regensteiner[12]	10	3	137.0	–
Mean % increase overall			76.1	90.4

SET: supervised exercise therapy

DISCUSSION

COMMUNITY-BASED SUPERVISED EXERCISE THERAPY

Supervised exercise therapy provided in a patient's home neighbourhood, in a so-called community-based physiotherapeutic setting, resulted in a highly statistically significant improvement in absolute claudication distance after 3 and 6 months. Although a comparison of these favourable results with historical studies should be regarded with caution because of the variability in the prescribed exercise regimens and treadmill walking tests used, supervised exercise therapy in a community-based setting seems to be at least as efficacious as programmes provided in a clinical setting.
Because we studied consecutive patients who were routinely referred to the new community-based supervised exercise programme, we were able to document carefully the reasons for programme discontinuation, as can also be done in routine clinical practice.

In our case, 37 patients (39.8%) who were referred to the community-based supervised exercise therapy did not continue the programme for the full 6-month period. Approximately a quarter of these patients stopped because of intercurrent disease, whereas in another quarter the supervised exercise therapy did not lead to adequate improvement and the patients had to undergo vascular intervention.

Overall, our recorded withdrawal rate seems to be comparable to those of trials studying supervised exercise therapy in a clinic-based setting, which have reported drop-out rates of up to 43%.[5,7,9]

One of the possible pitfalls of community-based supervised exercise therapy is the use of numerous physiotherapy practices (30) and physiotherapists (41), which results in a lower patient volume for each physiotherapist than occurs in a clinic-based setting. For this reason, we decided to implement the NETP and refer patients only to physiotherapists who participated in this network, instead of to any physiotherapist. Regular training sessions with all participating physiotherapists in the NETP programme ensures shared knowledge and experience. In addition, community-based supervised exercise therapy creates a larger capacity than clinic-based therapy, which means that a greater number of patients with intermittent claudication can be treated.

TREADMILL TESTS

The treadmill tests used to measure the walking distances vary widely between all reported studies. Overall, two contrasting treadmill protocols have been used to measure walking distance in patients with intermittent claudication. First, a constant-load test, with both a constant speed and a constant grade, has been developed.[18–20] It should, however, be noted that speed varies between 2.4 and 3.2 km per hour and incline between 0% and 12% in specific protocols and studies. Although this test is easy to administer, the variance coefficient lies between 30% and 40%.[19,21] Consequently, repeated measurements are needed for a sufficient assessment of walking distance. On the other hand, patients with a highly compromised circulation may be difficult to test at high initial workloads.[22]

A progressive treadmill test starts with a low initial workload that progressively increases until claudication pain forces a cessation of exercise.[20,23–25]

This low initial workload is achieved by a constant speed and increasing grade. Comparing the constant treadmill test with the progressive test, test process-related variances showed a comparable magnitude for both tests and were independent of the range of claudication distance.[22] However, for a subgroup of patients with a maximal walking distance of 100 m or less, measured by a constant treadmill test (3.2 km per hour, 12% incline), the workload of that test is suggested to be too high to allow for an appropriate separation of different claudication distances, resulting in a substantial drop in the

between-subject variance for the constant treadmill test.[22] Because the initial workload of the graded test is low, this problem can be avoided, and even patients with severe peripheral arterial disease can be tested with reasonable accuracy. For this reason, the current study used a progressive treadmill test instead of a constant-load treadmill test to evaluate walking distances after supervised exercise therapy.

FUTURE PERSPECTIVES

A multicentre, prospective randomized trial is currently being performed to determine the cost-effectiveness of community-based supervised exercise therapy, with or without therapy feedback (personal activity monitor), in comparison with non-supervised exercise therapy. Supervised exercise therapy has proven to be more effective than non-supervised therapy, but with uncertain cost-effectiveness. The feedback provided by the personal activity monitor might increase the intensity of supervised exercise therapy and lead to a reduction in the duration and number of physiotherapy sessions. Results are expected in 2008.

Another question that needs to be addressed concerns the effect of supervised exercise therapy on patients with recurrent complaints of intermittent claudication and a history of a previous vascular intervention. It is known that lower-extremity revascularization procedures in patients with peripheral arterial disease have a substantial failure rate over time,[26] and complaints of intermittent claudication may reoccur. The effectiveness of supervised exercise therapy in this specific population needs to be determined.

Likewise, little is known about the effect of supervised exercise therapy directly following a vascular intervention for peripheral arterial disease. Many patients still suffer or regain symptoms of intermittent claudication after vascular intervention, despite the fact that the treated segment is patent.[27–30] At this point, the possible value of supervised exercise therapy should be explored.

CONCLUSION

Supervised exercise therapy has significant benefits on treadmill-walking distance compared with non-supervised regimens. Non-supervised exercise therapy is, however, currently the main prescribed exercise therapy for people with intermittent claudication. Supervised exercise therapy for patients with intermittent claudication in a community-based setting seems to be as effective as the same therapy provided in a clinical setting.

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CHAPTER 3

FUNCTIONAL CLAUDICATION DISTANCE: A RELIABLE AND VALID MEASUREMENT TO ASSESS FUNCTIONAL LIMITATION IN PATIENTS WITH INTERMITTENT CLAUDICATION

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ABSTRACT

BACKGROUND

Disease severity and functional impairment in patients with intermittent claudication is usually quantified by the measurement of pain-free walking distance (initial claudication distance, ICD) and maximal walking distance (absolute claudication distance, ACD). However, the distance at which a patient would prefer to stop because of claudication pain seems a definition that is more correspondent with the actual daily life walking distance. We conducted a study in which the distance a patient prefers to stop was defined as the functional claudication distance (FCD), and estimated the reliability and validity of this measurement.

METHODS

In this clinical validity study we included patients with intermittent claudication, following a supervised exercise therapy program. The first study part consisted of two standardised treadmill tests. During each test ICD, FCD and ACD were determined. Primary endpoint was the reliability as represented by the calculated intra-class correlation coefficients. In the second study part patients performed a standardised treadmill test and filled out the Rand-36 questionnaire. Spearman's rho was calculated to assess validity.

RESULTS

The intra-class correlation coefficients of ICD, FCD and ACD were 0.940, 0.959, and 0.975 respectively. FCD correlated significantly with five out of nine domains, namely physical function (rho = 0.571), physical role (rho = 0.532), vitality (rho = 0.416), pain (rho = 0.416) and health change (rho = 0.414).

CONCLUSION

FCD is a reliable and valid measurement for determining functional capacity in trained patients with intermittent claudication. Furthermore it seems that FCD better reflects the actual functional impairment. In future studies, FCD could be used alongside ICD and ACD.

BACKGROUND

Intermittent claudication is a symptom of peripheral arterial disease (PAD), and is described as muscle pain in the lower extremities that is produced by exercise and relieved in rest. Patients with intermittent claudication have limited exercise and walking capacity, which reduces their functional capacity.[1]

Treadmill testing is a common way to quantify the grade of functional impairment. The Royal Dutch Society for Physiotherapists recommends the administration of treadmill tests to all patients with intermittent claudication, both to objectively document the degree of functional impairment, and to evaluate therapy effect.[2]

In general, two distances are measured during treadmill testing of patients with intermittent claudication. First is the distance walked at the onset of claudication pain, also known as the initial claudication distance (ICD), or pain-free walking distance. The second measurement is the distance at which claudication pain becomes so severe that the patient is forced to stop, also known as the absolute claudication distance (ACD), or maximal walking distance.[2-6] In the literature, both ICD and ACD are used to classify the degree of functional impairment. Both distances have been shown to be reliable measurements with good reproducibility. ICD appears to be less reliable in comparison with ACD.[7-13]

In patients with intermittent claudication both ICD and ACD correlate with different quality of life domains of the EuroQol,[14] the Short-form-36,[15,16] and several disease specific questionnaires.[17-19] However, the definition of both ICD and ACD is not correspondent with distances a patient would walk in daily life. Although most patients will continue to walk after appearance of the first signs of pain, few will walk until their maximum pain threshold is reached during the course of daily activities.

For this reason, the distance at which a patient prefers to stop because of claudication pain may be a better instrument by which to measure the functional impairment of patients with intermittent claudication. Bendermacher et al.[20] first used "the distance at which a patient prefers to stop because of claudication pain". We define this distance as the functional claudication distance (FCD).

We conducted this study, since the reliability and validity of FCD have never been tested. Furthermore we want to compare reliability and validity of FCD with both ICD and ACD to determine the value of FCD for testing functional impairment in patients with intermittent claudication.

METHODS

PATIENTS

Patients with intermittent claudication, following a supervised exercise program, were recruited from private physiotherapy practices in the Southern part of the Netherlands. Inclusion criteria were intermittent claudication with an ACD of < 1600 meters on a standard treadmill test. Patients had to have followed at least 3 months of community-based supervised exercise therapy according to the guidelines of the Royal Dutch Society of Physiotherapy to rule out therapy effect between the 2 study measurements. Exclusion criteria were the inability to walk on the standard treadmill protocol, serious cardiopulmonary comorbidity (NYHA 3 and 4)[21] and reasons for discontinuing the treadmill test other than intermittent claudication. The study was approved by the local research ethics committee from the Atrium medical centre Heerlen, and all patients provided informed consent.

STUDY PROTOCOL

The study consisted of two parts. In the first part, 57 patients were included who performed two standardised treadmill tests within three weeks. Patients rested for 10 minutes before each test to ensure that no claudication pain was present at the start. Handrail support was not allowed. In case of unbalance, the researcher gave the patient his hand to hold on to until balance was regained. During the treadmill tests, patients were blinded for the distance/time walked by covering the display of the treadmill. The data from the first part were used to determine reliability of ICD, FCD, and ACD.

In the second part, 25 patients were included who all performed a standardised treadmill test and filled out a Rand-36 questionnaire to determine quality of life. The Rand-36 is a general quality of life questionnaire and determines quality of life in 9 domains of functioning.[22] Data from the second part were used to determine validity of FCD, compared to ICD and ACD.

TREADMILL TESTING

A progressive treadmill test was used according to Gardner et al.[23] with a constant speed of 3.2 km/h and an increase in inclination of 2% every two minutes, beginning with 0% inclination. The inclination and testing duration were maximised to 10% and 30 minutes (1600 metres), respectively. Patients participating in the first part of the study performed two treadmill tests. Patients participating in the second part performed only one treadmill test. During treadmill testing all patients were supervised by one of two independent researchers. At each test all walking distances (ICD, FCD, and ACD) were measured.

Patients indicated the onset of claudication pain, the point of preferring to stop, and the point that maximum walking distance was reached.

ANALYSIS

Nominal and interval variables are presented as frequency (%) and mean ± standard deviation respectively, unless otherwise indicated. Differences in baseline characteristics between the two groups were assessed by a Chi-square test for nominal variables and a Paired Student's T-test for interval variables.

To determine the reliability of ICD, FCD, and ACD, an intra-class correlation coefficient (ICC) for absolute agreement was calculated, according to a two-way mixed effects model with random effects for subjects and a fixed effect for time.[24] Bland-Altman plots were used to visualize the repeated measurements.[25] Regression analysis was applied to assess whether the difference between the two measurements is dependent on the mean walking distance to determine if a log transformation of the Bland-Altman plots is necessary. The extent of variability between repeated measurements was assessed by the coefficient of variation for ICD, FCD and ACD separately.

In the validity study scatter plots were used to examine the linearity of the correlation and to detect possible outliers. Walking distance was plotted against the value of the different domains of the Rand-36 questionnaire for each patient individually. Outliers, appearing as points far away from the overall pattern were excluded. Validity was assessed using the Spearman's rho to calculate the degree of correlation between ICD, FCD, and ACD and the different domains of the Rand-36 questionnaire. Data were analysed using SPSS 12.0.

RESULTS

In total eighty-two patients were included in this study, of whom 57 in the reliability part and twenty-five in the validity part. The patient characteristics are shown in table 1, and as can be seen, no significant differences were present between the two patient groups.

For one patient participating in the reliability study no FCD was measured, for reasons unknown, resulting in 56 patients available for the reliability analysis of FCD. The mean walking distances (ICD, FCD, and ACD) are shown in table 2. For every patient the FCD laid in between ICD and ACD. The mean difference between FCD and ACD was 104 and 106 metres for the first and second treadmill test respectively.

Figure 1A, B, and 1C show Bland-Altman plots of ICD, FCD and ACD, respectively. The mean value of 2 measurements is plotted against the difference of measurement 1 mi-

Table 1. Clinical characteristics of the included population

Characteristic	Total Population N=82	Patients for reliability analysis N=57	Patients for validity analysis N=25	P-value
Male	49 (59.8%)	36 (63.2%)	13 (52.0%)	0.343
Age (years)	67 ± 10	68 ± 9	65 ± 12	0.213
ABI	0.69 ± 0.19	0.71 ± 0.20	0.66 ± 0.17	0.338
Weight (kg)	76 ± 14	76 ± 14	75 ± 15	0.797
Risk factors				
Hypertension	60 (78.9%)	39 (76.5%)	21 (84.0%)	0.449
Diabetes Mellitus	20 (26.3%)	10 (19.6%)	10 (40.0%)	0.058
Hypercholesterolemia	43 (56.6%)	25 (49.0%)	18 (72.0 %)	0.058
Smoking behaviour				0.669*
Current smoking	34 (44.7%)	22 (43.1%)	12 (48%)	
Former smoking	35 (46.1%)	24 (47.1%)	11 (44.0%)	
Never smoked	7 (9.2%)	5 (9.8%)	2 (8.0%)	

Kg: Kilograms, ABI: ankle brachial index

* Calculated with Kendall's-tau test

nus measurement 2. Regression analysis did not show that systematic differences between repeated measurements were dependent on mean walking distance, indicating that a log transformation of the Bland-Altman plots was unnecessary.[25] Differences between repeated measurements as presented in the Bland-Altman plots are equally divided above and below zero difference. This shows that no learning/therapy effect occurred between the two measurements.

The reliability measurements presented in table 2 show that the ICC of ACD (0.975, 95% CI 0.957 – 0.985) was significantly better than the ICC of ICD (0.940, 95% CI 0.899 – 0.964). The ICC of FCD was set in between these two, with a value of 0.959 (95% CI 0.931 – 0.976), not significantly different from ICD or ACD. The coefficients of variation showed corresponding results with values of 21.7%, 18.1% and 13.2% for the ICD, FCD and ACD, respectively.

Based on the scatter plots two patients were identified as outliers and excluded from the analysis, leaving 23 patients for validity analysis. The mean scores of the Rand-36 questionnaire and the correlations of the different walking distances with quality of life are shown in table 3. The ICD correlated significantly with the physical function (rho = 0.473, p = 0.022) and general health (rho = 0.518, p = 0.011) domain of the Rand-36 questionnaire. FCD correlated significantly with five out of nine domains, namely physical function (rho = 0.571, p = 0.004)), physical role (rho = 0.532, p = 0.009), vitality (rho = 0.416, p = 0.048), pain (rho = 0.416, p = 0.037) and health change (rho = 0.414, p = 0.050). ACD correlated with physical function (rho = 0.496, p = 0.016), physical role (rho = 0.519, p = 0.011) and health change (rho = 0.446, p = 0.033).

Table 2. Mean walking distances and reliability measurements

	Measurement one (metres ± SD)	Measurement two (metres ± SD)	ICC Value (95% CI)	Coefficient of variation (%)
ICD	271.6 ± 174.9	273.7 ± 162.2	0.940 (0.899 – 0.964)	21.7 %
FCD	531.2 ± 357.3	541.2 ± 339.6	0.959 (0.931 – 0.976)	18.8 %
ACD	635.4 ± 376.0	642.6 ± 368.8	0.975 (0.957 – 0.985)	13.2 %

SD: standard deviation, ICC: intra-class correlation coefficient, CI: confidence interval, ICD: initial claudication distance, FCD: functional claudication distance, ACD: absolute claudication distance

Table 3. Rand-36 scores and Spearman's correlations with walking distances

Domain	Rand-36 score	ICD		FCD		ACD	
	Median (IQR)	Correlation	P	Correlation	P	Correlation	P
Physical function	55.6 (50.0 - 72.2)	0.473*	0.022	0.571**	0.004	0.496*	0.016
Social function	87.5 (75.0 - 100.0)	-0.046	0.836	0.001	0.998	-0.065	0.768
Physical role	75.0 (0.0 - 100.0)	0.407	0.054	0.532**	0.009	0.519*	0.011
Emotional role	100.0 (100.0 - 100.0)	0.068	0.758	0.157	0.476	0.121	0.584
Mental health	84.0 (64.0 - 92.0)	0.014	0.948	0.132	0.549	0.092	0.676
Vitality	60.0 (55.0 - 70.0)	0.152	0.488	0.416*	0.048	0.366	0.086
Pain	67.3 (55.1 - 69.4)	0.338	0.114	0.437*	0.037	0.352	0.099
General health	50.0 (40.0 - 60.0)	0.518*	0.011	0.392	0.065	0.371	0.081
Health change	50 (25.0 - 75.0)	0.382	0.072	0.414*	0.050	0.446*	0.033

IQR: inter quartile range, ICD: initial claudication distance, FCD: functional claudication distance, ACD: absolute claudication distance.
* Correlation is significant at the 0.05 level, ** Correlation is significant at the 0.01 level.

DISCUSSION

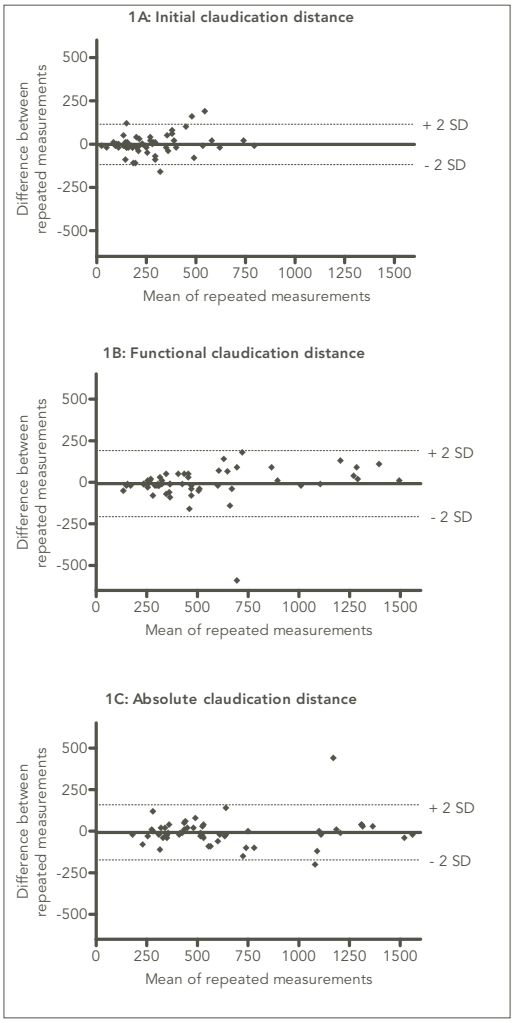
FCD, defined as the distance when the patient prefers to stop due to claudication, is a reliable and valid measurement to determine functional impairment in patients with intermittent claudication. The ICC of FCD was 0.959 and in between of the ICC of ICD and ACD, with ACD showing the most reproducible measurements. The coefficients of variation showed corresponding results. ACD showed the least variation, followed by FCD and ICD, respectively.

FCD correlated significantly with the physical function, physical role, vitality, pain and health change domain of the Rand-36 questionnaire. ICD correlated significantly with the physical function and general health domain. Significant correlations of ACD were found with physical function, physical role, and health change. These results indicate that FCD corresponds best with general quality of life as FCD correlated with five of nine domains compared to two and three domains for ICD and ACD respectively.

In our study, ACD is the most reliable measurement during a treadmill test. This conforms to results found in literature for several treadmill protocols.[7-13] Three studies from Gardner et al.[10,23] and Labs et al.[11] assessed the reliability of the treadmill protocol used in this study. The ICC of ICD and ACD in these studies ranges from 0.82 to 0.89 and from 0.93 to 0.96, respectively. The coefficients of variation in these studies range from 11.0% to 15.5% for ACD, and from 15.8% to 28.6% for ICD. These findings are in line with coefficients of variation found in our study, and indicate that ICD and ACD are both reliable measurements. However, the ICC found in our study tends to be better than those previously described in the literature. One possible explanation for this difference could be that our test population consisted of patients familiar with treadmill testing. Prior to this study, all patients received at least 3 months of community based supervised exercise therapy, consisting mainly of treadmill walking. This may have influenced the stability of the outcomes of the treadmill tests. It seems plausible that reliability between two measurements increases with treadmill training of the patients, as compared to untrained patients.

In our study FCD correlates best with quality of life, followed by ACD and ICD. In literature several studies determined correlations between QOL and walking distances. A recent study in 48 patients from Myers et al.[16] showed a significant correlation of ICD with both pain and social function whereas ACD correlated with physical function and vitality measured by the short-form-36. Izquierdo-Porrera et al.[15] determined Pearson's correlation coefficients between ACD and the different domains of the short-form-36. In this study ACD correlated significantly with physical function ($r = 0.43$), physical role ($r = 0.33$), and mental health ($r = 0.27$). Furthermore, ICD and ACD correlate with different domains

Figure 1. Walking distances, represented by Bland-Altman plots. For initial, functional, and absolute claudication distance respectively, the mean of the two measurements is plotted against the difference between the two measurements. SD: standard deviation.



of the PAVK-86,[19] the CLAUS questionnaire,[17] and the VascuQol.[17]

Limitation of the study is that we included patients familiar with treadmill walking, what could have influenced the reliability results. FCD results should therefore be measured in other patient populations and until then treated with caution in these populations. However, corresponding coefficients of variation for ICD and ACD from the literature (untrained patients) compared to our study (trained patients) may indicate that the results

from this study for FCD can be projected to patients unfamiliar with treadmill walking. A further limitation is the limited number of patients included in the validity study (n = 23 for the analysis). A study including more patients to confirm our results is desirable.

The definition of FCD, the distance at which a patient prefers to stop walking, assumes a better reflection of the functional capacity of patients than ICD or ACD. In practice, most patients do not stop walking at the first indication of claudication pain, neither do they walk until they reach their maximal pain threshold. In our study, comparison of FCD with the Rand-36, for the purpose of establishing the clinical relevance shows that FCD correlates better with quality of life than both ICD and ACD. Therefore we think that FCD is a more important outcome measurement from a patient's perspective. Furthermore, from a research perspective, FCD is a reliable and valid instrument that can be used in clinical trials. In the future it is conceivable that training programs using a global positioning system will be developed using a software program calculating walking distances and recuperation time.[26] Especially in such a training environment it is more likely that the average claudicant will stop when preferring so than until reaching a maximal pain threshold.

CONCLUSION

The functional claudication distance is a reliable measurement for determining functional capacity in trained patients with intermittent claudication. Furthermore it seems that FCD better reflects the actual functional impairment. In future studies, FCD could be used in conjunction with ICD and ACD.

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CHAPTER 4

SUPERVISED EXERCISE THERAPY FOR INTERMITTENT CLAUDICATION IN DAILY PRACTICE: ONE-YEAR RESULTS OF A COMMUNITY-BASED APPROACH

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ABSTRACT

OBJECTIVE

This study describes the results and functioning of community-based supervised exercise therapy (SET) at one year of follow-up.

METHODS

We conducted a prospective cohort study of community-based SET in regional physiotherapeutic practices. Consecutive patients with intermittent claudication referred for community-based SET were included. Exclusion criteria for SET were pain at rest or tissue loss. All patients received a diagnostic workup consisting of an ankle-brachial index at rest and after exercise. Interventions were exercise therapy according to the guidelines of the Royal Dutch Society for Physiotherapy. The primary outcome measurement was the increase in absolute claudication distance (ACD), assessed using a standardized treadmill protocol by a physiotherapist at baseline and at four, 12, 26, and 52 weeks of SET.

RESULTS

From January 2005 through September 2006, 349 patients were referred by vascular surgeons for community-based SET. A total of 272 patients with intermittent claudication began the program. Of the 349 initially referred patients, 52 could not perform a standard treadmill test but did start community-based SET at a lower level, and 25 patients never started the program. At one year, 129 of the original 272 patients who began community-based SET (47.4%) were available for analysis of walking distance. In the interim, 143 patients discontinued the program for the following reasons: satisfaction with the acquired walking distance (n=19); unsatisfying results (n=26); not motivated (n=22); (non)vascular intercurrent disease (n=48); and other reasons (n=28). ACD increased significantly from a median of 400 m at baseline to 1100 m after 12 months of follow-up ($P<0.001$), corresponding to a median increase of 107.8%.

CONCLUSION

Community-based SET seems as effective as SET in a hospital-based approach in improving walking distance, however, it has a high dropout rate.

INTRODUCTION

Intermittent claudication is a common symptom in patients with peripheral arterial disease (PAD). Treatment of patients suffering from intermittent claudication is based on two basic components: treatment of vascular risk factors to prevent future vascular events and treatment of symptoms.[1] Symptomatic relief of complaints of intermittent claudication can be achieved by exercise therapy, percutaneous transluminal angioplasty (PTA), and surgical revascularization. Exercise therapy is efficacious in improving walking distance[2] and is considered the first choice of treatment (Fontaine stage II). However, in cases of more proximal disease (e.g., aortic or iliac), primary revascularization is advised.[1]

The most common exercise therapy prescription consists of one-time oral advice to walk more, usually without supervision or follow-up.[3] However, the importance of supervised exercise therapy (SET) is increasingly recognized.[1,4] A recent Cochrane review reported a significant difference in favour of SET compared with an unsupervised exercise program in improving walking distance.[5] Trials included in this review provided SET programs at a department of physiotherapy or revalidation in a hospital. While this approach is appropriate in trials, there are some limitations in routine clinical practice. First, the capacity of a single department in a hospital is limited and not sufficient to provide SET to all claudication patients in the community. Second, attending at the hospital for two or three times a week is time consuming and expensive for the patient. These pitfalls can be solved using a community-based approach to SET,[6] consisting of a selected group of community-based physiotherapists especially trained in applying exercise therapy.

Implementation of community-based SET was first described by Willigendael et al,[7] and the first results in a selected group of patients were promising.[8]

This study describes the results of community-based SET at one year of follow-up compared with clinic-based SET with results known from literature. Furthermore, we give a status report on how community-based SET works in daily practice and describe the possible pitfalls of this approach.

PATIENTS AND METHODS

STUDY SETTING

All patients presenting at the vascular outpatient clinic with complaints of intermittent claudication receive a diagnostic workup consisting of an ankle brachial index (ABI) mea-

surement, which, if below 0.9, was followed by duplex ultrasound of the aortic-iliac tract. Patients with occlusive disease of the aortic-iliac tract were referred for diagnostic angiography and PTA or recanalization in the same procedure. Patients with more distal disease were primarily considered for community-based SET and referred to a physiotherapist participating in the Network for Exercise Therapy Parkstad (NETP).

The NETP provides community-based SET in private physiotherapy practices equally distributed over the region, instead of a department of physiotherapy and rehabilitation in a hospital or rehabilitation clinic. All participating physiotherapists are trained according to the guidelines of the Royal Dutch Society for Physiotherapy (table 1).[9] Training of physiotherapists, and the development and implementation of the NETP is described in more detail by Willigendael et al.[7]

Table 1. Summary of the Royal Dutch Society for Physiotherapy guideline 'Intermittent Claudication'

Facilities for SET	Equipment	Treadmill; Cycle ergometer; Indoor walking space; Small group exercise room
	Education	Course in exercise therapy according to the guideline
	Referral (general practitioner / specialist)	Fontaine classification; Ankle-Brachial Index (<0.9); Walking impairment; Cardiac risk and capacity; Contra-indications
Diagnostic process	Medical history	Disease specific; Co-morbidities; Patient specific complaints scale
	Physical examination	Disease specific; Co-morbidities
	Functional examination	Maximum treadmill test; Gait and specific function analysis
Therapeutic process	Objectives	Increase maximum walking distance; Increase aerobe endurance; Increase pain tolerance and reduce fear of pain; Improve gait and specific activities (stair climbing, etc); Provide information and induce life style changes
	Behavioural change	Increase pain tolerance; Reduce fear of pain; Induce active life style and improve risk factors
	Supply information	Disease specific; Exercise therapy; Life style
	Therapy mode and intensity	Primarily walking up to (sub)maximal pain; At least 6 months; At least 30 minutes per session; Walking 3 times a week (supervised or homework)
	Therapy evaluation	Continuous evaluation; Extensive evaluation at least after 4 and 12 weeks; Maximal treadmill test, Borg Ratings of Perceived Exertions; ASCM pain scale; Patient Specific Complaints Scale

ACSM: American College of Sports Medicine, SET: supervised exercise therapy

All patients with confirmed PAD received a platelet inhibitor and lipid-lowering medication. Diabetes mellitus and hypertension were treated according to current guidelines. Furthermore, smoking cessation and lifestyle advice were part of a cardiovascular prevention program initiated by a team of vascular nurse practitioners.

