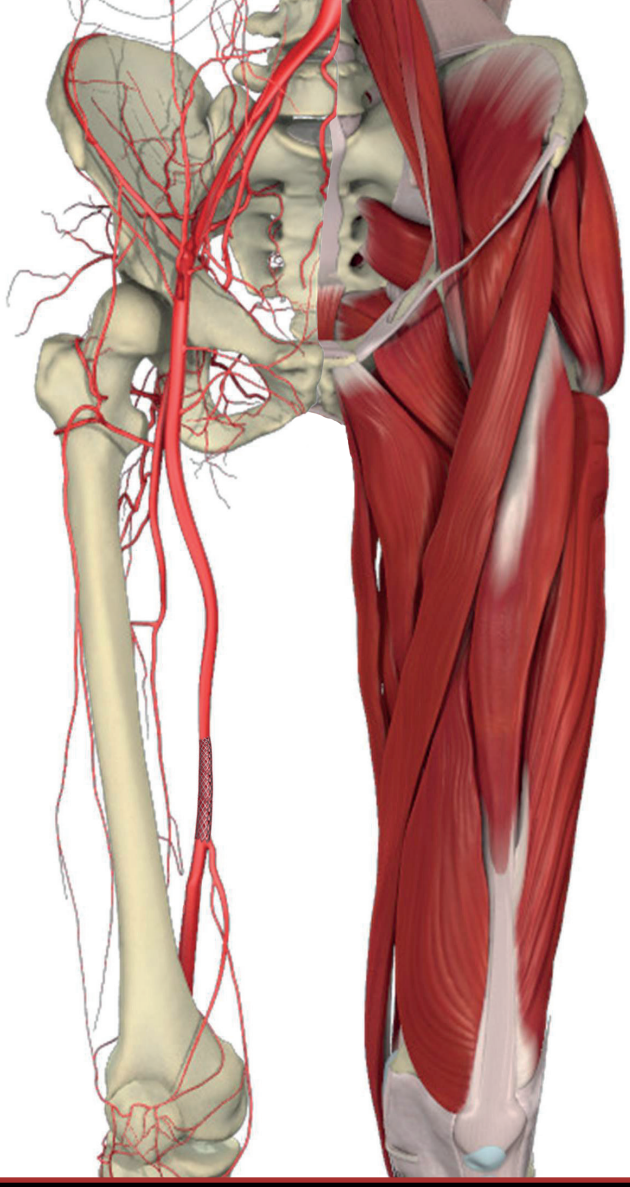

Treatment Strategies for Patients with Intermittent Claudication

Farzin Fakhry

Treatment Strategies for Patients with Intermittent Claudication

Farzin Fakhry

In loving memory of my mom

در خاطرات دوست داشتنی مادر جانم

Treatment Strategies for Patients with Intermittent Claudication

ISBN: 978-94-6380-161-4

Cover design: Ron Zijlmans
Cover photo's: Primal Pictures (reprinted with permission)
Lay-out: RON Graphic Power, www.ron.nu
Printing: ProefschriftMaken || www.proefschriftmaken.nl

Financial support for printing of this thesis was generously provided by the Departments of Epidemiology and Radiology of the Erasmus Medical Center, Bayer Netherlands, Stichting ClaudicatioNet, and the Erasmus University Rotterdam

Treatment Strategies for Patients with Intermittent Claudication

Behandelingsmogelijkheden voor patiënten met claudicatio intermittens

Thesis

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the rector magnificus

Prof. dr. R.C.M.E. Engels

and in accordance with decision of the Doctorate Board.
The public defense shall be held on

Wednesday the 19th of December 2018 at 11.30 am

by

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born in Kabul, Afghanistan

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The research in this thesis was funded by a grant from the Netherlands Organisation for Health Research and Development (ZonMw).

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

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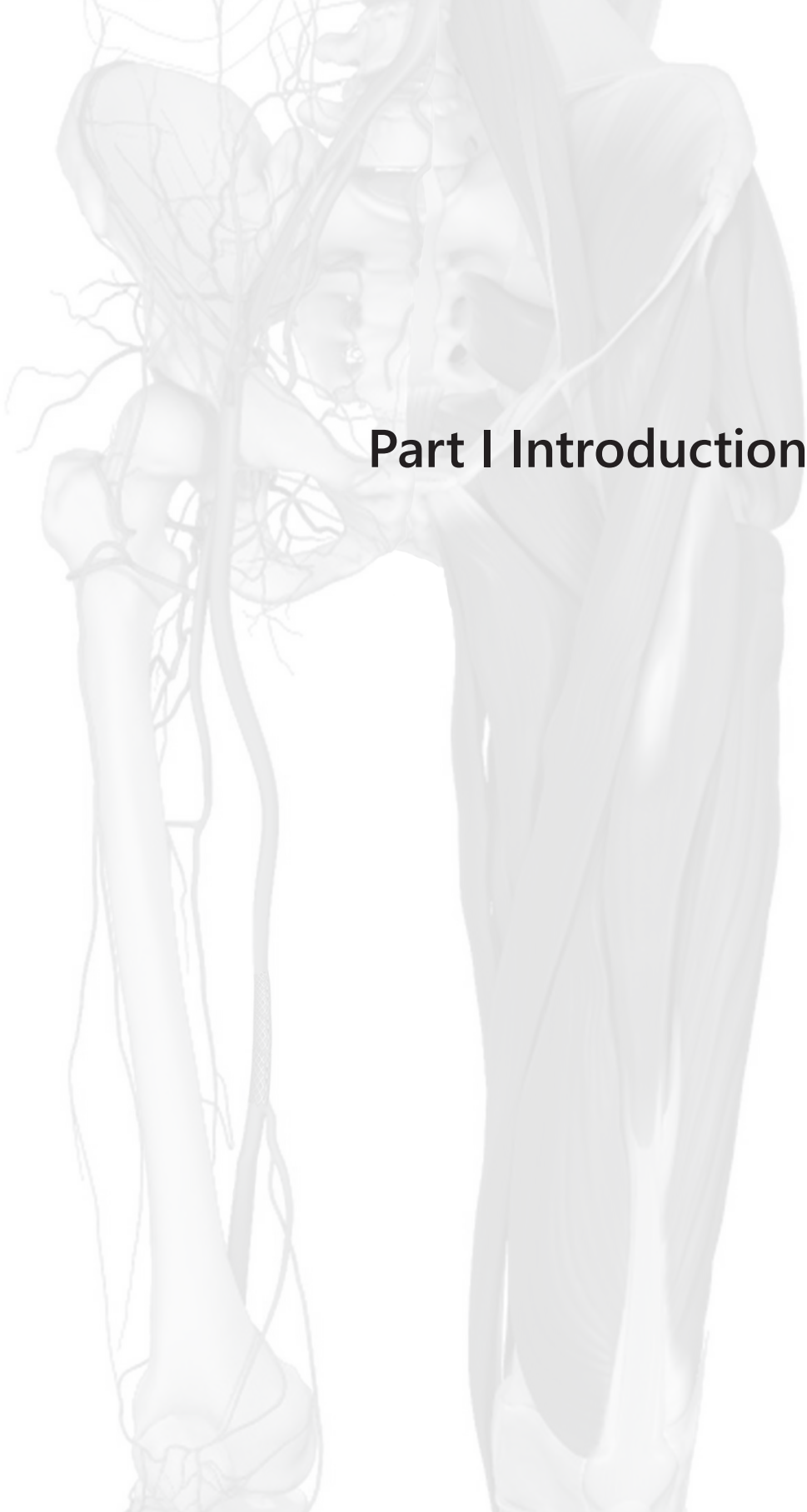

Part I Introduction

Chapter 1

General introduction, aims and outline

ETIOLOGY AND CLASSIFICATION

Lower extremity peripheral artery disease (PAD) is the clinical manifestation of systemic atherosclerosis affecting the infrarenal aorta and the lower limb arteries. Atherosclerosis is a chronic and slowly developing pathological process with formation of atherosclerotic plaques which results in progressive stenosis and occlusion of the arteries supplying oxygenated blood to the lower extremity muscles. There is a broad spectrum of clinical manifestations of PAD, ranging from asymptomatic patients with a decreased ankle-brachial index (ABI) to patients with classic intermittent claudication or atypical exercise-induced leg symptoms. End-stage PAD, critical limb ischemia, is characterized by ischemic rest pain in the foot, or lower limb ulceration or gangrene. Intermittent claudication, i.e. exertional pain in the calf or thigh of one or both legs that resolves after a short period of rest, is by far the most common symptomatic form of PAD.[1] The development and course of PAD are associated with risk factors which are identical to those for other forms of atherosclerotic disease such as coronary heart disease and cerebrovascular disease. These include smoking, hypertension, diabetes mellitus, dyslipidemia, and chronic kidney disease.[2] Smoking and diabetes are the strongest independent risk factors which are associated with the worst outcomes.[3]

EPIDEMIOLOGY AND CLINICAL COURSE

PAD is a highly prevalent, morbid, and mortal disease, affecting more than 200 million individuals globally.[4] The prevalence of PAD is strongly age-related with 3-10% of adults being affected and increasing to 15-20% in patients over 70 years.[2,5,6] The prevalence of PAD has enormously increased over a period of 10 years by 30% in low- and middle-income countries and by 15% in high-income countries.[4] In the absence of preventive efforts, the burden of PAD will rise even further to pandemic proportions. An estimated 10-30% of patients with PAD have the classic claudication manifestation, while the majority of the patients with PAD are asymptomatic or present with atypical leg symptoms.[7] Nevertheless, these estimations may be inaccurate given the different criteria used in studies to determine claudication and the limitations in mobility caused by other conditions. Furthermore, elderly patients deem to consider their complaints as part of normal ageing and consequently may not report claudication symptoms.

In general, the clinical course of intermittent claudication is relatively benign for the affected limbs; only 1 in 4 patients deteriorate to a more severe clinical stage[8] and the risk of limb loss is only 1-3% during the first 5 years after the onset of symptoms.[9] Nevertheless, patients with intermittent claudication experience significant functional disability over time associated with a diminished ability to perform their daily activities, resulting in a sedentary lifestyle[10,11] and impaired quality of life.[12,13] As opposed to the

relatively benign course for the legs, patients with PAD have a 3-fold higher all-cause mortality risk compared to individuals without PAD even after adjustment for the traditional cardiovascular risk factors.[14] PAD is strongly associated with other manifestations of atherosclerotic cardiovascular disease: over 50% of PAD patients have coronary heart disease, cerebrovascular disease, or both at presentation. In fact in data from registries patients with PAD even had a higher 1-year incidence of cardiovascular death, myocardial infarction or stroke as compared to patients with coronary heart disease (5.4% vs. 4.5%).[15] Within 5 years after the onset of claudication symptoms, 1 in 5 patients will die, mostly due to a cardiovascular cause, and 1 in 3 patients will experience a non-fatal cardiovascular event.[14,15] This stresses the importance of raising physician and patient awareness for detection of PAD and secondary prevention of cardiovascular events by managing the cardiovascular risk factors.

MANAGEMENT OF INTERMITTENT CLAUDICATION

Treatment for intermittent claudication should include a broad approach focusing on the prevention of future cardiovascular events as well as on the improvement of claudication symptoms and quality of life. Although cardiovascular risk management is crucial for the prognosis of the patient, in clinical practice patients with PAD are less likely than those with coronary artery or cerebrovascular disease to receive adequate secondary prevention measures.[16] All patients with PAD should receive an anti-platelet agent and aggressive medical management of hypertension, dyslipidemia, diabetes, and obesity, as well as lifestyle interventions to promote smoking cessation, healthy nutrition and physical activity according to current clinical guidelines.[1,17] The studies in this thesis will focus on treatment strategies to improve leg symptoms and quality of life in patients with intermittent claudication.

Pharmacotherapy

Three medications have been investigated for relief of claudication symptoms: cilostazol, pentoxifylline, and naftidrofuryl. The latter two have no or only very limited effects on walking distance compared to placebo.[18] Only cilostazol, a type 3 phosphodiesterase inhibitor, provides a modest improvement in pain-free and maximum walking distance of approximately 50% compared with placebo.[19] Yet, in clinical practice adherence to cilostazol is low due to frequent adverse effects including headache, palpitations and diarrhea.[20,21] Hence, there is no widely available effective medical agent to improve walking distance and quality of life in patients with claudication.

Exercise therapy

Exercise therapy has become the cornerstone in the management of intermittent

claudication. The potential mechanisms of exercise therapy to improve claudication symptoms are not completely clear. A variety of adaptive mechanisms in the lower extremity muscles have been suggested, including improved skeletal muscle mitochondrial metabolism, improved endothelial vasodilator function, lower blood viscosity, and more efficient biomechanics of walking.[22]

The first randomized clinical trial (RCT) describing the positive effects of exercise therapy on claudication was published in 1966 by Larsen et al.[23] Many RCTs with different types of exercise programs followed, all of them showing mainly positive effects on improving walking distances in patients with intermittent claudication. A Cochrane meta-analysis of these RCTs showed that exercise therapy on average improved the maximum walking distance by 150%, e.g. from 200 to 500 meters.[24] A second Cochrane systematic review showed that treadmill training supervised by an exercise therapist was superior to unsupervised training, i.e. a walking advice, in terms of improvement in maximum walking distance.[25] Although supervision seems to be an important aspect of exercise training, the optimal frequency, intensity, mode of exercise, and duration of the programs remains to be established.

Taken together, the evidence convincingly demonstrates that exercise therapy improves walking performance compared with no exercise and that supervised exercise gives superior results to unsupervised exercise. Current evidence-based clinical guidelines recommend supervised exercise therapy as the first-line treatment for all patients with intermittent claudication, regardless of the level of lower extremity arterial disease.[1,17] Despite these recommendations, the value of exercise therapy in routine clinical practice remains uncertain, as supervised exercise programs are underutilized due to slow results, reimbursement issues, poor patient compliance, and limited access in most countries. As a consequence, endovascular revascularization, though more expensive, is increasingly being performed as an attractive first-line alternative.[26]

Revascularization

Since the first endovascular revascularization procedure to restore blood flow in the lower extremity with balloon angioplasty by Dotter and Judkins in 1964[27], technological developments have advanced endovascular revascularization. The endovascular repertoire now includes bare metal and covered balloon-expandable and self-expandable stents, as well as drug-coated balloons, drug-eluting stents and bioabsorbable stents which have advanced endovascular revascularization as a safe and durable treatment option in the management of symptomatic PAD. In the literature effectiveness of endovascular revascularization is usually reported as procedural success rate and patency rates over time, which varies between different segments of the arterial tree. For aortoiliac procedures, the procedural success rate is over 90%, with 5-year primary patency rates ranging from 60-86%.[28] Femoropopliteal procedures have comparable procedural success rates, however much lower primary patency rates of 50-60% after 2-3 years of

follow-up. With the recent introduction of drug-coated balloons, the primary patency rate has improved to 70-80% after 2 years of follow-up.[29] While patency rates are reported as measures of success, clinical outcomes such as walking distances and quality of life are of more concern to patients with intermittent claudication.

The number of endovascular procedures performed in the United States for PAD increased by 400% between 1999 and 2007.[30] The higher rate of endovascular procedures has associated costs, risks of procedure-related morbidity and mortality, and re-intervention rates. A substantial proportion of patients require additional revascularization procedures for restenosis at the target lesion site and/or for other lesions in the ipsilateral or contralateral leg. Given the extent of the arterial lesions in PAD and the limited durability of endovascular revascularization, interventions beget more interventions. While endovascular or surgical revascularization is the treatment of choice for patients with critical limb ischemia to reduce pain, promote wound healing, and prevent amputation, the role of revascularization as first-line treatment for patients with intermittent claudication is still under debate. Several RCTs have compared endovascular revascularization versus supervised exercise therapy as initial treatment for intermittent claudication and have demonstrated no clear advantage for one of the treatment options in terms of improving walking distance and quality of life in the short-term, data with long-term follow up is scarce. In addition given the different mechanisms by which supervised exercise and endovascular revascularization improves walking distance and quality of life combining both treatment options might have the most beneficial effects.

AIMS AND OUTLINE OF THIS THESIS

The main objective of this thesis is to determine the optimal treatment for patients with intermittent claudication.

In *part I* we summarize the existing evidence regarding the management of intermittent claudication using systematic reviews and meta-analyses. In **chapter 2** we performed a systematic review and meta-analysis to first summarize the effectiveness of supervised walking therapy in the management of intermittent claudication and second identify the components including the duration, intensity and exact content of the walking therapy programs that provide maximal improvement in walking distances. A substantial number of patients with intermittent claudication are not able to perform supervised exercise which consists of walking therapy on a treadmill due to concomitant comorbidities. For these patients other modes of supervised exercise such as cycling, upper-arm ergometer exercise and strength training might be an plausible alternative. In **chapter 3** we performed a systematic review and meta-analysis to assess the effects of different modes of supervise exercise on walking distances and quality of life in patients with intermittent claudication. Endovascular revascularization is being considered as an

attractive alternative for conservative management (i.e. supervised exercise) as first-line treatment for intermittent claudication and the number of endovascular procedures has increased dramatically in the past 10 years. In **chapter 4** we performed a systematic review and meta-analysis to summarize the effect of endovascular revascularization versus or combined with conservative management.

In *part II* we assess the clinical effectiveness of different treatment strategies for intermittent claudication. Studies comparing long-term effectiveness of SE training and endovascular revascularization are scarce. In **chapter 5** we present the long-term results from a RCT comparing supervised exercise therapy with endovascular revascularization for intermittent claudication. As supervise exercise programs are not widely available and not fully reimbursed, in **chapter 6** we compare the effectiveness of a structured home-based exercise program with a supervised exercise program in patients with intermittent claudication. A combination therapy of endovascular revascularization and supervise exercise seems promising as it might combine the immediate improvement in claudication symptoms after revascularization with the added long-term benefits of exercise therapy. However level 1 evidence from a large RCT was missing to evaluate this hypothesis. In **chapter 7** we present the results from the Endovascular Revascularization And Supervised Exercise (ERASE) trial comparing a combination therapy of endovascular revascularization plus supervised exercise with supervised exercise therapy only in patients with intermittent claudication.

In *part III* we address the cost-effectiveness of different treatment strategies for intermittent claudication to better inform policymakers on implementation of these treatment strategies. In **chapter 8** we constructed a Markov model assessing the cost-effectiveness of supervised exercise therapy versus endovascular revascularization in the long-term. In **chapter 9** we perform a cost-effectiveness analysis of the ERASE trial to assess whether a combination therapy of endovascular revascularization and supervised exercise is cost-effective from a societal perspective compared to supervised exercise only.

We conclude the thesis by summarizing and discussing the main findings in **chapter 10** and providing future perspectives for clinical practice and research.

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Part II Systematic Reviews

Chapter 2

Supervised walking therapy in patients with intermittent claudication

Fakhry F, van de Luijtgaarden KM, Bax L, den Hoed PT, Hunink MGM, Rouwet EV, Spronk S.

J Vasc Surg. 2012 Oct; 56(4):1132-42

ABSTRACT

Objective

Exercise therapy is a common intervention for the management of intermittent claudication. However, considerable uncertainty remains about the effect of different exercise components such as intensity, duration, or content of the exercise programs. The aim of this study was to assess the effectiveness of supervised walking therapy as treatment in patients with Intermittent claudication and to update and identify the most important exercise components resulting in an optimal training protocol for patients with Intermittent claudication.

Methods

A systematic literature search using MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials databases was performed. Randomized controlled trials (RCTs) published between January 1966 and February 2012 were included if they evaluated the effectiveness of supervised walking therapy. Predefined exercise components were extracted, including treadmill use during training, claudication pain end point used during walking, length of the supervised walking therapy program, and total training volume. A meta-analysis and meta-regression was performed to evaluate the weighted mean difference in maximum walking distance (MWD) and pain-free walking distance (PFWD) between supervised walking therapy and noninterventional observation.

Results

Twenty-five RCTs (1054 patients) comparing supervised walking therapy vs noninterventional observation showed a weighted mean difference of 180 meters (95% confidence interval, 130-230 meters) in MWD and 128 meters (95% confidence interval, 92-165 meters) in PFWD, both in favor of the supervised walking therapy group. In multivariable meta-regression analysis, none of the predefined exercise components were independently associated with significant improvements in MWD or PFWD.

Conclusions

Supervised walking therapy is effective in improving MWD and PFWD in patients with intermittent claudication. However, pooled results from the RCTs did not identify any of the exercise components including intensity, duration, or content of the program as being independently associated with improvements in MWD or PFWD

Peripheral arterial disease (PAD) is prevalent in Western countries, affecting 4.3% of the population aged $40 years and increases with age to 14.5% in the elderly population aged $70 years.[1] Intermittent claudication (intermittent claudication), a common manifestation of PAD, defined as muscle discomfort in the legs that is elicited by exercise and relieved by a short period of rest, is associated with significant functional disability, reduced quality of life,[2] and an increased risk for nonfatal and fatal cardiovascular events.[3]

Treatment strategies for intermittent claudication include pharmacotherapy,[4] physical exercise therapy,[5] and surgical or percutaneous vascular interventions.[6,7] Considerable evidence is available to suggest that exercise therapy should have a central role in the management of intermittent claudication by significantly improving the pain-free walking distance (PFWD) and maximum walking distance (MWD) and lowering the risk for cardiovascular events.[5,8] In particular, supervised exercise therapy, which usually involves walking on a treadmill, is considered more effective than unsupervised exercise therapy,[9,10] and therefore, the general consensus is to initially treat patients with intermittent claudication with supervised exercise therapy.[6,7]

Although supervision and (treadmill) walking are considered important components of the exercise program, a lot of uncertainty remains about the intensity, duration, and content of the programs. In a 1995 meta-analysis, Gardner et al[11] determined the most important exercise components for providing optimal improvements in walking ability in patients with intermittent claudication. The authors concluded that the optimal exercise program consists of intermittent walking to near-maximal pain for a period of at least 6 months. However, these recommendations were based on results from nonrandomized (un)controlled studies. Since this publication 16 years ago, many randomized controlled trials (RCTs) evaluating the effectiveness of supervised walking therapy (supervised walking therapy) programs with a great variety in exercise protocols have been published. In addition, new methodologic evidence about meta-analytic approaches is available, and experience has accumulated since the last meta-analysis on this topic.

Therefore, the primary aim of this study was to determine whether supervised walking therapy in patients with intermittent claudication is effective in improving MWD and PFWD, and secondly, to update and identify the components of supervised walking therapy that provide maximal improvement in MWD and PFWD. Implementation of this state-of-the-art systematic review and meta-analysis of supervised walking therapy programs may optimize the therapeutic benefits of supervised walking therapy as a noninvasive first-line treatment in the large population of patients with intermittent claudication.

METHODS

Data sources

Two authors (F.F., K.L.) collaborated with a professional librarian to independently develop multiple search strategies to identify RCTs, which evaluated supervised walking therapy in patients with intermittent claudication, published between January 1966 and February 2012. We first performed an electronic search in MEDLINE and EMBASE. This search was subsequently reproduced using the Cochrane Central Register of Controlled Trials Register of Controlled Trials. Relevant keywords relating to disease of interest (claudica* and intermitten* or vascular disease* or peripheral arterial occlusive disease* or peripheral arterial disease* or peripheral artery disease* or ischemi* or ischaemi* or Fontaine 2) were used in combination with keywords relating to exercise program (exercise or exercise or training or walking or gymnast*) using a Boolean search strategy. Reference lists of all eligible studies were handsearched for additional studies, and no language restriction was applied.

Study selection

Identified studies were initially selected by a review of titles and abstracts by three reviewers (K.L., E.R., and S.S) independently. Final selection was based on a full-text evaluation of the selected studies by two reviewers (F.F., S.S.) independently. Disagreements between the reviewers were discussed and resolved by consensus. Studies were included if they were (1) an RCT comparing supervised walking therapy and noninterventional observation in patients with intermittent claudication and (2) assessed PFWD or MWD, or both, or time using a treadmill test before and after supervised walking therapy. When data from the same patient population were published in various journals, we examined the results and included the data only once in our systematic review.

Quality assessment

Methodologic quality of the included studies was assessed using the Physiotherapy Evidence Database (PEDro) scale.12 The following quality criteria are included and rated in the PEDro score: eligibility criteria specified, randomization of subjects, concealed allocation, baseline similarity of groups regarding the most important prognostic indicators, blinding of subjects, blinding of therapists, blinding of assessors, completeness of follow-up, outcomes analyzed by intention-to-treat principle, between-group statistical comparison reported, and point measures and measure of variability reported.

Data extraction

One reviewer (F.F.) extracted all required data from each included study using a standardized form that consisted of (1) study characteristics, including year of publication, study location, and number of patients in each group; (2) patient baseline characteristics,

including mean age and sex; and (3) primary outcomes, including MWD and PFWD before and after supervised walking therapy. If the walking performance was reported in a unit of time, this was converted to walking distances by using the reported tread-mill speed.

To evaluate supervised walking therapy we recorded the following components from each program:

- Mode of exercise, defined as "walking" or "walking plus," which was a combination of walking and alternative modes of exercises, including heel raises, knee bends, step-ups, and arm exercises, among others;
- Treadmill use during training;
- Length of walking program in weeks;
- Number of sessions per week;
- Duration of each session in minutes;
- Pain end point used during walking, which was defined as PFW, walking to mild or moderate claudication pain, or walking to (near) maximum claudication pain.

Training volume, which was the total duration of the supervised walking therapy program (in minutes), was calculated by multiplying the length of the program (in weeks), number of sessions per week, and duration per session (in minutes).

Data analysis

The primary and secondary outcomes of interest were the weighted mean difference in MWD and PFWD between the supervised walking therapy and control groups. Mean post-training MWD and PFWD from each trial were combined and weighted in a meta-analysis using a DerSimonian and Laird random effects model to estimate the pooled effect of the outcomes. These estimates were expressed as a weighted mean difference in MWD and PFWD, including 95% confidence intervals (95% CI).[13] Statistical heterogeneity was assessed for the mean differences in MWD and PFWD by calculating the *Q* statistics and the I^2 statistic.

Selective dissemination of evidence was assessed by plotting for each study the weighted mean difference in MWD and PFWD, against precision (1/standard error) in a plot with *P* value contours. Funnel plot asymmetry, specifically with apparent absent of studies in high *P* value areas of the plot, can be indicative of selective evidence dissemination.[14] Funnel plot asymmetry was formally evaluated by Begg and Egger tests.[15,16] If there was an indication of selective evidence dissemination, we performed a "trim and fill" procedure by imputing the potentially missing studies and checking whether this would change our results significantly.[17]

The heterogeneity of the weighted mean differences in MWD and PFWD between the supervised walking therapy programs and the potential effect of supervised walking therapy program components on this heterogeneity was first investigated by performing a subgroup meta-analysis of each supervised walking therapy program component

separately. Then, a multivariable random effects meta-regression model was used to determine whether an individual supervised walking therapy component or a combination of components would significantly explain the variation between the studies and thus was/ were independently associated with improvement in MWD and PFWD.

Individual study effect on the results was evaluated by an exclusion sensitivity analysis. In addition, sensitivity analysis by removing studies with a PEDro score 4 was performed to observe whether removing RCTs with a very low PEDro score would significantly change the results.

A two-sided $P = .05$ was considered statistically significant, except for the tests for selective evidence dissemination, for which the recommended levels are $P = .10$. Analyses were performed using SPSS 17 software (SPSS Inc, Chicago, Ill), STATA 12 (StataCorp, College Station, Tex), and MIX Professional 2.0.[18]

RESULTS

Literature search

From the original electronic search, 2778 citations published between January 1966 and February 2012 were retrieved (Fig 1). Of these, 992 studies were excluded because they were duplicates, and 1746 studies were excluded after the titles and abstracts were reviewed. Subsequently, of the 40 selected studies for full text review, another 15 studies were excluded for failing to meet predefined criteria (Fig 1); finally, 25 RCTs[19-43] met our inclusion criteria and were included in the analysis.

Study characteristics

The selected RCTs included 1054 patients (76% male), with studies ranging in sample size from 13 to 177 patients. The mean patient age was 66.0 7.0 years (Table I). Twenty-four RCTs offered supervised walking therapy-plus as intervention, whereas one RCT offered a supervised pole-striding program to the intervention group. The control groups in three RCTs were advised to walk as much as possible at home, but no exercise instructions were given. The control group patients in one RCT received placebo tablets (Table I).

Quality assessment

The methodologic quality of the included RCTs according to the PEDro scale is presented in Table I. Eight RCTs (32%) reported a proper concealment of randomization, whereas 18 (72%) reported baseline similarity between the intervention and control groups. None of the RCTs blinded the participants or the therapists who administrated the therapy, and only four RCTs (16%) reported blinding the assessors who measured one or more outcomes. In 17 RCTs (68%), measurement of at least one key outcome was obtained from 85% of the participants initially allocated to groups, and only five (20%) reported outcome

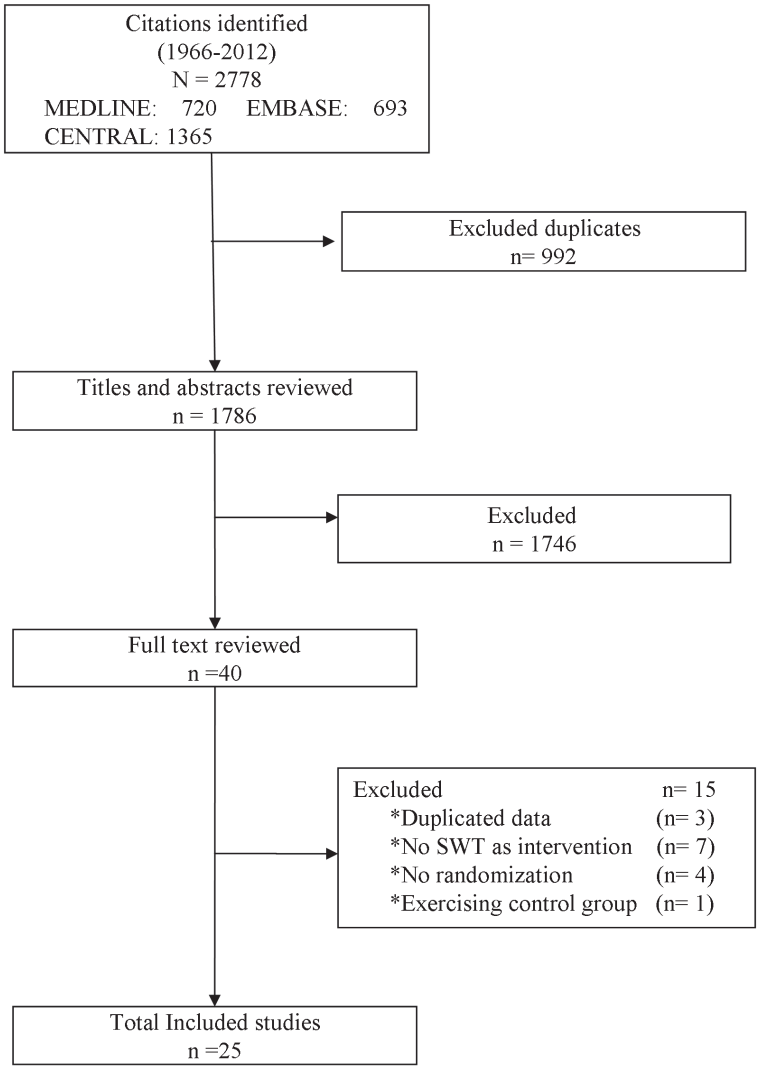

Figure 1. Flow diagram of studies identified from literature search. *SWT,* Supervised walking therapy.

analysis according to the intention-to-treat principle. Yet, 23 RCTs (92%) performed and reported between-group statistics for the main outcomes, and all included RCTs reported point measurements and measurements of variability for at least one of the key outcomes. Overall, the methodologic quality of the included RCTs was low, with an average PEDro score of 5 of 10 points. However, due to the nature of the comparison (supervised walking therapy vs no exercise) in the RCTs, it was impossible to blind the subjects and therapists for the randomized groups; therefore, the maximum PEDro score that could be achieved by the RCTs was 8 points.

Table I. Characteristics of the randomized controlled trials included in the systematic review

First author	*Year*	*Study location*	*Treatment group*	*Control group*	*Patients (No.)*	*Male (%)*	*Age[a] (years)*	*PEDro score[b]*
Dahllof[19]	1974	Sweden	SWT plus[c]	Placebo tablets	18	72	61 ±5	4
Hiatt[20]	1990	U.S.	SWT	No intervention	19	100	60 ±12	4
Jansen[21]	1991	Germany	SWT	No intervention	48	NR	NR	4
Hiatt[22]	1994	U.S.	SWT	No intervention	20	100	67 ±6	5
Tisi[23]	1997	U.K.	SWT	Advice to walk	39	69	68 NR	5
Gibellini[24]	2000	Italy	SWT	No intervention	40	90	67 ±7	3
Gardner[25]	2001	U.S.	SWT	No intervention	52	91	71 ±1	6
Gelin[26]	2001	Sweden	SWT	No intervention	177	67	67 NR	5
Gardner[27]	2002	U.S.	SWT	No intervention	31	NR	72 ±1	5
Langbein[28]	2002	U.S.	Pole-striding	No intervention	52	98	67 ±9	5
Tsai[29]	2002	Taiwan	SWT	No intervention	53	83	76 ±4	5
Mika[30]	2005	Poland	SWT	No intervention	80	83	61 ±6	5
Sandri[31]	2005	Germany	SWT	No intervention	18	NR	57 ±2	5
Hobbs[32]	2006	U.K.	SWT plus[c]	No intervention	14	71	72 NR	5
Mika[33]	2006	Poland	SWT	No intervention	55	87	59 ±8	6
Sanderson[34]	2006	Australia	SWT	No intervention	27	59	61 ±8	6
Wood[35]	2006	Australia	SWT	No intervention	13	69	60 ±8	4
Hobbs[36]	2007	U.K.	SWT plus[c]	No intervention	18	78	67 NR	5
Crowther[37]	2008	U.S.	SWT	No intervention	21	47	69 ±8	5
Hodges[38]	2008	U.K.	SWT	Advice to walk	28	NR	68 ±8	3
Treat-Jacobson[39]	2009	U.S.	SWT	Advice to walk	19	71	67 ±10	5
Schlager[40]	2011	Austria	SWT	No intervention	40	60	69 ±10	7
Leicht[41]	2011	Australia	SWT	No intervention	25	56	67 ±8	5
Gardner[42]	2011	U.S.	SWT	No intervention	79	49	66 ±11	5
Mika[43]	2011	Poland	SWT	No intervention	68	88	63 ±7	5

NR, Not reported; *SWT*, supervised walking therapy; *U.K.*, United Kingdom; *U.S.*, United States.

[a]Data presented as mean standard deviation.

[b]PEDro Score: Physiotherapy Evidence Database scale is a tool to assess the methodological quality of the included randomized controlled trials (score between 0 and 10).

[c]Therapy consisted of walking combined with additional lower limb aerobic exercises.

Supervised walking therapy program characteristics

Walking was the only mode of exercise used in 21 RCTs, a combination of walking and additional lower limb aerobic exercises was used in three RCTs, and polestriding was used as the mode of exercise in the intervention group in one RCT. Patients in 10 RCTs exercised till (near) maximum claudication pain before taking a short rest dur-ing the walking sessions, patients in 11 studies walked till mild/moderate claudication pain, and patients in four studies exercised pain free. Treadmill walking during the exercise sessions was reported in 19 of 25 programs (Table II). The total length of supervised walking therapy programs included varied between 4 and 104 weeks, with 60% of the programs lasting between 12 and 26 weeks. An average of four training sessions was held weekly, with an average duration of 49 minutes per session (range, 10-120 minutes; Table II).

Table II. Characteristics of supervised walking therapy from each study included in the systematic review

Author	*Year*	*Mode of exercise*	*Treadmill during SWT?*	*Walking pain end point*	*Length program (weeks)*	*Sessions/week (No.)*	*Duration each session (minutes)*	*Training volume[a] (minutes)*
Dahllof[19]	1974	Walking plus[b]	No	Mild/moderate pain	26	3	30	2340
Hiatt[20]	1990	Walking	Yes	Mild/moderate pain	12	3	60	2160
Jansen[21]	1991	Walking	Yes	Mild/moderate pain	104	2	120	24960
Hiatt[22]	1994	Walking	Yes	Mild/moderate pain	12	3	60	2160
Tisi[23]	1997	Walking	No	Maximum pain	4	1	60	240
Gibellini[24]	2000	Walking	Yes	Pain free	4	10	30	1200
Gardner[25]	2001	Walking	Yes	Maximum pain	26	3	60	4680
Gelin[26]	2001	Walking	No	Mild/moderate pain	52	0-26 wks: 3 sessions 27-52 wks: 2 sessions	30	3900
Gardner[27]	2002	Walking	Yes	Maximum pain	78	0-26 wks: 3 sessions 27-78 wks: 2 sessions	0-26 wks: starting with 15 minutes increased with 5 min per mon 27-52 wks: 40 min	6423
Langbein[28]	2002	Pole-striding	No	Maximum pain	20	0-4 wks: 3 sessions 5-12 wks: 2 sessions 13-16 wks: 1 session 16-20 wks: 1 session/2 wks	60	2040
Tsai[29]	2002	Walking	Yes	Mild/moderate pain	12	3	40	1440
Mika[30]	2005	Walking	Yes	Pain free	12	3	60	2160
Sandri[31]	2005	Walking	Yes	Maximum pain	4	5 days/wk 6 sessions daily	2 times walking until maximal claudication pain with 2 minutes rest in between (+/- 10 min/ session)	1200
Hobbs[32]	2006	Walking plus[b]	No	Mild/moderate pain	12	2	60	1440
Mika[33]	2006	Walking	Yes	Pain free	12	3	60	2160
Sanderson[34]	2006	Walking	Yes	Mild/moderate pain	6	3	40	720
Wood[35]	2006	Walking	Yes	Mild/moderate pain	6	3	40	720
Hobbs[36]	2007	Walking plus[b]	No	Mild/moderate pain	12	2	60	1440
Crowther[37]	2008	Walking	Yes	Maximum pain	52	3	25-40	5070

Table II. Continued.

Author	*Year*	*Mode of exercise*	*Treadmill during SWT?*	*Walking pain end point*	*Length program (weeks)*	*Sessions/week (No.)*	*Duration each session (minutes)*	*Training volume[a] (minutes)*
Hodges[38]	2008	Walking	Yes	Maximum pain	12	2	45	1080
Treat-Jacobson[39]	2009	Walking	Yes	Maximum pain	12	3	70	2520
Schlager[40]	2011	Walking	Yes	Mild/moderate pain	26	2	60	3120
Leicht[41]	2011	Walking	Yes	Maximum pain	52	3	25-40	5070
Gardner[42]	2011	Walking	Yes	Maximum pain	12	3	Starting with 15 min increased with 5 min/2 wks	990
Mika[43]	2011	Walking	Yes	Pain free	12	3	Starting with 30 min increased with 5 min/2 wks	1530

SWT, Supervised walking therapy.

[a]Training volume: Total duration SWT program = Length program *times* (average) number of sessions per week *times* (average) duration per session.

[b]Walking plus: Therapy consisted of walking combined with additional lower limb aerobic exercises.

Effect of supervised walking therapy on walking distance

Twenty-four RCTs reported MWD measurements before and after training from the intervention and control groups, and 20 RCTs also reported PFWD measurements (Table III). The weighted mean difference in MWD from 24 RCTs comprising 916 patients was 180 meters (95% CI, 130-230 meters), which was statistically significant in favor of supervised walking therapy compared with noninterventional observation (Fig 2). Similarly, the weighted mean difference in PFWD from 20 RCTs comprising 708 patients was statistically significant, with 128 meters (95% CI, 92-165 meters) in favor of the supervised walking therapy group (Fig 3).

Table III. Results of the randomized controlled trials included in the systematic review[a]

		Patients analyzed		*MWD (m) SWT group*	
First author	*Year*	*Intervention*	*Control*	*Pretraining*	*Post-training*
Dahllof[19]	1974	10	8	296±150	620±160
Hiatt[20]	1990	10	9	341±91	741±187
Jansen[21]	1991	24	24	191±27	320±50
Hiatt[22]	1994	10	8	515±306	789±392
Tisi[23d]	1997	22	17	104 (72-148)	175 (103-258)
Gibellini[24]	2000	20	20	217±79	451±170
Gardner[25]	2001	28	24	396±211	702±279
Gelin[26]	2001	73	76	258±142	247±111
Gardner[27]	2002	17	14	425±139	800±445
Langbein[28]	2002	27	25	505±433	1420±1156
Tsai[29]	2002	27	26	397±209	671±199
Mika[30]	2005	41	39	NR	NR
Sandri[31]	2005	9	9	152±34	210±47
Hobbs[32e]	2006	7	7	111 (69-237)	124 (74-352)
Mika[33]	2006	27	28	408±56	609±74
Sanderson[34]	2006	13	14	NR	Δ 180±46[c]
Wood[35]	2006	7	6	686±400	905±375
Hobbs[36]	2007	9	9	99 (81-241)	218 (122-339)
Crowther[37]	2008	10	11	300±125	661±278
Hodges[38]	2008	14	14	347±219	622±310
Treat-Jacobson[39]	2009	11	8	483±291	Δ 295±164[c]
Schlager[40]	2011	20	20	102 (66-155)	154 (97-230)
Leicht[41]	2011	8	9	NR	296±150
Gardner[42]	2011	33	33	289±150	480±250
Mika[43]	2011	30	31	551±57	848±61

Table III. Continued.

MWD (m) control group		*PFWD (m) SWT group*		*PFWD (m) control group*	
Pretraining	*Post-training*	*Pretraining*	*Post-training*	*Pretraining*	*Post-training*
340±253	340±253[b]	91±35	230±100	55±119	55±119[b]
320±107	379±155	NR	NR	NR	NR
145±16	171±25	116±14	196±26	89±9	111±13
395±176	389±144	177±107	360±231	203±123	165±69
110 (81-148)	126 (104-156)	70 (45-87)	112 (103-253)	80 (44-91)	107 (67-137)
230±110	226±123	128±46	308±163	112±65	111±79
379±254	425±296	172±127	402±274	163±122	203±228
272±153	261±131	NR	NR	NR	NR
430±139	425±278	195±139	580±445	190±139	210±178
535±184	499±226	NR	NR	NR	NR
384±171	405±203	177±166	333±145	155±139	171±181
NR	NR	87±38	192±95	87±40	102±50
148±51	146±38	104±34	175±51	98±59	87±47
84 (79-227)	145 (75-435)	59 (35-63)	92 (47-169)	47 (30-118)	56 (45-325)
382±63	401±68	178±32	359±56	181±18	187±25
NR	Δ-8±41[c]	309±188	455±277	293±308	335±332
966±596	1019±626	284±197	456±302	236±143	296±156
94 (79-162)	137 (94-175)	60 (45-95)	110 (66-194)	59 (48-72)	73 (46-80)
252±163	309±183	119±55	322±168	103±88	148±80
362±240	405±359	NR	NR	NR	NR
361±186	Δ 45±93[c]	200±151	Δ 92±148[c]	119±62	Δ4±45[c]
85 (50-150)	100 (40-150)	NR	NR	NR	NR
NR	244±172	NR	116±58	NR	107±93
449±192	439±213	174±128	321±235	200±140	186±149
551±62	516±89	260±52	542±72	258±71	258±89

MWD, Maximum walking distance; *NR*, not reported; *PFWD*, pain-free walking distance; *SWT*, supervised walking therapy.

[a]Data are presented as mean standard deviation or median (interquartile range).

[b]In the placebo-treated control patients, the walking distance remained unchanged.

[c]Mean change in walking distance after SWT.

[d]Reported post-training distances after 12-month follow-up.

[e]Reported post-training distance after 6-month follow-up.

Figure 2. Mean difference in maximum walking distance (MWD) from randomized controlled trials comparing super-vised walking therapy (SWT) vs noninterventional observation. *CI*, Confidence interval; *SD*, standard deviation

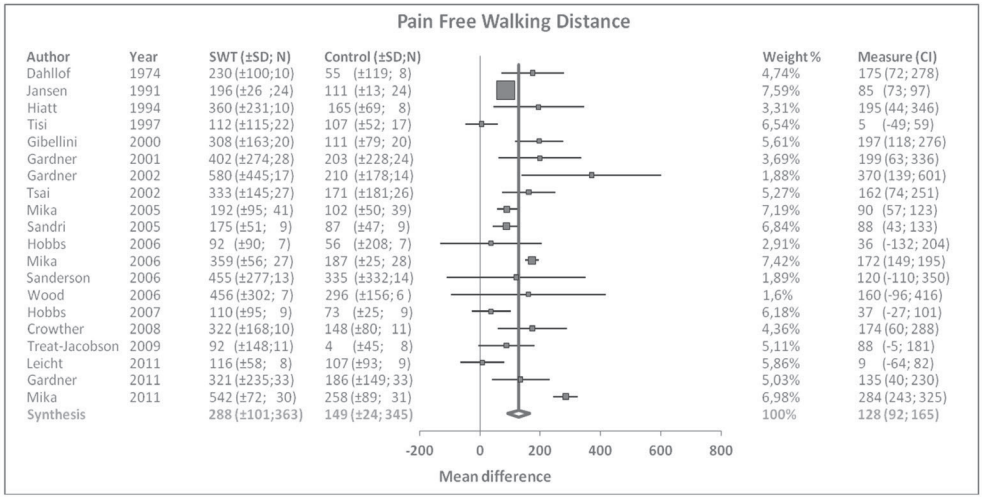

Figure 3. Mean difference in pain-free walking distance (PFWD) from randomized controlled trials comparing super-vised walking therapy (SWT) vs noninterventional observation. *CI*, Confidence interval; *SD*, standard deviation.

Assessment of selective evidence dissemination

The funnel plots (Fig 4 and Fig 5), the Begg tests, and the Egger regression tests were all suggestive of potential selective dissemination bias. The "trim and fill" correction changed the weighted mean differences in MWD and PFWD to 148 (95% CI, 136-160 meters) and 97 meters (95% CI, 92-165 meters), respectively, both still in favor of supervised walking therapy.

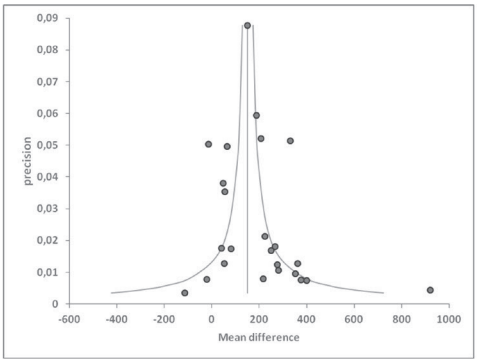

Figure 4. Heterogeneity funnel plot of the mean difference in max-imum walking distance (MWD) from the included randomized controlled trials.

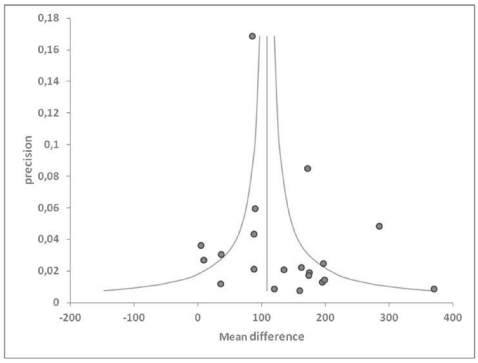

Figure 5. Heterogeneity funnel plot of the mean difference in pain-free walking distance (PFWD) from the included randomized controlled trials.

Table IV. Weighted mean changes in MWD and PFWD sorted by supervised walking therapy program component

Component SWT program	*Studies (No.)*	*Change in MWD*[a] *(meters)*	P	*Studies (No.)*	*Change in PFWD*[a] *(meters)*	P
Pain end point						
Pain free	3	257(164-351)	.01	4	128(92-165)	.01
Mild/moderate pain	11	151(85-217)	.01	8	101(63-140)	.01
Maximum pain	10	177(97-257)	.01	8	100(45-156)	.01
Length SWT program (weeks)						
Short-term (4-11)	5	123(41-204)	.01	5	100(20-179)	.01
Medium-term (12-26)	14	223(149-298)	.01	11	146(94-197)	.01
Long-term (26)	5	145(27-263)	.02	4	109(27-190)	.01
Total program volume (minutes)						
0-1080	5	105(6-205)	.04	4	128(-92-165)	0.1
1081-2340	11	237(151-323)	.01	10	146(95-198)	.01
2340	8	154(72-236)	.01	6	111(52-170)	.01
Treadmill use during SWT						
No	6	100(2-199)	.05	4	57(-13 to 126)	.11
Yes	18	200(150-250)	.01	16	128(92-165)	.01

MWD, Maximum walking distance; *PFWD*, pain-free walking distance; *SWT*, supervised walking therapy.
[a]Data are presented as mean (95% confidence interval).

