Supplementary Online Content


Trial protocol

This supplementary material has been provided by the authors to give readers additional information about their work.
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Project Title:

Cost-effectiveness of treatment strategies for intermittent claudication

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Summary:

Introduction:
Intermittent claudication (IC) is the first symptomatic manifestation of peripheral arterial disease and affects 275 000 people older than 50 years in the Netherlands alone. Despite developments in treatment for IC, the standard treatment is not optimal. This project examines alternative treatments.

Objective of the proposed RCT:
To evaluate the cost-effectiveness, from the perspectives of the health care system and of society at large, of supervised exercise compared to endovascular revascularization plus supervised exercise as first-line treatment of IC.

Specific research questions:
Comparing endovascular revascularization plus supervised exercise to supervised exercise alone
1. What is the gain in maximum walking distance (MWD)?
2. What is the gain in quality of life (QoL) and quality adjusted life years (QALYs)?
3. What are the additional costs (or are there cost-savings)?
4. What is the incremental cost-effectiveness ratio?

Study design: prospective multicenter Randomized Controlled Trial.

Study population: patients with symptoms of intermittent claudication (Rutherford I,II,III).

Intervention:
1. Supervised exercise at a physical therapy center;
2. Endovascular revascularization plus supervised exercise at a physical therapy center.

Outcome measures: Primary: maximum walking distance; Secondary: preference based utilities (EQ-5D and Rating Scale), health status QoL scores (SF-36 and VascuQol), ABI, maximum painless walking distance, clinical success, therapeutic and total costs, CVD risk factor score, number of events; all outcomes after 1-, 6-, and 12-months follow-up.

Sample size: 210 patients, 1 yr follow-up

Economic evaluation: In accordance with the Dutch guidelines. We will use the health care perspective and the societal perspective.

Time schedule: Months 1-5: preparation; 5-17: patient inclusion, treatment; 17-29: follow-up; 29-36: data-analysis and reporting
Peripheral arterial disease (PAD) is a chronic atherosclerotic occlusive disease of the lower extremities. The classical symptom in patients with PAD is intermittent claudication (IC) which is muscle discomfort in the lower limb produced by exercise and relieved by rest. Patients may describe muscle fatigue, aching or cramping on exertion in their limb or bottom. IC is a risk factor for more serious forms of cardiovascular disease (CVD), and death from cardiovascular events. IC has a prevalence of 4.5%, which increases with age and is predominant in males (1). In the Netherlands alone, IC affects approximately 275,000 people older than 50 years. Of these, half will have a cardiovascular event within 10 years (19% fatal and 27% non-fatal), killing over 2500 each year (3-4), which is a psychosocial burden to society (2). Most patients with IC have risk factors for arterial disease, such as smoking, hypertension, diabetes, or a dyslipidaemia. Patients with IC, suffer from functional limitations due to impaired walking ability (5), and also from serious quality of life limitations (6-7), which has a great impact on the patients daily functioning, whereas deterioration of PAD could lead to the need for arterial surgery or limb amputation. As the incidence of IC will increase over the next decades due to the aging population in Western societies, the economic impact of IC is expected to be substantial (3).

The treatment goals for patients with IC are to relieve symptoms, improve daily functional abilities, quality of life, and prevent future cardiovascular events. Previous studies have shown that exercise training should have a central role in the management of IC by significantly improving the maximum walking distance and quality of life, and lowering the risk for a cardiovascular event (8-9-10). There is considerable evidence which supports the clinical benefits of supervised exercise in improving exercise performance above home-based exercise (4, 5). The general consensus is therefore to initially treat IC with supervised exercise in addition to management of risk factors for atherosclerotic disease, which includes behavioral and lifestyle modification (smoking cessation, exercise), dietary measures, and pharmacotherapy targeted to specific goals. Pharmacotherapy includes antiplatelet agents, lipid-lowering agents (statins), anti-hypertensive agents, and glycemic control agents (6). However, despite the benefits of supervised exercise, the dropout rate is fairly high (from 10% up to 50%) (4, 7-9). Failure to respond to supervised exercise would lead to the next level of treatment, which is endovascular revascularization. In clinical practice, however, endovascular revascularization is commonly considered as initial treatment rather than awaiting the effect of exercise. Despite the guidelines, which only suggest initial endovascular revascularization for aorto-iliac lesions suitable for endovascular revascularization. Whereas 20 years ago only patients with disease of the suprainguinal arteries were considered for immediate endovascular revascularization, nowadays the indication has extended to infra-inguinal lesions. The reasons are the technical innovations, immediate success, and low risks of peri-procedural mortality and morbidity of endovascular revascularization. In addition, for many physicians the immediate benefit of endovascular revascularization enabling exercise and prevention of ‘unnecessary disability’ are reasons for this choice in combination with patient’s age, maximum walking distance, and whether the patient is still in the work process.
Early endovascular revascularization plus supervised exercise combines effective short-term relief of claudication symptoms with the added long-term benefits of a supervised exercise program. The results of a multicentre RCT provided promising evidence that the benefit of early endovascular revascularization over supervised exercise may now be sustained for a considerable period of time (10). The short-term benefits of endovascular revascularization keep patients motivated and can avoid high dropout rates during the supervised exercise training programme. The long term benefits of supervised exercise will improve patient’s walking distance and quality of life and lower the risk for future cardiovascular events. Despite the evidence in effectiveness of early endovascular revascularization plus supervised exercise, uncertainty remains as to the cost-effectiveness of this combination of treatments.

