Supervised exercise therapy after percutaneous transluminal angioplasty for intermittent claudication – associations and effects on physical function and health-related quality of life.

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Summary

Background: The main focus of this PhD thesis is the physical function and health-related quality of life (HRQoL) of patients with peripheral arterial disease (PAD) who are treated with supervised exercise therapy (SET) after percutaneous transluminal angioplasty (PTA) for intermittent claudication. PAD can not be cured, and effective treatment is not widespread available. Better utilization of existing treatments are of great importance. The aim was to investigate the associations between physical function and HRQoL in patients undergoing PTA, and evaluate the effect of SET after PTA.

Design, sample and methods: Three papers are included, and results from one cross-sectional study (Paper I) and one randomized controlled trial (Paper II and III) are presented. Fifty patients selected for PTA were included and randomized to an intervention (PTA+SET) or a control (PTA) group. The intervention group performed 12 weeks of SET after PTA. Assessments were conducted before the PTA (baseline), and three, six and twelve months after the PTA. Physical function was measured by the 6 Minutes Walk Test and a treadmill test. HRQoL was measured by the questionnaires Short Form 36 and the Claudication Scale.

Results: The associations between measures of walking distance and domains of HRQoL were small to medium in strength (Paper I). SET after PTA led to a greater improvement in walking distance after three months and statistically significant better results for walking distance and physical components of HRQoL in the intervention group compared to the control group during 12-months follow-up (Paper II and III). The improvements were clinically relevant to the participants.

Conclusion: The results from paper I demonstrate the usefulness of assessing HRQoL in addition to walking distance. The results from paper II and III show that SET after PTA yield better results than PTA alone for walking distance and physical domains of HRQoL. These findings are an important contribution to the evidence-based knowledge, particularly the emerging data on the additional effect of offering SET after PTA.
List of papers

Paper I


Paper II


Paper III


The papers are referred to by their Roman numerals throughout the thesis.
# List of abbreviations

<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>6MWT</td>
<td>Six Minute Walk Test</td>
</tr>
<tr>
<td>ABI</td>
<td>Ankle-Brachial Index</td>
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<tr>
<td>ADL</td>
<td>Activity of daily life</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>BMT</td>
<td>Best medical treatment</td>
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<tr>
<td>CAD</td>
<td>Coronary arterial disease</td>
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<tr>
<td>CLAU-S</td>
<td>The Claudication Scale</td>
</tr>
<tr>
<td>CONSORT</td>
<td>Consolidated Standards of Reporting Trials</td>
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<td>CTA</td>
<td>Computed tomography angiography</td>
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<tr>
<td>HRQoL</td>
<td>Health-related quality of life</td>
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<tr>
<td>ICF</td>
<td>International Classification of Function, Disability and Health</td>
</tr>
<tr>
<td>ICIDH</td>
<td>International Classification of Impairment, Disability and Health</td>
</tr>
<tr>
<td>MRA</td>
<td>Magnetic resonance Angiogram</td>
</tr>
<tr>
<td>MWD</td>
<td>Maximum walking distance</td>
</tr>
<tr>
<td>NICE</td>
<td>The National Institute for Health and Care Excellence</td>
</tr>
<tr>
<td>PAD</td>
<td>Peripheral arterial disease</td>
</tr>
<tr>
<td>PFWD</td>
<td>Pain-free walking distance</td>
</tr>
<tr>
<td>PRWD</td>
<td>Patient reported walking distance</td>
</tr>
<tr>
<td>PTA</td>
<td>Peripheral transluminal angioplasty</td>
</tr>
<tr>
<td>PVR</td>
<td>Pulse Volume Recording</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>SET</td>
<td>Supervised exercise therapy</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short form 36</td>
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<tr>
<td>TASC II</td>
<td>The Trans-Atlantic Inter-Society Consensus Document for the Management of Peripheral Arterial Disease II</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</table>
1. Introduction

The main focus of this PhD thesis is the physical function and health-related quality of life (HRQoL) of patients with peripheral arterial disease (PAD) who are treated with supervised exercise therapy (SET) after endovascular treatment for intermittent claudication.

Globally, 202 million people were living with PAD in 2010, and the estimated number for Europe was 40.5 million. Because the prevalence of PAD increases strongly with age, this number is expected to increase further in near future (1901). PAD is associated with an increased risk of total mortality, cardiovascular mortality and events (2), and it is the third leading cause of atherosclerotic vascular morbidity after coronary arterial disease (CAD) and stroke (1). Thirty percent of PAD patients have symptomatic disease, known as intermittent claudication, with known functional limitations such as limited walking capacity and reduced HRQoL compared with individuals without PAD (3, 4). Nevertheless, PAD is often ignored, as many people think their pain or aching is related to aging or other neurogenic or musculoskeletal disorders (5). PAD is widespread within the population, yet, remains a ‘silent’ cardiovascular disease (6). Previous research has documented that PAD is under-diagnosed and under-treated, and there is a general unawareness in the public of this common disease compared with other cardiovascular diseases (7, 8).

PAD cannot be cured; however, many of the current treatments for PAD are effective for reducing symptoms of the disease, optimizing or enhancing existing abilities and improving HRQoL. However, effective treatments are not widely available, and better utilisation of existing treatment and further searches for more and better knowledge are of utmost importance in light of the challenges ahead.

This thesis includes three papers from one trial of 50 participants in which the main focus was the effectiveness of SET after endovascular treatment, which is a treatment option that combines previously known and studied elements in a new way. It is hoped that the findings reported here will be an important contribution to existing evidence that can benefit both patients and the society in general.
2. Background

In the following chapter, the International Classification of Functioning, Disability and Health (ICF) is presented as a conceptual framework for the thesis (2.1). Further, Chapter 2.2 provides an overview of PAD and its symptoms, classification and consequences. The aims of treatment and existing treatment options are also presented. The terms physical function (2.3) and HRQoL (2.4) are presented in the context of the consequences of PAD and the existing treatment’s effectiveness. The associations between physical function and HRQoL in PAD are presented in Chapter 2.5, and a short orientation is provided regarding the main intervention of the study presented in Paper II and III (2.6).

2.1 International Classification of Functioning, Disability and Health

In 1980, the World Health Organisation (WHO) published the International Classification of Impairments, Disability and Handicaps (ICIDH), which was an attempt to better understand and describe the consequences of diseases in a way that was already published in the International Classification of Disease. In the ICIDH, the WHO attempted to incorporate the environment into the understanding of disability. Furthermore, the ICIDH introduced a classification system that used different dimensions of the bodily, individual and social consequences of disease and trauma. In 2001, the WHO published a major revision of the ICIDH, which was renamed the International Classification of Functioning, Disability and Health (ICF) (9). The ICF is not an explanatory theory for the development of disability, but a tool for describing both function and disability associated with health conditions (9, 10). It aimed to provide a unified and standard language and framework for the describing health and health-related states (9). The ICF was meant to complement the aetiology of diseases, disorders or other health conditions described in the International Classification of Disease with functioning information by presenting a continuum of function and environmental factors relevant to all conditions.