STUDY POPULATION

All consecutive patients referred for community-based SET from January 2005 through September 2006 were included. Patients with complaints of intermittent claudication were eligible for community-based SET after confirmation of PAD with an ABI measurement below 0.9 at rest or decreasing more than 0.15 after exercise. Signs of critical ischemia (e.g., pain in rest, tissue loss) were exclusion criteria for participating in community-based SET.

EXERCISE PROGRAM

All participating physiotherapists were participating in the NETP, a community-based program for SET in patients with intermittent claudication. SET was administered according to the guidelines of the Royal Dutch Society for Physiotherapy.[9]

The main goal of SET is to increase absolute claudication distance (ACD), the distance at which severe claudication pain forces cessation of exercise. This goal was achieved by means of interval training with treadmill walking up to (sub)maximal pain. Secondary goals are improving endurance, increasing strength, and correcting walking patterns.

Generally, patients started with a frequency of two to three sessions every week of approximately 30 minutes in the first three months. After this initial phase, the frequency was phased down to approximately once every two weeks at six months of follow-up and once every eight weeks at 12 months of follow-up, depending on patient progress and preference.

Patients were encouraged to walk on a daily basis to near maximal pain. Furthermore, all participating physiotherapists were instructed to emphasize as much as possible the importance of lifestyle adjustments and smoking cessation.

In The Netherlands, intermittent claudication is one of the chronic diseases that is considered for physiotherapy during the period of one year. Therefore, for every patient, from the tenth session through the period of one year, reimbursement is financed by the National Insurance of Health Care. Reimbursement for the first nine sessions of 30 minutes of exercise therapy depends on the patient's additional and voluntarily health insurance. The minimal advised charge of one session of physiotherapy is 32.07 USD (www.fysionet.nl). Approximately, the mean costs of one year of community-based SET lie in between 801.75 and 1282.80 USD, dependant on the frequency of the sessions.

THERAPY EVALUATION

Patients were evaluated by their physiotherapist at baseline and at 4, 12, 26, and 52 weeks of follow-up. Patients performed a standardized treadmill test, and their physiotherapists registered walking distances and possible reasons for dropping out of the SET program. A progressive treadmill test was used, with a constant speed of 3.2 km/h and an increase in incline of 2% every two minutes, starting at 0% incline.10 The incline and testing duration were maximized for practical reasons to 10% and 30 minutes (1600 m), respectively.

Outcomes of these evaluations were registered in a web-based electronic patient file, available for the physiotherapist as well as the vascular surgeons and nurse practitioners (www.fastguide.eu).

OUTCOME MEASUREMENTS

The primary outcome measurement was the percentage increase in ACD. Secondary outcome measurements were functional claudication distance (FCD), defined as the distance at which the patient prefers to stop because of claudication pain, and the number of invasive vascular interventions within one year after starting community-based SET. Furthermore, results were categorized as good, moderate, or unsatisfactory according to an objectively measured increase in ACD and according to the dropout reason of a patient. If patients stated that they were not satisfied with the walking distance at time of dropout, the result was classified as unsatisfactory. If patients stated that the reason of dropout was satisfaction with the regained walking distance, the result was classified as good.

ANALYSIS

All interval and ratio variables are presented as median and inter-quartile-range (IQR) because most variables were not normally distributed. Means are reported to allow comparison of the results of this study with results from the literature. Nominal variables are presented as absolute numbers and percentages.

For every patient, the percentage increase in FCD and ACD compared with baseline was calculated. Exclusion criteria for analysis of walking distances were the absence of a baseline measurement or the inability to walk according to the standardized treadmill protocol. All other patients were included in the analysis when data were available.

The statistical significance of this within-group difference was analyzed with a Wilcoxon signed-ranks test. Results were categorized as good, moderate, or unsatisfactory.[9] A good result was defined as an increase of 100% or more in ACD or dropping out of SET because of satisfaction with the regained walking distance. A moderate result was defined as an increase in ACD between 50% and 100%. The result was defined as unsatisfactory in cases

of an ACD increase of less than 50% or dropping out of SET because of patient dissatisfaction with the acquired walking distance. In patients undergoing a vascular intervention during the year, the last result before the vascular intervention was carried forward. In addition, the last result before dropping out for reasons other than (dis)satisfaction was carried forward.
Statistically significant differences between groups were calculated with a Mann-Whitney U test for ordinal and interval variables and a Chi^2 test for binominal variables. If criteria for a Chi^2 test were not fulfilled, a Fisher exact test was used. Comparison of more than two groups was performed using a Chi^2 test for trend. A value of $P < 0.05$ was considered to be statistically significant. Analyses were performed using SPSS 12.0 for Windows (SPSS, Inc, Chicago, Ill).

RESULTS

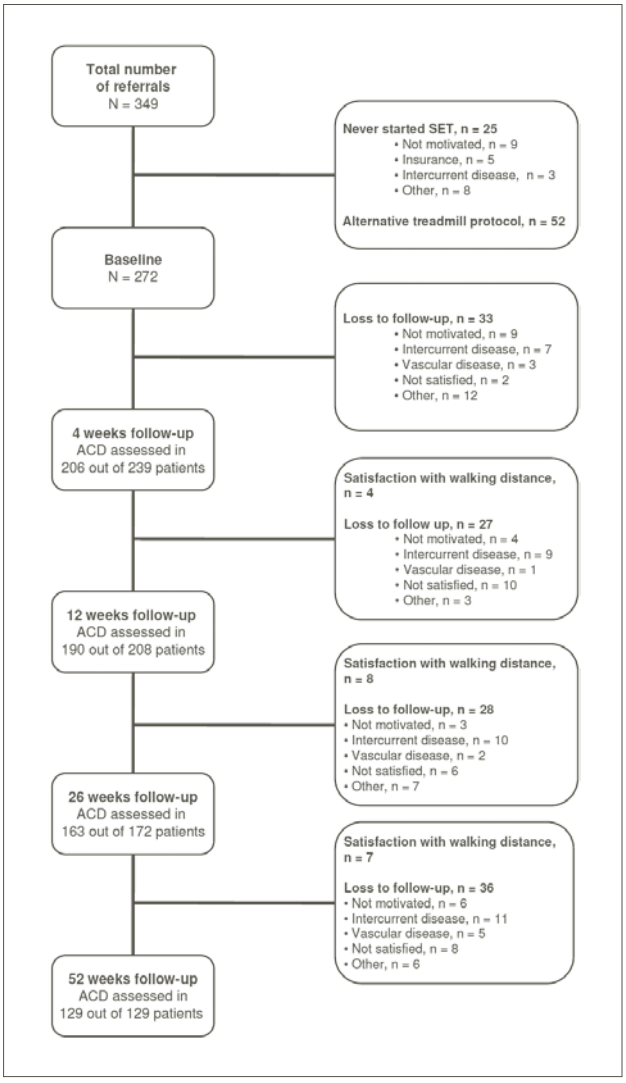
From January 2005 through September 2006, 349 patients with intermittent claudication were referred for community-based SET. Baseline characteristics of this population are summarized in table 2.
Fifty-two patients were not able to perform a standard treadmill test as described above and were excluded from further analysis. These patients did start community-based SET but at a lower level. Twenty-five patients never started community-based SET for various reasons (figure 1). These patients were also excluded from further analysis. A total of 272 patients with intermittent claudication started community-based SET. At one year, 129 patients (47.4%) were available for analysis of walking distance (figure 1). The remaining 143 patients discontinued the program for the following reasons: satisfaction with the acquired walking distance (n=19); unsatisfying results (n=26); not motivated (n=22); (non) vascular intercurrent disease (n=48); and other reasons (n=28). No differences in baseline characteristics were found between withdrawals and the population that completed 12 months of community-based SET, with the exception of the greater number of current smokers ($P = 0.046$) in the withdrawal group (table 2).

WALKING DISTANCES

The median FCD and ACD at baseline were 230.0 m (mean, 325.0 m) and 400.0 m (mean, 493.1 m), respectively. After 12 months of follow-up, the median walking distances significantly increased to 700.0 m (mean, 867.0 m) for FCD and 1100.0 m (mean, 1053.5 m) for ACD ($P<0.001$). This increase corresponds to a median increase of 166.7% (mean, 279.3%)

and 107.8% (mean, 196.9%) compared with baseline for FCD and ACD, respectively. Notably, most of the increase in walking distance occurred in the first six months of community-based SET. No further improvement in walking distance was seen between six and 12 months of follow-up. Table 3 shows more details about the different walking distances at 4, 12, and 26 weeks of follow-up.

Figure 1. Flow chart of the total population referred for community-based supervised exercise therapy. SET: Supervised exercise therapy, ACD: Absolute claudication distance

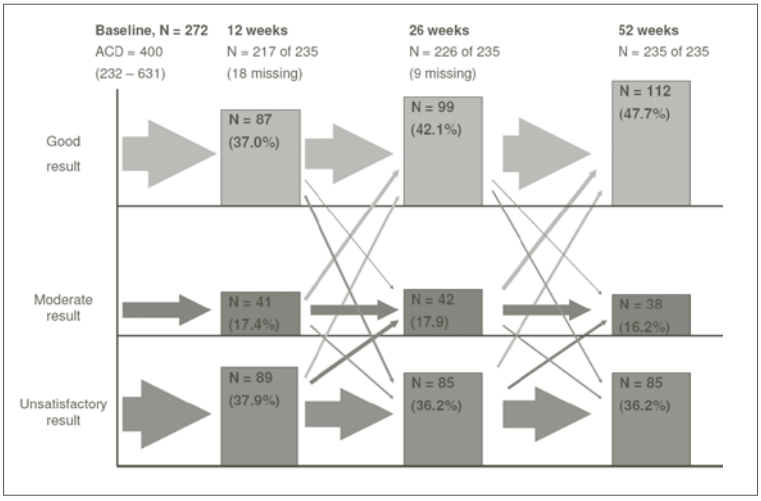


COURSE OF RESPONSE TO SET

The results of the total cohort (n=272) were categorized as good, moderate, or unsatisfactory. Because of the chosen definitions, 37 patients could not be classified. Of these, 33 dropped out before the first follow-up measurement, and four patients had a vascular intervention before four weeks of follow-up, resulting in 235 patients who were available for analysis.

The clinical course of the cohort is graphically represented in figure 2, in which the size of the arrows reflects the number of patients. As figure 2 shows, after 52 weeks of follow-up or at the moment a patient dropped out, 112 patients (47.7%) showed a good result, 38 (16.2%) had a moderate result, and 85 (36.2%) had an unsatisfactory result. Good or unsatisfactory results achieved at 12 weeks of follow-up were likely to persist at 26 and 52 weeks of follow-up.

Figure 2. Clinical course of the total cohort. The arrows represent movement of patients between different result categories in time and the blocks indicate the results at the different follow-up measurements. The size of the arrows and blocks reflect the number of patients. The upper, middle, and lower part represent patients with a good, moderate, and unsatisfactory result respectively. Good result: increase in ACD of ≥100% or patient satisfaction with the walking distance. Moderate result: increase in ACD ≥50% and <100%. Unsatisfactory result: increase in ACD <50% or patient dissatisfaction with the walking distance. ACD: Absolute claudication distance.



VASCULAR INTERVENTIONS

Out of 272 patients, 43 had a vascular intervention within the follow-up period of one year, of whom 33 received a PTA, six had bypass surgery, and four had other vascular interventions. In 39 patients (90.7%), the indication was intermittent claudication, and in

Table 2. Demographic and clinical characteristics

Characteristic	Total population, N = 349	Population completing 12 months, N = 137	Withdrawals, N = 212	P value
Age (year)	66.0 (58.6–74.0)	66.4 (58.6–73.7)	65.7 (58.5–74.3)	NS
Men	219/349 (62.8%)	88/137 (64.2%)	131/212 (61.8%)	NS
BMI	26.1 (23.6–29.0)	26.6 (23.9–29.4)	25.9 (23.1–28.9)	NS
	N = 331	N = 136	N = 195	
Resting ABI	0.70 (0.60–0.88)	0.71 (0.60–0.88)	0.70 (0.60–0.88)	NS
	N = 342	N = 135	N = 207	
Current smokers	168/341 (49.3%)	58/136 (42.6%)	110/ 205 (53.7%)	.046
Hypertension	266/349 (76.2)	103/137 (75.2%)	163/212 (76.9%)	NS
Diabetes mellitus	117/349 (33,5%)	48/137 (35.0%)	69/212 (32.5%)	NS
Hypercholesterolemia	267/349 (76.5%)	109/137 (79.6%)	158/212 (75.4%)	NS
Coronary heart disease	93/349 (26.6%)	35/137 (25.5 %)	58/212 (27.4%)	NS
Cerebrovascular disease	47/349 (13.5%)	13/137 (9.5%)	34/212 (16.0%)	NS
COPD	50/349 (14.3%)	22/137 (16.1%)	28/212 (13.2%)	NS
Arthrosis	19/349 (5.4%)	7/137 (5.1%)	12/212 (5.7%)	NS
Previous vascular intervention	113/349 (32.3%)	45/137 (32.8%)	68 (32.1%)	NS
Systolic blood pressure (mmHg)	150.0 (135.0–170.0) N = 344	150.0 (135.0–172.3) N = 136	150.0 (132.3–170.0) N = 208	NS
Glucose (mmol/l)	5.9 (5.3–7.1)	5.9 (5.2–7.1)	5.9 (5.3–7.0)	NS
	N = 330	N = 127	N = 203	
HbA1C (%)	6.0 (5.8–7.1)	6.2 (5.8–7.2)	6.0 (5.7–6.9)	NS
	N = 238	N = 94	N = 144	
Cholesterol (mmol/l)	5.2 (4.2–6.0)	5.1 (4.3–6.0)	5.2 (4.1–5.9)	NS
	N = 333	N = 130	N = 203	
HDL (mmol/l)	1.33 (1.12–1.60)	1.35 (1.12–1.67)	1.31 (1.09–1.58)	NS
	N = 316	N = 123	N = 193	
LDL (mmol/l)	2.8 (2.0–3.5)	2.6 (2.1–3.5)	2.9 (2.0–3.6)	NS
	N = 304	N = 119	N = 185	
Triglycerides (mmol/l)	1.60 (1.11–2.22)	1.52 (1.08–2.42)	1.67 (1.13–2.22)	NS
	N = 311	N = 122	N = 189	
FCD (metre)	230.0 (120.0–427.5)	260.0 (130.0–450.0)	205.0 (117.0–382.5)	NS
	N = 269	N = 127	N = 142	
ACD (metre)	400.0 (323.0–630.8)	276.0 (450.0–689.0)	370.0 (207.0–590.0)	NS
	N = 272	N = 129	N = 143	

NS: Not significant, BMI: body mass index, ABI: ankle-brachial index, COPD: chronic obstructive pulmonary disease, FCD: functional claudication distance, ACD: absolute claudication distance

four patients (9.3%), it was critical limb ischemia.

The distribution of the interventions in the different result categories showed a non-significant trend in those with an unsatisfactory result. The frequency of interventions in the group showing good results was 2.7%. In the groups showing moderate and unsatisfactory results, these percentages were 13.2% and 25.9%, respectively.

ADDITIONAL OBSERVATIONS

Fifty-two patients were not able to walk at the speed of 3.2 km/h of the standardized treadmill protocol. In general, these patients had poorer clinical characteristics; they were older (P<0.001), had diabetes more often (P=0.014), and had a significantly lower resting ABI (P=0.008) than patients starting the usual community-based SET. However, these 52 patients started community-based SET at their own level, with varying speeds and inclines during treadmill testing. Another striking difference between the group starting community-based SET at a low level and the group starting the usual SET was the dropout percentage. In the low level group, the dropout rate was 84.6% compared with 52.5% in the standard SET group (P<0.001). Seven patients from the lower-level group had a vascular intervention, all for intermittent claudication; four of these patients had PTA, and three had bypass surgery. This outcome was not significantly different from the standard SET group. Twenty-five patients never started community-based SET for different reasons (figure 1). Within one year after referral, three patients received a PTA and one patient received another vascular intervention. This outcome was not significantly different from the number of interventions in the group starting community-based SET. Patients never starting community-based SET were more likely to be men (P=0.012) compared with patients who did start SET. There were no other significant differences between these two groups.

DISCUSSION

In this study, we have shown that one year of community-based SET results in highly significant increases in FCD as well as ACD after 4, 12, 26, and 52 weeks of follow-up. However, community-based SET has a high dropout rate. These results for walking distance as well as for dropout are in line with the results after six months of community-based SET published recently by Bendermacher et al.[8]

Most reports on SET for patients with intermittent claudication are situated in an outpatient clinical setting, but these also show comparable results in improving walking distance.[2,5,11-20] Table 4 gives an overview of results of clinic-based SET after 6 and 12 months of follow up.[2,5] The overall mean percentages increase of clinic-based SET after 6 and 12 months of follow up are 92% and 108%, respectively. In our study, we found median increases in ACD of 88% (mean, 191%) and 108% (mean, 197%) after 6 and 12 months of follow up, suggesting community-based SET is as least equal to clinic-based SET.

Furthermore, an interesting observation is that a good or unsatisfactory result achieved after three months of community-based SET was unlikely to have changed at 6 and 12

Table 3. Walking distances

Median increase functional claudication distance*				
Follow up	N	Median (IQR) metres	Absolute median increase (IQR) metres	Median % increase (IQR)
Baseline	269	230.0 (120.0–427.5)	-	-
1 month	201	412.0 (275.0–630.0)	110.0 (30.0–245.0)	47.7% (8.3–115.6)
3 months	187	510.0 (324.0–840.0)	220.0 (90.0–430.0)	100.0% (34.5–260.9)
6 months	159	650.0 (350.0–1200.0)	340.0 (143.0–747.0)	140.0% (59.1–380.0)
12 months	125	700.0 (395.0–1600.0)	440.0 (172.0–905.0)	166.7% (79.4–342.2)

Median increase absolute claudication distance				
Follow up	N	Median (IQR) metres	Absolute median increase (IQR) metres	Median % increase (IQR)
Baseline	272	400.0 (232.0–630.8)	-	-
1 month	206	618.5 (407.5–985.0)	140.0 (40.0–330.0)	37.1% (10.5–77.6)
3 months	190	792.0 (487.5–1242.5)	265.0 (110.0–592.5)	79.4% (33.9–169.0)
6 months	163	900.0 (490.0–1600.0)	360.0 (149.0–850.0)	87.5% (33.3–229.2)
12 months	129	1100.0 (520.0–1600.0)	506.0 (185.5–890.0)	107.8% (47.8–201.9)

IQR: Interquartile range.
*In some patients, only absolute claudication distance was measured.

Table 4. Increase in absolute claudication distance / time in prior studies using clinic-based

Trial	**Patients**	**Duration SET (months)**	**Increase in ACD / ACT (%)**	
			6 months	12 months
Creasy[12]	16	12	110%	110%
Dahllof[13]	10	6	116%	-
Lundgren[15]	23	6 - 12	-	151%
Mannario[16]	10	6	86%	-
Tisi[18]	22	1	60%	68%
Cheetham[11]	28	6	129%	130%
Degischer[14]	19	3	70%	-
Kakkos[17]	8	6	52%	86%
Savage[20]	11	6	42%	-
Patterson[19]	25	3	159%	-
Mean % increase overall			92%	109%

SET: Supervised Exercise Therapy, ACD: Absolute claudication distance, ACT: Absolute claudication time

months. This finding could have consequences for clinical care and could lead to the notion that if results are unsatisfactory at 3 months of community-based SET, other treatment options should be considered. Naturally, at that time, severity of complaints and the risk of invasive interventions must be taken into account.

Patients referred for community-based SET are offered one year of exercise therapy, based on limited reimbursement up to one year. However, after 6 months of SET, walking distance had stabilized and FCD and ACD did not increase further. The reason for this phenomenon is unclear. A possible explanation is that after 6 months of community-based SET, patients achieve their maximum, entering into a plateau phase. Another explanation could be that within a year of community-based SET, the frequency of sessions gradually decreases, leading to maintenance of but not increases in walking distance. In a meta-analysis by Gardner et al, the best duration of a SET program was six months or longer, but no distinction was made between six and 12 months.[21] Dose-response research is needed to address this issue.

Another issue of discussion is the mode of exercise. Currently, the recommended mode of exercise mainly consists of treadmill walking to near maximal pain, according to the guidelines of the Royal Dutch Society for Physiotherapy.[9] However, recent research suggests that a pain-free mode of training also has significant effects on walking distance compared with a non-exercising control group.[22,23] Possible advantages of pain-free training could be better compliance and lower dropout rates. To determine if pain-free walking is as effective as walking to near maximal pain, further research is needed.

Comparing non-supervised exercise therapy with SET, the results with SET are statistically significantly better, leading to approximately 150-m and 225-m greater increases in ACD after three months[5] and six months[24] of follow-up, respectively. Ideally, according to the TransAtlantic Inter-Society Consensus Document on management of PAD (TASC-II), SET should be made available for all patients with intermittent claudication.[1] Implementing SET for intermittent claudication in an outpatient clinic, however, is very complicated or maybe even impossible, based on its disadvantages. First of all, the capacity of the usual department of rehabilitation and physiotherapy in a hospital is not sufficient for the numbers of patients with intermittent claudication who are eligible for non-invasive therapy. Furthermore, patients are often limited in their transport to the hospital in terms of costs and time. Community-based SET is an easy and good alternative for structurally implementing SET for every patient with intermittent claudication.

In addition to the effects on walking distance, SET could have a beneficial effect related to vascular risk factor management. Exercise has a known positive influence on vascular risk factors such as hypertension, hypercholesterolemia, and diabetes mellitus.[25] Furthermore, reports show that patients with PAD[26] (or more specifically, intermittent claudication)[27]

who are physically active are less likely to die compared with a group of sedentary patients with PAD.[26,27] After adjustments for age, ABI, and body mass index, these results are similar in patients with intermittent claudication.[27]
A possible disadvantage of community-based SET could be the large number of participating physiotherapists, leading to a lower volume of patients and less experience per physiotherapist. Thus, by referring patients only to specifically trained physiotherapists and not to just any physiotherapist, this problem can be addressed. Furthermore, by organizing SET in a community-based setting, an increasing number of patients with intermittent claudication can be treated, leading to greater numbers of experienced physiotherapists.
In addition, regular refresher courses with all participating physiotherapists can ensure adequate and shared knowledge. However, the number of referred patients, and thus the experience of the physiotherapists, is dependant on the utilization of the program.

The high number of dropouts (40.0% within six months and 52.6% within 12 months) is a disadvantage of community-based SET. However, in the literature, we find corresponding dropout percentages after six months of SET, from 10% up to 50%.[17,22,28-30] Only two studies report a dropout percentage after 12 months, ranging from 16% to 41%.[15,31] It should be realized that in the literature, dropout is observed in randomized controlled trials that have a highly selected patient population with strictly chosen inclusion and exclusion criteria. Presumably, dropout rates of community-based SET in usual practice seem not to be increased compared with clinic-based SET.

Although the presence of intermittent claudication leads to functional impairment for the patient, the clinical course as far as the leg is concerned is surprisingly stable in most cases.[1]
For this reason, it is usually acknowledged that invasive interventions with known morbidity and mortality should be used with restraint. The main reason for patients to stop community-based SET is intercurrent disease, and not unsatisfactory results. Thus, if a patient stops SET, the reason should be evaluated. The physician can use this moment to evaluate to the next level of decision making and consider an invasive intervention, if clinically indicated.
Our data suggest that after three months of SET, a physician can properly evaluate a patient's response to SET. In summary, SET represents a viable treatment for intermittent claudication with no known complications and has the potential to treat patients safely, preventing an invasive vascular intervention in a number of patients. Although many patients discontinue SET prematurely, its noninvasive nature and satisfactory improvement in the majority of patients are reasons to use it as the initial treatment in patients with intermittent claudication.

In case of unsatisfactory results, the option for PTA or surgical revascularization is still open if clinically indicated.

CONCLUSION

Community-based SET seems as efficacious as SET in a clinical study approach in improving walking distance in patients with intermittent claudication, however, has high drop-out rates. Furthermore, good and unsatisfactory results after three months are likely to persist, which could be useful for a physician in evaluating response to community-based SET and planning further treatment.

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CHAPTER 5

EFFECT OF SUPERVISED EXERCISE THERAPY FOR INTERMITTENT CLAUDICATION IN PATIENTS WITH DIABETES MELLITUS

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ABSTRACT

INTRODUCTION

Primary treatment for patients with intermittent claudication is exercise therapy. Diabetes mellitus (DM) is a frequent occurring co-morbidity in patients with intermittent claudication and in these patients exercise tolerance is decreased. However, there is little literature about the increase in walking distance following supervised exercise therapy (SET) in patients with both intermittent claudication and DM. The objective of this study was to determine the effectiveness of SET for intermittent claudication in patients with diabetes mellitus (DM).

MATERIAL AND METHODS:

Consecutive patients with intermittent claudication who started SET were included. Exclusion criteria were Rutherford stage 4 – 6, and the inability to perform the standardised treadmill test. SET was administered according to the guidelines of the Royal Dutch Society for Physiotherapy. At baseline and at 1, 3 and 6 months of follow up a standardised treadmill exercise test was performed. The primary outcome measurement was the absolute claudication distance (ACD).

RESULTS

We included 775 patients of whom 230 had DM (29.7%). At 6 months of follow up, data of 451 patients (58.0%) were available. Both ACD at baseline and 6 months of follow up were significantly lower in patients with DM ($P<0.001$). However, increase in ACD after 6 months of SET did not differ significantly ($P=0.48$) between the DM-group and non DM-group, and was 270 and 400 metres respectively.

CONCLUSION

In conclusion, SET for patients with intermittent claudication is equally effective in improving walking distance for both patients with and without DM, although absolute ACD remains lower in patients with DM.

INTRODUCTION

Primary conservative treatment for patients with intermittent claudication is exercise therapy.[1-3] Recently, several randomised controlled studies have documented the additional effect of supervised exercise therapy (SET).[4-7] In literature, mean increases in maximal walking distance or absolute claudication distance (ACD) range from 50% up to 191% after 6 months of SET.[4, 6-8]

A frequently occurring co-morbidity in patients with peripheral arterial disease (PAD) is diabetes mellitus (DM), with a prevalence ranging from 20 up to 41% compared to 7.8% in the general population.[8-11] It is well established that diabetes is associated with a more rapid progression of PAD,[12] and a decreased exercise tolerance.[13-16] However, in several studies examining the effect of SET, patients with DM are excluded.[7, 17-23]

Current hypotheses on the physiological mechanisms suggest that SET increases walking distance in patients with intermittent claudication due to beneficial effects on skeletal muscle metabolism, endothelial function and inflammatory response.[24, 25] Since DM is associated with metabolic changes in skeletal muscle and endothelial function,[26, 27] this already suboptimal metabolic environment might result in a lower effectiveness of SET in patients with DM and claudication compared to patients with only intermittent claudication. However, only little information is available regarding the influence of diabetes on the result of exercise therapy.

The objective of the current study was to determine if the increase in walking distance following SET for intermittent claudication is equal in patients with DM compared to non-DM patients.

PATIENTS AND METHODS

STUDY SETTING

Patients who visited the outpatient clinic of the department of vascular surgery with complaints of intermittent claudication receive a diagnostic workup, consisting of an ankle brachial index (ABI) measurement and / or duplex ultrasound.

Patients with PAD, Rutherford stage 1 – 3 without signs of significant occlusive disease in the aorta-iliac tract were primarily considered for community-based SET. Community-based refers to the location where SET is administered. Instead of restriction to the department for physiotherapy and rehabilitation in the hospital, patients can train with an

educated private physiotherapist within the area of their homes. More details about community-based SET (implementation, training of physiotherapists) are previously described by Willigendael et al.[28]

STUDY POPULATION

Consecutive patients with PAD, Rutherford stage 1 – 3 who started community-based SET in the period from January 2005 to November 2007 were eligible for inclusion. Exclusion criteria were the presence of Rutherford stage 4 – 6 and the inability to perform the standardised treadmill test.