Relevance (5000)

Atherosclerosis is a systemic disease, and the manifestation of IC is a strong marker of CVD, which places the patient at significantly increased risk of sudden death from stroke or myocardial infarction. The “all cause mortality” for patients with IC is approximately 30% at 5 years, 50% at 10 years, and 70% at 15 years (11). This gives a prognosis similar to that following resection of Duke’s B carcinoma of the colon. Non-fatal events are also common, with approximately one quarter of patients suffering a CVD event over an 11-year period. The standard treatment for patients with IC is not optimal. Despite developments in treatment for IC, this group of patients still has a high mortality and morbidity, which is a financial burden to society.

We know from previous studies that the response rate in supervised exercise programs is higher than in home-based exercise programs and that some level of supervision is necessary to achieve optimal clinical benefit (4). The supervised exercise program in itself has psychosocial aspects to it which enhance patients’ compliance with the program. Many affected patients are housebound or dependent on others due to lack of physical fitness which impacts their psychosocial wellbeing and the psychosocial aspects of the training program are helpful secondary benefits.

The effectiveness of early revascularization over and above supervised exercise has been shown to benefit patients with IC in a multi center RCT from the UK (10). The findings of this RCT showed significant improvement in functional capacity of early revascularization plus supervised exercise compared to supervised exercise alone for up to 24 months. In addition, the effectiveness of early revascularization plus exercise training was also demonstrated in a RCT from Norway (12). The results of this RCT showed that early revascularization in addition to optimal medical treatment (which included exercise training) seems to have more positive effect compared to optimal medical treatment only, on functional capacity as well as quality of life for up to 24 months.

The cost-effectiveness of early revascularization plus supervised exercise compared to supervised exercise alone has not yet been explored. Revascularization has higher initial costs than supervised exercise, whereas, the patient costs (due to the time investment of
the patient and traveling) are higher after supervised exercise (8). However, whatever the
treatment considered, if the initial procedure fails, total costs during 12-month follow-up
are 2-to 4-fold higher than if the initial procedure is successful (13). In the proposed
project, potential differences in total costs after 12 months follow-up between the two
treatment groups are likely the result from less dropouts during supervised exercise in the
group with early revascularization. Dropouts can potentially increase the additional
imaging and treatment costs, in particular when lesions are no longer suitable for
endovascular (re-)intervention after failure of exercise. Finally a surgical intervention
may be needed, which is much more expensive. The early revascularization and the
availability of supervised exercise close to the patient’s home address are advantages and
are most likely to substantially improve therapy participation, compliance, and
effectiveness. Starting with revascularization may enable and motivate patients to make the
best use of an exercise program which will result in less dropouts, an increase in maximum
walking distance and quality of life, a reduction in cardiovascular events, and a reduction
in societal costs.

To determine the value of performing more research in this field, we performed a value
of information analysis of our RCT comparing revascularization with supervised
exercise. The results suggested that further research in this area is justified (14). The total
expected value of perfect information expressed in net monetary benefit was €249 per
patient. This means that after eliminating uncertainty we can expect an improvement in net
monetary benefit of 249 euro per patient. The population expected value of perfect
information for the Netherlands was €11 million. This implies that the maximum amount
worth spending on future research to decrease current uncertainty clearly exceeds the
anticipated research costs.

The proposed study will fill a gap in our knowledge concerning the treatment of IC. It is
complementary to our previous RCT in Rotterdam (revascularization vs supervised
exercise) (8), a multicentre RCT in the UK (early revascularization plus supervised
exercise vs supervised exercise alone), and to an ongoing RCT in Heerlen (supervised
exercise vs home-based exercise). The added value of performing the proposed project
will be enumeration of the costs, effectiveness, and cost-effectiveness of early
endovascular revascularization plus supervised exercise from the perspective of the
health care system and from a societal perspective.

**Objective/Research questions (2500)**

**Objective of the proposed RCT:**
To evaluate the cost-effectiveness, from the perspectives of the health care system and of
society at large, of early endovascular revascularization plus supervised exercise
compared to supervised exercise alone as first-line treatment of intermittent claudication.