The ICF states that it takes a biopsychosocial approach based on an integration of previous medical and social models of disability. The biopsychosocial model’s core
components are biological, personal/psychological and social factors, and it seeks to
develop a basis for a relational or non-dualistic understanding of the body by merging
sociological aspects with biological sciences (11). The biopsychosocial approach is a
response to the over-medicalisation of the preceding models and the tendency for social
models to detach disablement from its biomedical foundations (12). This difference in
the theoretical underpinning of the ICF has been viewed as a paradigm shift, as it
attempts to reconcile established scientific paradigms in disability and rehabilitation
research that are quite contrary (13).

The application of the ICF to clinical practice and research has been strongly
recommended (14). In this thesis, we will apply the ICF as a framework, specifically to
categorise the outcome measure variables according to their main correspondence with
the ICF components.

Definitions of the concept and components of ICF:

• **Health condition** refers to diseases, disorders, injuries and traumas.

• **Body functions** are the physiological functions of the body’s system (including
psychological functions). **Body structures** are anatomical parts of the body, such as
organs, limbs and their components. **Impairments** are problems with body function
or structure, such as significant deviations or loss.

• **Activity** is the execution of a task or action by an individual. **Activity limitations** are
difficulties an individual may have with executing activities.

• **Participation** is involvement in a life situation. **Participation restrictions** are
problems an individual may experience with involvement in life situations.

• **Environmental factors** make up the physical, social and attitudinal environment in
which people live and conduct their lives.

• **Personal factors** comprise the particular background of an individual’s life and living
and include individual features that are not part of a health condition or health
status.

• **Functioning** is an umbrella term that encompasses all body functions, activities and
participation.
• **Disability** is an umbrella term for impairments, activity limitations or participation restrictions.

The ICF is organised into two parts, and each part has two components (see Figure 1). Part 1: Functioning and disability includes the components a) body functions and structures and b) activities and participation. Part 2: Contextual factors includes the components a) environmental factors and b) personal factors.

![Diagram of ICF components](image)

**Figure 1. Interactions between the components of ICF (9)**

Although the ICF represents a great step forward from the ICIDH, there are still shortcomings regarding its use. The personal factors domain has not been developed, and there is no clear conceptual differentiation between the activities and participation components, which leads to several possible ways to operationalise these concepts. These shortcomings have led to much debate and uncertainty among users (15).
2.2 Peripheral arterial disease

PAD is a vascular disease, further defined as stenosis or occlusion of upper- or lower extremity arteries (16). It is limited to artery disease, however, excludes renal, coronary, cerebral, mesenteric aneurysms (16). In the most common usage, PAD implies disease of the arteries that supply the lower extremities. PAD results from an atherosclerotic process in which the inner lumen of the peripheral arteries narrows or is blocked by a build-up of fatty deposits, a phenomenon that is most common in the pelvis and the legs. PAD is defined as an at-rest ankle-brachial index (ABI) of less than 0.9 or, if the index is normal at rest, a drop after activity (2).

2.2.1 Symptoms and classification

The severity of the symptoms depends on the location and extent of the arterial lesions, collateral circulation and the vigour of exercise (17). The most prominent symptom of PAD is characterised by, but not limited to, muscle cramping and pain in the calf, thighs or buttocks during walking or exercise that is relieved by rest within ten minutes. This symptom is called intermittent claudication (2). However, PAD can also be asymptomatic, or the pain can be atypical. At the other end of the scale, PAD can lead to critical limb ischemia, gangrene and minor or major tissue loss.

PAD is commonly categorised according to the Fontaine stage (18) or Rutherford categorical classification (19) systems (Table 1). Both classification systems are universally accepted for grading the severity of PAD. The Fontaine stage was originally introduced in Europe in 1954 by Fontaine. The Rutherford classification system was introduced in 1986 by the First Society for Vascular Surgery / the International Society for Cardio Vascular Surgery (SVS/ISCVS). Both systems address the range of severity from asymptomatic disease to tissue loss; however, the two systems differ in some ways. The Fontaine system features four increasing stages of severity, whereas the Rutherford system has seven categories. Originally, the Rutherford system included an objective criterion in each clinical category that distinguished the system from the Fontaine stage; however, in the first Trans-Atlantic Inter-Society Consensus (TASC) Document on Management of PAD in 2000 (20), these criteria were removed, and only
the categories were retained (21). It has been stated that with this change, the Rutherford system actually lost its strength compared with the Fontaine stage. Nevertheless, both systems offer an objective framework that provides guidelines for treatment and are useful tools for scientific reporting (22).

Table 1. The Fontaine stage and Rutherford categorical classification systems of peripheral arterial disease

<table>
<thead>
<tr>
<th>Fontaine</th>
<th>Rutherford</th>
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<tr>
<td>Stage</td>
<td>Symptoms</td>
</tr>
<tr>
<td>I</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>II a</td>
<td>Mild claudication</td>
</tr>
<tr>
<td>II b</td>
<td>Moderate to severe claudication</td>
</tr>
<tr>
<td>III</td>
<td>Ischemic rest pain</td>
</tr>
<tr>
<td>IV</td>
<td>Ulceration or gangrene</td>
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*Modified table from Dormandy JA, Rutherford RB, for the Trans Atlantic Inter-Society Consensus (TASC) Working Group, Management of peripheral arterial disease (20).*

2.2.2 Prevalence

As stated above, the global prevalence of PAD was estimated at 202 million people in 2010, and the prevalence estimated for Europe was 40.5 million (1). The number of people affected globally increased by approximately 23% between 2000 and 2010. This increase was mostly caused by increased life expectancy worldwide, as the prevalence of PAD increases greatly with age, from approximately 5% among people under the age of 50 to approximately 15% among those over the age of 80 years (1). Approximately 10 to 20% of people with PAD have intermittent claudication, and approximately 50% are asymptomatic or have atypical leg symptoms (1). In Norway, an epidemiologic investigation of 20 000 people aged 40-69 showed an age-adjusted prevalence of intermittent claudication of 1.2% and an overall PAD prevalence of 6% (23). Separate prevalence rates for men and women have been inconsistently reported; however, any possible gender difference might blur with increasing age (24). Some studies have noted male gender as an independent risk factor for PAD; however, these conclusions are based on data from 1985 (25). In contrast, most recent studies have reported that the PAD prevalence in women is higher than or similar to the prevalence among men.
According to a recent study, the conflicting prevalence data for men and women might be a result of the underrepresentation of women in clinical studies and the underreporting of symptoms in women (26). Nonetheless, women clearly have a statistically significant higher prevalence of asymptomatic PAD than men do (26).