Association between supervised walking therapy components and walking distance

Subgroup analysis

In subgroup meta-analysis, supervised walking therapy programs selected by their predefined components showed statistically significant improvements in MWD and PFWD

compared with their control groups, except for studies in which no treadmill was used during the supervised walking therapy and the total supervised walking therapy volume was 1080 minutes (Table IV).

Multivariable meta-regression

Multivariable random effects meta-regression, which included all the supervised walking therapy components listed in Table IV as covariables, indicated that only a small fraction of the heterogeneity in the weighted mean difference in MWD or PFWD between the included RCTs could be explained by the covariables entered in the random effects meta-regression model. In other words, none of the entered components from supervised walking therapy programs were independently associated with the improvements in MWD or PFWD.

None of the studies had excessive effect on the results, as evaluated by an exclusion sensitivity analysis. Furthermore, sensitivity analysis by removing studies with a PEDro score 4, did not have a major effect on the results.

DISCUSSION

We evaluated the effectiveness of supervised walking therapy as initial treatment in patients with intermittent claudication by performing a systematic review and meta-analysis of RCTs that compared supervised walking therapy with non-interventional observation. In addition, we performed multivariable meta-regression to identify the most important exercise components in supervised walking therapy programs.

Results from our meta-analysis, based on RCTs comparing supervised walking therapy with noninterventional observation, demonstrated that supervised walking therapy is associated with significantly greater improvement in both MWD and PFWD. These results are consistent with two previous systematic reviews that demonstrated that supervised exercise therapy improves walking distance compared with unsupervised exercise therapy[9] or usual care.[10] We only included RCTs evaluating walking programs and excluded other modes of exercise therapies, such as strength training, cycling, pneumatic calf compression, and upper limb exercises, to make the exercise studies more comparable.

In multivariable meta-regression, none of the exercise components, including treadmill use during training, claudication pain end point used during walking, length of the supervised walking therapy program, or total training volume, seemed to be independently associated with significant mean improvements in MWD or PFWD. Yet in subgroup analysis, there seemed to be a tendency to greater mean improvement in MWD and PFWD in supervised walking therapy programs with a middleterm length (12-26 weeks) compared with the shorter (12 weeks) or longer (26 weeks) programs.

This tendency was also observed in total training volume (Table IV). This suggests that supervised walking therapy between 12 and 26 weeks, with three sessions per week and 30 minutes of walking per session, would give the best results. However, these results were not confirmed by meta-regression analysis and need to be evaluated properly in an RCT.

A meta-analysis based on RCTs to evaluate the effect of various exercise components on clinical improvement is difficult, given the lack of RCTs directly comparing different exercise components. In a previous systematic review from 1995 that combined results from RCTs and uncontrolled studies, Gardner et al[11] determined that the optimal exercise program for patients with intermittent claudication consists of intermittent walking to near-maximal pain for at least 6 months. Although the present systematic review used results from RCTs only and therefore is less prone to confounding due to selection bias, our results do not support these prior recommendations: no single exercise component was independently associated with a significant improvement in walking distance. In line with the present study, a more recent review by Parmenter et al[44] on the same topic concluded that improvements in MWD were not related to various components of exercise training; however, the focus in the review by Parmenter et al was not on supervised walking therapy but on any mode of exercise therapy for patients with intermittent claudication.

The recommended supervised exercise therapy programs,[6,7] consisting of walking 30 to 60 minutes to (maximum) claudication pain three to five times weekly for a duration of 3 to 6 months, are usually experienced as very intensive and time-consuming. Consequently, these recommended programs are affiliated with low patient compliance and high dropout rates.[45]

In addition to improving walking ability, exercise training is also effective in preventing cardiovascular events,[8,46] and this can fulfill an important role in cardiovascular risk factor management in patients with intermittent claudication by encouraging patients to quit smoking and adhere to prescribed medication. Hence, every attempt to increase patient compliance with supervised walking therapy programs should be considered and evaluated carefully. The results of this systematic review suggest that low-intensity (pain-free) supervised walking therapy or a shorter training duration, or both, might be as equally beneficial as high-intensity exercise programs with a relatively long duration, while promoting patient compliance with the supervised walking therapy. However, clinical RCTs evaluating each component from supervised walking therapy independently are essential to determine the optimal supervised walking therapy protocol, resulting in improvement in walking distance and higher patient compliance.

A full economic evaluation of the supervised walking therapy components from patient and societal perspectives is necessary to determine the cost-effectiveness of different supervised walking therapy programs. van Asselt et al[47] evaluated the cost-effectiveness of supervised exercise therapy compared with "go home and walk" advice and concluded that at the willingness-to-pay threshold of €40,000 per quality-adjusted

life-year, exercise therapy is likely to be a cost-effective treatment option. This was based on exercise therapy consisting of two to three sessions of 30 minutes weekly for 1 year, the frequency of which could be adjusted depending on the patient's progress and need. The remaining question is whether a less intensive supervised walking therapy program is going to be cost-effective compared with the recommended supervised walking therapy programs at regular intensity.

Some limitations of this systematic review should be addressed. The results of the systematic review are limited by the methodologic quality of the original studies. The mean PEDro score was low (average, 5 points), with most studies not reporting allocation concealment or data analysis according to the intention-to-treat principle. The sample size of the included studies was relatively small (average, 42 patients), which might have resulted in lack of statistical representation or precision in effect estimation. Negative or nonsignificant studies with low precision seem to be missing in the funnel plot, which might be an indication of selective reporting or publication. Still, performing a "trim and fill" procedure by imputing the potentially missing studies did not change our results significantly. Another issue was missing data, especially data on compliance or adherence to the supervised walking therapy programs were lacking. Next, the studies did not use similar standardized treadmill tests to assess the walking distances before and after supervised walking therapy. The recommendation is to use a standardized progressive tread-mill test with a constant walking speed of 3.2 km/h and gradual increase in inclination of 2% every 2 minutes till a maximum grade of 10%.[48] However, most of the included studies used other treadmill test protocols with varying speed and gradual incline of the treadmill, which might have resulted in inaccurate outcome assessment in several RCTs.

Results on the effectiveness of exercise programs from our systematic review and previous systematic reviews are based on pooled results from RCTs evaluating nonstandardized exercise programs with very diverse training components regarding duration, mode, and intensity of the programs. Nevertheless, our results confirm the suggestion that, despite the diversity in supervised walking therapy, these studies have one thing in common: they all show significant clinical benefits for patients with intermittent claudication independent of the frequency, duration, mode, or intensity of the programs.

CONCLUSIONS

This systematic review showed that supervised walking therapy is effective in improving MWD and PFWD in patients with intermittent claudication. However, pooled results from the RCTs evaluating supervised walking therapy programs did not identify a statistically significant association between the improvements in MWD or PFWD and individual supervised walking therapy program components.

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Chapter 3

Modes of exercise training for intermittent claudication

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Cochrane Database of Systematic Reviews 2014, Jul 4; 7

ABSTRACT

Background

According to international guidelines and literature, all patients with intermittent claudication should receive an initial treatment of cardiovascular risk modification, lifestyle coaching, and supervised exercise therapy. In most studies, supervised exercise therapy consists of treadmill or track walking. However, alternative modes of exercise therapy have been described and yielded similar results to walking. Therefore, the following question remains: Which exercise mode gives the most beneficial results?

Objectives

Primary objective: To assess the effects of different modes of supervised exercise therapy on the maximum walking distance (MWD) of patients with intermittent claudication.
Secondary objectives: To assess the effects of different modes of supervised exercise therapy on pain-free walking distance (PFWD) and health-related quality of life scores (HR-QoL) of patients with intermittent claudication.

Search methods

The Cochrane Peripheral Vascular Diseases Group Trials Search Coordinator searched the Cochrane Peripheral Vascular Diseases Group Specialised Register (July 2013); CENTRAL (2013, Issue 6), in The Cochrane Library; and clinical trials databases. The authors searched the MEDLINE (1946 to July 2013) and Embase (1973 to July 2013) databases and reviewed the reference lists of identified articles to detect other relevant citations.

Selection criteria

Randomised controlled trials of studies comparing alternative modes of exercise training or combinations of exercise modes with a control group of supervised walking exercise in patients with clinically determined intermittent claudication. The supervised walking programme needed to be supervised at least twice a week for a consecutive six weeks of training.

Data collection and analysis

Two authors independently selected studies, extracted data, and assessed the risk of bias for each study. Because of different treadmill test protocols to assess the maximum or pain-free walking distance, we converted all distances or walking times to total metabolic equivalents (METs) using the American College of Sports Medicine (ACSM) walking equation.

Main results

In this review, we included a total of five studies comparing supervised walking exercise and alternative modes of exercise. The alternative modes of exercise therapy included cycling, strength training, and upper-arm ergometry. The studies represented a sample size of 135 participants with a low risk of bias. Overall, there was no clear evidence of a difference between supervised walking exercise and alternative modes of exercise in maximum walking distance (8.15 METs, 95% confidence interval (CI) -2.63 to 18.94, P = 0.14, equivalent of an increase of 173 metres, 95% CI -56 to 401) on a treadmill with no incline and an average speed of 3.2 km/h, which is comparable with walking in daily life. Similarly, there was no clear evidence of a difference between supervised walking exercise and alternative modes of exercise in painfree walking distance (6.42 METs, 95% CI -1.52 to 14.36, P = 0.11, equivalent of an increase of 136 metres, 95% CI -32 to 304). Sensitivity analysis did not alter the results significantly.

Quality of life measures showed significant improvements in both groups; however, because of skewed data and the very small sample size of the studies, we did not perform a meta-analysis for health-related quality of life and functional impairment.

Authors' conclusions

There was no clear evidence of differences between supervised walking exercise and alternative exercise modes in improving the maximum and pain-free walking distance of patients with intermittent claudication. More studies with larger sample sizes are needed to make meaningful comparisons between each alternative exercise mode and the current standard of supervised treadmill walking. The results indicate that alternative exercise modes may be useful when supervised walking exercise is not an option for the patient.

BACKGROUND

Description of the condition

Peripheral arterial occlusive disease (PAOD) is a chronic arterial occlusive disease caused by progressive atherosclerosis. Several arterial segments can be affected, such as the aorta; iliac; and femoral, popliteal, and tibial arteries in the limbs. The most common symptom is intermittent claudication, defined as a cramping pain in the muscles of the leg(s) that occurs during exercise and is relieved by a short period of rest. Because of this condition, patients have a diminished maximum and pain-free walking capacity, leading to diminished health-related quality of life[1]. The incidence of intermittent claudication increases with age, with an annual incidence rate of 0.7%, 3.9%, and 10.6% among 35- to 44-year-old men, 45- to 54-year-old men, and 55- to 64-year-old men, respectively[2]. In women, the incidence rates are approximately 50% lower[2]. Intermittent claudication restricts patients' activity and mobility and considerably reduces their health-related quality of life[1,3]. In addition, because of the ongoing generalised atherosclerotic process, intermittent claudication is closely associated with cardiovascular morbidity and mortality. Patients with intermittent claudication have a five-year all-cause mortality rate of 10% to 15% and a 20% chance of a non-fatal cardiovascular event[4]. When intermittent claudication progresses to critical limb ischaemia, an even higher mortality rate of 25% after one year is found[5].

Description of the intervention

Because of the serious health risks, all patients with intermittent claudication should receive a multicomponent therapy consisting of cardiovascular risk modification, lifestyle coaching, and exercise therapy[5]. Several randomised controlled trials and systematic reviews compared walking exercise supervised by a physical or exercise therapist to non-supervised exercise, usual care, placebo, single walking advice, endovascular interventions, or bypass surgery[6-10]. The current evidence supports supervised exercise therapy as the primary treatment for improvement of walking capacity and health-related quality of life in patients with intermittent claudication. Furthermore, community-based supervised exercise appears to be at least as efficacious as programmes provided in a hospital setting[11-13]. However, less attention has been paid to the mode of (supervised) exercise. Besides walking, alternative modes of supervised exercise training, such as cycling, upper-extremity cycle ergometer exercise and strength training exist and are associated with a significantly improved walking capacity[14-16].

How the intervention might work

A number of potential mechanisms have been suggested for the reduced functional capacity in intermittent claudication, such as blood flow limitation due to arterial obstruction, disruption of endothelial function, altered skeletal muscle phenotype by

mitochondrial dysfunction, increased blood viscosity, and inflammatory activation[17]. Exercise has the potential to reverse these pathological events and thereby interrupt the clinical course toward disability[17].

Why it is important to do this review

In most studies, supervised exercise programmes involve treadmill or track walking that is of sufficient intensity to bring on claudication pain. Walking exercise is alternated with rest over the course of a 30- to 60-minute session. Exercise therapy for intermittent claudication is recommended at least three times a week for three months, although there does not seem to be a clear dose-response relationship between exercise volume or intensity and symptom relief[5,18]. Unfortunately, some groups of patients with intermittent claudication are not capable of completing the exercise protocol because of concomitant comorbidities, such as arthrosis, chronic obstructive pulmonary disease, stroke, or cardiac complaints. For these patients, an adjusted protocol or alternative exercise regime may be proposed.

Recently, a systematic review comparing any mode of exercise, whether supervised or unsupervised, was published[18]. It suggested that alternative modes of aerobic exercise, other than walking, appear equally beneficial compared to walking exercise, while the effects of progressive resistance training and upper body exercise seem only promising. The effect size of each exercise mode was calculated and compared to the effect size of walking exercise. However, because of heterogeneity, no meta-analysis was performed on specific randomised controlled trials (RCTs) comparing the standard of supervised walking exercise to alternative exercise regimes.

Therefore, the question regarding which exercise mode gives the most beneficial results in walking distance, health-related quality of life, or both, in patients with intermittent claudication remains to be answered. Previous Cochrane systematic reviews focused on the effect of exercise compared with usual care and the value of a supervised exercise programme in relation to non-supervised exercise[7,19]. This systematic review will determine the effect of alternative exercise modes by analysing randomised controlled trials comparing the current standard of supervised walking exercise to alternative modes of exercise. Studies focusing on this research topic are increasing, implicating the need for a regular update of this review in the upcoming years.

Objectives

Primary objective: To assess the effects of different modes of supervised exercise therapy on the maximum walking distance (MWD) of patients with intermittent claudication.

Secondary objectives: To assess the effects of different modes of supervised exercise therapy on pain-free walking distance (PFWD) and health-related quality of life scores (HR-QoL) of patients with intermittent claudication.

METHODS

Criteria for considering studies for this review

Types of studies

We We included parallel-group, randomised controlled trials (RCTs) comparing (combinations of) alternative modes of exercise training (for example, ergometry, strength training, aerobic exercise, etc.) with supervised walking exercise in patients with intermittent claudication. We excluded crossover, factorial, or cluster RCTs.

Types of participants

The study population consisted of adults (18 years and older) with clinically determined intermittent claudication, according to Fontaine stage II or Rutherford stages 1 to 3, who were considered for conservative treatment. We excluded studies of participants with asymptomatic lower-limb atherosclerosis identified by testing. When studies described a mixture of asymptomatic and symptomatic participants, we contacted the authors to ask if a subanalysis was available. If not, we excluded these studies.

Types of interventions

We included all RCTs comparing alternative modes of exercise training (e.g. arm ergometry, strength training, cycling, etc.) or combinations of exercise modes with a control group of supervised walking exercise. Supervised walking exercise needed to be supervised at least twice a week for a consecutive six weeks of training. We excluded studies reporting an exercise programme with a duration of less than six weeks of training or with less than two supervised walking sessions a week.

Since different types of alternative exercise modes are associated with an increased walking capacity, we combined all studies with different alternative exercise modes in one analysis. However, to analyse the effect of each individual or combined alternative exercise modes, we performed a subgroup analysis on the exercise mode (or combination) if more than one study was available. We excluded all types of mechanical intermittent compression treatments as we did not consider them to be exercise training. Furthermore, we did not include studies comparing different types of walking exercise (supervised versus unsupervised, community versus hospital-based) or comparisons of different walking protocols (low- versus high-frequency training, low- versus high-intensity training, different treadmill exercise protocols).

Types of outcome measures

Primary outcomes

The primary outcome measurement was the maximum walking distance (MWD) measured by a treadmill test. Outcome measurements needed to be available at baseline and after

at least six weeks of follow up. In case of different treadmill test protocols, we converted walking times or distances to total metabolic equivalents (total METs or sum of METs during the walking period).

Secondary outcomes

Secondary outcome measurements were the pain-free walking distance (PFWD) and health-related quality of life (HR-QoL) scores. Besides a baseline measurement, results needed to be available after at least six weeks of follow up. In case of different treadmill test protocols, we converted walking times or distances to METs.

Search methods for identification of studies

We applied no language restrictions.

Electronic searches

The Cochrane Peripheral Vascular Diseases Group Trials Search Coordinator (TSC) searched the Cochrane Peripheral Vascular Diseases Group Specialised Register (last searched July 2013) and the Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 6, part of The Cochrane Library, www.thecochranelibrary.com. The Specialised Register is maintained by the TSC and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used are described in the Specialised Register section of the Cochrane Peripheral Vascular Diseases Group module in The Cochrane Library www.thecochranelibrary.com.

The TSC searched the following trial databases (July 2013) for details of ongoing and unpublished studies using the terms exercise and claudication:

- The World Health Organization International Clinical Trials Registry (ICTRP) platform (apps.who.int/trialsearch/).
- The US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov).
- The metaRegister of Controlled Trials (www.controlledtrials.com/isrctn/).

Searching other resources

The authors searched MEDLINE (1946 to 15 July 2013) and Embase (1973 to 15 July 2013). We reviewed the reference lists of articles identified by the above search strategies to identify other relevant citations.

Data collection and analysis

Selection of studies

GJL and FF independently selected trials for this review. SS and JT confirmed the suitability of selected trials for inclusion in the review. We sought additional information for included trials, if necessary.

Data extraction and management

GJL and FF independently extracted data using a standard data collection form created for this review. We entered the data into Review Manager (RevMan 5.2). We resolved disagreements between the review authors by discussion. SS acted as arbiter if no consensus was achievable. The extracted study data consisted of the following:

- Study characteristics, including study design, method of randomisation, exclusions postrandomisation, publication year, country, and study period;
- Baseline characteristics, including number of participants, losses to follow up, mean age, gender distribution, and inclusion and exclusion criteria;
- Type of interventions, including mode(s) of exercise, duration of programme, number of sessions, number of supervised sessions, and exercise protocol; and
- The mean maximum walking distance or time, mean painfree walking distance or time, and mean quality of life scores at baseline and follow-up periods.

Assessment of risk of bias in included studies

The authors (GJL and FF) assessed the risk of bias for each study as described in the Cochrane Handbook for Systematic Reviews of Interventions[20] for each of the following domains:Randomisation and sequence generation.

- Allocation concealment.
- Blinding (of participants, personnel, and outcome assessors).
- Incomplete outcome data.
- Selective outcome reporting.
- Publication and other sources of bias.

For each of the six domains, we assessed risk of bias as 'low' or 'high', or as 'unclear' when available information was insufficient to permit judgement on risk of bias.

Measures of treatment effect

To analyse treatment effect, we assessed the MWD, PFWD, and HR-QoL scores after participation in the exercise programme. In the case of different treadmill test protocols, we converted walking times or distances to total METs (sum of METs during the walking period) using the American College of Sports Medicine (ACSM) walking equation[21]. The ACSM walking equation includes the time, speed, and inclination of the treadmill test.

Since direct conversion of the walking times or distances to METs was not possible because of the absence of individual participant data, we simulated a new dataset for each study. We used post intervention walking distances and variances from the intervention and control group to simulate a new dataset assuming a normal distribution. For each simulated individual, we calculated the number of METs using the ACSM walking equation. We used the summary measures (mean METs and variances) from each simulated dataset as post intervention outcomes from the included studies.

Unit of analysis issues

We searched for RCTs with at least six weeks' duration of training and a parallel-group design. We included no crossover trials in this review. In assessment of the primary and secondary outcomes, we considered the participant the unit of analysis.

Dealing with missing data

We expected missing standard deviations for walking distances. In the case of missing data, we requested data from the original investigators, if appropriate. We did not impute missing outcome data for the primary and secondary outcomes.

Assessment of heterogeneity

For all the outcome measures, we assessed statistical heterogeneity by calculating the Q-statistic or Chi2 test ($P < 0.10$ considered as heterogeneous) and the I^2 statistic (I^2 statistic greater than 50% considered as moderate to substantial risk of heterogeneity) in order to assess to what degree the data from the included studies were heterogeneous[20].

Assessment of reporting biases

In case of sufficient studies (> 10 studies), we planned to assess publication bias with a funnel plot with the maximum walking distance on the X axis and the standard error of each study on the Y axis[20]. If there is bias, for example, because smaller studies without statistically significant effects remain unpublished, this will lead to an asymmetrical appearance of the funnel plot. In this situation, the effect calculated by the meta-analysis will tend to overestimate the intervention effect. Therefore, we also planned to evaluate funnel plot asymmetry using Begg and Egger tests[22,23] performed with Stata statistical software[24].

Data synthesis

To analyse treatment effect, we used the DerSimonian and Laird random-effects model. This model takes the variance between studies and the variance within a study into account[25]. We summarised the data of each study in forest plots and calculated summary estimates with a 95% confidence interval. We considered a two-sided $P < 0.05$ as statistically significant, except for the test of publication bias for which the recommended levels are $P < 0.10$. We performed analyses using RevMan 5.2.

Subgroup analysis and investigation of heterogeneity

We performed a subgroup analysis of each type of alternative exercise mode if we found more than one trial comparing the specific exercise mode with walking exercise. Furthermore, because most studies and international guidelines advise a 12-week supervised exercise programme, we reported outcomes both at the end of training and at 12 weeks of training. Finally, we performed a subgroup analysis on the combination of alternative exercise modes in relation to supervised walking exercise.

Sensitivity analysis

We examined individual study effects on the results by removing each study one at a time to examine whether removing a particular study would significantly change the results. In addition, we planned to perform sensitivity analyses on the methodological quality of the studies. We planned to exclude studies with apparent methodological flaws and risk of bias and examine whether removing these studies significantly changed results.

RESULTS

Results of the search

See Figure 1.

Included studies

We identified 10 publications comparing an alternative exercise regime to supervised walking exercise for intermittent claudication. Of these 10 publications, we identified five primary studies[15,16,26-28]. These five randomised controlled trials published in peer-reviewed journals fulfilled the inclusion criteria, and we considered these for inclusion in this review. Five additional publications described the results of three of the primary studies more extensively[29-33].

Three trials compared supervised walking exercise to an exercise or progressive resistance regime[26-28], one trial compared arm ergometry to supervised walking exercise[16] and one trial compared cycling exercise to supervised walking exercise[15]. These five trials randomised a total of 184 participants with intermittent claudication, with 135 participants randomised to the treatment arms relevant to this review. The number of participants per study was small, with a variation of between 29 and 45 participants. The mean age of the participants in the included trials varied between 62.0 and 71.7 years, and all trials included both men and women. The trials were conducted in the United States (3), Brazil (1), and Australia (1).

Enrolment criteria were rather homogeneous. All trials included participants if a declination in ankle brachial index was present with coinciding limiting or disabling symptoms of intermittent claudication. One trial[26] assessed claudication symptoms by a questionnaire (San Diego Claudication Questionnaire). In all trials, the presence of critical limb ischaemia was an exclusion criterion. Participants were also excluded if the exercise capacity was limited by another factor than intermittent claudication (e.g. angina, chronic obstructive pulmonary disease, arthrosis). In three of the five trials, claudication symptoms needed to be stable for, respectively, three months[27] six months[28], or more than 12 months[15]. Two trials[27,28] excluded participants if a revascularisation procedure was performed in the previous year. One RCT[16] excluded participants if a coronary or lower-extremity revascularization procedure was performed within the past three months. The

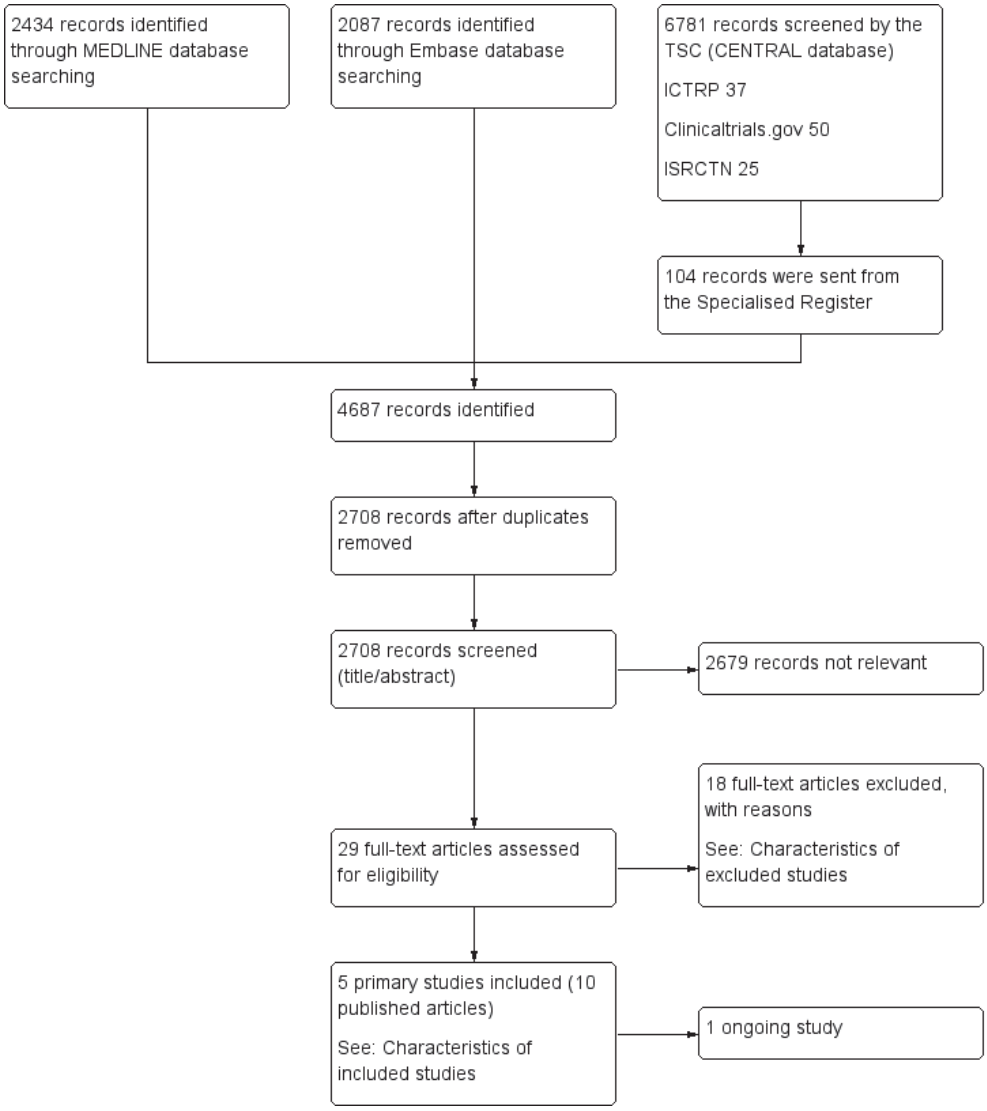


Figure 1. Study flow diagram.

two remaining trials[15,26] excluded participants if they recently underwent surgery or a cardiovascular event. Treatment duration varied between studies ranging from six weeks' training[15] ,12-week training[16,27,28] to 24-week training periods[26].

Excluded studies

After title/abstract screening, we excluded 3626 studies. After full text assessment, we excluded another 18 studies for various reasons. We excluded three studies as they were not randomised controlled trials[34-36]. We excluded four studies[37-40] as they were meeting

posters with a limited description of the methods and results; no articles of these meeting posters were published yet. We excluded nine studies[40-48] because they did not assess (adequate) supervised exercise therapy according to our inclusion criteria for this review. Five studies[41,43,44,46,49] did not report the primary and secondary outcome measures of this review. We excluded one study[50] because the outcome measures were unclearly described. We tried to contact the authors but did not receive additional information. We excluded one study[51] because we did not consider the intervention (pole walking) an alternative exercise regime in comparison to supervised walking.

Risk of bias in included studies

See Figure 2 for a summary of the risk of bias in each included study.

Allocation

Two studies described adequate sequence generation and allocation concealment by means of computer randomisation[26,28]. Two studies an adequate sequence generation, but did not describe the allocation concealment[15,16]. One study did not describe the randomisation process[27].

Blinding

In the included studies, participants and direct personnel could not be blinded to the intervention (exercise). For this reason, bias could be introduced. However, since all studies experienced the same limitation, we considered the risk of bias to be low for all studies. Detection bias can be avoided by blinding the outcome assessors. Three studies achieved this[16,16,28].

Incomplete outcome data

Most studies well-described reasons for missing data, and we considered these plausible and well distributed among the groups. One study addressed asymptomatic participants with PAOD as well as symptomatic participants[26]. After contacting the authors, we derived the data of the sole symptomatic group with intermittent claudication. However, it is unclear which of the missing data described in the article related to the symptomatic group. For this reason, we considered the incomplete outcome data in this study to be unclear.

Selective reporting

All studies described relevant outcomes. For three studies[15,16,26], we retrieved additional outcome data by contacting the authors.

Other potential sources of bias

Since we identified only five studies, we could not detect publication bias with a funnel plot. Additional Begg and Egger tests did also exclude any indication of publication

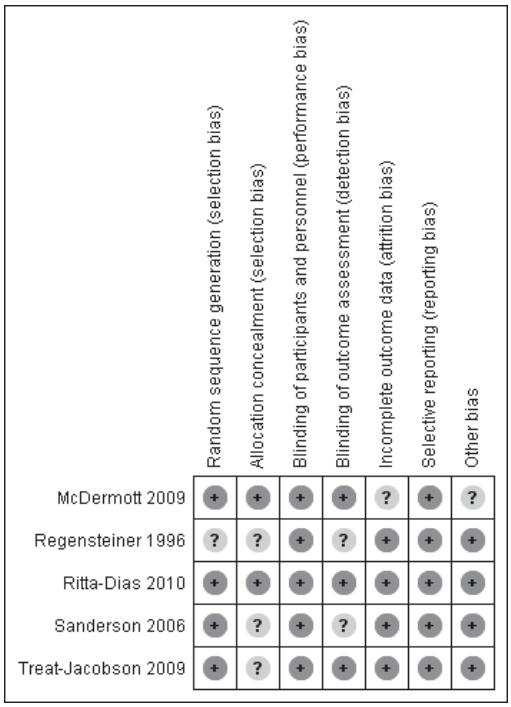


Figure 2. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study

bias (Begg: adjusted Kendall's score = 4, P = 0.462; Egger: bias 1.11, 95% confidence interval (CI) 0.43 to -2.77, P = 0.430). One of the studies[26] did not describe the baseline characteristics of the subgroup of participants with intermittent claudication. This was due to the study setting. (The study included participants with asymptomatic as well as symptomatic peripheral arterial disease.) However, we identified no other potential sources of bias in the included trials.

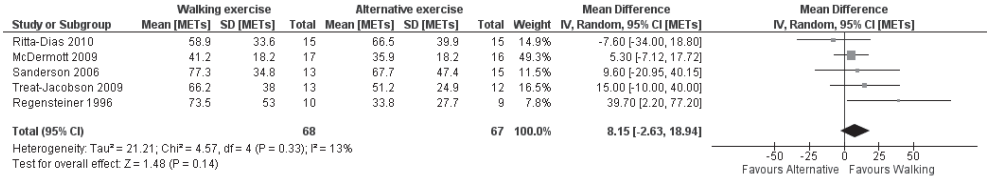
Effects of interventions

Walking exercise versus alternative exercise

Maximum walking distance [METs]

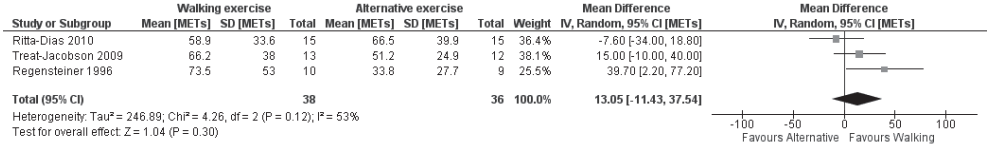
Data for the maximum walking distance (MWD) obtained at the end of each study were available in all of the included trials, with a total sample size of 135 participants. We calculated the pooled treatment effect after standardising the reported walking distances. For this reason, we converted all distances to metabolic equivalents (METs) using the American College of Sports Medicine (ACSM) formulas for metabolic calculations. We considered the impact of heterogeneity as low with an I2 statistic of 13%. At the end of

training, the pooled MWD increased with an overall non-significant effect size of 8.15 METs (95% confidence interval (CI) -2.63 to 18.94, P = 0.14) in favour of walking exercise. This is the equivalent of an increase of 173 metres (95% CI -56 to 401metres) on a treadmill with no incline and an average speed of 3.2 km/h, which is comparable with walking in daily life (Analysis 1.1). However, because of the width of the CI of the pooled MWD, we could not identify any clear evidence of difference between interventions.



Analysis 1. 1 Walking exercise versus alternative exercise, Maximum walking distance at the end of training.

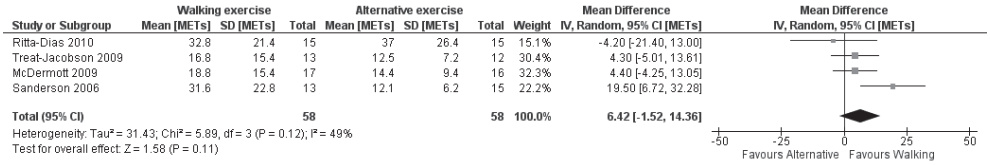
Furthermore, we calculated the effect size after 12 weeks of training. After this follow-up period, data from three trials on MWD were available with a sample size of 74 participants[16,27,28]. We considered the impact of heterogeneity as moderate to substantial with an I^2 statistic of 52%. In these trials, the pooled MWD increased with a non-significant effect size of 13.05 METs (95% CI -11.43 to 37.54, P = 0.30) in favour of walking exercise. This correlates with 276 metres (95% CI -242 to 795 metres) on a treadmill with no incline and an average speed of 3.2 km/h (Analysis 1.2).



Analysis 1.2. Walking exercise versus alternative exercise, Maximum walking distance after 12 weeks of training.

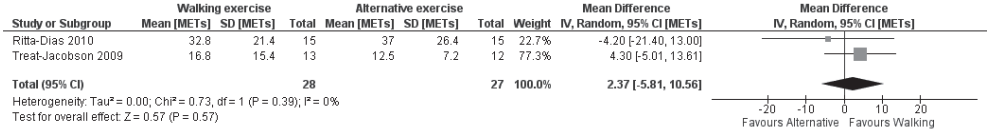
Pain-free walking distance [METs]

Data for the pain-free walking distance (PFWD) obtained at the end of each study were available in four of the five included trials, with a total sample size of 116 participants[15,16,26-28]. We calculated the effect after converting the reported walking distances to standardised METs. We considered the impact of heterogeneity as moderate with an I^2 statistic of 49%. At the end of training, the PFWD increased with an overall non-significant effect size of 6.42 METs (95% CI -1.52 to 14.36, P = 0.11) in favour of walking exercise. This is the equivalent of an increase of 136 metres (95% CI -32 to 304 metres) on a treadmill with no incline and an average speed of 3.2 km/h, which is comparable with walking in daily life (Analysis 1.3). However, because of the width of the CI of the pooled PFWD, we could not identify any clear evidence of a difference between interventions.



ANALYSIS 1.3. Walking exercise versus alternative exercise, Pain-free walking distance at the end of training.

Furthermore, we calculated the effect size after 12 weeks of training. After this followup period, data for two trials for PFWD were available, with a sample size of 55 participants[16,28]. We considered the impact of heterogeneity as low with an I^2 statistic of 0%. In these trials, the pooled PFWD increased with a non-significant effect size of 2.37 METs (95% CI -5.81 to 10.56, P = 0.57) in favour of walking exercise. This correlates with 50 metres (95% CI -123 to 224 metres) on a treadmill with no incline and an average speed of 3.2 km/h (Analysis 1.4).



Analysis 1.4. Walking exercise versus alternative exercise, Pain-free walking distance after 12 weeks of training.

Health-related quality of life (HR-QoL) and functional impairment

Two of the included studies described HR-QoL and functional impairment[26,27]. One study used the Medical Outcomes Study (MOS) SF-20; another study used the SF-36 Physical Functioning score to collect HR-QoL data. Both studies used the Walking Impairment Questionnaire (WIQ) to describe functional impairment.

Data on HR-QoL and functional impairment (WIQ) from one study, with a total sample size of 19 participants, showed an increase in HR-QoL with a significant effect size of 26.50% (95% CI 2.67 to 50.33, P = 0.03) in favour of walking exercise[27]. WIQ distance score increased with an effect size of 2.00% (95% CI -16.04 to 20.04, P = 0.83) in favour of walking exercise. WIQ speed score decreased with an effect size of -4.50% (95% CI -27.34 to 18.34, P = 0.70) in favour of alternative exercise. WIQ stair-climbing score decreased with an effect size of -29.50%(95% CI -51.65 to -7.35, P = 0.009) in favour of alternative exercise.

Unfortunately, both the SF-36 Physical Functioning score and WIQ data from the second study were not normally distributed. SF-36 Physical Functioning score improved in both the strength (n = 14) and treadmill walking group (n = 17), with a median of, respectively, 12.5 points (interquartile range = -5.00 to 20.00) and 10.0 points (interquartile

range = 5.00 to 20.00), P = 0.811. WIQ distance score improved in both the strength (n = 15) and treadmill walking group (n = 15), with a median of, respectively, 14.0 points (interquartile range = 1.56 to 26.6) and 7.46 points (interquartile range = -0.36 to 25.0), P = 0.431. WIQ speed score improved in both the strength (n = 15) and treadmill walking group (n = 16), with a median of, respectively, 3.26 points (interquartile range = -7.61 to 26.1) and 1.63 points (interquartile range = -3.80 to 28.8), P = 0.736. WIQ stair-climbing score improved in the strength training group (n = 15), with a median of, respectively, 12.5 points (interquartile range = 4.17 to 25.0), while we saw no improvement in the median score in the treadmill walking group (n = 16, median score of 0.00 points, interquartile range = 0.00 to 14.6), P = 0.136[26]. Because of the skewed data of one of the studies and the small sample size of both studies, we did not transform these data to perform a meta-analysis of the two studies.

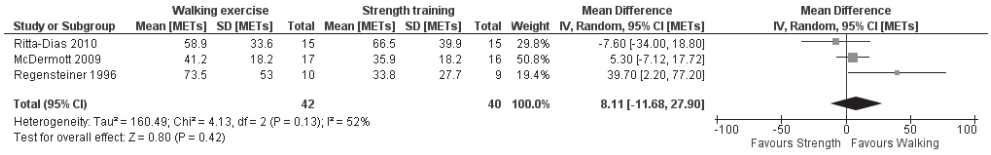
Sensitivity analysis

We performed a sensitivity analysis to assess whether excluding an individual study would significantly change the main results on MWD and PFWD at the end of the study. For MWD, removing any individual study did not alter the results significantly, although by removing one study[28], the MWD increased almost significantly, in favour of walking exercise, with an overall effect size of 10.16 METs (95% CI -0.40 to 20.71, P = 0.06). This is the equivalent of an increase of 215 metres (95% CI - 8 to 439 metres) on a treadmill with no incline and an average speed of 3.2 km/h. For PFWD, removing one of the studies did not alter the results significantly, although by removing one study[28], the PFWD increased almost significantly in favour of walking exercise, with an overall effect size of 8.30 METs (95% CI -0.26 to 16.86, P = 0.06). This is the equivalent of an increase of 176 metres (95% CI -6 to 357 metres) on a treadmill with no incline and an average speed of 3.2 km/h. We did not perform a sensitivity analysis on the methodological quality of the studies because of the limited number of studies.

Walking exercise versus alternative exercise

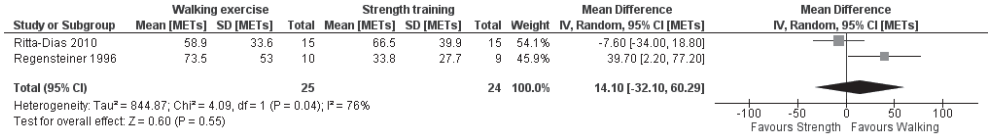
Maximum walking distance [METs]

Data for MWD obtained at the end of each study were available in three of the five included trials, with a total sample size of 82 participants[26-28]. We considered the impact of heterogeneity as moderate to substantial with an I^2 statistic of 52%. At the end of the study, the pooled MWD increased with an overall non-significant effect size of 8.11 METs (95% CI -11.68 to 27.90, P = 0.42) in favour of walking exercise. This is the equivalent to an increase of 172 metres (95% CI -247 to 591 metres) on a treadmill with no incline and an average speed of 3.2 km/h, which is comparable with walking in daily life (Analysis 2.1).



Analysis 2.1. Walking exercise versus strength training, Maximumwalking distance at the end of training

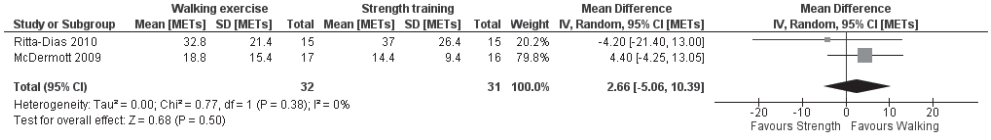
Furthermore, we calculated the effect size after 12 weeks of training. After this followup period, data for two trials for MWD were available, with a sample size of 49 participants[27,28]. We considered the impact of heterogeneity as substantial with an I^2 statistic of 76%. The pooled MWD increased with a non-significant effect size of 14.10 METs (95% CI -32.10 to 60.29, P = 0.55) in favour of walking exercise. This correlates with 299 metres (95% CI -680 to 1277 metres) on a treadmill with no incline and an average speed of 3.2 km/h (Analysis 2.2).



Analysis 2.2. Walking exercise versus strength training, Maximum walking distance after 12 weeks of training.

Pain-free walking distance [METs]

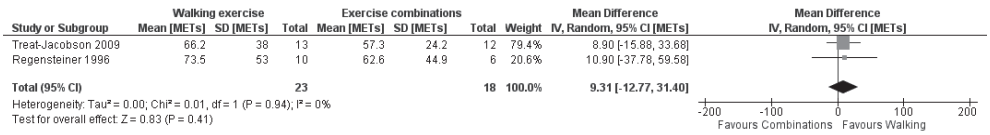
Data for the PFWD at the end of the study were available in two of the included trials, with a total sample size of 63 participants[26,28]. We considered the impact of heterogeneity as low with an I^2 statistic of 0%. At the end of the study, the pooled PFWD increased with an overall non-significant effect size of 2.66 METs (95% CI -5.06 to 10.39, P = 0.50) in favour of walking exercise. This is the equivalent of an increase of 56 metres (95% CI -107 to 220 metres) on a treadmill with no incline and an average speed of 3.2 km/h, which is comparable with walking in daily life (Analysis 2.3).



Analysis 2.3. Walking exercise versus strength training, Pain-free walking distance at the end of training.

Walking exercise versus a combination of exercise modes

Maximum walking distance [METs]
Two trials analysed the effect of a combination of exercise modes in relation to supervised walking exercise on the MWD[16,27]. One trial compared a combination of walking exercise and arm ergometry to sole walking exercise[16]. The second trial compared a combination of walking exercise and strength training to sole walking exercise[27]. In total, the two trials had a sample size of 41 participants for analysis of the MWD at the end of the studies. We considered the impact of heterogeneity as low with an I^2 statistic of 0%. The pooled MWD increased with an overall non-significant effect size of 9.31METs (95%CI -12.77 to 31.40, P = 0.41) in favour of sole walking exercise. This is the equivalent of an increase of 197 metres (95% CI -270 to 665 metres) on a treadmill with no incline and an average speed of 3.2 km/h, which is comparable with walking in daily life (Analysis 3.1).



Analysis 3.1. Walking exercise versus a combination of exercise modes , Maximum walking distance at the end of training

Pain-free walking distance [METs]
Data for PFWD obtained at the end of each study were available in one of the included trials with a total sample size of 25 participants.16 At the end of this study, the PFWD increased with an overall non-significant effect size of 3.30 METs (95% CI -6.01 to 12.61, P = 0.49) in favour of sole walking exercise. This is the equivalent of an increase of 70 metres (95% CI - 127 to 267 metres) on a treadmill with no incline and an average speed of 3.2 km/h, which is comparable with walking in daily life.

DISCUSSION

Summary of main results

We included five RCTs in this review, with a total of 135 participants. We could not find any clear evidence of a statistical difference in maximum or pain-free walking distance when comparing supervised treadmill walking with an alternative exercise regime. Furthermore, sensitivity analysis did not significantly alter the results. Regarding quality of life, two studies described health related quality of life and functional impairment[26,27]. However, the data in one of the two studies were not normally distributed[26]. Therefore, we could not make any meaningful comparison between studies.

Overall completeness and applicability of evidence

Although the topic of this review is contemporary[18], this review identified only five RCTs, with a total of 135 participants. The five RCTs described only three alternative exercise modes: strength training[26-28], arm-ergometry[16] , and cycling exercise[15]. In total, three of the five studies[26-28] compared strength training to supervised treadmill walking, for which we performed a subanalysis. Eventually, more studies are needed to make meaningful comparisons between each alternative exercise mode and the current standard of supervised treadmill walking. Therefore, the applicability of the current evidence is limited.

Quality of the evidence

The risk of bias of the included studies was, in general, low (see Figure 2), reflecting good methodological quality of the included studies. We could not detect publication bias because we could not assess asymmetry in a funnel plot with the limited number of studies. The quality of this review is however limited because of the small sample size of 135 participants. At analysis, we experienced some heterogeneity in Analysis 1.2, Analysis 2.1, and Analysis 2.2 using the I^2 statistic and in Analysis 2.2 using the Q-statistic or Chi^2 test. Sensitivity analysis did not significantly alter the results of the review.

Potential biases in the review process

We tried to limit all potential biases in the review process. To limit bias and make a meaningful comparison, we standardised maximum walking distance (MWD) and pain-free walking distance (PFWD) from each study by converting walking distances to total metabolic equivalents (METs) according to the American College of Sports Medicine (ACSM) formulas for metabolic calculations[21]. However, direct conversion of the walking times or distances to METs was not possible due to the absence of individual participant data. We therefore simulated a new dataset for each study to make a meaningful comparison. It is unclear to what extent this could have biased our findings.

We excluded one study solely because it did not report the correct outcome measures[49]. Although we were careful to ascertain that relevant outcomes were not available because they were not measured rather than not reported, this could be a potential bias in the review process. In future updates, we will pay further attention to this potential source of bias

Agreements and disagreements with other studies or reviews

We agree with a previous published systematic review 18 that there was no clear evidence of difference between alternative exercise modes and supervised walking exercise for intermittent claudication. Results seem promising, but additional studies are urgently needed to validate these exercise modes in relation to the standard of supervised walking exercise.

AUTHOR'S CONCLUSIONS

Implications for practice

Few studies were found and there was no clear evidence of a difference between supervised walking exercise and alternative exercise modes. More studies with larger sample sizes are needed to make meaningful comparisons between each alternative exercise mode and the current standard of supervised treadmill walking. The results indicate that alternative exercise modes may be useful when supervised walking exercise is not an option for the patient.

Implications for research

More studies are urgently needed to make meaningful comparisons between each alternative exercise mode and the current standard of supervised treadmill walking.