**Specific research questions:**
Comparing early endovascular revascularization plus supervised exercise to supervised
exercise alone
1. What is the gain in maximum walking distance?
2. What is the gain in quality of life and quality adjusted life years?
3. What are the additional costs (or are there cost-savings)?
4. What is the incremental cost-effectiveness ratio?

**Implementation (5000)**

We intend to convey the results of the study to patients, providers, health insurance companies, and health care policy-makers.

Providers are health care professionals that either advice or refer individuals for treatment and treat those identified to be patients with IC, in particular vascular surgeons, radiologists, and general practitioners.

The health insurance companies include a wide range of companies, which are covering endovascular revascularization and considering IC as chronic disease for which physiotherapy during the period of one year is indicated.

Health care policy-makers are those involved in regulating treatment strategies in the context of the CBO (Centraal Begeleidings Orgaan), in particular the Dutch Guidelines for Cardiovascular Risk Management, and those providing advice, in particular the Dutch Health Council (Gezondheidsraad).

Activities:
1) Develop a user-friendly website with relevant information which can be useful for patients, providers, health insurance companies, and policy-makers
2) Write articles for newspapers and popular magazines to reach out to patients. 
3) Publish papers in professional journals
4) Present our results at professional meetings
5) Provide a summary report to the CBD Committee concerned with IC, the Dutch Health Council, and to Health Insurance Companies.

**Study design (60000)**

We will use what we have learned from prior and/or ongoing studies:

**Prior study 1 – cohort study (Kruidenier et al 2008):**

This study described the results and functioning of community-based supervised exercise at one year of follow-up (7). Trials in a Cochrane review (15) provided supervised exercise programs at a department of physiotherapy in a hospital. While this approach is appropriate in clinical trials, there are some limitations in routine clinical practice. First, the capacity of a single department in a hospital is limited and not sufficient to provide supervised exercise to all patients in the community. Second, attending a program at the hospital for two or three times a week is time consuming and expensive for the patient. This problem can be solved using a community-based approach to supervised exercise which was first implemented by Willegendael et al, and the first results published in 2005 were promising. The community-based approach is also evaluated by Kruidenier et al, who concluded that community-based supervised exercise seems as efficacious as supervised exercise in a clinical study approach (7). Therefore, the supervised exercise at the physical therapist should be accessible close to the patients home address in the proposed study.
Prior study 2 – RCT (Spronk et al 2008):
We recently performed a single centre RCT comparing endovascular revascularization to supervised exercise training, which demonstrated that after 6- and 12-months follow-up patients with IC benefited equally from either endovascular revascularization or supervised exercise, whereas improvement was more immediate following revascularization (8). However, the results of this RCT led to new questions such as whether supervised exercise in addition to early endovascular revascularization would be cost-effective compared to supervised exercise alone, which will be answered in the proposed study.

An ongoing study 3- (the CLEVER trial, Murphy et al 2008):
This multi-centre RCT is an ongoing study in the US to evaluate the effect of three different treatment strategies for patients with IC from the aortoiliac segments: 1. a primary medical therapeutic approach; 2. endovascular revascularization; 3. supervised exercise. In addition to the three study arm comparisons, there is also interest in a possible additive effect of combined therapy with stenting and supervised exercise compared to stenting alone. CLEVER will randomize 42 such patients to evaluate this secondary hypothesis (16). The primary outcome is maximum walking distance and secondary outcomes are quality of life and cost-effectiveness. Personal communication with Murphy exists to share our expertise in this context.

The proposed study will be complementary to the CLEVER study in that we will address questions through comparing different treatment strategies (endovascularization plus supervised exercise versus supervised exercise alone) and different levels of disease (aortoiliac and femoropopliteal) that will not be addressed in the CLEVER trial. More specifically, we will study a representative Dutch population by performing a multicentre RCT, we will evaluate treatment strategies that are currently relevant, we will evaluate clinical success, quality of life and functional capacity, we will determine the effect of prevention of events (which also includes secondary treatment for failure of initial treatment of IC), and we will calculate cost-effectiveness.

Prior Study 4 – Value of information analysis (Groot-Koerkamp et al 2008):
In a value of information (VOI) analysis we evaluated whether the non-significant difference between endovascular revascularization and supervised exercise in patients with IC merits additional quantitative research (14). We applied a net benefit framework to patient-level data on costs and quality-of-life of the previous RCT. We estimated the total population expected value of perfect information (total EVPI), assuming that patients would benefit from the results for 5 years, and discounted these benefits at 3% per year. In the Netherlands the population that can benefit is about 46 000 patients with a corresponding population EVPI of 11 million euro. Because the EVPI for the population exceeds the expected costs of an additional study, it is potentially justified to perform some sort of additional study, which supports the proposed study.