2.2.3 Risk factors
The most important risk factors associated with PAD are similar to those of other cardiovascular diseases. In addition to age and family history, risk factors include smoking, diabetes mellitus, hypertension and dyslipidaemia (1, 2). For PAD in particular, smoking has been shown to be a very important risk factor; it is more highly correlated with PAD than with other cardiovascular disease (27-29). In addition, a graded association has been shown between the number of modifiable risk factors present and the prevalence of disease in specific vascular territories, such as PAD, carotid artery stenosis and abdominal aortic aneurysms. This association implies that every additional modifiable risk factor that is present significantly increases the prevalence of vascular disease; furthermore, in contrast to some other aspects of the disease, this association was similar for men and woman (30). Regarding gender differences, the most important risk factors are the same between men and women. Other described risk factors, such as race and obesity, differ between the genders; affected women are more likely to be older, obese and black, but the reasons for these differences are unknown (31).

2.2.4 Consequences
Whether symptomatic or not, PAD is associated with a five- to sixfold increase in total mortality and cardiovascular mortality and events (2, 7). This rate is reported to be even higher than the cardiovascular mortality and cardiovascular event rates in patients with CAD (32). The increased mortality and cardiovascular event risk may result from greater vasodilator impairment, which might contribute to an adverse cardiovascular prognosis in PAD patients (33). Because atherosclerosis is a systemic disease, the presence of the disease at one site, such as in the peripheral arteries, increases the frequency of symptomatic and asymptomatic disease at another site. The cardiovascular morbidity and mortality rate is particularly ominous when exacerbated by the presence of CAD, cerebrovascular disease and/or diabetes (34).
According to the ICF model and terminology, the presence of intermittent claudication might be associated with disturbances in body functions and structure, otherwise known as impairments. Intermittent claudication may have impact on a person’s activities and participation, which could be observed as limitations in activities and also restrict participation in society. However, the degree of impairment, activity limitations and restricted participation varies considerably among individuals affected by intermittent claudication. This variation depends on the degree of the symptoms and on circumstances linked to the individual or the environment. Other specific possible consequences or phenomena associated with PAD in terms of physical functioning and HRQoL are described in later sections (Chapter 2.3 and 2.4). In addition to the consequences for each patient, there are societal consequences in terms of increased healthcare resources use and costs arising from the number of physician visits and hospitalisations, treatment and medication (35).

2.2.5 Aim of treatment

In keeping with the consequences of PAD, the aims of PAD treatment are preventing future cardiovascular events and related mortality and improving function and HRQoL (2, 24, 36). For intermittent claudication specifically, it is especially important to improve physical function, particularly walking (2). Furthermore, because PAD is a chronic disease that cannot be cured, improved quality of life (QoL) is of great importance to those living with the disease (37).

2.2.6 Treatment

PAD treatment comprises multiple components. Therapy without intervention, mainly endovascular treatment or surgery, has traditionally been described as conservative treatment. The more precise term that is currently used is medical treatment or best medical treatment (BMT). BMT consists of exercise therapy, the modification of risk factors and, in some countries, specific medications; it should be offered to all patients with PAD independent of their symptoms (38). General recommendations for risk factor modification include smoking cessation, lipid-lowering and antiplatelet medications; medications for hypertension and coexistent diabetes mellitus may also be needed (2,
24). Additional descriptions of exercise, endovascular treatments and specific medication for intermittent claudication are provided below.

2.2.6.1 Exercise
In many older adults with disabilities, part of the loss in function they experience may be related to sedentary behaviour and a reduction in physical fitness (39, 40). Most people do not obtain the recommended amount of physical activity necessary to maintain health, and the level of inactivity among people with disabilities is higher than that of the general population (40). Even a small reduction in strength or endurance can diminish physical independence (41). Thus, there is a greater need to address the physical activity needs of middle-aged and older adults with disabilities than those of the general population (42, 43). Exercise rehabilitation is a Class I, Evidence Level A, recommendation for the treatment of intermittent claudication in patients with PAD (25). Exercise is defined as planned, structured and repetitive physical activity, and its final or intermediate objective is to improve or maintain physical fitness (44). Although the first reported RCT took place in 1966 (45), Erb suggested exercise for intermittent claudication as early as 1898 (46). The current recommended exercise regimen for intermittent claudication is walking (2). Each training session should include walking until moderate pain occurs, usually after three to five minutes, followed by rest until the claudication pain is gone. The intervals should be repeated until the total training time reaches 35 minutes at the beginning of the training programme and should increase until the total training time reaches 60 minutes. An exercise frequency of three times per week for three months is recommended (2). Other possible exercise regimens suggested in the literature include upper-limb training, resistance training and pole-striding (47). There is no consensus about what type, intensity, duration and frequency of exercise is most efficient (48, 49); however, a Cochrane review on this specific topic is in progress (50).

A Cochrane review found that SET was more effective than non-supervised exercise for this patient-group (51), a finding that was recently updated with no change to the conclusion (52). Suggested explanations for the effectiveness of SET have included the availability of instruction, oversight and accountability for compliance, the presence of
favourable facilities and the availability of encouragement and motivation from and social interactions with other participants (34, 52).

In order to increase effort and motivation for physical activity and exercise, the meaningfulness of the activity, achievement of personal goals and physical well-being are central to a sustained adherence. A person’s level of physical activity will be affected by factors such as what the person can do, the exercise task to be performed and what the person wants to do (53). Our motivation for movement and activity is controlled in part by our interests, experiences and mood, which will therefore be of great importance to a person’s physical activity level. Motivation as a separate topic will not be further addressed in this thesis; however, it is important to be aware of its influence and importance.

Most SET interventions take place in hospitals and clinics, which could be a barrier to availability. Home-based exercise has not been as extensively studied as SET, and because of methodological limitations, unsupervised home-based exercise was given a Class IIb, Evidence Level B recommendation in 2005. This recommendation was reviewed and upheld in 2011, which indicates conflicting efficacy evidence based mostly on non-randomized trials (25). The results of a recent systematic review (54) confirm the low-level evidence and state that although home-based exercise can improve walking capacity and HRQoL compared with usual care or observation, it is most likely less effective than SET. Another recent single-study of a home-based exercise program combined with cognitive behavioural intervention has yielded good results; however, this intervention has not been compared with SET (55). Hence, at present, home-based exercise is recommended when SET is unavailable or unfeasible (54, 56).