CHARACTERISTICS OF STUDIES

Characteristics of included studies

McDermott 2009

Methods	RCT
Participants	1009 participants with asymptomatic and symptomatic PAOD were assessed for eligibility; 156 participants were randomised; after contacting authors, 33 randomised participants were affected by intermittent claudication
Interventions	Group 1: 24 weeks of supervised treadmill walking Group 2: 24 weeks of supervised lower-extremity resistance training Group 3 (control group): 11 nutritional information sessions over 6 months
Outcomes	6-minute walk test, Short physical performance battery, Brachial artery flow-mediated dilation, Physical activity (accelerometry), Maximum treadmill walking time, Treadmill time to onset of leg symptoms, SF-36 physical functioning score, Walking Impairment Questionnaire, Knee extension isometric strength/power, Plantarflexion isometric strength
Notes	We contacted the authors for more information regarding study results for the subgroup of participants with intermittent claudication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised by computer using a randomly permuted block method. Randomisation was stratified by the presence versus absence of intermittent claudication
Allocation concealment (selection bias)	Low risk	Participants were randomised by computer using a randomly permuted block method
Blinding of participants and personnel (performance bias) All outcomes	Low risk	In all of the included studies, participants and direct personnel could not be blinded to the intervention (exercise). For this reason, bias could be introduced. However, since all studies experienced the same limitation, we considered the risk of bias to be low for all studies
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Examiners were blinded to participant group assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat analyses were performed for dropouts. Analyses were repeated using multiple imputation for persons who died or dropped out before completing 6-month follow-up testing. However, because of the study setting, it is not clear which participants with intermittent claudication (instead of asymptomatic peripheral arterial disease) dropped out. The paper stated that missing data at follow-up were more common in more frail participants. On the other hand, the authors performed a sensitivity analysis and showed that the missing data were not likely to have significantly altered the findings
Selective reporting (reporting bias)	Low risk	All relevant outcomes were described. Although not all secondary outcomes were mentioned in the trial registration, all outcomes mentioned in the study protocol were reported in the final draft of the paper
Other bias	Unclear risk	Because of the study setting (the study included participants with asymptomatic or symptomatic peripheral arterial disease), the baseline characteristics of the subgroup of participants with intermittent claudication were not described. We identified no other forms of bias

Regensteiner 1996

Methods	RCT
Participants	44 participants evaluated: 15 were excluded before randomisation; 29 participants were enrolled and randomised
Interventions	Group 1: 12 weeks of supervised walking exercise. Secondly, 12 weeks of additional supervised walking exercise Group 2: 12 weeks of strength training. Secondly, 12 weeks of additional supervised walking exercise Group 3 (control group): no treatment for 12 weeks. Secondly, 12 weeks of a combination of supervised walking exercise and strength training
Outcomes	Peak treadmill walking time, Ankle brachial indices (in rest and after exercise), Walking Impairment Questionnaire score, Physical Activity Recall score, Medical Outcomes Study Questionnaire score, Vitalog activity monitor
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	In all of the included studies, participants and direct personnel could not be blinded to the intervention (exercise). For this reason, bias could be introduced. However, since all studies experienced the same limitation, we considered the risk of bias to be low for all studies
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	To minimise the potential for bias in the self-evaluation of walking ability and functional status, questionnaires were administered before the treadmill test. Thus, participants' questionnaire responses were not influenced by their treadmill exercise performance. In addition, the interviewer and participant were blinded to previous questionnaire scores. The paper did not describe whether examiners were blinded to participant group assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants in the control group were not available for follow-up at the 12-week evaluation. They were excluded from further analysis. In the supervised walking and strength training group, no missing outcome data were described
Selective reporting (reporting bias)	Low risk	All relevant outcomes were described
Other bias	Low risk	No significant differences in baseline characteristics were found. We identified no other forms of bias

Ritta-Dias 2010

Methods	RCT
Participants	34 participants were randomised; 4 participants did not complete training; 30 participants completed the study protocol (15 per group)
Interventions	Group 1: 12 weeks of supervised treadmill exercise Group 2: 12 weeks of strength training
Outcomes	Initial claudication distance, Total walking distance, Peak VO_2, VO_2 at the first stage of treadmill test, Ischaemic window, Leg strength with lower ABI, Leg strength with higher ABI
Notes	No intention-to-treat analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by computer random number generation
Allocation concealment (selection bias)	Low risk	Randomisation was performed by computer random number generation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	In all of the included studies, participants and direct personnel could not be blinded to the intervention (exercise). For this reason, bias could be introduced. However, since all studies experienced the same limitation, we considered the risk of bias to be low for all studies
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants were evaluated at baseline (pre-training) and after 12 weeks of exercise training (post-training) by a physician who was blinded to the exercise programme performed by participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 participants (2 in the strength training groups and 2 in the walking exercise groups) did not complete the training programmes for the following reasons: inguinal hernia (n = 1), gastrointestinal infection (n =1), ongoing treatment for lung cancer (n = 1), and diagnosis of abdominal aneurysm (n = 1) Although no intention-to-threat analysis was performed, reasons for missing data were plausible and well distributed among intervention groups
Selective reporting (reporting bias)	Low risk	All relevant outcomes were described in the study results
Other bias	Low risk	No significant differences in baseline characteristics were found. We identified no other forms of bias

Sanderson 2006

Methods	RCT
Participants	694 participants were assessed for eligibility; 43 participants were randomised
Interventions	Group 1: 6 weeks of supervised treadmill walking Group 2: 6 weeks of supervised cycling Group 3 (control group): cardiovascular risk management and exercise advice
Outcomes	Maximum walking time, Pain-free walking time, Maximum cycling time, Pain-free cycling time, Submaximal and peak heart rate/VO_2/respiratory exchange ratio/minute ventilation
Notes	We contacted the authors and received relevant outcome data, which were not clearly described in the paper

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A closed-envelope system was used to randomise participants from the stratified groups to a control group, a cycle-training group, or a treadmill training group
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	In all of the included studies, participants and direct personnel could not be blinded to the intervention (exercise). For this reason, bias could be introduced. However, since all studies experienced the same limitation, we considered the risk of bias to be low for all studies
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessment was described
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant in the treadmill training group withdrew after 1 week of training. The baseline data have been omitted
Selective reporting (reporting bias)	Low risk	Relevant outcome data for this review (maximum and pain-free walking time) were only presented in a figure; no numerical data were given. However, after contacting the authors, we collected these data
Other bias	Low risk	No significant differences in baseline characteristics were found. We identified no other forms of bias

Treat-Jacobson 2009

Methods	RCT
Participants	102 participants were assessed for eligibility; 45 participants were randomised
Interventions	Group 1: 12 weeks of arm ergometry Group 2: 12 weeks of supervised treadmill walking Group 3: 12 weeks of a combination of arm ergometry and supervised treadmill walking Group 4 (control group): usual care (cardiovascular management and exercise advice)
Outcomes	Maximum walking distance, Pain-free walking distance, Resting ankle-brachial index/heart rate/blood pressure, Functional capacity (Peak VO_2)
Notes	The study paper mentioned only the change in walking distances. To retrieve all data, we contacted the authors and received the exact outcome data at follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible participants were randomised by simple randomisation tables to 1 of the 4 study groups
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	In all of the included studies, participants and direct personnel could not be blinded to the intervention (exercise). For this reason, bias could be introduced. However, since all studies experienced the same limitation, we considered the risk of bias to be low for all studies
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The physician supervising the treadmill tests was blinded to treatment group assignment. However, other staff assisting with testing were not blinded. To mitigate for this limitation, care was taken to ensure standardisation of exercise-testing protocols
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete outcome data are well described and equally distributed among intervention groups. 4 of the 45 participants withdrew from the study before completing exercise training (2 participants in the arm- ergometry group and 2 participants in the treadmill walking group). Therefore, only 41 participants completed the 12-week follow-up. 31 participants completed the 24-week follow-up
Selective reporting (reporting bias)	Low risk	All relevant outcomes were described in the study results
Other bias	Low risk	No significant differences in baseline characteristics were found. We identified no other forms of bias

ABI: ankle brachial index.

RCT: randomised controlled trial.

Characteristics of excluded studies

Study	Reason for exclusion
Collins 2012	Alternative exercise regime
Dedes 2010	Meeting poster; no journal article available
Gardner 2011	Commentary on other journal article; not a RCT
Jones 1996	Outcome measures unclearly described; no information from authors
Kim 2006	Commentary on other journal article; not a RCT
Kuwabara 2010	Meeting poster; no article available
Nawaz 2001	No intervention group with adequate supervised walking therapy; no correct outcome measures
Ornelas 2011	Meeting poster; no article available
Parr 2009	No intervention group with adequate supervised walking therapy
Roitman 2010	Editorial; not a RCT
Saxton 2008	No control group with adequate SET, no correct outcome measures
Saxton 2011	No control group with adequate SET, no correct outcome measures (MWD assessed by shuttle-walk test instead of protocolised treadmill test)
Tebbutt 2011	No control group with adequate SET
Treat-Jacobson 2011	No correct outcome measures
Treat-Jacobson 2012	Meeting poster; no journal article available; no control group with adequate SET
Walker 2000	No control group with adequate SET; no correct outcome measures (no treadmill test)
Wang 2008	No control group with SET
Zwierska 2005	No control group with adequate SET

MWD: maximum walking distance.

RCT: randomised controlled trial.

SET: supervised exercise therapy.

Characteristics of ongoing studies

NCT00895635

Trial name or title	Exercise training to reduce claudication: arm ergometry versus treadmill walking. Evaluating two exercise training programs to reduce leg pain in people with peripheral arterial disease (The EXERT study)
Methods	Allocation: randomised End point classification: efficacy study Intervention model: parallel assignment Masking: single-blind (outcomes assessor) Primary purpose: treatment
Participants	150 participants of both gender, 18 to 90 years old, who comply with the inclusion and exclusion criteria Inclusion criteria • Has lifestyle-limiting claudication • Able to walk on a treadmill at 2 mph • Able to perform arm-ergometry exercise • Able to complete a 12-week exercise programme Exclusion criteria • Physical activities are limited for reasons other than claudication • Uncontrolled high blood pressure • Uncontrolled diabetes • Unstable coronary heart disease • Ischaemic rest pain or tissue loss • Recent (in the 3 months before study entry) coronary or peripheral revascularisation
Interventions	Study arms: Experimental: treadmill exercise training Participants will take part in a 12-week supervised treadmill exercise training programme Intervention: behavioural: treadmill exercise training Experimental: arm-ergometry exercise training Participants will take part in a 12-week supervised aerobic arm-ergometry exercise training programme Intervention: behavioural: arm-ergometry exercise training Active comparator: usual care control group Participants will receive usual care for PAD from their doctor Intervention: behavioural: usual care
Outcomes	Primary outcome measures • Maximal walking distance (time-frame: measured at baseline and weeks 6, 12, and 24) • Pain-free walking distance (time-frame: measured at baseline and weeks 6, 12, and 24) • Secondary outcome measures • Limb blood flow (time-frame: measured at baseline and weeks 6, 12, and 24) • Cardiovascular function (time-frame: measured at baseline and weeks 6, 12, and 24) • Quality of life (time-frame: measured at baseline and weeks 6, 12, and 24)
Starting date	January 2009
Contact information	Contact: Diane J Treat-Jacobson, PhD, RN612-624-7613treat001@umn.edu Contact: Laura N Kirk, PhD, RN612-626-4687kirk0013@umn.edu
Notes	-

mph: miles per hour.

PAD: peripheral arterial disease.

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Chapter 4

Endovascular revascularisation versus conservative management for intermittent claudication

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Cochrane Database of Systematic Reviews 2018, Mar 8; 3

ABSTRACT

Background

Intermittent claudication is the classic symptomatic form of peripheral arterial disease affecting an estimated 4.5% of the general population aged 40 years and older. Patients with intermittent claudication experience limitations in their ambulatory function resulting in functional disability and impaired quality of life (QoL). Endovascular revascularisation has been proposed as an effective treatment for patients with intermittent claudication and is increasingly performed.

Objectives

The main objective of this systematic review is to summarise the (added) effects of endovascular revascularisation on functional performance and QoL in the management of intermittent claudication.

Search methods

For this review the Cochrane Vascular Information Specialist (CIS) searched the Specialised Register (February 2017) and the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 1). The CIS also searched trials registries for details of ongoing and unpublished studies.

Selection criteria

Randomised controlled trials (RCTs) comparing endovascular revascularisation (± conservative therapy consisting of supervised exercise or pharmacotherapy) versus no therapy (except advice to exercise) or versus conservative therapy (i.e. supervised exercise or pharmacotherapy) for intermittent claudication.

Data collection and analysis

Two review authors independently selected studies, extracted data, and assessed the methodological quality of studies. Given large variation in the intensity of treadmill protocols to assess walking distances and use of different instruments to assess QoL, we used standardised mean difference (SMD) as treatment effect for continuous outcome measures to allow standardisation of results and calculated the pooled SMD as treatment effect size in meta-analyses. We interpreted pooled SMDs using rules of thumb (< 0.40 = small, 0.40 to 0.70 = moderate, > 0.70 = large effect) according to the Cochrane Handbook for Systematic Reviews of Interventions. We calculated the pooled treatment effect size for dichotomous outcome measures as odds ratio (OR).

Main results

We identified ten RCTs (1087 participants) assessing the value of endovascular revascularisation in the management of intermittent claudication. These RCTs compared endovascular revascularisation versus no specific treatment for intermittent claudication or conservative therapy or a combination therapy of endovascular revascularisation plus conservative therapy versus conservative therapy alone. In the included studies, conservative treatment consisted of supervised exercise or pharmacotherapy with cilostazol 100 mg twice daily. The quality of the evidence ranged from low to high and was downgraded mainly owing to substantial heterogeneity and small sample size.

Comparing endovascular revascularisation versus no specific treatment for intermittent claudication (except advice to exercise) showed a moderate effect on maximum walking distance (MWD) (SMD 0.70, 95% confidence interval (CI) 0.31 to 1.08; 3 studies; 125 participants; moderate-quality evidence) and a large effect on pain-free walking distance (PFWD) (SMD 1.29, 95% CI 0.90 to 1.68; 3 studies; 125 participants; moderate-quality evidence) in favour of endovascular revascularisation. Long-term follow-up in two studies (103 participants) showed no clear differences between groups for MWD (SMD 0.67, 95% CI -0.30 to 1.63; low-quality evidence) and PFWD (SMD 0.69, 95% CI -0.45 to 1.82; low-quality evidence). The number of secondary invasive interventions (OR 0.81, 95% CI 0.12 to 5.28; 2 studies; 118 participants; moderate-quality evidence) was also not different between groups. One study reported no differences in disease-specific QoL after two years.

Data from five studies (n = 345) comparing endovascular revascularisation versus supervised exercise showed no clear differences between groups for MWD (SMD -0.42, 95% CI -0.87 to 0.04; moderate-quality evidence) and PFWD (SMD -0.05, 95% CI - 0.38 to 0.29; moderate-quality evidence). Similarliy, long-term follow-up in three studies (184 participants) revealed no differences between groups for MWD (SMD -0.02, 95% CI -0.36 to 0.32; moderate-quality evidence) and PFWD (SMD 0.11, 95% CI -0.26 to 0.48; moderate-quality evidence). In addition, high-quality evidence showed no difference between groups in the number of secondary invasive interventions (OR 1.40, 95% CI 0.70 to 2.80; 4 studies; 395 participants) and in disease-specific QoL (SMD 0.18, 95% CI -0.04 to 0.41; 3 studies; 301 participants).

Comparing endovascular revascularisation plus supervised exercise versus supervised exercise alone showed no clear differences between groups for MWD (SMD 0.26, 95% CI -0.13 to 0.64; 3 studies; 432 participants; moderate-quality evidence) and PFWD (SMD 0.33, 95% CI -0.26 to 0.93; 2 studies; 305 participants; moderate-quality evidence). Long-term follow-up in one study (106 participants) revealed a large effect on MWD (SMD 1.18, 95% CI 0.65 to 1.70; low-quality evidence) in favour of the combination therapy. Reports indicate that disease-specific QoL was comparable between groups (SMD 0.25, 95% CI -0.05 to 0.56; 2 studies; 330 participants; moderate-quality evidence) and that the number of secondary invasive interventions (OR 0.27, 95% CI 0.13 to 0.55; 3 studies; 457 participants; high-quality evidence) was lower following combination therapy.

Two studies comparing endovascular revascularisation plus pharmacotherapy (cilostazol) versus pharmacotherapy alone provided data showing a small effect on MWD (SMD 0.38, 95% CI 0.08 to 0.68; 186 participants; high-quality evidence), a moderate effect on PFWD (SMD 0.63, 95% CI 0.33 to 0.94; 186 participants; high-quality evidence), and a moderate effect on disease-specific QoL (SMD 0.59, 95% CI 0.27 to 0.91; 170 participants; high-quality evidence) in favour of combination therapy. Long-term follow-up in one study (47 participants) revealed a moderate effect on MWD (SMD 0.72, 95% CI 0.09 to 1.36; P = 0.02) in favour of combination therapy and no clear differences in PFWD between groups (SMD 0.54, 95% CI -0.08 to 1.17; P = 0.09). The number of secondary invasive interventions was comparable between groups (OR 1.83, 95% CI 0.49 to 6.83; 199 participants; high-quality evidence).

Authors' conclusions

In the management of patients with intermittent claudication, endovascular revascularisation does not provide significant benefits compared with supervised exercise alone in terms of improvement in functional performance or QoL. Although the number of studies is small and clinical heterogeneity underlines the need for more homogenous and larger studies, evidence suggests that a synergetic effect may occur when endovascular revascularisation is combined with a conservative therapy of supervised exercise or pharmacotherapy with cilostazol: the combination therapy seems to result in greater improvements in functional performance and in QoL scores than are seen with conservative therapy alone.

BACKGROUND

Description of the condition

Lower extremity peripheral arterial disease (PAD) is a manifestation of systemic atherosclerosis and is considered a major cause of morbidity in the elderly population.[1] Intermittent claudication, the most frequent symptomatic presentation of PAD, is defined as discomfort in the legs with exertion that resolves after a short period of rest. Intermittent claudication is highly prevalent in Western countries, affecting an estimated 4.5% of the general population aged 40 years and older[2], and is likely to become more prevalent given the ageing population. Although individuals with claudication have a relatively benign prognosis for their affected limb, with a major amputation risk of only 1% to 3% over a five-year period[2], their functional performance deteriorates significantly, and this results in a sedentary lifestyle[3], along with severely limited quality of life (QoL)[4,5]. Additionally, claudication is associated with significantly increased risk of all-cause and cardiovascular mortality independent of other atherosclerotic risk factors[6,7].

Description of the intervention

Treatment of intermittent claudication consists of multiple components that focus on preventing future cardiovascular events and related mortality, as well as on ameliorating claudication symptoms. Pharmacotherapy and exercise therapy are established as effective first-line conservative treatment options, improving walking distance and QoL in patients with claudication[8-10]. However, in clinical practice, endovascular revascularisation is considered an attractive first-line alternative owing to its immediate effect and relatively low complication rates. Although both exercise therapy and endovascular revascularisation are effective in improving symptoms, it should be noted that neither therapy completely removes the disability in most patients[11]. In 1964 Dotter and Judkins first performed and reported on endovascular revascularisation of the lower extremities[12]. Since that time, important technological developments including the introduction of balloon angioplasty and drugeluting balloons and stents has advanced endovascular revascularisation as a safe and durable treatment option for management of symptomatic PAD. Endovascular revascularisation is performed with the patient under local anaesthesia, and access to the stenosed or occluded peripheral artery is usually gained via the common femoral artery. Subsequently, an angioplasty procedure that involves (balloon) dilatation of a stenosed peripheral artery or recanalisation of an occluded peripheral artery is performed. This is followed by stent placement if suboptimal results are achieved with angioplasty only[13]. After a successful endovascular revascularisation procedure, patients are usually ambulatory on the same day and are able to resume all normal activities within a few days. Furthermore, procedure-related morbidity and mortality is reported to be lower than 0.5%[14], and haematoma at the puncture site and embolization are reported as the most common procedure related complications.

How the intervention might work

After successful revascularisation, whereby the obstruction or occlusion in the peripheral artery is resolved and improved blood flow is restored, arterial perfusion in the lower extremity improves significantly. This is confirmed by significant improvement in the ankle brachial index (ABI) immediately after the procedure. Randomised controlled trials (RCTs) have demonstrated the effectiveness of endovascular revascularisation in improving functional performance (i.e. walking distance and ABI) and QoL in individuals with intermittent claudication[16-18].

Why it is important to do this review

Intermittent claudication is a serious lifestyle-limiting symptom of PAD that has a large impact on patients' functional performance and QoL. Conservative treatment strategies, including pharma-cotherapy and supervised exercise therapy, are recommended as first-line therapy for claudication[2,19]. Yet their value in clinical practice remains uncertain, as medical drugs for claudication (e.g. cilostazol, pentoxifylline, naftidro-furyl) have limited effects[20], and supervised exercise programmes are underutilised in clinical practice owing to limited access[21], reimbursement issues, and poor patient compliance[8]. Consequently, researchers are noting an enormous increase in the use of endovascular revascularisation as first-line therapy for claudication[22,23]. Nonetheless, the (long-term) effectiveness of endovascular revascularisation as first-line therapy for intermittent claudication remains debatable. The only Cochrane review on this topic, which included two studies with a total of 98 participants comparing angioplasty versus non-surgical therapy, concluded that limited data suggest short-term benefit in favour of angioplasty[24]. Since the last update of this review, new randomised trials assessing the efficacy of endovascular revascularisation compared with conservative treatment have published their findings. Furthermore, new clinical studies have investigated the combination of exercise therapy and endovascular revascularisation, which takes advantage of immediate short-term effects of revascularisation and long-term benefits of exercise therapy[17,25,26]. However, clinical studies rarely have sufficient power to detect intervention effectiveness in terms of clinical outcomes such as functional performance, QoL, or cardiovascular events. Therefore, a Cochrane review identifying these studies systematically, evaluating their results independently, and updating results when new studies are published is important for reducing uncertainty about the (added) value of endovascular revascularisation in the management of patients with intermittent claudication.

Objectives

The main objective of this systematic review is to summarise the (added) effects of endovascular revascularisation on functional performance and QoL in the management of intermittent claudication.

METHODS

Criteria for considering studies for this review

Types of studies

We systematically searched for and included only RCTs with parallel-group design comparing outcomes of endovascular revascularisation (with and without conservative therapy) versus no specific therapy or versus conservative therapy (i.e. supervised exercise or pharmacotherapy) in patients with intermittent claudication.

We included only studies comparing endovascular revascularisation (± conservative therapy) versus conservative therapies or no specific therapy for intermittent claudication. We excluded studies providing any kind of surgical revascularisation in the comparison group. We also excluded studies comparing different types of endovascular revascularisation procedures (e.g. angioplasty vs angioplasty plus stenting).

Types of participants

Patients with stable intermittent claudication, according to Rutherford category 1 to 3 or Fontaine stage II[2], who are eligible for both endovascular revascularisation and conservative management.

Types of interventions

In the intervention group, participants underwent endovascular revascularisation (± conservative therapy). We considered all percutaneous endovascular revascularisation procedures including angioplasty (any type, e.g. balloon, laser) or angioplasty plus (selective) stent placement (any type of stent including drugeluting) for atherosclerotic lesion(s) in arteries of the lower extremity. In the comparison group, participants received only conservative therapy or no specific therapy for intermittent claudication. Conservative therapy included specific pharmacotherapy for intermittent claudication (e.g. cilostazol, pentoxifylline, naftidrofuryl) or supervised exercise therapy.

We considered the following comparisons.

- Endovascular revascularisation versus no specific therapy for intermittent claudication except verbal advice to exercise.
- Endovascular revascularisation versus conservative therapy (pharmacotherapy or supervised exercise).
- Endovascular revascularisation plus conservative therapy versus conservative therapy.

When investigators provided cardiovascular risk factor modification (e.g. lipid control, hypertension control, anti-smoking advice) in the intervention group, it was also provided equally in the comparison group.

Types of outcome measures

Primary outcomes

- Functional performance outcomes
  - Maximum walking distance (MWD), as assessed on a treadmill
  - Pain-free walking distance (PFWD), as assessed on a treadmill
- Secondary invasive interventions during follow-up
  - Endovascular or surgical revascularisation
  - Amputation

Secondary outcomes

- Quality of life, including health-related (general and disease-specific) QoL measures
- Procedure related complications (e.g. local haematoma, artery dissection, embolisation)
- Cardiovascular events (e.g. myocardial infarction, stroke)
- Functional performance measures not assessed on a treadmill (e.g. six-minute walk test, selfreported walking distance)
- Mortality

Search methods for identification of studies

We applied no language restrictions.

Electronic searches

The Cochrane Vascular Information Specialist (CIS) searched the following databases for relevant trials.

- Cochrane Vascular Specialised Register (21 February 2017).
- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 1) via the Cochrane Register of Studies Online.

The Cochrane Vascular Specialised Register is maintained by the CIS and is constructed from weekly electronic searches of MEDLINE Ovid, Embase Ovid, the Cumulative Index to Nurs-ing and Allied Health Literature (CINAHL), and the Allied and Complementary Medicine Database (AMED), and through handsearching of relevant journals. We have provided the full list of databases, journals, and conference proceedings searched, as well as the search strategies used, in the Specialised Register section of the Cochrane Vascular Module in the Cochrane Library (www.cochranelibrary.com).

The CIS also searched the following trials registries for details of ongoing and unpublished studies (21 February 2017).

- ClinicalTrials.gov (www.clinicaltrials.gov).
- World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch).
- International Standard Randomised Controlled Trial Number (ISRCTN) Register (www.isrctn.com/)

Searching other resources

We handsearched the reference lists of all eligible studies for additional relevant studies.

Data collection and analysis

Selection of studies

Two review authors (FF and HF) initially selected identified studies independently upon reviewing titles and abstracts. Final selection was based on full-text evaluation of selected studies by the two review authors (FF and HF) working independently. Review authors discussed and resolved disagreements by consensus. If no consensus was reached, a third review author (MH) acted as arbiter.

Data extraction and management

Two review authors (FF and HF) extracted all required data from each included study using a standardised form, which consisted of (1) study characteristics including study design, year of publication, study location, source of funding, sample size estimation, follow-up, and applied inclusion and exclusion criteria; (2) participant baseline characteristics including number of participants in each group, mean age, and gender distribution; (3) intervention characteristics, compliance, and losses to follow-up; and (4) primary and secondary outcomes, as specified under Types of outcome measures.

Assessment of risk of bias in included studies

Two review authors (FF and HF) independently assessed the methodological quality of included studies, as described in the Cochrane Handbook for Systematic Reviews of Interventions[27], for the following domains.

- Randomisation and sequence generation.
- Allocation concealment.
- Blinding (of participants, personnel, and outcome assessors).
- Incomplete outcome data.
- Selective outcome reporting.
- Publication and other sources of bias.

For each of the six domains, we assessed risk of bias as 'low' or 'high', or as 'unclear' when available information was insufficient to permit judgement on risk of bias.

Measures of treatment effect

To analyse the treatment effect of endovascular revascularisation in each study for continuous outcome measures, including the primary outcomes MWD and PFWD and the secondary outcome QoL, we extracted the value of each outcome measure at different time points (6 to 12 months and over the long term) for both intervention and comparison groups. For studies reporting treadmill walking time instead of treadmill walking distance, we calculated MWD and PFWD by converting walking time to distance using the reported treadmill speed.

Given large variation in the intensity of treadmill protocols to assess MWD and PFWD and use of different instruments to assess QoL in each study, we used standardised mean differences (SMDs) and 95% confidence intervals (CIs) as treatment effects for these outcome measures to allow standardisation of results to a uniform scale. We calculated the pooled SMD, which is the pooled treatment difference between groups normalised to the pooled standard deviation of the difference, as treatment effect size in meta-analysis. We interpreted pooled SMDs using rules of thumb (< 0.40 = small effect, 0.40 to 0.70 = moderate effect, > 0.70 = large effect), as described in the Cochrane Handbook for Systematic Reviews of Interventions[27].

For dichotomous outcome measures, including secondary invasive intervention, procedurerelated complications, cardiovascular events, or death during follow-up in each treatment group, we calculated odds ratios (ORs) and corresponding 95% CIs as measures of treatment effect, if appropriate.

Unit of analysis issues

In this systematic review, we included only RCTs with parallel-group design. The unit of randomisation was the individual participant.

Dealing with missing data

In the case of missing data on dropouts, withdrawals, and outcome measures, we contacted the original investigators and requested data when appropriate. If studies reported medians and interquartile ranges (IQRs) as measures of variance for walking distance, we converted these values to means and standard deviations (SDs), assuming a normal distribution for walking distance so we could include these studies in the meta-analysis. We tested this assumption by performing sensitivity analysis. Missing data indicating the variance of outcome measures (e.g. SD, CI) were to be expected, in which case we used the methods described in the Cochrane Handbook for Systematic Reviews of Interventions[27] to calculate or impute these data.

Assessment of heterogeneity

We assessed the statistical heterogeneity of outcome measures by calculating the Q statistics and the I^2 statistic, as suggested in the Cochrane Handbook for Systematic Reviews of Interventions[27].

Assessment of reporting biases

We created a funnel plot providing enough studies were included for each outcome measure, with effect size on the x-axis and precision on the y-axis to investigate possible publication bias.

Data synthesis

We calculated treatment effects using corresponding 95% CIs for both continuous and dichotomous outcome measures by applying random-effects models. Subsequently, when appropriate, we calculated the pooled treatment effect size from the random-effects model meta-analysis and presented this as a forest plot for each outcome measure separately. We considered two-sided $P \leq 0.05$ as statistically significant and performed all data analyses using RevMan 5.3[28], when appropriate.

Subgroup analysis and investigation of heterogeneity

We considered the following subgroup analyses for primary outcomes, provided we identified enough studies for each subgroup.

- Types of endovascular revascularisation procedures (e.g. angioplasty, angioplasty plus stenting).
- Types of pharmacotherapy (e.g. cilostazol, pentoxifylline, naftidrofuryl).
- Types of exercise therapy (i.e. supervised or non-supervised programme).
- Separate segments (i.e. aortoiliac, femoropopliteal, or combined).

Sensitivity analysis

We planned to perform several sensitivity yses provided we could include enough studies in the meta-analysis. We assessed individual study effects by excluding each study separately from the analysis to examine whether exclusion of an individual study would significantly change the results. Likewise we planned to perform sensitivity analysis on the methodological quality of studies by removing studies with high risk of (methodological) bias to observe whether excluding these studies would significantly change the results. In addition, in performing sensitivity analyses, we removed from meta-analysis studies reporting only median and IQR walking distances, to observe whether excluding these studies would significantly change the results.

RESULTS

Results of the search

See Figure 1.

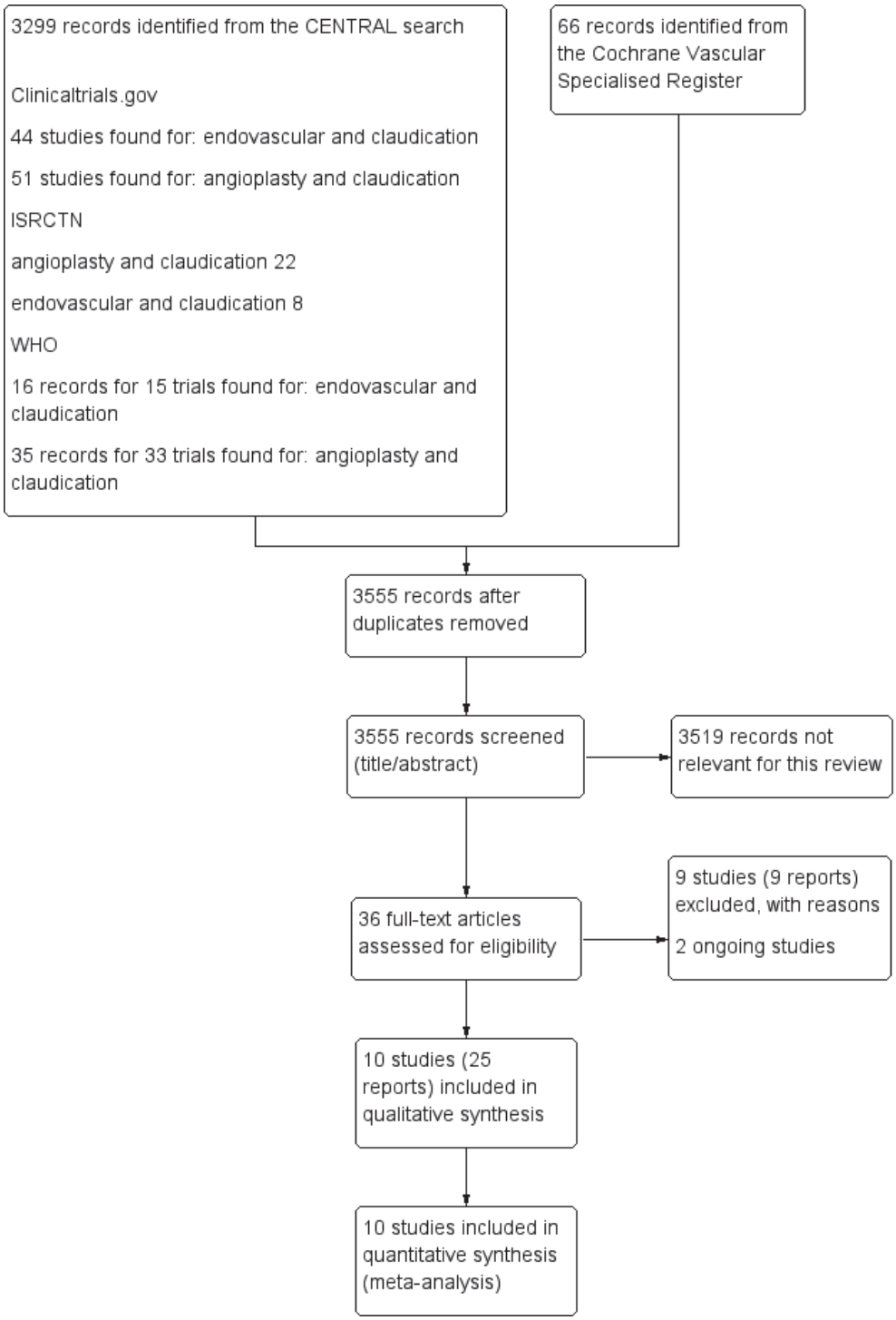


Figure 1. Study flow diagram.

Included studies

After fulltext assessment, we included in this systematic review ten studies described in 25 publications assessing the value of endovascular revascularisation in the management of patients with intermittent claudication[25,26,29-36]. Results from all included studies had been published in peer-reviewed journals. Greenhalgh reported two separate trials that included participants in one of the two trials on the basis of lesion site (femoropopliteal or aortoiliac) and consequently randomised them to one of two treatment arms[26]. Nordanstig randomised participants to a non-invasive treatment group or an invasive treatment group that included both open surgical or endovascular revascularisation procedures at baseline[33]. To include this study in this systematic review, we sought and received from study authors outcome data from the subgroup of participants undergoing endovascular revascularisation.

All included studies used a parallel-group design, with seven studies randomising between two arms comparing endovascular revascularisation versus cardiovascular risk factor management alone (i.e. no specific therapy for intermittent claudication except verbal advice to exercise)[34,36], endovascular revascularisation versus supervised exercise[29,35], endovascular revascularisation plus supervised exercise versus supervised exercise alone[26,26], or endovascular revascularisation plus cilostazol 100 mg twice daily versus cilostazol 100 mg twice daily[33]. Three studies had three arms comparing endovascular revascularisation versus cardiovascular risk factor management alone (i.e. no specific therapy for claudication) versus supervised exercise[30], endovascular revascularisation versus supervised exercise versus endovascular revascularisation plus supervised exercise[31], or endovascular revascularisation plus cilostazol 100 mg twice daily versus cilostazol 100 mg twice daily alone versus supervised exercise plus cilostazol 100 mg twice daily[32]. All studies were conducted in Europe (n = 9) and North America (n = 1) and recruited a total number of 1087 participants, ranging from 23 to 212 participants in each individual study. All participants had stable intermittent claudication, and most were recruited from outpatient clinics in university and non-university hospitals. Seven out of ten studies included participants with claudication due to both aortoiliac and femoropopliteal disease[25,26,29,33-36], two studies included only participants with femoropopliteal disease[30,31], and one study included only participants with aortoiliac disease[32]. Most included participants were male (61%) with an average age ranging from 61 to 70 years. All studies except one study[29] reported to a greater or lesser extent some sort of cardiovascular risk factor management (e.g. providing smoking cessation advice, promoting physical activity, providing dietary advice or medical therapy for cardiovascular risk factors) offered to participants in each treatment arm at the start of the study, in addition to their specific treatment for intermittent claudication, if applicable. In all studies, endovascular revascularisation consisted of balloon angioplasty; in four studies, investigators placed a stent if initial balloon angioplasty results were unsatisfactory (selective stenting)[25,26,34,35]; in one study always placed a stent after initial balloon angioplasty (primary stenting)[32]; in one

study always placed a stent in the aortoiliac segment (primary stenting) but placed a stent in the femoropopliteal segment only if angioplasty results were unsatisfactory (selective stenting)[33]; and four studies placed no stent and performed only balloon angioplasty (no stenting)[29-31,36]. In studies comparing endovascular revascularisation (± conservative therapy) versus conservative therapy for intermittent claudication, conservative treatment consisted of pharmacotherapy with cilostazol 100 mg twice daily in two studies[32,33], comprised a supervised exercise programme in six studies[25,26,29-31,35], and included a combination of cilostazol 100 mg twice daily and supervised exercise in one study[32]. The duration of supervised exercise programmes varied between studies, with most studies offering a programme of 12 weeks with a frequency of two to three sessions per week. In two studies[21,35] the supervised exercise programme continued until six months, and in one study[25] the programme continued up to 12 months, with a declining number of sessions per week after the initial three months of training depending on participants' progress.

Duration of follow-up was homogeneous between studies, with all studies reporting a follow-up duration of at least six months. Eight out of ten studies recorded outcome measures at 12 months' follow-up[25,26,29,31-35]; six studies reported long-term follow-up (longer than 12 months), with follow-up duration of 18 months in one study[32], two years in three studies[31,34,36], six years in one study[29], and seven years in another study[35].

In assessing functional performance measures (i.e. MWD and PFWD), studies used different treadmill protocols with varying treadmill speed and incline and total duration of assessment. Six studies used a 10% incline with treadmill speed between 2.5 km/h and 4 km/h and duration from 5 to 20 minutes[26,29,30,31,34,36]. Two studies used a treadmill protocol with constant speed of 3.2 km/h and graded incline starting at 0%, increasing each two minutes up to a maximum of 10%[25,32]. One study[25] recorded walking distances up to 30 minutes walking on the treadmill, and one study[32] limited this time to 12 minutes. One study[33] used a treadmill protocol with progressively increasing incline (0 to 12%) and speed (1.5 to 4.5 km/h). In the final study[35], the treadmill protocol allowed no graded incline and used a constant speed of 3.5 km/h, permitting participants to walk up to 30 minutes on the treadmill.

Nine out of ten studies reported secondary invasive (endovascular or surgical) interventions during follow-up[25,26,29,31-36], but only four studies explicitly reported data on numbers of amputations[25,32,33,35]. Seven studies reported data on general QoL[25,26,31-35], and six studies presented data on disease-specific QoL[25,31-35], yet the validated questionnaires used to assess QoL were quite heterogeneous between studies.

Excluded studies

After fulltext assessment, we excluded nine studies[37-45]. One study[40] reported outcome measures for participants randomised to open or endovascular revascularisation as one invasive treatment group, and corresponding authors could provide no data for the subgroup of participants receiving endovascular revascularisation. For this reason, we

decided to exclude this study from further evaluation. We excluded another eight studies for not including a non-interventional control group[37-39,44], not providing relevant outcome measures for this systematic review[42,43], not using a formal randomisation process[41], or publishing only abstract data, with study authors not able to provide additional data[45].

Ongoing studies

We classified two studies as ongoing studies[46,47].

Risk of bias in included studies

See Figure 2 and Figure 3 for a graphical summary of risk of bias for the ten included studies.

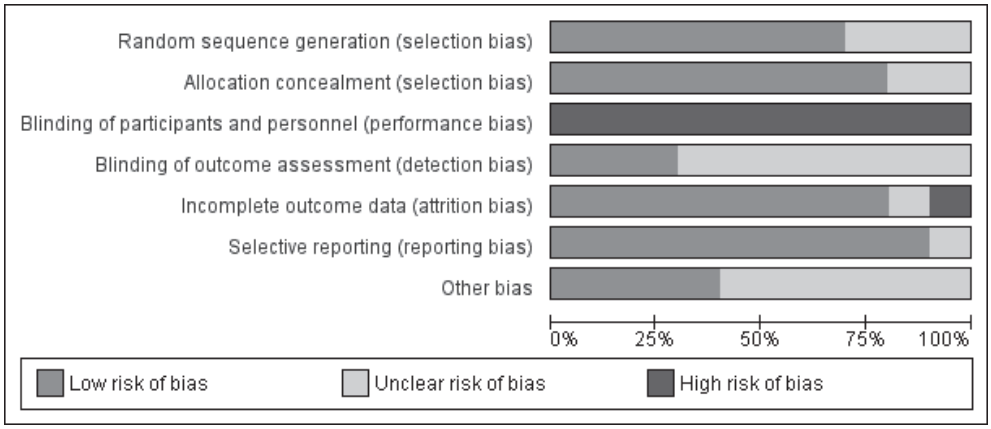


Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

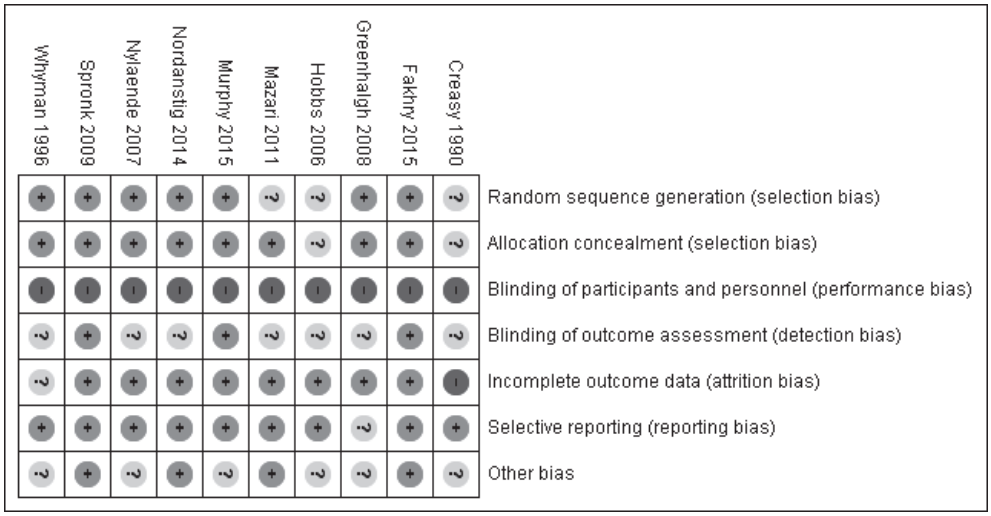


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

Although all ten included studies were RCTs, seven studies described an adequate sequence generation method performed by means of computerised randomisation[25,26,32-36]. In the remaining three studies, researchers randomised participants to one of the treatment arms, yet did not report the exact sequence generation methods used, making adequate judgement of risk of bias impossible[29-31]. Similarly, most studies reported an adequate allocation concealment method[25,26,31-36]. Two studies provided insufficient information to allow a definitive judgement on concealment[29,30].

Blinding

None of the included studies performed blinding of participants and personnel to the allocated treatment, given the nature of endovascular revascularisation as the intervention in each study. This might have introduced performance bias. Detection bias could be avoided by blinding outcome assessors, which three studies adequately performed and described[25,32,35]. The remaining seven studies provided no information on assessor blinding; thus we determined risk of detection bias to be unclear in these studies.

Incomplete outcome data

We determined risk of attrition bias to be low in eight studies, as censoring at 6 to 18 months' follow-up (if applicable) was minimal to moderate, and numbers and reasons for censoring across allocated groups were well balanced[25,26,30-35]. For one study, we assessed risk of attrition bias to be high, as at 12 months' follow-up, a significant number of participants were not available for primary outcome assessment and information provided on distribution and reasons for dropouts was insufficient[29]. One study[36] excluded from analysis participants in the control group who underwent endovascular or open revascularisation, which might have introduced attrition bias, yet information on characteristics of these participants was insufficient to allow judgement for risk of bias.

Selective reporting

In nine studies[25,29-36], investigators reported all relevant and expected outcome measures in the results section. In contrast to maximum walking distance, one study[26] reported no absolute values for pain-free walking distance but rather percentage of participants attaining 200 metres without claudication pain; this was not prespecified in the methods section of this study.

Other potential sources of bias

One study[34] received unrestricted grants from the industry, and two studies[32,36] received partial support from the industry. Owing to slow recruitment in five studies[26,29,30,32,34], investigators were unable to include their prespecified intended sample size based on power calculations for the primary outcome measure of walking distance, and this may have biased the results.

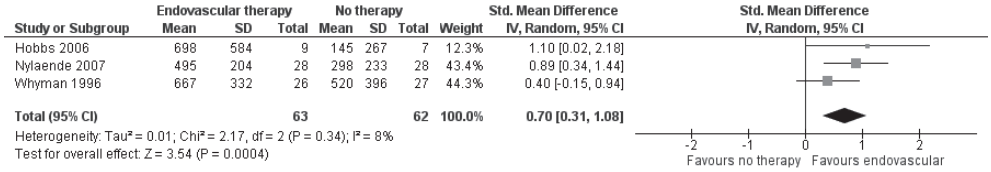
Effects of interventions

Comparison 1. Endovascular revascularisation versus no specific therapy for intermittent claudication except verbal advice to exercise

Data from three studies comparing endovascular revascularisation versus no specific therapy for intermittent claudication (i.e. only cardiovascular risk factor management and verbal advice on ex-ercise) were eligible for inclusion with a total sample size of 134 participants[30,34,36].

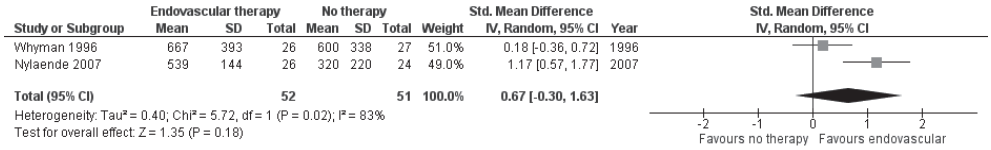
Maximum walking distance

After 6 to 12 months' follow-up, use of a random-effects model and pooled data from three studies (n = 125) showed that participants had higher MWD following endovascular revascularisation than after no specific therapy (Analysis 1.1), with a pooled SMD of 0.70 (95% CI 0.31 to 1.08; P = 0.0004), which is equivalent to a moderate effect in favour of endovascular revascularisation. There was little heterogeneity (I^2 = 8%).



Analysis 1.1. Endovascular revascularisation versus no specific therapy except verbal advice to exercise, outcome: Maximum walking distance.

After long-term follow-up, use of a random-effects model and pooled data from two studies (n = 103) showed no clear differences in MWD between participants following endovascular revascularisation compared with those given no specific therapy (pooled SMD 0.67, 95% CI -0.30 to 1.63; P = 0.18) (Analysis 1.2). Het-erogeneity was substantial (I^2 = 83%).



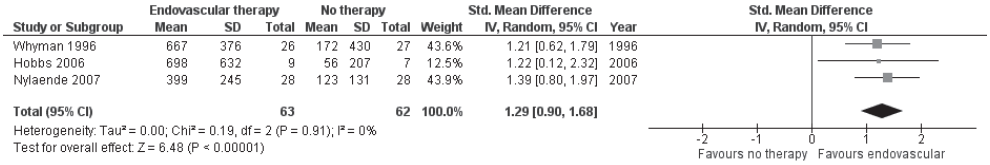
Analysis 1.2. Endovascular revascularisation versus no specific therapy except verbal advice to exercise, outcome: Maximum walking distance (long-term)

Pain-free walking distance

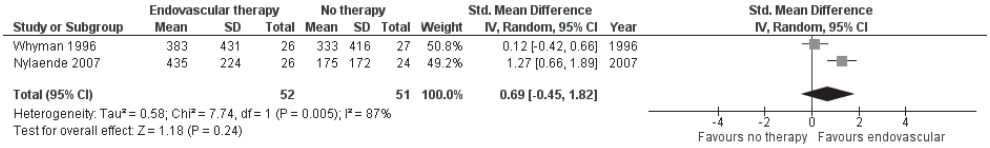
After 6 to 12 months' follow-up, use of a random-effects model and pooled data from three studies (n = 125) showed that participants following endovascular revascularisation

had higher PFWD compared with those given no specific therapy (Analysis 1.3), with a pooled SMD of 1.29 (95% CI 0.90 to 1.68; P < 0.00001); this is equivalent to a large effect in favour of endovascular revascularisation. There was little heterogeneity (I^2 = 0%).

After long-term follow-up, use of a random-effects model and pooled data from two studies (n = 103) showed no clear differences in PFWD between participants following endovascular revascularisation and those given no specific therapy (pooled SMD 0.69, 95% CI -0.45 to 1.82; P = 0.24) (Analysis 1.4). Heterogeneity was considerable (I^2 = 87%).