The proposed study will be a prospective, multicenter RCT comparing different treatment modalities in patients with symptoms of IC stage 1-3 (Rutherford), who will be randomly assigned to:
1. Supervised exercise at a physical therapy center;
2. Endovascular revascularization plus supervised exercise at a physical therapy center.

For all participating centers separately, all regional physiotherapy practices of each center will be invited to attend a symposium regarding supervised exercise in a physiotherapeutic setting. This symposium has already been developed by the Atrium MC and has been also used for other centers in other regions for the development of a network of physical therapists. The symposium provides the necessary knowledge and skills to give professional supervised exercise training. The symposium covers topics on the theoretical background, therapeutic benefits, and an introduction to the Royal Dutch Society for Physiotherapy guideline on supervised exercise. An important issue of the symposium will be the formation of a network of physical therapists to facilitate supervised exercise for patients referred by vascular surgeons from the participating centers. At the end of the symposium, attending physiotherapists interested in providing exercise training, and in the possession of, or the willingness to acquire, a treadmill will be asked to register. We know that the team in the Atrium MC has the expertise in this context and that developing and the implementation of a network of physical therapists for each participating center is feasible in a relatively short period of time.

**Inclusion criteria:**
1. Rutherford category 1, 2, or 3 (> 3 months duration);
2. ABI <0.9 at rest or ABI decreasing by >0.15 after treadmill test;
3. Maximum walking distance <500m on a treadmill test (Gardner protocol);
4. ≥1 vascular stenoses of >50% diameter reduction at the iliac or femoro-popliteal level;
5. Informed consent.

**Exclusion criteria:**
1. Lesions deemed unsuitable for revascularization;
2. Abdominal aortic aneurysm >5 cm or iliac aneurysm >1.5 cm;
3. Life-incapacitating cardiac disease (NYHA classification III and higher);
4. Prior treatment for the same lesion (including exercise training);
5. Contra indication for revascularization (allergy to iodinated contrast);
6. Ambulation limited by co-morbid condition;
7. Inability to walk on a treadmill without grade at a speed of at least 3.2 km/h for at least 2 minutes.

**Group 1: Supervised exercise training.**
Generally, patients will receive CVD risk factor management according to the 2006 CBO guidelines for CVD, including blood pressure control, aspirin therapy, lipid modification, and advice on smoking cessation, diet, and physical activity (17). Patients will be offered a supervised exercise program at the physical therapy center of the hospital or at participating physiotherapists from a network list who are all trained and certified to treat patients with IC. In advance, all participating physiotherapists, hospital-based or community-based, are instructed how to support the supervised exercise. Participating physiotherapists are invited for a course that covers the necessary theoretically
background, and practical skills that follow the guidelines of the Royal Dutch Society for Physiotherapy (KNGF) (18) (new update 2009) for the treatment of patients with IC. In addition, the course will pay extra attention to the evaluation of the maximum walking distance using a standardized walking treadmill test in order to create consistency across the different participating physiotherapists. The main goal of supervised exercise according to these guidelines is to increase maximum walking distance. This goal will be achieved by means of interval training with treadmill walking up to (sub)maximal pain. Secondary goals are improving endurance, increasing strength, and correcting walking patterns.

Patients will start with a frequency of two to three sessions every week of approximately 30 minutes in the first three months. After this phase, the frequency will be phased down to approximately once every two weeks at six months follow-up and once every eight weeks at 12 months follow-up, depending on patients progress and preference. Patients will also be encouraged to walk on a daily basis to near maximal pain. Furthermore, all participating physiotherapists will be instructed to emphasize as much as possible the importance of lifestyle adjustments and smoking cessation.

**Group 2: Endovascular revascularization plus supervised exercise.**

Patients will receive the same CVD risk factor management as group 1. Patients will be offered an endovascular revascularization according to the most recent standards, performed by an interventional radiologist. In addition, patients will be offered the same supervised exercise program as group 1, within two weeks after the revascularization procedure.

**Failures in the supervised exercise group**

In case of progressive complaints (Rutherford stage IV or more) in the supervised exercise group and a decreased ABI (>15%), the patient may cross-over to the endovascular revascularization group. Diagnostic imaging will be repeated and if the lesion is not treatable with endovascular revascularization, operative treatment will be considered.

In case of progressive complaints without a decrease in ABI, the patient should be motivated to continue the supervised exercise programme.

**Failures in the endovascular revascularization group**

If the lesion is not treatable with endovascular revascularization, the patient may cross-over to the supervised exercise group (without early intervention) and this will be reported.

If recurrent or residual symptoms are reported in the treated limb after endovascular revascularization and there is a < 0.1 improvement in ABI, diagnostic imaging will be repeated and a second selective DSA with intervention will be considered.

In case of critical limb ischemia a surgical intervention will be considered if endovascular revascularization is not feasible.