Some studies suggest possible physiological adaptations that occur in PAD patients in response to an exercise intervention (34, 57, 58). These adaptations include specific outcomes for intermittent claudication symptoms and more general gains with regard to the risk of further cardiovascular events, manifested disease and general health. These outcomes are listed in table 2.
Table 2. Benefits of exercise

**General gains and cardiovascular risk factor reduction**
- Improvement in exercise capacity
- Improvement in lipid profiles (primarily increased HDL and decreased triglycerides)
- Improvement in insulin sensitivity if reduced
- Reduction in obesity indices
- Reduction in blood pressure if mild hypertension
- Reduction in inflammatory and hemostatic markers
- Reduction in depression and psychosocial stress

**Specific outcomes for symptoms of intermittent claudication**
- Improvement in walking distance (maximum and pain-free)
- Improvement in vaso-responsiveness of the arteries
- Improvement in blood rheology
- Improvement in oxygen delivery and metabolic responses within the limb (angiogenesis*, arteriogenesis** and mitochondrial synthesis)
- Potentially delayed progression of the disease

*Angiogenesis = growth of new blood vessels; **arteriogenesis = collateral artery growth; HDL = high-desity lipoprotein. Table based on (34, 57, 58).

2.2.6.2 Endovascular treatment

For mild to moderate intermittent claudication (see table 1), there is general agreement that exercise and risk-factor modification should be the first-line treatment (2). When the patient responds inadequately to BMT, endovascular treatment can be considered (2, 24). In cases of aortoiliac lesions, endovascular treatment can also be considered without initial extensive conservative treatment. However, the use of endovascular treatment to treat intermittent claudication has become more common as an alternative to conservative treatment (2, 59). The first percutaneous vascular intervention was performed in 1964 (60). Since then, the technique has been further developed, and percutaneous transluminal angioplasty (PTA) is now a well-established method that aims to dilate the narrowed or occluded area in the arterial vessel, first reported in Norway in 1981 (61). In addition, a stent may be placed within the artery to keep the vessel open. The advantage of PTA is the immediate increase in blood flow; in contrast other treatments for intermittent claudication, such as medication and exercise, offer much slower results. Due to its immediate effect, PTA is an attractive treatment for intermittent claudication as the patient is usually able to resume normal activities within few days (61).
Compared with surgery, PTA is a relatively safe procedure. However, as with all invasive procedures, there is a risk of complications. Complications can be classified as major or minor, with a quite similar frequency rate of approximately 5% (62). The minor complications include minor infections, minor bleeding after the procedure, or slight discomfort at the procedure site; however, these complications are usually resolved with minimal treatment. Major complications include pseudo-aneurisms and distal embolization, in which fragments of the plaque loosen and follow the vessel further down the leg. If these pieces are large enough, they can restrict the blood flow (2). PTA can be performed repeatedly if required.

Reports of patency rates (the vessel’s degree of openness) in the literature show that from a hemodynamic point of view, the technical and initial clinical success rate of iliac stenosis exceeds 90% (2, 62). The patency rate of femoropopliteal stenosis is slightly lower compared with the aortoiliac level, (approximately 90%); however, patency rate is lower with more distal and longer stenosis or occlusions (2, 63). At three years follow-up, the patency rates are reportedly considerably worse; 60-75% and 50-60% for aortoiliac and femoropopliteal stenosis, respectively (62).

2.2.6.3 Pharmacological interventions
Specific medications exist for improving walking performance in PAD patients. Two medications, pentoxifylline and cilostazol, are currently approved in the United States (64), and naftidofuryl has been available for use in Europe for over 25 years (65, 66). According to the National Institute for Health and Care Excellence (NICE) guidelines in the United Kingdom (66), naftidofuryl is recommended over cilastazol; however, it is reserved for those who have failed to improve with exercise and do not want to be referred for endovascular treatment. In Norway, neither of these medications are in widespread use, nor are other medications labelled specifically for intermittent claudication.
2.3 Physical function

Function, as defined in the ICF classification (9), is an umbrella term that encompasses all body functions, activities and participation, including physical, mental and cognitive function. Physical function has also been defined as an individual’s ability to perform activities required in their daily life. Function is determined by many factors, including physical fitness, sensory function, clinical condition, environmental and behavioural factors (67). Physical function may also be a prerequisite for the capability to engage in physical activity, which again may help maintain and possibly improve physical function (40). In this thesis, the main focus is physical function, specifically walking performance.

Physical function covers many important functions and activities. Intermittent claudication in particular is linked to walking, as pain when walking is the most prominent symptom of the disease (68). Walking is a very central physical function, as it is essential to activities of daily living and is a prerequisite to participation in many normal daily routines and community-based social and physical activities in all ages (69). Limited walking ability may therefore have causal effect on disability by reducing activities of daily living that are linked to a person’s autonomy and that affect social life, role achievements, mood and QoL (5, 70).

Walking is closely linked to physical independence, specifically in older people. Cohen et al. (71) recommended 360 metres as a minimum walking distance needed to function independently; that is, to be able to navigate within the community to do one’s own shopping and errands. Others, exemplified by Medicare, the government health insurance program for the elderly and disabled in the United States, Newman (72) and Buchner (73), has also proposed ¼ mile (approximately 400 metres) as a cut-off point for defining mobility limitation and disability. Walking is also recognised as one of the most common and best forms of physical activities for older adults in terms of health benefits, simplicity and availability (69). It is also associated with greater adherence than more vigorous activities (74). In relation to intermittent claudication walking is a cornerstone in the exercise treatment (2, 75).
2.3.1 Physical function in patients with peripheral arterial disease

Patients with intermittent claudication have functional limitations, such as reduced walking endurance and velocity, reduced balance, lower proximal and distal muscle strength and lower distal muscle endurance compared with individuals without PAD (3, 4). Studies have also reported reduced walking activity in these patients, which may result from efforts to avoid pain (76, 77). Despite information and recommendations, many patients do not follow exercise recommendations given. In a study by Bartelink (78), walking exercise was not carried out by almost half of the patients with intermittent claudication. Other data by Gardner (76) have shown that this patient group is found generally very inactive with as little as 16% of their daily energy expenditure resulting from physical activity. Lack of specific advice and supervision were found to be important barriers to taking walking exercise (78). Notwithstanding having good intentions, the translation to action of the intentions is often hard as another barrier to exercise is the experience of pain during walking which is very specific for this group of patients (68). Additionally, PAD patients without symptoms or with atypical pain have greater functional limitations and faster functional decline compared with individuals without PAD (79, 80). More severe PAD is associated with more frequent limitations and increasing severity (81, 82). Women were found to have a shorter maximal walking distance (MWD), to walk more slowly and to have greater impairment in calf microcirculation compared with men (58, 83); furthermore, because women are more likely to have asymptomatic PAD and therefore a delayed start of treatment, their symptoms and dysfunction are usually more severe (84).