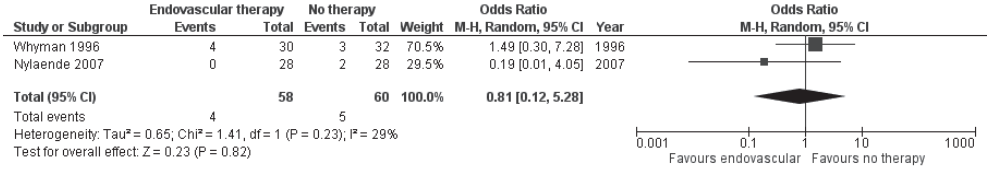
Analysis 1.3. Endovascular revascularisation versus no specific therapy except verbal advice to exercise, outcome: Pain-free walking distance.



Analysis 1.4. Endovascular revascularisation versus no specific therapy except verbal advice to exercise, outcome: Pain-free walking distance (long-term).

Secondary invasive interventions

Two studies reported data on the number of secondary invasive interventions during follow-up. During two-year follow-up, investigators performed a secondary invasive intervention in 4 of 58 participants in the endovascular revascularisation group and in 5 of 60 participants in the no specific therapy group (OR 0.8, 95% CI 0.12 to 5.28; P = 0.82). There was little heterogeneity (I^2 = 29%) (Analysis 1.5).



Analysis 1.5. Endovascular revascularisation versus no specific therapy except verbal advice to exercise, outcome: Secondary invasive interventions.

Quality of life

One study assessed disease-specific QoL using Claudication Scale (CLAU-S) forms and reported no significant differences in all seven domains of the questionnaire between the two study groups after two years of follow-up[34].

Two studies assessed and reported on general health-related QoL. One study used Nottingham Health Profile scores (six domains) to show no significant differences between groups in any domains during follow-up (P > 0.05) [36]. The second study used the Short Form-36 (SF-36) questionnaire to show statistically significant differences between groups in the domains of physical functioning in favour of the no specific therapy group and emotional role functioning in favour of the endovascular revascularisation group[34].

Procedure related complications

None of the three studies provided data on the number of complications following endovascular revascularisation. However, two studies reported that no major procedure-related complications had occurred[34,36].

Cardiovascular events

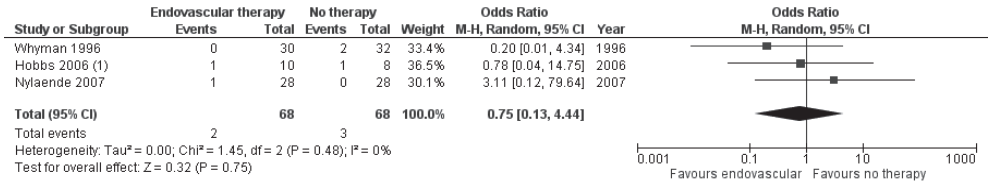
None of the included studies reported data on cardiovascular events during follow-up.

Non-treadmill functional performance measures

Two studies reported non-treadmill functional performance measures. One reported on self-reported walking distance and number of participants with at least 1 kilometre reported walking distance. At two years' fol-low-up for both outcome measures, study authors reported no statistically significant differences between groups (P ≥ 0.70)[36]. After two years' follow-up, the second study reported a higher visual analogue scale (VAS) score (functional status) following endovascular compared with no therapy[34].

Mortality

Three studies reported data on all-cause mortality. During follow-up, 2 of 68 participants in the endovascular revascularisation group and 3 of 68 participants in the no therapy group had died (OR 0.75, 95% CI 0.13 to 4.44; P = 0.75) (Analysis 1.6). There was little heterogeneity (I^2 = 0%).



Analysis 1.6. Endovascular revascularisation versus no specific therapy except verbal advice to exercise, outcome: Mortality.

Subgroup analysis

Given the limited number of studies, we performed no subgroup analysis.

Sensitivity analysis

Given the limited number of studies, we performed no sensitivity analysis.

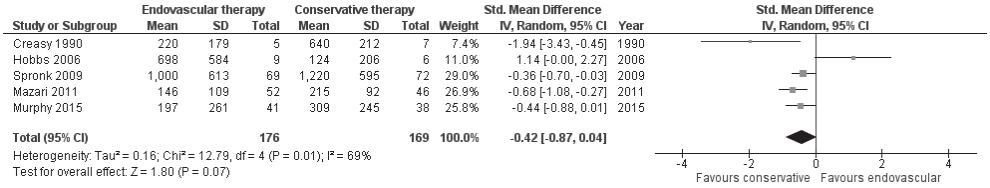
Comparison 2. Endovascular revascularisation versus conservative therapy

Data from five studies comparing endovascular revascularisation versus conservative therapy for intermittent claudication were eligible for inclusion, with a total sample size of 412 participants[29,30-32,35]. The conservative therapy provided in these five studies was supervised exercise therapy.

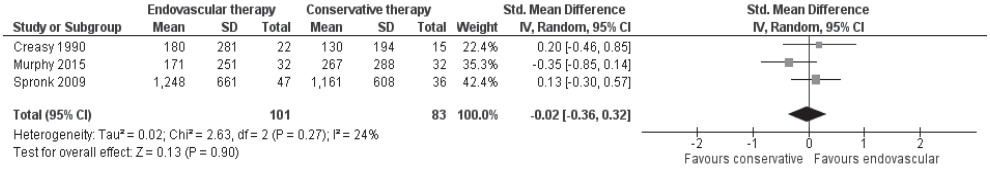
Maximum walking distance

After 6 to 12 months' follow-up, use of a random-effects model and pooled data from five studies (n = 345) showed no clear differences in MWD between participants following endovascular revascularisation and those given supervised exercise therapy (SMD -0.42, 95% CI -0.87 to 0.04; P = 0.07; Analysis 2.1). Heterogeneity was substantial (I^2 = 69%).

After long-term follow-up, use of a random-effects model and pooled data from three studies (n = 184) showed no clear differences in MWD between participants following endovascular revascularisation and those given supervised exercise therapy (pooled SMD -0.02, 95% CI -0.36 to 0.32; P = 0.90; Analysis 2.2). There was little heterogeneity (I^2 = 24%).



Analysis 2.1. Endovasular revascularisation versus conservative therapy in form of supervised exercise, outcome: Maximum walking distance.



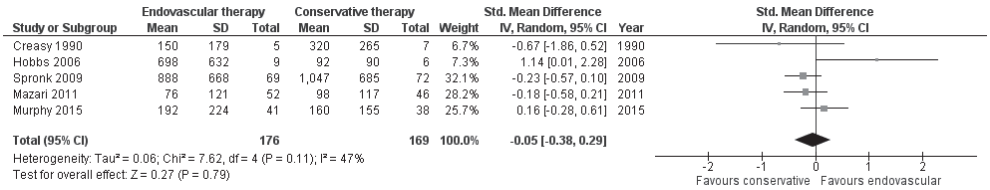
Analysis 2.2. Endovasular revascularisation versus conservative therapy in form of supervised exercise, outcome: Maximum walking distance (long-term).

Pain-free walking distance

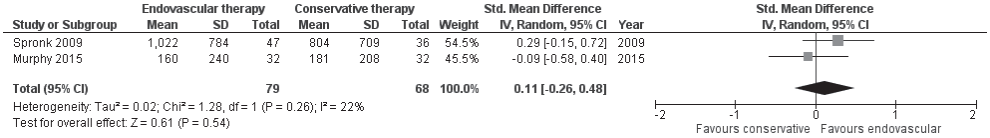
After 6 to 12 months' follow-up, use of a random-effects model and pooled data from five studies (n = 345) showed no clear differences in PFWD between participants following endovascular revascularisation and those given supervised exercise therapy (SMD -0.05, 95% CI -0.38 to 0.29; P = 0.79; Analysis 2.3). Heterogeneity was substantial (I^2 = 53%).

After long-term follow-up, use of a random-effects model and pooled data from two studies (n = 147) showed no clear differences in PFWD between participants following endovascular revascularisation and those given supervised exercise therapy (pooled SMD 0.11, 95% CI -0.26 to 0.48; P = 0.54; Analysis 2.4). There was little heterogeneity (I^2 = 22%).

One study[29] also assessed long-term PFWD (after 6 years' follow-up) but provided no data on PFWD except for the statement that data showed no significant differences between groups over the long term.



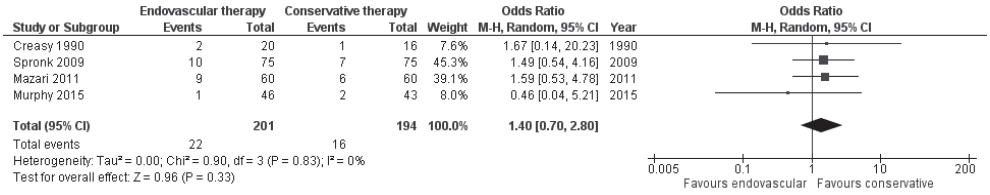
Analysis 2.3. Endovasular revascularisation versus conservative therapy in form of supervised exercise, outcome: Pain-free walking distance.



Analysis 2.4. Endovasular revascularisation versus conservative therapy in form of supervised exercise, outcome: Pain-free walking distance (long-term).

Secondary invasive interventions

Four studies reported data on the number of secondary invasive interventions during follow-up. During 6 to 18 months' follow-up, a secondary invasive intervention was performed in 22 of 201 participants in the endovascular revascularisation group, and in 16 of 194 participants in the supervised exercise therapy group (OR 1.40, 95% CI 0.70 to 2.80; P = 0.33). There was little heterogeneity (I^2 = 0%) (Analysis 2.5).

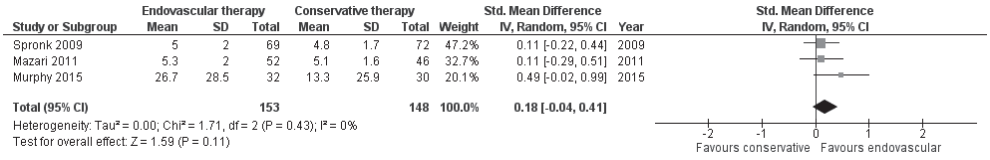


Analysis 2.5. Endovasular revascularisation versus conservative therapy in form of supervised exercise, outcome: Secondary invasive interventions.

Two studies reported data on the number of secondary invasive interventions during long-term follow-up (29; Spronk 2009). In one study[29], after six years' follow-up, 8 of 30 participants in the endovascular revascularisation group and 9 of 30 participants in the control group needed a secondary invasive revascularisation procedure. In the other study[35], after seven years' follow-up, 17 of 75 participants in the endovascular revascularisation group and 32 of 75 participants in the control group needed a secondary revascularisation procedure.

Quality of life

Three studies assessed and reported disease-specific QoL. In two studies[31,35] the VascuQol questionnaire was used, and in one study[32] the Peripheral Artery Questionnaire (PAQ) was used. Pooled data from these studies (n = 301) produced a pooled SMD of 0.18 (95% CI -0.04 to 0.41; P = 0.11) showing no clear differences between study groups. There was little heterogeneity (I^2 = 0%) (Analysis 2.6).



Analysis 2.6. Endovasular revascularisation versus conservative therapy in form of supervised exercise, outcome: Quality of life (disease-specific).

Three studies assessed and reported general health-related QoL. Two studies[31,35] used one or more domains of Short Form-36, and one study[32] used Short Form-12. We have provided a summary of their findings in Figure 4. None of the domains showed a clear difference between study groups.

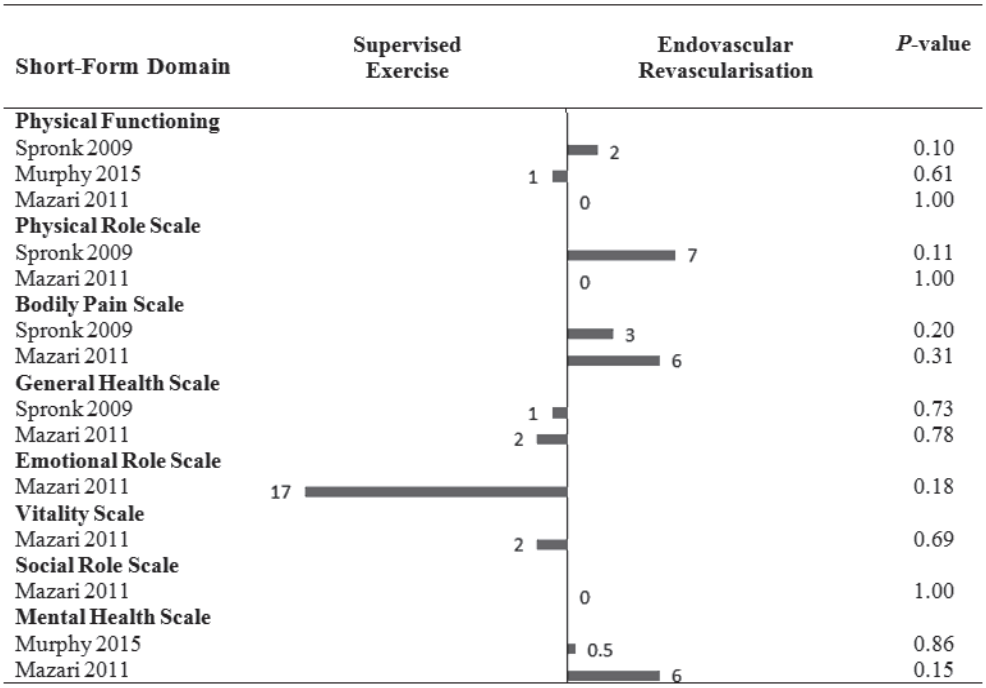


Figure 4. Health-related quality of life (mean differences between groups).

Procedure related complications

Three studies provided data on the number of minor complications following endovascular revascularisation (Table 1)[29,32,35]. Two studies[29,35] reported one arterial perforation during the procedure, which needed surgical revision. One study[32] stated that no major procedure related complications had occurred.

Table 1. Minor complications after endovascular revasuclarisation

Study	Groin haematoma	Artery dissection
Creasy 1990	3/20	1/20
Fakhry 2015	5/106	2/106
Greenhalgh 2008	8/67	1/67
Murphy 2015	nr	2/46
Nordanstig 2014	1/52	nr
Spronk 2009	6/75	1/75

nr: not reported

Cardiovascular events

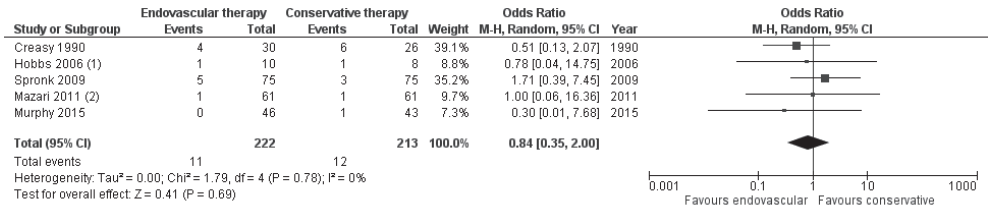
No study reported data on cardiovascular events during follow-up.

Non-treadmill functional performance measures

Two studies reported non-treadmill functional performance measures including self-reported walking distance, hourly free-living steps measured with a pedometer, and functional status assessed with the walking impairment questionnaire (WIQ) and with PAQ[31,32]. One reported no clear differences in self-reported walking distance between the two study groups at one year of follow-up[31]. After six months' follow-up, the second study found no clear differences between study arms for change in hourly free-living steps. Similarly in this study, at 18 months' follow-up, PAQ and WIQ scores for all domains were comparable between groups, except for the PAQ physical limitation score and the PAQ summary score, both of which favoured the endovascular revascularisation group ($P < 0.05$)[32].

Mortality

Five studies reported data on all-cause mortality[29-32,35]. During follow-up, 11 of 222 participants in the endovascular revascularisation group and 12 of 213 participants in the supervised exercise therapy group had died (OR 0.84, 95% CI 0.35 to 2.00; P = 0.69). There was little heterogeneity (I^2 = 0%) (Analysis 2.7).



Footnotes

(1) As no events had occurred in both treatment groups, +1 was added to the number of events and total participants in both groups to allow calculation of the Odds Ratio

(2) As no events had occurred in both treatment groups, +1 was added to the number of events and total participants in both groups to allow calculation of the Odds Ratio

Analysis 2.7. Endovasular revascularisation versus conservative therapy in form of supervised exercise, outcome: Mortality.

Subgroup analysis

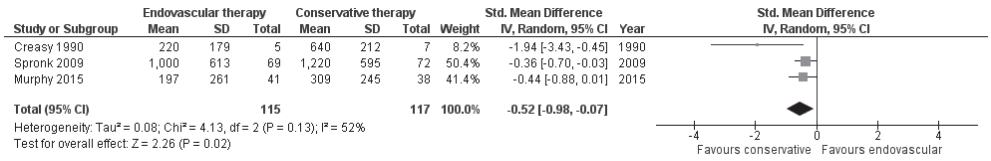
Given the limited number of studies and fact that conservative therapy in all studies consisted of supervised exercise therapy, we performed no subgroup analysis.

Sensitivity analysis

In sensitivity analysis excluding two studies[30,31], which reported only median (IQR) MWD or PFWD; or which measured walking distances on a treadmill during only five minutes,

which probably underestimated the treatment effect, results compared with the main analysis showed changes for the following outcome: At 6 to 12 months' follow-up, pooled results for MWD from the three remaining studies[29,32,35] (n = 232) showed higher MWD in the supervised exercise therapy group than in the endovascular revascularisation group, with SMD of -0.52 (95% CI -0.98 to -0.07; P = 0.024) (Analysis 2.8). For all other outcomes, results from sensitivity analysis did not differ substantially from results obtained by the main analysis.

We did not perform sensitivity analysis on the methodological quality of studies or on individual study effects owing to the limited number of included studies.



Analysis 2.8. Endovasular revascularisation versus conservative therapy in form of supervised exercise, outcome: Sensitivity analysis: maximum walking distance.

Comparison 3. Endovascular revascularisation plus conservative therapy versus conservative therapy

Data from three studies[26,26,31] (n = 457) comparing endovascular revascularisation plus supervised exercise versus supervised exercise alone and data from two studies[32,33] (n = 199) comparing endovascular revascularisation plus pharmacotherapy (i.e. cilostazol) versus pharmacotherapy for intermittent claudication were eligible for inclusion.

Maximum walking distance

After 6 to 12 months' follow-up, use of a random-effects model and pooled data from three studies (n = 432) showed no clear differences in MWD between participants following combination therapy versus supervised exercise therapy alone (SMD 0.26, 95% CI -0.13 to 0.64; P = 0.19; Analysis 3.1). Heterogeneity was substantial (I^2 = 70%).

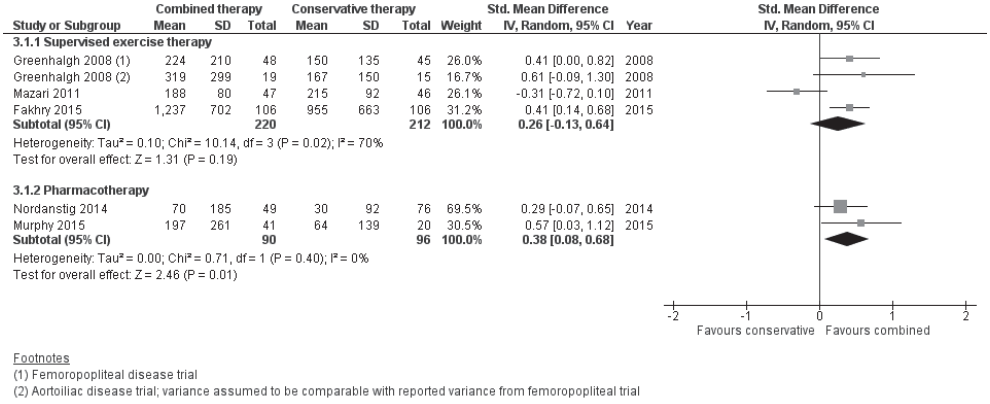
After 6 to 12 months' follow-up, use of a random-effects model and pooled data from two studies (n = 186) showed that participants following combination therapy had a higher MWD than those given pharmacotherapy alone (Analysis 3.1), with an SMD of 0.38 (95% CI 0.08 to 0.68; P = 0.014), which is equivalent to a small effect in favour of combination therapy. There was little heterogeneity (I^2 = 0%).

One study[26] provided long-term data for MWD at two years' follow-up for comparison of combination therapy versus supervised exercise therapy alone, which showed a higher MWD in the combination therapy group than in the supervised exercise therapy alone group (SMD 1.18, 95% CI 0.65 to 1.70; P < 0.0001; 106 participants; Analysis 3.2).

One study[32] provided long-term data for MWD at 18 months' follow-up for comparison of combination therapy versus pharmacotherapy alone, which showed a higher MWD in the combination therapy group than in the pharmacotherapy alone group (SMD 0.72, 95% CI 0.09 to 1.36; P = 0.02; 47 participants; Analysis 3.2).

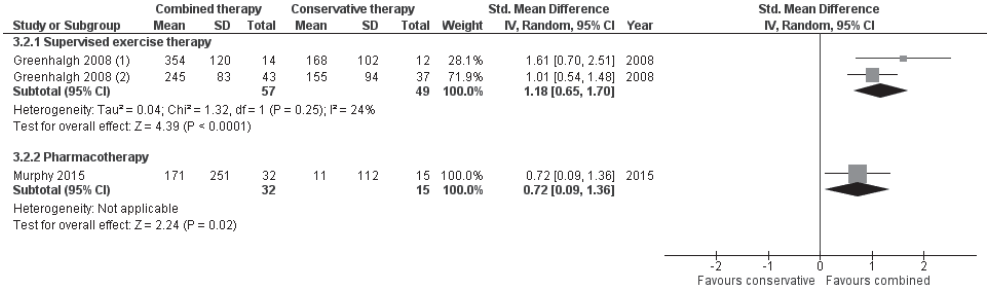
Pain-free walking distance

After 6 to 12 months' follow-up, use of a random-effects model and pooled data from two studies (n = 305) showed no clear differences in PFWD between participants following combination therapy and those given supervised exercise therapy alone (pooled SMD 0.33, 95% CI -0.26 to 0.93; P = 0.27; Analysis 3.3). Heterogeneity was substantial (I^2 = 83%).



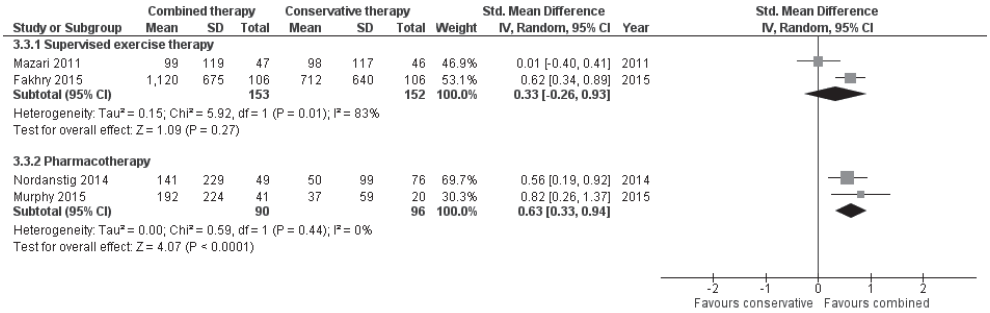
Footnotes
(1) Femoropopliteal disease trial
(2) Aortoiliac disease trial; variance assumed to be comparable with reported variance from femoropopliteal trial

Analysis 3.1. Endovascular revascularisation plus conservative therapy versus conservative therapy, outcome: Maximum walking distance.



Footnotes
(1) Aortoiliac disease trial; variance assumed to be comparable with reported variance from femoropopliteal trial
(2) Femoropopliteal disease trial

Analysis 3.2. Endovascular revascularisation plus conservative therapy versus conservative therapy, outcome: Maximum walking distance (long-term).



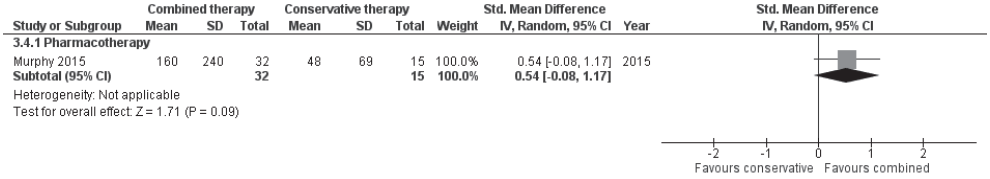
Analysis 3.3. Endovascular revascularisation plus conservative therapy versus conservative therapy, outcome: Pain-free walking distance.

4

After 6 to 12 months' follow-up, use of a random-effects model and pooled data from two studies (n = 186) showed that participants following the combination therapy had a higher PFWD than those given pharmacotherapy alone (Analysis 3.3), with SMD of 0.63 (95% CI 0.33 to 0.94; P < 0.0001), which is equivalent to a moderate effect in favour of combination therapy. There was little heterogeneity (I^2 = 0%).

One study[26] compared combination therapy versus supervised exercise therapy alone in two separate trials - the aortoiliac trial and the femoropopliteal trial - and reported data on long-term PFWD after two years' follow-up. In the femoropopliteal trial, 63% of participants in the combination therapy group and 22% of those in the supervised exercise therapy group attained 200 metres without claudication pain, corresponding to an adjusted hazard ratio of 3.11 (95% CI 1.42 to 6.81; P < 0.01) in favour of combination therapy. Similarly, in the aortoiliac trial, 61% of participants in the combination therapy group and 25% of those in the supervised exercise therapy group attained 200 metres without claudication pain, corresponding to an adjusted hazard ratio of 3.6 (95% CI 1.0 to 12.8; P = 0.05) in favour of combination therapy.

One study[32] provided long-term data for PFWD at 18 months' follow-up comparing combination therapy versus pharmacotherapy alone showing no clear differences between study groups (SMD 0.54, 95% CI -0.08 to 1.17; P = 0.09; 47 participants; Analysis 3.4).

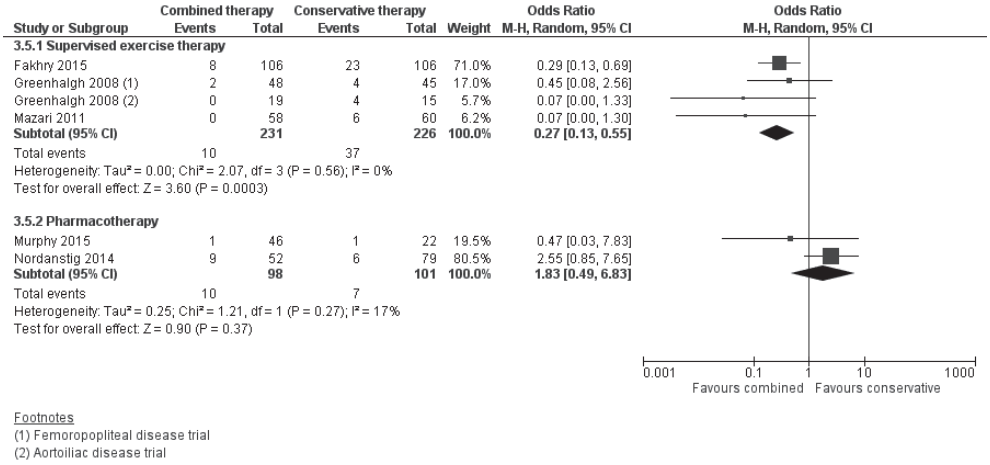


Analysis 3.4. Endovascular revascularisation plus conservative therapy versus conservative therapy, outcome: Pain-free walking distance (long-term).

Secondary invasive interventions

Three studies comparing combination therapy versus supervised exercise therapy alone reported data on the number of secondary invasive interventions during follow-up. During 12 to 24 months' follow-up, investigators performed a secondary invasive intervention in 10 of 231 participants in the combination therapy group and in 37 of 226 participants in the supervised exercise therapy group (OR 0.27, 95% CI 0.13 to 0.55; P = 0.0003) (Analysis 3.5). There was little heterogeneity (I^2 = 0%).

Two studies comparing combination therapy versus pharmacotherapy alone reported data on the number of secondary invasive interventions during follow-up. During 12 to 18 months' follow-up, researchers performed a secondary invasive intervention in 10 of 98 participants in the combination therapy group and in 7 of 101 participants in the pharmacotherapy group (OR 1.83, 95% CI 0.49 to 6.83; P = 0.37) (Analysis 3.5). There was little heterogeneity (I^2 = 17%).



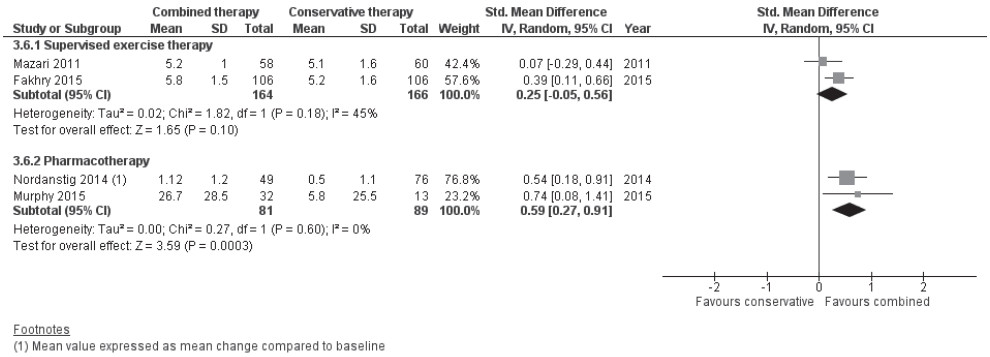
Analysis 3.5. Endovascular revascularisation plus conservative therapy versus conservative therapy, outcome: Secondary invasive interventions.

Quality of life

Four studies assessed and reported disease-specific QoL. Three of them[25,31,33] used the VascuQol questionnaire, and one[32] used the Peripheral Artery questionnaire.

Pooled data from two studies (n = 330) comparing combination therapy versus supervised exercise therapy alone produced a pooled SMD of 0.25 (95% CI -0.05 to 0.56; P = 0.10) (Analysis 3.6). Heterogeneity was moderate (I^2 = 45%).

Pooled data from two studies (n = 170) comparing combination therapy versus pharmacotherapy alone produced a pooled SMD of 0.59 (95% CI 0.27 to 0.91; P = 0.0003) (Analysis 3.6), which is equivalent to a small effect in favour of combination therapy. There was little heterogeneity (I^2 = 0%).



Analysis 3.6. Endovascular revascularisation plus conservative therapy versus conservative therapy, outcome: Quality of life (disease-specific).

Five studies assessed and reported general health-related QoL using one or more domains of Short Form-36 or Short Form-12[25,26,31-33]. We have provided a summary of findings from these five studies in Figure 5. For domains assessed on the physical functioning scale, the physical role scale, and the bodily pain scale, data show statistically significant differences in favour of combination therapy.

Procedure related complications

Four studies provided data on the number of minor complications (Table 1) following endovascular revascularisation[25,26,32,33]. One study[32] reported one arterial perforation during the procedure, which needed a surgical revision. One study[33] reported an emergency surgical exploration due to access site bleeding and one study[31] stated that no major procedure related complications had occurred.

Cardiovascular events

No study reported data on cardiovascular events during follow-up.

Non-treadmill functional performance measures

Three studies reported non-treadmill functional performance measures including self-reported walking distance, hourly free-living steps measured with a pedometer, and functional status assessed with WIQ and PAQ[31-33]. At one year of follow-up, one study[31] reported no statistically significant difference in self-reported walking distance between study groups, and one study[33] reported a significant difference in self-reported MWD in favour of combination therapy over pharmacotherapy alone ($P < 0.01$). After six months' follow-up, one study[32] reported no statistically significant differences between groups for change in hourly free-living steps. At 18 months' follow-up, one study[31] reported that for all domains of WIQ and PAQ summary score, a statistically significant greater improvement favoured combination therapy ($P < 0.05$) over pharmacotherapy alone.

Short-Form Domain	Conservative Therapy	Endovascular Revascularisation *plus* Conservative Therapy	*P*-value
Physical Functioning			
Greenhalgh 2008 (A)[1]		1,7	0.82
Greenhalgh 2008 (B)[1]		7,8	0.02
Murphy 2015[2]		4,3	0.05
Mazari 2011[1]		7	0.30
Fakhry 2015[1]		9,8	0.00
Nordanstig 2014[2]		14,5	0.00
Physical Role Scale			
Mazari 2011[1]		0	1.00
Fakhry 2015[1]		14	0.02
Nordanstig 2014[2]		11	0.26
Bodily Pain Scale			
Mazari 2011[1]		10	0.09
Fakhry 2015[1]		7,6	0.02
Nordanstig 2014[2]		12,1	0.00
General Health Scale			
Mazari 2011[1]	5		0.33
Fakhry 2015[1]		4,1	0.11
Nordanstig 2014[2]		6,5	0.05
Emotional Role Scale			
Mazari 2011[1]		0	1.00
Nordanstig 2014[2]	1,9		0.29
Vitality Scale			
Mazari 2011[1]	5		0.34
Nordanstig 2014[2]		6,6	0.09
Social Role Scale			
Mazari 2011[1]		13	0.06
Nordanstig 2014[2]		5,6	0.05
Mental Health Scale			
Greenhalgh 2008 (A)[1]		3,9	0.25
Greenhalgh 2008 (B)[1]		4,3	0.12
Murphy 2015[2]		0,7	0.71
Mazari 2011[1]		6	0.20
Nordanstig 2014[2]		0,5	0.71

A: Femoropoliteal trial.B: Aortoiliac trial.

1 In this study, the comparison was endovascular revascularisation plus supervised exercise versus supervised exercise.

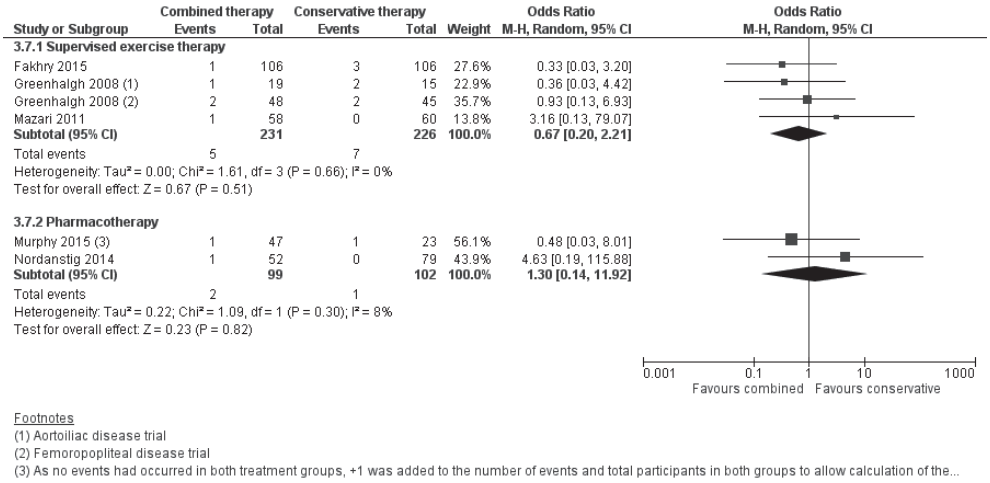
2 In this study, the comparison was endovascular revascularisation plus pharmacotherapy with cilostazol versus cilostazol.

Figure 5. Health-related quality of life (mean differences between groups).

Mortality

Three studies comparing combination therapy versus supervised exercise therapy reported data on all-cause mortality showing that 5 of 231 participants in the combination therapy group and 7 of 226 participants in the supervised exercise therapy alone group had died (OR 0.67, 95% CI 0.20 to 2.21; P = 0.51) (Analysis 3.7) (25; 26; 31). There was little heterogeneity (I^2 = 0%).

Two studies comparing combination therapy versus pharmacotherapy reported data on all-cause mortality showing that 5 of 99 participants in the combination therapy group and 1 of 102 participants in the pharmacotherapy alone group had died (OR 1.30, 95% CI 0.14 to 11.92; P = 0.82) (Analysis 3.7). There was little heterogeneity (I^2 = 8%).



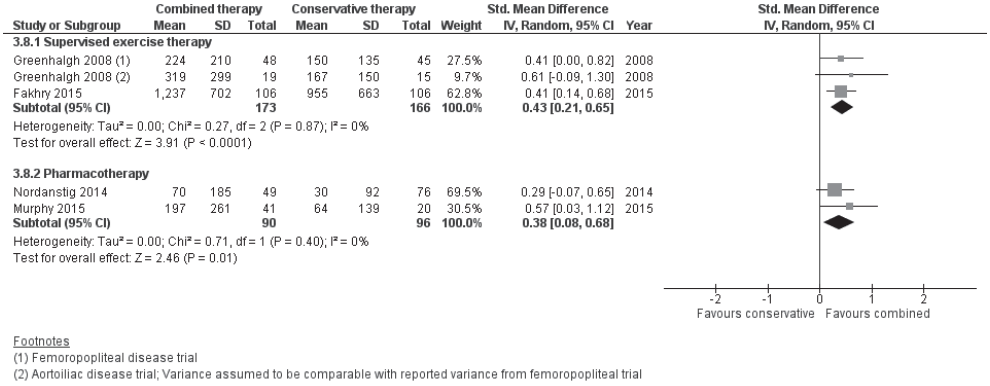
Analysis 3.7. Endovascular revascularisation plus conservative therapy versus conservative therapy, outcome: Mortality.

Subgroup analysis

Given the limited number of studies, we performed no subgroup analysis.

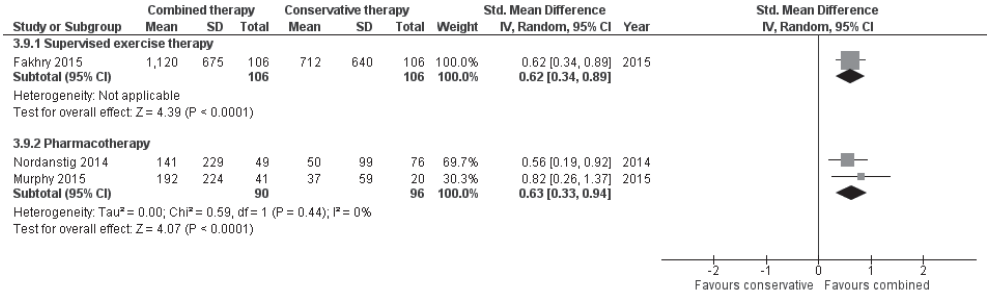
Sensitivity analysis

In sensitivity analysis excluding one study[31], which reported only median (IQR) MWD or PFWD and measured walking distances on a treadmill during only five minutes (probably underestimating the treatment effect), results compared with those of the main analysis showed changes in the following outcome: For the comparison of endovascular revascularisation plus supervised exercise versus supervised exercise alone, pooled results for MWD from the two remaining studies (n = 339) showed higher MWD in the combination therapy group than in the supervised exercise alone group, with SMD of 0.43 (95% CI 0.21 to 0.65; P < 0.0001) (Analysis 3.8), which is equivalent to a moderate effect in favour of combination therapy. For PFWD, results from one study[25] showed higher PFWD in the combination therapy group than in the supervised exercise alone group (SMD 0.62, 95% CI 0.34 to 0.89; P = 0.0001; 212 participants) (Analysis 3.9).



Footnotes
(1) Femoropopliteal disease trial
(2) Aortoiliac disease trial; Variance assumed to be comparable with reported variance from femoropopliteal trial

Analysis 3.8. Endovascular revascularisation plus conservative therapy versus conservative therapy, outcome: Sensitivity analysis: maximum walking distance.



Analysis 3.9. Endovascular revascularisation plus conservative therapy versus conservative therapy, outcome: Sensitivity analysis: pain-free walking distance.

DISCUSSION

In this review, we included ten RCTs with a total of 1087 participants assessing the (added) effect of endovascular revascularisation in the management of patients with stable intermittent claudication. It should be stated that overall the studies included are relatively small and show considerable heterogeneity in outcome assessment and outcome reporting; therefore trial results must be interpreted with caution.

Summary of main results

After comparing endovascular revascularisation versus no therapy (except exercise advice) for intermittent claudication, three studies (n = 134) provided data showing a moderate to large effect on walking distances in favour of endovascular revascularisation in the short term up to 12 months. However, after long-term follow-up, this short-term

advantage of endovascular revascularisation was uncertain upon pooling of results from two studies. In addition, as reported in these two studies, quality of life (QoL) and the number of secondary invasive interventions during follow-up were not substantially different between study groups.

After comparing endovascular revascularisation versus supervised exercise for intermittent claudication, five studies (n = 412) provided data showing no specific preference for one of the two treatment options. Overall, participants in the supervised exercise therapy group tended to have higher walking distances, and participants in the endovascular revascularisation group tended to have better general and disease-specific QoL, yet these differences were not statistically significant. Similarly, the number of secondary invasive interventions during follow-up was comparable between the two study groups. Sensitivity analysis excluding studies reporting only median walking distances and one study that measured walking distances on a treadmill during only five minutes, which probably underestimated the treatment effect, showed that participants following supervised exercise had a higher maximum walking distance (MWD) after 6 to 12 months when compared with participants following endovascular revascularisation.

After comparing endovascular revascularisation plus conservative therapy versus conservative therapy alone for intermittent claudication, three studies (n = 457) comparing endovascular revascularisation plus supervised exercise versus supervised exercise alone provided data showing no clear difference in walking distances and in disease-specific QoL between groups up to 12 months' follow-up, and one study reported better walking distances in favour of combination therapy at 24 months' follow-up. In addition, participants following endovascular revascularisation plus supervised exercise tended to have higher general health-related QoL in favour of combination therapy for some of the Short Form (SF)-36 domains. Finally, the number of secondary invasive interventions during follow-up was significantly lower following combination therapy compared with supervised exercise alone. Sensitivity analysis excluding one study reporting only median walking distances and measuring walking distances on a treadmill during only five minutes, which probably underestimated the treatment effect, showed that participants following endovascular revascularisation plus supervised exercise had higher maximum walking distance (MWD) and pain-free walking distance (PFWD) after 6 to 12 months compared with participants following supervised exercise only.

When comparing endovascular revascularisation plus cilostazol versus cilostazol alone, two studies (n = 199) provided data showing a small to moderate effect on short- and long-term walking distances in favour of combination therapy. In addition, participants following combination therapy had higher disease-specific and general health-related QoL with differences favouring endovascular revascularisation plus cilostazol for some of the SF-36 domains. The number of secondary invasive interventions during follow-up was not different between participants in the combination therapy group and those in the cilostazol only group.

Six studies with a total of 366 participants randomised to an endovascular revascularisation procedure provided data on the number of procedure related complications. Overall endovascular revascularisation for claudication seems to be a relatively 'safe' procedure with an incidence of 8% (30/366) for minor procedure related complications (groin haematoma and artery dissection) requiring conservative management only. Three studies reported one arterial perforation each during the procedure that required a surgical revision. None of the studies reported any major procedure related complications leading to permanent disability or death. Yet, it should be noted that these data are based on complications within clinical studies, and complication rates in clinical practice might be much higher.

Overall completeness and applicability of evidence

In general, the ten included studies provided sufficient information on the predefined primary and secondary outcomes of this review, except for the number of cardiovascular events during follow-up, which was not reported by any of the studies.

Considerable heterogeneity in outcome assessment was evident between studies. The treadmill protocol (speed, grade, and time) used to assess primary outcome functional performance measures (i.e. MWD and PFWD) differed significantly between studies; therefore we used SMD as treatment effect for these outcomes to allow standardisation of study results to a uniform scale. In addition, some heterogeneity in outcome reporting was evident between studies, including three studies[30,31,36] reporting only median (interquartile range (IQR)) MWD and PFWD. In sensitivity analysis excluding these studies and one study[31] limiting treadmill time to assess MWD and PFWD to only five minutes, the main results changed significantly for three analyses as summarised above.

Given the limited number of studies included in this review, we were unable to perform all of the predefined subgroup analyses to investigate existing clinical heterogeneity between studies based on the selected population (femoropopliteal vs aortoiliac vs combined disease) or heterogeneity due to the endovascular revascularisation procedure performed (angioplasty vs stenting).

Given these restrictions, applicability of this review is limited to the general population of patients with intermittent claudication, and review findings do not allow robust conclusions for specific groups of participants or specific types of interventions given.

Quality of the evidence

We used GRADE criteria according to Schünemann[48] and Atkins[49] to assess the quality of evidence for the outcomes MWD, PFWD, secondary invasive interventions, and disease-specific QoL.

For the comparison endovascular revascularisation versus no specific therapy for intermittent claudication, we rated the quality of evidence as low (MWD and PFWD at long term) or moderate (MWD and PFWD at 6 to 12 months and secondary invasive

interventions). We downgraded the quality of evidence for this comparison mainly because of small study sample sizes and the possibility of serious risk of bias in two studies with three or more risk of bias domains labelled as having 'unclear' risk.

For the comparison endovascular revascularisation versus conservative therapy (i.e. supervised exercise), quality assessment ranged from moderate (MWD and PFWD at 6 to 12 months and at long term) to high (secondary invasive interventions and disease-specific QoL). We downgraded the quality of evidence for this comparison mainly owing to substantial heterogeneity between studies and high risk of attrition bias in one[29] of the five studies included in the analysis.

For the final comparison of combination therapy of endovascular revascularisation followed by conservative therapy versus conservative therapy alone, the quality assessment for the comparison combination therapy versus supervised exercise alone ranged from low (MWD at long term) to moderate (MWD and PFWD at 6 to 12 months and disease-specific QoL) to high (number of secondary invasive interventions). We downgraded the quality of evidence for this comparison mainly owing to substantial heterogeneity between studies. We assessed quality for the comparison combination therapy versus pharmacotherapy alone as high (MWD and PFWD at 6 to 12 months, disease-specific QoL, and number of secondary invasive interventions).

The Cochrane Vascular Information Specialist conducted a comprehensive search to identify all relevant studies for inclusion in this review. In addition, review authors handsearched the reference lists of all eligible studies and reviews for additional relevant studies. Nevertheless, unpublished studies or data may have been missed. We had to exclude two eligible studies because one[40] reported no outcome measures for the subgroup of participants receiving endovascular revascularisation, and one[45] published only abstract data with incomplete results. We attempted to contact study authors to ask for relevant data but received no response. Study authors from one study[33] provided data on the subgroup of participants receiving endovascular revascularisation, which allowed us to include this study in the quantitative analysis. However, it should be noted that this study was not powered to detect a difference in outcomes between the subgroup of participants receiving endovascular revascularisation and control group participants.

A potential bias that deserves attention is the limitation of maximum walking time on a treadmill test for assessment of the primary outcomes MWD and PFWD during follow-up, which varied between studies and ranged from 5 minutes to 30 minutes. Particularly in studies, which limited maximum walking time to only 5 minutes[31], and to 10 minutes[36], this may have caused serious underestimation of treatment effect, as participants might have been able to walk farther. This might explain the non-significant differences between treatment groups as reported by these studies[31,36]. In addition, to pool trial data, we assumed normal distribution for walking distances in three studies[30,31,36] and used reported median values in the meta-analysis; this may have biased pooled results. In sensitivity analysis excluding these studies, the main results changed significantly for three analyses, as summarised above.

Agreements and disagreements with other studies or reviews

Results of this review are in line with those of two previously published systematic reviews comparing treatment strategies for patients with intermittent claudication[50,51]. Both reviews concluded that endovascular revascularisation alone provides no significant benefit over supervised exercise therapy alone, and combination therapy of endovascular revascularisation plus supervised exercise therapy may be superior to supervised exercise therapy alone. Since then, results from three sizeable RCTs have been published and are included in this review[25,32,33], overall confirming the conclusions provided by those two earlier systematic reviews.

AUTHOR'S CONCLUSIONS

Implications for practice

In the management of patients with intermittent claudication, endovascular revascularisation does not provide significant benefits compared with supervised exercise therapy alone in terms of improvement in functional performance or quality of life. Although the number of studies is small with presence of some clinical heterogeneity, evidence suggests a possible synergetic effect when endovascular revascularisation is combined with a conservative therapy of supervised exercise or pharmacotherapy with cilostazol: the combination therapy seems to result in greater improvements in functional performance and quality of life scores when compared with conservative therapy alone.

Implications for research

More large (and long-term) studies assessing the added effect of endovascular revascularisation over and above supervised exercise therapy, or assessing the effectiveness of a stepped care approach with supervised exercise followed by endovascular revascularisation if needed, are required to define the optimal treatment strategy for the growing population of patients with intermittent claudication. In addition, health economic analyses of these combined treatment strategies are scarce and are urgently needed.