**Randomization**

After all diagnostic tests have been performed, the indication for treatment will be made at the vascular conference by the vascular surgeons and interventional radiologists in
each centre and patients will be assessed for meeting the selection criteria. Patients will be registered at the time that diagnostic imaging is requested. Randomization will take place through the Trial Coordinating Center of the Department of Radiology at the Erasmus MC.

Patients will be registered at the time that treatment is requested. Patients will be informed about the trial and will have to give written informed consent. They will be registered centrally in Erasmus MC by telephone or fax and will be assigned a treatment strategy at that time. They will also get a unique identifying code. A computer generated list for the strategy assignments will be used. Randomization will be stratified for hospital.

**Primary outcome parameter:**

*Maximum walking distance*

Maximum walking distance will be measured by the physiotherapist following treadmill walking (speed 3.2 km/h, 10% incline max; Gardner protocol) (19) after 1-, 6-, and 12-months follow-up. The graded treadmill protocol is more effective than a standard constant grade protocol in distinguishing the severity of the claudication in a reproducible manner as well as providing a tool to analyze the effect of interventions. A progressive treadmill test will be used, with a constant speed of 3.2 km/h and an increase in incline of 2% every two minutes, starting at 0% incline. The incline and testing duration will be maximized for practical reasons to 10% and 30 minutes (1600 m), respectively.

**Secondary outcomes**

*Preference-based utilities (EQ-5D and Rating Scale)*

Utilities will be assessed using a self-administered questionnaire which will include the EQ-5D and the Rating Scale. The EQ-5D is a multi-attribute utility instrument that assesses quality-of-life values from the societal perspective and classifies patients into a health-state (20). For each health-state, a value will be calculated using the Dutch scoring algorithm, which is derived from the general population (21): 0 equates to death and 1 equates to maximum health. The rating scale requires the respondent to rate their overall health on a scale from 0-100, where 0 represents death and 100 perfect health (22). Both utilities will be evaluated after 1-, 6-, and 12-months.

*Health-status Quality-of-life scores (SF-36 and VascuQol)*

Quality-of-life scores will be assessed using a self-administered questionnaire, which will include the SF-36 and the VascuQol. The SF-36 evaluates physical-, social-, and physical-role functioning of patients and elicits their perceptions of their general health and well-being in eight different health dimensions (23). The scoring per dimension is valued on a 100-point scale from 0 (worst-outcome) to 100 (best-outcome). The VascuQol is a questionnaire especially developed for patients with PAD and is responsive to subtle treatment effects (24). The questionnaire contains 35 questions subdivided into five dimensions (activity, symptom, pain, emotion, and social
functioning). Each question has a 7-point response option. Patients’ responses will be converted to a scale ranging from 1 (worst-outcome) to 7 (best-outcome). Both quality-of-life scores will be evaluated after 1-, 6-, and 12-months.

**Functional capacity (ABI, maximum painless walking distance)**
In addition to our primary outcome (maximum walking distance) we will also measure the ABI and maximum painless walking distance. The ABI will be measured at rest and following treadmill walking (speed 3.2 km/h, 10% incline), and maximum- and pain-free walking distances will be reported after 1-, 6-, and 12-months.

**Clinical success**
With clinical success defined as an improvement of at least one category in the Rutherford scale above the pre-treatment level, measured after treadmill walking (3.2 km/h, 10% incline; Gardner protocol) and based on post ankle pressure and maximum walking distance evaluated after 1-, 6-, and 12-months (25).

**Therapeutic and total costs,**
Costs (health care costs and non-health care costs) of all relevant items used during the entire trial will be collected. Health care costs includes costs of all therapeutic procedures, personnel, materials, equipment, additional associated diagnostic or therapeutic procedures, and associated hospital admissions during 12-months follow-up. Personnel costs will be computed by multiplying time spent with the mean wage rate of the appropriate personnel-category and adding 37% social-security (26). Costs of materials will be summed cost prices. Equipment costs will be calculated as: [time spent on a procedure] x [hourly cost]. The annuitized hourly costs of equipment will be summed with servicing costs and divided by the proportion of total available room time (26). Non-health care costs includes costs of supporting departments, housing, overhead, transportation costs, and patient time costs. The costs of supporting departments will be obtained from records of our financial department; housing and overhead will be estimated at 45% of direct assignable costs (26). Transportation costs includes parking costs and mean estimated gasoline costs. Patient-time costs will be [hourly wage rate] x [number of hours in-hospital]. The hourly wage rate will be estimated with the published mean hourly wage rate for Dutch men and women given for different age categories (25-44, 45-54, 55-64, >65). The time required for treatment was based on the mean length of hospitalization, which was estimated from the records of patients undergoing revascularization (8 hours) and/or the exercise program (30min*number of sessions). In addition, time invested in unsupervised exercise at home will be also reported and included in the patient-time cost analysis.