2.3.2 Effect of treatment on physical function

Extensive research has been performed on the effect of treatment on physical function in patients with intermittent claudication. In contrast to the gender difference in the clinical manifestation of PAD, very few studies have investigated whether there is any gender difference in treatment effect (58). Table 3 describes the most important meta-analysis, systematic reviews and Cochrane reviews on the effect of exercise and PTA on physical function and HRQoL; however, there is some overlap in the studies that were evaluated. A literature search was conducted using the search terms peripheral arterial disease, intermittent claudication, endovascular treatment, percutaneous transluminal
angioplasty, exercise, function, health-related quality of life, meta-analysis and systematic review. The derived studies were screened according to the title and abstract, and eventually, the full text was read. In addition, some of the reference lists were screened for eligible studies. Fifteen studies are presented in table 3, which includes from two to 42 studies with a number of participants ranging from 98 to 7475. Nine of these review studies reviewed exercise alone (47, 48, 52, 54, 85-89), one review study reviewed PTA alone (90), and five review studies examined both exercise and PTA (91-95).

The most frequently measured function in interventional studies on intermittent claudication is walking distance, time or speed, or a combination of those factors (91, 96). The NICE guidelines for lower limb PAD suggests that the minimal important difference between maximum walking distance (MWD) and pain-free walking distance (PFWD) is a doubling of the baseline distance (66). The EU guideline suggests a >30% increase from baseline in MWD and PFWD (97). Hedeager-Momsen (98) states that 50% improvement is based on the rationale that with a baseline of 200 metres, a value of 50% is at least 100 metres, and a walking distance of 300 metres is considered clinically meaningful to help maintain essential activity of daily living. However, this specific distance is again lower than what was suggested previously in this chapter. The Cochrane review on exercise for intermittent claudication (85) showed that exercise programs were of significant benefit in improving walking time and distance (an improvement of 50-200% in walking distance, i.e., an average increase in PFWD of 82 metres and an average increase in MWD of 113 metres) in patients with intermittent claudication. These improvements were seen for up to two years (85). Other reviews showed similar results for exercise interventions when compared with the usual care (48, 86-88, 91). Endovascular treatment alone showed moderate effects on MWD compared with the usual care (91). For PFWD, exercise training and endovascular treatment both showed large effects. However, neither exercise nor PTA were statistically superior when compared with each other for MWD or PFWD; however, PTA combined with SET was found superior to either treatment alone with regards to physical function (91-93) (Table 4).
Increases in blood flow after PTA, measured by increased ABI, are expected and are fairly self-explanatory. Several studies have found an increase in ABI after successful PTA (99-101). A Cochrane review from 2000 (90) on the use of PTA for intermittent claudication showed increased ABI compared with control groups six months after PTA. At 24 months, the ABI was still higher; however, it was not statistically significantly different from the control group. After six years, there was no difference between the PTA groups and the control groups. In contrast with the Cochrane review, a more recent study by Fakhry et al. (102) reported long-term results that found a statistically significant increase in ABI compared with the baseline sustained at seven years, yet there was no significant difference between the PTA and exercise groups. Nylænde et al. (99) also found that the increase in ABI found at three months after PTA was sustained at statistically significantly levels at 24 months.

Regarding changes in blood flow after exercise interventions, the majority of the results are different from the results after PTA. Studies have shown that ABI values are not usually altered by exercise interventions (85, 103-105). However, a few studies have shown an increase after exercise compared with the baseline-values (59, 102, 106). Other studies did not find any significant increase in ABI measured at rest, but found increases in ABI post-exercise (107).

The effect of medications such as cilostazol, pentoxifylline and naftidrofuryl on physical function is under debate. Some studies have found cilostazol more effective than pentoxifylline (108, 109), and have found naftidrofuryl more effective than both cilastazol and pentoxifylline (64). However, these medications have been associated with quite serious side effects, and a recent systematic review found that the improvement was only modest - 15-25% improvement in MWD on a treadmill (64) - which is much lower than the improvement found with other treatment modalities, such as exercise and endovascular treatment (110).
2.4 Health-related quality of life

QoL has become an increasingly important focus of theory, research, and practice in rehabilitation counselling (111-113). The development of welfare states in Europe and North America in the 1970s introduced the measurement of QoL in general populations. In the 1980s, the term HRQoL was introduced (114). In 1995, the WHO recognised the importance of evaluating and improving people’s QoL (115). HRQoL goes beyond direct measures of population health, life expectancy and causes of death, and are used increasingly to supplement objective, clinical or biological measures of disease and focuses on the impact disease and treatment has on the lives of people (114).

There is no consensus on a unified definition of HRQoL, however, there seems to be a generally acceptance that generic HRQoL is a subjective and multidimensional construct. HRQoL consists of the person’s own perceptions, and it takes into account various domains that include levels of physical, mental and social health status, role functioning, abilities, life satisfaction, and well-being (116). Ware (117) suggested five distinct dimensions that should be included when measuring HRQoL: physical health, mental health, everyday functioning in social and in role activities, and general perceptions of well-being.

In cases of terminal or chronic illness where no effective cure is available, an emphasis is placed on improving HRQoL through interventions such as symptom relief, palliative care, rehabilitation or adaptive technology (37). HRQoL instruments may reveal issues that are important to patients but are difficult to capture with other instruments. In terms of cost-effectiveness, HRQoL is important to consider given the unsolved challenges of reimbursement and the availability of treatment, particularly SET, for many PAD patients.