CHARACTERISTICS OF STUDIES

Characteristics of included studies

Creasy 1990

Methods	Study design: parallel 2-arm RCT Number of sites: 1 Sample size estimation: not reported Follow-up: 3, 6, 9, 12, 15 months and 6 years
Participants	Country and setting: United Kingdom, Oxford Regional Vascular Service Inclusion criteria - Stable unilateral claudication, with failure of conservative treatment for ≥ 3 months - Treadmill claudicating distance < 375 meters - Angiographically significant lesion(s) suitable for treatment by angioplasty, as agreed upon by both surgeon and radiologist Exclusion criteria: none Number of participants assessed and randomised: 36 participants fulfilled the entry criteria and were randomised Demographics - Age (years): Group 1: mean 63.6 (SD 8.9); Group 2: mean 62.2 (SD 8.6) - Gender (male): Group 1: 15 (75%); Group 2: 12 (75%)
Interventions	Group 1: endovascular revascularisation without stenting, n = 20 (n = 30 at 6 years' follow-up) Group 2: supervised exercise therapy for 6 months (2 sessions/week, 30 minutes/session), n = 16 (n = 26 at 6 years' follow-up) Compliance with interventions - Group 1: Two angioplasties were not successful - Group 2: Mean attendance over 6 months of exercise therapy was 0.89 sessions/week Mortality - Group 1: 4 participants after 6 years' follow-up - Group 2: 6 participants after 6 years' follow-up Loss to follow-up - Group 1: 4 participants after 6 years' follow-up - Group 2: 5 participants after 6 years' follow-up
Outcomes	Maximum walking distance, pain-free walking distance, number of secondary interventions, procedure-related complications
Notes	Source of funding: Oxford District Research Committee Notes: New participants were added to the study after initial publication in 1990. Meta-analysis for long-term walking distances used numbers of participants at 6 years' follow-up. Authors' conclusion: "In patients with mild or moderate claudication, who do not require an immediate therapeutic response, supervised exercise therapy may ultimately produce greater symptomatic improvement than PTA."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Simple randomisation" was performed according to trial authors; exact randomisation technique was not reported
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment process
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not possible given the nature of the intervention (endovascular revascularisation)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors not adequately discussed in the study
Incomplete outcome data (attrition bias) All outcomes	High risk	Not analysed according to intention-to-treat principle; participants who had technically unsuccessful angioplasties were excluded from analysis; at 1-year follow-up, walking distance in only 5 participants (25%) in the revascularisation group and in 7 participants (44%) in the exercise group assessed; characteristics of withdrawals not adequately discussed; new participants added to study after 1 year of follow-up
Selective reporting (reporting bias)	Low risk	All relevant outcome measures as specified in the methods section were reported
Other bias	Unclear risk	Sample size estimation not adequately discussed; low number of participants in whom primary endpoint was assessed (study underpowered)

Fakhry 2015

Methods	Study design: parallel 2-arm RCT Number of sites: 10 Sample size estimation: 210 participants to detect 30% difference in maximum walking distance between the 2 treatment groups based on 90% power, type I error rate of 0.01, and anticipating 10% censoring Follow-up: 1, 6, and 12 months
Participants	Country and setting: Netherlands, university and non-university hospitals Inclusion criteria - Patients with stable intermittent claudication - One or more vascular stenoses > 50% diameter reduction at the aortoiliac and/or femoropopliteal level established by non-invasive vascular imaging - Maximum walking distance between 100 and 500 meters as assessed on a graded treadmill Exclusion criteria - Targeted lesion deemed unsuitable for revascularisation - Prior treatment for the targeted lesion (including exercise therapy) - Limited life expectancy - Limited ambulation due to any other condition than intermittent claudication not allowing participant to follow treadmill training Number of participants assessed and randomised: 666 participants assessed, 212 participants randomised to 1 of the treatment groups Demographics - Age (years): Group 1: mean 64 (SD 9); Group 2: mean 66 (SD 10) - Gender (male): Group 1: 60 (57%); Group 2: 72 (68%)
Interventions	Group 1: endovascular revascularisation with selective stenting plus supervised exercise therapy, n = 106 Group 2: supervised exercise therapy for 12 months (2 to 3 sessions/week 0 to 3 months, 1 session/week 3 to 6 months, 1 session/mo 6 to 12 months, 60 minutes/session), n = 106 Compliance with interventions - Group 1: endovascular revascularisation technically successful in 102 (96%) participants, on average per participant 30 sessions exercise followed - Group 2: on average per participant 43 sessions exercise followed Mortality - Group 1: 1 participant - Group 2: 3 participants Loss to follow-up - Group 1: 5 participants - Group 2: 8 participants
Outcomes	Maximum walking distance, pain-free walking distance, number of secondary interventions, procedure-related complications, SF-36 Physical Functioning, SF-36 Physical Role, SF-36 Bodily Pain, SF-36 General Health, VascuQol
Notes	Source of funding: grant from Netherlands organization for health research and development Authors conclusion: "Among patients with intermittent claudication after 1 year of follow-up, a combination therapy of endovascular revascularization followed by supervised exercise resulted in significantly greater improvement in walking distances and health-related quality-of-life scores compared with supervised exercise only."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation using Web-based randomisation software based on minimisation method
Allocation concealment (selection bias)	Low risk	Central Web-based allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not possible given the nature of the intervention (endovascular revascularisation)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Independent outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis based on an intention-to-treat principle, censoring at 12 months low (6%) and comparable between groups
Selective reporting (reporting bias)	Low risk	All requested relevant outcome measures provided by study authors
Other bias	Low risk	No other forms of bias identified

Greenhalgh 2008

Methods	Study design: parallel 2-arm RCTs: (1) femoropopliteal disease trial; (2) aortoiliac disease trial Number of sites: 9 Sample size estimation: 170 participants in each trial based on 90% power and significance level of 0.05 to detect a difference of 60 metre improvement in absolute walking distance between groups Follow-up: 6, 12, and 24 months
Participants	Country and setting: United Kingdom, university and non-university hospitals Inclusion criteria - Positive outcome on the Edinburgh Claudication Questionnaire - ABPI < 0.9 or > 0.9 with a positive stress test (fall of > 30 mmHg in Doppler blood pressure following a treadmill test at 4 km/h, 10 slope for 1 minute) - Aortoiliac or femoropopliteal target lesion amenable to endovascular revascularisation as demonstrated by duplex mapping or diagnostic arteriography Exclusion criteria - Symptoms too mild to consider angioplasty or so severe that intervention was mandatory - Critical limb ischaemia (absolute Doppler blood pressure < 50 mmHg or presence of ulcers or gangrene with Doppler pressure > 50 mmHg) - Concomitant disease such as musculoskeletal or cardiac that was prohibitive to exercise Number of participants assessed and randomised: 144 participants assessed, 127 participants randomised (93 participants in the femoropopliteal trial and 34 participants in the aortoiliac trial) Demographics Femoropopliteal disease trial - Age (years): Group 1: 63.9 (SD: 9.0); Group 2: 68.5 (SD: 9.4) - Gender (male): Group 1: 33 (69%); Group 2: 26 (58%) Aortoiliac disease trial - Age (years): Group 1: mean 63.9 (SD 8.6); Group 2: mean 62.5 (SD 9.8) - Gender (male): Group 1: 12 (62%); Group 2: 10 (67%)
Interventions	Group 1: endovascular revascularisation with selective stenting plus supervised exercise therapy, n = 48 (femoropopliteal disease trial), and n = 19 (aortoiliac disease trial) Group 2: supervised exercise therapy for 6 months (≥ 1 session/week, 30 minutes/session), n = 45 (femoropopliteal disease trial), and n = 15 (aortoiliac disease trial) Compliance with interventions Femoropopliteal trial - Group 1: in 11/44 participants, endovascular revascularisation recorded as failed, 62% attended available weekly exercise classes - Group 2: 61% attended available weekly exercise classes Aortoiliac trial - Group 1: in 2/19 participants, endovascular revascularisation recorded as failed, 53% attended available weekly exercise classes - Group 2: 48% attended available weekly exercise classes Mortality Femoropopliteal trial - Group 1: 2 participants - Group 2: 2 participants Aortoiliac trial - Group 1: 1 participants - Group 2: 2 participants Loss to follow-up Femoropopliteal trial - Group 1: 3 participants - Group 2: 6 participants Aortoiliac trial - Group 1: 4 participants - Group 2: 1 participants

Outcomes	Absolute walking distance, initial claudication distance, number of secondary interventions, SF-36 physical health score , SF-36 physical mental score, procedure-related complications
Notes	Source of funding: Camelia Botnar Arterial Research Foundation with independent educational grants from Bard Ltd., Boston Scientific Ltd., and Cook Authors' conclusion: "PTA confers adjuvant benefit over supervised exercise and best medical therapy in terms of walking distances and ABPI 24 months after PTA in patients with stable mild to moderate intermittent claudication."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate randomisation technique using "randomly permuted blocks of unequal size generated by Stata"
Allocation concealment (selection bias)	Low risk	Central allocation, "performed by the trial manager via a laptop computer whilst on site at each centre"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not possible given the nature of the intervention (endovascular revascularisation)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors not adequately discussed in the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis based on an intention-to-treat principle, censoring at 24 months moderate (17%) and comparable between groups
Selective reporting (reporting bias)	Unclear risk	Prespecified maximum walking distance reported; for pain-free walking distance, no absolute distances reported during follow-up
Other bias	Unclear risk	Intended recruitment based on power calculations 170 participants in each trial, eventually including 93 participants in the femoropopliteal trial and 34 participants in the aortoiliac trial

Hobbs 2006

Methods	Study design: parallel 3-arm RCT Number of sites: 4 Sample size estimation: 21 participants (7 per group) required to detect a 75% reduction in the thrombin antithrombin complex in treatment groups with 80% power and a P value of 0.05 Follow-up: 3 and 6 months
Participants	Country and setting: United Kingdom, Department of Vascular Surgery at University of Birmingham Inclusion criteria - Confirmed mild to moderate intermittent claudication (defined as absolute claudication distance (of 50 to 500 m on a treadmill) due to infrainguinal disease - Suitable for unilateral infrainguinal endovascular revascularisation and participation in a supervised exercise programme - 3 to 6 months stabilised on best medical therapy before consideration for study entry Exclusion criteria - Significant aortoiliac disease - Equally severe bilateral symptoms (making them unsuitable for unilateral angioplasty) - Previous ipsilateral infrainguinal intervention - Unable to exercise to absolute claudication distance on treadmill Number of participants assessed and randomised: 372 participants screened for entry; from them 23 participants randomised to 1 of 3 treatment arms Demographics - Age (years): Group 1: median 67 (IQR 57 to 77); Group 2: median 67 (IQR 58 to 71); Group 3: median 67 (IQR 57 to 77) - Gender (male): Group 1: 6 (67%); Group 2: 6 (86%); Group 3: 4 (57%)
Interventions	Group 1: endovascular revascularisation without stenting plus best medical therapy, n = 9 Group 2: supervised exercise therapy plus best medical therapy for 12 weeks (2 sessions/week, 60 minutes/session), n = 7 Group 3: best medical therapy based on cardiovascular risk factor management, n = 7 (for analysis, this group was labelled as 'no therapy') Compliance with interventions: not reported Mortality - Group 1: 0 participants - Group 2: 0 participants - Group 3: 0 participants Loss to follow-up - Group 1: 0 participants - Group 2: 1 participant - Group 3: 0 participants
Outcomes	Maximum walking distance, pain-free walking distance
Notes	Source of funding: Health Technology Assessment Grant Authors' conclusion: "The addition of lower limb revascularization by PTA to best medical therapy in patients with intermittent claudication due to infra-inguinal disease results in a medium-term improvement in the resting procoagulant and hypo fibrinolytic state."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants underwent "central randomisation", yet exact randomisation technique not specified
Allocation concealment (selection bias)	Unclear risk	Study did not address allocation concealment process
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not possible given the nature of the intervention (endovascular revascularisation)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors not adequately discussed in the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	During 6-month follow-up, only 1 participant withdrew (4%) from the study
Selective reporting (reporting bias)	Low risk	All relevant outcome measures as specified in the methods section were reported
Other bias	Unclear risk	Study was not powered to consider walking distances as primary endpoint; study was closed early including only 10% of required participants

Mazari 2011

Methods	Study design: parallel 3-arm RCT Number of sites: 1 Sample size estimation: 60 participants in each treatment arm based on 80% power, α = 0.05, and anticipating a 20% dropout rate to detect a 20% difference between treatment arms in physical function domain of SF-36 Follow-up: 1,3, 6, and 12 months
Participants	Country and setting: United Kingdom, Vascular Surgical Unit of a university hospital Inclusion criteria - Symptomatic unilateral intermittent claudication - Femoropopliteal lesion amenable to angioplasty (as discussed in a multi-disciplinary meeting) - Symptoms stable after 3 months on best medical therapy Exclusion criteria - Critical limb ischaemia - Incapacitating systemic disease - Inability to tolerate treadmill testing (unrelated to limb ischaemia) - Significant Ischaemic changes on ECG during treadmill testing - Ipsilateral vascular surgery or peripheral angioplasty within previous 6 months Number of participants assessed and randomised: 1157 participants were assessed for inclusion; from them 178 participants were randomised to 1 of 3 treatment arms Demographics - Age (years): Group 1: median 69.5 (95% CI 64 to 79); Group 2: median 70 (95% CI 63 to 75); Group 3: median 69 (95% CI 63 to 76) - Gender (male): Group 1: 33 (57%); Group 2: 37 (62%); Group 3: 37 (62%)
Interventions	Group 1: endovascular revascularisation without stenting plus supervised exercise therapy, n = 58 Group 2: endovascular revascularisation without stenting, n = 60 Group 3: supervised exercise therapy for 12 weeks (3 sessions/week), n = 60 Compliance with interventions: not reported Mortality - Group 1: 1 participant - Group 2: 0 participants - Group 3: 0 participants Loss to follow-up - Group 1: 10 participants - Group 2: 8 participants - Group 3: 14 participants
Outcomes	Maximum walking distance, pain-free walking distance, number of secondary interventions, SF-36 Physical Function, SF-36 Role Physical, SF-36 Bodily Pain, SF-36 General Health, SF-36 Vitality, SF-36 Social, SF-36 Emotional, SF-36 Mental, VascuQol, self-reported maximum walking distance
Notes	Source of funding: BJS research bursary, European Society of Vascular Surgery research grant, and support from the Academic Vascular Surgical Unit, University of Hull Authors' conclusion: "For patients with intermittent claudication due to femoropopliteal disease, PTA, supervised exercise and PTA plus supervised exercise were all equally effective in improving walking distance and quality of life after 12 months."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were "randomised into one of the three treatment arms"; exact sequence generation method not reported
Allocation concealment (selection bias)	Low risk	Sealed envelopes were used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not possible given the nature of the intervention (endovascular revascularisation)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors not adequately discussed in the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Sufficient number of participants (82%) analysed after 1 year of follow-up; censoring comparable between groups
Selective reporting (reporting bias)	Low risk	All relevant outcome measures as specified in the methods section were reported
Other bias	Low risk	No other forms of bias identified

Murphy 2015

Methods	Study design: parallel 4-arm RCT Number of sites: 22 Sample size estimation: Allowing 30% premature withdrawal, 252 participants would be needed to have 80% power to detect relevant difference between supervised exercise and stenting groups. Sample size was adjusted to 217 after removal of stenting plus supervised exercise arm owing to slow enrolment. Follow-up: 6 and 18 months
Participants	Country and setting: United States, university and non-university hospitals Inclusion criteria - Symptoms of moderate to severe intermittent claudication (ability to walk 2 to 11 minutes on a graded treadmill test) - Objective evidence of a haemodynamically significant aortoiliac arterial stenosis established by non-invasive vascular testing Exclusion criteria - Critical limb ischaemia - Comorbid conditions limiting participants' walking ability - More than 25% deviation between 2 treadmill tests at baseline - Total aortoiliac occlusion from the level of the renal arteries to the inguinal ligaments Number of participants assessed and randomised: 999 participants screened, 119 participants randomised to 1 of 4 treatment arms Demographics - Age (years): Group 1: mean 65 (SD 10); Group 2: mean 64 (SD 10); Group 3: mean 62 (SD 8) - Gender (male): Group 1: 32 (70%); Group 2: 21 (49%); Group 3: 16 (73%)

Interventions	Group 1: endovascular revascularisation with primary stenting plus claudication pharmacotherapy (cilostazol), n = 46 Group 2: supervised exercise therapy for 26 weeks (3 sessions/week, 1 hour/session) supplemented by 12-month telephone-based (1 to 2 calls/mo) programme to adhere and maintain adherence plus claudication pharmacotherapy (cilostazol), n = 43 Group 3: claudication pharmacotherapy, including cilostazol 100 mg twice daily and advice on home exercise and diet, n = 22 Group 4: endovascular revascularisation plus supervised exercise therapy and claudication pharmacotherapy (cilostazol), n = 8 (inclusion in this study arm stopped prematurely and study arm excluded from further analysis) Compliance with interventions - Group 1: 43 participants received assigned intervention, all procedures technically successful, > 90% adherence to cilostazol treatment - Group 2: 29 (71%) participants attended at least 70% of 78 scheduled exercise sessions, > 90% adherence to cilostazol treatment - Group 3: > 90% adherence to cilostazol treatment Mortality - Group 1: 0 participants - Group 2: 1 participant - Group 3: 0 participants Loss to follow-up - Group 1: 5 participants - Group 2: 8 participants - Group 3: 4 participants
Outcomes	Maximum walking distance, pain-free walking distance, number of secondary interventions, procedure-related complications, SF-12 Physical, SF-12 Mental, Walking Impairment Questionnaire Score, Peripheral Artery Questionnaire Score, hourly free-living steps on pedometer
Notes	Source of funding: grants from National Heart, Lung, and Blood Institute. Financial support from Cordis/Johnson & Johnson (Warren, NJ), eV3 (Plymouth,MN), and Boston Scientific (Natick, MA). Cilostazol was donated to all study participants by Otsuka America, Inc (San Francisco, CA). Pedometers were donated by Omron Healthcare, Inc (Lake Forest, IL). Krames Staywell (San Bruno, CA) donated print materials on exercise and diet. Notes: The endovascular revascularisation plus supervised exercise therapy treatment arm was stopped after including 8 participants owing to slow enrolment. Authors' conclusion: "Both supervised exercise and endovascular revascularization had better 18-month outcomes than medical treatment. Both treatments provided comparable durable improvement in functional status and in quality of life up to 18 months. The durability of claudication exercise interventions merits its consideration as a primary claudication treatment."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A real-time Web-based randomisation programme was used to randomise participants
Allocation concealment (selection bias)	Low risk	Central Web-based allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not possible given the nature of the intervention (endovascular revascularisation)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study reported to be an "observer-blinded" randomised trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	All analyses according to intention-to-treat principle; censoring was moderate (10%) after 6 months' follow-up and was well balanced between treatment groups
Selective reporting (reporting bias)	Low risk	All relevant outcome measures as specified in the methods section were reported
Other bias	Unclear risk	Intended recruitment based on power calculations was 252 participants; eventually 119 participants were included in the study

Nordanstig 2014

Methods	Study design: parallel 2-arm RCT Number of sites: 1 Sample size estimation: From power calculations, a total sample size of 158 participants was needed with the assumption of a maximum dropout rate of 25% and 80% power to detect relevant differences between the 2 groups. Follow-up: 6 and 12 months
Participants	Country and setting: Sweden, Department of Vascular Surgery at university hospital Inclusion criteria - Stable (≥ 6 months) intermittent claudication, without any other important activity-limiting medical condition - Aged ≤ 80 years Exclusion criteria - Very mild claudication symptoms - Severe claudication symptoms making invasive treatment mandatory - Weight > 120 kg - ≥ 2 previously failed ipsilateral vascular interventions - Inability to understand the Swedish language Number of participants assessed and randomised: 464 participants screened for inclusion; of these, 205 participants were eligible, and eventually 158 participants were randomised in the trial Demographics - Age (years): Group 1: mean 68 (SD 7); Group 2: mean 68 (SD 6) - Gender (male): Group 1: 41 (52%); Group 2: 38 (48%)
Interventions	Group 1: invasive vascular procedure including open surgery or endovascular revascularisation with primary stenting in the aortoiliac segment and selective stenting in the femoropopliteal segment plus claudication pharmacotherapy (cilostazol 100 mg twice daily), home-based exercise training advice, and cardiovascular risk factor management, n = 79 (of these, 52 participants received an endovascular revascularisation procedure) Group 2: non-invasive management including claudication pharmacotherapy (cilostazol 100 mg twice daily), home-based exercise training advice, and cardiovascular risk factor management, n = 79 Compliance with interventions - Group 1: 70 participants received invasive treatment; from them, 52 participants received an endovascular intervention, 60% adherence to cilostazol treatment at 12 months, no data on exercise adherence - Group 2: 60% adherence to cilostazol treatment at 12 months; no data on exercise adherence Mortality - Group 1: 1 participant of the 52 participants receiving endovascular revascularisation - Group 2: 0 participants Lost to follow up: - Group 1: 2 participants of 52 participants receiving endovascular revascularisation - Group 2: 3 participants
Outcomes	Maximum walking distance, intermittent claudication distance, number of secondary interventions, procedure-related complications, SF-36 Physical Function, SF-36 Role Physical, SF-36 Bodily Pain, SF-36 General Health, SF-36 Vitality, SF-36 Social, SF-36 Emotional, SF-36 Mental Health, and VascuQol

Notes	Source of funding: Study was funded by the Fred G. and Emma E. Kanolds Foundation/Gothenburg Medical Society; Helena Ahlin Foundation; Odd Fellow, Karlstad, Sweden; Swedish Heart and Lung Foundation; and Hjalmar Svensson Foundation. Notes: Outcome data from the subgroup of 52 participants who received an endovascular revascularisation at baseline in the invasive treatment group were provided by study authors and were included in the analyses in this systematic review. Authors' conclusion: "An invasive treatment strategy improves health-related quality of life and intermittent claudication distance after 1 year in patients with stable lifestyle-limiting claudication receiving current medical management. Long-term follow-up data and health-economic assessments are warranted to further establish the role for revascularization in intermittent claudication."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed via computerised randomisation software based on minimisation method
Allocation concealment (selection bias)	Low risk	Allocation sequence was concealed using computerised randomisation software
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not possible given the nature of the intervention (endovascular revascularisation)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors not adequately discussed in the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All analysis performed by intention-to-treat principle; censoring during 12-month follow-up low and well balanced between treatment groups
Selective reporting (reporting bias)	Low risk	All relevant outcome measures as specified in the methods section were reported in the results section
Other bias	Low risk	No other forms of bias identified

Nylaende 2007

Methods	Study design: parallel 2-arm RCT Number of sites: 1 Sample size estimation: approximately 100 participants in each group; thus a total of 200 participants to detect a difference of 20% in QoL between groups assuming type I error of 5% and power of 80% Follow-up: 3, 12, and 24 months
Participants	Country and setting: Norway, Centre of Vascular Surgery at university hospital Inclusion criteria - < 80 years of age - Symptomatic IC > 3 months - Ankle brachial index < 0.9 without pain at rest and/or ischaemic skin changes - Lesion feasible for angioplasty evaluated by angiography - Subjective pain-free walking distance < 400 metres - Ability to exercise on a treadmill Exclusion criteria - Previous vascular or endovascular surgery - Diabetic skin ulceration - Renal insufficiency (defined as serum creatinine > 150 mmol/L) - Oral anticoagulant medication - Suffering from a physical or mental disorder expected to impede compliance Number of participants assessed and randomised: 826 participants were assessed for inclusion; finally 56 participants could be included and randomised to 1 of 2 treatment groups. Demographics - Age (years): Group 1: median 68 (25 to 75 percentiles: 56 to 72); Group 2: median 69 (25 to 75 percentiles: 61 to 75) - Gender (male): Group 1: 16 (57%); Group 2: 15 (54%)
Interventions	Group 1: endovascular revascularisation with primary stenting for iliac occlusions and selective stenting for iliac stenoses plusoptimal medical treatment, n = 28 Group 2: optimal medical treatment including active smoking cessation, advice on home-based exercise therapy, individual nutritional advice, and acetylsalicylic acid 160 mg daily to all participants and cardiovascular risk factor management, n = 28 (for analysis, this group was labelled as 'no therapy') Compliance with interventions - Group 1: All procedures were technically successful. - Group 2: No data were provided on home-based exercise therapy compliance. Mortality - Group 1: 1 participant - Group 2: 0 participants Loss to follow-up - Group 1: 1 participant - Group 2: 4 participants
Outcomes	Maximum walking distance, pain-free walking distance, number of secondary interventions, SF-36 Physical Function, SF-36 Role Physical, SF-36 Bodily Pain, SF-36 General Health, SF-36 Vitality, SF-36 Social, SF-36 Emotional, SF-36 Mental, SF-36 Health Transition, Claudication Score (5 domains), visual analogue scale
Notes	Source of funding: unrestricted grants from Pfizer AS, Norway Authors conclusion: "Early intervention with PTA in addition to optimal medical treatment seems to have a generally more positive effect compared to optimal medical treatment only, on haemodynamic, functional as well as quality of life aspects during the first 2 years in patients with intermittent claudication."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A "computerized randomisation list" was used
Allocation concealment (selection bias)	Low risk	Sealed envelopes were used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not possible given the nature of the intervention (endovascular revascularisation)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors not adequately discussed in the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All relevant outcome measures as specified in the methods section were reported
Selective reporting (reporting bias)	Low risk	Censoring during 12-month follow-up minimal (9%) and well balanced between groups
Other bias	Unclear risk	Intended recruitment based on power calculations was 200 participants; eventually 56 participants were included in the study, Source of funding: unrestricted grants from Pfizer AS, Norway

Spronk 2009

Methods	Study design: parallel 2-arm RCT Number of sites: 1 Sample size estimation: 68 participants in each arm based on 80% power and significance level of 0.05 to detect 25% difference in improvement in physical functioning dimension of SF-36 between the 2 groups Follow up: 1, 6, 12 months and 7 years
Participants	Country and setting: Netherlands, outpatient clinic at a non-university hospital Inclusion criteria - Rutherford category 1, 2, or 3 claudication with duration ≥ 3 months - Maximum pain-free walking distance < 350 metres - Ankle-brachial index < 0.9 at rest or decreasing by more than 0.15 after the treadmill test - ≥ 1 vascular stenoses of > 50% diameter reduction at the iliac or femoropopliteal level on magnetic resonance angiography Exclusion criteria - Abdominal aortic aneurysm, life-incapacitating cardiac disease (New York Heart Association Class III and higher) - Multi-level disease (i.e. same-side stenoses at both iliac and femoral levels, requiring multiple revascularisation procedures) - Isolated tibial artery disease - Lesions deemed unsuitable for revascularisation - Prior treatment for the lesion (including exercise therapy) Number of participants assessed and randomised: 293 participants assessed, 151 participants randomised to 1 of 2 treatment groups Demographics - Age (years): Group 1: mean 65 (SD 11); Group 2: mean 66 (SD 9) - Gender (male): Group 1: 44 (59%); Group 2: 39 (52%)
Interventions	Group 1: endovascular revascularisation with selective stenting, n = 76 Group 2: supervised exercise therapy for 24 weeks (2 sessions/week, 30 minutes/session), n = 75 Compliance with interventions - Group 1: In 4 participants, revascularisation failed technically - Group 2: Per participant, on average 33 (SD 10) sessions of exercise followed Mortality - Group 1: 5 participants (after 7 years: 15) - Group 2: 3 participants (after 7 years: 17) Loss to follow-up - Group 1: 2 participants (after 7 years: 14) - Group 2: 0 participants (after 7 years: 22)
Outcomes	Maximum walking distance, pain-free walking distance, number of secondary interventions, procedure-related complications, SF-36 Physical Functioning, SF-36 Physical Role, SF-36 Bodily Pain, SF-36 General Health, VascuQol
Notes	Source of funding: not applicable Authors conclusion: "After 6 and 12 months, patients with intermittent claudication benefited equally from either endovascular revascularization or supervised exercise."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A "computer generated block-randomized list" was used, prepared in advance by an independent statistician
Allocation concealment (selection bias)	Low risk	Allocation was "sealed for every particular participant."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not possible given the nature of the intervention (endovascular revascularisation)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Walking distance evaluated by an independent assessor blinded to assigned treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All analysis according to intention-to-treat principle; after 12 months' follow-up, censoring minimal (7%) and well balanced between the 2 groups
Selective reporting (reporting bias)	Low risk	All relevant outcome measures as specified in the methods section were reported
Other bias	Low risk	No other forms of bias identified

Whyman 1996

Methods	Study design: parallel 2-arm RCT Number of sites: 1 Sample size estimation: 54 participants based on 90% power and significance level of 0.05 to detect 40% difference in number of participants with symptomatic improvement between intervention and control groups Follow-up: 3, 6, and 24 months
Participants	Country and setting: United Kingdom, outpatient department of a university hospital Inclusion criteria - Predominantly unilateral intermittent claudication - Lesion suitable for endovascular revascularisation Exclusion criteria - Previous angioplasty or arterial surgery to the symptomatic leg - Iliac occlusion or > 10 cm length femoropopliteal occlusion, multiple stenoses or diffuse disease with long stenoses - Participants taking oral anticoagulants - Duration of symptoms < 1 month - Inability to manage the treadmill examination - Any psychiatric illness or other reason making follow-up difficult. Number of participants assessed and randomised: 425 participants assessed, 62 participants randomised Demographics - Age (years): Group 1: mean 60.6 (range 44 to 73); Group 2: mean 62.6 (range 45 to 78) - Gender (male): Group 1: 23 (77%); Group 2: 28 (88%)
Interventions	Group 1: endovascular revascularisation without stenting, n = 30 Group 2: conventional medical treatment including low-dose aspirin plus advice on smoking and exercise, n = 32 (for analysis, this group was labelled as 'no therapy') Compliance with interventions: not reported Mortality - Group 1: 0 participants - Group 2: 2 participants Loss to follow-up - Group 1: 1 participant - Group 2: 2 participants
Outcomes	Maximum walking distance, pain-free walking distance, number of secondary interventions, Nottingham health profile scores, self-reported maximum walking distance
Notes	Source of funding: grant from the Scottish Home and Health Department, cost of balloon catheters from Meadox, UK Authors' conclusion: "Two years after PTA, patients had less extensive disease than medically treated patients, but this did not translate into a significant advantage in terms of improved walking or quality of life."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was carried out via a computerised random allocation system
Allocation concealment (selection bias)	Low risk	Allocation was carried out via a computerised random allocation system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not possible given the nature of the intervention (endovascular revascularisation)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors not adequately discussed in the study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Censoring minimal (5%) and comparable between groups, yet participants in the control group who underwent angioplasty or surgery excluded from analysis
Selective reporting (reporting bias)	Low risk	All relevant outcome measures as specified in the methods section were reported
Other bias	Unclear risk	Source of funding: cost of balloon catheters from Meadox, UK

ABI: ankle brachial pressure index.

IC: intermittent claudication.

IQR: interquartile range.

PTA: percutaneous transluminal angioplasty.

QoL: quality of life.

RCT: randomised controlled trial.

SD: standard deviation.

SF-36: Short Form-36.

Characteristics of excluded studies

Study	Reason for exclusion
Bo 2013	All participants received endovascular revascularisation
Brodmann 2013	Two endovascular revascularisation techniques were compared; no non-interventional treatment group was included
Gabrielli 2012	Two endovascular revascularisation techniques were compared; no non-interventional treatment group was included
Gelin 2001	Intervention group included participants with open and endovascular revascularisation; no data could be provided for the subgroup of participants receiving endovascular revascularisation
Giugliano 2013	Participant assignment to a specific group of treatment was not randomised
Heider 2009	Participants were followed up to 4 weeks. No relevant outcome measures for this systematic review were reported
Husmann 2008	Walking distances were recorded only up to 1 month follow-up; no long-term data were provided. In addition, no other relevant outcome measures for this systematic review were reported
Kruidenier 2011	All participants received endovascular revascularisation
Thomson 1999	Abstract data only with incomplete results; no additional data could be provided

Characteristics of ongoing studies

Frans 2012a

Trial name or title	SUPERvised Exercise Therapy or Immediate PTA for Intermittent Claudication in Participants With an Iliac Artery Obstruction
Methods	Study design: multi-centre randomised controlled trial Sites: 15 Dutch hospitals Sample size estimation: 400 participants to detect a clinically relevant difference in quality-adjusted life-years between the 2 groups based on 90% power and 2-sided significance level of 0.05 Follow up: 1 week, 1, 6, and 12 months
Participants	Consecutive outpatients with intermittent claudication due to aortoiliac disease with a walking distance between 100 and 300 metres on a treadmill at 3.2 km/h and 10% incline. All participants must have an iliac artery obstruction with a diameter reduction ≥ 50%
Interventions	Group 1: endovascular revascularisation with selective stenting Group 2: supervised exercise therapy for 6 months
Outcomes	Maximum walking distance, pain-free walking distance, complications, treatment failures, additional interventions, costs, AMC linear disability score, VascuQol, Short-Form 36, EuroQol
Starting date	Inclusion started in September 2011
Contact information	m.j.koelemaij@amc.uva.nl
Notes	Owing to slow enrolment, inclusion stopped prematurely (241 participants included per May 2015; www.superstudie.nl).

NCT01230229

Trial name or title	Primary Stenting vs Conservative Treatment in Claudicants - A Study on Quality of Life (NCT01230229)
Methods	Study design: randomised controlled trial Estimated enrolment: 100 participants Follow-up: 12 and 24 months
Participants	Patients with stable intermittent claudication (Fontaine IIa and IIb) due to superficial femoral artery disease
Interventions	Group 1: endovascular revascularisation with primary stenting (self-expanding stent) Group 2: best medical treatment including an exercise programme
Outcomes	Primary: improvement in quality of life scores (Short Form-36 and EuroQol-5D surveys) Secondary: ABI, walking distances, cost parameters
Starting date	January 2010
Contact information	Hans Lindgren, MD; e-mail: hanslindgren@gmail.com
Notes	Planned recruitment and randomisation of 100 participants; estimated study completion date June 2017 (https://clinicaltrials.gov/ct2/show/study/NCT01230229?term=endovascular+and+claudication#desc)

ABI: ankle brachial pressure index.

AMC: academic medical centre.

PTA: percutaneous transluminal angioplasty.

QoL: quality of life.

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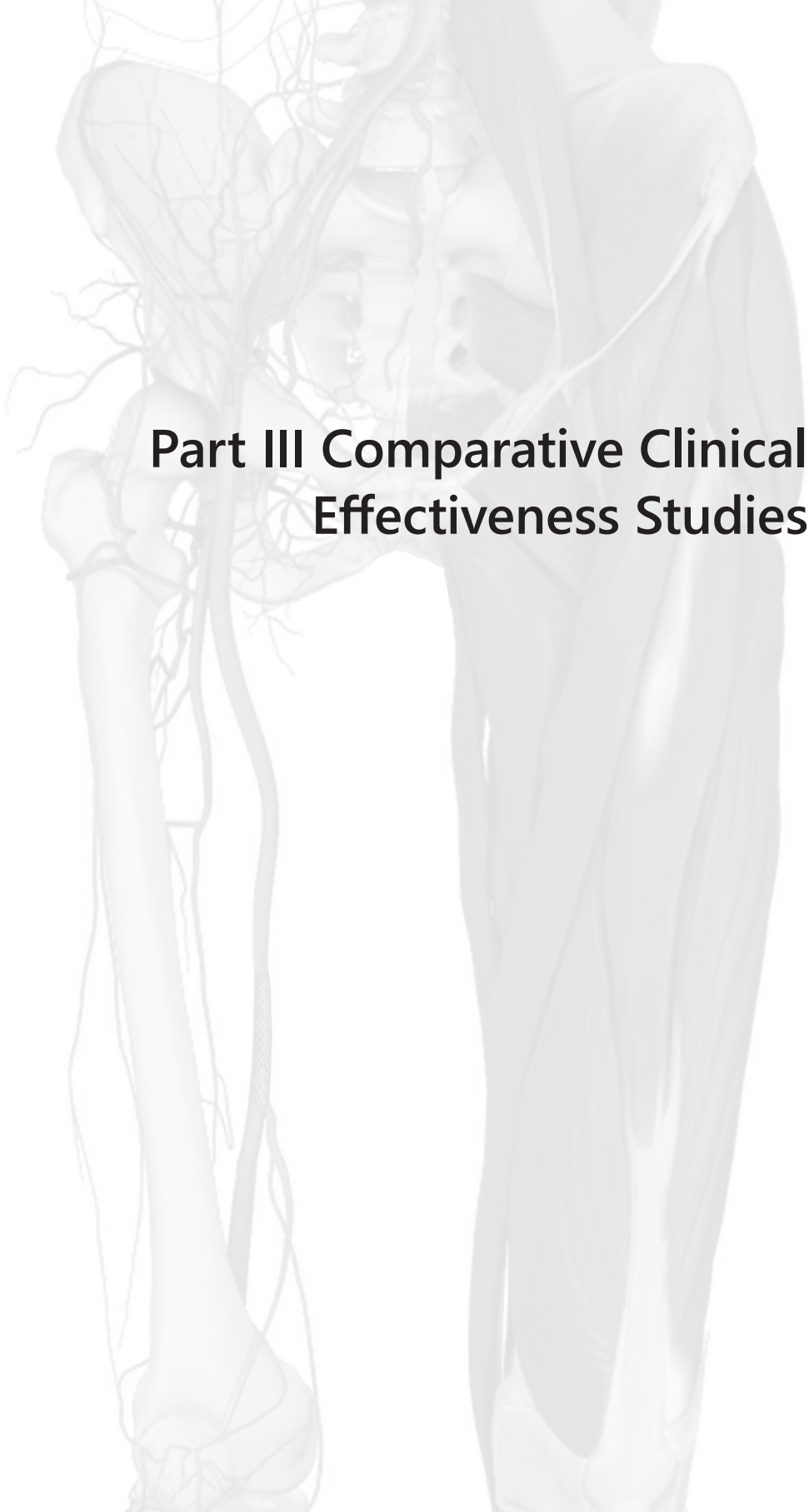

Part III Comparative Clinical Effectiveness Studies

Chapter 5

Long-term clinical effectiveness of supervised exercise therapy versus endovascular revascularization for intermittent claudication from a randomized clinical trial

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Br J Surg 2013 Aug; 100: 1164–1171

ABSTRACT

Background

Long-term comparisons of supervised exercise and endovascular revascularization for patients with intermittent claudication are scarce. The long-term clinical effectiveness of supervised exercise therapy and endovascular revascularization was assessed in patients from a randomized trial.

Methods

Consenting patients with intermittent claudication were assigned randomly to either supervised exercise therapy or endovascular revascularization. Outcome measures on functional performance (pain-free and maximum walking distance, ankle : brachial pressure index), quality of life (QoL) and number of secondary interventions were measured at baseline and after approximately 7 years of follow-up. Repeated-measurement and Kaplan–Meier methods were used to analyse the data on an intention-to treat-basis.

Results

A total of 151 patients were randomized initially to either supervised exercise therapy or endovascular revascularization. After 7 years, functional performance (P <0·001) and QoL (P ≤0·005) had improved after both supervised exercise therapy and endovascular revascularization. Long-term comparison showed no differences between the two treatments, except in the secondary intervention rate, which was significantly higher after supervised exercise therapy (P=0.001). Nevertheless, the total number of endovascular and surgical interventions (primary and secondary) remained higher after endovascular revascularization (P <0·001).

Conclusions

In the longer term, supervised exercise therapy-first or endovascular revascularization-first treatment strategies were equally effective in improving functional performance and QoL in patients with intermittent claudication. The substantially higher number of invasive interventions in the endovascular revascularization-first group supports a supervised exercise therapy-first treatment strategy for intermittent claudication. Registration number: NTR199 (http://www.trialregister.nl).

Intermittent claudication, Rutherford categories 1–3[1], is the classical symptom of peripheral arterial disease (PAD). intermittent claudication affects about 2 per cent of the population aged 40–44 years, increasing to 8 per cent in people aged 70–74 years[2]. Patients with intermittent claudication have significant functional disability due to their impairedwalking[3], and suffer reduced quality of life (QoL), which is comparable to the situation in other forms of cardiovascular disease[4]. Previous studies have established both supervised exercise therapy and endovascular revascularization to be effective in improving walking performance and QoL in patients with intermittent claudication[5,6]. Consequently both strategies are recommended as treatment options by the TransAtlantic Inter-Society Consensus (TASC) II and the American College of Cardiology/American Heart Association Practice guidelines for the management of patients with PAD[2,7]. supervised exercise therapy has the advantage of being a safe non-invasive treatment, whereas endovascular revascularization is attractive because of its immediate effect, if successful. Direct comparison of these two options in the long term can help determine which treatment is more durable and should be offered as initial therapy for intermittent claudication.

Controlled trials comparing supervised exercise therapy and endovascular revascularization, especially in the long term, are scarce. Previously, the Comparing Exercise Therapy with Angioplasty for Claudication (CETAC) trial[8] and a systematic review, with results from three other controlled trials comparing supervised exercise therapy and endovascular revascularization for intermittent claudication[9], concluded that the clinical effectiveness of supervised exercise therapy and endovascular revascularization was equivalent after 12 months. However, owing to lack of long-term data, it remains unclear whether the improvements gained in the first 12 months are sustained.

This study was a late evaluation of patients from the CETAC trial. The aim was to compare the long-term clinical effectiveness of a supervised exercise therapy-first or an endovascular revascularization-first treatment strategy in patients with intermittent claudication.

METHODS

The study design and methods of the CETAC trial have been published previously[8]. The CETAC trial was a single-centre randomized trial comparing the clinical effectiveness of supervised exercise therapy versus endovascular revascularization as initial treatment for patients with intermittent claudication. The study was approved by the institutional review board and guidelines of Good Clinical Practice and the Consolidated Standards of Reporting Trials were followed[10]. The study was registered as an international standard randomized controlled trial (ISRCTN 64443682)[11].

Study patients and randomization

In brief, patients with stable intermittent claudication visiting the outpatient clinic were considered for inclusion in the trial if they were suitable candidates for both supervised exercise therapy and endovascular revascularization, and agreed to participate in the trial. Inclusion and exclusion criteria have been published previously[8]. Patients with both iliac and femoropopliteal disease diagnosed on magnetic resonance angiography were included. After providing informed consent, patients were randomized to either supervised exercise therapy or endovascular revascularization using a computer-generated block-randomized list. For the purposes of the present study, participants in the CETAC trial were contacted again, and those willing to be reinvestigated signed a new consent form. Those who could not attend the clinic were contacted by telephone, and asked to fill in a QoL questionnaire and return it by mail.

Interventions

At baseline, patients with one or more risk factors for cardiovascular disease were referred to an internal medicine physician for secondary prevention according to the European Society of Cardiology guidelines on cardiovascular risk factor management in clinical practice[8,12].

The supervised exercise therapy programme consisted of 24-weeks of supervised treadmill exercise, two sessions per week, each lasting 30 min[8]. In addition, patients were encouraged to walk for at least 30min three times a week at home and to continue walking for at least 1 h per day after completing the 24-week programme.

Endovascular revascularization was performed by an experienced interventional radiologist. For iliac revascularization, a self-expanding nitinol stent was placed if the initial balloon angioplasty was not technically successful. For femoral revascularization, a self-expanding nitinol stent was placed if the residual lumen diameter was less than 50 per cent after the initial balloon angioplasty. After the procedure all the patients were given general recommendations concerning lifestyle changes and were strongly advised to walk regularly.

Outcome measures and assessments

Consenting patients attended for a standard treadmill walking test (speed 3·5 km/h, no graded incline) to assess functional performance, which included maximum walking distance (MWD), pain-free walking distance (PFWD), and ankle : brachial index (ABI) at rest and after the treadmill walking test. They also completed a patientreported QoL questionnaire.

The questionnaire consisted of the rating scale[13], Short Form 36 (SF-36; QualityMetric, Lincoln, Rhode Island, USA)[14] and the PAD-specific vascular QoL score (VascuQoL)[15] instruments. As physical functioning, role functioning limitations due to physical problems, bodily pain and general health domains of the SF-36 instrument are the most relevant for

describing the health status of patients with PAD[8,16], the present analysis was restricted to these four domains. For all reported QoL instruments, higher scores correspond to better QoL as perceived by the patient.

Secondary interventions and outcomes

To gather information on the type, date and cause of any subsequent secondary intervention following initial randomization, the patients' medical records were reviewed by two authors independently. Disagreements were resolved by consensus. A secondary intervention was defined as an additional invasive treatment offered to the patient during follow-up as a result of primary randomized treatment failure. This included any surgical or endovascular intervention. The number of patients who required leg amputations as a consequence of limb ischaemia was registered for each treatment group. If a patient had died during follow-up, the hospital records were searched and, if necessary, the patient's general practitioner was contacted to determine the exact date and cause of death.

Statistical analysis

The main analyses were conducted according to the intention-to-treat principle. Completeness of long-term follow-up in each treatment group was calculated as the ratio of the total observed person-time of follow up to the potential maximum[17]. For the continuous outcome measures of physical performance and QoL, the significance of mean change within and between each treatment group at follow-up compared with baseline was analysed using mixed models for repeated measures. The significance of differences between the two treatment groups regarding survival and having one or more secondary intervention(s) was evaluated using Fisher's exact test, Kaplan–Meier methods, and Cox regression analysis to calculate hazard ratios (HRs) with 95 percent confidence intervals (c.i.). In the Kaplan–Meier analysis for secondary interventions, patients without a secondary intervention were censored at death, loss to follow-up or at the end of the study. The log rank test was used to compare the Kaplan–Meier curves. Post hoc perprotocol analyses were performed, which included data from patients who completed the allocated treatment and finished the study without any secondary intervention.

Furthermore, a sensitivity analysis excluding patients with missing values in the long term was performed (completecase analysis) to determine whether this might affect the main results. For all analyses a significance level of 0.050 (two-sided) was considered statistically significant. Analyses were carried out using SPSS version 17 software (IBM, Armonk, New York, USA) and SAS version 9.2 (SAS Institute, Cary, North Carolina,USA).

RESULTS

A total of 151 patients were initially assigned randomly to supervised exercise therapy

(75) or endovascular revascularization (76). In the endovascular revascularization group one patient refused further participation after randomization, but before undergoing the intervention and baseline data collection; this patient was therefore excluded from further analysis. There were no significant differences in baseline characteristics regarding demographic data and co-morbidities between the supervised exercise therapy and endovascular revascularization groups[8]. Baseline functional performance measures and QoL scores were also comparable between groups, except for PFWD (P=0.043)[8]. Similarly, baseline characteristics of the patients available for long-term follow-up were comparable in the supervised exercise therapy and endovascular revascularization groups, except for PFWD (P =0.024).

In the supervised exercise therapy group, adherence to the supervised exercise therapy programme was good, with a mean(s.d.) of 33(10) sessions followed. In the endovascular revascularization group, revascularization failed technically in four patients. Therefore, two patients underwent a surgical procedure as initial intervention, and two were offered a home-based exercise programme.

After a median follow-up of approximately 7 (range 0.07–9.17) years, 17 patients in the supervised exercise therapy group and 15 in the endovascular revascularization group had died. Completeness of long-term follow-up was 70.9 per cent (236 of 333 weeks) and 83.8 per cent (279 of 333 weeks) respectively. Thirtysix patients were available for review in the supervised exercise therapy group and 47 in the endovascular revascularization group. Sixtyfive patients agreed to attend for treadmill testing; the remaining 18 (7 supervised exercise therapy, 11 Endovascular revascularization) were interviewed by telephone on their general health and returned a completed QoL questionnaire by mail.

Functional performance

In both the supervised exercise therapy and endovascular revascularization groups, MWD and PFWD had increased significantly after 7 years compared with baseline values (*P* <0.001). The mean long-term improvement in the supervised exercise therapy group was 975 (95 percent c.i. 772 to 1177)m for MWD and 700 (461 to 941)m for PFWD. Similarly, in the endovascular revascularization group the improvement in MWD and PFWD was sustained after 7 years, with a mean increase of 1074 (881 to 1267) and 940 (710 to 1171) m respectively compared with baseline (Table 1). There were no significant differences in MWD and PFWD between the groups after 7 years. The ABI, both at rest and after exercise, increased significantly after 7 years in both groups compared with baseline values (*P* <0.001). There were no significant differences in ABI between the groups after 7 years of follow-up (Table 1).

Quality of life

In both groups the VascuQoL score increased significantly after approximately 7 years. The mean long-term improvement was 0.6 (95 percent c.i. 0.2 to 1.1) in the supervised

Table 1. Baseline scores and mean changes within, and difference between, the treatment groups in measures of functional performance.