**CVD risk factor score (Euro SCORE risk charts and Framingham CVD risk score (d’Agostino 2008))**
The sex-specific multivariable risk factor algorithm from d’Agostino et al will be used to assess general CVD risk and risk of individual CVD events will be evaluated after 6-, and 12-months(27). In addition the Euro SCORE risk charts will be used, which estimates
the 10-year risk of a first fatal atherosclerotic event, whether heart attack, stroke, aneurysm of the aorta, or other (28, 29).

**Medication use**
Anticoagulants, antithrombotic agents, statins, beta-blockers, angiotensin converting enzyme inhibitors, angiotensin-II receptor antagonists evaluated after 6-, and 12-months.

**Number of events**
With an event defined as failure of the revascularization procedure, failure to improve symptoms, restenosis, recurrence of symptoms, amputations, complications due to a diagnostic or therapeutic procedure, and CVD events evaluated after 1-, 6-, and 12-months.

**Sample size:**
Based on previous studies we expect a difference in maximum walking distance in terms of long-term outcomes for the two different trial arms and, therefore, it is expected to demonstrate a clinically relevant difference in maximum walking distance. With adequate treatment, the improvement in maximum walking distance after 12 months for patients with IC was on average 124% after early intervention plus supervised exercise, whereas after supervised exercise only the improvement was on average 26% (mean percentage difference 98%)(10). A mean percentage difference of 30-35% would be considered clinically relevant, which can be translated to an important effect size in practical terms of day-to-day living (r>0.5)(15) meaning that these mostly elderly patients with symptomatic PAD become psychosocially more independent.

To demonstrate a difference of 30% with an alpha of 0.01, a power of 0.90, and a 2-sided test of differences in unpaired proportions, would require 95 patients in each trial arm. With 2 trial arms this implies recruiting 190 patients for the trial. Anticipating 5-10% loss to follow-up, we will include 210 patients.

**Feasibility:**
In total, 600 potential subjects are seen each year in the participating centers combined. Based on our previous RCT, comparing endovascular revascularization to supervised exercise in patients with IC, 50% are expected to be eligible (300 subjects) which makes 210 inclusions within one year feasible (Table 3).

Most of the participating centers have worked together previously on a study in this area, so we know that the collaboration works and that measuring the outcome parameters is feasible in this context. All six centers have access to up-to-date technology and have the infra-structure (physical therapists (hospital-based or/and community-based), radiologists, vascular surgeons, internists, logistics) to perform this study.

**Blinding**
Blinding of the physicians for clinical decision-making is not feasible and not desired in this empirically-based setting. Because patients are randomized across strategies that represent clinical practice, this will not be a problem. The researchers involved in
collecting outcome data and in performing the data analysis will be blinded to the treatment strategy assigned. Clinical success, maximum walking distance, maximum painless walking distance, and ABI will be evaluated by an independent observer blinded to the specific treatment that is assigned, and patients will be instructed not to discuss their assigned treatment.

**Economic evaluation:**
The economic evaluation will be performed in accordance with Dutch guidelines for the performance of cost-effectiveness analyses. We will use the health care perspective and the societal perspective. Time-frame of the analysis will be 1 year, and extrapolation with Markov modeling to long-term outcomes will be performed. In cost-effectiveness analysis from the health-care perspective we will consider QALYs and health care costs and discount both future costs and effectiveness at 4% and 1.5% respectively (26, 30-32), which is in accordance with the Dutch recommendations (33). The cost-effectiveness analysis from the societal perspective will be performed according to the Dutch recommendations which, in addition to the above, also takes productivity losses (friction costs) into account. A threshold willingness-to-pay of €50 000/QALY (range €20 000-€80 000) will be used.

**Analysis:**
Results will be analyzed according to the intention-to-treat principle: once a patient is randomly allocated, the patient remains in the allocated group for analysis regardless of whether cross-overs occur or whether follow-up is completed. The data will be analyzed and reported in accordance with the CONSORT statement. A flowchart will be made to describe the participant flow, number of procedures performed, and reasons for exclusion or loss to follow up (see Figure 1 for a temporary flowchart of the proposed study).

Patient characteristics will be analysed using descriptive statistics. We will calculate the means and 95% confidence intervals of change in each of the outcomes and compare them using a repeated measurement technique, such as a mixed linear model. We will use the bootstrap method to calculate 95% confidence intervals.

**Systematic review:**
We reviewed systematically the published data on the short- and long-term effects of functional capacity or quality of life of early endovascular revascularization plus exercise compared to exercise alone in patients with IC. A literature search was performed using Medline (1966 to date), EMBASE (1980 to date), the Cochrane Library, Cinaih, PiCarta, Web of Science and the reference lists of articles. There was no restriction on language of publication.