SUPERVISED EXERCISE THERAPY

SET was administered, according to the guidelines of the Royal Dutch Society for Physiotherapy[29] by trained private physiotherapists. The main goal of SET is to increase the patient's walking distance. This is mainly achieved by walking in intervals up to sub-maximal pain (intense pain, distraction not possible), followed by a short resting period. Generally, patients start with 2 – 3 sessions of 30 minutes every week during the first 3 months. From 3 – 6 months the frequency gradually decreases to 1 session every two weeks. Treadmill walking was the main mode of exercise. Furthermore, patients were encouraged to walk on a daily basis to sub-maximal pain. Further details about the training program and results are previously described.[8, 30]

BASELINE CHARACTERISTICS

At baseline, all patients underwent an intake performed by a nurse practitioner of the department of vascular surgery. Vascular risk factors (smoking, diabetes, hypertension, hypercholesterolemia, cardio- and cerebrovascular disease) were registered. Other relevant co-morbidities such as pulmonary and musculoskeletal disease were recorded, as well as a history of vascular interventions. Blood pressure was measured and body mass index (BMI) was calculated. A routine blood screen test was performed to determine fasting glucose, a lipid spectrum, and HbA1c% levels. Hypertension was defined as a blood pressure ≥ 140/90 mmHg or the use of antihypertensive drugs. Presence of DM was recorded in case of serum fasting glucose level ≥ 6 mmol/l or the use of anti diabetic drugs. Hypercholesterolemia was defined as a fasting cholesterol level ≥ 5 or the use of cholesterol lowering drugs.

WALKING DISTANCES

To evaluate therapy progress, walking distances were assessed at baseline and at 1, 3, and 6 months of follow up. We used a standardised treadmill protocol with a constant

speed of 3.2 km/h and an increasing slope of 2% every 2 minutes to a maximum slope of 10%.[31, 32] The maximum testing duration was 30 minutes. Prior to the baseline measurement all patients performed a separate treadmill training session in order to familiarize them with the treadmill protocol.
We measured two distances; the functional claudication distance (FCD) and the absolute claudication distance (ACD). The FCD is defined as the moment patients preferred to stop walking because of claudication pain. The ACD is defined as the maximal possible walking distance. Both FCD and ACD are reliable measurements for evaluating walking distance in patients with intermittent claudication.[33] All data were prospectively recorded in a web based database designed and secured by the Centre for Evidence Based Physiotherapy (www.cebp.nl) and Fastguide® (www.fastguide.eu).

STATISTICAL ANALYSIS

Interval variables were presented as mean ± standard deviation for normal distributed data and as median (inter-quartile-range) for not normal distributed data. Nominal variables are presented as frequency (percentage). To identify statistical significant differences in baseline characteristics between two groups a student's T-test (normal distribution), a Mann-Whitney test (skewed distribution) or a Chi-square test (dichotomous variables) was used.
FCD and ACD were both expressed as absolute distance in meters and as increase compared to baseline. Repeated measures ANOVA was used to analyse the change in walking distance over time. To identify a significant difference in change in walking distance between groups, the grouping variable (DM) was taken as between subject factor. Covariates in the analyses included coronary heart disease, cerebrovascular disease, BMI, smoking behaviour, ABI, and age. FCD and ACD were both transformed to a logarithmic scale, as both outcome measurements were not normally distributed. We used polynominal contrasts to adjust for the different time intervals between the follow up measurements and in case the sphericity assumptions were violated a Greenhouse-Geisser correction was used. P-values of <0.05 were considered to be statistically significant. Analyses were performed using SPSS 15.0.

RESULTS

From January 2005 to November 2007, 775 patients with intermittent claudication started community-based SET and were included in the present study. The total study population consisted of 230 patients (29.7%) with DM and 528 (68.1%) patients without DM. In

Table 1. Baseline characteristics of all patients with and without diabetes

Characteristic	DM (N = 230)	No DM (N = 528)	P-value	Missing data DM	Missing data No DM
Age	67.5 ± 9.3	66.7 ± 10.5	0.28	1 (0.4)	3 (0.6)
Men	154 (67.0)	321 (60.8)	0.11	-	-
BMI	28.3 ± 4.4	25.8± 4.1	<0.001	8 (3.5)	25 (4.7)
Current smoker	75 (32.6)	240 (45.5)	0.001	2 (0.9)	8 (1.5)
Hypertension	191 (83.0)	413 (78.2)	0.13	-	-
Hypercholesterolemia	171 (74.3)	381 (72.2)	0.53	-	-
Coronary heart disease	93 (40.4)	131 (24.8)	<0.001	-	-
Cerebrovascular disease	44 (19.4)	61 (11.6)	0.005	3 (1.3)	4 (0.8)
Pulmonary disease	36 (16.1)	68 (13.0)	0.26	6 (2.6)	4 (0.8)
Musculoskeletal disease	22 (9.7)	56 (10.6)	0.70	3 (1.3)	2 (0.4)
Previous vascular intervention	88 (38.6)	177 (33.6)	0.19	2 (0.9)	1 (0.2)
ABI	0.75 ± 0.22	0.71 ± 0.20	0.01	18 (7.8)	32 (6.1)
SBP (mmHg)	157.3± 21.8	156.5 ± 25.9	0.70	14 (6.1)	31 (5.9)
HbA1c (%)	7.5 ± 1.6	5.8 ± 0.38	<0.001	32 (13.9)	242 (45.8)
Glucose (mmol/L)	8.8 ± 3.3	5.5 ± 0.6	<0.001	14 (6.1)	76 (14.4)
Cholesterol (mmol/L)	4.8 ± 1.5	5.2 ± 1.2	0.001	11 (4.8)	55 (10.4)
LDL (mmol/L)	2.6 ± 1.2	3.0 ± 1.0	<0.001	30 (13.0)	89 (16.9)
HDL (mmol/L)	1.3 ± 0.6	1.4 ± 0.5	0.012	22 (9.6)	76 (14.4)
Triglycerides (mmol/L)	2.0 ± 1.0	1.7 ± 1.0	<0.001	26 (11.3)	84 (15.9)
Baseline FCD (m)	180.0 (100.0-317.5)	230.0 (110.0-440.0)	0.001	6 (2.6)	10 (1.9)
Baseline ACD (m)	315.0 (180.0-512.5)	440.0 (280.0-720.0)	<0.001	-	-

DM: Diabetes mellitus, BMI: Body mass index, ABI: Ankle brachial index, SBP: Systolic blood pressure, LDL: Low density lipoprotein, HDL: High density lipoprotein, FCD: Functional claudication distance, ACD: Absolute claudication distance

17 patients (2.2%) presence of diabetes was not recorded and these patients were excluded from further analysis. Baseline characteristics are summarized in table 1. Patients with DM had significantly higher BMI, ABI, triglyceride-, blood glucose- and HbA1c-levels compared to non DM patients and patients with DM had more often coronary- and cerebrovascular disease. Cholesterol-, low-density-lipoprotein-, and high-density-lipoprotein-levels were significantly lower in DM patients. Furthermore, patients with DM had a significantly lower baseline FCD and ACD and were less often smokers compared to patients without DM.

At 6 months follow up, 324 patients (42%) discontinued SET early because of reasons summarized in table 2. Patients that did not complete the 6 months training program showed significantly higher percentages of musculoskeletal disease, cerebrovascular dis-

ease and hypercholesterolemia. For all other baseline characteristics, including diabetes, no statistical significant difference was found.

WALKING DISTANCES

At baseline, walking distances for patients with DM were significantly lower (P<0.001) compared to patients without DM. The median FCD was 180 and 230 meters for the DM group and the non DM group respectively. The median ACD for patients with and without DM was 315 and 440 meters. This difference in FCD and ACD persisted at every follow up moment in time.

However, increase from baseline of FCD and ACD was not significantly different between the diabetes and non-diabetes group. At 6 months of follow up FCD increased with a median of 280 meters for the DM group compared to 332 meters for the group without DM (P=0.72). The median ACD increased with 270 metres and 400 metres for the DM group and the non DM group respectively (P=0.48). After adjusting for coronary heart disease, cerebrovascular disease, BMI, smoking behaviour, ABI, and age increase in FCD and ACD did not differ between the two groups with P-values of 0.63 and 0.56 respectively. More details about the walking distances are presented in table 3.

Table 2. Reasons for withdrawal

Reasons	Withdrawals* (n=324)
Reason not recorded	109 (33.6)
Musculoskeletal disease	19 (5.9)
Cardiovascular disease	22 (6.8)
Pulmonary disease	6 (1.9)
Sufficient result of SET	23 (7.1)
Lack of motivation	39 (12.0)
Insufficient progress	22 (6.8)
Death	4 (1.2)
Insurance or logistical problems	8 (2.5)
Other	66 (20.4)

SET = supervised exercise therapy

* Data are represented as number of patients (%)

Table 3. Walking distance in diabetics compared to non-diabetics

Functional claudication distance*				
	Absolute distance		Increase in walking distance	
Follow up	Diabetes	Non-diabetes	Diabetes	Non-diabetes
Baseline	180 (100-318) (N=224)	230 (110-440) (N=518)	-	-
1 month	330 (200-520) (N=139)	400 (245-612) (N=350)	90 (30 – 220) (N=139)	110 (30 – 220) (N=344)
3 months	400 (240-600) (N=137)	500 (317-750) (N=335)	180 (78 – 300) (N=137)	200 (90 – 420) (N=331)
6 months	500 (300-893) (N=126)	600 (380-1150) (N=311)	280 (110 – 510) (N=123)	332 (140 – 650) (N=306)

Absolute claudication distance*				
	Absolute distance		Increase in walking distance	
Follow up	Diabetes	Non-diabetes	Diabetes	Non-diabetes
Baseline	315 (180-513) (N=230)	440 (280-720) (N=528)	-	-
1 month	540 (350-837) (N=141)	640 (450-1030) (N=357)	110 (47 – 317) (N=141)	150 (30 – 340) (N=357)
3 months	610 (375-1030) (N=137)	800 (530-1350) (N=342)	200 (80 – 496) (N=137)	300 (106 – 590) (N=342)
6 months	650 (410-1600) (N=127)	1010 (600-1600) (N=314)	270 (120 – 685) (N=126)	400 (166 – 811) (N=314)

* All distances are represented as median (first - third interquartile range)

DISCUSSION

Results of this study show that patients with and without DM have a similar increase in walking distance after 6 months of community-based SET. This indicates that SET as primary treatment for intermittent claudication is equally effective in improving walking distance in patients with and without diabetes.
However, we found that absolute walking distance at baseline was significantly lower in patients with DM compared to non DM patients ($P<0.001$ for both ACD and FCD) and that this difference continued to exist at every follow up moment.

Our results are in contradiction with research by Ubels et. al.,[34] who reported that SET has a greater relative gain in patients with DM. A possible explanation for the different results is the small number of diabetic patients (n=33) included in that study. Secondly, Ubels

et. al. used a 6 km/h corridor test to measure walking distance which is more difficult to standardize.[34]
Other studies did not concern SET but limited their research to the influence of diabetes on exercise tolerance in patients with intermittent claudication.[13, 15, 35-37]
Evidence in literature is conflicting. Carter et. al. [22] and Katzel et. al.[25] did not report any difference in exercise tolerance between diabetic and non diabetic patients. However, results of these studies might have been biased by the fact that patients with severe co-morbidities were excluded, including patients with poorly controlled diabetes. More recent studies, that did not exclude patients with poorly regulated DM, did report lower exercise performance in patients with DM.[13, 15, 37]

We hypothesised that an already sub optimal metabolic environment can contribute to a lower exercise performance in patients with intermittent claudication and DM. Skeletal muscle metabolism might be less efficient in DM patients which can result in a more rapid appearance of ischemic pain and thus decreasing FCD and ACD. Results of our study support this hypothesis only partially. Despite that absolute walking distance in diabetic patients is lower than in non diabetic patients, we found that increase in walking distance was similar in both groups. This latter suggests that the beneficial effect of SET is not negatively influenced by presence of diabetes.

In literature, different studies describe a significant correlation between BMI and walking distance in patients with intermittent claudication.[15, 38] In our study, BMI in the DM group was significantly higher compared to the non DM group. This might be a reason for the lower walking distance in the diabetes group. However, after adjusting for this difference in a multivariate analysis, increase in walking distance after 6 months of SET is not significantly different between the two groups. Another possible explanation for lower exercise performance in the diabetes group might be that patients with a chronic condition such as diabetes are overall less conditioned than non DM patients.
At last, PAD patients with DM are more likely to have crural disease compared to patients without DM.[39] This could have influence on the response to exercise therapy. There is some suggestion in literature that patients with femoral disease have more benefit from exercise therapy compared to patients with aorto-iliac disease.[40] However, the difference in response to exercise of crural disease compared with other anatomic locations is not known.

LIMITATIONS OF THE STUDY

A major limitation of this study was the high number of missing measurements due to patients who discontinued before 6 months of SET were completed. At 6 months, 42% of patients had dropped out, resulting in missing data which leads to loss of power. Several statistical options for imputing data are available to handle missing data.[41, 42] However, missing data in our study are likely to be not missing at random. Therefore, any form of imputing data would potentially lead to unacceptable bias. To minimize this bias, we deferred from imputation.

High drop out percentages are a common phenomenon in SET program for intermittent claudication. In literature drop out percentages after 6 months of SET range from 7 – 40% in randomised controlled trials.[4, 5,11] Our drop out percentage was 42% in a study setting describing daily practice. Previous literature about community-based SET show similar drop out percentages.[8, 30] It should be realized that the dropout percentages observed in randomised controlled trials could be lower than in daily practice because of the inclusion of a highly selected population and the exclusion of patients with multiple co-morbidities. In our study SET was part of the regular care for patients with intermittent claudication and therefore presence of major co-morbidities was not a reason for exclusion from the exercise program.

A second limitation is that we did not record changes in medical treatment of diabetes, nor did we repeat measurements of fasting glucose and HbA1c at 6 months of follow up. Hence, it is possible that our subgroup of PAD patients without diabetes included some patients with undiagnosed diabetes, which might have reduced the differences between patients with and without diabetes. Thus, the absence of a significant difference in increase in walking distance could be biased by altered diabetes control instead of SET.

Furthermore, as we can conclude from table 1, baseline measurements were not complete in every patient. This might have biased our analysis. Collection of baseline characteristics was dependent on vascular nurses and although prospectively collected, measurements in our study were performed as part of regular care for PAD patient and not as part of a controlled trial.

Also, treadmill measurements were not repeated, so variability between repeated tests in this population are not known. However, previous literature about variability of FCD and ACD show that variability is small and both are reliable instruments to measure walking ability.

CONCLUSION

SET as primary treatment for intermittent claudication seems as effective in patients with DM compared to patients without DM in improving walking distance. However, in absolute terms, patients with both DM and PAD perform on a lower level.

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CHAPTER 6

PREDICTORS OF WALKING DISTANCE AFTER SUPERVISED EXERCISE THERAPY IN PATIENTS WITH INTERMITTENT CLAUDICATION

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ABSTRACT

OBJECTIVE
To identify predictors variables for results after supervised exercise therapy (SET), and to develop a clinical prediction model that aims to predict a target walking distance for individual patients.

DESIGN
Retrospective analyses on prospectively collected data

MATERIALS
Patients with intermittent claudication who participated in a SET program.

METHODS
SET was conducted according to the guidelines of the Royal Dutch Society for Physiotherapy. The main outcome measurement was the absolute claudication distance (ACD) after 6 months of SET. Linear regression analyses were conducted to identify independent predictor variables for ACD.

RESULTS
Four-hundred-and-thirty-seven patients were analyzed. Independent predictor variables for post-treatment ACD were baseline ACD ($P<0.001$), smoking behaviour ($P=0.012$), and body-mass-index ($P=0.041$). A better baseline ACD was associated with a longer post-treatment ACD whereas current smoking, and a higher body-mass-index were associated with a shorter post-treatment ACD. The final regression equation included baseline ACD, age, body-mass-index, smoking, and pulmonary disease and was translated into several clinical prediction models. However, only 24.8 – 33.6% of the patients had an ACD within the calculated target range.

CONCLUSION
Predictive variables for post-treatment ACD after SET are baseline ACD, age, body-mass-index, pulmonary disease, and smoking behaviour. However, translating the regression equation into a clinical prediction model did not lead to a valid model for use in clinical practice.

INTRODUCTION

A common symptom, experienced by patients with peripheral arterial disease (PAD) is intermittent claudication, defined as discomfort in the muscles of the lower extremities that is repeatedly produced by exercise and relieved when at rest. Complaints of intermittent claudication have a considerable negative influence on a patient's walking ability and quality of life.[1-3]

Exercise therapy is an effective treatment to increase walking distance in patients with intermittent claudication,[4, 5] and according to a recent Cochrane review, better results are obtained with supervised exercise therapy (SET) compared with non supervised exercise therapy.[6]

The Dutch physiotherapy guideline, "Intermittent Claudication" from the Royal Dutch Society for Physiotherapy provides a practical tool for physiotherapists who supervise patients in exercise training. According to the guideline, an increase in maximal walking distance of more than 100%, evaluated on a treadmill, is considered to be a good result after SET.[7] In a previously conducted cohort study from our research group, about 48% of patients achieved a good result and 36% of patients achieved an unsatisfactory result (< 50% improvement) after SET.[8]

Research on patient-related factors that could influence the results of SET is scarce. However, if clinical variables that influence the results of SET can be identified, it may be possible to identify a subgroup of patients that will not benefit from SET. As a consequence, an alternative course of treatment could be planned for these patients.

We hypothesized that patient-related baseline variables can influence results of SET. Therefore, the objective of this study was to identify clinical predictors of results after SET and to develop a clinical prediction model based on patient-related variables that exist at baseline.

METHODS

STUDY POPULATION

In patients with a complaint of intermittent claudication who were referred to the vascular outpatient clinic, the diagnosis of PAD was confirmed with an ankle-brachial-index (ABI) measurement and / or a duplex ultrasound. Patients with complaints of intermittent claudication and confirmation of PAD with an ABI measurement below 0.9 at rest or decreasing more than 0.15 after exercise were eligible for community-based SET. Ischemic pain in rest and tissue loss were exclusion criteria for participation in community-based

SET. Vascular nurse practitioners performed an intake of every patient, recording smoking behaviour, co-morbidities, height, weight, and blood pressure. Furthermore, all patients received a prescription for a platelet inhibitor and lipid-lowering medication (statins).
Data were prospectively recorded in an electronic patient database developed by the centre of evidence based physiotherapy (www.cebp.nl) and Fastguide® (www.fastguide.eu).
All patients who started community-based SET were potentially eligible for inclusion. Exclusion criteria to participate in the current study were the inability to walk the standardised treadmill test, and a baseline ACD of more than 1600 meters. These patients however did start community-based SET.
Registration of the patients' medical data in the electronic patient database is part of the usual care program and all patients provided their oral informed consent to register and use their medical data.

BASELINE VARIABLES

Smoking behaviour was recorded as current smoker or non-current smoker (never and previous smokers). Diabetes mellitus (DM) was considered present if serum fasting glucose levels were above 7.0 mmol/l and/or glucose lowering medication was prescribed. Hypertension was defined as the use of blood pressure lowering medication and/or a systolic blood pressure over 140 mmHg. Orthopaedic disease was defined as the presence of at least one of the following: arthrosis, rheumatoid arthritis, poly-arthritis, osteoporosis, or arthroplasty in the lower extremities. Cardiac disease was considered to be present in patients with one of the following conditions in their medical history: angina pectoris, heart failure, myocardial infarction, coronary arterial bypass graft, percutaneous transluminal coronary angioplasty, valvular disease or rhythm disorders. Pulmonary disease was defined as the presence of at least one of the following: asthma, chronic obstructive pulmonary disease, emphysema, or interstitial pulmonary disease. Patients with a cerebrovascular accident or a transient ischemic attack in their medical history were considered to have neurological disease.

SUPERVISED EXERCISE THERAPY PROGRAM

All patients received SET according to the guidelines of the Royal Dutch Society for Physiotherapy[7] in a community-based setting as a part of the usual care program. Detailed information on the community-based training program is extensively reported previously by our research group.[8-10]

THERAPY EVALUATION

Patients were evaluated by their physiotherapist at baseline and after 1, 3, 6, 9, and 12

months of follow up. Walking distances were measured by a standardized graded treadmill test with a constant speed of 3.2 km/h. The incline starts at 0% and is increased by 2% every 2 minutes. In practical considerations slope and testing duration are maximized at 10% and 30 minutes respectively. Results were registered by the physiotherapists in the web-based electronic patient database.
The primary outcome measurement of community-based SET is the ACD, defined as the distance walked before a patient is forced to stop exercise. Post-treatment ACD was measured at least 6 months after the initiation of SET.

ANALYSIS
Categorical variables are presented as frequencies with percentages. Nominal variables are presented as the mean ± standard deviation (normal distribution) or as median and interquartile-range (IQR) for a skewed distribution. For walking distance, means and standard deviations are reported for the purpose of comparison with the literature. Change in walking distance over time in the total cohort was analyzed using repeated measurement ANOVA.
Univariable and multivariable linear regression analyses were conducted to identify variables predictive of the absolute post treatment ACD and the percentage increase in ACD. In the univariable regression analysis each variable is included in a separate regression analysis. In the multivariable regression analysis, all pre-specified variables are included in one regression analysis, using the enter method. With the enter method all variables are included in one step. Pre-specified variables that were included in the regression models were baseline ACD, age, smoking behaviour, ABI, BMI, DM, pulmonary disease, neurological disease, cardiac disease and orthopaedic disease.
Finally, multivariable linear regression analyses using the backward elimination method were used to identify the variables included in the final regression equations. The backward method starts with all the variables in the equation and in every step variables that do not have a statistically significant influence are excluded. The criterion for removal from the regression model was a P-value of more than 0.10. The final regression equations were formulated to predict post treatment ACD and percentage increase in ACD. The regression equation with best quality was translated into different clinical prediction models to explore the best way to predict post-treatment ACD. The quality of the regression equation was described with R^2, and lays between 0 – 100%, with 0 and 100% being worst and best quality, respectively. R^2 can be interpreted as the percentage of variability existing in the original cohort that can be explained with the included predictor variables in the regression equation.
The quality of the different clinical prediction models was tested by comparing the predicted and real values for each individual patient.

RESULTS

From January 2005 until January 2008, 760 patients met the inclusion criteria and were included in the study. At 6 months of follow up, 437 patients (57.5%) were available for the analysis. For 323 patients a post-treatment ACD was not available. These patients discontinued SET early for the following reasons: co-morbidity (n=63, 19.5%), good result (n=26, 8.0%), unsatisfactory result (n=32, 9.9%), insurance/transport problems (n=14, 4.3%), not motivated (n=38, 11.8%), death (n=5, 1.5%), other reasons (n=40, 12.4%), no reason recorded (n=105, 32.5%). There were no significant differences in baseline characteristics between the analyzed patients and the patients that discontinued community-based SET early, as can be seen in table 1. Further baseline characteristics of the study population are also described in table 1.

The median ACD of the total cohort increased significantly (P <0.001) from 380 (IQR 250 – 570) meters at baseline (mean ± SD, 449 ± 292 m) to a median of 850 (IQR 505 – 1600)

Table 1. Clinical characteristics of the study population

Characteristic*	Total population (N=760	Analyzed population (N=437)	Early dropouts (N=323)	P-value	Missing values n (%)
Men	474 (62.4)	266 (60.9)	208 (64.4)	0.321	-
Age, years	66.0 ± 10.0	65.6 ± 9.9	66.6 ± 10.0	0.170	5 (0.7)
BMI	26.6 ± 4.4	26.5 ± 4.4	26.8 ± 4.4	0.316	45 (5.9)
Resting ABI	0.72 ± 0.20	0.71 ± 0.20	0.72 ± 0.21	0.815	66 (8.7)
SBP (mmHg)	156.7 ± 25.1	156.7 ± 26.0	156.7 ± 24.0	0.998	59 (7.8)
Current smokers	307 (41.3)	180 (42.1)	127 (40.3)	0. 634	17 (2.2)
Hypertension	592 (79.1)	335 (78.1)	257 (80.6)	0.410	12 (1.6)
DM	221 (29.9)	119 (28.1)	102 (32.3)	0.216	20 (2.6)
Pulmonary disease	127 (17.3)	71 (16.7)	56 (17.9)	0.669	24 (3.2)
Neurological disease	106 (14.3)	52 (12.2)	54 (17.1)	0.062	19 (2.5)
Cardiac disease	260 (34.7)	146 (34.2)	112 (34.9)	0.911	10 (1.3)
Orthopedic disease	106 (14.3)	52 (12.2)	54 (17.1)	0.058	17 (2.2)
Baseline ACD**	390 (240 – 590)	380 (250 – 570)	400 (220 – 600)	0.574	-

BMI: Body mass index, ABI: Ankle brachial index, SBP: Systolic blood pressure, DM: Diabetes mellitus, ACD: Absolute claudication distance

* Dichotomous variables are presented as n (%), and continuous variables as mean ± standard deviation, unless otherwise indicated.

** Baseline ACD reported as median (inter-quartile range).

meters post-treatment (mean ± SD, 949 ± 495 m). More details on walking distance can be found in table 2.

Table 2. Median absolute claudication distance for the total cohort

Follow up	N	Absolute ACD* metre Median (inter quartile range)	Absolute increase in ACD, metre Median (inter quartile range)
Baseline	437	380 (250 - 570)	-
1 month	339	620 (420 – 900)	190 (64 - 360)
3 months	348	725 (512 - 1170)	320 (130 - 590)
6 months	437	850 (505 - 1600)	390 (188 - 805)

ACD: Absolute claudication distance. * P value < .001 for the increase in ACD

CLINICAL PREDICTORS FOR POST-TREATMENT ACD

In table 3, the associations between the different baseline characteristics with post-treatment ACD are presented. In the multivariable regression analysis that included all selected variables, baseline ACD (P<0.001) and current smoking (P=0.008) were independent predictor variables for post-treatment ACD. A better baseline ACD was associated with a longer post-treatment ACD, whereas current smoking was associated with a lower post-treatment ACD. The R^2 of the multivariable regression was 29.3%, including 10 variables.
The final regression equation had a R^2 of 29.4% with 5 variables instead of 10. Baseline ACD (P<0.001), current smoking (P=0.012), and BMI (P=0.041) were significant predictors. Besides these variables, the final regression equation for post-treatment ACD consisted of age, and pulmonary disease. In the final regression equation, a better baseline ACD was associated with a better post-treatment ACD whereas older age, current smoking, higher BMI, and presence of pulmonary disease were associated with a lower post-treatment ACD. The following regression equation was determined:

ACD post-treatment = 1218 + 0.9 * ACD baseline – 5 * Age – 11 * BMI – 124 * Current smoking – 114 * Pulmonary disease.

For baseline ACD, age, BMI, smoking behaviour and pulmonary disease, the baseline values of an individual patient can be inserted into the regression equation to calculate post-treatment ACD. For the dichotomous variables, zero means the condition is not present and one means that the condition is present.

Table 3. Regression models for post-treatment absolute claudication distance

Variables	Univariable regression		Multivariable regression*		Final regression**	
	P value	Beta per unit #	P value	Beta per unit #	P value	Beta per unit #
Total model	-	-	<.001	-	<.001	-
Continuous variables						
Baseline ACD	<.001	0.899	<.001	0.858	<.001	0.879
Age	<.001	-9.831	.110	-4.092	.062	-4.686
ABI	.104	203.587	.221	137.813	-	-
Body-mass-index	.179	-7.424	.119	-8.597	.041	-10.760
Dichotomous variables						
Current smoking	.120	-75.523	.008	-134.110	.012	-123.708
DM	.004	-154.867	.200	-67.973	-	-
Pulmonary disease	.005	-180.826	.071	-110.014	.059	-114.194
Neurological disease	.069	-133.317	.748	-22.277	-	-
Cardiac disease	.242	-58.777	.326	-49.195	-	-
Orthopaedic disease	.096	-121.533	.704	-27.099	-	-

ACD: Absolute claudication distance, ABI: Ankle-brachial-index, DM: Diabetes mellitus
* R^2 = 29.3%, * R^2 = 29.4%,
# The Beta gives information about the direction of the association and the influence of each individual variable. The bigger the beta, the bigger the influence per unit on the dependant variable.