2.4.1 Health-related quality of life in patients with peripheral arterial disease

HRQoL was introduced to the field of vascular surgery with the development of disease-specific instruments in the 1990s (101, 118). PAD has a considerable impact
Table 3. Description of meta-analysis, systematic reviews and Cochrane reviews on the effect of exercise and percutaneous transluminal angioplasty in patients with intermittent claudication on physical function and health-related quality of life.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Incl studies/participants (year)</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brandsma et al. 1998 (87)</td>
<td>Meta-analysis</td>
<td>10/291 (1966 - 1996)</td>
<td>Exercise</td>
<td>PF: Improvements in walking distance or time 105% (SD 55.8%, range 28-210%).</td>
</tr>
<tr>
<td>Spronk et al. 2005 (94)</td>
<td>Systematic review of RCTs</td>
<td>8/672 (1980 - 2003)</td>
<td>Exercise vs PTA</td>
<td>PF: Mean change in ABI significantly differed between groups (p=.01). PTA sign improved ABI, exercise did not. HRQoL: Both groups improved, no difference between groups.</td>
</tr>
<tr>
<td>Watson et al. 2008 (85)</td>
<td>Cochrane-review</td>
<td>22/1200 (1966 - April 2008)</td>
<td>Exercise, usual care and placebo</td>
<td>PF: Exercise groups &gt; usual care and placebo. Overall improvement in walking ability of 50-200%. Exercise showed no effect on ABI</td>
</tr>
<tr>
<td>Frans et al. 2011 (93)</td>
<td>Systematic review</td>
<td>8/702 (1966 - Jan 2010)</td>
<td>PTA vs (supervised) exercise or combination</td>
<td>PF: PTA and (S)ET equally effective. HRQoL: PTA and (S)ET equally effective. PTA+SET may be superior in walking distance and some domains of QoL, but need to be confirmed*.</td>
</tr>
<tr>
<td>Ahimastos et al. 2011 (92)</td>
<td>Meta-analysis</td>
<td>9/873 (Until June 2010)</td>
<td>PTA vs non-invasive treatments (medical therapy and SET)</td>
<td>PF: PTA &gt; medical therapy. PTA vs SET no difference. PTA+SET &gt; SET alone*.</td>
</tr>
<tr>
<td>Reference</td>
<td>Design</td>
<td>Incl studies / participants (year)</td>
<td>Intervention</td>
<td>Results</td>
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<td>----------------------</td>
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</tr>
<tr>
<td>Kruidenier et al. 2012 (95)</td>
<td>Meta-analysis</td>
<td>42/3106 (Until 2009)</td>
<td>Angioplasty, surgery, SET, non-SET or no treatment</td>
<td>PF: Angioplasty, surgery and SET increased walking distance sign &gt; no treatment. HRQoL: Angioplasty, surgery and SET increased physical QOL &gt; no treatment. Only SET had additional value over no treatment</td>
</tr>
<tr>
<td>Fokkenrood et al. 2013 (52)</td>
<td>Cochrane review</td>
<td>14/1002 (Until Sept 2012)</td>
<td>Exercise – SET vs non-SET</td>
<td>PF: SET &gt; non-SET for maximal walking distance. Difference of 180 m in favour of SET. HRQoL: No difference between SET and non-SET. (Update of the 2006-review with no change to the conclusion)</td>
</tr>
</tbody>
</table>

AWD = Absolute walking distance; ABI = Ankle brachial index; HRQoL = Health-related quality of life; MWD = maximum walking distance; MWT = maximum walking time; non-SET = non supervised exercise therapy; PF = physical function (including ABI and/or walking distance); PFWD = pain-free walking distance; PTA = Percutaneous transluminal angioplasty; SET = Supervised exercise therapy; SWT = Supervised walking training. * Further description in table 4.
on HRQoL, particularly in the domains of pain, physical function and physical role, which mirror difficulties with activities of daily life, work deficits, mobility, energy, fatigue and discomfort (4, 119-123). Studies have reported that QoL is decreased in PAD patients to the same extent that it is in patients with other cardiovascular diseases (4). Some studies have found that the QoL of patients with PAD is further compromised by disease severity and comorbidities (124, 125). However, there are differing conclusions in the literature, as other studies show that asymptomatic PAD patients and patients with atypical leg pain have scores that are similar of those of patients with symptomatic PAD (79, 121, 126).

2.4.2 Effect of treatment on health-related quality of life
Six of the presented review studies in table 3 showed results for HRQoL. The review by Guidon and McGee (89) of exercise-based interventions from 1989 to 2008 reported that exercise had a positive impact on physically aspects; yet, the authors found a more ambivalent picture regarding effects on the more psychological dimensions of the HRQoL instruments used. Disease-specific measures revealed greater improvements than generic instruments did. HRQoL effects after PTA have not been as thoroughly investigated as HRQoL after exercise interventions; however, improved HRQoL after PTA was found in several single studies (127-132) and reported in reviews, as shown in table 3 (93-95).

None of the specific treatments stood out as statistically superior with regards to HRQoL, and while the combination of PTA and SET was shown to improve physical function, its effect on HRQoL has been less clear (91, 92, 94, 133).

2.5 Associations between physical function and health-related quality of life

Physical function is said to be an important building block to other aspects of QoL (67, 68). A basic conceptual framework presented in Painter et al. (67), implied that physical function was very basic and important for participation in activities of daily life (ADL) and social, vocational and recreational activities. If a patient is unable to meet the physical
demands of these activities, his or her QoL might be diminished. However, QoL is
definitely not a result of physical function alone, as the preceding chapter noted.

2.5.1 Associations between physical function and health-related quality of life in patients
with peripheral arterial disease
The full influence and consequences of PAD from both a patient perspective and a
societal perspective might not be captured by outcome measurements. A wide variety
of measurements will present a broader picture than measurements of only one aspect
will. Therefore, it is important to study the associations between different
measurements to ensure that most aspects will be covered without measuring the same
aspect multiple times.

It has been stated that clinical and laboratory outcome measures such as ABI, walking
ability, graft patency and limb salvage may not accurately reflect HRQoL in patients with
PAD (126, 134). The literature regarding this association between measures of physical
function and HRQoL is not unanimous; poor, moderate and good correlations between
these measurements have all been reported. Moderate to good correlations are found
in many studies that measure walking ability and HRQoL, especially the physical domains
of HRQoL measured with the Short Form-36 (SF-36) physical function, physical role,
bodily pain and general health domains (124, 135-138). However, some studies have
also reported a poor correlation between walking ability and HRQoL (80, 100, 139-141).
The correlation found between ABI and HRQoL have been predominantly poor (100,
135, 137, 140-144). In summary, there is generally better correlation between measures
of walking ability and HRQoL than between ABI and HRQoL.

2.6 Supervised exercise therapy after percutaneous transluminal angioplasty

Based on previous research, in which the best mode of intervention was inconclusive
and yet to be established, and on the promising results of newly emerging research
(table 4), the combination of PTA followed by SET has been suggested as a possible area
of future research by other researchers (51, 59, 145). A PTA should diminish the main
limiting factor for exercise training in intermittent claudication. However, exercise is still
very important as it plays a preventive role by treating risk factors for further manifestation of cardiovascular disease and has a therapeutic effect on other possible concomitant diseases that are common among PAD patients (42, 44, 96). More conventional principles of exercise training could therefore be applied, possibly including exercise principles for older people (42).

Exercise for older people should include aerobic, muscle strengthening and flexibility exercises (42). Aerobic exercise in particular can influence risk factors for cardiovascular disease (146). The frequency of moderate-intensity activities should reach 30-60 minutes per day in bouts of at least ten minutes, in addition to vigorous-intensity activities of 20-30 minutes per day until an accumulated 150-300 minutes of moderate intensity exercise and 75-150 minutes of vigorous intensity exercise weekly is reached. However, the optimal intensity is not clear (147, 148). High-intensity exercise is not necessary to reduce the risks of developing further cardiovascular and metabolic diseases, although it is most likely more effective than lower-intensity exercise (42), as has been shown for both a general population (149) and for patients with such diseases as heart failure (150) and intermittent claudication (151).

The possible advantage of adding SET after PTA is most likely therefore the twofold focus on locally increased blood flow in the treated area during activity and the general positive effects of exercise. In this way, the patient may benefit from the different timing of the two treatments’ effects, namely, the immediate effect of the PTA and the effect of exercise training, which develop more gradually.