*Key words and Medical Subject Headings:*
("intermittent claudication" OR claudicants) AND (angioplasty OR PTA OR revascularization OR “balloon dilatation” OR exercise OR gymnastics OR walking OR training) AND ("quality of life" OR qol OR “health status” OR "functional capacity"
OR "ankle brachial index" OR "walking distance") AND ("Randomized controlled trial" OR "RCT").

Selected articles:
The studies were included if they met the following criteria: All patients with IC were randomized between (a) early endovascular revascularization applied to lesions in the aortoiliac or femoropopliteal arterial segments plus an exercise program, or (b) an exercise program alone including walking or gymnastics etc., and (c) functional capacity, such as the walking distance or the ABI, or quality of life scores of at least 3 months follow-up were reported.
Many studies (n=204) were excluded on the basis of the abstract because there was no combination of early endovascular revascularization and exercise training in patients with IC investigated or the study was not a RCT.
Table 1 shows the characteristics of the two remaining studies.

**RCT-1 (the OBACT trial, Nylaende et al, 2006)**
This single centre RCT was instigated to evaluate the effect of optimal medical treatment (which included home-based exercise) compared with endovascular revascularization plus optimal medical treatment (which also included home-based exercise) in patients with IC (12). The primary outcome was quality of life and secondary outcomes were ABI, and walking distance after 24 months of follow-up (see Table 2). The results were in favor of early endovascular revascularization plus optimal medical treatment, compared to optimal medical treatment alone. Further analyses are required on whether the benefit presented here is also cost-effective.

**RCT-2 (the MIMIC trial, Greenhalgh et al 2008):**
This multi-centre RCT was instigated to evaluate the effect of early endovascular revascularization over supervised exercise, smoking cessation advice and best medical therapy in patients with stable, mild to moderate symptoms of IC caused by aortoiliac or femoropopliteal lesions suitable for endovascular revascularization (10). The outcomes were specified in terms of treadmill walking distances, ankle-brachial pressure indices (ABI) and quality of life after 24 months of follow-up (see Table 2). The results were in favor of early endovascular revascularization plus supervised exercise, compared to supervised exercise alone. Further analyses are required on whether the benefit presented here is also cost-effective.

The proposed study will be complementary to this studies in that we will address questions through performing cost-effectiveness analysis that were not addressed in this RCT’s. More specifically, we will study a representative Dutch population by performing a multicentre RCT, we will evaluate treatment strategies that are currently more relevant, we will evaluate clinical success, quality of life and functional capacity, we will determine the effect of prevention of events (which also includes secondary treatment for failure of initial treatment of IC), and we will calculate cost-effectiveness.
Figure 1. A temporary Flowchart of the proposed RCT

Registered (n=600)

Eligible (n=300)

Not eligible;
Possible reasons (n=300)
Not meeting inclusion criteria

Randomized (n=210)

Not randomized;
Possible reasons (n=90)
Refused to participate

Endovascular revascularization plus supervised exercise (n=105)

Supervised exercise (n=105)

Strategy 1 not received;
Possible reason(n=1)
Refused to continue participation prior to baseline data collection and prior to intervention

Strategy 1 not received;
(n=0)

Possible events during follow up (n=9)
failure of the revascularization procedure n=3
restenosis n=2
recurrence of symptoms n=1
complications due to a diagnostic or therapeutic procedure n=1
CVD events n=2

Withdrawn;
Possible reasons(n=4)
Lost to follow-up
Death

Included in analysis n=104

Possible events during follow up (n=12)
failure to improve symptoms n=8
CVD events n=4

Withdrawn;
Possible reasons(n=10)
Lost to follow-up
Death

Included in analysis n=105
**Required Data**

1. Data of presentation, date of completion of the therapeutic work-up (i.e. date of last therapeutic study), performed therapeutic methods, date and type of the treatment-decision, date of treatment, date that normal activities were resumed, date of recurrence of symptoms and symptom severity, data and type of events. These will be tracked with a case record form (CRF) which will be filled out by the trial co-ordinator of the department of Surgery. The information will be complemented with data from the hospital information system and patient questionnaires at baseline, 1 month, 6 months and 12 months.

2. All patients with lifestyle-limiting IC, evaluated at the weekly vascular conference, will be registered and baseline characteristics will be recorded so that we can evaluate generalizability and the percentage of patients eligible and the percentage randomized. Figure 1 indicates the patient flow chart.

3. Patient characteristics, diagnostic results, TASC classifications, and therapeutic results will be documented including age, sex, smoking, symptoms (according to the Rutherford classification), co-morbidities (symptoms of angina, arthritis, diabetes mellitus, hypertension, hypercholesterolemia, palpitations, dyspnoe). Lifestyle changes will be documented including quit smoking, lose weight (Body Mass Index) and do more exercise.

4. Quality of life: Quality of life will be measured at baseline, 1 month, 6 months and one year follow-up with general and disease-specific descriptive instruments.