CLINICAL PREDICTORS OF PERCENTAGE INCREASE IN ACD

The associations of the different baseline characteristics with percentage increase in ACD are presented in table 4. In the multivariable regression analysis that included all pre-specified variables, baseline ACD (P<0.001) and BMI (P=0.022) were independent predictors for percentage increase in ACD. The multivariable regression model that included all 10 variables had a R^2 of 0.94%. The final regression model had a R2 of 10.7% with inclusion of baseline ACD (P<0.001) and BMI (P=0.022) as the only variables. Both variables had a negative association with percentage increase in ACD, meaning that a lower baseline ACD and a lower BMI were associated with a higher percentage increase in ACD. The regression equation derived from this model is:
Percentage increase ACD = 653 – 0.4 * ACD baseline – 11 * BMI.

For baseline ACD and BMI, the baseline values of an individual patient can be inserted into the regression equation to calculate percentage increase in ACD.

CLINICAL PREDICTION MODEL FOR POST-TREATMENT ACD

The regression equation for post treatment ACD was translated into several clinical prediction models, that included all variables of the final regression model, and aimed to predict a target ACD for each patient. However, even in the original cohort only 24.8 – 33.6% of the patients had the ACD within the calculated (325 – 400 m wide) target range.

Table 4. Regression models for percentage increase in absolute claudication distance

Variables	Univariable regression		Multivariable regression*		Final regression**	
	P value	Beta per unit #	P value	Beta per unit #	P value	Beta per unit #
Total model	-	-	<.001	-	<.001	-
Continuous variables						
Baseline ACD	<.001	-0.632	<.001	-0.392	<.001	-0.397
Age	.334	3.601	.778	-0.587	-	-
ABI	.129	-306.938	.920	-9.253	-	-
Body-mass-index	.017	-9.191	.022	-10.335	.007	-11.076
Dichotomous variables						
Current smoking	.819	-13.902	.866	6.902	-	-
DM	.730	29.157	.452	-32.440	-	-
Pulmonary disease	.757	-31.477	.957	-2.661	-	-
Neurological disease	.038	239.866	.288	60.182	-	-
Cardiac disease	.750	25.151	.922	-4.003	-	-
Orthopaedic disease	.904	-13.923	.297	60.535	-	-

ACD: Absolute claudication distance, ABI: Ankle-brachial-index, DM: Diabetes mellitus

* R^2 = 0.94%, ** R^2 = 10.7%

The Beta gives information about the direction of the association and the influence of each individual variable. The bigger the beta, the bigger the influence per unit on the dependant variable.

DISCUSSION

This study shows that baseline ACD is the strongest predictive variable for post-treatment ACD as well as percentage increase in ACD, although the correlations are in the opposite direction. A higher baseline ACD predicts for a longer post-treatment ACD, but a lower percentage increase in ACD. Besides baseline ACD, other independent predictor variables were BMI and current smoking for post-treatment ACD and BMI for percentage increase in ACD.

In literature several studies can be found about clinical variables that predict treatment outcome. In line with our studie, Andriessen et al.[11] and Rosfors et al.[12], found that baseline ACD was an independent predictor for ACD after a SET program.
However, Lundgren et al.[13] and Gardner et al.[14] found no independent association between the baseline walking distance with post-treatment ACD after SET in patients with intermittent claudication. Possible explanation for this difference is that sample sizes are very small in comparison with our study.
Other proposed predictor variables from literature are walk symptoms on baseline and toe pressure to predict walk symptoms after treatment.[15] Furthermore Amighi et al.[16] found that the female sex, diabetes and a low ABI were associated with less clinical improvement after conservative treatment of intermittent claudication.

Based on the regression equation for post-treatment ACD, we developed several clinical prediction models to calculate a minimum and maximum expected post-treatment ACD for an individual patient. However, using varying clinical models, maximal one third of the cases was predicted correctly. In our opinion, the quality of the different clinical prediction models that we have tried, is poor and the prediction based on the baseline variables in the final regression equation is not accurate. This indicates that besides the variables discussed, other factors influence a large part of treatment outcome. Therefore, a clinical prediction model, based on baseline ACD, age, smoking behaviour, BMI, and pulmonary disease, does not seem sufficient for use in clinical practice.

Other possible factors influencing treatment outcome could be training related factors, the level of occlusive disease, or cognitive factors. Cheetham et al.[17] found that walking more frequent was associated with a better result. Furthermore, Gardner et al.[18] found that 87% of the variance in increase in ACD was explained by training related factors. In this study, training to near maximal pain, a program of at least 6 months, and walking as the main mode of exercise were associated with more increase in ACD. In our cohort, these exercise components may also have had a predictive value for post-treatment ACD. The guideline from the Royal Dutch Society for Physiotherapy provides general instructions about treatment components that are adapted by a physiotherapist for every patient. Therefore, in our study variation exists in the frequency, length of the program, and mode of exercise.
In this study, the level of occlusive disease was not studied. However, there are some indications that SET is more effective in femoral disease compared with more proximal disease.[19] Additional research to study the association of the after-SET results with the level of occlusive disease would be interesting.
The patient's belief that training is beneficial for their disease is positively associated

with the percentage increase in walking distance,[12] and presence of depressive symptoms is negatively associated with ACD.[20] Furthermore, patients with a type D personality (a tendency to have negative feelings combined with a lack of expression of those feelings) remain more impaired after conservative or invasive treatment compared with non-type D patients with intermittent claudication.[21] However, these cognitive factors were not registered in our study. Regression analyses that include these variables would be interesting in future research.

LIMITATIONS OF THE STUDY

A major limitation of the study was that for many patients no post-treatment ACD was available, due to a high number of patients that discontinued SET within the first 6 months. Before 6 months of follow up 323 patients (42.5%) did not continue with the training program. This could have caused bias in our analysis, assuming that patients who did not continue with the training program would have relatively poor results. This could lead to underestimation of the negative influence from age, BMI, current smoking and pulmonary disease. However, no statistical significant differences in baseline variables existed between the analyzed population and the drop outs.

In literature drop out percentages range from 10 – 50% within 6 months of SET in randomized controlled studies.[22-26] In our study, a corresponding drop out percentage was found (42.5%) in a setting describing a regular care program instead of a controlled study. These percentages are also in line with previous reported results of community-based SET.[8,9]

A second limitation of this study is that we did not record the exact training program for the individual patients. According to the Dutch Physiotherapy guideline, general instructions for therapy components were adapted by the physiotherapist for the individual patient. Therefore, the possible influence of variation in therapy components on the outcome of SET cannot be determined in the current study.

IMPLICATIONS FOR CLINICAL PRACTICE

In general, SET is a safe and effective treatment for patients with intermittent claudication, although not all patients benefit from a training program.[8] If we could identify a group of patients that are less likely to benefit from SET, early adaptations to the treatment plan could be made. However, our study shows that a valid prediction of the SET results is not possible based on simple clinical baseline variables. As long as we cannot adequately predict if patients will or will not benefit from SET, starting with SET as the primary treatment should be the first option for all patients with intermittent claudication. When SET does not lead to sufficient relief of symptoms, other treatment options are still available.

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PART TWO **TREATMENT OF INTERMITTENT CLAUDICATION COMPARED AND IMPROVED**

CHAPTER 7

TREATMENT FOR INTERMITTENT CLAUDICATION AND THE EFFECTS ON WALKING DISTANCE AND QUALITY OF LIFE: A NETWORK META-ANALYSIS

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ABSTRACT

BACKGROUND

Treatment of intermittent claudication aims for improvement in functional capacity and quality of life. However, studies on radiological and surgical interventions often focus on hemodynamic outcomes. Therefore, the objective of this network meta-analysis is to provide an overview of the most common treatments for intermittent claudication and to determine the effectiveness in improving walking distance and quality of life based on a combination of direct and indirect evidence.

METHODS

We included trials that compared: angioplasty, surgery, exercise therapy or no treatment for intermittent claudication. Outcome measurements were walking distance (maximum, pain-free) and quality of life (physical, mental). We used a network meta-analysis model for the combination of direct and indirect evidence.

FINDINGS

We included 42 studies, presenting the results of 3106 participants. The network meta-analysis showed that supervised exercise therapy (Δ=1.62, P<0.01), angioplasty (Δ=1.89, P<0.01) and surgery (Δ=2.72, P=0.02) increased walking distance significantly more than no symptomatic treatment therapy. Furthermore, supervised exercise therapy (Δ=0.60, P<0.01), angioplasty (Δ=0.91, P=0.01) and surgery (Δ=1.07, P<0.01) increased physical quality of life more than no symptomatic treatment. However, in the sensitivity analysis, only supervised exercise therapy had additional value over no symptomatic treatment (Δ=0.66, P<0.01). None of the treatments had any effect on mental health.

INTERPRETATION

This network meta-analysis indicates that supervised exercise therapy is more effective in both increasing walking distance and physical quality of life, compared to no treatment. Angioplasty and surgery also increase walking distance, compared to no treatment, but, results for physical quality of life are less convincing.

INTRODUCTION

Intermittent claudication is a symptom of peripheral arterial occlusive disease and is described as an uncomfortable or painful feeling in the calves, buttocks, or thighs that is experienced while walking and that is relieved by a short rest. The prevalence of intermittent claudication is approximately 3% among 40 to 45 year olds, with an increase to 7% in individuals older than 70 years.[1] Survival of patients with intermittent claudication is decreased, mainly due to cardiac and cerebrovascular co-morbidity.[2] The prognosis of the leg, however, is favourable; in 70 – 80% of the patients complaints remain stable over a 5 year period,[3] and the long term amputation rate for patients with intermittent claudication is less than 4%.[4] Hence, in the vast majority of cases, intermittent claudication is not a limb-threatening condition. Nevertheless, it has a considerable negative influence on the patient's functional capacity, ambulatory activity and quality of life.[5-7] Therefore, treatment of intermittent claudication aims for functional improvement and increase in quality of life rather than limb-salvage.

Exercise therapy is the oldest suggested therapy for intermittent claudication.[8] More recently, surgical[9] and endovascular interventions[10] were described. Traditionally, studies evaluating invasive interventions for intermittent claudication mainly focussed on results of increased blood flow rather than functional improvement and changes in quality of life. However, objective indices of peripheral arterial disease (e.g. ankle-brachial-index, angiographic extent of the disease) only correlate weakly with functional capacity and quality of life.[11] More importantly, correlations between hemodynamic improvements and improvement in functional capacity, quality of life and symptoms are only modest.[12-14] This indicates that outcome measurements other than hemodynamics would be more valuable to describe the results of treatment for intermittent claudication. Furthermore, as recently was described by Cao and De Rango[15], the discussion about the best treatment of intermittent claudication is ongoing and lack of evidence of more recent developed techniques was underlined.

The objective of this meta-analysis is to provide an overview of the most frequently used treatments for intermittent claudication and to determine their effectiveness in improving walking distance and quality of life based on a combination of direct and indirect evidence.

MATERIAL AND METHODS

SELECTION CRITERIA

All clinical trials that compared at least two of the following treatments for intermittent claudication: angioplasty, surgery, exercise therapy, or no treatment were potentially eligible for inclusion in the meta-analysis. Additional inclusion criteria were presence of intermittent claudication (Fontaine stage 2 / Rutherford stages 1 – 3), and walking distance (assessed on a treadmill) and / or quality of life as an outcome measurement.
Exclusion criteria were a follow-up duration less than 3 months, and stages of peripheral arterial disease other than intermittent claudication. Furthermore, studies in languages other than English, German or Dutch were excluded.

SEARCH STRATEGY

We conducted a search in Pubmed and Embase with the following search terms: (peripheral arterial disease, intermittent claudication, peripheral arterial obstructive disease, peripheral vascular disease, peripheral arterial occlusive disease, PAD, PAOD) and (angioplasty, exercise, walking, endarterectomy, bypass) and (quality of life, QOL, short form 36, SF-36, Rand 36, euroqol, sickness impact profile, SIP, vascuqol, walking distance). Reference lists of relevant articles were hand-searched for additional studies.
One author (LK) selected potentially eligible trials based on the abstracts. These studies were then independently assessed for suitability by two additional authors (LK, SN). If necessary a third reviewer (MP) was asked for conclusive advice.

INTERVENTIONS

Interventions were categorised into no treatment, non-supervised exercise therapy (nonSET), supervised exercise therapy (SET), angioplasty, surgery, conservative treatment or invasive treatment by two reviewers (LK, MP).
No treatment was defined as no treatment or the use of placebo tablets with or without treatment of vascular risk factors (e.g. platelet inhibitors) and without any advice to exercise. NonSET was defined as a single or repeated advice and / or information on exercise. Supervision of exercise was considered to be present if a nurse or physiotherapist was present during the training sessions. Within the definition of angioplasty both angioplasty alone and angioplasty with (primary or selective) stent placement or laser assisted an-

gioplasty were accepted. The surgical category consisted of bypass surgery as well as endarterectomy.
Conservative and invasive treatment are categories with mixed treatment modalities. Studies for which it was not clear what the exact treatment was or no differentiation was made between the various invasive or conservative treatments were categorised in a mixed category (e.g. angioplasty and surgery).

OUTCOME MEASUREMENTS

The primary outcome measurement was the absolute claudication distance (maximum walking distance) as measured by a treadmill test. A progressive treadmill test (constant speed, increasing slope) was preferred, but if not available a continuous treadmill test (constant speed and slope) was an alternative.
Secondary outcome measurements were the initial claudication distance (pain-free walking distance) and quality of life. The preferred quality of life assessment was the medical outcomes study 36-item short-form health survey (SF-36), but other quality of life instruments were also eligible. The SF-36 was summarised into a physical health component and a mental health component.[16] Alternative quality of life questionnaires were also summarised into physical and mental health components.

ASSESSMENT OF QUALITY OF THE REPORTS

One reviewer assessed (LK) and a second confirmed (SN) the quality of each trial according to the criteria of Jadad et al.[17] Studies could score one point for all the following items: randomisation, correct description of randomisation and description of dropouts. Double blinding was not considered, because in trials comparing conservative and invasive treatments blinding is not possible. We gave each trial a summary score ranging from 0 to 3.

DATA EXTRACTION AND CALCULATION

If available, we extracted from each treatment arm of each study the number of patients, baseline standard deviation, baseline mean and follow up mean for walking distance (absolute and initial claudication distance) and quality of life (mental- and physical health). Data of the last assessment in the study were used for the analyses. If these data were not available authors were contacted. If authors did not respond to our request or did not have the requested data available, the data were, if possible, calculated based on other information presented in the articles using various methods.[18] A description of the calculations and methods used can be found in appendix 1.

Table 1. Characteristics of the included studies

Study	Design	Jahad points	Treatment	N	Loss to follow up	Follow up (months)	Outcome	Treadmill protocol
Aquarius 2005 [55]	Cohort	1	nonSET	107	22%	12	SF-36	X
			Invasive	77				
Brothers 2007 [56]	Cohort	0	Conservative	77	NA	12	SF-36	X
			Surgery	30				
			Angioplasty	6				
Cheetham 2004 [21]	RCT	3	nonSET	30	7%	12	ACD, SF-36	3.5 km/h, 12%
			SET	29				
Collins 2005 [57]	RCT	2	No treatment	25	12%	6	SF-36	X
			SET	27				
Crowther 2008 [22]	RCT	1	nonSET	11	NA	12	ACD, ICD	3.2 km/h, every 2 minutes 2% increase
			SET	10				
Currie 1995 [58]	Cohort	1	nonSET	78	8%	3	SF-36	X
			Angioplasty	74				
			Surgery	34				
Dahllof 1974 [23]	RCT	1	No treatment	8	NA	6	ICD, ACD	4.0 km/h, 0%
			SET	10				
Dahllöf 1976 [24]	RCT	1	No treatment	11	29%	12	ICD, ACD	4.0 km/h, 0%. After 10 minutes 6.0 km/h
			SET	23				
Degischer 2002 [25]	CT	1	nonSET	23	14%	6	ICD, ACD	3.2 km/h, every 2 minutes 2% increase
			SET	46				
Feinglass 2000 [59]	Cohort	1	Conservative	145	18%	18	SF-36	X
			Surgery	60				
			Angioplasty	44				
Gardner 2002 [26]	RCT	2	No treatment	30	49%	18	ICD, ACD	3.2 km/h, every 2 minutes 2% increase
			SET	31				
Gardner 2001 [60]	RCT	2	No treatment	30	49%	6	SF-36	X
			SET	31				
Gelin 2001 [27]	RCT	3	No treatment	89	15%	12	ACD	Unknown speed with increasing slope
			SET	88				
			Invasive	87				
Gibellini 2000 [28]	RCT	1	No treatment	20	8%	6	ICD, ACD	3.0 km/h, 0%
			SET	20				
Regensteiner 1990	RCT	2	No treatment	9	24%	3	ICD, ACD	3.2 km/h, every 3 minutes 3.5% increase
			SET	10				
Hiatt 1994 [29]	RCT	2	No treatment	10	10%	3	ICD, ACD	3.2 km/h, every 3 minutes 3.5% increase
			SET	10				

Study	Design	Jahad points	Treatment	N	Loss to follow up	Follow up (months)	Outcome	Treadmill protocol
Hobbs 2006 [30]	RCT	3	nonSET	7	4%	6	ICD, ACD	3.0 km/h, 10%
			SET	7				
			Angioplasty	9				
Hobbs 2007 [31]	RCT	1	nonSET	9	NA	6	ICD, ACD	3.0 km/h, 10%
			SET	9				
Hodges 2008 [32]	RCT	2	nonSET	14	NA	3	ACD	3.2 km/h, every 2 minutes 2% increase
			SET	14				
Holm 1973 [33]	RCT	1	No treatment	6	NA	4	ICD, ACD	Unknown
			SET	6				
Imfeld 2006 [61]	CT	1	nonSET	20	20%	6	SF-36	X
			SET	18				
Izquierdo-Porrera 2000 [34]	Cohort	0	No treatment	14	NA	6	ICD, ACD	3.2 km/h, every 2 minutes 2% increase
			SET	34				
Jansen 1991 [35]	RCT	1	No treatment	24	NA	24	ICD, ACD	3.5 km/h, 10%
			SET	24				
Kakkos 2005 [37]	RCT	3	nonSET	9	38%	12	ICD, ACD, SF-36	3.5 km/h, 10%
			SET	12				
Langbein 2002 [38]	RCT	2	No treatment	25	12%	6	ACD	3.0 km/h, every 0.5 minute 0.5% increase. After 6 minutes every 3 minutes 0.32 km/h increase
			SET	27				
Larsen 1966 [8]	RCT	2	No treatment	7	0%	6	ICD, ACD	4.6 km/h, 0% or 8% or 16%
			nonSET	7				
Lee 2006 [39]	CT	0	nonSET	37	NA	6	ICD, ACD, SF-36	3.8 km/h, 10%
			SET	33				
Lundgren 1989 [9]	RCT	3	SET	25	16%	12	ICD, ACD	4.0 km/h, 0%
			Surgery	25				
Mannario 1989 [41]	CT	0	No treatment	8	NA	6	ICD, ACD	2.0 km/h, 12%
			SET	8				
Mannario 1991 [40]	RCT	1	No treatment	10	NA	6	ICD, ACD	2.0 km/h, 12%
			SET	20				
Mika 2005 [54]	RCT	2	No treatment	49	18%	3	ICD	3.2 km/h, 12%
			SET	49				
Mika 2006 [42]	RCT	2	No treatment	30	8%	3	ICD, ACD	3.2 km/h, every 3 minutes 3.5% increase
			SET	30				
Nielsen 1975 [43]	RCT	3	nonSET	26	12%	3	ACD	3.8 km/h, 8%
			SET	25				
Nylaende 2007 [44]	RCT	3	nonSET	28	14%	24	ICD, ACD	3.0 km/h, 10%
			Angioplasty	28				
Patterson 1997 [45]	RCT	2	nonSET	30	37%	6	ICD, ACD, SF-36	1.6 km/h, 5%. Every 5 minutes increase in speed and slope
			SET	30				

Study	Design	Jahad points	Treatment	N	Loss to follow up	Follow up (months)	Outcome	Treadmill protocol
Pell 1997 [62]	Cohort	1	Conservative	119	22%	6	SF-36	X
			Surgery	19				
			Angioplasty	19				
Perkins 1996 [46]	RCT	2	SET	26	34%	70	ACD	3.0 km/h, 10%
			PTA	30				
Regensteiner 1996 [63]	RCT	2	No treatment	10	10%	3	SF-20	X
			SET	10				
Regensteiner 1997 [47]	RCT	2	nonSET	10	0%	3	ICD, ACD,	3.2 km/h, every 3 minutes 3.5% in
			SET	10			SF-20	
Savage 2001 [48]	RCT	1	nonSET	10	NA	6	ICD, ACD,	3.2 km/h, every 2 minutes 2% incr
			SET	11			SF-36	
Spronk 2009 [49]	RCT	3	SET	75	7%	12	ICD, ACD,	3.5 km/h, 0%
			Angioplasty	75			SF-36	
Stewart 2008 [50]	RCT	3	nonSET	26	8%	6	ICD, ACD	2.5 km/h, 10%
			SET	29				
Taft 2001 [64]	RCT	3	No treatment	57	32%	12	SIP	X
			SET	61				
			Invasive	53				
Tisi 1997 [51]	RCT	1	nonSET	17	NA	12	ICD, ACD	3.0 km/h, 10%
			SET	22				
Tsai 2002 [52]	RCT	2	No treatment	32	17%	3	ICD, ACD,	3.2 km/h, every 2 minutes 2% incr
			SET	32			SF-36	
Wann-Hansson 2004 [65]	Cohort	1	Angioplasty	18	21%	12	SF-36	X
			Surgery	30				
Whyman 1997 [53]	RCT	3	nonSET	32	11%	24	ICD, ACD	4.0 km/h, 10%
			Angioplasty	30				

NonSET: Non-supervised exercise therapy, SET: Supervised exercise therapy, RCT: Randomised controlled trial, CT: Controlled trial, NA available, SF: Short form, ACD: Absolute claudication distance, ICD: Initial claudication distance, SIP: Sickness impact profile

STATISTICAL ANALYSIS

For all outcome measurements, the standardised mean change between the baseline and follow-up assessment for each treatment arm in the individual studies was calculated (i.e., mean at follow-up minus baseline mean, divided by the baseline standard deviation).

The direct evidence about the relative effectiveness of one intervention compared to another was then expressed in terms of the difference between the standardised mean change values. These effect sizes were then meta-analysed based on a random-effects model using restricted maximum-likelihood estimation when at least three effect size estimates were available (with only two estimates, a fixed-effects model was used).

For the combination of the direct and indirect evidence, we used an arm-based network

meta-analysis model[19] for each outcome measure (the network of evidence for the mental health component of quality of life yielded two disconnected sets of interventions, which were examined separately). A single parameter for the random effects variance and a constant correlation of 0.5 between the random effects within a study was assumed, so that the amount of heterogeneity between all pair wise intervention contrasts was constrained to be equal.[20] The models were fitted with restricted maximum-likelihood estimation. Based on the fitted models, a relative intervention effectiveness can then be obtained for any two interventions connected with each other via the network of evidence, even if no direct evidence is available to compare those two treatments. For the network meta-analysis, we also conducted sensitivity analyses, leaving out all studies with Jadad scores below 2 (all non-randomised trials).

RESULTS

One-hundred-and-forty-three potential eligible articles were identified up to September 2008. We had to exclude 96 articles for the following reasons: no intermittent claudication (n = 9), cohort study evaluating just one treatment (n = 29), other treatments described than included in the meta-analysis (n = 10), no treatment specified (n = 15), outcome measurement other than walking distance or quality of life (n = 13), duplicate publications (n=10), follow up less than 3 months (n = 7), and other reasons (n = 3), leaving 42 studies, reported in 47 articles for inclusion in the meta-analysis. References of the excluded articles are listed in appendix 2.

DESCRIPTION OF THE STUDIES

The main characteristics of the included studies are presented in table 1. Thirty-six articles reported results of randomised controlled trials, 4 articles concerned controlled trials and 7 studies were cohort studies, presenting the results of a total of 3106 participants.

ABSOLUTE CLAUDICATION DISTANCE

Data for the absolute claudication distance at the end of study were available for 35 studies, reporting on 39 direct comparisons.[8, 9, 21-53] The majority of the included trials compared SET with either nonSET (n=14) or no treatment (n=15).

Figure 1a presents the results using only direct evidence. The most obvious result is that SET is on average better in increasing the absolute claudication distance than both nonSET ($P<0.01$) and no treatment ($P<0.01$) based on 14 and 15 studies respectively. The

other comparisons only included 1 – 3 studies.
The combined direct and indirect evidence is presented in figure 2a and shows that results for SET are robust. Furthermore, the combined analysis suggests that angioplasty and surgery increase absolute claudication distance more than nonSET and no treatment, although the comparison of surgery with nonSET just failed to reach statistical significance (P=0.06).
In the sensitivity analysis, 14 studies were excluded. Six of the excluded studies compared nonSET with SET and 8 studies compared no treatment with SET. Combining direct and indirect evidence, the results for all comparisons remained. Results of the sensitivity analysis are presented in table 2.

*Table 2. Results of the sensitivity analyses**

	Absolute claudication distance	**Initial claudication distance**	**Physical health component**
Surgery	Δ = 2.84 (0.17 - 5.50)	Δ = 10.4 (4.86 - 15.95)	X
Angioplasty	Δ = 2.18 (0.72 - 3.65)	Δ = 4.55 (1.23 - 7.88)	Δ = 0.81 (-0.21 - 1.84)
SET	Δ = 1.74 (0.89 - 2.58)	Δ = 3.16 (1.45 - 4.88)	Δ = 0.66 (0.20 - 1.13)
Invasive	Δ = 1.35 (-0.58 - 3.27)	X	Δ = 0.16 (-0.68 - 1.00)
NonSET	Δ = 0.76 (-0.33 - 1.86)	Δ = 2.38 (0.04 - 4.73)	Δ = 0.29 (-0.46 - 1.04)
Conservative	X	X	X

SET: Supervised exercise therapy, NonSET: Non super vised exercise therapy
* Data are presented as difference in standardised change (Δ) and 95% confidence interval.
All data shown use no symptomatic treatment as referent treatment.

INITIAL CLAUDICATION DISTANCE

Data from 30 studies, reporting 32 comparisons on the initial claudication distance were available (figure 1b).[8, 9, 22-26, 28-31, 33-37, 39-42, 44, 45, 47-54] Most trials compared SET with nonSET (n=11) or SET with no treatment (n=14).
The most obvious result is that SET increases initial claudication distance more than both no treatment and nonSET. The results based on only the direct comparisons for initial claudication distance are depicted in figure 1b.
Combining both direct and indirect evidence, SET, angioplasty, and surgery are more effective when compared to no treatment in increasing initial claudication distance. Additionally, surgery performs better than nonSET, SET, and angioplasty.

In the sensitivity analyses (table 2), 14 studies were excluded. Six of the excluded studies compared nonSET with SET and 8 studies compared no treatment with SET. Combining direct and indirect evidence SET, angioplasty, and surgery remain better in improving initial claudication distance compared to no treatment. Surgery is still more effective than nonSET, SET, and angioplasty, although the comparison with angioplasty just failed to reach statistical significance (P=0.06).

Figure 1. Results of the direct comparisons
In this figure only direct evidence is gathered for all outcome measurements. In the grey blocks the different treatments are indicated. In the white blocks the number of studies (n), the difference in standardised change (Δ) with a 95%-confidence interval, and the P-value are noted. The arrows indicate the direction of the effect and the head of the arrow points to the more effective treatment. Figure 1a, b, and c describe the results of the absolute claudication distance, initial claudication distance, and physical health.
SET: Supervised exercise therapy.