	Supervised Exercise (n=75)	**Endovascular Revascularization** (n=75)	**Mean Difference** (between groups)	***P***†
Maximum Walking Distance (m)				
Baseline	186 (164 ; 208)	174 (157 ; 191)		
1 year	1041 (892 ; 1189)*	829 (674 ; 984)*	212 (-4 ; 426)	0.063
7 years	975 (772 ; 1177)*	1074 (881 ; 1267)*	-99 (-379 ; 180)	0.481
Pain Free Walking Distance (m)				
Baseline	104 (89 ; 119)	82 (71 ; 93)		
1 year	916 (743 ; 1090)*	784 (599 ; 968)*	133 (-121 ; 386)	0.302
7 years	700 (461 ; 941)*	940 (710 ; 1171)*	-240 (-573 ; 93)	0.156
Ankle Brachial Index (at rest)				
Baseline	0.62 (0.58 ; 0.66)	0.63 (0.59 ; 0.67)		
1 year	0.05 (0.01 ; 0.09)*	0.18 (0.14 ;0.23)*	-0.14 (-0.19 ; -0.08)	0.000
7 years	0.20 (0.12 ; 0.27)*	0.21 (0.14 ; 0.28)*	-0.01 (-0.12 ; 0.09)	0.809
Ankle Brachial Index (post- exercise)				
Baseline	0.42 (0.37 ; 0.47)	0.41 (0.36 ; 0.46)		
1 year	0.17 (0.11 ; 0.23)*	0.32 (0.26 ; 0.38)*	-0.15 (-0.24 ; -0.07)	0.001
7 years	0.22 (0.14 ; 0.30)*	0.31 (0.23 ; 0.38)*	-0.09 (-0.19 ; 0.02)	0.123

Data are presented as mean improvement compared to baseline (95 per cent confidence interval), Measures of functional performance after 7 years assessed in 29 out of 36 patients in the supervised exercise group and in 36 out of 47 patients in the endovascular revascularization group.

* P <0.050 (mean change versus baseline, Fisher's least significant difference test from mixed model).

† Wald test for fixed effects in mixed model

exercise therapy group (P =0.005) and 0.9 (0.5 to 1.3) in the endovascular revascularization group (P <0.001), with no significant difference between the two treatments (Table 2). The rating score did not improve significantly in either group after 7 years of follow-up, and there were no significant differences between the groups (Table 2). Some of the SF-36 health domain scores showed significant improvement after 7 years of follow-up in both groups. Nonetheless, there were no significant differences in SF-36 scores between the groups (Table 2).

Survival and secondary interventions

During follow-up, 17 patients in the supervised exercise therapy group and 15 in the endovascular revascularization group died. The cumulative survival probability for 7 years after randomization was 68 percent in the supervised exercise therapy group and 74 percent in the endovascular revascularization group; the survival rates were not significantly different between the two groups (HR 1.35, 95 percent c.i. 0.67 to 2.70; P =0.402).

Seven years after randomization, the proportion of patients who had not needed a secondary intervention (endovascular or surgery) was 47 percent in the supervised exercise therapy group and 73 percent in the endovascular revascularization group (Figure 1); the

Table 2. Baseline scores and mean changes within, and difference between, the treatment groups in measures of quality of life.

	Supervised Exercise (n=75)	**Endovascular Revascularization** (n=75)	**Mean Difference** (between groups)	***P***†
Vascular QoI score (1-7)				
Baseline	4.3 (4.0 ; 4.6)	4.2 (4.0 ; 4.4)		
1 year	0.6 (0.2 ; 1.0)*	0.7 (0.4 ; 1.1)*	-0.1 (-0.6 ; 0.4)	0.634
7 years	0.6 (0.2 ; 1.1)*	0.9 (0.5 ; 1.3)*	-0.3 (-0.9 ; 0.3)	0.290
Rating Score (0-100)				
Baseline	65.4 (61.3 ; 69.5)	62.3 (58.4 ; 66.2)		
1 year	6.5 (2.0 ; 11.0)*	4.5 (0.0 ; 8.9)*	2.0 (-4.3 ; 8.3)	0.527
7 years	-0.3 (-6.8 ; 6.0)	4.3 (-1.6 ; 10.2)	-4.6 (-13.3 ; 4.0)	0.292
SF-36 Physical Functioning (0-100)				
Baseline	49.4 (44.8 ; 54.0)	42.0 (36.1 ; 47.9)		
1 year	12.7 (7.6 ; 17.8)*	17.1 (12.0 ; 22.1)*	-4.4 (-11.6 ; 2.8)	0.228
7 years	4.9 (-3.7 ; 13.4)	11.1 (3.2 ; 18.9)*	-6.2 (-17.8 ; 5.3)	0.287
SF-36 Role Physical Score (0-100)				
Baseline	49.0 (38.7 ; 59.3)	36.7 (24.9 ; 48.5)		
1 year	5.9 (-4.9 ; 16.8)	20.7 (9.8 ; 31.5)*	-14.7 (-30.0 ; 0.6)	0.059
7 years	-2.5 (-13.5 ; 18.5)	18.0 (3.1 ; 32.9)*	-20.5 (-42.3 ; 1.3)	0.065
SF-36 Bodily Pain (0-100)				
Baseline	54.8 (50.0 ; 59.9)	50.1 (45.4 ; 54.7)		
1 year	9.7 (3.6 ; 15.7)*	11.3 (5.3 ; 17.3)*	-1.7 (-10.2 ; 6.9)	0.702
7 years	6.3 (-1.5 ; 14.2)	10.6 (3.3 ; 18.0)*	-4.3 (-15.0 ; 6.5)	0.431
SF-36 General Health (0-100)				
Baseline	53.8 (49.4 ; 58.2)	53.1 (48.0 ; 58.2)		
1 year	4.9 (0.4 ; 9.4)*	2.1 (-2.5 ; 6.6)	2.8 (-3.6 ; 9.2)	0.384
7 years	-6.9 (-12.4 ; -1.4)*	-3.2 (-8.5 ; 2.0)	-3.7 (-11.3 ; 3.9)	0.341

Data are presented as mean improvement compared to baseline (95 per cent confidence interval), QoL, Quality of Life; SF-36, Short-Form 36; Measures of Quality of Life after 7 years reported by 34 out of 36 patients in the supervised exercise group and by 43 out of 47 patients in the endovascular revascularization group.

* P <0.050 (mean change versus baseline, Fisher's least significant difference test from mixed model).

† Wald test for fixed effects in mixed model

secondary intervention rate was significantly higher in the supervised exercise therapy group (HR 2.56, 1.41 to 4.63; P =0.001). Nevertheless, the total number of endovascular and surgical procedures performed at baseline (primary) plus those performed during followup (secondary) were significantly higher in the endovascular revascularization group (P <0.001) (Table 3)

Thirty-two patients in the supervised exercise therapy group underwent one or more secondary intervention(s) during follow-up. In the majority of patients (27 of 32) this was intervention for a pre-existing lesion that had already been identified at baseline; in only five patients was the intervention for a new atherosclerotic lesion. The secondary interventions were endovascular in 20 of 32 patients and the majority (19 of 32) were done for stenosis in the aortoiliac segment. Seventeen patients in the endovascular

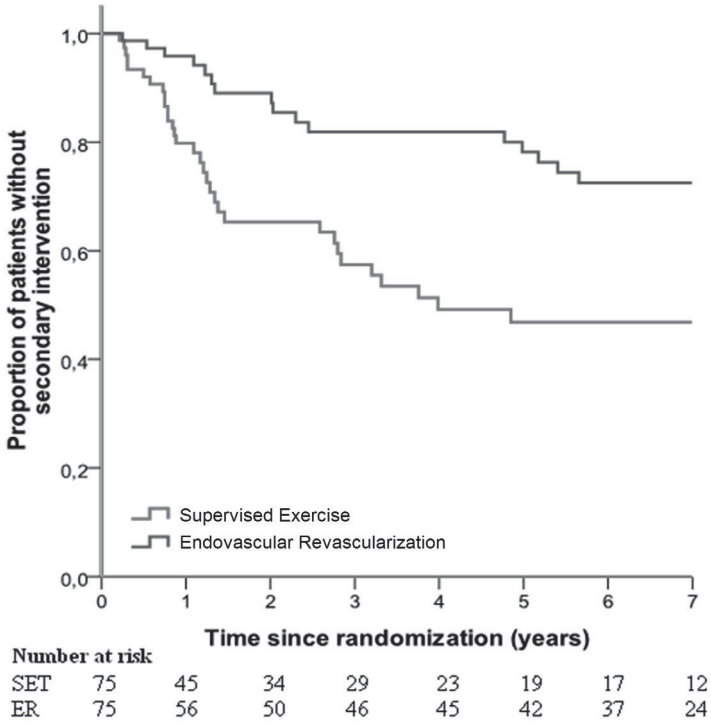

Figure 1. Kaplan–Meier estimates of the proportion of patients without secondary intervention during follow-up in supervised exercise and endovascular revascularization groups. P <0.001 (log rank test)

Table 3. Secondary endovascular or surgical interventions.

	Supervised Exercise (n=75)	**Endovascular Revascularization** (n=75)	***P*** ‡
No. of patients with one or more secondary intervention(s)	32	17	0.01
Secondary intervention lesion	27		
Intervention on pre-existing lesion	5	13	0.70
Intervention on new lesion		4	
Secondary intervention segment	19		
Aortoiliac segment	13	7	0.25
Femoropopliteal segment		10	
Secondary intervention procedure	20		
Endovascular procedure	12	8	0.37
Surgical procedure	2.0 (1 – 6)	9	
Average number of secondary interventions*	64	2.8 (1 - 7)	
Total no. of interventions (primary and secondary)†		121	0.10§
No. of patients with amputation	2		<0.01
Minor amputation	-	-	1.00
Major amputation		3	

*Mean (range) number of secondary interventions (endovascular or surgical procedure) during follow-up once a patient needed a secondary intervention. †Total number of endovascular and surgical procedures at baseline (primary) and during follow-up (secondary). ‡Fisher's exact test, except §Student's t test.

revascularization group required one or more secondary endovascular or surgical intervention(s), including 13 who had reintervention for a previously treated lesion and four who underwent intervention for a new lesion. The secondary interventions in the endovascular revascularization group were endovascular in eight of 17 patients and the majority (10 of 17) were for (re)stenosis in the femoropopliteal segment (Table 3).
Although there was no significant difference in amputation rates between the two groups, the severity of the amputations differed; there were two minor amputations in the supervised exercise therapy group and three major amputations in the endovascular revascularization group (Table 3).

The per-protocol analysis, which included data from patients who completed the allocated treatment and finished the study without having any secondary intervention, did not change the results regarding mean difference between the groups in functional performance measures and QoL scores compared with the results of the main analysis. Similarly, the complete-case analysis, which excluded patients with missing values in the long term, yielded similar results to the main analysis in terms of mean difference in functional performance measures and QoL scores.

DISCUSSION

This report examined the long-term clinical effectiveness of supervised exercise therapy and endovascular revascularization as initial treatment for patients with intermittent claudication due to aortoiliac or femoropopliteal disease. After a median follow-up of approximately 7 years, supervised exercise therapy-first treatment was equivalent to endovascular revascularization-first treatment in achieving improvements in functional performance and QoL.

Long-term benefits in functional performance have been demonstrated previously for supervised exercise therapy[18-20], as well as for endovascular revascularization[21,22], in cohort studies; the only randomized clinical trial (RCT) published so far found no significant difference in walking capacity between supervised exercise therapy and endovascular revascularization[23]. However, that study did not show any increase in MWD or PFWD after approximately 6 years, possibly due to the limited number of patients. In addition to a persistent increase in walking distance, the present study also demonstrated a sustained improvement in QoL after both supervised exercise therapy and endovascular revascularization. In contrast to the VascuQoL, the SF-36 instrument failed to demonstrate (sustained) improvements, especially after supervised exercise therapy. VascuQoL is a disease-specific instrument that was developed and validated in patients with intermittent claudication[15], and may be better for detecting disease-related QoL improvement.

Another interesting observation was that ABI values at rest and after exercise in the supervised exercise therapy group were significantly higher after 7 years than at

baseline, which resulted in the similar ABI improvements in the two treatment groups after 7 years; this contrasts with the 12-month results[8]. This significant improvement in ABI after supervised exercise therapy was not the result of the supervised exercise therapy programme itself, and was explained by the appreciable number of patients in the supervised exercise therapy group who received a secondary intervention (endovascular or surgical revascularization) during follow-up. Although the high crossover rate to endovascular revascularization is not desirable in a clinical study, it does reflect real-world clinical practice. Per-protocol analysis, including only data from patients who completed their allocated treatment without crossover, did not affect the conclusion of the main intention-to-treat analysis.

A positive finding of this study was that, after 7 years, almost half of the patients with intermittent claudication randomized to supervised exercise therapy initially had sustained improvement in functional performance and QoL without the need for any secondary intervention. The mean number of subsequent interventions after the initial treatment failure tended to be higher in the endovascular revascularization group, and the long-term prognosis for the leg seemed poorer, with three major amputations compared with only two minor amputations in the supervised exercise therapy group. These findings support the conservative supervised exercise therapy-first approach, without exposing patients to invasive endovascular or surgical treatments and their complications[24,25].

With respect to the level of disease, ten of 20 patients in the endovascular revascularization group with one or more lesions in the femoropopliteal segment required secondary intervention in this arterial segment, whereas seven of 55 patients with aortoiliac disease underwent a secondary intervention for restenosis in the aortoiliac segment during follow-up. This finding is expected, confirming a higher long-term patency rate for endovascular revascularization of aortoiliac compared with femoropopliteal lesions[2,24]. Given the high patency rate and relative ease of endovascular aortoiliac procedures, patients with aortoiliac disease may be considered for endovascular revascularization-first treatment, yet in the supervised exercise therapy group almost two thirds of the patients with intermittent claudication due to aortoiliac disease did not require a secondary intervention during follow up. The 6-month results of the Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) trial, a multicentre RCT comparing supervised exercise therapy and endovascular revascularization for patients with intermittent claudication due to aortoiliac disease, demonstrated that supervised exercise therapy resulted in better walking performance than endovascular revascularization[26]. Another RCT, comparing supervised exercise therapy, endovascular revascularization or both for patients with intermittent claudication due to femoropopliteal disease, concluded that all treatment regimens were equally effective in improving walking distance and QoL[27]. Results from these two recent trials combined with the present data justify supervised exercise therapy-first treatment for patients with intermittent claudication due to both aortoiliac and femoropopliteal disease.

The present study had some limitations. First, not all patients were available for long-term follow-up, which might have caused bias. However, baseline characteristics, functional performance and QoL measures were similar after 12 months in patients who withdrew and those who completed the long-term follow-up. Second, a high mortality and attrition rate among patients in the study decreased its power to detect small significant differences between the supervised exercise therapy and endovascular revascularization groups. Third, to avoid multiple revascularization procedures, patients with ipsilateral multilevel disease (stenoses at both iliac and femoral levels) were excluded from the present study. It is not known whether the findings of the present study are generalizable to this group. Finally, there was no information from participants on regular exercise performance after the trial. Therefore, only endovascular and surgical procedures, but not exercise, were considered as secondary interventions.

One year cost-effectiveness analysis, comparing supervised exercise therapy and endovascular revascularization for intermittent claudication, based on data from the present study has shown that, from a societal perspective and using a willingness-to-pay threshold of €50.000 per quality adjusted life year, supervised exercise therapy is cost-effective compared with endovascular revascularization[28]. Given the higher baseline costs for an endovascular revascularization-first approach compared with supervised exercise therapy[28], and the relatively large number of patients in the endovascular revascularization group who had a secondary surgical procedure, it is likely that supervised exercise therapy remains cost-effective in the long term.

This study suggests that in the long-term supervised exercise therapy-first or endovascular revascularization-first treatment strategies are equivalent in improving functional performance and QoL in patients with intermittent claudication. Although the secondary intervention rate was higher in patients who had supervised exercise therapy as initial treatment, the total number of invasive interventions (primary and secondary) remained substantially lower, and hence this study supports the use of a supervised exercise therapy-first approach for patients with intermittent claudication.

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Chapter 6

Long-term effects of structured home-based exercise program on functional capacity and quality of life in patients with intermittent claudication

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Arch Phys Med Rehabil. 2011 Jul; 92(7):1066-73

ABSTRACT

Objectives:

To evaluate effects of a structured home-based exercise program on functional capacity and quality of life in patients with intermittent claudication after 1-year follow-up, and to compare these results with those from a concurrent control group who received supervised exercise therapy.

Design: Comparative longitudinal cohort study.
Setting: Referral center.
Participants: Patients (N=142) with intermittent claudication.
Interventions: Structured home-based exercise therapy or supervised exercise therapy.

Main Outcome Measures:

The maximum- and pain-free walking distance and the ankle-brachial index (at rest and postexercise) were measured at baseline and after 6 and 12 months' follow-up. Additionally, quality of life was evaluated using a self-administered questionnaire consisting of the Euroqol-5D (scale 0 –1), rating scale (scale 0 –100), Short-Form Health Survey (SF-36; scale 0 –100), and the Vascular Quality of Life Questionnaire (VascuQol; scale 1–7). Comparison of the groups was performed with adjustment for the nonrandomized setting using propensity scoring.

Results

One hundred forty-two patients with intermittent claudication started the structured home-based exercise program, of whom 95 (67%) completed 12 months' follow-up. The mean relative improvement compared with baseline was statistically significant after 12 months' follow-up for the maximum- and pain-free walking distance (342%, 95% confidence interval [CI], 169–516; P=0.01 and 338%, 95% CI, 42–635; P=0.03, respectively) and for the ankle-brachial index post exercise (mean change, 0.06; 95% CI,0 .01–0.10; P=.02). For the quality of life outcomes, the improvement compared with baseline was statistically significant after 12 months for the VascuQol (mean change, 0.42; 95% CI, 0.20 –0.65; P<0.01) and for the SF-36 physical functioning (mean change, 5.17; 95% CI, .77–9.56; P=0.02). Compared with the structured home-based exercise program, patients in the control group showed significantly better results in the mean relative improvement of maximum- and pain-free walking distance and change in the ankle-brachial index at rest after 12 months' follow-up.

Conclusions

Structured home-based exercise training is effective in improving both functional capacity and quality of life in patients with intermittent claudication and may be considered as a feasible and valuable alternative to supervised exercise therapy, since supervised exercise programs are not often available.

Pripheral arterial disease a chronic atherosclerotic occlusive disease of the lower extremities. The classic symptom in patients with PAD is intermittent claudication (ie, Rutherford category 1, 2, or 3)[1], affecting approximately 275,000 people older than 50 years in The Netherlands alone. Of these, half will have a cardiovascular event within 10 years (19% fatal, 27% nonfatal), resulting in more than 2500 deaths each year[2]. Patients with intermittent claudication have functional limitations because of impaired walking ability[3], and diminished quality of life (QoL)[4].

The treatment goals for patients with intermittent claudication are to relieve symptoms and improve daily functional abilities and QoL. Previous studies have shown that exercise training should have a central role in the management of intermittent claudication by significantly improving the MWD[5-7] and QoL[8]. A Cochrane review and a recent systematic review showed that supervised exercise therapy is more effective than "go home and walk" advice[9,10]. Furthermore, the American College of Cardiology and American Heart Association guidelines recommend supervised exercise therapy as the initial treatment modality for patients with intermittent claudication[11]. In clinical practice, however, supervised exercise therapy programs have a limited capacity in many centers[12]. In addition, reimbursement for supervised exercise sessions depends on the patient's health insurance. Because of these limitations, many physicians in routine practice still advise their patients with intermittent claudication to "go home and walk." This approach, however, has many shortcomings including a high dropout rate and inadequate exercise as a result of minimal instruction. A better alternative to this simple "go home and walk" advice may be a structured home-based exercise program in which additional instructions, encouragement, and motivation are offered to the patient during the program. Since the patient can exercise in a self-chosen environment, a structured homebased exercise program does not require the infrastructure and the logistics of supervised exercise programs and thus, if efficacious, may be implemented in current practice more easily.

The objective of this study was to evaluate the effectiveness of a structured home-based exercise program on both functional capacity and QoL in patients with intermittent claudication after 6 and 12 months' follow-up, and to compare these results with those for a concurrent control group who received supervised exercise therapy.

METHODS

Study Design and Participants

This study was a comparative longitudinal cohort study following up patients with intermittent claudication (Rutherford category 1, 2, or 3) for a period of 12 months. All patients with intermittent claudication referred to the Department of Vascular Surgery by their general practitioner were considered for recruitment. Patients met the following

inclusion criteria for a structured home-based exercise program: (1) older than 18 years; (2) Rutherford category (1, 2, or 3); (3) ankle-brachial index (ABI) less than 0.9 at rest, or ABI with a decrease of more than 30% after the treadmill test; (4) pain-free walking distance (PFWD) less than 350m during a treadmill test; (5) and informed consent. Exclusion criteria were (1) patient eligible for concurrent RCT[13,14]; (2)life-incapacitating cardiac disease; and (3) inability to complete a treadmill walking test for reasons other than claudication.

Patients who were eligible for a concurrent randomized controlled trial (RCT) and were allocated to supervised exercise therapy served as controls. In this RCT, which was performed at the same hospital, results of supervised exercise therapy and endovascular revascularization for patients with intermittent claudication were compared after 12 months of follow-up[13,14]. Inclusion criteria of this RCT were (1) Rutherford category 1, 2, or 3, with a duration of 3 months or more; (2) PFWD less than 350m; (3) ABI less than 0.9 at rest, or ABI decreasing by greater than .15 after the treadmill test; (4) 1 or more vascular stenoses of greater than 50% diameter reduction at the iliac or femoropopliteal level; and (5) informed consent. Exclusion criteria were (1) abdominal aortic aneurysm; (2) life-incapacitating cardiac disease (New York Heart Association classification II and higher); (3) multilevel disease (ie, same-side stenoses at both the iliac and femoral levels, requiring multiple revascularization procedures); (4) isolated tibial artery disease; (5) lesions deemed unsuitable for revascularization (iliac or femoropopliteal Trans-Atlantic Inter-Society Consensus for the Management of PAD (TASC) type D and some TASC type B and/or C lesions24); and (6) prior treatment for the lesion (including exercise training). Institutional review board approval was obtained, and all patients gave written informed consent.

Risk Factor Modification

Before starting either a structured home-based exercise program or a supervised exercise program, baseline data were obtained for all patients including cardiovascular risk factors, concomitant diseases, medical therapy use, previous vascular interventions, and a self-administered QoL assessment by questionnaire. Patients with one or more risk factors for cardiovascular disease were referred to a physician for secondary prevention according to the European Society of Cardiology guidelines on cardiovascular disease prevention in clinical practice[15] .

Interventions

Structured home-based exercise program

Before initiating the exercise program, a treadmill test at the vascular laboratory established patients' initial PFWD and maximum walking distance (MWD). The patients were instructed to accomplish daily exercise sessions, at least 1 session daily, during 24

weeks in a self-chosen environment. In addition, patients were advised to include regular walks in their daily routine. Each subject received an information sheet with instructions regarding the exercise regimen, which consisted of approximately 30 minutes of walking during each exercise session, started with the initial walking speed, and involved walking near-maximum claudication pain, alternated with 1 minute of walking at a very low pace until the pain abated[16]. Evaluation of the walking distance took place after 2, 8, 16, and 24 weeks at the vascular laboratory by a vascular technologist. During these 1-hour individual follow-up sessions, the patient's progress was assessed by establishing the patient's MWD and PFWD, and discussing the approximate number of sessions and duration of each exercise session the patient had performed. New targets regarding walking speed, walking distance, and compliance were given to the patient. Problems experienced by the patient during the exercise program were discussed, and additional instruction on exercise performance was given. Education about the treatment of intermittent claudication and the presently known results and advantages of exercise training on intermittent claudication and atherosclerotic risk factors was given to the patients every session. The patients were also strongly encouraged to keep up the recommended exercise program and to perform at least ome exercise session daily. After completion of the 24-week program, patients were advised to include home-based exercise training in their daily routine.

Control group

All patients in the nonrandomized control group started with supervised exercise therapy for a period of 24 weeks, 2 sessions weekly. The exercise session consisted of 30 minutes of walking on a treadmill at a workload of 3.5km/h without a graded incline and was supervised by a vascular technologist. Patients walked to near-maximum claudication pain, then decreased the workload and continued exercising at this reduced workload until the pain subsided, after which the workload was increased again[13]. After completion of the 24-week supervised program, these patients were also advised to walk on a daily basis.

Outcomes

The outcome variable was effectiveness, which was defined as improvement compared with baseline in both functional capacity and QoL after 6- and 12-month follow-up. Improvement in functional capacity was assessed by MWD and PFWD after treadmill walking (speed 3.5 km/h, no graded incline), and by the ABI at rest and postexercise determined by Doppler pressure measurements. Trained vascular technicians assessed these parameters. For practical reasons the maximum walking time was 30 minutes.

Improvement in QoL was assessed by a self-administered questionnaire. This patient-reported questionnaire consisted of the Euroqol-5D, rating scale, Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), and the Vascular Quality of Life

Questionnaire (VascuQol) instruments. The Euroqol-5D instrument assesses QoL values from the societal perspective and classifies patients into a health-state. It covers 5 QoL dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression[17]. We used the Dutch scoring algorithm, which was derived from the general population, to value each health state between 0 and 1, where 0 indicates death and 1 indicates maximum health[18]. The rating scale instrument asked the patients to rate their overall health on a scale from 0 to 100, where 0 represents death and 100 perfect health[19]. The SF-36 instrument contains 36 questions and evaluates the general health and well-being of patients through 8 different health domains[20]. Previous studies demonstrated that only physical functioning, role-functioning limitations caused by physical problems, bodily pain, and general health are the most relevant health domains to describe the health status of patients with peripheral arterial disease (PAD)[14,21], so we restricted this analysis to these 4 domains. The SF-36 was valued on a 0- to 100-point scale; 0 reflected worst health, and 100 indicated maximum health. The VascuQol instrument consists of 25 questions[22]. For each question there is a 7-point response scale, with 1reflecting the worst possible QoL and 7 the best possible QoL.

Statistical Analysis

Continuous data are presented as means and SDs. Discrete data are given as numbers and percentages. Changes in the outcome measures are expressed as mean improvements compared with baseline and 95% CIs, except for the dependent variables MWD and the PFWD which are given as mean relative improvements due to the skewness of these data[13].

To assess the differences in baseline characteristics between the patients who received the structured home-based exercise program and the control group, we used the unpaired t test or the Mann-Whitney U test, as appropriate, whereas dichotomous outcomes were assessed with the chi-square test. Significance of change in the outcome measures was assessed with mixed effects models for repeated measures. An advantage of this repeated-measures approach is that it allows for inclusion of patients with missing follow-up data, due to random withdrawal, in the analysis. Where applicable, a linear mixed model was applied to the original outcome. Otherwise, in case of the MWD and the PFWD, we used a transformation to a relative improvement compared with baseline. We adjusted the model for the following potential confounders, based on clinical judgment and the literature: sex, age, smoking, hypertension, diabetes mellitus, and hyperlipidemia[24].

To compare the differences in outcome measures between the structured home-based exercise program and the control group, we performed a propensity score–adjusted repeated measures analysis. We first computed a propensity score by using a multivariable logistic regression analysis with treatment group as the dependent variable and baseline characteristics related to the outcome as independent variables[25]. We then

entered the propensity score into a linear mixed model as a continuous variable to adjust for all observed potential imbalance between the two treatment groups. In our modeling approach, we first assumed a general model for the mean structure, and sought the simplification of the variance-covariance matrix structure. After all possible dependencies were eliminated, we proceeded with an elimination of the mean structure parameters.
A significance level of 0.05 (2-sided) was considered statistically significant. Calculations were performed with SPSS 14.0 for Windows and SAS 9.2.

RESULTS

Patients

A total of 298 patients with intermittent claudication were referred to the Department of Surgery. One hundred fifty-one patients were excluded based on the exclusion criteria. Five patients never started the structured home-based exercise program for various reasons and were therefore also excluded from further analysis. Thus, the final study population consisted of 142 patients. Ninety-five of the 142 patients (67%) completed 12 months' follow-up. The remaining 47 patients discontinued the study for various reasons (Figure 1).

The baseline characteristics of the patients are presented in Table 1. There were no statistical significant differences in baseline characteristics between patients from the structured home-based exercise program group and patients from the control group, except for smoking and level of disease (Table 1).

Outcomes

The adjusted mean relative improvement in MWD compared with baseline after 6 months of structured home-based exercise was 364% (95% confidence interval [CI], 200–528; P<0.01) and was statistically significant (Table 2). After 12 months' follow-up, this adjusted relative improvement was still statistically significant (improvement 342%; 95% CI, 169–516; P<0.01). The adjusted mean relative improvement in PFWD after 6 months compared with baseline was 269% (95% CI, –60 to 597; P=0.10), which was not statistically significant. After 12 months' follow-up, this adjusted mean relative improvement was statistically significant with an improvement of 338% (95% CI, 42–635; P=0.03) (Table 2). Although there were no significant differences in the ABI at rest after 6 and 12 months' follow-up, the mean change in ABI after exercise was significantly better after follow-up compared with baseline. After 6 months, the mean change was 0.04 (95% CI, 0.00 –0.07; P=.04). After 12 months, this improvement was still statistically significant and increased to 0.06 (95% CI, 0.01–0.10; P=.02).

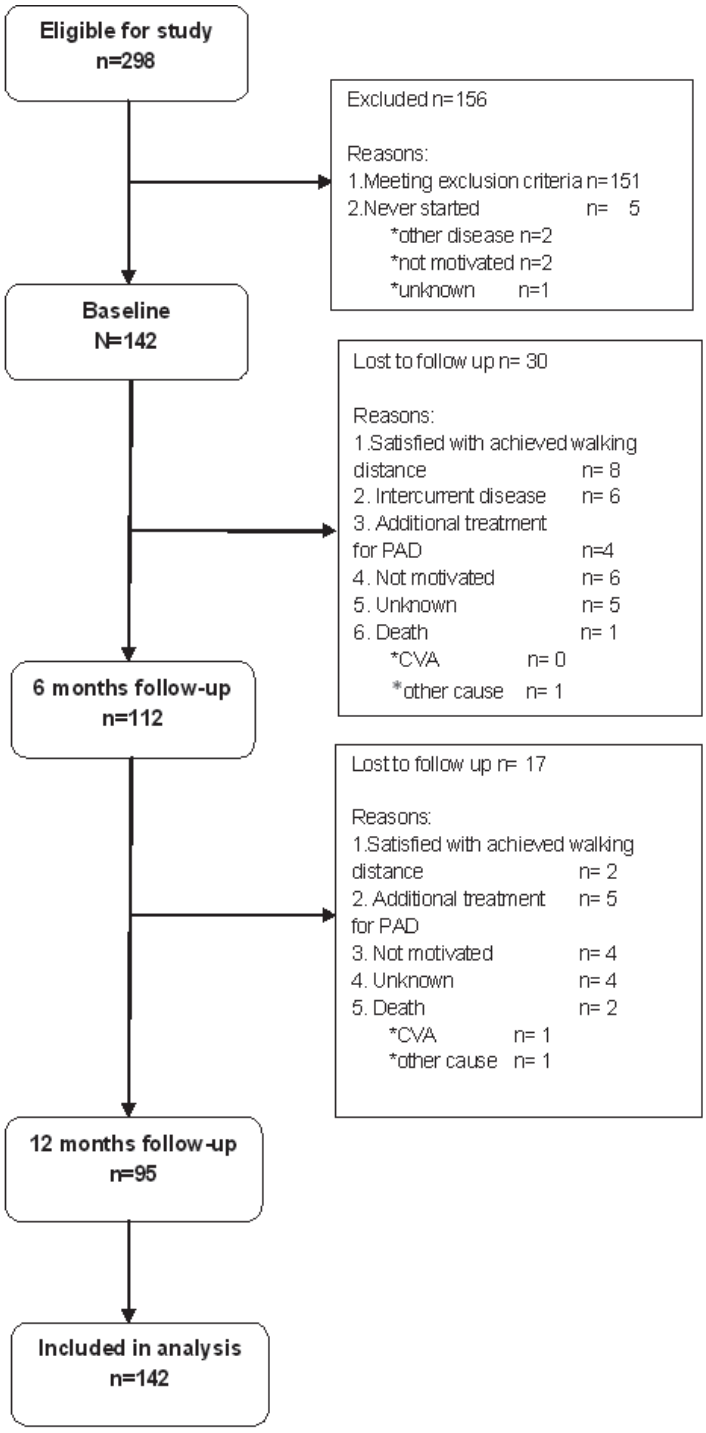

Figure 1. Flow chart of the total population eligible for structured home-based exercise program.

Table 1. Baseline patient characteristics

Characteristic	Structured Home-Based Exercise (n=142)	Control group, Supervised Exercise (n=75)	*P*
Age (years)	68.1 +/- 10.1	66.9 +/- 8.9	NS
Body Mass Index (kg/m^2)	26.8 +/- 5.6	25.5 +/- 4.6	NS
Male sex	91/142 (64)	44/75 (59)	NS
Arterial hypertension	67/134 (50)	30/75 (40)	NS
Diabetes Mellitus	44/142 (31)	14/75 (19)	NS
Hyperlipidemia	66/128 (52)	43/75 (57)	NS
History of ischemic heart disease	44/142 (31)	22/75 (29)	NS
History of cerebrovascular disease	23/141 (16)	5/75 (7)	NS
Pulmonary disease	17/142 (12)	9/75 (12)	NS
Renal disease	4/140 (3)	4/74 (5)	NS
Osteoarthritis of lower limb	21/139 (15)	5/75 (7)	NS
Smoking			
Never	11/139 (8)	37/75 (49)	< 0.01
Current/Former	128/139 (95)	38/75 (51)	
Level of disease			
Aortoiliac	23/139 (17)	34/69 (49)	
Femoropopliteal	98/139 (71)	35/69 (51)	< 0.01
Infrapopliteal	18/139 (12)	0/69 (0)	
Rutherford classification			NS
1 or 2	79/142 (56)	33/73 (45)	
3	63/142 (44)	40/73 (55)	
Pain-free walking distance (m)	106 (+/- 88.2) n=120	108 (+/- 69) n=71	NS
Maximum walking distance (m)	201 (+/- 177) n=123	191 (+/- 97) n=71	NS
Ankle Brachial Index			
at rest	0.62 (+/- 0.20) n=139	0.62 (+/- 0.18) n=75	NS
after exercise	0.42 (+/- 0.22) n=125	0.42 (+/- 0.20) n=75	
SF-36 quality of life score#			
Physical functioning	48 (+/- 21) n=137	49 (+/- 20) n=75	
Physical role functioning	45 (+/- 42) n=134	51 (+/- 43) n=75	NS
Bodily pain	56 (+/- 22) n=140	55 (+/- 22) n=75	
General health	53 (+/- 19) n=140	54 (+/- 19) n=75	
EuroQol total score**	0.70 (+/- 0.20) n=140	0.68 (+/- 0.21) n=75	NS
Rating scale total score#	62 (+/- 18) n=128	64 (+/- 18) n=74	NS
VascuQol total score&	4.3 (+/- 1.16) n=142	4.2 (+/- 1.26) n=75	NS

Values are mean ± SD or n (%) unless otherwise indicated.

Abbreviation: SF-36= Short Form-36; NS, not significant.

*Score, 0 to 100 (worst-best) scale.

†Score, 0 to 1 (worst-best) scale.

‡Score, 1 to 7 (worst-best) scale.

Score= 0-100 (worst-best) scale

** Score= 0-1 (worst-best) scale

& Score=1-7 (worst-best) scale

Table 2. Mean change in measures of functional capacity, 6 and 12 months compared with baseline, after a structured home-based exercise program (n=142)

Measure of functional capacity	Adjusted mean change (95% CI)**	Adjusted *p*-value**
Maximum walking distance (%)*		
After 6 months	364 (200 to 528)	< 0.01
After 12 months	342 (169 to 516)	< 0.01
Pain-free walking distance (%)*		
After 6 months	269 (-60 to 597)	NS
After 12 months	338 (42 to 635)	0.03
ABI at rest		
After 6 months	0.001 (-0.03 to 0.03)	NS
After 12 months	-0.001 (-0.04 to 0.04)	NS
ABI after exercise		
After 6 months	0.04 (0.00 to 0.07)	0.04
After 12 months	0.06 (0.01 to 0.10)	0.02

Abbreviation: CI=Confidence Interval; ABI=Ankle Brachial Index; NS= Not Significant

* Presented as mean relative improvement

** Adjusted for sex, age, smoking, hypertension, hyperlipidemia, and diabetes mellitus.

The adjusted mean change in QoL after 6 months compared with baseline was statistically significant for the VascuQol (scale 1–7) with a mean change of 0.37 (95% CI, 0.17–0.56; P<0.01), and for the SF-36 physical functioning scores (scale 0–100) with a mean change of 5.96 (95% CI, 2.04 –9.87; P<0.01). After 12 months, this improvement was still statistically significant for the VascuQol (mean change, 0.42; 95% CI, 0.20 –0.65; P<0.01) and for the SF-36 physical functioning score (mean change, 5.17; 95% CI, 0.77–9.56; P=0.02) (Table 3).

Comparison of Groups

After adjustment for potential confounders, the patients in the control group showed significantly better results in functional capacity outcomes except for ABI after exercise (Table 4). However, after adjustment, there were no significant differences in the QoL scores between the 2 groups at 6 or 12 months' follow-up, except for SF-36 general health domain (P=0.03) and rating scale (P<0.01) at 6 months' follow-up (Table 5).
Table 4 and 5

Table 3. Mean change in measures of quality of life, 6 and 12 months compared to baseline, after a structured home-based exercise program (n=142)

Measure of quality of life	Adjusted mean change (95% CI)*	Adjusted P *
VascuQol total score&		
After 6 months	0.37 (0.17 to 0.56)	< 0.01
After 12 months	0.42 (0.20 to 0.65)	< 0.01
SF-36 Physical functioning#		
After 6 months	5.96 (2.04 to 9.87)	< 0.01
After 12 months	5.17 (0.77 to 9.56)	0.02
SF-36 Physical role functioning#		
After 6 months	0.07 (-0.09 to 1.84)	NS
After 12 months	0.09 (0.04 to 2.12)	0.04
SF-36 Bodily pain#		
After 6 months	2.31 (-1.88 to 6.50)	NS
After 12 months	4.10 (-0.93 to 9.11)	NS
SF-36 General health#		
After 6 months	-1.53 (-4.53 to 1.47)	NS
After 12 months	-0.99 (-4.24 to 2.24)	NS
Rating scale total score#		
After 6 months	-0.38 (-4.06 to 3.29)	NS
After 12 months	2.38 (-0.93 to 5.69)	NS
EuroQol total score**		
After 6 months	-0.00 (-0.21 to 0.20)	NS
After 12 months	0.04 (-0.02 to 0.44)	NS

Abbreviation: NS= Not Significant; CI= Confidence Interval; SF-36= Short Form-36

* Adjusted for sex, age, smoking, hypertension, hyperlipidaemia, and diabetes mellitus.

& Score=1-7 (worst-best) scale

Score= 0-100 (worst-best) scale

** Score= 0-1 (worst-best) scale

Table 4. Mean change in measures of functional capacity after 6 and 12 months follow-up compared to baseline and differences between a structured home-based exercise program and the control group

Measure of functional capacity	Mean change compared to baseline		Adjusted mean difference (95% CI)**	Adjusted P**
	Structured home-based exercise (95% CI) n=142	Control group, Supervised exercise (95% CI) n=75		
Maximum walking distance (%)*				
After 6 months	265 (180 to 350)	750 (599 to 901)	-433 (-665 to -200)	< 0.01
After 12 months	268 (140 to 396)	666 (523 to 809)	-361 (-604 to -118)	< 0.01
Pain-free walking distance (%)*				
After 6 months	308 (139 to 478)	1241 (894 to 1587)	-938 (-1495 to -381)	< 0.01
After 12 months	370 (223 to 516)	1286 (908 to 1663)	-953 (-1565 to -341)	< 0.01
ABI at rest				
After 6 months	0.00 (-0.04 to 0.04)	0.07 (0.04 to 0.09)	-0.07 (-0.14 to -0.00)	0.05
After 12 months	0.00 (-0.03 to 0.03)	0.09 (0.07 to 0.12)	-0.11 (-0.19 to -0.04)	< 0.01
ABI after exercise				
After 6 months	0.05 (0.01 to 0.09)	0.13 (0.08 to 0.19)	-0.09 (-0.20 to 0.02)	NS
After 12 months	0.08 (0.03 to 0.13)	0.16 (0.10 to 0.21)	-0.09 (-0.21 to 0.12)	NS

Abbreviation: CI= Confidence Interval; ABI=Ankle Brachial Index; NS= Not Significant

Negative difference indicates the difference between the two groups in favour of the control group

* Presented as mean relative improvement.

** Adjusted for sex, age, smoking, hypertension, hyperlipidemia, diabetes mellitus, and propensity score

Table 5. Mean change in measures of Quality of Life after 6 and 12 months follow-up compared with baseline and differences between a structured home-based exercise program and the control group

Measure of QoL	Mean change compared to baseline		Adjusted mean difference (95% CI)**	Adjusted P**
	Structured home-based exercise (95% CI) n=142	Control group, Supervised exercise (95% CI) n=75		
VascuQol total score&				
After 6 months	0.31 (0.09, 0.53)	0.66 (0.33, 0.99)	-0.32 (-0.98, 0.35)	NS
After 12 months	0.45 (0.21, 0.69)	0.60 (0.28, 0.91)	-0.14 (-0.80, 0.53)	NS
SF-36 Physical functioning#				
After 6 months	5.74 (2.06, 9.42)	12.20 (6.78 17.62)	-8.81 (-18.55, 0.92)	NS
After 12 months	6.88 (2.85,10.91)	12.68 (7.33, 18.03)	-7.90 (-18.44, 2.63)	NS
SF-36 Physical role#				
After 6 months	6.78 (-0.68,14.24)	13.93 (3.49, 24.38)	-13.64 (-32.45, 5,18)	NS
After 12 months	8.89 (0.57, 17.21)	5.93 (-4.74 16.61)	3.32 (-16.23, 22.87)	NS
SF-36 Bodily pain#				
After 6 months	3.51 (-0.55, 7.57)	6.56 (0.96, 12.16)	-6.50 (-16.55, 3.55)	NS
After 12 months	6.55 (1.54, 11.56)	9.67 (3.85, 15.49)	-5.08 (-15.26, 5.10)	NS
SF-36 General health#				
After 6 months	-0.79 (-3.64, 2.10)	5.13 (0.81, 9.46)	-8.39 (-16.11, -0.68)	0.03
After 12 months	-1.19 (-4.45, 2.07)	4.88 (0.81, 8.95)	-6.32 (-14.22, 1.57)	0.12
Rating scale total score#				
After 6 months	0.86 (-2.52, 4.24)	5.49 (0.79, 10.18)	-10.03 (-17.19, -2.88)	<0.01
After 12 months	2.80 (-0.58, 6.18)	6.50 (1.59, 11.40)	- 5.66 (-13.17, 1.86)	NS
EuroQol total score**				
After 6 months	0.01 (-0.03, 0.05)	0.09 (0.03, 0.16)	-0.07 (-0.16, 0.01)	NS
After 12 months	0.05 (0.03, 0.09)	0.07 (-0.00, 0.14)	-0.02 (-0.11, 0.06)	NS

Abbreviation: CI= Confidence Interval; QoL= Quality of Life; SF-36=Short Form-36; NS= Not Significant

Negative difference indicates the difference between the two groups in favour of the control group.

** Adjusted for sex, age, smoking, hypertension, hyperlipidemia, diabetes mellitus, and propensity score.

& Score=1-7 (worst-best) scale

Score= 0-100 (worst-best) scale

** Score= 0-1 (worst-best) scale

DISCUSSION

The objective of this study was to evaluate the effectiveness of a structured home-based exercise program for patients with intermittent claudication and to compare these results with those for a concurrent control group who received supervised exercise therapy. We determined the improvement in both functional capacity and QoL after 6 and 12 months' follow-up and showed that a structured home-based exercise program was of significant benefit in improving MWD, PFWD, the ABI postexercise, and the QoL in patients with intermittent claudication. The improvement achieved in MWD and PFWD can also be considered clinically relevant, as patients improved their pre-training adjusted MWD and PFWD by 342% and 338%, respectively, after 12 months' follow-up, This is comparable with walking an additional 6 to 7 blocks until maximum claudication pain and can be considered as substantial improvement for patients with intermittent claudication. However, compared with a supervised exercise program, the structured home-based exercise program was inferior in improving functional capacity.

Studies evaluating both functional capacity and QoL after structured home-based exercise program are scarce, and to our knowledge this is the first study that evaluated all these outcomes by using an unsupervised but structured approach. There are no meta-analyses on the effectiveness of structured home-based exercise programs. However, our results were consistent with those from previous RCTs, in which minimal supervision was added to their home-based exercise training group[26,27]. The results from the literature evaluating the effectiveness of the simple "go home and walk" advice are not comparable with our results because of the supportive element in our study. The improvement achieved in MWD after 12 months was larger in our study compared with studies evaluating the simple "go home and walk" advice[28,29]. An explanation for this difference is probably that our home-based exercise program was structured by intervening visits during the program in which we evaluated patients' progress, offered patients additional instructions, and motivated them to continue. Patients who follow the "go home and walk" advice but do not get any form of supervision and encouragement are more likely to stop the program than patients who get supervised exercise therapy[30]. The dropout rate in our study (33%) was low and comparable with the dropout rates from RCTs evaluating supervised exercise therapy[31-33]. An explanation for this "good" compliance might be that in our structured home-based exercise program the patient could perform the exercise sessions in a self-chosen environment and time, which might facilitate continuation of the program.

Study Limitations

Although we demonstrated significant improvement in functional capacity and QoL, there were some limitations of our study, which could have affected our results. First, our study sample was relatively small, which may limit the level of evidence of our study. Second,

our study was a single-center study, nonblinded and nonrandomized. To adjust for the effect of nonrandomization we used a propensity score–adjusted analysis to compare the structured home-based exercise group with a control group. Although propensity score risk adjustment controls for the observed imbalance on background covariates between the treatment and control group, it does not take into account nonmeasured confounding variables that may have still caused a treatment selection bias. Next, we excluded the patients eligible for a concurrent RCT, which might have established an inherent bias in the selection of patients. However, at baseline, there were no statistically significant differences in severity of disease, functional capacity, and QoL outcomes between the patients in our study and patients from the concurrent RCT.

Furthermore, we did not ask the patients to keep daily programrecords of their exercise sessions, and because the patients were not completely supervised, there could be a level of uncertainty about their exercise compliance. Because exercise compliance in an unsupervised exercise therapy program is very important but difficult to measure, a suggestion for future studies might be to use devices such as pedometers to monitor patients' activity. Since patients in a structured home-based exercise program have the freedom to exercise in the convenience of their home setting, the patient compliance and QoL can be favorably influenced. For many patients it is difficult to attend regular activities that are outside their daily routine. Many patients with intermittent claudication are physically inactive, which could reduce a patient's motivation to participate in a supervised exercise therapy program, and emphasizes the need to explore the most convenient and feasible program in daily practice. Next, our analyses were limited to only those who completed the study. To deal with this limitation we included all patients in the analyses and used a repeatedmeasures approach, which has the advantage of allowing for the inclusion of patients with random missing follow-up data because of withdrawal. Still the possibility that those who withdrew from the study would have responded less favorably to exercise cannot be ruled out.

Furthermore, at the time of the study protocol, a graded treadmill test was not available, and instead we used a speed of 3.5 km/h with a maximum of 30 minutes for practical reasons. However, a significant number of patients were able to walk longer than the limited 30 minutes, and the demonstrated improvement in the MWD after 6 and 12 months' follow-up may have been underestimated. Whereas patients in the control group exercised on a treadmill, patients in the structured home-based exercise program did not. This might have caused a familiarization for treadmill walking in the control group with a subsequent better performance when they were tested during follow-up, which could have led to overestimation of the difference in MWD and PFWD between the 2 groups in favor of the control group.

It is important to emphasize that our study was not designed to compare the effectiveness of a structured home-based exercise training group with a supervised exercise therapy group. Our goal was to evaluate a structured home-based exercise

program when a supervised program is not available. Implementing supervised exercise therapy for intermittent claudication in daily practice can be complicated. Many vascular surgeons do not have access to a rehabilitation center for carrying out supervised exercise therapy because of limited capacity at the centers. A recent published study showed that despite all the recommendations from the TASC, and the American College of Cardiology and the American Heart Association guidelines to use supervised exercise therapy in the management of intermittent claudication[11,24],only 24% of surgeons have access to supervised exercise therapy[12]. Furthermore, patients are often limited in their transport to the hospital or rehabilitation center in terms of costs and time. These limitations force the current practice of care for most patients to still consist of advice to "go home and walk."