5. Functional capacity: ABI, maximum walking distance, and maximum painless walking distance be measured at baseline, 1 month, 6 months and one year follow-up.

6. Costs of the therapeutic work-up: Resource utilisation of all therapeutic procedures will be tracked with case record forms, filled out by the Trial co-ordinator, and complemented with data from the hospital information system and patients questionnaires. The costs of supervised exercise, endovascular revascularization, personnel, and materials needed are important to this analysis. Other costs per unit of resource will be analysed independently of the patient data collection.

7. Non-medical costs like time costs for the patient: the time that the patient spends on waiting, exercising, and undergoing procedures, and friction costs.

**Documentation**

1. A case record form will be filled out by the Trial co-ordinator of the department of Surgery based on data from the referring and treating physicians.

2. A questionnaire will be administered at baseline immediately following randomization and at 1 month, 6 months and one year.

3. Time, personnel and expensive materials (stents, contrast, catheters) required for each therapeutic procedure will be recorded per patient. Personnel costs for supervised exercise will be recorded.

4. Functional capacity will be determined at baseline and at 1 month, 6 months and one year.
5. Events: CVD events, CVD death, secondary revascularization procedures, failures to improve symptoms, restenosis, recurrence of symptoms, amputations, and complications due to a diagnostic or therapeutic procedure will be documented in the CRF.

6. Diagnostic imaging of the treated artery when recurrent symptoms are reported and additional treatments. The results will be documented in the CRF

**Ethical Issues**

All patients will receive written information and an oral explanation and will be required to give informed consent prior to inclusion (in compliance with Good Clinical Practice). The patient will be informed about potential risks and benefits. All data will be entered into a computer database and checked for consistency and completeness. The database will only be accessible by researchers working on this project.

All patients participating in this trial will undergo a treatment workup with well-developed, generally accepted techniques. Half of the patients will undergo the strategy with early endovascular revascularization followed by supervised exercise at the physiotherapist. They will need observation for 4-6 hours or hospital admission after catheterization, substituted with an outpatient procedure of approximately 30 minutes. The other half will be immediately referred to the physiotherapist for supervised exercise. Treatment results expected and unexpected, and the additional therapeutic options will be explained to the patient by his/her vascular surgeon. The physicians involved in the care of the patients will not be blinded to the treatment options – only the investigators collecting outcome data and performing the data analysis will be blinded – so the care of patients will not be unduly influenced by the blinding procedure in the trial.

All treatment decisions will be discussed at the weekly Vascular Surgery conference and progress of the trial will be discussed at a regular management meeting of the Participating Centers. Should unexpected problems arise with performing endovascular revascularization or supervised exercise or with the protocol, these will be addressed at these meetings.
Expertise (7500)

Most of the participating centers have worked together previously on a study in this area, so we know that the collaboration works and that measuring the outcome parameters is feasible in this context. All seven centers have access to up-to-date technology and have the infra-structure (physical therapists (hospital-based or/and community-based), radiologists, vascular surgeons, internists, logistics) to perform this study.

Spronk performed a RCT of endovascular revascularization versus supervised exercise between 2002-2006 which resulted in a PhD thesis in 2008. Hunink, Bosch, Pattynama, and den Hoed worked cooperatively on this project.


Bosch is the PI on multiple projects concerning cardiovascular disease including a study assessing health-related quality of life after angioplasty and stent placement in patients with iliac artery occlusive disease. She has multiple publications in high-impact journals relevant to this project.

Pattynama is an interventional radiologist at the Erasmus MC, which is an innovative center for high-quality research. Pattynama is renowned with multiple appointments on international committees and boards.

Verhagen is chairman of Surgery and an internationally renowned vascular surgeon with many publications, mostly of high-impact.
Dees has extensive vascular risk factor expertise and collaborates with multiple different specialists.

Benda has expertise with supervised exercise programs at the physical center and will be involved with the network list of the participating physical centers.

In Atrium MC in Heerlen different treatment strategies concerning IC have been studied and studies are ongoing (Teijink JAP, kruidenier LM, Nicolai SP). Kruidenier and Nicolai have experience with community-based exercise.

**Publications** (7500)

Selected publications from the research group:

Clinical effectiveness of endovascular revascularization versus supervised hospital-based exercise training for intermittent claudication: A Randomized, Controlled Trial. **Spronk S, Bosch JL, den Hoed PT, Veen HF, Pattynama PMT, Hunink MGM.** Radiology, in press.


Multicenter randomized controlled trial of the costs and effects of noninvasive diagnostic imaging in patients with peripheral arterial disease: the DIPAD trial. Ouwendijk R, de Vries M, Stijnen T, **Pattynama PM, van Sambeek MR, Buth J, Tielbeek AV, van der Vliet DA, SchutzeKool LJ, Kitslaar PJ, de Haan MW, van Engelshoven JM, Hunink**


References (7500)