Figure 1a. Absolute claudication distance

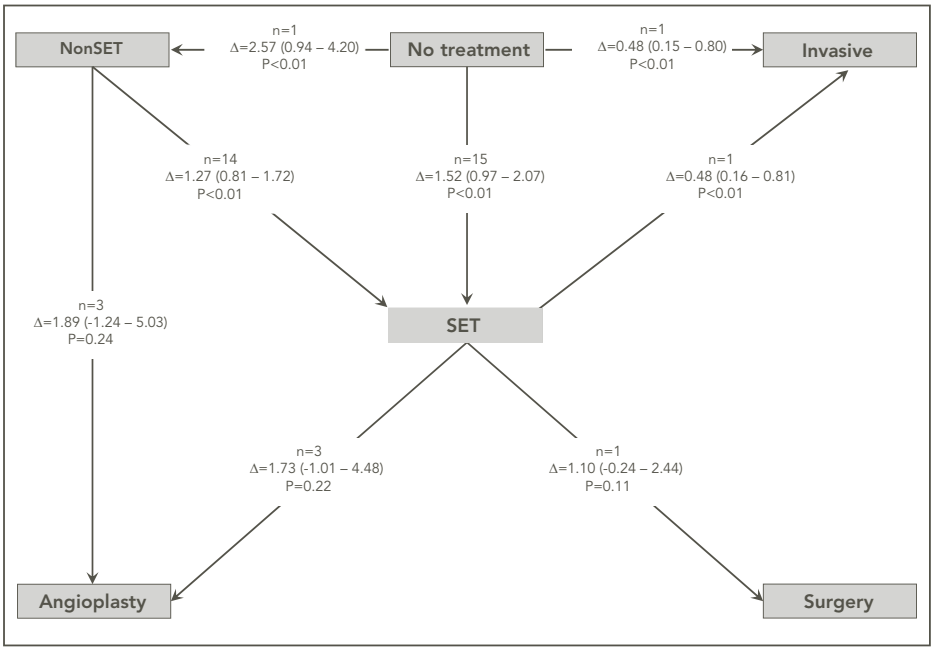


Figure 1b. Initial claudication distance

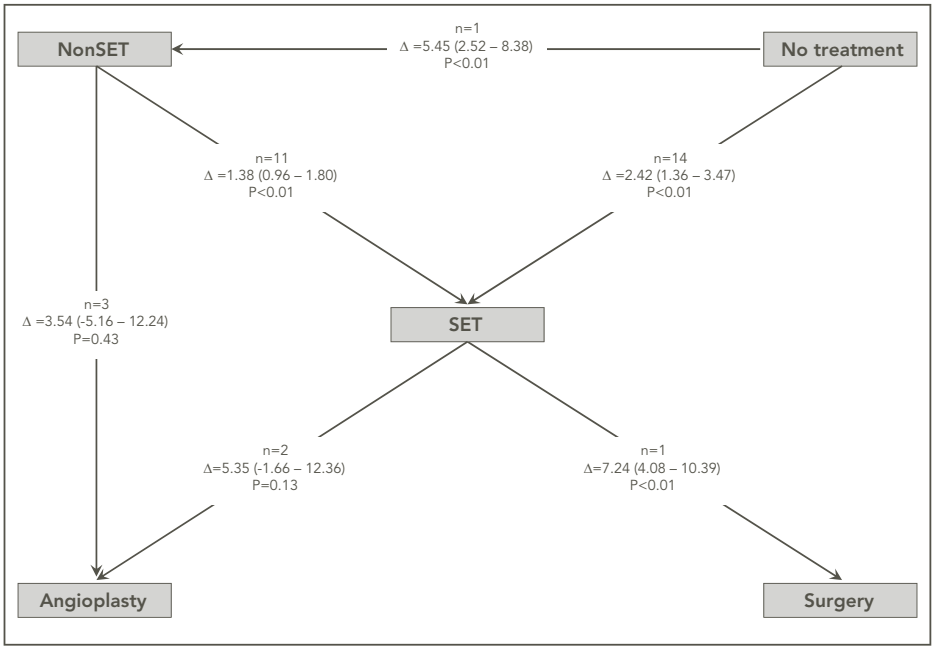
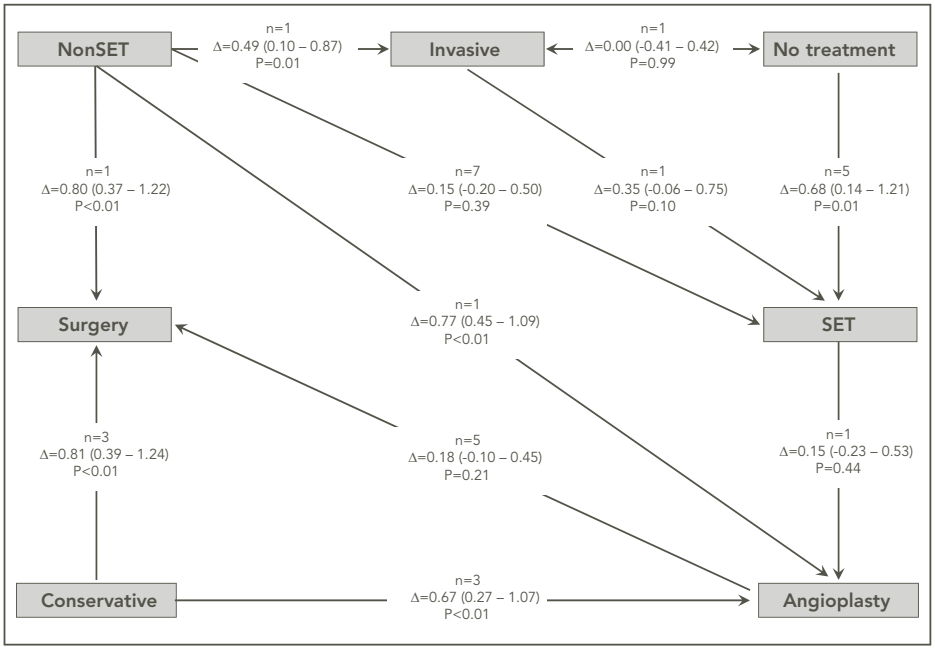


Figure 1c. Physical health component



PHYSICAL HEALTH

Data from 19 studies reported 29 direct comparisons for physical health (figure 1c).[21, 37, 39, 45, 47-49, 52, 55-65] Most of the trials compared SET with nonSET (n=7), SET with no treatment (n=5), or surgery with angioplasty (n=5). Using only direct evidence, SET increases physical health more than no treatment (P=0.01). Other direct results for physical health are presented in figure 1c.

Combining direct and indirect evidence, SET, angioplasty, and surgery are more effective in improving physical health when compared to no treatment. Furthermore, angioplasty and surgery are more effective than both nonSET and conservative treatment. The difference between SET and nonSET almost reaches significance (P=0.09) in favour of SET. The results of the combined direct and indirect evidence are presented in figure 2c.

For the sensitivity analysis 8 studies were excluded, leaving 11 studies describing 12 direct comparisons. SET was compared to no treatment (n=5), nonSET (n=4), angioplasty (n=1), and invasive treatment (n=1). Furthermore, invasive treatment was compared to no treatment. In the sensitivity analysis the results of SET compared to no treatment remain in favour of SET with a difference in standardised change of 0.66 (95% CI 0.20 – 1.13). All other treatments are not significantly different from each other, or comparisons are excluded from the analysis as part of the sensitivity analysis.

MENTAL HEALTH

Data from 14 studies reported 20 direct comparisons for mental health.[37, 39, 45, 47, 48, 52, 55-57, 60, 62-65] None of the included treatments differed significantly from each other in the direct, indirect, and sensitivity analysis (data not shown).

INTERPRETATION

This network meta-analysis shows that SET, angioplasty, and surgery are more beneficial in increasing pain-free and maximum walking distance as compared to no treatment. For physical health SET has an additional benefit compared to no treatment. For angioplasty and surgery improvements in physical health are less convincing. None of the studied treatments had any effect on mental health. Moreover, no obvious differences in effectiveness were found when comparing SET, angioplasty and surgery with each other. Only for increasing pain-free walking distance, surgery seems more effective than SET. However, these results are based on a very limited number of studies.

Figure 2. Results of the network meta-analysis
In this figure both direct and indirect evidence is combined for all outcome measurements. In the right blocks forests plots are shown that compare the treatments with no symptomatic treatment as reference. Results are indicated as difference in standardised change (◆) with a 95%-confidence interval. In the left blocks the other treatments are compared with each other. Results are indicated as the difference in standardised change (Δ) with the P-value. A positive Δ indicates that the treatment modality in the column (bold) is superior to the treatment modality in the row (cursive). A negative Δ indicates the opposite. SET: supervised exercise therapy, nonSET: non supervised exercise therapy.
Figure 1a, b, and c, describe the results of the absolute claudication distance, initial claudication distance, and physical health respectively.

Figure 2a. Absolute claudication distance

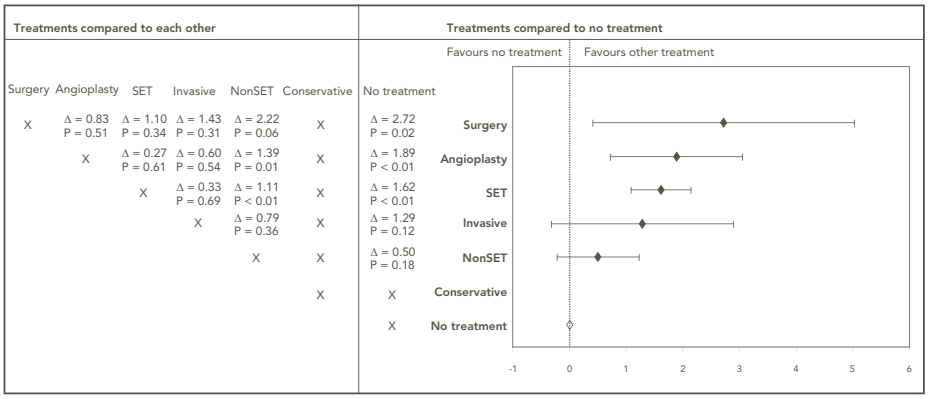


Figure 2b. Initial claudication distance

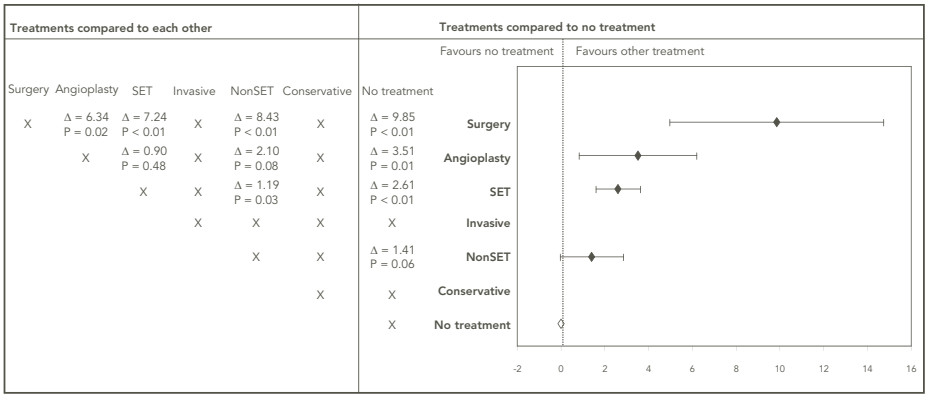
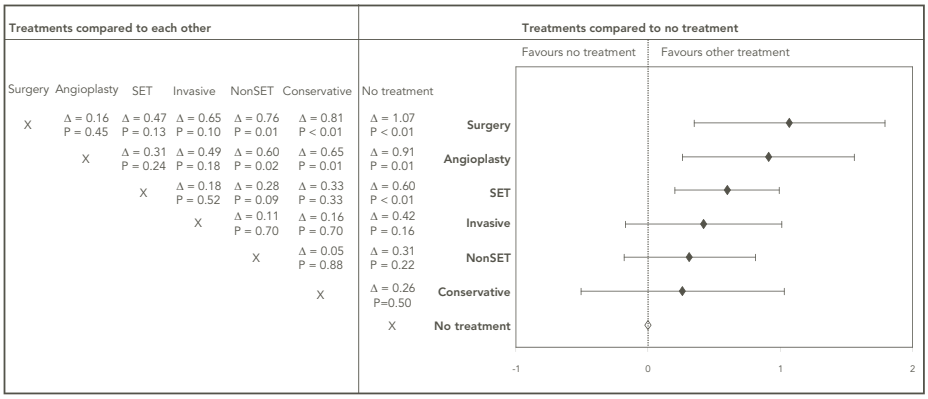


Figure 2c. Physical health component



Watson et al.[66] compared exercise therapy with other treatments and concluded that compared to no treatment, exercise therapy significantly improves maximum walking distance. No distinction was made between nonSET and SET in this meta-analysis, although only one study[8] reported results from nonSET compared to no treatment. Evidence for exercise compared to other treatments was limited.

A meta-analysis of Fowkes et al.[67] compared angioplasty with nonsurgical management. Two studies are included in this meta-analysis and with the nonSET based study results, angioplasty was significantly better than nonsurgical management. However, as in our meta-analysis, with the SET based study results, no significant difference was found between angioplasty and nonsurgical management. Spronk and collegues[14] compared exercise therapy with angioplasty and found that both treatments brought about improvements in physical health related quality of life. However, no differences between exercise and angioplasty were found.

One meta-analysis compared bypass surgery with other treatments for patients with chronic lower limb ischaemia.[68] The authors concluded that there is limited evidence for a superior effectiveness of bypass surgery compared to other treatments and that further large trials are required.

The results from the literature mentioned above are in line with the results of our current network meta-analysis. However, the network approach adds the possibility of combining both direct and indirect available evidence within a single analysis. For example, the direct evidence indicates that the difference in effectiveness between nonSET and no treatment is rather big (Δ=2.57) and significant in favour of nonSET, but this finding is based on only one small study (figure 1a). On the other hand, based on the direct evidence of

SET versus no treatment (n=15;Δ=1.52) and SET versus nonSET (n=14;Δ=1.27), we can estimate the effectiveness of nonSET versus no treatment using indirect evidence. The network-based estimate of nonSET versus no treatment is a combination of the direct and indirect evidence. In this case, the indirect evidence is much stronger than the direct evidence, as there is only one direct comparison based on a very small study, while there are many studies providing indirect evidence. The combined evidence therefore suggests no significant difference between nonSET and no treatment.

A striking finding of this meta-analysis is the discrepancy between the number of trials studying the effect of exercise therapy (n=43) compared to the number that studied the effect of angioplasty / surgery (n=14). This imbalance had implications for the sensitivity analyses as almost no studies remained in the analyses to compare angioplasty and surgery with other treatments. Therefore further research is needed to assess the functional- and quality of life outcomes of especially angioplasty and surgery.

LIMITATIONS

To establish the effectiveness of an intervention, direct evidence from randomised controlled trials should be used whenever possible. However, due to the limited number of high quality direct comparisons, indirect evidence was added to the current meta-analysis, bringing uncertainty to our results.

Another potential limitation is the inclusion of several non-randomised and cohort studies in the meta-analysis. Lack of randomization may result in biased effect size estimates, especially when patient characteristics play a role in selecting the treatment. To address this problem, we performed sensitivity analyses that excluded all non-randomised trials.

Finally, we used end-of-study data as the primary outcome instead of a fixed follow-up time for each study. The reason was that many studies differed in follow-up and that the number of studies was not sufficient to do the analyses for the different follow-up periods separately. Clearly, follow-up time could have an influence on the results of the different interventions (e.g. the time until maximum treatment effect for angioplasty is different than for SET). We examined this issue by including follow-up time as a potential moderator in the meta-analyses of the direct comparisons. However, no moderating effects of follow-up time were found.

According to the current meta-analysis, three treatments options for increasing walking distance in patients with intermittent claudication are effective, namely SET, angioplasty and surgery. However, not only the effectiveness of a treatment, but also the complication risks should be taken into consideration when making a treatment plan for an individual patient.

SET is an effective as well as safe option to treat patients with intermittent claudication given that it is a non-invasive treatment. On the other hand, both angioplasty and bypass surgery are invasive treatment options with known morbidity and mortality. Taking the results from this meta-analysis plus the known complication risks from invasive treatment into account, the clinical implication should be that patients with intermittent claudication should first be treated with supervised exercise therapy. Accordingly, efforts should be made to make supervised exercise programs universally available for patients with intermittent claudication. In conclusion, supervised exercise therapy is more effective in both increasing walking distance and physical health when compared to no treatment in patients with intermittent claudication. Angioplasty and surgery also increase walking distance, compared to no treatment, but, results for physical quality of life are less convincing.

Large randomised controlled trials comparing supervised exercise therapy, angioplasty and bypass surgery in terms of walking distance and quality of life are necessary to establish the potential extra benefits of angioplasty and bypass surgery in the treatment of intermittent claudication.

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APPENDIX 1 – DETAILED DESCRIPTION OF DATA CALCULATION

When medians and inter-quartile-ranges (IQR) were reported, the mean and SD were estimated by assuming that the median was equal to the mean and the SD was the IQR divided by 1.35 (Cochrane Handbook).[18]

WALKING DISTANCE

One trial, Cheetham et al.,[21] did not report standard deviations for walking distances and data were calculated using the reported P-values. Dahllöf et al. 1974[23] and Holm et al.[33] did not report complete data for the control group. We estimated the walking distances for the control group based on the text and the results for the intervention group. The follow up means for walking distance of Dahllöf et al. 1976[24] and Stewart et al.[50] were calculated using the percentage increase and the mean on baseline. Gibellini et al.[28] reported the walking distance of the supervised exercise group for symptomatic and asymptomatic patients separately. For these groups one common mean and standard deviation was calculated. In the study of Larsen et al.[8] individual patients performed different treadmill tests and for each patient the total amount of consumed calories was calculated and then extrapolated to the walking distance of one treadmill protocol. Mannario et al. 1991[40] reported the results of SET versus SET combined with antiplatelet therapy in different groups. For these groups one common mean and standard deviation was calculated and included in the meta-analysis.

QUALITY OF LIFE

The physical and mental health component were calculated from the 8 subscales according to the scoring algorithm[16], taking correlations between subscales into account. Five studies only reported parts of the subscales. Component scores were then calculated in a similar way, but using only the available subscales. Spronk et al.[49] reported all 4 subscales of the physical health component (physical function, bodily pain, physical role and general health), but no subscales of the mental health component. Currie et al.[58] reported physical function, bodily pain and physical role, whereas Feinglass et al.[59] and Imfeld et al.[61] reported physical function and bodily pain. Cheetham et al.[21] only reported physical function. Two studies of Regensteiner et al.[36,63] used the SF-20, reporting 5 of 6 subscales (physical function, social function, role functioning, overall health and well being). The subscales physical function and overall health were merged to physical health and social function and well being were merged to form the mental health component. Taft et al.[64] reported a physical and mental component score of the SIP. Quality of life measurements from

Nylaende et al.[44] and Whyman et al.[53] using the SF-36 and the Nottingham health profile respectively, were excluded from the analysis due to lack of data reported in the articles.

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CHAPTER 8

PREDICTORS FOR FUNCTIONAL RESULTS AFTER A PERCUTANEOUS VASCULAR INTERVENTION FOR INTERMITTENT CLAUDICATION

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ABSTRACT

PURPOSE

The objective of this study was to determine clinical variables that would be predictive for the functional outcome after a percutaneous vascular intervention (PVI) for intermittent claudication.

METHODS

Patients with peripheral arterial disease (PAD), Rutherford stage 1 – 3, selected for treatment with PVI were included. Exclusion criteria were other stages of PAD, serious cardiopulmonary co-morbidity, and the inability to walk the standardized treadmill test. Primary outcome was the absolute claudication distance (ACD), measured with treadmill testing, within three weeks post-PVI. Secondary outcome was the persistence of complaints of claudication. Linear and logistic regression analyses were conducted to identify variables associated with post-PVI claudication complaints and ACD.

RESULTS

Eighty-nine patients were included. In the final prediction model for post-PVI ACD, presence of isolated iliac disease (P=0.007), a higher baseline ACD (P<0.001), and a younger age (P=0.044) were associated with a higher ACD after the vascular intervention. The likelihood of persisting claudication complaints increased with a lower baseline ACD (P=0.070), existence of multi-segment disease (P=0.007), current smoking (P=0.015), presence of a stenosis (instead of an occlusion; P=0.026), and the presence of diabetes (P=0.030). Presence of COPD decreased the likelihood of post-PVI claudication complaints (P=0.067).

CONCLUSION

Several predictor variables for the functional result after PVI could be identified. A lower baseline ACD, increased age, multi-segment disease, current smoking, and the presence of diabetes are all associated with less functional benefit after PVI.

INTRODUCTION

Exercise therapy is the first choice of treatment for symptoms of intermittent claudication according to several guidelines.[1-3] However, since the first description by Dotter et. al.[4], percutaneous transluminal angioplasty (PTA) is increasingly used for the treatment of intermittent claudication, especially for patients with aorto-iliac occlusive disease. Various alternative and additional techniques have been described since (e.g. stenting, recanalisation). For this reason we refer to these procedures as percutaneous vascular interventions (PVI). Several studies describe an improvement in both walking distance and quality of life following PVI for intermittent claudication.[5-8] Initial technical success rates range between 80 and 98 percent, depending on lesion site and severity.[9] Reported primary patencies at one year follow up for femoral and iliac angioplasty are 62% and 90% respectively.[9] Suggested predictors for patency and hemodynamic improvement after PVI are lesion site, lesion severity, smoking, severity of symptoms and diabetes. Better results were reported for claudication patients, patients with aorto-iliac disease instead of femoro-popliteal disease, patients having a stenosis (instead of an occlusion), and for patients without diabetes.[10-15] However, since patency and hemodynamics moderately correlate with functional outcome [5,16-18], predictors for walking distance would be of more clinical importance. Therefore, the objective of this study was to investigate if clinical variables predictive for patency would also be predictive for functional outcome. Furthermore, additional clinical variables, predictive of functional results were searched for.

MATERIAL AND METHODS

STUDY POPULATION

Consecutive patients diagnosed with peripheral arterial disease, Rutherford stage 1 – 3, and selected for PVI as primary treatment for their complaints of intermittent claudication were potentially eligible for inclusion in the study.

The diagnosis PAD was confirmed with an ankle-brachial-index (ABI) measurement below 0.9 in rest or an ABI decreasing 0.15 after exercise. Further diagnostics for lesion site and severity were done by duplex ultrasound or magnetic resonance angiography. Exclusion criteria were signs of critical ischemia (Rutherford 4 – 6), asymptomatic PAD (Rutherford 0), serious cardiopulmonary co-morbidity (NYHA 3 and 4), and the inability to walk the standardized treadmill test.

BASELINE VARIABLES

Baseline variables were prospectively recorded by a vascular nurse during intake of a patient. Lesion site was recorded as isolated iliac disease or multi-segment stenosis (combined iliac and / or femoro-popliteal and / or crural disease) and the lesion severity as stenosis versus occlusion. We did not use the TASC classification, because the expected number of patients to include did not meet the number necessary to analyze 4 classes of lesion site/severity. Smoking behavior was recorded as current non-smoker (never and previous smoker) or current smoker. The severity of symptoms was assessed with treadmill testing. Diabetes mellitus (DM) was defined as the use of glucose lowering medication or a serum fasting glucose above 7.0 mmol/l.

Besides the above mentioned variables, known from literature, the following potential predictor variables were recorded during intake: age, body-mass-index (BMI), chronic obstructive pulmonary disease (COPD), cerebrovascular disease, coronary heart disease, and orthopedic disease.

Cerebrovascular disease was defined as a history of cerebrovascular accident (CVA) or a transient ischemic attack (TIA). A medical history of angina pectoris or myocardial infarction was defined as coronary heart disease. Furthermore, orthopedic disease was considered to be present when patients had arthrosis, rheumatoid arthritis, poly-arthritis or arthroplasty of the lower extremities.

INTERVENTION

All PVIs were planned based on the results of duplex ultrasound and / or magnetic resonance angiography, after a multidisciplinary meeting of interventional radiologists, vascular surgeons, vascular nurses, and vascular technicians. The procedure was performed by an experienced interventional-radiologist. After angioplasty of iliac stenoses, stent placement was only used if necessary (selective stent placement). Stent placement was routinely used after angioplasty of femoral stenoses, and after recanalisation of iliac and femoral occlusions.

OUTCOME MEASUREMENTS

The primary outcome measurement was the absolute claudication distance (ACD) post-PVI , measured with treadmill testing. The ACD is defined as the moment severe claudication pain or other reasons (e.g. dyspnoea) forces cessation of exercise. We used a standardized treadmill test with a constant speed of 3.2 km/h and an increasing slope, starting with 0% increasing every 2 minutes with 2% until a maximum of 10%.[19] The maximum testing duration was 30 minutes (1600 meters).

Secondary outcome measurement is the presence of claudication complaints post-PVI,

measured during the treadmill test. The reason for stopping the treadmill test was recorded and patients stopping for other reasons than claudication complaints were considered to be symptom free. Treadmill testing was performed two weeks pre-PVI and within three weeks post-PVI.

ANALYSIS

Nominal variables are presented as mean ± standard deviation and categorical variables as frequency with percentage. Walking distances are presented as median and interquartile-range (IQR), as walking distances are not normally distributed. The change in walking distance of the total cohort is analyzed using a paired T-test. Logarithmic transformation of walking distances was used to meet the requirements of a T-test.

Univariable and multivariable linear and logistic regression analyses were conducted to identify predictor variables for ACD post-PVI and presence of claudication complaints. Suggested predictor variables from literature (lesion site, lesion severity, smoking, severity of symptoms, and diabetes) were included in the analyses. In addition, age, ABI, BMI, COPD, cerebrovascular disease, coronary heart disease, and orthopedic disease were included in the analyses to inventory potential new predictor variables.

To reduce the effect of potential over fitting, regression analyses using the backward method were carried out to identify the variables having most influence on the outcome measurement. The quality of the regression models were expressed with the R^2 (explained variance) for linear regression analysis and the Nagelkerke R^2 for logistic regression analysis. The (Nagelkerke) R^2 can range from 0 to 100 percent and the higher the better the quality of the regression model.

A student's T-test was used to analyze differences in walking distances between groups that are based on significant dichotomous predictor variables for ACD after vascular intervention.

RESULTS

A total of 89 patients, 54 men, were included in the study with a mean age of 61.3 ± 10.2 years. Baseline characteristics of the included patients are presented in table 1. Seventy-one patients (79.8%) were treated for a stenosis, 12 patients (13.5%) for an occlusion and 6 patients (6.7%) were treated for both a stenosis and occlusion. Thirty-two patients had a stent placement. The majority of interventions was for aorto-iliac lesions (86.5%). Further details of the procedures are listed in table 2.

Table 1. Baseline characteristics of the study population

Characteristic	Population (N=89)
Men	54 (60.7%)
Age	61.3 ± 10.2
ABI	0.72 ± 0.19
BMI	26.7 ± 4.1
Diabetes Mellitus	15 (16.9%)
Hypertension	62 (69.7%)
Hypercholesterolemia	78 (87.6%)
Current smoking	50 (56.2%)
CVA or TIA	6 (6.7%)
COPD	10 (11.2%)
Orthopedic disease	14 (15.7%)
Coronary heart disease	22 (24.7%)
Previous vascular intervention	
PVI	9 (10.1%)
Surgical intervention	3 (3.4%)
Both	4 (4.5%)
Isolated iliac disease	49 (55.1%)

ABI: Ankle-brachial-index, BMI: Body mass index, CVA: Cerebro vascular attack, TIA: Transient ischemic attack, COPD: Chronic pulmonary obstructive disease, PVI: Percutaneous vascular intervention

Table 2. Percutaneous vascular interventions

Intervention characteristic	Population
Procedure	
Angioplasty	71 (79.8%)
Recanalisation	12 (13.5%)
Both angioplasty and recanalisation	6 (6.7%)
Stent placement	32 (26.0%)
Location intervention	
Aorto-iliac	77 (86.5%)
Femoro-popliteal	7 (7.9%)
Both aorto-iliac and femoro-popliteal	5 (5.6%)

The median ACD on baseline was 300 (190 – 575) meters. Post-PVI the ACD increased significantly (P<0.001) with a median of 251 (IQR 113 to 570) meters to 676 (IQR 422 to 1250) meters (table 3). Most patients (47.2%) had to stop the post-PVI treadmill test for complaints other than claudication (e.g. dyspnoea, joint pain). Twenty-one percent of the patients walked the complete treadmill test (30 minutes). Complaints of claudication after PVI were still present in 28 patients (31,5%).