2.6.1 Effect of treatment on physical function and health-related quality of life
To the best of our knowledge, no published research results regarding the combined treatment of PTA and SET were available at the commencement of this present project. An ongoing multicentre study in the United States, the CLEVER-study (152) that aimed to compare the effects of medication, SET and PTA for intermittent claudication initially included a fourth treatment arm examining SET and PTA in combination. However, the researchers concluded this fourth arm shortly after the study’s commencement because of slow recruitment. Since the commencement of our study in 2010, two other
studies of SET following PTA have been published (153, 154) (Table 4). Mazari et al. (154) used a three-month training intervention and reported statistically significant improvements in walking distance at three months for all of the studied treatment arms (PTA alone, SET alone and PTA+SET), with the PTA+SET group performing statistically significantly better than either treatment alone. At the 12-month follow-up, this advantage was not sustained. For HRQoL, statistically significant improvements were reported throughout the 12-month follow-up, though with no difference between the three treatment arms. Kruidenier et al. (153) used a six-month training intervention, but no further follow-up beyond the end of the intervention was reported. After the six-month intervention period, the authors found an increased walking distance with additional SET after PTA compared with PTA alone. However, no additional improvement in HRQoL was observed.

In addition to these two published studies, the preliminary results of the ERASE-trial in the Netherlands were presented at a conference in November 2013 (155). This study aimed to compare the clinical effectiveness of PTA+SET with that of SET alone in patients with intermittent claudication. The results indicated that PTA+SET led to a greater improvement in walking distance, as measured with a graded treadmill test, and in HRQoL, as measured with the by SF-36 and VascuQoL; however, these results have not yet been published.
Table 4. Description of randomized control trials evaluating the effect of percutaneous transluminal angioplasty followed by exercise on physical function and health-related quality of life in participants with intermittent claudication.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country, population, Mean age (SD), % men</th>
<th>Outcome measurement and follow-up</th>
<th>Intervention (n)</th>
<th>Statistical analyses</th>
<th>Results</th>
</tr>
</thead>
</table>
| Kruidenier et al. 2011 (153) | Netherlands, Both aortoiliac and/or infrapopliteal 62.3 (9.8) years, 61.4% men | **Primary:** ACD (max 30 min / 1600 m)  
**Secondary:** FCD, persisting claudication complaints, WIQ, number of patients finishing treadmill, ABI, primary patency, re-interventions, SF-36 and EuroQoL-5D  
**Follow-up assessment:** 3 weeks, 3 and 6 months | **PVI alone** (n=35)  
**PVI + SET 6 months** (n=35): Community-based SET for IC, 6 months (Dutch guidelines*) | Independent t-test or x² or Fishers exact test  
Multiple regression analysis adjusted for age, sex, ABI and baseline values  
Intention-to-treat principle | PVI+SET sign, improved walking distance for both FCD and ACD at 3 and 6 months compared to PVI alone.  
Physical QoL improved after PVI, but showed no further improvement in PVI+SET.  
PVI+SET no additional effect on hemodynamic parameters (ABI, restenosis or occlusions). |
| Mazari et al. 2011 (154) | UK, Femoropopliteal 70 years (median), 60% men | **Primary:** MWD (max 5 min / 215 m)  
SF-36 PF domain at 12 months  
**Secondary:** ICD, MWD, PRWD, ABI, restenosis, re-intervention, SF-36, VascuQoL and ISCVS outcome criteria  
**Follow-up assessment:** 1, 3, 6 and 12 months | **PTA alone** (n=60)  
**SET alone** (n=60): Specific claudicant training, 12 weeks (Gardner 1995 ***)  
**PTA + SET** (n=58) | Univariate non-parametric tests | PTA+SET performing better than PTA alone and SET alone at 3 months  
All groups effective, yet, no stat.sign diff between PTA alone, SET alone and PTA+SET in improving walking distance and QoL after 12 months |

*ABI = Ankle Brachial Index; ACD = absolute claudication distance; FCD = functional claudication distance; ICD = Intermittent claudication; IC = Initial claudication distance; ISCVS = International Society for Cardiovascular Surgery Scores; MWD = maximum walking distance; PRWD = Patient-reported walking distance; PAD = Peripheral arterial disease; PTA = Percutaneous transluminal angioplasty; PVI = Percutaneous vascular intervention; SD = Standard deviation; SET = Supervised exercise therapy; WIQ = Walking Impairment Questionnaire. * 30 min x2-3 per week and encouraged to walk on a daily basis. Walking interval training (3-5 min up to submax pain). ** Closed-circuit training of six stations of 2 min with 2 min of brisk walking between stations, x 3 per week. One circuit first 6 weeks, additional one station per week for the next six weeks to two full circuits at 12 weeks.
3. Aims of the thesis

The overall aim of this thesis was twofold. We wanted to investigate the associations between physical function and HRQoL in patients who were selected to undergo PTA and to describe and evaluate the effect of SET after PTA on physical function and HRQoL in patients with severe intermittent claudication.

In Paper I, the specific aim was to investigate the association between walking distance and HRQoL in PAD patients. In addition, we aimed to explore the possible differences in HRQoL regarding the Fontaine stage.

In Paper II, the specific aim was to compare the effects of 12 weeks of SET after PTA with those of PTA alone on physical function, limb hemodynamics and HRQoL in patients with intermittent claudication.

In Paper III, the specific aim was to explore the effects during one year of 12 weeks of SET (not claudicant specific) after PTA and to compare them with those of PTA alone on physical function, limb hemodynamics and HRQoL in patients with severe claudication.
4. Material and methods

In the following chapter, the studies’ material and methods are presented in terms of the designs (4.1), sample (4.2), inclusion and exclusion criteria (4.3), and randomisation and blinding (4.4). Furthermore, an overview of the endovascular treatment and post-operative care (4.5) and the intervention (4.6) is provided. The outcome measurements used are presented (4.7), and the chapter concludes with the statistical methods used (4.8) and ethical considerations (4.9).

4.1. Designs

In Paper I, a cross-sectional design was used. This design is characterised by showing observations of a population at one point in time (156), and it was here used to describe physical function and HRQoL, and to explore the possible association between physical function and HRQoL in patients with intermittent claudication who were selected for PTA.

In Papers II and III, a RCT with a parallel group design was used to evaluate the effectiveness of adding SET after PTA. The RCT was reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement criteria for reporting clinical trials (157). Further description of elements related to the RCT design is provided later in the chapter.