Economic evaluation of (structured) home-based exercise training versus supervised exercise therapy is important but still relatively rare. A recent article from van Asselt et al evaluating the cost-effectiveness of supervised exercise therapy compared with "go home and walk" advice concluded that at a willingness-to-pay threshold of €40.000 per quality-adjusted life year, supervised exercise therapy is likely to be a costeffective therapeutic option[34]. However, in this study, supervised exercise therapy was compared with advice to "go home and walk" and not with a structured home-based exercise program as we described. Although one would expect the structured home-based exercise to be less expensive, additional treatment costs after failure of a structured home-based exercise program need to be taken into account and could raise the costs. Therefore, further research with a full economic evaluation that includes consideration of all costs and consequences is needed.

To improve current practice, we showed that a structured home-based exercise program can be clinically more effective than the simple "go home and walk" advice and should be used instead. We suggest that all patients with symptoms of intermittent claudication should be treated with a supervised exercise therapy program. If a supervised exercise therapy program is not feasible, a structured home-based exercise program should be considered instead of the "go home and walk" advice.

CONCLUSIONS

A structured home-based exercise program is effective in improving both functional capacity and QoL in patients with intermittent claudication and may be considered as a feasible and valuable alternative to a supervised exercise therapy program, since supervised exercise programs are not often available in clinical practice.

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Chapter 7

Endovascular revascularization and supervised exercise for peripheral artery disease and intermittent claudication: a randomized clinical trial

Fakhry F, Spronk S, van der Laan L, Wever JJ, Teijink JAW, Hoffmann WH, Smits TM, van Brussel JP, Stultiens GNM, Derom A, den Hoed PT, Ho GH, van Dijk LC, Verhofstad N, Orsini M, van Petersen A, Woltman K, Hulst I, van Sambeek MRHM, Rizopoulos D, Rouwet EV, Hunink MGM.

JAMA. 2015 Nov 10;314(18):1936-44

ABSTRACT

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

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

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

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

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

Results
Endovascular revascularization plus supervised exercise (combination therapy) was associated with significantly greater improvement in maximum walking distance (from 264m to 1501m for an improvement of 1237m) compared with the supervised exercise only group (from 285m to 1240mfor improvement of 955 m) (mean difference between groups, 282m; 99% CI, 60-505 m) and in pain-free walking distance (from 117m to 1237m for an improvement of 1120m vs from 135m to 847m for improvement of 712m, respectively) (mean difference, 408 m; 99%CI, 195-622 m). Similarly, the combination therapy group demonstrated significantly greater improvement in the disease-specific VascuQol score (1.34 [99% CI, 1.04-1.64] in the combination therapy group vs 0.73 [99% CI, 0.43-1.03] in the exercise group; mean difference, 0.62 [99%CI, 0.20-1.03]) and in the score for the

SF-36 physical functioning (22.4 [99%CI, 16.3-28.5] vs 12.6 [99%CI, 6.3-18.9], respectively; mean difference, 9.8 [99% CI, 1.4-18.2]). No significant differences were found for the SF-36 domains of physical role functioning, bodily pain, and general health perceptions.

Conclusions and relevance

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

Intermittent claudication is the classic symptomatic form of peripheral artery disease, affecting approximately 20 to 40 million people worldwide and is increasing rapidly with the aging world population[1]. Patients with claudication experience significant functional disability resulting in a sedentary lifestyle and reduced quality of life[2-4].

Supervised exercise is an effective first-line treatment for claudication[5] and is recommended by international guidelines as the standard of care[6-9]. Yet, in clinical practice, its value remains uncertain because supervised exercise programs are underused due to limited access in most countries, reimbursement issues, and poor patient compliance[5,10]. As a consequence, endovascular revascularization is an increasingly attractive first-line alternative due to its immediate effect and potential to prevent disability[11]. Studies have suggested that endovascular revascularization is not significantly different from supervised exercise for improving functional performance and quality of life[12,13]. Hence, to date, the optimal first-line treatment in clinical practice for the increasing population of patients with claudication remains uncertain.

A combination therapy of early endovascular revascularization followed by supervised exercise seems promising because it combines the immediate improvement in claudication symptoms after revascularization with the added longterm benefits of exercise therapy. Two systematic reviews on this topic concluded that combination therapy might be superior to supervised exercise or endovascular revascularization alone[12,13]. However, this conclusion was based on limited data and needed to be confirmed in a larger randomized clinical trial (RCT). To address this question, the Endovascular Revascularization And Supervised Exercise (ERASE) RCT was designed to compare both the effectiveness and costeffectiveness of endovascular revascularization plus supervised exercise in patients with intermittent claudication with supervised exercise only. The outcomes on effectiveness are reported in this article. The cost-effectiveness analysis will be presented in the future.

METHODS

Study Design

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

Participants

Patients with peripheral artery disease and stable claudication (≥3 months) referred to the outpatient clinic in the participating centers were potentially eligible. Patients were included if they had a resting ankle brachial index (ABI) of 0.90 or less or if their ABI decreased by

more than 0.15 after treadmill testing regardless of their ABI at rest. All participants also had 1 or more vascular stenoses at the aortoiliac level, the femoropopliteal level, or both, as established by noninvasive vascular imaging. Furthermore, their maximum walking distance had to be between 100 m and 500 m as assessed on a graded treadmill using the protocol by Gardner et al.[14] Patients were excluded if their target lesions were unsuitable for revascularization or if they had received prior treatment for the target lesions. Patients with limited life expectancy or ambulation due to a condition other than peripheral artery disease also were excluded.

Randomization

Eligible patients were assigned in a 1:1 ratio to either endovascular revascularization plus supervised exercise or supervised exercise only. Randomization and allocation was performed using web-based randomization software (TenALEA, Amsterdam, the Netherlands) based on the Pocock and Simon minimization method.[15,16]

Intervention

Supervised Exercise

Exercise was provided to the patients by trained physiotherapists in a network of physiotherapy clinics in each patient's neighborhood or at the physiotherapy center of the participating site. All physiotherapists were required to have completed a 2-day course on supervised exercise for claudication certified by the Royal Dutch Society for Physical Therapy and follow the society's guideline on treatment of claudication.[17] Most of the selected physiotherapists (82%) also participated in ClaudicatioNet, a national network of integrated care to improve the quality and accessibility of supervised exercise for patients with claudication in which the participating physiotherapists receive regular training and monitoring.[18] The exercise program consisted primarily of treadmill walking to near-maximum claudication pain. The physiotherapists were advised to start with a frequency of 2 to 3 sessions every week and approximately 30 to 45 minutes per session during the first 3 months. After this phase, the frequency was reduced to at least 1 session per week between months 3 and 6 and then to a frequency of 1 session per 4 weeks at 12 months, depending on patients' progress and preference.

Endovascular Revascularization Plus Supervised Exercise

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

Outcomes and Assessment

Outcome assessment was performed at baseline and at the 1-, 6-, and 12-month follow-up visits. Baseline medical history and demographic data, including sex and race, were obtained by patient report to allow external generalizability of the study results. In addition, lipid profile, weight, height, and waist circumference were measured at the study visit and patient reported smoking and physical activity level were recorded. Physical activity was patient reported as number of hours physical activity (walking, running, bicycling, or other form of physical activity) performed per week. Vascular imaging, assessment of treadmill walking distances, ABI, and patientreported quality of life also were recorded.

The primary outcome was maximum walking distance at 12 months assessed during a graded treadmill test[14] (maximum duration, 30 minutes). To ensure blinded outcome assessment, the treadmill test was overseen by an independent person, who was unaware of the specific treatment assigned, and patients were advised not to discuss their assigned treatment.

Secondary outcomes included pain-free walking distance, ABI (at rest and after exercise), and additional interventions (defined as any surgical or endovascular revascularization procedure, or both) offered to the patient during follow-up as a result of primary randomized treatment failure, number of leg amputations, and recurrent stenosis detected at 12 months by duplex ultrasonography in the endovascular revascularization plus supervised exercise group. Patientreported generic quality of life was obtained using the Rating score, which is based on a single question in which patients rate their health state on a scale from 0 (worst imaginable) to 100 (best imaginable),[19] and the 36-item Short-Form Health Survey domain scores for physical functioning, physical role function (ie, limitations due to physical problems), bodily pain, and general health perceptions on a scale from 0 (severe limitation) to 100 (no limitation)[20]; these are the most relevant health domains to describe the health status of patients with peripheral artery disease.[21] In addition, disease-specific quality of life was measured using the VascuQol questionnaire, which consists of the following 5 domains of activities, symptoms, pain, emotional, and social scored on a scale from 1 (worst outcome) to 7 (best outcome).[22]

Statistical Analysis

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

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

A significant number of patients reached the maximum of 30 minutes of walking on the treadmill during follow-up, causing a nonnormal distribution for walking distances. To address this ceiling effect and account for the correlations in the repeated measurements for each patient, we used the Tobit mixed-effects model.[28] The computations were performed in SAS procedure NLMIXED using the general likelihood option. Between-group differences for additional interventions during follow-up were compared using Kaplan-Meier methods and Cox proportional hazards models. The proportional hazards assumptions were evaluated and met to estimate hazard ratios with corresponding 99% confidence intervals. To account for multiple testing, we used a stringent significance level of 0.01 (2-sided) as statistically significant for all analyses. The statistical analyses were performed using SPSS version 21 (SPSS Inc) and SAS version 9.3 (SAS Institute Inc).

RESULTS

A total of 666 patients were screened for inclusion. Of these, 212 patients were randomly assigned to supervised exercise (n = 106) or endovascular revascularization plus supervised exercise (n = 106; combination therapy group) (Figure 1). The 2 groups were well matched at baseline (Table 1). The mean (SD) age was 65 (10) years, 132 patients (62%) were men, and noninvasive imaging identified 112 (53%) patients with predominant aortoiliac disease and 100 (47%) patients with predominant femoropopliteal disease. The types of noninvasive imaging used were duplex ultrasonography (n = 155), magnetic resonance angiography (n = 8), and computed tomography angiography (n = 49).

In the combination therapy group, endovascular revascularization at baseline was technically successful in 102 patients (96%). Procedure-related minor complications occurred in 7 patients (7%), including groin hematoma (n = 5) and localized arterial dissection (n = 2); however, no major complications were recorded. Of the 4 patients in whom endovascular revascularization technically failed, 3 underwent an open surgical procedure, including endarterectomy (n = 2) and bypass (n = 1) procedures, and 1 received only supervised exercise.Among the 102 patients with technically successful endovascular revascularization, balloon angioplasty was followed by selective stent placement in 63 patients (62%).

Table 1. Baseline characteristics of the study population according to treatment group

Baseline Characteristics	Supervised Exercise (n= 106)	Endovacular Revascularization *plus* Supervised Exercise (n= 106)
Age (years)	66 (10)	64 (9)
Gender (male)	72 (68%)	60 (57%)
Ethnicity		
White	98 (92%)	102 (96%)
Black	2 (2%)	2 (2%)
Other	6 (6%)	2 (2%)
Smoking		
Current	55 (52%)	65 (61%)
Former	42 (40%)	33 (31%)
Lipids (mg/dL)		
Total cholesterol	189 (46)	193 (58)
LDL-C	108 (43)	112 (50)
HDL-C	50 (23)	54 (31)
Triglycerides	195 (133)	168 (133)
Hyperlipidemia[a]	44 (42%)	47 (44%)
BMI (kg/m^2)	26.2 (4.4)	27.0 (4.1)
Waist size (cm)	102 (18)	102 (14)
Hypertension	66 (62%)	62 (58%)
Diabetes	27 (26%)	17 (16%)
History of ischemic cardiac disease	42 (40%)	35 (33%)
History of cerebrovascular disease	14 (13%)	11 (10%)
Pulmonary disease	17 (16%)	15 (14%)
Renal insufficiency	7 (7%)	7 (7%)
Lower limb osteoarthritis	12 (11%)	11 (10%)
Physical activity (hours/week)[b]	4.0 (1.0-8.0)	4.0 (1.0-9.0)
Duration IC (months)[b]	12.0 (6.0-24.0)	12.0 (5.0-24.0)
Fontaine classification[c]		
IIa	24 (23%)	18 (17%)
IIb	82 (77%)	88 (83%)
Dominant lesion		
Aortoiliac	54 (51%)	58 (55%)
Femoropopliteal	52 (49%)	48 (45%)
Maximum Walking Distance (m)	285 (165)	264 (145)
Pain Free Walking Distance (m)	135 (88)	117 (83)
Ankle Brachial Index[d]		
At rest	0.68 (0.16)	0.71 (0.18)
Post exercise	0.40 (0.24)	0.43 (0.21)
VascuQol score[e]	4.51 (1.02)	4.48 (0.92)
Rating score[f]	64.9 (17.8)	67.9 (17.8)
SF36- Physical Functioning[g]	52.7 (21.0)	51.4 (16.4)
SF36- Role Physical Score[g]	53.4 (40.9)	59.2 (40.2)
SF36- Bodily Pain[g]	53.1 (20.7)	52.7 (17.6)
SF36- General Health[g]	53.9 (20.3)	59.3 (15.4)

Data are presented as number of patients (%) or means (standard deviations)

Abbreviations: SE, supervised exercise; ER, endovascular revascularization; LDL-C low density lipoprotein- cholesterol; HDL-C, high density lipoprotein- cholesterol; BMI, body mass index; IC, intermittent claudication; VascuQol, vascular quality of life questionnaire score; SF-36, the 36-item short form health survey score

a: Defined as total cholesterol level ≥ 193 mg/d

b: Data presented as median (interquartile range)

c: Fontaine stage IIa is defined as pain-free walking distance >200 meters, Fontaine stage IIb is defined as pain- free walking distance ≤200 meters

d: Minimum value of those for right and left legs

e:The VascuQol consists of 25 questions on five domains including activities, symptoms, pain, emotional and social domain, scored on a 1 (worst outcome) and 7 (best outcome) scale.

f:Rating score consists of a single question in which patients score their health state on a 0 (worst imaginable health state) to 100 (best imaginable health state) point scale.

g: In this study the SF-36 questionnaire consists of four separate domain scores, which are the weighted sums of the questions in each domain. Each domain score is expressed on a 0 (severe limitation) to 100 (no limitation) scale.

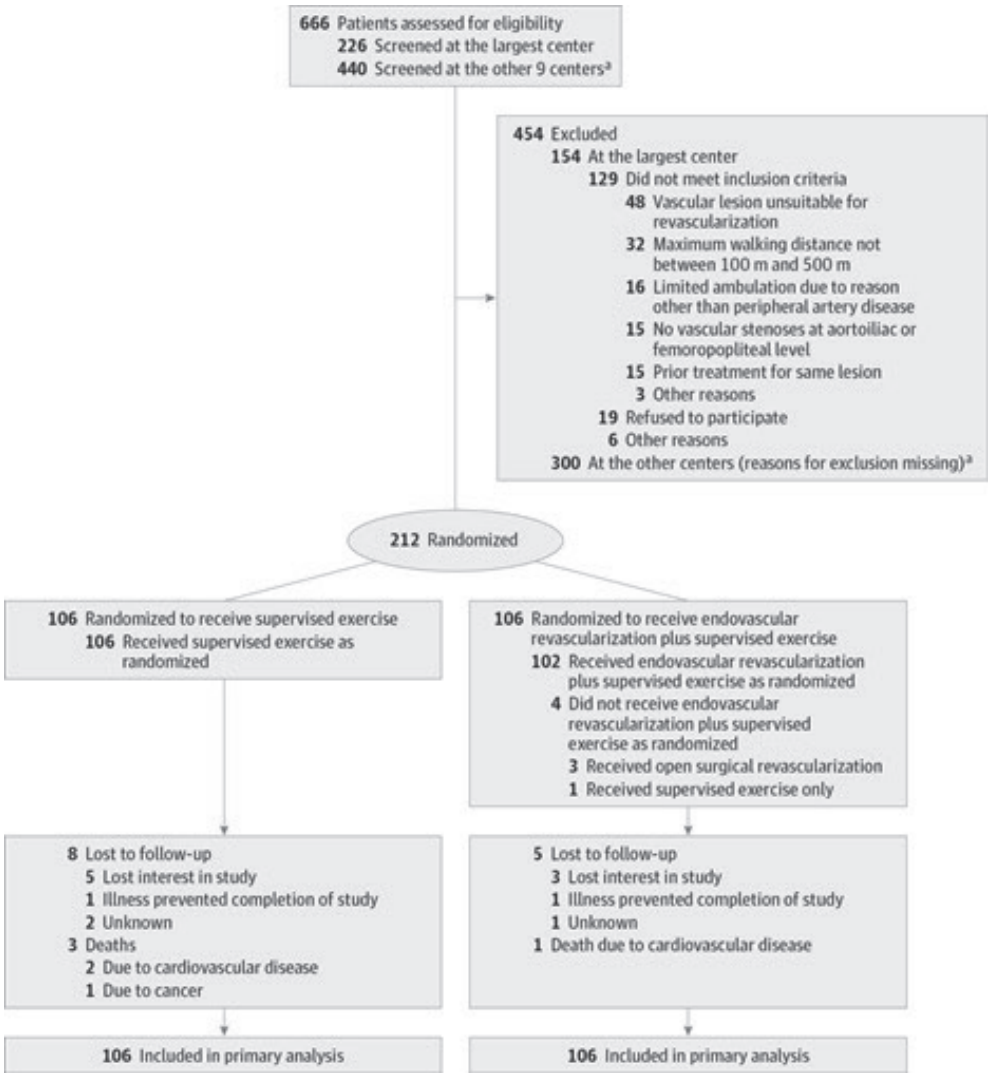

Figure 1. Flow of Patients in the Endovascular Revascularization and Supervised Exercise Trial

The average number of completed exercise sessions in the combination therapy group was 30 sessions compared with the recommended 46 to 59 sessions during the 1-year follow-up. In the supervised exercise group, the average number of completed exercise sessions was 43 sessions compared with the recommended 46 to 59 sessions during the 1-year follow-up. The completeness of 1-year follow up was 96% (5211/5438 person-weeks) in the exercise group and 97% (5329/5518 person-weeks) in the combination therapy group (Figure 1).

Table 2. Mean changes compared to baseline and mean difference between the treatment groups for measures of functional performance

Functional Performance Measures	Supervised Exercise (n=106)	Endovascular Revascularization *plus* Supervised Exercise (n=106)	Between-Group Difference	*P* Value[a]
Maximum Walking Distance (meters)				
Baseline	285 (244 ; 326)	264 (228 ; 300)		
1 month	438 (282 ; 595)	1004 (835 ; 1174)	566 (358 ; 774)	<0.001
6 months	851 (683 ; 1018)	1260 (1076 ; 1444)	409 (183 ; 636)	<0.001
12 months	955 (786 ; 1124)	1237 (1058 ; 1418)	282 (60 ; 505)	0.001
Pain Free Walking Distance (meters)				
Baseline	135 (113 ; 157)	117 (96 ; 138)		
1 month	181 (23 ; 339)	724 (561 ; 886)	543 (340 ; 744)	<0.001
6 months	542 (378 ; 707)	1071 (900 ; 1243)	529 (315 ; 743)	<0.001
12 months	712 (549 ; 876)	1120 (948 ; 1293)	408 (195 ; 622)	<0.001
Ankle Brachial Index[b] (at rest)				
Baseline	0.68 (0.64 ; 0.72)	0.71 (0.67 ; 0.76)		
1 month	-0.02 (-0.07 ; 0.02)	0.19 (0.15 ; 0.23)	0.21 (0.15 ; 0.27)	<0.001
6 months	0.04 (-0.01 ; 0.09)	0.16 (0.11 ; 0.20)	0.12 (0.05 ; 0.17)	<0.001
12 months	0.03 (-0.02 ; 0.08)	0.16 (0.11 ; 0.21)	0.13 (0.06 ; 0.19)	<0.001
Ankle Brachial Index[b] (post- exercise)				
Baseline	0.40 (0.34 ; 0.46)	0.43 (0.38 ; 0.48)		
1 month	0.03 (-0.02 ; 0.09)	0.36 (0.30 ; 0.42)	0.33 (0.25 ; 0.40)	<0.001
6 months	0.12 (0.06 ; 0.18)	0.33 (0.27 ; 0.39)	0.21 (0.13 ; 0.29)	<0.001
12 months	0.11 (0.05 ; 0.18)	0.33 (0.27 ; 0.40)	0.22 (0.13 ; 0.31)	<0.001

Data are presented as mean improvement compared to baseline (99% confidence intervals)

a: P values represent the difference between the two treatment groups for functional performance measures

b: Minimum value for right and left legs

Primary Outcome

During follow-up, the maximum treadmill walking distance improved significantly in both the supervised exercise only group and in the endovascular revascularization plus supervised exercise group. Compared with the supervised exercise only group, the improvement was significantly greater in the combination therapy group with a mean difference of 566 m (99% CI, 358-774 m) at 1 month, 409 m (99% CI, 183-636 m) at 6 months, and 282 m (99% CI, 60-505 m) at 12 months (Table 2).

Secondary Outcomes

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

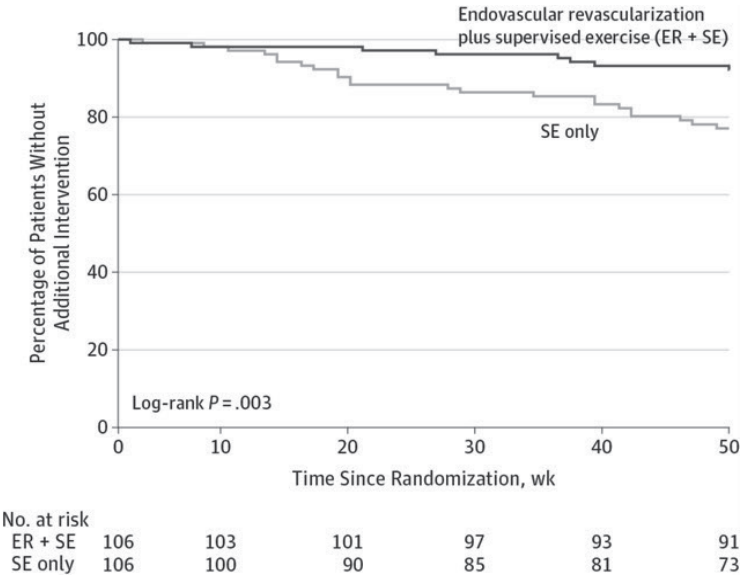

Figure 2. Kaplan-Meier Estimates of the Proportion of Patients Without Additional Intervention During Follow-up

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

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

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

DISCUSSION

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

To our knowledge, the ERASE trial is the first adequately powered RCT assessing the effectiveness of a combination therapy of endovascular revascularization plus supervised exercise vs supervised exercise only in patients with aortoiliac and femoropopliteal peripheral artery disease. In the Claudication: Exercise vs Endoluminal Revascularization trial,[30,31] which was funded by the National Institutes of Health and assessed the effectiveness of treatment strategies for aortoiliac disease, the fourth treatment group combining endovascular revascularization plus supervised exercise was prematurely stopped and removed from the analysis due to slow enrollment. Similarly, in the Mild to Moderate Intermittent Claudication trial[23] that assessed the adjuvant benefit of endovascular revascularization above supervised exercise, recruitment was stopped prematurely due to slow enrollment. The authors included 67 patients in the combination therapy group and demonstrated that after 24 months of follow-up, patients in the endovascular revascularization plus supervised exercise group had significantly higher maximum walking distance compared with the patients in the exercise only group. A more recent trial by Mazari et al[32] that assessed the effectiveness of a combination therapy of endovascular revascularization plus supervised exercise compared with a monotherapy of endovascular revascularization or supervised exercise in patients with femoropopliteal disease showed that the combination therapy was not different after 1 year regarding improvement in walking distance and quality of life. The lack of a statistically significant difference in walking distance between the groups might have been due to a ceiling effect because the treadmill test duration was limited to only 5 minutes (215 m).

The present study reopens the debate for revascularization in patients with claudication, in particular in terms of an approach using endovascular revascularization

Table 3. Mean changes compared to baseline and mean difference between the treatment groups for measures of quality of life

Quality of Life Measures	Supervised Exercise (n=106)	Endovascular Revascularization *plus* Supervised Exercise (n=106)	Between-Group Difference	*P* Value[a]
VascuQol score[b]				
Baseline	4.51 (4.25 ; 4.77)	4.48 (4.25 ; 4.71)		
1 month	0.27 (0.04 ; 0.50)	1.52 (1.29 ; 1.76)	1.25 (0.94 ; 1.56)	<0.001
6 months	0.62 (0.37 ; 0.88)	1.41 (1.16 ; 1.66)	0.79 (0.45 ; 1.13)	<0.001
12 months	0.73 (0.43 ; 1.03)	1.34 (1.04 ; 1.64)	0.62 (0.20 ; 1.03)	<0.001
Rating score[c]				
Baeline	64.9 (60.4 ; 69.4)	67.9 (63.4 ; 72.4)		
1 month	1.1 (-3.9 ; 6.2)	9.9 (5.1 ; 14.7)	8.7 (2.4 ; 15.1)	<0.001
6 months	-0.5 (-5.5 ; 4.5)	10.1 (5.2 ; 15.0)	10.6 (4.3 ; 17.0)	<0.001
12 months	-1.4 (-3.5 ; 6.3)	7.9 (3.0 ; 12.8)	6.5 (0.2 ; 12.7)	0.008
SF-36 Physical Functioning[d]				
Baseline	52.7 (47.4 ; 58.0)	51.4 (47.3 ; 55.5)		
1 month	4.0 (-0.7 ; 8.6)	27.3 (22.7 ; 31.8)	23.3 (17.3 ; 29.4)	<0.001
6 months	12.7 (7.7 ; 17.7)	27.2 (22.3 ; 32.2)	14.6 (7.9 ; 21.2)	<0.001
12 months	12.6 (6.3 ; 18.9)	22.4 (16.3 ; 28.5)	9.8 (1.4 ; 18.2)	0.002
SF-36 Role Physical Score[d]				
Baseline	53.4 (43.2 ; 63.7)	59.2 (49.1 ; 69.3)		
1 month	2.6 (-7.2 ; 12.3)	19.7 (10.0 ; 29.4)	17.1 (4.5 ; 29.7)	<0.001
6 months	5.9 (-4.4 ; 16.1)	18.9 (8.8 ; 28.9)	13.0 (-0.1 ; 26.1)	0.011
12 months	5.0 (-6.4 ; 16.5)	19.0 (7.8 ; 30.2)	14.0 (-0.8 ; 28.7)	0.015
SF-36 Bodily Pain[d]				
Baseline	53.1 (47.9 ; 58.3)	52.7 (48.3 ; 57.1)		
1 month	-3.1 (-8.1 ; 2.0)	22.7 (17.7 ; 27.8)	25.8 (19.2 ; 32.4)	<0.001
6 months	6.6 (1.2 ; 11.9)	21.0 (15.7 ; 26.3)	14.4 (7.4 ; 21.5)	<0.001
12 months	10.4 (4.3 ; 16.5)	17.9 (12.0 ; 23.9)	7.6 (-0.6 ; 15.7)	0.017
SF-36 General Health[d]				
Baseline	53.9 (48.9 ; 59.0)	59.3 (55.4 ; 63.2)		
1 month	-0.6 (-4.7 ; 3.5)	5.0 (0.8 ; 9.1)	5.6 (0.1 ; 11.0)	0.009
6 months	1.6 (-2.8 ; 5.9)	5.8 (1.5 ; 10.1)	4.2 (-1.6 ; 9.9)	0.061
12 months	-2.4 (-7.3 ; 2.5)	1.7 (-3.1 ; 6.5)	4.1 (-2.4 ; 10.6)	0.106

Data are presented as mean improvement compared to baseline (99% confidence intervals) Abbreviations: VascuQol, vascular quality of life questionnaire score; SF-36, the 36-item short form health survey score

a: P values represent the difference between the two treatment groups for quality of life measures

b: The VascuQol consists of 25 questions on five domains including activities, symptoms, pain, emotional and social domain, scored on a 1 (worst outcome) and 7 (best outcome) scale. The minimal clinically important difference for VascuQol has been established to be > 0.36 to 0.48 points[39]

c: Rating score consists of a single question in which patients score their health state on a 0 (worst imaginable health state) to 100 (best imaginable health state) point scale. For patients with peripheral arterial disease the minimum clinically important difference for rating score has not been established yet.

d: In this study the SF-36 questionnaire consists of four separate domain scores, which are the weighted sums of the questions in each domain. Each domain score is expressed on a 0 (severe limitation) - 100 (no limitation) scale. The minimal clinically important difference for the SF-36 score is suggested to be >2 to 2.5 points[29]

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

In addition to demonstrating benefits of a combination therapy, this study also confirmed the beneficial effects of exercise in the management of claudication with significant improvements in walking distances and quality of life in patients receiving supervised exercise only with the majority requiring no revascularization procedure up to 1 year. A cost-effectiveness analysis based on the ERASE results is required and is under way to address the question of whether the incremental benefit of the combination therapy as demonstrated in this study will also be cost-effective given the substantially higher costs of endovascular revascularization compared with supervised exercise.[33-35]

In clinical practice, especially in the United States, endovascular revascularization alone is being performed more frequently than the recommended care of supervised exercise. This is mainly due to reimbursement issues and unavailability of supervised exercise. Previous studies have shown exercise alone to be no different than[24,32] or even superior to endovascular revascularization alone.[30,31] Thus, in the ERASE trial we chose to study the treatment strategy of combining supervised exercise and endovascular revascularization. We believe this was the most relevant comparison from a scientific point of view and also the most relevant comparison in the context of recommended clinical practice as formulated in the guidelines.[6-9]

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

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

Fifth, the number of supervised exercise sessions followed by the patients was lower compared with the number of sessions as recommended by the guideline,[7] which might have resulted in a less effective supervised exercise. Nonetheless, significant improvement was demonstrated in walking distance and quality of life in the supervised exercise group, which was comparable or even superior to previously published RCTs assessing the effectiveness of supervised exercise.[23,24,30,32,36,38] In addition, the optimal number of supervised exercise sessions to complete remains unknown.[5] The supervised exercise program in the ERASE study was in accordance with the single RCT on this issue, which suggests an important role for intensive training offered during the first 2 months of supervised exercise.[39]

CONCLUSIONS

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

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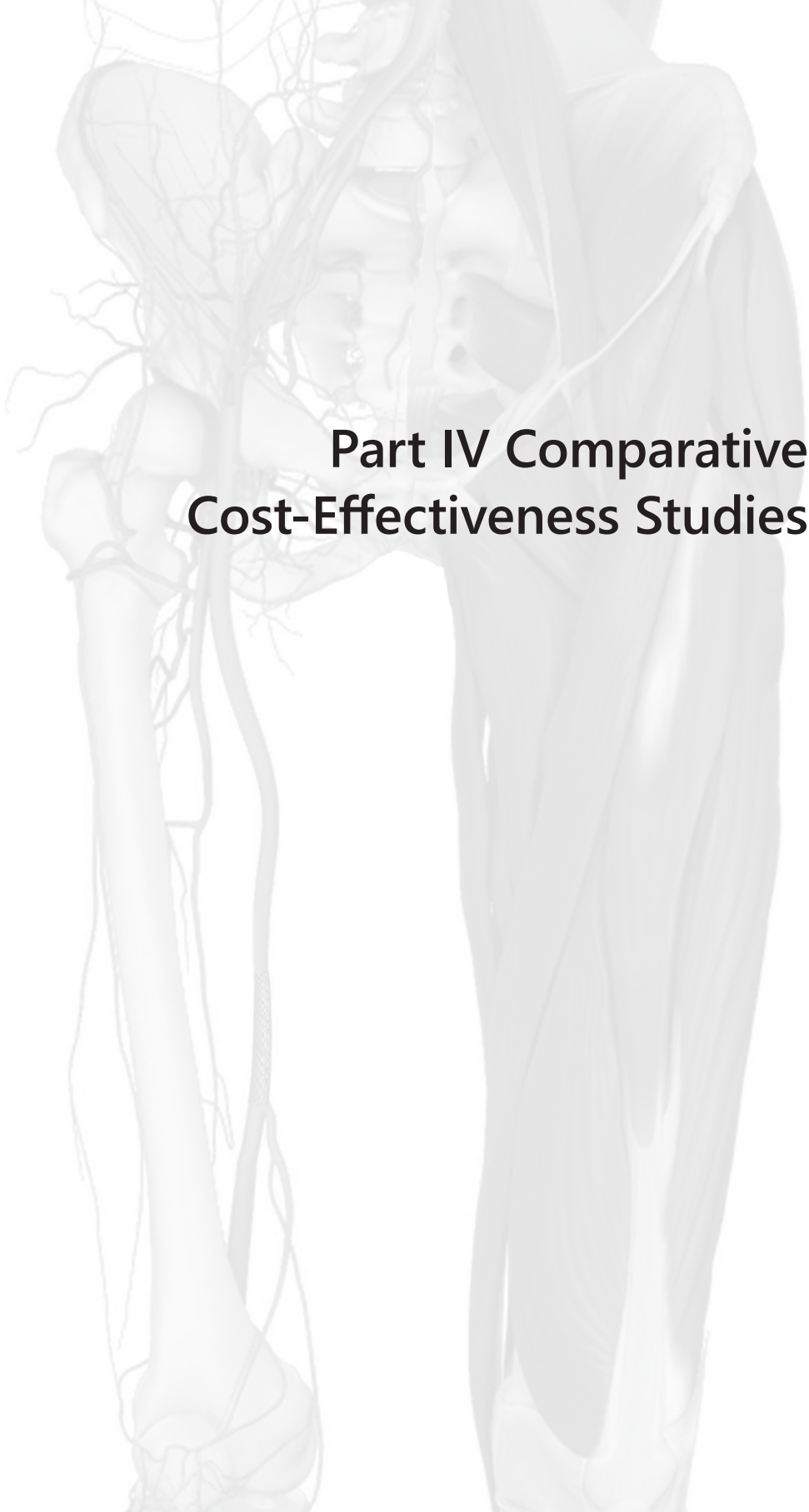

Part IV Comparative Cost-Effectiveness Studies

Chapter 8

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

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Br J Surg. 2016 Nov;103(12):1616-1625

ABSTRACT

Background

Current guidelines recommend supervised exercise therapy as the preferred initial treatment for patients with intermittent claudication. The availability of supervised exercise therapy programmes is, however, limited and such programmes are often not reimbursed. Evidence for the long-term cost-effectiveness of supervised exercise therapy compared with endovascular revascularization as primary treatment for intermittent claudication might aid widespread adoption in clinical practice.

Methods

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

Results

Considering a 5-year time horizon, probabilistic sensitivity analysis revealed that supervised exercise therapy was associated with cost savings compared with endovascular revascularization (– €6412, 95 percent credibility interval (CrI) – €11874 to – €1939). The mean difference in effectiveness was −0.07 (95 percent CrI −0.27 to 0.16) QALYs. Endovascular revascularization was associated with an additional €91600 per QALY gained compared with supervised exercise therapy. One-way sensitivity analysis indicated more favourable cost-effectiveness for endovascular revascularization in subsets of patients with low quality of life scores at baseline.

Conclusions

supervised exercise therapy is a more cost-effective primary treatment for intermittent claudication than endovascular revascularization. These results support implementation of supervised exercise programmes in clinical practice.

Intermittent claudication is the most common manifestation of peripheral arterial disease (PAD). Its prevalence is around 2 percent in the population aged 40–44 years, increasing to 8 per cent at 70–74 years[1]. With the ageing population in Western societies, the prevalence of intermittent claudication is increasing[2] and it will place a growing burden on healthcare resources. Treatment of intermittent claudication aims to improve quality of life (QoL) and walking distance. Over the past decade, several studies have compared supervised exercise therapy, endovascular revascularization or a combination of these treatments. In general, most studies found no difference between supervised exercise therapy and endovascular revascularization with respect to walking distance or QoL, even after 7 years of follow-up[3-8]. Supervised exercise therapy is a relatively safe, non-invasive treatment[9]. Accordingly, current international guidelines recommend supervised exercise therapy as the primary treatment in the management of intermittent claudication1,[10–12]. However, access to adequate supervised exercise therapy programmes worldwide is limited[13,14]. Furthermore, in contrast to endovascular revascularization they are often not, or only partially, reimbursed by insurance plans[15,6]. As a result, supervised exercise therapy remains underutilized in the treatment of intermittent claudication.

Considering the equal effectiveness of supervised exercise therapy and endovascular revascularization, other aspects such as costs, mortality and morbidity of the intervention can play a decisive role in choosing the initial treatment strategy. Previous cost-effectiveness studies[17-19] found a supervised exercise therapy-first approach to be less expensive than endovascular revascularization, and equally effective. Implementation of a supervised exercise therapy-first approach in the treatment of intermittent claudication could lead to significant savings in terms of healthcare resources[16]. However, these studies either considered a limited time horizon of 12–15 months[18,19], or did not include effectiveness[16,17].

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

The purpose of the present study was to incorporate current evidence on the costs and effectiveness of supervised exercise therapy and endovascular revascularization into a clinical decision model, and to evaluate the cost-effectiveness of a supervised exercise therapy-first strategy (with endovascular revascularization in the event of supervised exercise therapy failure) compared with an endovascular revascularization-first strategy for the management of intermittent claudication.

METHODS

Study design

A Markov model was developed using Microsoft Excel 2010 (Microsoft Corporation, Redmond,Washington,USA) to assess the cost-effectiveness, from the perspective of the Dutch healthcare payer, of supervised exercise therapy and endovascular revascularization for patients with newly diagnosed intermittent claudication (PAD Fontaine II, Rutherford 1–3). The model was designed to simulate the effect of both treatment strategies on the clinical course of a hypothetical cohort of patients. It consisted of seven health states: asymptomatic PAD, mild claudication, moderate claudication, severe claudication, critical limb ischaemia (CLI), post major amputation and death (Fig. 1).

All patients started with an intervention, either supervised exercise therapy or endovascular revascularization. With each cycle, representing 3 months, transition probabilities determined whether patients would relocate to a different health state or remain in the same state. The decision model kept track of costs, time spent in each health state and impact on QoL. Subsequent analysis over a 5-year time horizon (20 cycles) provided results regarding the cost-effectiveness of supervised exercise therapy and endovascular revascularization. Outcomes of interest were total quality adjusted life years (QALYs), total costs (reported in euros) and the incremental cost-effectiveness ratio (ICER).

Treatment strategies

Two primary treatment strategies were analysed: supervised exercise therapy and endovascular revascularization. supervised exercise therapy, lasting 1 year, was performed by a physiotherapist trained in supervised exercise therapy according to the guidelines of the Royal Dutch Society for Physical Therapy[21]. A typical session included interval training to near-maximal pain, as well as strength and endurance training, and focused on risk factor modification and improving self-management. endovascular revascularization comprised a percutaneous transluminal angioplasty followed by a stent when balloon dilatation was inadequate.

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

Model input sources

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

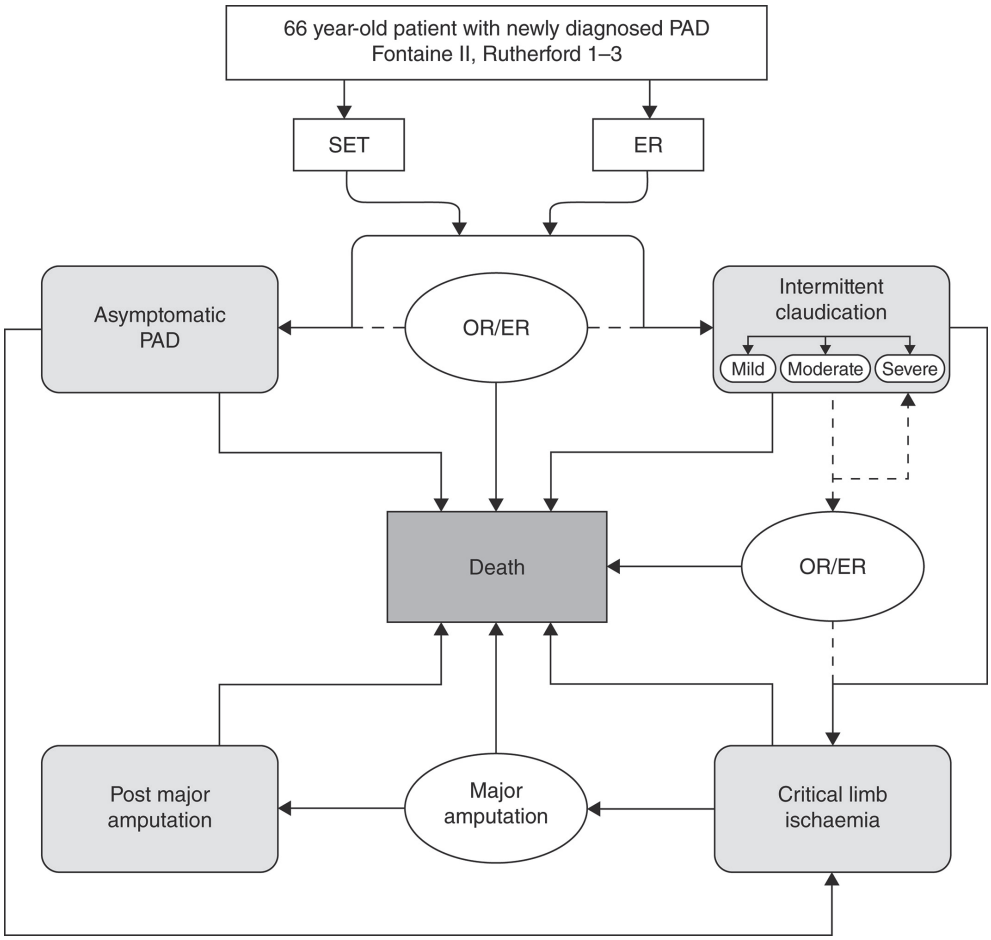

Figure 1. Simplified diagram of the Markov structure. Patients start the cycle in one of the intermittent claudication health states and will receive primarily either supervised exercise therapy (SET) or endovascular revascularization (ER). The shaded boxes represent a health state. The oval boxes represent a possible secondary intervention: major amputation, open revascularization (OR) or ER. The arrows indicate possible transitions between health states. Transition probabilities define how patients may move during a cycle. Both the supervised exercise therapy and ER groups have distinct transition probabilities. For clarity, simplifications have been made. The intermittent claudication health states are represented in a single box. In the model, intermittent claudication was split into three groups (mild, moderate, severe) based on symptom severity as defined by quality of life. Each health state had possible transitions to itself not shown in the figure.

with Angioplasty for Claudication) study[3]. The EXITPAD study was a multicentre RCT that included 304 patients from 11 outpatient vascular surgery clinics throughout the Netherlands. Patients were randomized to either verbal walking advice or supervised exercise therapy performed by a local physiotherapist. The CETAC study was a single-centre RCT; 151 consecutive patients who presented with symptoms of intermittent claudication due to iliac or femoropopliteal arterial stenosis were included. Patients with lesions unsuitable for revascularization were excluded. Patients were assigned randomly to either hospital-based supervised exercise therapy or endovascular revascularization. Further details of trial methodology were published previously[3,37].

The baseline and 12-month follow-up data from the supervised exercise therapy treatment arms of the EXITPAD study (159 patients), and both the endovascular revascularization and supervised exercise therapy arms of the CETAC study (150 patients), were used. A comparison of baseline characteristics can be found in Table S1 (supporting information online). Their respective institutional review boards approved both trials and all patients gave written informed consent. The authors of both trials approved use of their data in the present study.

Health states

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

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

Input parameters

Transition probabilities

Tables S2 and S3 (supporting information online) show the input transition probabilities with their corresponding sources and ranges used for probabilistic sensitivity analysis. Some assumptions had to be made where data sources were insufficient, as described below.

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

The model structure allowed for only one type of secondary intervention. To be able to incorporate outcome and costs for both endovascular revascularization and OR, weighted averages of cost and effectiveness outcomes were calculated, and the results combined based on observed ratios of OR:ER (10 : 29316 for intermittent claudication and 10 : 2729 for CLI).

Transitions for a patient in the CLI health state differed depending on type of treatment received. A study by Frans and colleagues[29] found that, of 150 consecutive patients with CLI, 7.3 percent received conservative treatment, 3.3 percent required a major amputation, 24.1 percent were treated with OR and 65.3 per cent with endovascular revascularization. Accordingly, different transition probabilities, from different sources, were used for patients with CLI who had conservative treatment (wound care and pharmacotherapy alone)[25], after endovascular revascularization or OR[26] and after amputation[28] (Tables S2 and S3, supporting information online).

Costs

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

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

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

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

Values in parentheses are standard errors. *All values are presented per year. They were converted into 3-monthly values to fit the cycle length of the model. †Based on a range of values from different studies reported by Barshes et al.26 ‡Estimated standard error owing to lack of published data. §Cost of secondary intervention endovascular revascularization (ER)/open revascularization (OR) was calculated by combining separate costs, assuming an OR:ER ratio of 10 : 29316 for intermittent claudication and 10 : 2729 for critical leg ischaemia. PAD, peripheral arterial disease; SET, supervised exercise therapy.

Quality of life

To assess the effect of treatment on QoL, utility scores were assigned to each health state (Table 1). A utility is the valuation of a person's health ranging from 0 (worst possible) to 1 (perfect). Utility scores for mild, moderate and severe claudication as well as asymptomatic PAD were derived from the EXITPAD and CETAC data by calculating median EQ-5D™ values for these states. Utilities for post major amputation[41] and CLI[26] were drawn from the literature.

Analysis

Validation

The internal validity of the model was tested by comparing the health state distribution after 1 simulated year with the distribution in the observed data from the EXITPAD and CETAC studies. The external validity was verified by comparing important simulated

outcome parameters with values described in the practice guidelines from the Society for Vascular Surgery[12].

Base-case analysis

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

Uncertainty

To account for the uncertainty of the model outcome, a probabilistic sensitivity analysis was performed using Monte Carlo simulation. A probability distribution was derived for each parameter, from either reported standard errors, confidence intervals, alternative probabilities found in the literature or expert opinion (Table 1; Tables S2 and S3, supporting information online). The simulation ran 1000 times for a hypothetical cohort of 100 000 patients for each treatment strategy. Each time, the value for each parameter differed based on random selection from their respective distributions. The mean costs and QALYs from the 1000 simulations were reported, along with their 95 percent credibility interval (CrI). The CrI is the Bayesian statistics equivalent of a confidence interval.

The probability of supervised exercise therapy or endovascular revascularization being cost-effective at different willingness-to-pay (WTP) thresholds was presented in cost-effectiveness acceptability curves (CEACs). There is no consensus on an appropriate threshold for the costs society is willing to pay per QALY gained. In the Netherlands a WTP threshold range of €20 000 – €80 000/QALY has been suggested[43]. A threshold WTP for a QALY of €40 000 was used as this is close to the commonly used threshold of €50 000/QALY[44]. Various one-way sensitivity analyses were performed to evaluate the effect of alternative inputs and assumptions on the outcomes of the model. In particular, sensitivity analyses were carried out by varying the time horizon, using alternative discount rates, varying the age of the patients, alternating the frequency of supervised exercise therapy sessions (according to National Institute for Health and Care Excellence guideline recommendations[11]), using different costs or secondary intervention rates, applying cardiovascular health benefits after supervised exercise therapy[45], and isolating patients with mild, moderate or severe disease (as defined by EQ-5D™ scores).

RESULTS

The outcome of 1000 Monte Carlo Markov model simulations of a hypothetical cohort of 100000 patients with intermittent claudication was calculated (Figure 2). Over a 5-year time horizon, the mean total costs of supervised exercise therapy and endovascular revascularization were €10219 and €16631 respectively. Mean total QALYs were 2.78 for supervised exercise therapy and 2.85 for endovascular revascularization. The distribution of virtual patients across health states after 5 years is shown in Table S4 (supporting information online). Probabilistic sensitivity analysis showed that supervised exercise therapy saved costs compared with endovascular revascularization (−€6412, 95 percent CrI −€11874 to −€1939). There was no statistically significant difference in effectiveness (−0.07 (95 percent CrI −0.27 to 0.16) QALYs). Endovascular revascularization was associated with an additional €91600 per QALY gained compared with supervised exercise therapy. This exceeds the Dutch WTP threshold of €20 000–80 000/QALY. There were no statistically significant differences in the number of secondary interventions (endovascular revascularization/OR and major amputations) between supervised exercise therapy and endovascular revascularization.

Figure 3: shows the CEACs for the supervised exercise therapy-first and endovascular revascularization-first treatment strategies. The probability of endovascular revascularization being cost-effective increased with a rising WTP threshold. Even so, with WTP thresholds of up to €100 000, the probability that endovascular revascularization was the optimal primary treatment choice did not exceed 53 percent.