Table 3. Walking distances

Follow up	Absolute ACD	Absolute increase in ACD
Total cohort*		
Baseline	300 (190 - 575)	-
Post - PVI	676 (422 - 1250)	251 (113 - 570)
Isolated iliac disease**		
Baseline	280 (190 - 615)	-
Post - PVI	917 (433 - 1600)	390 (153 - 865)
Multiple affected segments**		
Baseline	310 (181 - 543)	-
Post - PVI	580 (383 - 837)	205 (73 - 373)

ACD: absolute claudication distance, PVI : percutaneous transluminal angioplasty

* Significant increase in walking distance ($P < 0.001$)

** Significant difference in increase of ACD between patients with isolated iliac disease compared to multiple affected segments ($P < 0.001$)

PREDICTOR VARIABLES FOR POST-PVI WALKING DISTANCE

The different associations between baseline variables and the ACD post-PVI are presented in table 4. Variables predictive for patency and significantly associated with the ACD post-PVI in the univariable analyses were; severity of symptoms (baseline ACD), diabetes and lesion site (isolated iliac disease versus multi-segment stenosis). No significant association was found for smoking behavior and lesion severity (occlusion versus stenosis). Additional predictor variables for ACD post-PVI were age and ABI. In the multivariable regression analysis that included all selected variables symptom severity (baseline ACD), lesion site (isolated iliac disease versus multi-segment stenosis), and age turned out to be independent predictor variables. The R^2 of the multivariable model was 45.1%.

The final regression model included baseline ACD, age and isolated iliac disease and the R^2 of this model was 47.9% with only 3 predictor variables. A higher baseline ACD, the presence of isolated iliac disease, and a younger age are associated with a higher ACD post-PVI.

PREDICTOR VARIABLES FOR POST-PVI CLAUDICATION COMPLAINTS

Table 5 presents the associations of the different baseline variables with the presence of persisting post-PVI claudication.

In the univariable regression analyses, only lesion site was associated with the persistence of claudication complaints post-PVI. For the other variables associated with patency (smoking, symptom severity, DM, and lesion severity) no univariable association was found with persistence of claudication complaints. However, in the multivariable analyses lesion

site as well as smoking, DM, and lesion severity were significant predictors. COPD was an additional significant predictor variable. The multivariable model had a Nagelkerke R^2 of 44.7%, indicating reasonable quality of the regression model.
The final model included baseline ACD (P=0.070)), current smoking (P=0.015), diabetes (P=0.030), COPD (P=0.067), isolated iliac disease (P=0.007), and presence of an occlusion (P=0.026). The final model had a Nagelkerke R^2 of 35.1%.
The likelihood of persisting claudication complaints increases with a lower baseline ACD, existence of multi segment stenosis, current smoking, presence of a stenosis (instead of an occlusion), and the presence of diabetes. The presence of COPD decreases the likelihood of post-PVI claudication complaints, since the increase in walking distance post-PVI seems to be limited by the pulmonary factor.

WALKING DISTANCE ACCORDING TO LESION SITE

For patients with multiple segment stenosis and patients with isolated iliac disease, walking distances were separated. Results are presented in table 3. At baseline, no significant differences in walking distance existed between the two groups (P = 0.916). Patients with isolated iliac disease increased with a median of 390 meters, compared to 205 meters for patients with multiple segment stenosis (P < 0.001).

Table 4. Regression analyses post-PVI walking distance

	Univariable		Multivariable*		Final model**	
	P-value	Beta	P-value	Beta	P-value	Beta
Total model	-	-	<0.001	-	<0.001	-
Continuous variables						
Baseline ACD	< 0.001	0.879	<0.001	0.807	<0.001	0.827
Age	0.004	-14.609	0.031	-11.496	0.044	-8.247
ABI	0.014	692.728	0.901	32.293	-	-
BMI	0.123	-19.720	0.194	-13.838	-	-
Dichotomous variables						
Current smoking	0.306	108.936	0.175	-134.697	-	-
DM	0.008	-366.220	0.951	-8.004	-	-
COPD	0.625	-81.975	0.308	140.400	-	-
CVA / TIA	0.287	-224.392	0.604	-88.831	-	-
Cardiac disease	0.090	-206.367	0.377	-97.268	-	-
Orthopedic disease	0.443	-111.351	0.869	20.030	-	-
Isolated iliac disease	0.002	315.794	0.024	209.518	0.007	228.917
Recanalisation	0.155	-187.484	0.966	4.897	-	-

PVI: Percutaneous vascular intervention, ACD: Absol ute claudication distance, ABI: Ankle-brachial-index, BMI: Body mass index, DM: Diabetes mellitus, CVA: Cerebro vascular attack, TIA: Transient ischemic attack, COPD: Chronic pulmonary obstructive disease

* Model explains 45.1% of the variance in post-PVI walking distance

** Model explains 47.9% of the variance in post-PVI walking distance

DISCUSSION

Results from this study show that known predictors for patency are also predictive for functional outcomes after a PVI. Lesion site and symptom severity are associated with post-PVI walking distance. Furthermore, lesion site, symptom severity, diabetes, smoking behaviour, and lesion severity are associated with persistence of claudication complaints.
Additional identified predictor variables are age (for post-PVI walking distance) and COPD (for persistence of claudication complaints).
Summarizing; patients who are younger, who have isolated iliac disease and who have a higher baseline ACD, benefit most from a vascular intervention in terms of walking distance. Furthermore, a shorter baseline ACD, current smoking, presence of diabetes, multi-segment stenosis, and the presence of a stenosis (instead of an occlusion) were associated with persisting post-PVI claudication complaints. The presence of COPD is associated with less post-PVI claudication complaints. This is in line with earlier studies suggesting that multi-segment disease[15], smoking[15], and the presence of diabetes[11] are predictive variables for a worse clinical outcome post-PVI.
Johnston et al.[13] showed that lesion severity was a predictor variable for clinical outcome post-PVI, however he found that an occlusion was associated with worse outcome compared to stenosis. In this study however, occlusion was associated with a better outcome compared to stenosis. A possible explanation is that in this study recanalisation was routinely followed by stent placement in contrast with the study of Johnston et al.[13] who used recanalisation only. Predictive variables for post-PVI walking distance have not been previously described.
Other suggested predictive variables for worse clinical outcome post-PVI from literature are TASC C/D lesions[15,20,] critical limb ischemia[11,13-15], chronic renal failure with hemodialysis[15], no aspirin treatment[21], a residual stenosis post-PVI[21,22,] femoropopliteal disease[11,13,] bad runoff[11,13,] and a low ABI post-PVI.[14] These studies all included patients with both intermittent claudication and critical limb ischemia. However, defining predictor variables for outcome after PVI for only patients with intermittent claudication is important, since the treatment goal for claudicants is evidently different from the treatment goal for patients with critical limb ischemia.
On average every patient increases in walking distance after a PVI, however, patients with unfavorable baseline characteristics (e.g. multi-segment disease, smoking, diabetes) benefit less from a PVI. For this group of patients additional therapy (e.g. supervised exercise therapy) could contribute to more benefit and better functional outcomes. Lundgren et al.[23] and Badger et al.[24] studied the effect of additional supervised exercise therapy after bypass surgery and concluded that combination of surgery with exercise was better than

surgery alone for improving walking distance. Literature about additional therapy after PVI is not known, and it would be interesting to study the effect of additional treatment after PVI. Currently, our research group is conducting a randomized clinical trial to study the effect of additional supervised exercise therapy after a PVI.

Table 5. Logistic regression analyses post-PVI claudication complaints

	Univariable		Multivariable*		Final model**	
	P-value	Beta	P-value	Beta	P-value	Beta
Total model	-	-	0.001	-	0.001	-
Continuous variables						
Baseline ACD	0.063	-0.002	0.115	-0.002	0.070	-0.002
Age	0.814	-0.005	0.809	0.010	-	-
ABI	0.329	-1.207	0.105	-3.202	-	-
BMI	0.963	0.003	0.224	-0.094	-	-
Dichotomous variables						
Current smoking	0.298	0.489	0.013	2.286	0.015	1.653
DM	0.052	1.127	0.024	2.400	0.030	1.835
COPD	0.414	-0.674	0.032	-2.422	0.067	-1.854
CVA / TIA	0.432	-0.880	0.241	-1.837	-	
Cardiac disease	0.108	0.819	0.127	1.230	-	
Orthopedic disease	0.800	-0.163	0.862	0.146	-	-
Isolated iliac disease	0.045	-0.937	0.027	-1.528	0.007	-1.712
Recanalisation	0.332	-0.602	0.016	-2.233	0.026	-1.7 02

PVI: Percutaneous vascular intervention, ACD: Absolute claudication distance, ABI: Ankle-brachial-index, BMI: Body mass index, DM: Diabetesmellitus, CVA: Cerebral vascular attack, TIA: Transient ischemic attack, COPD: Chronic obstructive pulmonary disease

* Nagelkerke R^2 is 44.7%

** Nagelkerke R^2 is 35.1%

LIMITATIONS OF THE STUDY

A limitation of the study is that the follow up time after PVI is only 3 weeks. Predictive variables for long term functional outcome would be interesting. However, short term results are important since limited functional results post-PVI demand accurate adjustments in treatment planning at short term.

A second limitation is the small number of participants. Ideally, for every potential predictor variable, inclusion of 10 patients is desirable to reduce the effect of over fitting. To overcome this problem regression analysis using the backward method was done to exclude variables with less influence.

A third limitation could be that we included both patients with an aorto-iliac as well as a femoro-popliteal PVI as these subgroups are very different in literature for long-term

patency results. However, repeating the analyses with only patients with an aorto-iliac PVI did not alter any of the conclusions. Although in the final model for persisting claudication complaints for patients with aorto-iliac disease, both ABI as BMI were included. The likelihood of persisting claudication complaints increased with lower BMI and ABI. Furthermore, baseline ACD was not included in the final regression model for persisting claudication complaints (data not shown).

CONCLUSION

Several predictor variables for functional results after PVI were identified. A lower baseline walking distance, older age, multi-segment disease, current smoking, and the presence of diabetes are all associated with less benefit after PVI. Further research into the effectiveness of additional treatment, especially for these subgroups, is needed.

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CHAPTER 9

ADDITIONAL SUPERVISED EXERCISE THERAPY AFTER A PERCUTANEOUS INTERVENTION FOR PERIPHERAL ARTERIAL DISEASE: A RANDOMISED CLINICAL TRIAL

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ABSTRACT

BACKGROUND

It is not known whether combination therapy of supervised exercise therapy (SET) and percutaneous vascular intervention (PVI) is more effective than either treatment modality alone. Therefore, the objective of the current randomised trial was to determine whether PVI and supplemental SET is more effective than PVI alone in improving walking ability in patients with symptomatic peripheral arterial disease (PAD).

METHODS

Patients with PAD, Rutherford stage 1 – 4, treated with a PVI, and a post-PVI maximum walking distance <1600 metres were potentially eligible. Exclusion criteria were: major amputation/tissue loss, serious co-morbidity preventing physical activity, insufficient knowledge of the Dutch language, no insurance for SET, and participation in a SET program. All patients participating in the study were treated with a PVI. After the PVI patients were randomised in either the PVI alone or PVI + additional SET. Primary outcome was the maximum walking distance (absolute claudication distance, ACD). Secondary outcome was, among others, quality of life.

RESULTS

We included 35 patients in each group. The mean difference in ACD at 6 months of follow up was 271.3 metres (95%-CI 64.0 to 478.6, P =0.011) in favour of additional SET. In the control group 1 patient (3.7%) finished the complete treadmill test compared to 11 (32.4%) in the intervention group (P=0.005). Physical health related quality of life score was 44.1 ± 7.8 in the control group, compared to 41.9 ± 9.5 in the intervention group which was a non significant difference (P=0.34).

CONCLUSIONS

Supervised exercise therapy following a PVI is more effective in increasing walking distance compared to a PVI alone. These data indicate that SET is useful adjunct after a PVI.

Trial registration: Clinical trials.gov, NCT00497445

INTRODUCTION

Peripheral arterial disease (PAD) of the lower extremities describes atherosclerotic disease that affects the arteries in the legs.[1] PAD is a common health issue with a prevalence of 18-20% in the general population aged over 55 years.[2] Symptoms of PAD range from intermittent claudication, defined as fatigue or discomfort in calve, buttock or thigh muscles on exertion that is relieved by rest, to critical limb ischemia, defined as distal leg pain at rest with or without ischemic ulcers.[1]

Treatment of PAD consists of modification of atherosclerotic risk factors and symptomatic treatment. First choice for the treatment of symptoms, according to the TASC-II guideline is supervised exercise therapy (SET). However, in case of more proximal disease revascularisation can be a good first option.[3] The latter consists of either surgical or endovascular revascularisation. Percutaneous vascular interventions (PVI), including angioplasty, stent placement, and recanalisation of occluded arteries, are increasingly used for the treatment of PAD. The immediate technical success of PVI exceeds 90%.[3] However, a significant number of patients have persistent or recurrent symptoms after PVI, despite patency of the treated arterial segment.[4, 5] SET has been reported to be an effective alternative to revascularisation for improving walking distance in patients with symptoms of intermittent claudication.[6-8] Since it is not known whether combination therapy of SET and PVI is more effective than either treatment modality alone, the objective of the current randomised clinical trial was to determine whether PVI and supplemental SET is more effective than PVI alone in improving walking ability in patients with symptomatic PAD.

METHODS

In this single centre randomised clinical trial[9] we compared the effectiveness of PVI alone (control group) with PVI followed by additional SET (intervention group). We hypothesised that additional SET after a PVI will increase walking distance and quality of life compared to PVI alone.

Eligible patients were randomised to either treatment arm using a computer generated block randomised list (block size 5) for every individual patient using consecutively numbered and sealed envelopes. The sealed envelopes were prepared in advance of the study by one of the researchers (SN), and the block randomised list was not accessible for the local trial coordinator (LK) who enrolled patients and assigned patients to their

groups. Inherent to the study design, participants, physiotherapists administering SET and assessing outcomes, and the local trial coordinator (LK) were not blinded to the group assignment.
The study was approved by the institutional review board of the Atrium medical centre and registered at clinical trials.gov, NCT00497445.

PATIENTS
Patients were recruited at the vascular surgery outpatient clinic of the Atrium medical centre. Patients were eligible for the study if they fulfilled all of the following criteria: (1) PAD Rutherford stage 1 – 4, (2) planned for a PVI, and (3) maximum walking distance post-PVI less then 1600 m as measured by a standardised treadmill test. Exclusion criteria were: (1) history of or current participation in a SET program, (2) serious cardiopulmonary co-morbidity (NYHA 3–4), (3) other serious co-morbidity preventing physical activity, (4) insufficient knowledge of the Dutch language, (5) no insurance for SET, and (6) major amputation or tissue loss.
All patients that were eligible were asked for written informed consent to participate in the study.

INTERVENTIONS
The choice for primary PVI for the individual patient was based on the results of duplex ultrasound and/or magnetic resonance angiography as discussed in a multidisciplinary meeting of interventional radiologists and vascular surgeons. All PVIs were performed by an experienced interventional radiologist, and consisted of iliac angioplasty with selective stent placement for iliac stenoses, angioplasty and stenting for superficial femoral artery stenoses, or recanalisation with stenting for iliac and femoral occlusions.
In addition, all patients received cardiovascular risk factor modification, including a platelet inhibitor and a statin, and treatment of hypertension and/or diabetes as required. All smoking patients were repeatedly advised to quit smoking and were offered a smoking-cessation program. Furthermore, all patients were advised concerning life style changes (physical activity, weight, diet) according to the Dutch standard for cardiovascular risk management.[10]

For patients in the intervention group, the SET program aimed to start within 3 weeks after the PVI. The SET program was performed in a community-based setting, meaning that patients followed exercise therapy by a trained physiotherapist in proximity to their homes. Organisation and results of community based SET have been described previously.[11-13] SET was administered according to the guidelines of the Royal Dutch Society

for Physiotherapy.[14] The main goal is to increase a patient's walking distance by interval training with short (3 – 5 minutes) walking intervals up to sub-maximal pain (distraction not possible). Secondary goals are increasing endurance and strength, and improving walking patterns. In general, patients started with a frequency of 2 to 3 sessions of 30 minutes a week. Frequency of the sessions was phased down according to the patient's progress. Furthermore, patients were encouraged to walk on a daily basis besides the physiotherapy sessions.

OUTCOME PARAMETERS

The primary outcome measurement was the absolute claudication distance (ACD). Secondary outcome measurements were the functional claudication distance (FCD), functional results (persisting claudication complaints, walking impairment questionnaire, number of patients finishing the treadmill test), hemodynamic results (ankle brachial index, primary patency, re-interventions), and health-related quality of life.

Walking distances, persisting claudication complaints, and the ankle brachial index (ABI) were measured pre-PVI, within 3 weeks post-PVI , and at 3 and 6 months of follow up. Health-related quality of life and walking capacity questionnaires were performed pre-PVI, and at 3 and 6 months of follow up. Patency of the re-vascularised segment and potential re-interventions were assessed at 6 months of follow up.

The ACD was defined as the walking distance after which a patient had to stop walking to relieve claudication pain. The FCD was defined as the distance a patient would prefer to stop because of claudication pain.[15] If patients were symptom-free and had no pain with walking, FCD was equal to ACD. Both FCD and ACD were measured with a standardised treadmill test with a constant speed of 3.2 km/h and an increasing slope, starting at 0% and increasing 2% every 2 minutes until a maximum of 10%. The test time was maximised at 30 minutes (1600 metres). Both walking distances (FCD and ACD) and the treadmill test are reproducible and valid tools to objectify walking capacity in patients with intermittent claudication.[15, 16]

Persistence of claudication complaints post-PVI was measured during the treadmill test. The reason for stopping the treadmill test was recorded and patients stopping for claudication were considered to have persisting claudication complaints.

Furthermore, functional results were measured by the walking impairment questionnaire (WIQ), that has recently been validated in the Dutch language.[17, 18] The WIQ assesses functional capacity in 3 domains, namely distance, speed and walking stairs.[19]

Health-related quality of life was measured with the medical outcomes study 36-item short-form health survey (SF-36),[20] and the Euroqol-5D questionnaire.[21] The SF-36 is a generic quality of life questionnaire that assesses 8 health dimensions (physical function,

physical role, pain, general health, social function, emotional role, mental health, vitality). The scoring per dimension is valued between 0 – 100 meaning worst and best outcome, respectively. These 8 dimensions can be summarised into a physical summary score and a mental summary score.[22] The Euroqol-5D questionnaire is also a generic quality of life questionnaire that classifies patients into a health state based on 5 domains (mobility, self care, daily activities, pain, state of mind). For each health state a value ranging from 0 – 1 was calculated, reflecting worst and best health, respectively.[21] Furthermore, a rating scale from 0 – 100 is used to rate the overall health of a respondent, where 0 represents worst health and 100 represents maximum health.[21]

STATISTICAL ANALYSES

The mean increase of the ACD after SET was estimated at 1200 meters (standard deviation 600 meters). Inclusion of 40 patients per group would approximately result in 33 patients to be evaluated (20% loss to follow up). This could demonstrate a difference of 450 meters in ACD between the 2 groups with =0.05 and a power of 0.80.

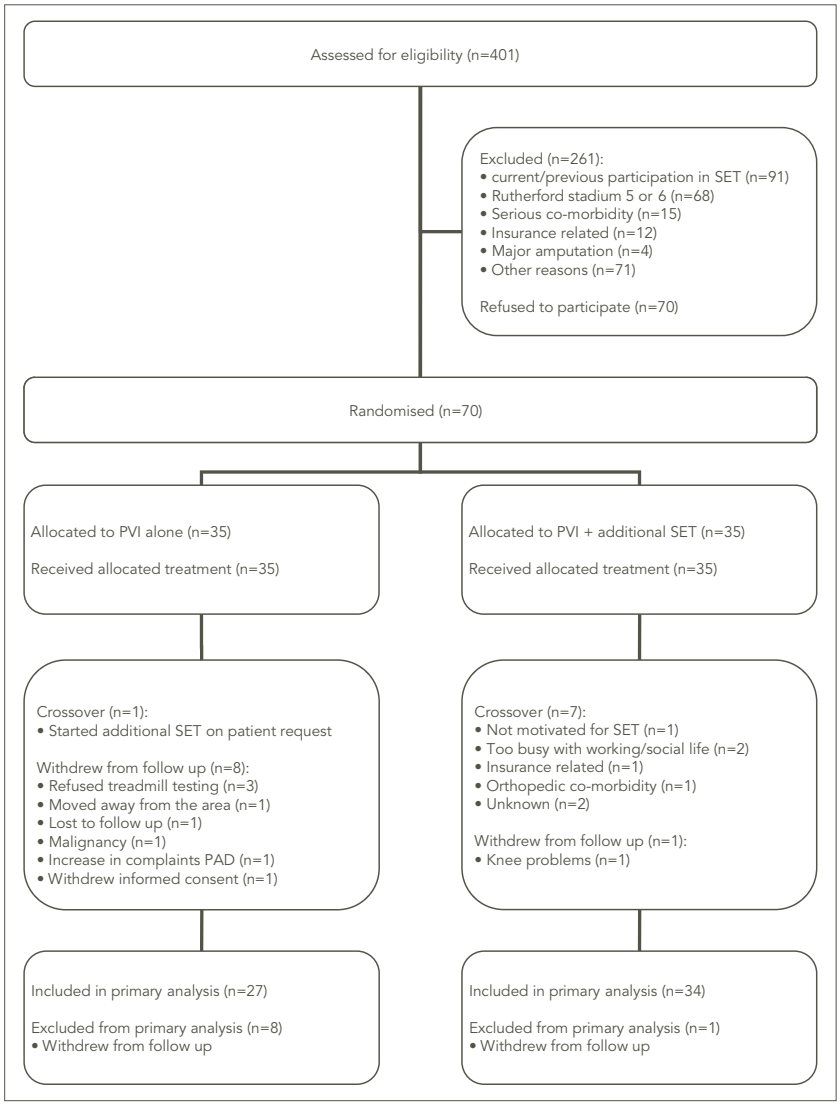
Interval and ratio variables are presented as mean ± standard deviation and nominal variables are presented as absolute number and percentages.

Results were analysed according to the intention-to-treat principle. Patients allocated to a certain group were analysed as part of their allocated group, regardless if crossover occurred. For health-related quality of life questionnaires and the WIQ multiple imputation methods were used to impute missing data, under the condition that at least 50% of the questions in the questionnaire were answered. If more answers were missing a patient was excluded for the analysis for the particular questionnaire.

Statistical significance of differences between 2 groups was determined using an independent T-test for continuous variables and a Chi^2 test for nominal variables. If criteria for a Chi^2 test were not fulfilled, a Fisher exact test was used. With multivariable regression analysis we adjusted for age, sex, ABI and the baseline value.

A value of $P < 0.05$ was considered to be statistically significant. Analyses were performed using SPSS 16.0 for Windows (SPSS Inc, Chicago, Ill).

Figure 1. Flow chart participants



RESULTS

Between July 2007 and July 2008 all patients planned for a PVI were checked for eligibility (n=401). We excluded 261 patients for reasons listed in figure 1, leaving 140 eligible patients. Of these patients, 70 refused to participate, hence 70 patients were randomised. Thirty-five patients were allocated to the control group (only PVI) and 35 patients to the intervention group (PVI and additional SET). At the end of the follow up period of 6 months 27 patients in the control group and 34 patients in the intervention group were included in the primary analysis. Nine patients withdrew from follow up for reasons specified in figure 1.

Table 1. Baseline characteristics of the study population

Characteristic	Control group N=35	Intervention group N=35	P-value
Men	21 (60.0%)	22 (62.9%)	0.806
Age	60.2 ± 10.0	64.5 ± 9.3	0.067
BMI	27.5 ± 4.9	26.6 ± 3.4	0.384
ABI $_{\text{pre PVI}}$	0.71 ± .18	0.69 ± 0.21	0.747
ABI $_{\text{post PVI}}$	0.91 ± .22	0.87 ± 0.22	0.418
Current smokers	21 (60.0%)	18 (51.4%)	0.470
Previous vascular intervention	7 (20.0%)	9 (25.7%)	0.569
Hypertension	24 (68.6%)	25 (71.4%)	0.794
Hypercholesterolemia	31 (88.6%)	30 (85.7%)	1.000
CVA / TIA	2 (5.7%)	4 (11.4%)	0.673
COPD	5 (14.3%)	3 (8.6%)	0.710
Diabetes	5 (14.3%)	9 (25.7%)	0.232
Orthopedic disease	4 (11.4%)	8 (22.9%)	0.205
Coronary heart disease	7 (20.0%)	13 (37.1%)	0.112
Walking distances			
FCD $_{\text{pre PVI}}$	282.2 ± 292.8	186.1 ± 116.2	0.078
FCD $_{\text{post PVI}}$	562.5 ± 356.8	484.6 ± 285.5	0.317
ACD $_{\text{pre PVI}}$	343.3 ± 247.9	293.4 ± 189.6	0.347
ACD $_{\text{post PVI}}$	650.5 ± 327.5	550.2 ± 289.0	0.179
SF-36 quality of life score			
Physical functioning	41.6 ± 17.5	43.6 ± 19.4	0.660
Physical role	39.1 ± 43.5	33.3 ± 39.9	0.582
Pain	43.0 ± 16.4	41.4 ± 19.9	0.725
General health	52.2 ± 13.2	51.5 ± 11.3	0.809
Physical summary score	31.0 ± 9.1	30.5 ± 7.7	0.802
Social functioning	69.1 ± 28.0	64.0 ± 22.8	0.413
Emotional role	83.9 ± 35.4	80.8 ± 38.2	0.741
Mental health	72.8 ± 18.3	72.2 ± 20.8	0.905
Vitality	51.2 ± 18.8	57.4 ± 20.2	0.206
Mental summary score	53.8 ± 11.6	53.8 ± 11.7	0.981
Euroqol			
Total score	0.63 ± .19	0.55 ± .27	0.181
General health	64.3 ± 15.8	56.3 ± 18.2	0.057
Walking impairment questionnaire			
Distance	0.34 ± .20	0.24 ± .26	0.112
Speed	0.41 ± .18	0.34 ± .24	0.162
Stairs	0.51 ± .23	0.49 ± .30	0.724
Total score	0.42 ± .17	0.35 ± .23	0.161

BMI: Body mass index, ABI: Ankle brachial index, CVA: Cerebro vascular attack, TIA: Transient ischemic attack, COPD: Chronic obstructive pulmonary disease, FCD: Functional claudication distance, ACD: Absolute claudication distance, PVI: Percutaneous vascular intervention

The mean age of the included patients was 62.3 ± 9.8 years. The median ACD before intervention was 318.4 ± 220.5 meters. Forty-three patients (61.4%) were male. Baseline characteristics of the two groups are listed in table 1. There were no significant differences at baseline in demographic data, co-morbidities, walking capacity and quality of life.

Table 2 shows the Rutherford stages and the characteristics of the PVI. Three patients from the intervention group had complications as a consequence of the PVI, whereas no complications occurred in the control group. Complications of PVI included contralateral leg embolism requiring acute surgical thrombectomy, aortic rupture requiring emergency aorto-bifemoral bypass surgery, and persistent bleeding from the femoral artery necessitating surgical intervention. No SET related complications occurred.

Table 2: Characteristics of the percutaneous vascular intervention

Characteristic	Control group N=35	Intervention group N=35	P-value
Rutherford stage			0.441
Stage 1	0 (0.0%)	1 (3.3%)	
Stage 2	20 (62.5%)	15 (50.0%)	
Stage 3	12 (37.5%)	13 (43.3%)	
Stage 4	0 (0.0%)	1 (3.3%)	
Procedure			0.387
Angioplasty	29 (82.9%)	25 (71.4%)	
Recanalisation	3 (8.6%)	7 (20.0%)	
Both	3 (8.6%)	3 (8.6%)	
Side PVI			0.450
Left leg	12 (34.3%)	9 (25.7%)	
Right leg	13 (37.1%)	11 (31.4%)	
Both legs	10 (28.6%)	15 (42.9%)	
Localisation PVI			0.792
Aorto-iliac	31 (88.6%)	29 (82.9%)	
Femoro-popliteal	2 (5.7%)	3 (8.6%)	
Both aorto-iliac and femoro-popliteal	2 (5.7%)	3 (8.6%)	
Stent placement	12 (34.3%)	16 (45.7%)	0.329
Hemostasis			0.598
Compression bandage	5 (16.7%)	7 (23.3%)	
Closure device	25 (83.3%)	22 (73.3%)	
Complications			0.239
Bleeding	0 (0.0%)	1 (2.9%)	
Embolism	0 (0.0%)	1 (2.9%)	
Aortic rupture	0 (0.0%)	1 (2.9%)	

PVI: percutaneous vascular intervention

ADHERENCE TO THE PROTOCOL

All patients in both the control group and the intervention group underwent a PVI. One of the patients randomised to the control group (PVI alone) followed additional SET on his own request. In the intervention group 7 patients discontinued SET early for reasons mentioned in figure 1. Patients in the intervention group followed a mean of 20 sessions of SET within the follow up period of 6 months.

WALKING DISTANCE

The ACD in the control group increased from 343.3 metres pre-PVI to 650.5 metres post-PVI. Six months post-PVI the ACD in the control group remained at a stable level of 685.0 metres. The ACD in the intervention group increased from 293.4 metres pre-PVI to 550.2 metres post-PVI. With the additional SET program the ACD increased further to a mean of 956.3 metres at 6 months of follow up. The difference in ACD at 6 months follow up between the control and intervention group was significant with a mean difference of 271.3 metres (95%-CI 64.0 – 478.6, P =0.011) in favour of the intervention group receiving additional SET. After adjustment for ACD post PVI, age, sex, and ABI, the P-value was 0.001.

The FCD in the control group increased from a mean of 282.2 metres pre-PVI to 562.5 metres post-PVI and remained stable with a median of 547.2 metres at 6 months of follow up. The FCD in the intervention group increased from 186.1 metres pre-PVI to 484.6 metres post-PVI and increased further to a mean of 842.4 metres at 6 months of follow up. The mean difference in FCD at 6 months of follow up was 295.1 metres (95%-CI 101.7 – 488.5, P=0.003). After adjustment for FCDpost PVI, age, sex, and ABI the difference remained significant with a P-value of 0.001.

More details about walking distances are listed in table 3.

FUNCTIONAL RESULTS

As shown in table 3, intermittent claudication persisted in 9 patients in the control group compared to 10 patients in the intervention group at 6 months of follow up (P=0.743, adjusted P=0.601).

The total WIQ score, summarising the domains walking distance, speed, and climbing stairs, did not differ significantly between the two groups. However, the adjusted P-value for the difference at 6 months of follow up was 0.032 in favour of the intervention group. More details about the WIQ score are listed in table 3.

At 6 months of follow up 1 patient in the control group compared to 11 patients in the intervention group finished the complete treadmill test (P=0.002).

Table 3. Results for functional and hemodynamic parameters

	Control group		Intervention group		P-value	Adjusted P-value*
	N	Value	N	Value		
Walking distance						
FCD 3 months	28	660.4 ± 399.0	32	896.0 ± 520.8	0.052	0.001
FCD 6 months	27	547.2 ± 263.5	34	842.4 ± 478.3	0.003	0.001
ACD 3 months	29	782.9 ± 384.9	32	974.0 ± 512.6	0.103	0.001
ACD 6 months	27	685.0 ± 313.5	34	956.3 ± 490.4	0.011	0.001
Functional results						
Persisting claudication complaints 3 months	29	7 (24.1%)	32	8 (25.0%)	0.983	0.592
Persisting claudication complaints 6 months	27	9 (33.3%)	34	10 (29.4%)	0.743	0.601
Finished treadmill test 3 months	29	2 (6.9%)	32	9 (28.1%)	0.031	0.033
Finished treadmill test 6 months	27	1 (3.7%)	34	11 (32.4%)	0.005	0.018
Walking impairment questionnaire						
Distance 3 months	30	0.81 ± 0.21	29	0.78 ± 0.28	0.634	0.149
Distance 6 months	28	0.78 ± 0.22	32	0.83 ± 0.21	0.497	0.032
Speed 3 months	26	0.68 ± 0.22	27	0.61 ± 0.21	0.241	0.933
Speed 6 months	26	0.66 ± 0.25	31	0.65 ± 0.21	0.938	0.104
Stairs 3 months	31	0.79 ± 0.24	29	0.80 ± 0.24	0.777	0.199
Stairs 6 months	28	0.86 ± 0.15	31	0.80 ± 0.22	0.208	0.691
Total score 3 months	26	0.76 ± 0.17	26	0.71 ± 0.21	0.455	0.205
Total score 6 months	26	0.76 ± 0.18	30	0.76 ± 0.17	0.946	0.175
Hemodynamic results						
ABI 6 months	33	0.93 ± 0.18	30	0.88 ± 0.19	0.356	0.755
Re-intervention within 6 months	33	2 (6.1%)	35	0 (0.0%)	0.232	0.997
Re-stenosis > 70% / re-occlusion within 6 months	32	3 (9.4%)	34	3 (8.8%)	1.000	0.402

FCD: Functional claudication distance, ACD: Absolute claudication distance, ABI: Ankle brachial index
* Adjusted for baseline value, age, sexe and ABI

HEMODYNAMIC RESULTS

The ABI in the control group improved from 0.71 pre-PVI to 0.91 post-PVI and remained stable at a level of 0.93 at 6 months of follow up. In the intervention group the ABI improved from 0.69 pre-PVI to 0.87 post-PVI and was 0.88 at 6 months of follow up. The mean difference between the two groups was 0.044 (P=0.356), remaining similar after adjustment for baseline variables (P=0.755).

The number of re-interventions for PAD and the number of re-stenoses / occlusions were not significantly different between the two groups with P-values of 0.232 and 1.000, re-

spectively. More details about the hemodynamic results are displayed in table 3.

HEALTH RELATED QUALITY OF LIFE

Results for health related quality of life at 6 months of follow up are displayed in table 4. The physical health summary score of the SF-36 improved after PVI in both the control and the intervention group. Additional SET did not increase the improvement in physical health (P=0.340).

The difference in mental health summary score was 4.8 (95%-CI .7 – 10.3) in favour of the intervention group (P=0.085). After adjustment for baseline variables the difference was statistically significant with a P-value of 0.035. Additional analyses indicated that this difference was not the result of an increase of mental health summary score in the intervention group, but a decrease in the control group (P=0.045). Data at 3 months of follow up did not reveal any difference in quality of life between the intervention and control group (data not shown).

Table 4. Results for health-related quality of life at 6 months of follow up

	Control group		Intervention group		P-value	Adjusted P-value*
	N	Value	N	Value		
Short Form 36						
Physical functioning	29	72.2 ± 18.0	33	72.7 ± 22.3	0.928	0.281
Physical role	29	71.6 ± 37.0	32	56.3 ± 40.2	0.128	0.594
Pain	29	64.7 ± 26.0	33	70.0 ± 22.8	0.393	0.082
General health	28	53.7 ± 12.5	33	56.9 ± 12.6	0.325	0.086
Physical summary score	28	44.1 ± 7.8	31	41.9 ± 9.5	0.340	0.897
Social functioning	29	77.2 ± 31.0	33	80.7 ± 19.8	0.591	0.157
Emotional role	29	77.0 ± 40.9	32	82.3 ± 35.9	0.593	0.255
Mental health	29	68.0 ± 19.5	32	79.4 ± 17.5	0.020	0.003
Vitality	29	57.1 ± 20.0	32	67.3 ± 17.7	0.038	0.043
Mental summary score	28	49.0 ± 11.7	31	53.8 ± 9.2	0.085	0.035
Euroqol						
Total score	29	0.77 ± 0.20	33	0.79 ± 0.19	0.660	0.196
General health	34	73.6 ± 12.1	35	74.2 ± 11.9	0.817	0.122

* Adjusted for baseline value, age, sex and ankle brachial index

DISCUSSION

The results of the current randomised clinical trial show that SET in addition to PVI significantly improves walking distance by approximately 300 m compared with PVI alone at 3 and 6 months of follow up, for both FCD and ACD. The additional improvement in walking ability of approximately 300 m was not accompanied by additional improvement in quality of life.

METHODOLOGICAL ASPECTS OF THE STUDY

Although the study was randomised and the allocation was adequately concealed before randomisation, the study had to be open because of the nature of the intervention. In addition, physiotherapists evaluating the walking distance were not blinded for the intervention. However, the primary outcome measurement was defined as the ACD measured with a standardised treadmill protocol which is considered as an objective measurement of walking capacity.

For practical reasons the treadmill test was maximised at 30 minutes. After 6 months of follow up, 1 patient in the control group improved beyond these 30 minutes compared to 11 patients in the intervention group. This indicates that the difference in walking distance between the 2 groups is likely to underestimate the real difference. An important limitation of the study is the difference in withdrawal from follow up between the control (n=8) and intervention group (n=1). This could have led to bias in our analysis. However, the patients who withdrew from the follow up in the control group did not differ in walking distance (last data before withdrawal, data not shown) compared to the patients in the control group that completed the follow up. Therefore, it is likely that if these patients could be included in the analysis, the difference between the control group and intervention group would not alter substantially.

A second limitation is that this study is conducted in a single centre in the Netherlands, which may limit the generalisability of the results. In our centre, a supervised exercise program in a community-based setting is available for all patients with intermittent claudication as part of standard care. In the current study mainly iliac stenoses were treated, which might have been influenced by the easy availability of SET. Therefore, results might be different for patients with a femoro-popliteal PVI.

COMPARISON WITH LITERATURE

Little is known about the effects of exercise therapy following invasive treatment for PAD. A beneficial effect of SET on walking distance has been reported following bypass surgery

as compared with bypass surgery alone[23,24] In line with these results, the present study demonstrates that SET causes an additive improvement in walking capacity following a PVI.
A recent study by Spronk et al. showed that SET is as effective as PVI for increasing walking distance and physical quality of life after 6 and 12 months of follow up.[7]
Several studies[7, 25] have evaluated the effect of PVI and SET on physical quality of life, and have demonstrated that both treatments result in an increase in different domains of physical quality of life. In our study, physical quality of life improved after the PVI, but did not further improve with additional SET in spite of an improvement in walking capacity. This discrepancy may be explained by a lack of sensitivity to detect subtle changes by the general quality of life questionnaires.

IMPLICATIONS FOR CLINICAL PRACTICE AND CONCLUSION

The results of the present study indicate that SET is a useful adjunct to PVI for the treatment of peripheral arterial disease. Since this study mainly included patients treated for iliac lesions, it remains to be established whether patients with more distal lesions would also benefit from such a combination therapy. Furthermore, based on our findings and the recently reported similar efficacy of SET and PVI,[7] a combination of these treatments is expected to be more effective than SET alone in increasing walking capacity. We recommend that this should be subject of future research.

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CHAPTER 10

GENERAL DISCUSSION

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The general objective of this thesis was to describe the effectiveness of exercise therapy and endovascular treatment for intermittent claudication, focussing on walking distance and quality of life. Effectiveness of treatment, implementation in clinical practice, and differences between patients are perspectives that we planned to study.
To address this objective, different clinical studies have been performed on the functioning of community-based supervised exercise therapy (SET) in daily practice (part one).To explore other treatment options a systematic review to asses the effectiveness of different PAD treatments and a randomised clinical trial were conducted (part two).
In this chapter we describe the main findings of the studies presented in this thesis. In addition, methodological considerations concerning the validity of the studies will be discussed. Then, implications for clinical practice and suggestions for future research will come up for discussion. Methodological considerations and implications for practice and research are described separately for the two parts of the thesis. Finally, the overall conclusions are presented.

MAIN FINDINGS

PART ONE: SUPERVISED EXERCISE THERAPY IN DAILY PRACTICE

Exercise therapy is, according to several guidelines, first choice of therapy for patients with intermittent claudication.[1-3] The importance of supervised training programmes is increasingly recognised.[2] However, implementing SET for every patient with intermittent claudication is difficult and supervised exercise programmes are sporadically available.[4]
Chapter 2 gives a summary of the results from studies performed previously by our research group. Results from a meta-analysis support the superiority of SET compared to non SET in increasing walking distance.[5] Furthermore, implementation of SET in a community-based setting as part of the regular care for patients with intermittent claudication is described.[6] Results for walking distance of community-based SET appear comparable to results we know from literature at 6 months of follow up.[7]
Chapter 3 describes the results of a validity study for the functional claudication distance (FCD), defined as the distance at which a patient prefers to stop because of claudication pain. As the FCD was used as an outcome measurement in our studies, validity had to be assessed. We demonstrated that the FCD is a reproducible and valid measurement, comparable to maximum- and pain-free walking distance. Furthermore, FCD correlated better with quality of life, indicating that FCD may better reflects actual functional impairment.
In chapter 4 we showed that 12 month results from community-based SET in the field

of walking distance are comparable to results we know from literature about SET for intermittent claudication. The most increase in walking distance occurred during the first 6 months of SET. After 6 months no further increase in walking distance was seen. It is unclear what mechanism is responsible for this plateau phase.
The Royal Dutch Society for Physiotherapy classifies the results of SET in the field of walking distance in good (≥ 100% increase), moderate (50% ≤ increase < 100%), and unsatisfactory (< 50% increase).[8] Following these definitions about 36% of the patients starting community-based SET had an unsatisfactory result. Remarkably, a good or unsatisfactory result at 3 months of follow up was likely to persist. To investigate what patients would have unsatisfactory results, two studies were conducted in which patient related variables and their influence on walking distance were explored. The first study (chapter 5) showed that patients with intermittent claudication and diabetes mellitus (DM) have corresponding improvement in walking distance compared to patients with intermittent claudication alone after 6 months of community-based SET. However, the walking distance in metres is lower in diabetic patients at every follow up moment in time.
The second study (chapter 6) explored patient related variables predictive of walking distance after SET. Baseline walking distance, body-mass-index, and smoking behaviour were independent predictors for the walking distance after SET. Patients with a better walking distance at baseline also walked better at follow up, whereas a higher body-mass-index and current smoking were associated with a lower walking distance. However, predicting individual results based on these variables was inaccurate, with only 25 to 34% of the actual walking distance within the predicted target range.

PART TWO: TREATMENT OF PERIPHERAL ARTERIAL DISEASE COMPARED AND IMPROVED

In recent guidelines, SET is recommended as first choice therapy for intermittent claudication,[1-3] although several other treatment options are increasingly used. In the second part of the thesis treatment options other than SET are explored and we tried to identify variables that can improve endovascular treatments.
Chapter 7 provides an overview of the most frequently used treatments for intermittent claudication and their effectiveness on walking distance and quality of life. In this network meta-analysis we used both direct as indirect evidence to determine the effectiveness of the different treatment modalities. SET, angioplasty and surgery are all better in improving walking distance compared to both no treatment and non SET. This indicates that solely treatment of vascular risk factors with an advice to exercise is not sufficient for relieving symptoms of intermittent claudication. For improving physical quality of life SET was of additional value compared to no treatment. Results of angioplasty and surgery for

physical quality of life were less obvious, as only very few studies could be included for these treatment modalities.
The Trans-Atlantic Inter-Society Consensus Document on the management of PAD (TASC-II)[2] advices to localise the lesion, and if a proximal lesion is found, to consider primary revascularisation, instead of SET. Also the Dutch guideline on diagnosis and treatment of PAD[3] recommends to perform angioplasty in selected patients with short lesions without trying exercise. However, only little evidence is available on variables that affect functional results after angioplasty. In the clinical study, described in chapter 9, we explored what patient related variables would influence functional outcome after a percutaneous vascular intervention (PVI) for intermittent claudication. Patients with a younger age, longer baseline walking distance, and isolated iliac disease had a better functional outcome in terms of walking distance. Old age, short baseline walking distance and multi-segment disease were associated with a shorter walking distance following the PVI. Furthermore, persistence of claudication complaints after treatment with a PVI was more likely with multi-segment disease, diabetes mellitus, current smoking, and existence of a stenosis (instead of occlusion).
In chapter 10, SET following a PVI is explored as variable that possibly can improve results compared to PVI alone for the treatment of PAD. In a randomised controlled trial PVI alone was compared to PVI with additional SET. After 6 months of follow up walking distance improved most in the group receiving additional SET with a mean difference of 270 metres. Furthermore, in the control group (PVI alone) 1 patient was able to finish the treadmill test, compared to 11 patients in the intervention group (PVI with additional SET). The further improvement in walking distance was not accompanied by additional improvement in quality of life.

METHODOLOGICAL CONSIDERATIONS – PART ONE

In the first part of this thesis three studies concerning a cohort of patients following community-based SET were described. In this section we first describe methodological considerations that apply on all these cohort studies. After that, more study specific considerations will be discussed.

A cohort study is obviously not the 'gold standard' for investigating effectiveness of a treatment. In our cohort study, for lack of a control group, results were compared to results of SET literature in a clinic-based setting. Limited capacity in the department of

rehabilitation and physiotherapy of our centre was the main practical barrier preventing implementation of clinic-based SET. However, SET in general is extensively studied and the effectiveness in the treatment of intermittent claudication has been demonstrated for different programs and exercise modalities.[5, 9] Therefore, we do not expect that community-based SET would perform worse than clinic-based SET.

More importantly, all patients following SET were included in the cohort without strict in- or exclusion criteria, as our objective was to describe usual care. On the contrary, in literature patients with co-morbidities as diabetes[10-14], coronary heart disease[10, 12-18], pulmonary disease[12-14, 16] and cerebrovascular disease[15, 16] often are excluded. However, these co-morbidities are frequently present in the population of patients with intermittent claudication.[2] Furthermore, these co-morbidities are no absolute contra-indication for exercise.[19] Therefore, in our cohort also patients with various co-morbidities were prescribed exercise therapy. Hence, we expect that our results can be easily generalised to other populations suffering from intermittent claudication. A side note that should be made is that in our centre we tend to treat patients having aorto-iliac disease more often with a PVI instead of SET. Therefore it is plausible that in our cohort of community based SET patients with more distal PAD are overrepresented. However, we are not sure as we did not record the site of the lesion. Therefore, we should be conservative with generalisation to a population with mainly aorto-iliac disease.

It is possible that in daily practice loss to follow up or early cessation of the exercise program can be increased compared to literature, due to more frequent presence of co-morbidities. Important motives for patients to stop the program were other diseases that originated besides intermittent claudication. In all three cohort studies the number of patients discontinuing SET was high, ranging from 37% to 43% after 6 months of follow up. High numbers of patients who drop out are a common phenomenon in literature about SET with percentages ranging from 10% to 50% after 6 months of follow up.[14, 20-23] These percentages are consistent with the drop out percentages of our own study.
In our cohort studies we choose not to impute any data, although several methods for data imputation are available.[24] Missing data in our studies were likely to be dependent on unobserved data (not missing at random), and therefore we choose to analyse only the data available, as imputation could potentially lead to unacceptable bias.

All patients were prescribed community-based SET according to the guideline of the Royal Dutch Society of Physiotherapy that provides an evidence based background for training and evaluating patients with intermittent claudication.[8] However, this guideline

lacks specific advice about training schedules in terms of frequency, duration, and work strain. Also, training modality can vary (e.g. walking, cycling, strength, endurance, interval) extensively. As a consequence, training is adjusted to the individual needs of a patient and differs between patients and physiotherapists. Unfortunately, we did not record the exact training program. Differences in results between patients could therefore be the consequence of differences in training program, instead of patient related variables. Furthermore, we could not address the dose-response question with this study set-up.

In chapter 3 reproducibility and validity of the FCD was determined. In this study two small cohorts (n=57 and n=25) of patients familiar with treadmill walking were studied. Both cohorts were small, and so results (especially validity; n=25) should be treated with some caution. The reliability results of the pain-free and maximum walking distance were better than those reported in literature.[25-27] A possible explanation could be that we included patients familiar with treadmill walking, what could have influenced the reliability results. Therefore, extrapolation of our results to a population without treadmill experience should be treated with caution.
Chapter 5 compares the effectiveness of SET in patients with intermittent claudication alone to patients with both DM and intermittent claudication. In this study we only measured fasting glucose and HbA1C at baseline. Furthermore we did not record medication use or alterations in medication during follow up. Results from literature indicate that the level of regulation of DM influences exercise tolerance.[28-32] Also in our study patients with inadequately regulated DM at baseline had lower exercise performance than patients with adequately regulated DM (data not shown). It could be that patients without DM developed this condition during follow up. Vice versa, patients with severe DM (HbA1C > 7.0%) at baseline could be adequately regulated due to alterations in medication. This could have influenced the results, most likely decreasing the potential difference between DM and nonDM patients.

IMPLICATIONS FOR CLINICAL PRACTICE – PART ONE

Part one of this thesis mainly describes results of SET in a community-based setting. We experienced that community-based SET is easy to implement in clinical practice and solves the capacity problem we experienced with clinic based SET. Hence, we think that community-based SET is a useful and effective approach that can be used in other regions in daily care for patients with intermittent claudication.

However, with the drop out percentages mentioned above, the question arises if SET should be the treatment of first choice for patients having symptoms of intermittent claudication. Percutaneous vascular interventions are increasingly used, and give an instant improvement of walking distance and quality of life.[33, 34] On the other hand, one should realise that not all lesions are suitable for endovascular therapy. Furthermore, PVIs have complication rates ranging from <0.5% - 5% of complications needing re-intervention and 8% - 15% of minor complications.[34-36] Additionally, patients who discontinued SET early, did not necessary had an unsatisfactory outcome. It appeared that the majority of dropouts did not receive an additional vascular intervention and a small group of patients stopped because of satisfaction with the regained walking distance. Furthermore, after only 3 months a physician can properly evaluate a patient's response to SET, as unsatisfactory or satisfactory results are likely to persist in the further follow up. Therefore we recommend that all patients with intermittent claudication try SET for a period of 3 months, before evaluating the need for a revascularisation procedure.

Two studies describe the influence of different patient related variables on the effectiveness of SET in terms of walking distance. Although some patient related variables had some influence, we could not identify a subgroup of patients who were not likely to benefit from SET. Consequently, all patients should start SET in order to assess the effectiveness of SET in an individual patient. We recommend that every patient, regardless of body-mass-index (BMI), DM, smoking, and baseline walking distance, starts with SET. When SET turns out to be ineffective in an individual patient, the need for an endovascular or surgical procedure can be further evaluated.

IMPLICATIONS FOR FUTURE RESEARCH – PART ONE

After performing the studies in community-based SET, some further research questions arose that will be discussed below.
First, the training program used in the studies differed for the individual patient and physiotherapist. We know from a meta-analysis of Gardner and Poehlman[37] that walking to near maximal pain for a period of at least 6 months is more effective in improving walking distance than other modes of exercise, e.g. not reaching near maximal pain and/or a shorter training period. However, questions about optimal frequency of the sessions, the duration per session, time of the intervals until claudication pain, and optimal frequency of reaching claudication pain remain unanswered. Dose-response research and research

more focussed on the content of exercise therapy is necessary to address the issues about the most optimal training program.

Furthermore, more specific research about the reasons for dropping out the exercise program should be considered. In our studies we could not identify any predicting variables for drop out (data not shown). However, we only studied patient related baseline variables. A suggestion for further studies could be research to patients' satisfaction for exploring variables in the process of diagnosis, information services, and treatment related variables that could influence drop out.

The predictor variables BMI, smoking and baseline walking distance did only explain about one third of the variation existent in walking distance after SET. This suggests that other variables are of importance in predicting outcome after SET. In literature psychological factors (type D personality, depressive symptoms, patient's belief)[38-40] and level of occlusive disease (aorto-iliac versus femoro-popliteal)[41] are suggested variables that could influence results of SET. Especially the level of occlusive disease is important to study. There is some indication that SET is more effective in femoro-popliteal disease[41] whereas this thesis suggests that a PVI would be more effective in aorto-iliac disease in the field of walking distance. Hence, a randomised clinical trial comparing SET with PVI for aorto-iliac and femoro-popliteal disease separately would be interesting and results of such a trial will contribute to the optimisation of the care for patients with intermittent claudication.

METHODOLOGICAL CONSIDERATIONS – PART TWO

In the second part of this thesis, where we focus more on endovascular treatment of intermittent claudication, some methodological aspects need to be discussed.
Chapter 7 describes the results of a meta-analysis, in general acknowledged as the best possible evidence. However, in our meta-analysis we combined both direct and indirect evidence, as for the comparison of the most frequently used therapies for intermittent claudication the number of head to head randomised controlled trials was limited. Furthermore, we also included non randomised trials and cohort studies for the same reason. However, we performed sensitivity analyses, excluding all non randomised trials, and observed corresponding results for walking distance. For physical health, results of angioplasty and surgery altered, failing to show an improvement in physical health compared to

no treatment. Another point of attention is that the majority of trials were not very recent. By now, techniques for endovascular and surgical interventions have been altered, possibly improving the effectiveness. If trials were available, including these in the meta-analysis could alter the results, possibly leading to an increased effect of endovascular and surgical interventions compared to no treatment / exercise therapy.

In chapter 8 several variables that can predict functional outcome after PVI were identified, albeit at short term (ca. 3 weeks). These variables are not necessarily predicting for long term outcome. Hence, we can not state that patients with good short term outcome will be better of eventually, compared to patients with worse short term outcome. Although it is unlikely that patients with worse short term outcome will improve spontaneous over time, patients with better functional results at short term could deteriorate over time leading to an equal effect at long term.

Chapter 9 describes the results of a randomised clinical trial comparing PVI alone with PVI followed by additional SET. A randomised clinical trial is generally acknowledged as an appropriate study design, as both known and unknown confounding variables are likely to be equally divided between the groups. The most correct procedure is to blind patients and health care professionals for the allocated treatment to prevent bias. However, our study was an open randomised clinical trial, due to the nature of the intervention (exercise therapy). Physiotherapists and physicians were aware of the treatment allocated to the patients, allowing to (subconsciously) treating patients in the control and intervention group in a different way. However, we tried to evaluate the patients in the most standardised way possible, with a standardised treadmill test.

The external validity of the studies described in both chapter 8 and 9 should be considered shortly. Both studies were conducted in a single centre in the Netherlands where community-based SET is available for patients with intermittent claudication as standard care. Based on current guidelines, our general policy is that we tend to treat patients with aorto-iliac disease primarily with a PVI, whereas patients with femoro-popliteal disease are treated with SET. Hence, in the studies described in chapter 8 and 9 mainly iliac disease was treated. However, in other centres, that have no easy access to SET, more patients with femoro-popliteal disease might be treated with PVI. Consequently, in these centres, the population of patients treated with PVI might be substantially different. Therefore, our results are most likely to apply for patients with aorto-iliac disease.

IMPLICATIONS FOR CLINICAL PRACTICE – PART TWO

Part two of this thesis mainly describes the results of PVIs for intermittent claudication. From the comparison with other treatments we can say that for the treatment of symptoms of intermittent claudication a wait and see policy, or only an advice to exercise without supervision is not an adequate treatment. Supervised exercise therapy, PVI and surgery are all three effective treatment modalities. However, we recommend, considering both effectiveness and complication rate, that SET is the treatment of first choice for patients with intermittent claudication.

Then, if a PVI is planned for the treatment of intermittent claudication, location and extensiveness of the disease should be taken into consideration. Patients with only iliac disease have better outcomes in both walking distance and claudication complaints compared to patients with multi-segment disease. Patients with multi-segment disease should therefore be informed about less chance of success or the possibility of additional treatment.

Following PVI, SET can additionally improve walking distance in patients with intermittent claudication. Hence, if a PVI is performed for intermittent claudication it is useful to prescribe additional SET.

IMPLICATIONS FOR FUTURE RESEARCH – PART TWO

In the first place, although SET, PVI, and surgery are all three effective treatments for intermittent claudication, no difference between these treatments could be determined in the field of walking distance and quality of life. However, there were only a limited number of trials with regard to these outcomes. Hence, there is still uncertainty of the possible additional value of PVI and surgery compared to SET. More importantly, based on the findings in chapter 9 and reports from literature regarding SET following bypass surgery being more effective than surgery alone[42, 43], a combination of SET and invasive treatments is expected to be more effective than SET alone in increasing walking capacity. We recommend that this should be subject of future research.

CONCLUSIONS

At this point supervised exercise therapy should be the treatment of first choice for all patients with intermittent claudication as we have no strong evidence that a percutaneous vascular intervention or surgery is more effective. Furthermore, subgroups in which SET is less beneficial could not be identified.
In case a percutaneous vascular intervention is performed, effectiveness can be increased with additional supervised exercise therapy, and should therefore be prescribed supplemental to PVI.

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SUMMARY

The general purpose of this thesis is to describe exercise and endovascular treatment for intermittent claudication from different perspectives. From a patient perspective we focus on walking distance and quality of life as outcome measurements. From a research perspective we focus on effectiveness of treatments and exploring variables that influence effectiveness. From a health care perspective we focus on implementation of exercise therapy in daily care.

PART ONE – SUPERVISED EXERCISE THERAPY IN PRACTICE

Supervised exercise therapy (SET) is extensively studied, and a proven effective treatment for intermittent claudication. However, SET programmes are not universally available and implementation of SET in daily clinical practice stays behind. In the Netherlands, an evidence based guideline from the Royal Dutch Society for Physiotherapy is available. All clinical studies described in this thesis, perform SET according this guideline.