One-way sensitivity analysis

The supervised exercise therapy-first approach would remain the most cost-effective option, given a hypothetical WTP threshold of €40 000, in all one-way sensitivity analyses, except one alternative scenario in which all patients started in the severe claudication health state (Table 2). Alternative input values regarding cost estimations for endovascular revascularization and secondary intervention rates, as well as applying cardiovascular health benefits to the supervised exercise therapy-first treatment arm, markedly improved the cost-effectiveness of supervised exercise therapy. Changing the time horizon to lifetime decreased the probability that supervised exercise therapy was cost-effective compared with the base case (Fig. S1,supporting information online). However, this would assume a continued treatment effect of the initial intervention well beyond the follow-up time span of available trial data, increasing the uncertainty concerning incremental QALYs. This is illustrated by the wide spread of simulation results on the incremental cost-effectiveness plane of lifetime analysis (Fig. S2, supporting information online).

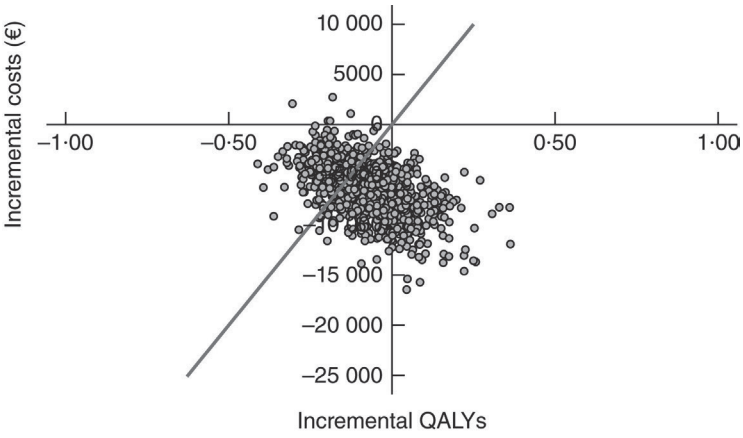

Figure 2. Incremental cost-effectiveness plane for supervised exercise therapy versus endovascular revascularization (ER). The x-axis shows the incremental quality-adjusted life-years (QALYs), and the y-axis the incremental costs, for supervised exercise therapy compared with ER. The differences in costs (incremental costs) and QALYs (incremental QALYS) are calculated for each of the 100 000 hypothetical patients and represented as a dot. The diagonal line represents a €40 000 willingness-to-pay threshold. Supervised exercise therapy was the preferable treatment in all samples below this line, constituting 73 per cent of the 1000 simulations

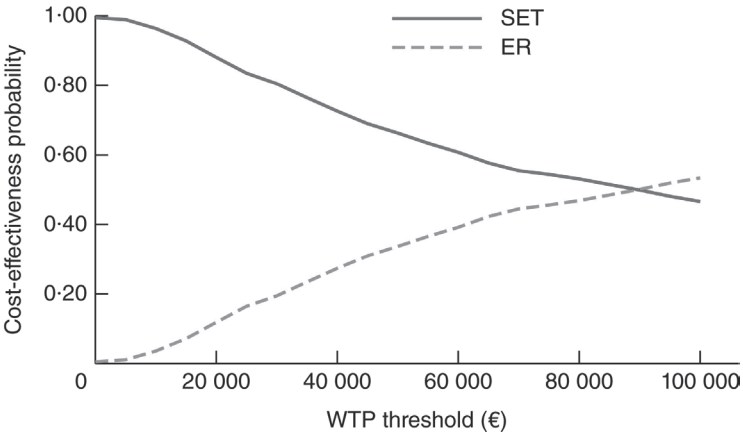

Figure 3. Cost-effectiveness acceptability curves for a range of willingness-to-pay (WTP) thresholds for the treatment of intermittent claudication. The x-axis shows different WTP thresholds that society may be willing to pay to gain 1 quality-adjusted life-year. The y-axis shows the proportion of samples that demonstrated cost-effectiveness for supervised exercise therapy and endovascular revascularization (ER)

Table 2. Input and outcomes of one-way sensitivity analyses

Parameters	Incremental costs (€)*	Incremental QALYs*	CEP†
Base case analysis	-6412 (-11 874;-1939)	-0.07 (-0.27;0.16)	73%
Cost of ER			
€12 51231	-11 353 (-16 098;-6624)	-0.07 (-0.27;0.14)	93%
Cost of SET			
24 sessions (2/week for 3 mo)48	-6832 (-12 058;-1848)	-0.07 (-0.27;0.14)	76%
2x 1-h session/wk for 3 mo11‡	-6084 (-14 522;2572)	-0.07 (-0.53, 0.36)	72%
Discount rates			
Costs 3%, outcome 3%	-6619 (-11 744;-1827)	-0.06 (-0.26;0.15)	77%
Costs 5%, outcome 5%	-6462 (-11 606;-1963)	-0.07 (-0.26;0.12)	75%
Age			
55 years	-6445 (-12 166;-1387)	-0.07 (-0.31;0.17)	72%
75 years	-6637 (-11 662;-2334)	-0.06 (-0.23;0.10)	81%
Time horizon			
Lifetime horizon	-6341 (-13 707;424)	-0.09 (-0.54;0.35)	61%
10 years	-6220 (-12 570;62)	-0.10(-0.44;0.26)	59%
Secondary intervention rate			
SET 6.4%, ER 35.2%16	-8207 (-14 371;-2848)	-0.09 (-0.30;0.14)	78%
Cardiovascular health benefits SET			
52% mortality reduction45	-6036 (-11 029;-1649)	0.01 (-0.19;0.23)	87%
Starting health state			
Mild Claudication	-8051 (-13 219;-2380)	0.04(-0.18;0.26)	93%
Moderate Claudication	-6193 (-12 603;-735)	-0.08 (-0.30;0.17)	63%
Severe Claudication	-4618 (-10 319;1250)	-0.23 (-0.55;0.14)	29%

Value in parentheses are 95 per cent credibility intervals. *Incremental values are shown for supervised exercise therapy (SET) minus endovascular revascularization (ER). †Cost-effectiveness probability (CEP): the probability that supervised exercise therapy is cost-effective compared with ER considering a willingness-to-pay threshold of €40 000. ‡National Institute for Health and Care Excellence guidelines. QALY, quality-adjusted life-year; PAD, peripheral arterial disease.

Validation

The model adequately predicted the health state distributions after 1 simulated year as observed in the EXITPAD and CETAC studies, and after 5 simulated years compared with outcomes presented by Conte and colleagues[12] (Table S5, supporting information online).

DISCUSSION

This cost-effectiveness analysis, comparing supervised exercise therapy and endovascular revascularization as primary treatment in patients with newly diagnosed intermittent claudication, showed that supervised exercise therapy is more cost-effective than endovascular revascularization. The mean costs of a supervised exercise therapy-first treatment strategy over a 5-year interval were lower per patient, but there was no statistically significant difference in effectiveness. Submitting a new patient with intermittent

claudication to endovascular revascularization as opposed to supervised exercise therapy would cost an additional €91600 per QALY gained. This exceeds most international WTP thresholds. These results, therefore, support a supervised exercise therapy-first approach in the treatment of intermittent claudication.

The outcome of this model-based cost-effectiveness analysis is in line with previous economic evaluations. Reynolds and co-workers[46] used a Markov model to extrapolate the results of a recent trial comparing supervised exercise therapy, stenting and optimal medical care for intermittent claudication. Data from one trial, containing a small sample of patients, were used. Consequently, comparisons between supervised exercise therapy and endovascular stenting lacked statistical power to detect small differences. Furthermore, their model did not include PAD progression to CLI and secondary interventions such as repeated endovascular revascularization,OR or amputation. In their analysis, stenting demonstrated an ICER of US $122600 per QALY gained (€109754; exchange rate 1 June 2016) compared with supervised exercise therapy. These results are analogous to the ICER for endovascular revascularization versus supervised exercise therapy of €91600 found in the present study (US $102322), despite differences in setting and scope between the two studies. Likewise, a previous study[16] used invoice data from a large Dutch health insurance company and demonstrated that implementation of supervised exercise therapy as initial treatment would amount to yearly cost savings of up to €6677 per patient. Two trial-based economic analyses[18,19] found supervised exercise therapy to be as effective as endovascular revascularization and less costly. A retrospective analysis of costs by O'Brien-Irr and colleagues[17] showed that a trial of supervised exercise therapywas cost-effective, even if 80 percent of patients still required endovascular revascularization afterwards. Thus, the present study confirms the findings of previous cost-effectiveness research on supervised exercise therapy versus endovascular revascularization. Moreover, it adds that potential cost savings can be achieved over an extended time horizon and without a detrimental effect on QoL, secondary intervention rate or mortality.

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

Four international guidelines recommend supervised exercise therapy as primary treatment for intermittent claudication[1,10-12]. However, in practice there are several important impediments to routine implementation of supervised exercise therapy. First, availability of supervised exercise therapy programmes is lacking[13]. This study again supports the

implementation of a network of trained supervised exercise therapy providers to improve accessibility. Moreover, it indicates that the initial investment required to develop the necessary infrastructure for a supervised exercise therapy programme will be compensated by the economic benefits supervised exercise therapy yields. Second, insurance coverage is poor for supervised exercise therapy, as opposed to endovascular revascularization[15,16]. The present results, in accordance with previous analyses[16-19,46], advocate the allocation of healthcare resources to support reimbursement by health insurers.

Finally, it has been postulated that patients with intermittent claudication generally favour endovascular revascularization, as it provides a 'quick fix'[15].However, others have reported that supervised exercise therapy improves patients' walking capacity rapidly in the first 2 months[47], achieving maximal effectiveness at 3 months[48]. Emphasizing these short-term benefits could help motivate patients for supervised exercise therapy. In addition, the costs of supervised exercise therapy decrease when fewer training sessions are required to achieve the same effectiveness.

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

Third, treatment arms were compared using combined data from two different studies. Although baseline characteristics were generally similar, significant differences between baseline walking distances and smoking status were found. This could be a cause of heterogeneity. Fourth,most input parameters were based on data spanning 1 year. In the present model, a continued effect from both endovascular revascularization and supervised exercise therapy up to 5 years was assumed, as opposed to lifetime analysis. Sensitivity analysis using a lifetime horizon, assuming a continuous effect of treatment, showed this assumption had a moderate effect on outcome. Fifth, a recent trial[49] showed a greater improvement in walking distances and health-related QoL after endovascular revascularization followed by supervised exercise therapy compared with supervised exercise therapy alone. These results raise the question of whether the observed improved effectiveness of combined treatment is associated with an acceptable increase in costs. The present analysis does not address this.

Finally, owing to lack of sound evidence, the benefits of exercise on cardiovascular health and QoL were not included in the base-case model. The effect on outcome of a 52 percent reduction in cardiovascular mortality after 12 weeks of supervised exercise therapy[45] was investigated in one-way sensitivity analysis. This provided an expected

dramatic increase in the relative cost-effectiveness of supervised exercise therapy. Future research should further clarify the potentially beneficial effect supervised exercise therapy provides on general cardiovascular health in this patient population.

This study has shown that supervised exercise therapy is a more cost-effective primary treatment for intermittent claudication than endovascular revascularization. These results add to an impressive body of evidence and consequent guideline recommendations advocating a supervised exercise therapy-first approach in the treatment of intermittent claudication. Policymakers' efforts and further research should focus on realizing implementation of supervised exercise therapy in clinical practice.

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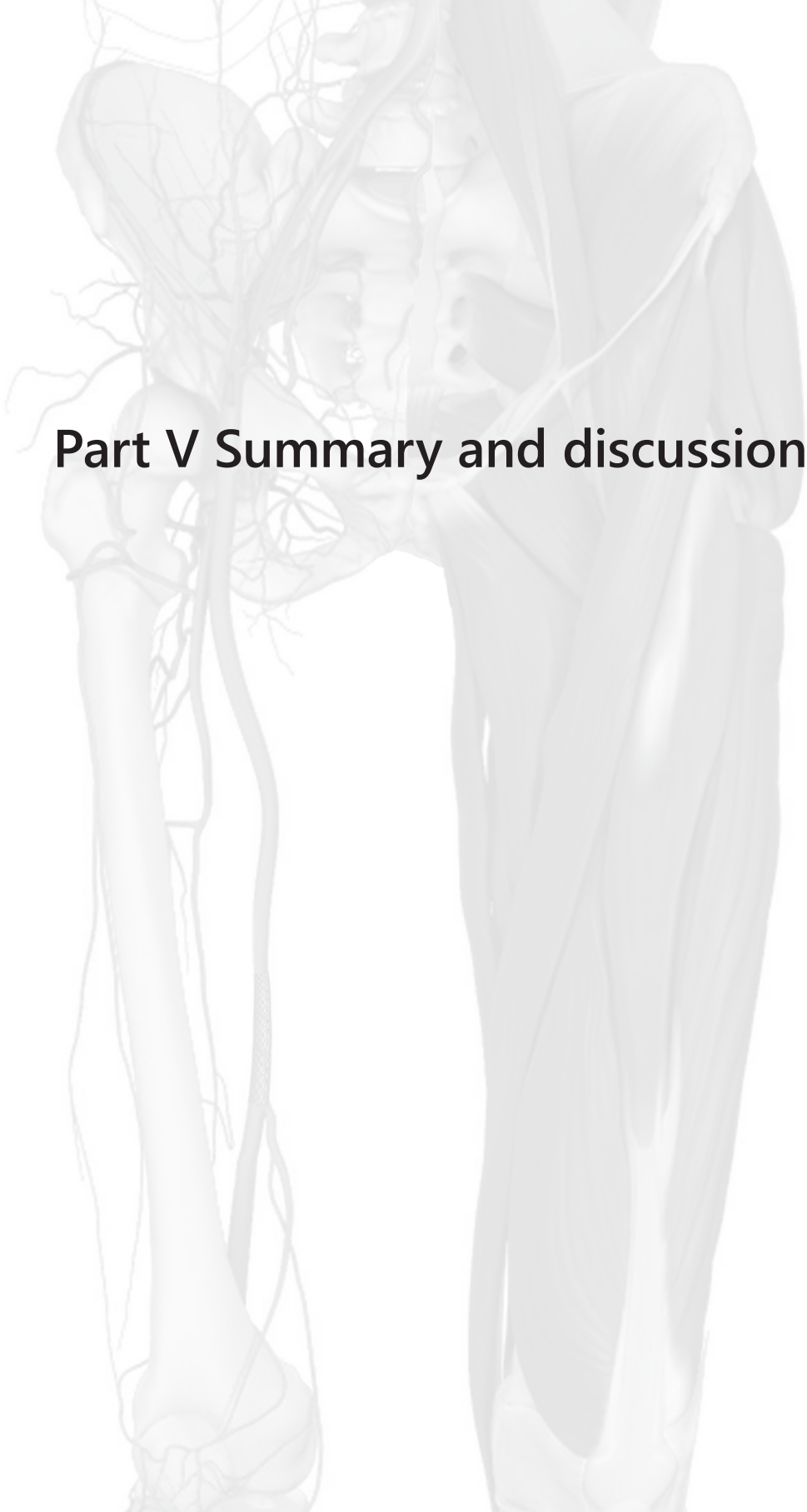

Part V Summary and discussion

Chapter 10

Summary and general discussion

Summary and general discussion

Part I Introduction

Peripheral artery disease (PAD) which is caused by systemic atherosclerosis of the infrarenal aorta and the lower limb arteries is a major global burden with a prevalence of 200 million people worldwide and is increasing rapidly with the ageing world population. Intermittent claudication, i.e. exertional leg pain that resolves with rest, is the symptomatic form of PAD, affecting approximately 20-40 million people worldwide.[1] Patients with claudication experience significantly limited walking ability and diminished ability to perform their daily activities leading to a sedentary lifestyle and impaired quality of life.[2,3] Moreover, these patients face increased cardiovascular morbidity and mortality.[4,5] In order to tackle these challenges, two policies need to be followed: improving limb symptoms and quality of life and reducing the risk for cardiovascular events. Modalities to improve limb symptoms are supervised exercise therapy or (endovascular) revascularization, either alone or in combination. The aim of this thesis was to determine the optimal treatment for improving walking ability and quality of life in patients with intermittent claudication. We first summarized the existing evidence regarding treatment options, then assessed the effectiveness of a novel treatment strategy compared to the standard care, and finally assessed the cost-effectiveness of this novel treatment strategy to better inform policymakers on implementation.

Part II Systematic reviews

Supervised exercise therapy is being recommended as first-line treatment for intermittent claudication. However, uncertainty remains about the effect of supervised walking therapy and the different exercise components (e.g. treadmill use, intensity, duration and content). In **chapter 2** we performed a meta-analysis and meta-regression to summarize the effectiveness of supervised walking therapy for intermittent claudication and identify the components of the walking program that provide maximal improvement in walking distances. Pooled data from 25 randomized controlled trials (RCT) with more than 1000 patients showed an improvement in maximum walking distance of about 200 meters in patients who followed a supervised walking program as compared to those who did not. No specific component of the exercise program in isolation was responsible for the improvement in walking capacity.

Although supervised walking therapy is an effective first-line treatment for intermittent claudication, a substantial number of patients cannot train on a treadmill due to common comorbidities, such as pulmonary disease, heart failure, back pain, or osteoarthritis. For these patients, other modes of exercise therapy (e.g. cycling, upper-arm ergometer and strength training) might be a suitable alternative. In **chapter 3** we performed a systematic

review and meta-analysis to compare alternative modes of supervised exercise with supervised walking therapy. Pooled results from five RCTs (135 patients) showed similar improvements in walking distance in patients who followed a supervised walking program and those who performed alternative modes of exercise.

The benefit of supervised exercise in the management of intermittent claudication is well established and international guidelines recommend supervised exercise as first-line treatment for intermittent claudication. Supervised exercise requires patient motivation and time in order to be successful, while on the on the other hand endovascular revascularization offers instant symptom relief without patient compliance and is highly profitable for the physician. Endovascular revascularization provides an attractive alternative and the number of endovascular procedures for PAD has increased dramatically in the past 10 years. To assess the value of endovascular revascularization in the management of intermittent claudication, in **chapter 4** we performed a systematic review and meta-analysis to summarize the comparative efficacy of endovascular revascularization versus conservative management. Pooled results from three studies (125 patients) showed a moderate to large effect on improvement in walking distances in favor of revascularization as compared to a walking advice. Pooled data from five studies (345 patients) showed equal effectiveness for endovascular revascularization and supervised exercise therapy in terms of improving walking distances and quality of life. Finally, pooled data from five studies (618 patients) showed a moderate to large effect on improvement in walking distance and quality of life in patients receiving combination therapy (endovascular revascularization combined with supervised exercise or pharmacotherapy) as compared to conservative therapy (supervised exercise or pharmacotherapy) only.

Part III Clinical effectiveness

Most of the clinical trials comparing endovascular revascularization with supervised exercise have limited their follow-up to one year, making long-term recommendations difficult. In **chapter 5** we presented the 7-year results from a randomized controlled trial of supervised exercise versus endovascular revascularization. Patients in both groups showed comparable and sustained improvements in their walking distance and quality of life at long-term follow-up, which suggests that both therapies are also equivalent in the long term.

Supervised exercise programs are not widely available and not reimbursed in most countries. To overcome this issue of limited access, home-based exercise programs are being investigated. In **chapter 6** we evaluated the effectiveness of a structured home-based exercise program for patients with intermittent claudication and compared these results with those from a concurrent control group who received supervised exercise. At one year follow up the 142 patient receiving structured home-based exercise showed significant improvement in their walking distances and quality of life compared to their baseline values, yet patients in the control group receiving supervised exercise showed

significantly better results. In **chapter 7** we presented results from the Endovascular Revascularization And Supervised Exercise (ERASE) trial, which compared the combination therapy of endovascular revascularization plus supervised exercise with supervised exercise only for claudication. In this multicenter study, 212 patients were randomized to the combination therapy or supervised exercise only. At one year follow up, patients receiving the combination therapy showed greater improvements in maximum and pain-free walking distances of 300 and 400 meters, respectively. Similarly, patients in the combination therapy group showed greater improvement in quality of life. A combination therapy of early endovascular revascularization followed by supervised exercise thus seems promising because it combines the immediate improvement in claudication symptoms after revascularization with the potentially long-term benefits of exercise therapy.

Part IV Cost-effectiveness

Data on long-term cost-effectiveness of supervised exercise versus endovascular revascularization for intermittent claudication is sparse. In **chapter 8** we constructed a Markov model to assess the cost-effectiveness of supervised exercise versus endovascular revascularization from the healthcare perspective considering a 5-year time horizon. Supervised exercise was associated with significant cost-savings as compared to endovascular revascularization. Per quality adjusted life year (QALY) gained, an additional € 91.600 (incremental cost-effectiveness ratio) had to be paid for endovascular revascularization as compared to supervised exercise. Supervised exercise was determined as cost-effective primary treatment option for intermittent claudication as compared to endovascular revascularization. To address the question of whether the clinical benefit of the combination therapy (endovascular revascularization plus supervised exercise) as demonstrated in the ERASE trial was also cost-effective compared with supervised exercise only, we performed an extensive cost-effectiveness analysis in **chapter 9**. As compared with supervised exercise, the combination therapy cost an additional € 1.462 from the healthcare perspective and an additional € 161 from the societal perspective over a time-frame of 1 year. The clinical benefit of combination therapy translated into an 0.042 increase in accumulated QALYs during the study time horizon of 12 months. This resulted in an incremental cost-effectiveness ratio of € 34.810 / QALY gained from the healthcare perspective and € 3.833 / QALY gained from the societal perspective, which is well below the willingness-to-pay threshold of € 80.000. The probability of the combination therapy being cost-effective was 87% and 95% from the healthcare and societal perspective, respectively. Our data indicated that the combination therapy was less cost-effective in patients over 65 years of age, males and patients with femoropopliteal disease.

RECOMMENDATIONS AND FUTURE PERSPECTIVES

Cardiovascular risk management

In the management of PAD the main focus should be on prevention of future cardiovascular events, as at 5 years 15% to 20% of PAD patients will die, most of them due to a cardiovascular event, and another 20% of them will experience a nonfatal cardiovascular event.[4,6] Despite strong recommendations in the excellent guidelines on cardiovascular risk management in patients with PAD[7,8], these patients remain to be undertreated compared to patients with coronary heart disease.[5] Studies assessing the efficacy of a guideline recommended risk reduction programs have shown improved limb outcomes, reduction of myocardial infarction and stroke, and improvement in overall survival in patients with PAD receiving guideline-based secondary prevention.[9,10] We should put our efforts into optimizing guideline adherence in routine clinical care. Current guidelines recommend that all patients with PAD should cease smoking, receive antiplatelet agents, high-density statin agents, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers, blood pressure- and diabetic glycemic control if needed.[7,8] The most important lifestyle intervention remains discontinuation of smoking in patients with PAD with regard to improved limb outcomes (prevention of progression to critical limb ischemia or amputation) and prevention of major cardiovascular events.[9,11] Thus all patients with PAD should be advised to quit smoking during each medical visit and assisted in developing a plan to cease smoking. New initiatives developing step-wise standardized intervention methods to help the clinician addressing smoking cessation in PAD patients are being conducted and should be supported in future research projects.[11] Antiplatelet therapy is the cornerstone of drug therapy in patients with PAD. Antiplatelet monotherapy with Aspirin or Clopidogrel is being recommended in all patients with PAD.[7,8] Antiplatelet therapy with Aspirin alone is recommended in all patients with PAD based on results from a meta-analysis of 18 trials involving 5,269 PAD patients which showed a statistically nonsignificant decrease in cardiovascular events and a statistically significant reduction in nonfatal strokes in patients receiving Aspirin.[12] In the subgroup of patients with symptomatic PAD in the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) trial Clopidogrel monotherapy was shown to be more effective in reducing cardiovascular events as compared to monotherapy with Aspirin.[13] And the recently published EUCLID (Examining Use of Ticagrelor in Peripheral Artery Disease) showed no superiority of monotherapy with Ticagrelor as compared to Clopidogrel in patients with symptomatic PAD.[14] Based on this evidence Clopidogrel monotherapy is the preferred antiplatelet therapy to prevent cardiovascular events in patients with symptomatic PAD. More uncertainty remains on the use of dual antiplatelet therapy (DAPT) with Aspirin and Clopidogrel versus monotherapy with either one of the medications. Although no conclusive evidence exists on the use of DAPT after endovascular or surgical revascularization most clinicians prescribe DAPT for usually 1 to

3 months post revascularization. The ongoing Antiplatelet Strategy for Peripheral Arterial Interventions for Revascularization of Lower Extremities (ASPIRE-PAD) trial comparing at least one month of DAPT versus an additional 12 months of DAPT post endovascular revascularization will determine the optimal duration of DAPT use post revascularization. It should be noted that most of the recommendations on antiplatelet therapy in patients with PAD are based on trials in patients with clinical evidence of cardiovascular disease including subgroup of patients with PAD. This usually results in limited statistical power to show a significant effect of a certain antiplatelet regimen in the subgroup of patients with PAD. For this reason trials including exclusively patients with PAD are needed to determine the optimal antiplatelet regimen in these patients. Further elaboration on recommendations on cardiovascular risk factor management in patients with PAD are beyond the scope of this thesis. We focused on treatment options to improve walking distance and quality of life in PAD patients with intermittent claudication.

Pharmacotherapy

Cilostazol is the single medication that is recommended for relief of claudication symptoms.[8] However, its benefits in terms of improving walking distance are only modest, and its use is frequently discontinued due to side effects. Hence, there is great interest in the development of alternative pharmacological therapies. Since claudication symptoms are caused by ischemia of the leg muscles, interventions that promote angiogenesis are potential therapeutic candidates. Administration of colony-stimulating factors induces mobilization of endothelial progenitor cells from bone marrow and spleen, which may subsequently stimulate angiogenesis and improve endothelial cell function, thus improving blood flow. In spite of promising preliminary studies, however, the recently published PROPEL trial (Progenitor Cell Release Plus Exercise to Improve Functional Performance in PAD) did not support using granulocyte-macrophage colony-stimulating factor (GM-CSF) to treat walking impairment in patients with claudication.[15] Repeated subcutaneous administration of GM-CSF did not significantly improve walking performance, either when used alone or when combined with supervised exercise. Thus, although cell-based and angiogenic therapies for improving claudication symptoms are theoretically promising, their value in clinical practice remains to be determined. Given the absence of an effective widely used medication for intermittent claudication more effort on the development of medical therapies for claudication symptoms is highly needed and should be one of the main focuses of PAD research.

Exercise therapy

Supervised exercise

Exercise therapy is the cornerstone in the management of intermittent claudication and is being recommended by all guidelines as first-line treatment.[7,8] Although the benefit of

supervised treadmill exercise is clear, a lot of uncertainty remains on the exact duration and content of the exercise program. In our review we showed the beneficial effects of supervised walking therapy yet none of the exercise components (e.g. intensity, duration or content) was independently associated with significant improvement in walking distances. This might have been caused by the limited number of studies in our meta-regression analysis and the heterogeneity between the studies for the different exercise components, yet it is interesting that less intensive programs might be as beneficial as high-intensity training where patients are stimulated to walk to near-maximum claudication pain. The only RCT comparing supervised treadmill exercise programs of different duration concluded that the highest gain in walking distances is achieved within the first two months of exercise therapy[16], suggesting that a relatively short-term exercise program may be preferred above extended programs with associated higher costs and patient burden. Future RCTs should focus on the comparative effectiveness of different types of supervised walking therapy programs.

Home-based exercise

In spite of their reported efficacy, supervised exercise programs are underutilized due to limited access and reimbursement issues. Previous studies showed supervised exercise to be superior to a "go home and walk" advice.[17] Recent evidence, however, supports structured home-based exercise regimens as valuable alternatives to supervised exercise programs.[18] One trial comparing supervised exercise with structured home-based exercise in which patients were monitored by an activity monitor to record their walking performance and seen on a regular basis by a healthcare professional to motivate them to achieve their walking goals, showed the home-based program to be equally effective as the supervised exercise program.[19] In the Group Oriented Arterial Leg Study (GOALS) showed that a home-based group-mediated cognitive behavioral walking intervention was superior to a health education control group to improve walking performance in patients with PAD.[20] With the recent developments in implementation of electronic health portals, personal health records and monitoring options by eHealth technologies, the role of widely accessible home-based exercise programs will evolve and need further attention as it might overcome the barriers associated with supervised exercise programs. In addition to providing (remote) coaching by dedicated healthcare professionals, such home-based exercise programs should incorporate behavioural change interventions, including goal setting and self-monitoring. The clinical challenge is to effectuate home-based exercise programs that maximize improvements in walking endurance and achieve a durable physically active lifestyle, while minimizing the use of healthcare resources.

Endovascular revascularization

Endovascular revascularization continues to evolve as an attractive first-line treatment for intermittent claudication with the development of new devices and techniques.

Although supervised exercise is the recommended first-line treatment, endovascular revascularization has evolved as an attractive alternative due to high procedural success rates, insurance coverage, and immediate relief of ischemic symptoms. As a result, the number of endovascular procedures for claudication has increased dramatically over the past decade.[21] Yet, it should be noted that endovascular procedures have limited durability with high rates of re-intervention and associated costs and complications in the long-term as compared to supervised exercise.[22,23] In chapter 4 we showed from pooled data from RCTs comparing endovascular revascularization with supervised exercise that both therapies are equally effective in terms of improving walking distances and quality of life, even in the long-term. This underlines the need for a stepped-care approach, reserving revascularization for those patients who are unable to exercise or receive insufficient benefit from supervised exercise.

All trials comparing supervised exercise and endovascular revascularization so far, only used conventional balloons or stents in the intervention arm, which are associated with high restenosis rates, particularly in the femoropopliteal arteries. Over the past few years, the domain of endovascular intervention has expanded with the introduction of new technologies, such as drug-coated balloons and drug-eluting stents. Recent trials show that these new technologies have better arterial patency, but are more expensive.[24-27] To date, no comparisons have been made between the recommended supervised exercise-first strategy and revascularization with drug-eluting balloons. In addition, most studies evaluating the effectiveness of endovascular revascularization techniques have focused on patency rates of the treated segments as the primary endpoint rather than clinically relevant endpoints, including improvements in walking capacity and quality of life. Future research should focus on the question whether revascularization with drug-coated balloons and stents confers any clinical benefits over supervised exercise in the course of time, i.e. are these invasive strategies really helpful or just expenditure of substantial health care resources?

Combination therapy

Exercise therapy for PAD takes time, motivation, and compliance, whereas revascularization provides instantaneous symptom relief and requires little patient effort or intrinsic motivation. The two therapies also have different working mechanisms: exercise improves skeletal muscle mitochondrial metabolism, endothelial function and biomechanics of walking[28], whereas revascularization increases blood flow to the affected muscles. We showed that the combination therapy of endovascular revascularization plus supervised exercise had superior clinical outcomes as compared to supervised exercise only at 12 months of follow up. This approach combined the synergistic effects of these treatment modalities in the short term. However, during the 12-month follow up the results between the treatment modalities began to approximate each other while the majority of the patients in the supervised exercise group showed sustained improvement without the

need of a revascularization procedure during the follow up. This confirmation of the beneficial effects of both treatment modalities has important clinical implications and in clinical practice both treatment modalities with their pros and cons should be discussed with the patient. Further studies are needed to identify the best treatment strategy for specific subgroups of patients, based on their anatomical and clinical characteristics in order to realize a personalized treatment of intermittent claudication.

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Chapter 11

Thesis conclusions

Thesis conclusions

- Supervised walking therapy is an effective first-line treatment to improve walking distance in patients with intermittent claudication.

- The improvement in walking capacity seems unrelated to any particular component of a supervised walking program.

- Other modes of supervised exercise therapy, such as cycling or strength training are suitable alternatives to supervised walking therapy for patients who cannot train on a treadmill due to common comorbidities, such as pulmonary disease, heart failure, back pain, or osteoarthritis.

- Supervised exercise therapy and endovascular revascularization are equally effective to improve walking distance and quality of life in the short and long-term.

- Compared to endovascular revascularization, supervised exercise therapy is more cost-effective as primary treatment for intermittent claudication considering a 5-year time horizon.

- A structured, unsupervised, home-based exercise program improves the walking distance and quality of life, though less so than a supervised exercise program.

- Combination therapy of endovascular revascularization plus supervised exercise offers greater improvements in walking distance and quality of life than supervised exercise monotherapy, at least in the short term.

- Combination therapy is also cost-effective in the short term as compared with supervised exercise monotherapy.

Chapter 12

Nederlandse samenvatting

List of publications

PhD portfolio

Dankwoord

About the author

Nederlandse samenvatting

Deel I Introductie

Perifeer arterieel vaatlijden (PAV) is een aandoening die veroorzaakt wordt door atherosclerose (slagaderverkalking) van de lichaamsslagader (aorta) en de beenslagaders. Het is een veel voorkomende aandoening: naar schatting lijden 200 miljoen mensen wereldwijd aan PAV en dit aantal neemt snel toe met de vergrijzing van de wereldbevolking. Ongeveer 20-40 miljoen mensen met PAV hebben last van claudicatio intermittens (etalagebenen), d.w.z. pijn in de benen bij inspanning die met stilstaan weer overgaat. Door deze klachten worden patiënten met claudicatio intermittens aanzienlijk beperkt in hun loopafstand, met als gevolg een verminderd vermogen om hun dagelijkse activiteiten uit te voeren, immobiliteit en een slechtere kwaliteit van leven. Bovendien hebben deze patiënten een sterk verhoogd risico op een hartinfarct of een beroerte en een verhoogde kans op voortijdig overlijden.

Bij de behandeling van deze patiëntengroep moet dan ook een tweesporenbeleid worden gevolgd: het verbeteren van de claudicatio klachten en kwaliteit van leven enerzijds en het verminderen van het risico op hartinfarct, beroerte en overlijden anderzijds. Behandelingsmogelijkheden om claudicatio klachten te verbeteren zijn medicatie, (gesuperviseerde) looptherapie, herstel van de doorbloeding met behulp van een dotterbehandeling of (bypass)operatie, of een combinatie van deze behandelingen. Het doel van dit proefschrift was om de optimale behandeling te bepalen voor het verbeteren van de loopafstand en de kwaliteit van leven bij patiënten met claudicatio intermittens. Om dit te bereiken hebben we eerst de wetenschappelijke literatuur van de bestaande gangbare behandelopties systematisch samengevat, vervolgens de effectiviteit van een nieuwe behandelstrategie vergeleken met de standaardzorg en uiteindelijk de kosteneffectiviteit van deze nieuwe behandelstrategie berekend om beleidsmakers beter te kunnen informeren over implementatie ervan in de dagelijkse praktijk.

Deel II Systematisch literatuuronderzoek

Gesuperviseerde looptherapie wordt aanbevolen als eerstelijnsbehandeling voor claudicatio intermittens. Er blijft echter onzekerheid bestaan over de effectiviteit van gesuperviseerde looptherapie in de praktijk en de effectieve componenten van het loopprogramma (bijvoorbeeld het gebruik van een loopband, intensiteit, duur of inhoud van het programma). In **hoofdstuk 2** hebben we een meta-analyse uitgevoerd om de effectiviteit van gesuperviseerde looptherapie voor claudicatio intermittens samen te vatten en de componenten van het loopprogramma te identificeren die zorgen voor maximale verbetering in loopafstanden. Analyse van de resultaten van 25 gerandomiseerde gecontroleerde studies (RCTs) met meer dan 1000 patiënten toonde

een verbetering van de maximale loopafstand van ongeveer 200 meter bij patiënten die een gesuperviseerd loopprogramma volgden in vergelijking met degenen die dat niet deden. Uit deze analyse bleek verder dat deze verbetering van de loopcapaciteit niet het gevolg was van een afzonderlijk onderdeel van het trainingsprogramma, maar eerder van het samenspel van alle componenten.

Hoewel gesuperviseerde looptherapie dus een effectieve eerstelijnsbehandeling is voor claudicatio intermittens kan een aanzienlijke deel van de patiënten niet trainen op een loopband vanwege bijkomende aandoeningen, zoals een longziekte, hartfalen, rugpijn of artrose van de heupen of knieën. Voor deze patiëntengroep kan een andere vorm van oefentherapie (bijvoorbeeld fietsen, roeien of krachttraining) een geschikt alternatief bieden. In **hoofdstuk 3** hebben we een systematisch literatuuronderzoek en meta-analyse uitgevoerd om alternatieve vormen van gesuperviseerde oefentherapie te vergelijken met de standaard behandeling van gesuperviseerde looptherapie. De verzamelde resultaten van vijf studies toonden vergelijkbare verbetering in loopafstanden bij patiënten die een alternatieve vorm van oefentherapie hadden gevolgd ten opzichte van patiënten die looptherapie hadden gevolgd.

Gezien deze gunstige effecten wordt gesuperviseerde looptherapie in de (inter) nationale richtlijnen aanbevolen als behandeling van eerste voorkeur voor claudicatio intermittens. Echter, gesuperviseerde looptherapie kost tijd, motivatie en inspanning van de patiënt. Daarentegen biedt endovasculaire revascularisatie (dotterbehandeling) snel en direct symptoomverlichting, zonder dat dit inspanning van de patiënt vereist. Endovasculaire revascularisatie biedt om deze reden een aantrekkelijk alternatief als eerstelijnsbehandeling voor claudicatio intermittens en is het aantal endovasculaire procedures voor PAV in de afgelopen 10 jaar dan ook dramatisch toegenomen.

Om de waarde van endovasculaire revascularisatie in de behandeling van claudicatio intermittens te evalueren hebben we in **hoofdstuk 4** een systematisch literatuuronderzoek en meta-analyse uitgevoerd naar de effectiviteit van endovasculaire revascularisatie vergeleken met conservatieve, niet-invasieve, behandeling. Samengevoegde resultaten van drie onderzoeken toonden een matige tot grote verbetering in de loopafstand bij patiënten die een endovasculaire revascularisatie ondergingen ten opzichte van de patiënten die alleen een wandeladvies kregen. De resultaten van vijf studies tezamen lieten zien dat endovasculaire revascularisatie net zo effectief is als gesuperviseerde looptherapie, zowel ter verbetering van loopafstand als verbetering van kwaliteit van leven. Ten slotte bleek ook een combinatie van endovasculaire revascularisatie en gesuperviseerde looptherapie of medicatie tot een grotere toename in loopafstand en kwaliteit van leven te leiden dan alleen behandeling met gesuperviseerde looptherapie of medicatie.

Deel III Klinische effectiviteit

De meeste klinische studies waarin endovasculaire revascularisatie wordt vergeleken met gesuperviseerde looptherapie voor claudicatio intermittens hebben een beperkte follow-up van maximaal 1 jaar waardoor aanbevelingen op de lange termijn niet mogelijk zijn. In **hoofdstuk 5** onderzochten we de 7-jaars resultaten van een gerandomiseerde gecontroleerde studie onder patiënten met claudicatio intermittens die eerder waren behandeld met ofwel gesuperviseerde looptherapie ofwel endovasculaire revascularisatie. De verbeteringen in loopafstand en kwaliteit van leven 7 jaar na de behandeling waren vergelijkbaar in beide groepen. Dit suggereert dat beide therapieën ook op de lange termijn gelijkwaardig zijn ter behandeling van claudicatio intermittens.

Gesuperviseerde loopprogramma's zijn niet overal beschikbaar en worden in de meeste landen niet vergoed door zorgverzekeraars. Om dit probleem van beperkte toegang te verhelpen wordt er onderzoek gedaan naar alternatieven, waaronder looptraining door de patiënt zelf thuis. In **hoofdstuk 6** vergeleken we de effectiviteit van een gestructureerd looptherapieprogramma voor thuis met de resultaten van een controlegroep van patiënten met claudicatio intermittens die gesuperviseerde looptherapie hadden gevolgd in het ziekenhuis. De 142 patiënten die een thuisprogramma volgden, hadden na 1 jaar wel een verbetering van hun loopafstand en kwaliteit van leven, maar deze waren aanzienlijk minder dan de verbeteringen die hierin werden bereikt door patiënten die gesuperviseerde looptherapie ontvingen.

In hoofdstuk 7 worden de resultaten beschreven van de Endovascular Revascularization And Supervised Exercise (ERASE) studie waarin de combinatietherapie van endovasculaire revascularisatie plus gesuperviseerde looptherapie werd vergeleken met de standaardbehandeling van gesuperviseerde looptherapie alleen. In dit onderzoek dat in meerdere Nederlandse ziekenhuizen werd uitgevoerd, werden 212 patiënten met claudicatio intermittens gerandomiseerd naar combinatietherapie of alleen gesuperviseerde looptherapie. Na één jaar follow-up toonden patiënten die de combinatietherapie ontvingen grotere verbetering in hun maximale- en pijnvrije loopafstand van respectievelijk 300 en 400 meter meer in vergelijking met patiënten die enkel gesuperviseerde looptherapie hadden ontvangen. Evenzo vertoonden patiënten in de combinatietherapie groep grotere verbetering in hun kwaliteit van leven in vergelijking met de patiënten uit controlegroep die enkel gesuperviseerde looptherapie hadden gevolgd. Een combinatietherapie van vroege endovasculaire revascularisatie gevolgd door gesuperviseerde looptherapie lijkt dus veelbelovend omdat het zeer waarschijnlijk de onmiddellijke verlichting van claudicatio symptomen na revascularisatie combineert met de potentiële lange termijn voordelen van gesuperviseerde looptherapie.

Deel IV Kosteneffectiviteit

Gegevens over de kosteneffectiviteit op lange termijn van gesuperviseerde looptherapie ten opzichte van endovasculaire revascularisatie voor claudicatio intermittens zijn schaars. In **hoofdstuk 8** construeerden we een Markov-model om de kosteneffectiviteit van gesuperviseerde looptherapie ten opzicht van endovasculaire revascularisatie te evalueren vanuit het gezondheidszorg perspectief over een tijdsbestek van 5 jaar. Gesuperviseerde looptherapie ging gepaard met aanzienlijke kostenbesparing in vergelijking met endovasculaire revascularisatie. Per gewonnen levensjaar, gecorrigeerd voor kwaliteit van leven, (QALY) bedroegen de extra kosten voor endovasculaire revascularisatie € 91.600 in vergelijking met gesuperviseerde looptherapie. Gesuperviseerde looptherapie werd dan ook geduid als de meest kosteneffectieve primaire behandelingsoptie voor claudicatio intermittens in vergelijking met endovasculaire revascularisatie.

Om de vraag te beantwoorden of het klinisch voordeel van de combinatietherapie (endovasculaire revascularisatie plus gesuperviseerde looptherapie) zoals aangetoond in de ERASE-studie kosteneffectief zou zijn in vergelijking met alleen gesuperviseerde looptherapie hebben we een uitgebreide kosteneffectiviteitsanalyse uitgevoerd in **hoofdstuk 9**. Vergeleken met gesuperviseerde looptherapie kostte de combinatietherapie € 1.462 extra per patiënt vanuit het gezondheidszorg perspectief en € 161 extra vanuit het maatschappelijk perspectief over een tijdsbestek van 1 jaar. Het klinisch voordeel van combinatietherapie leidde tot een toename van 0,042 gewonnen levensjaar, gecorrigeerd voor kwaliteit van leven, (QALY) tijdens de follow-up van 1 jaar. Omgerekend kostte het klinisch voordeel van de combinatietherapie €34.810 per QALY vanuit het gezondheidszorg perspectief en €3.833 per QALY vanuit het maatschappelijk perspectief wat ruim onder de betalingsdrempel van €80.000 per QALY ligt wat we als maatschappij accepteren. In 87% van de gevallen berekend vanuit een gezondheidszorg persepectief en in 95% van de gevallen berekend vanuit een maatschappelijk perspectief was de combinatietherapie kosteneffectief in vergelijking met gesuperviseerde looptherapie alleen. Verdere analyse van de gegevens toonde aan dat alleen gesuperviseerde looptherapie wel kosteneffectief is voor patiënten ouder dan 65 jaar, mannen en patiënten met een vernauwing of verstopping van de bovenbeens- of knieslagaders en dus voor deze patiënten een gesuperviseerde looptherapie mogelijk geadviseerd zou kunnen worden.

List of publications

Fakhry F, Fokkenrood HJ, Spronk S, Teijink JA, Rouwet EV, Hunink MGM. Endovascular revascularisation versus conservative management for intermittent claudication. *Cochrane Database Syst Rev.* 2018 Mar 8;3

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Fakhry F, Spronk S, van der Laan L, Wever JJ, Teijink JA, Hoffmann WH, Smits TM, van Brussel JP, Stultiens GN, Derom A, den Hoed PT, Ho GH, van Dijk LC, Verhofstad N, Orsini M, van Petersen A, Woltman K, Hulst I, van Sambeek MR, Rizopoulos D, Rouwet EV, Hunink MGM. Endovascular Revascularization and Supervised Exercise for Peripheral Artery Disease and Intermittent Claudication: A Randomized Clinical Trial. *JAMA*. 2015 Nov 10;314(18):1936-44.

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Klaphake S, **Fakhry F,** Rouwet EV, van der Laan L, Wever JJ, Teijink JA, Hoffmann WH, van Petersen A, van Brussel JP, Stultiens GN, Derom A, den Hoed PT, Ho GH, van Dijk LC, Verhofstad N, Orsini M, Hulst I, van Sambeek MR, Rizopoulos D, van Rijn MJ, Verhagen HJM, Hunink MGM. Long-term follow-up of a randomized clinical trial comparing endovascular revascularization plus supervised exercise with supervised exercise only for intermittent claudication. *Submitted*

PhD portfolio

Name PhD student: Farzin Fakhry
Erasmus MC Department: Epidemiology and Radiology
Promotor: Prof. dr. M.G.M. Hunink
Copromotor: Dr. E.V. Rouwet

Research skills

- Clinical Epidemiology Program, Individual research project and various methodological, statistical and program specific (advanced) courses: Principles of Research in Medicine and Epidemiology, Data-analysis, Regression Analysis, Methods of Clinical Research, Clinical Trials, Topics in Meta-analysis, Health Economics, Survival Analysis, Cohort Studies, Case-control studies, Decision making in Medicine, Topics in Health and Disease in the Elderly, Study Design, Modern Statistical Methods, Clinical Research, Pharmaco-epidemiology and Drug Safety, Intervention Research, Diagnostic Research, Repeated Measurements in Clinical Studies, Prognosis Research, Planning and Evaluation of Screening, Netherlands Institute for Health Sciences, Rotterdam, The Netherlands, 2007-2010 (Workload 120 ECTS)

Scientific presentations

- 'Exercise or endovascular revascularization for intermittent claudication', Invited lecture at the Vascular Rounds, Rotterdam, the Netherlands, 2012 (Workload 1 ECTS)
- 'Long-term clinical effectiveness of supervised exercise therapy versus endovascular revascularization for intermittent claudication: Results from a randomized controlled trial', Oral presentation at the Scientific Sessions of the American Heart Association, Los Angeles, USA, 2012 (Workload 1 ECTS)
- 'Supervised exercise for intermittent claudication in the Netherlands', Invited lecture at the Scientific Sessions of the American Heart Association, Los Angeles, USA, 2012 (Workload 1 ECTS)
- 'Results from the Endovascular Revascularization And Supervised Exercise for claudication study', Oral presentation at the Late-Breaking Clinical Trial session of the Scientific Sessions of the American Heart Association, Dallas, USA, 2013 (Workload 1 ECTS)
- Interview with Dr. Duane S. Pinto on the results of the Endovascular Revascularization and Supervised Exercise (ERASE) Trial at Clinical Trial Results TV, 2013 (Workload 1 ECTS)

- Discussion with Professor Gerhard Hindricks and Professor Mary McDermott on the results of the ERASE trial and its implications for the clinical practice, European Heart Journal – EHJ today TV, 2013 (Workload 1 ECTS)
- 'Role of endovascular revascularization in the management of peripheral arterial disease' Invited lecture at the Netherlands Annual Conference on Vascular Surgery, Noordwijkerhout, the Netherlands, 2015 (Workload 1 ECTS)

Teaching activities

- Teaching Assistant for the course 'Principles of Research in Medicine and Epidemiology', Faculty: Prof. dr. A. Hofman, Erasmus Summer Programme, Netherlands Institute for Health Sciences (NIHES), Rotterdam, the Netherlands, 2012-2013 (Workload 4 ECTS)
- Teaching Assistant for the course 'Advanced Topics in Decision Making in Medicine', Faculty: Prof. dr. M.G.M. Hunink, Erasmus Winter Programme, Netherlands Institute for Health Sciences (NIHES), Rotterdam, the Netherlands, 2011-2013 (Workload 6 ECTS)
- Teaching evidence-based medicine courses to first and fourth year medical students, Erasmus University, Medical School, Rotterdam, the Netherlands, 2011-2013 (Workload 6 ECTS)
- Supervising fourth year medical students during their research period, Erasmus University, Medical School, Rotterdam, the Netherlands, 2012-2014 (Workload 12 ECTS)