In chapter 2 an overview is given of recent studies conducted by our research group about implementing SET in clinical practice. The first results of this so called community-based approach are presented. The main findings from our previous research were that SET programmes have significant benefits compared with non-supervised programmes, and that SET in a community-based setting both has economic and logistic advantages over clinic-based SET. Furthermore, community-based SET programmes seem to be as effective as SET provided in a clinic-based setting and are a promising approach to providing conservative treatment for patients with intermittent claudication close to their home.

Chapter 3 describes the validity of an alternative outcome measurement for the effectiveness of treatment for intermittent claudication. Disease severity and functional impairment in patients with intermittent claudication is usually quantified by the measurement of pain-free walking distance (intermittent claudication distance, ICD) and maximal walking distance (absolute claudication distance, ACD). However, the distance at which a patient would prefer to stop because of claudication pain seems more correspondent with the actual walking distance in daily life. In this chapter the distance a patient prefers to stop was defined as the functional claudication distance (FCD). To assess reliability and validity of the FCD we included patients with intermittent claudication following a SET program. First we studied patients performing a standardised treadmill test twice. During each test ICD, FCD and ACD were determined. Reliability was represented by the calculated intra-class correlation coefficients. In the second part of the study patients performed a standardised treadmill test and filled out the Rand-36 questionnaire. Spearman's rho was calculated to assess validity.

The intra-class correlation coefficients of ICD, FCD and ACD were 0.940, 0.959, and 0.975 respectively. FCD correlated significantly with five out of nine domains, namely physical function (rho = 0.571), physical role (rho = 0.532), vitality (rho = 0.416), pain (rho = 0.416) and health change (rho = 0.414).
Based on these results we concluded that the FCD is a reliable and valid measurement for determining functional capacity in trained patients with intermittent claudication. Furthermore it seems that FCD better reflects the actual functional impairment. In future studies, FCD could be used alongside ICD and ACD.

In chapter 4 we conducted a prospective cohort study of community-based SET in regional physiotherapeutic practices. This study describes the results and functioning of community-based supervised exercise therapy (SET) at one year of follow-up.
Consecutive patients with intermittent claudication referred for community-based SET were included. Exclusion criteria for SET were pain at rest or tissue loss. At baseline and at 1, 3, 6, and 12 months of follow up, the ACD was assessed with a standardised treadmill test.
From January 2005 through September 2006, 349 patients were referred by vascular surgeons for community-based SET. A total of 272 patients with intermittent claudication started with the program. Of the 349 initially referred patients, 52 could not perform a standard treadmill test and did start community-based SET at a lower level, and 25 patients never started the program. At one year, 129 of the original 272 patients who began community-based SET (47.4%) were available for analysis of walking distance. During the study period, 143 patients discontinued the program for the following reasons: satisfaction with the acquired walking distance (n=19); unsatisfying results (n=26); not motivated (n=22); (non)vascular intercurrent disease (n=48); and other reasons (n=28). ACD increased significantly from a median of 400 m at baseline to 1100 m after 12 months of follow-up ($P<0.001$), corresponding to a median increase of 107.8%. This increase is correspondent with results we know from literature about clinic-based SET. We concluded that community-based SET seems as effective as SET in a hospital-based approach in improving walking distance, however, it has a high dropout rate.

Chapter 5 describes the effect of SET for intermittent claudication in patients with diabetes mellitus (DM). Diabetes is a frequent occurring co-morbidity in patients with intermittent claudication and in these patients exercise tolerance is decreased. However, there is little literature about the increase in walking distance following SET in patients with both intermittent claudication and DM.
We included consecutive patients with intermittent claudication who started SET. Exclusion criteria were pain at rest, tissue loss, and the inability to perform the standardised

treadmill test. At baseline and at 1, 3 and 6 months of follow up a standardised treadmill exercise test was performed. The primary outcome measurement was the ACD.
We included 775 patients of whom 230 had DM (29.7%). At six months of follow up, data of 451 patients (58.0%) were available. Both ACD at baseline and 6 months of follow up were significantly lower in patients with DM (P<0.001). However, increase in ACD after 6 months of SET did not differ significantly (P=0.48) between the DM-group and non DM-group, and was 270 and 400 metres respectively.
Supervised exercise therapy for patients with intermittent claudication is equally effective in improving walking distance for both patients with and without DM, although absolute walking distances remain lower in patients with DM.

In chapter 6 we try to identify predictive variables for results after SET and developed a clinical prediction model that aims to predict a target walking distance for individual patients.
We included patients with intermittent claudication who participated in a SET program. The main outcome measurement was the ACD after 6 months of SET. Linear regression analyses were conducted to identify independent predictor variables for ACD.
Four-hundred-and-thirty-seven patients were analysed. Independent predictor variables for post-treatment ACD were baseline ACD (P<0.001), smoking behaviour (P=0.012), and body-mass-index (P=0.041). A better baseline ACD was associated with a longer post-treatment ACD whereas current smoking, and a higher body-mass-index were associated with a shorter post-treatment ACD. The final regression equation included baseline ACD, age, body-mass-index, smoking, and pulmonary disease and was translated into several clinical prediction models. However, only 24.8 – 33.6% of the patients had an ACD within the calculated target range, so translating the regression equation into a clinical prediction model did not lead to a valid model for use in clinical practice.

PART TWO – TREATMENT FOR INTERMITTENT CLAUDICATION COMPARED AND IMPROVED

Treatments, other than exercise training, are increasingly used for symptomatic relief of intermittent claudication, especially endovascular treatments. However, there is an ongoing discussion about the effectiveness of other treatments than exercise training for intermittent claudication.

In chapter 7 a network meta-analysis is conducted to describe the effect of different treatments for intermittent claudication. Treatment of intermittent claudication aims for improvement in functional capacity and quality of life. However, studies on radiological and

surgical interventions often focus on hemodynamic outcomes. Therefore, the objective of this network meta-analysis is to provide an overview of the most common treatments for intermittent claudication and to determine the effectiveness in improving walking distance and quality of life based on a combination of direct and indirect evidence.
We included trials that compared: angioplasty, surgery, exercise therapy or no treatment for intermittent claudication. Outcome measurements were walking distance (maximum, pain-free) and quality of life (physical, mental). We used a network meta-analysis model for the combination of direct and indirect evidence.
We included 42 studies, presenting the results of 3106 participants. The network meta-analysis showed that supervised exercise therapy (Δ=1.62, P<0.01), angioplasty (Δ=1.89, P<0.01) and surgery (Δ=2.72, P=0.02) increased walking distance significantly more than no symptomatic treatment therapy. Sensitivity analyses, excluding all non-randomised trials, showed corresponding results. Furthermore, supervised exercise therapy (Δ=0.60, P<0.01), angioplasty (Δ=0.91, P=0.01) and surgery (Δ=1.07, P<0.01) increased physical quality of life more than no symptomatic treatment. However, in the sensitivity analysis, excluding all non-randomised trials, only supervised exercise therapy had additional value over no symptomatic treatment (Δ=0.66, P<0.01) for improving physical quality of life. None of the treatments had any effect on mental health.
This network meta-analysis indicates that supervised exercise therapy is more effective in both increasing walking distance and physical quality of life, compared to no treatment. Angioplasty and surgery also increase walking distance, compared to no treatment, but, results for physical quality of life are less convincing.

In chapter 8 we search variables that would be predictive for the functional result after a percutaneous vascular intervention (PVI) for intermittent claudication. Patients with peripheral arterial disease (PAD), Rutherford stage 1 – 3, selected for treatment with PVI were included. Primary outcome was the absolute claudication distance (ACD), measured with treadmill testing, within three weeks post-PVI. Secondary outcome was the persistence of complaints of claudication. Linear and logistic regression analyses were conducted to identify variables associated with post-PVI claudication and ACD.
Eighty-nine patients were included. In the final prediction model for post-PVI ACD, presence of isolated iliac disease (P=0.007), a higher baseline ACD (P<0.001), and a younger age (P=0.044) were associated with a higher ACD after the vascular intervention. The likelihood of persisting claudication complaints increased with a lower baseline ACD (P=0.070), existence of multi-segment disease (P=0.007), current smoking (P=0.015), presence of a stenosis (instead of an occlusion; P=0.026), and the presence of diabetes (P=0.030). Presence of COPD decreased the likelihood of post-PVI claudication com-

plaints (P=0.067).
This study shows that several predictor variables for the functional result after PVI could be identified. A lower baseline ACD, increased age, multi-segment disease, current smoking, and the presence of diabetes are all associated with less functional benefit after PVI.

Chapter 9 describes the results of a randomised clinical trial that investigates the value of additional SET after a PVI, compared to PVI alone. Patients with PAD, Rutherford stage 1 – 4, treated with a PVI, and a post-PVI maximum walking distance <1600 metres were potentially eligible. All patients participating in the study were treated with a PVI. After the PVI patients were randomised to PVI alone or PVI + additional SET. Primary outcome was the ACD. Secondary outcome was, among others, quality of life.
We included 35 patients in each group. The mean difference in ACD at 6 months of follow up was 271.3 metres (95%-CI 64.0 to 478.6, P =0.011) in favour of additional SET. In the control group 1 patient (3.7%) finished the complete treadmill test compared to 11 (32.4%) in the intervention group (P=0.005). Physical health related quality of life score was 44.1 ± 7.8 in the control group, compared to 41.9 ± 9.5 in the intervention group which was a non significant difference (P=0.34).
In conclusion, supervised exercise therapy following a PVI is more effective in increasing walking distance compared to a PVI alone. These data indicate that SET is a useful adjunct after a PVI.

CONCLUSIONS
At this point supervised exercise therapy should be the treatment of first choice for all patients with intermittent claudication as we have no strong evidence that a percutaneous vascular intervention or surgery is more effective. Furthermore, subgroups in which SET is less beneficial could not be identified.
In case a percutaneous vascular intervention is performed, effectiveness can be increased with additional supervised exercise therapy.

SAMENVATTING

Het doel van dit manuscript is om vanuit verschillende perspectieven de primaire behandeling van claudicatio intermittens te beschrijven, waarbij zowel looptherapie als endovasculaire behandeling aan bod komt.
Vanuit het perspectief van de patiënt wordt gekeken naar voor de individuele patiënt belangrijke uitkomstmaten, zoals loopafstand en kwaliteit van leven. Vanuit onderzoeksperspectief kijken we naar de effectiviteit van verschillende behandelingen en onderzoeken we patiënt gerelateerde variabelen die de effectiviteit van een behandeling kunnen beïnvloeden. Tot slot wordt vanuit een gezondheidszorg perspectief gekeken naar de implementatie van gesuperviseerde looptherapie in de dagelijkse klinische praktijk.

DEEL ÉÉN – GESUPERVISEERDE LOOPTHERAPIE IN DE PRAKTIJK
Gesuperviseerde looptherapie is uitgebreid bestudeerd in de literatuur en een bewezen effectieve behandeling voor patiënten met claudicatio intermittens. Sinds 2003 is in Nederland een fysiotherapie richtlijn beschikbaar, uitgegeven door het Koninklijk Nederlands Genootschap voor Fysiotherapie (KNGF), waarin invulling wordt gegeven aan looptherapie. Deze op wetenschappenlijk onderzoek gebaseerde richtlijn stelt een kader op waarin de minimale randvoorwaarden en trainingsvormen worden uiteengezet voor het geven van gesuperviseerde looptherapie. De in dit proefschrift beschreven studies zijn gebaseerd op gesuperviseerde looptherapie zoals beschreven in deze richtlijn. In de dagelijkse praktijk blijkt een gesuperviseerd looptrainingsprogramma lang niet voor iedere patiënt met claudicatio intermittens beschikbaar.

In hoofdstuk 2 worden een aantal studies betreffende looptherapie beschreven die werden uitgevoerd door onze onderzoeksgroep. Wij toonden aan dat gesuperviseerde looptherapie effectiever blijkt dan niet gesuperviseerde training voor wat betreft het verbeteren van de loopafstand. Daarnaast bleek gesuperviseerde looptherapie in een georganiseerd netwerk van perifere fysiotherapeuten zowel economische als logistieke voordelen te hebben vergeleken met looptherapie gegeven op een afdeling revalidatie / fysiotherapie in een ziekenhuis. Met het geven van gesuperviseerde looptherapie door perifere fysiotherapeuten in de woonomgeving van de patiënt wordt de capaciteit dusdanig vergroot dat alle patiënten met claudicatio intermittens gesuperviseerde looptherapie kunnen volgen. Op grond van bestaande literatuur over gesuperviseerde looptherapie in een ziekenhuis setting vonden wij dat gesuperviseerde looptherapie in een georganiseerd netwerk in de woonomgeving van de patient vergelijkbare resultaten geeft. Het aanbieden van gesuperviseerde looptherapie in de woonomgeving van de patient en binnen een netwerk van geschoolde fysiotherapeuten blijkt een veelbelovende manier om gesuperviseerde looptherapie in de dagelijkse klinische praktijk beschikbaar te maken voor alle patiënten met claudicatio intermittens.

In hoofdstuk 3 wordt een alternatieve uitkomstmaat voor het meten van de effectiviteit van behandelingen voor claudicatio intermittens gepresenteerd. De ernst van de ziekte en de functionele belemmering worden meestal beschreven met de initiële claudicatio afstand (ICA, pijnvrije loopafstand) en de absolute claudicatio afstand (ACA, maximale loopafstand). In het dagelijks leven stoppen de meeste patiënten echter niet bij het voelen van de eerste pijn, maar lopen ook niet door tot de maximale pijngrens is bereikt. Daarom definieerden wij de afstand die een patiënt in het dagelijks leven zou lopen alvorens te stoppen als de functionele claudicatio afstand (FCA).
Patiënten met claudicatio intermittens die deelnamen aan een gesuperviseerd looptherapieprogramma ondergingen tweemaal een loopbandtest waarbij de ICA, FCA en de ACA werden gemeten. De betrouwbaarheid van de verschillende uitkomstmaten werd uitgedrukt met de intra-class correlatie coëfficiënt voor zowel ICA, FCA en ACA. Om de validiteit te bepalen lieten we een tweede groep patiënten een gestandaardiseerde loopbandtest doen en een kwaliteit van leven vragenlijst invullen (Rand-36). Met een Spearman's rho werden de correlaties tussen de verschillende loopafstanden en de kwaliteit van leven berekend.
De intra-class correlatie coëfficiënten van de ICA, FCA en ACA waren respectievelijk 0,940, 0,959 en 0,975. Verder bleek de FCA significant te correleren met 5 van de 9 domeinen van kwaliteit van leven, namelijk fysieke functie (rho=0,571), fysieke rol (rho=0,532), vitaliteit (rho=0,416), pijn (rho=0,416) en gezondheidsverandering (rho=0,414).
Gebaseerd op deze resultaten kunnen we concluderen dat de FCA zowel een betrouwbaar als valide uitkomstmaat is voor het bepalen van de functionele capaciteit van patiënten met claudicatio intermittens die meedoen aan een trainingsprogramma. Verder lijkt het dat de FCA de werkelijke functionele belemmering beter beschrijft in vergelijking met ICA en ACA. In de toekomst kan de FCA gebruikt worden naast de ICA en ACA.

Hoofdstuk 4 beschrijft de resultaten van een prospectieve cohort studie over regionaal georganiseerde gesuperviseerde looptherapie voor patiënten met claudicatio intermittens. Deze studie rapporteert de resultaten en het functioneren van regionaal georganiseerde looptherapie na een follow up periode van één jaar.
We includeerden opeenvolgende patiënten met claudicatio intermittens die werden verwezen voor looptherapie in een regionale setting. Patiënten werden doorverwezen naar een perifere fysiotherapeut in de nabijheid van hun woonomgeving en geschoold om looptherapie volgens de KNGF-richtlijn aan te bieden. Exclusie criteria voor looptraining waren ischemische rustpijn en weefselverlies. Op baseline en na 1, 3, 6 en 12 maanden werd de loopafstand bepaald met behulp van een gestandaardiseerde loopbandtest.
In de periode van januari 2005 tot en met september 2006 werden 349 patiënten verwezen

voor gesuperviseerde looptherapie. In totaal zijn 272 patiënten gestart met het programma. Van de initieel verwezen patiënten waren 52 patiënten niet in staat de gestandaardiseerde loopbandtest te lopen. Zij zijn wel gestart met gesuperviseerde looptherapie, echter op een lager niveau. Vijfentwintig patiënten zijn nooit gestart met het programma om uiteenlopende redenen.
Na de periode van één jaar waren 129 patiënten van de initieel gestarte patiënten (47,4%) beschikbaar voor analyse van de loopafstand. Tijdens de studieperiode stopten 143 patiënten vroegtijdig met het looptherapie programma. De redenen om vroegtijdig te stoppen waren als volgt: tevreden over de behaalde loopafstand (n=19), ontevreden over de behaalde loopafstand (n=26), niet gemotiveerd (n=22), comorbiditeit (n=48) en andere redenen (n=28). De maximale loopafstand verbeterde significant van een mediane 400 meter op baseline tot 1100 meter na 12 maanden follow up (P<0,001), wat overeenkomt met 107,8% toename. Deze toename komt overeen met de resultaten die we kennen van de literatuur over gesuperviseerde looptherapie gegeven in een klinische setting. Concluderend kunnen we zeggen dat gesuperviseerde looptherapie in een regionale setting even effectief lijkt te zijn als looptherapie gegeven in de klinische setting van een ziekenhuis. Gesuperviseerde looptherapie in een regionale setting kent een hoog uitvalspercentage.

In hoofdstuk 5 wordt het effect van gesuperviseerde looptherapie voor claudicatio intermittens vergeleken tussen patiënten met en zonder diabetes mellitus (DM). Diabetes is een veelvoorkomende comorbiditeit bij patiënten met claudicatio intermittens en we weten dat het bewegingsniveau van patiënten met DM verlaagd is. Over de toename in loopafstand na looptherapie bij patiënten met zowel claudicatio intermittens als DM is weinig bekend. Opeenvolgende patiënten met claudicatio intermittens die zijn gestart met gesuperviseerde looptherapie werden geïncludeerd. Exclusie criteria voor looptherapie zijn ischemische rustpijn, wonden en het niet kunnen lopen van de gestandaardiseerde loopbandtest. Op baseline en na 1, 3 en 6 maanden voerden de patiënten een loopbandtest uit waarbij primair de maximale loopafstand werd bepaald.
We includeerden 775 patiënten, waarvan 230 (29,7%) bekend waren met DM. Na 6 maanden follow up waren de data van 451 patiënten (58,0%) beschikbaar. De maximale loopafstand bij baseline en bij 6 maanden follow up was significant lager bij patiënten met DM (P<0,001). De toename in loopafstand na het volgen van 6 maanden gesuperviseerde looptherapie was 270 meter in de DM groep en 400 meter in de non DM groep. Dit verschil was niet significant (P=0,48).
Uit deze resultaten blijkt dat gesuperviseerde looptherapie voor patiënten met claudicatio intermittens even effectief is in het verbeteren van loopafstand bij patiënten met en zonder DM. De absolute loopafstand blijft echter lager bij patiënten met DM.

In hoofdstuk 6 proberen we voorspellende variabelen voor het resultaat van gesuperviseerde looptherapie te identificeren. Daarbij wordt een klinisch predictie model ontwikkeld om voor individuele patiënten de te halen loopafstand na gesuperviseerde looptherapie te voorspellen.
We includeerden patiënten met claudicatio intermittens die participeerden in een regionaal opgezet programma voor gesuperviseerde looptherapie. De primaire uitkomstmaat was de maximale loopafstand na 6 maanden looptherapie. Met lineaire regressie analyses identificeerden we variabelen die de maximale loopafstand na 6 maanden training konden voorspellen.
In totaal werden 437 patiënten geanalyseerd. Onafhankelijke voorspellende variabelen voor loopafstand na behandeling met looptraining waren de baseline loopafstand (P<0,001), rookgedrag (P=0,012) en body-mass-index (P=0,041). Een grotere baseline loopafstand was geassocieerd met een grotere loopafstand na 6 maanden looptraining. Roken en een hoge body-mass-index waren geassocieerd met een geringere loopafstand na 6 maanden looptraining. Het uiteindelijke regressiemodel includeerde baseline loopafstand, leeftijd, body-mass-index, roken en longziekten als voorspellende variabelen. De regressievergelijking van dit model werd vertaald naar verschillende klinische predictie modellen, waarmee we bij 24,8 tot 33,6% van de patiënten de loopafstand correct konden voorspellen. Hieruit concludeerden we dat het vertalen van de regressievergelijking naar een klinisch predictie model niet leidt tot een valide model dat we kunnen gebruiken in de dagelijkse praktijk.

DEEL TWEE – BEHANDELING VOOR CLAUDICATIO INTERMITTENS VERGELEKEN EN VERBETERD

(Endo)vasculaire behandelingen worden frequent gebruikt om symptomen van claudicatio intermittens te bestrijden. De discussie over de effectiviteit van andere behandelingen voor claudicatio intermittens in vergelijking met looptherapie persisteert ook in 2010.

In hoofdstuk 7 voeren we een netwerk meta-analyse uit om de effectiviteit van verschillende behandelingen voor claudicatio intermittens in kaart te brengen. De behandeling van claudicatio intermittens heeft als doel het verbeteren van de functionele capaciteit en kwaliteit van leven. Studies naar minimaal invasieve en conventioneel vaatchirurgische behandelingen concentreren echter vaak op hemodynamische uitkomsten. Met deze meta-analyse geven we een overzicht van de meest gebruikte behandelingen voor claudicatio intermittens en bepalen we de effectiviteit in het verbeteren van loopafstand en kwaliteit van leven.
Studies die geen behandeling, looptherapie, angioplastiek of chirurgie voor claudicatio in-

termittens met elkaar vergeleken werden geïncludeerd. Uitkomstmaten waren loopafstand (maximaal en pijnvrij) en kwaliteit van leven (fysiek en mentaal). We gebruikten een netwerk meta-analyse model dat direct en indirect bewijs kan combineren.
We includeerden 42 studies die de resultaten van 3106 patiënten beschreven. De netwerk meta-analyse liet zien dat gesuperviseerde looptherapie (Δ =1,62, P<0,01), angioplastiek (Δ =1,89, P<0,01), en chirurgische behandeling (Δ =1,07, P<0,01) effectiever zijn in het verbeteren van de loopafstand vergeleken met geen behandeling. De sensitiviteitsanalyse, waarbij alle niet gerandomiseerde studies werden geëxcludeerd liet overeenkomstige resultaten zien.
In het verbeteren van fysieke kwaliteit van leven hadden gesuperviseerde looptherapie (Δ =0,60, P<0,01), angioplastiek (Δ =0,91, P=0,01) en chirurgische behandeling (Δ =1,07, P<0,01) meerwaarde boven geen behandeling. Echter, in de sensitiviteitsanalyses, die alle niet gerandomiseerde studies excludeert, had alleen gesuperviseerde looptherapie additionele waarde boven geen behandeling (Δ =0,66, P<0,01) in het verbeteren van fysieke kwaliteit van leven. Geen van de behandelingen had een effect op mentale gezondheid.
De resultaten van deze netwerk meta-analyse laten zien dat gesuperviseerde looptherapie effectiever is dan geen behandeling in het verbeteren van zowel loopafstand als kwaliteit van leven. Angioplastiek en chirurgische behandeling zijn effectiever in het verbeteren van de loopafstand vergeleken met geen behandeling, echter de meerwaarde in het verbeteren van fysieke kwaliteit van leven is minder overtuigend.

In hoofdstuk 8 wordt gezocht naar variabelen die voorspellend zijn voor het functionele resultaat na een percutane vasculaire interventie (PVI) voor claudicatio intermittens. Patiënten met claudicatio intermittens die geselecteerd waren voor behandeling met PVI werden geïncludeerd. De primaire uitkomstmaat was de maximale loopafstand, bepaald met een gestandaardiseerde loopbandtest binnen 3 weken na de PVI. Secundaire uitkomstmaat was het persisteren van claudicatio klachten na de behandeling. Met lineaire en logistische regressie analyse werden variabelen, voorspellend voor het functionele resultaat geïdentificeerd.
We includeerden 89 patiënten in deze studie. In het uiteindelijke regressiemodel waren de aanwezigheid van geïsoleerd iliacaal lijden (P=0,007), een lange baseline loopafstand (P<0,001) en jonge leeftijd (P=0,044) geassocieerd met een betere loopafstand na de vasculaire interventie. De kans op het persisteren van claudicatio klachten was hoger bij een lage baseline loopafstand (P0,070), multipele aangedane vaatsegmenten (P=0,007), roken (P=0,015), aanwezigheid van een stenose in plaats van occlusie (P=0,026) en de aanwezigheid van DM (P=0,030). De aanwezigheid van COPD verlaagde de kans op persisterende claudicatio klachten (P=0,067).

In deze studie werden verschillende voorspellende variabelen voor functionele resultaten na PVI geïdentificeerd. Een lage baseline loopafstand, hoge leeftijd, multipele aangedane vaatsegmenten, roken en DM zijn geassocieerd met minder goede functionele resultaten na PVI.

Hoofdstuk 9 beschrijft de resultaten van een gerandomiseerde klinische studie die de waarde van additionele gesuperviseerde looptherapie na een PVI vergelijkt met alleen PVI. Patiënten met claudicatio intermittens die werden behandeld met PVI en die een loopafstand van < 1600 meter hadden na PVI waren potentieel geschikt. Alle patiënten die participeerden in de studie werden behandeld met PVI. Na PVI werden de patiënten gerandomiseerd naar alleen PVI of naar PVI met additionele gesuperviseerde looptherapie. De primaire uitkomstmaat was de maximale loopafstand en één van de secundaire uitkomstmaten kwaliteit van leven.
In elke groep werden 35 patiënten geïncludeerd. Het gemiddelde verschil in maximale loopafstand na 6 maanden follow up was 271,3 meter (95%-BI 64,0 – 478,6, P=0,011) in het voordeel van additionele gesuperviseerde looptherapie. In de controle groep was 1 patiënt (3,7%) in staat de loopbandtest volledig uit te lopen vergeleken met 11 patiënten (32,4%) in de interventiegroep (P=0,005). De fysieke kwaliteit van leven score in de controlegroep was 44,1 ± 7,8 en in de interventiegroep 41,9 ± 9,5, wat een niet significant verschil was (P=0,34).
Concluderend kunnen we zeggen dat een PVI gevolgd door gesuperviseerde looptherapie effectiever is in het verbeteren van de loopafstand vergeleken met alleen PVI. Deze resultaten laten zien dat het zinvol is tesamen met een PVI gesuperviseerde looptherapie voor te schrijven.

CONCLUSIES
Op dit moment zou gesuperviseerde looptherapie de eerste behandelingskeuze voor iedere patiënt met claudicatio intermittens moeten zijn, aangezien we geen overtuigend bewijs hebben dat een percutane vasculaire interventie of een chirurgische behandeling effectiever zijn in het verbeteren van de functionele capaciteit. Verder kunnen we op dit moment geen subgroepen identificeren waarvoor gesuperviseerde looptherapie minder effectief is.
Indien toch een percutane interventie wordt gedaan kan de effectiviteit hiervan vergroot worden door aanvullend gesuperviseerde looptherapie aan te bieden.

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CURRICULUM VITAE

Lotte Mathilde Kruidenier werd geboren op 29 augustus 1980 te Groenlo, Nederland. Na het afsluiten van het eindexamen Atheneum aan het Assink scholengemeenschap te Haaksbergen in 1999 startte zij met de propedeuse Gezondheidswetenschappen aan de Universiteit Maastricht. Na een tweede loting in het kader van de numerus fixus kon zij in 2000 starten met de studie Geneeskunde aan diezelfde universiteit.

Tijdens haar wetenschapsstage onder leiding van Prof. Dr. Kitslaar werd de eerste interesse voor het wetenschappelijk onderzoek gewekt. In 2006 behaalde ze haar artsexamen en begon aansluitend met haar promotie onderzoek in het Atrium medisch centrum onder de bezielende leiding van Prof. Dr. Martin Prins en Dr. Joep Teijink in nauwe samenwerking met het Nederlands Platform voor Perifeer Arterieel Vaatlijden.

Op 1 juli 2009 is zij gestart met de opleiding tot algemeen chirurg in het Orbis Medisch Centrum te Sittard (opleider: Dr. A.G.M. Hoofwijk).