4.2 Sample

The participants were recruited among patients at the vascular surgery out-patient clinic who were selected to undergo PTA because of intermittent claudication (Fontaine Stage II) as the results of BMT were not satisfactory. BMT consisted of an urgent request for smoking cessation, appropriate medication for lowering lipids and for treating diabetes mellitus and hypertension if present and, most important, strong advise to start or continue exercise. The lesions were determined by clinical examination, ABI and ultrasound triplex as a part of the assessment by the vascular specialist. If there were
indications for further investigations, the participants were referred for a magnetic resonance angiogram (MRA) or, when MRA was contraindicated, computed tomography angiography (CTA) to better estimate the options for possible endovascular treatment. The inclusion of the participants commenced in March 2010 and concluded in June 2012. The final follow-up assessment for the last included participants was completed in June 2013.

4.3 Inclusion and exclusion criteria

In addition to being scheduled for PTA treatment at either the aortoiliac or the femoropopliteal level, the participants had to be available to return for hospital-based exercise twice weekly for three months after the PTA to be included in the study. The exclusion criteria were previous endovascular treatment on the same leg during the previous two years, a present unsuccessful attempt at endovascular treatment, asymptomatic PAD (Fontaine Stage I), critical limb ischemia (Fontaine Stage III or IV) and reduced walking ability caused by factors other than PAD (i.e., orthopaedic problems, spinal stenosis, angina pectoris or dyspnoea).

4.4 Randomisation and blinding

Because of different patency rates, the treatment site (aortoiliac or femoropopliteal) is a factor that might influence the outcome of the study. The participants were therefore stratified according to the treatment site to ensure that the groups were balanced within each stratum. The patients were then randomly allocated after the PTA to an intervention group or a control group. We decided to allocate unequal numbers to each group, with an intervention-to-control ratio of 3:2. This ratio was chosen considering the greater demands on the intervention group and the possibility of a higher drop-out rate. The allocation to groups was concealed using a consecutively numbered randomised computer-generated block list and sealed envelopes. Administrative staff prepared the sealed envelopes in advance, and the block size and randomisation list were inaccessible to the project coordinator (E.B.), who enrolled the participants and assigned them to the groups.
It is not possible to blind participants to an exercise-training intervention, but the assessors performing the baseline and the follow-up tests were blinded to the group assignment, and the participants were also specifically told not to reveal the group to which they belonged. The physiotherapists conducting SET were not blinded to the group assignments.

4.5 Percutaneous transluminal angioplasty and post-operative care

Since first introduced in the 1960s, the endovascular treatment technique of PTA has been further developed and is now a well-established method that involves dilating the narrowed or occluded arena of the chosen vessel (2, 158). For this study, PTA was performed by vascular interventional radiologists in accordance with the hospital’s guidelines. Access was gained by puncturing the common femoral artery; the access was retrograde for lesions in the aortoiliac segment and antegrade for lesions in the femoropopliteal segment. A six-french sheath was introduced, and a balloon catheter was inserted over a guidewire to the site of the obstruction. Inflating the balloon lead to the rupture and flattening of the atherosclerotic plaque. In conjunction with the PTA, lesions in iliac arteries were primarily treated with stents. In femoropopliteal lesions, balloon angioplasty was performed, and a stent was implanted only in cases of flow-limiting dissection or significant residual stenosis. Both groups received post-operative care in agreement with the ward’s usual procedures and were discharged either the same day or on the first post-operative day. The physician responsible for discharge and the responsible nurse gave general advice on the importance of exercise, smoking cessation and diet.

4.6 Intervention

There is mounting of evidence that aerobic exercise is beneficial for health, and it is prescribed as part of treatment for a number of diseases, including metabolic syndrome-related disorders, heart and pulmonary diseases, muscle, bone and joint diseases, cancer and depression (42, 96). As described in 2.2.6.1, exercise training, primarily
walking, is recommended as a primary treatment for intermittent claudication. However, after PTA, the main symptom of intermittent claudication should be diminished and more conventional principles of exercise training, such as the exercise principles for older people (42) described in 2.6, may be applicable.

The intervention group participated in hospital-based SET two days per week for 12 weeks, as also described in Paper II and III. In addition, the participants underwent one home-based exercise session every week. After the 12-week period of hospital-based SET, the participants were strongly urged to conduct three home-based exercise sessions every week for an additional 12 weeks.

The group-based SET was based on The Norwegian Ulleval Model (159), a modified cardiac rehabilitation program, and was slightly adjusted to be applicable to this patient group. It is designed to improve physical capacity, body awareness and emotional well-being and is an interval training program with high and moderate intervals in addition to warm-up and cool-down exercises. Each SET session lasted for 60 minutes and consisted of warm-up exercises, three high-intensity intervals (each lasting five to ten minutes), two moderate-intensity intervals (each lasting five to ten minutes) and cool-down exercises, including stretching. The exercises were generally simple aerobic dance movements and walking and involved the use of both upper and lower extremities. The warm-up exercises included large muscle movements that were repeated later in the higher-intensity intervals, but with greater force and a larger range of movement. The high-intensity intervals focused mainly on endurance, and the moderate-intensity intervals focused on flexibility and strength. During walking, the participants alternated among walking in a circle in the gym, walking in the corridor or climbing stairs. The instructor walked the opposite direction within the circle or close to the participant in the corridor and on the stairs to monitor the participants. The cool-down exercises were decreased in intensity to diminish lactic acid in the working muscles and to prepare for stretching the large muscle groups. No extra equipment was required for this program. Each session had between two and twelve participants.
The exercise intensity used to improve aerobic capacity was adjusted using the Borg scale of perceived exertion and the beats per minute of the music pace (159). The Borg scale is a participant self-report scale that rates perceived exertion on a scale ranging from six to 20 (160). The participants were motivated to gradually increase their exercise intensity towards 15-17 on the Borg scale during the high-intensity SET exercises and to 11-13 on the Borg scale during the moderate-intensity intervals. The choice of music was important. The music was melodious and varied, chosen to roughly fit the age group represented. It had a strong and steady rhythmic component that allowed it to be easily followed. Especially during the high-intensity intervals, the music had an upbeat and faster rhythm to encourage hard work.

After 12 weeks of SET, the intervention group was strongly urged to undertake three home-based exercise sessions over the next 12 weeks. They were encouraged to focus mainly on endurance training and to monitor intensity using the Borg scale. They were also encouraged to use elements from the group-based exercise, which was intentionally simple and required no special equipment to allow carry-over to other environments and situations. The control group did not receive any additional follow-up regarding exercise at discharge beyond the general advice about the importance of exercise that is routinely provided at the hospital.

4.7 Outcome measurements

Traditionally, in early studies on the effect of endovascular or surgical treatment for intermittent claudication and critical limb ischaemia, the measured variables were patency rates and limb salvage. Later, functional performance gained increased importance as a measured outcome of interventions and their influence on QoL (161). The assessment of physical functions and HRQoL consisted of laboratory measures, performance-based tests and self-reported questionnaires. HRQoL can be measured in several ways; however, self-reported questionnaires are most frequently used in interventional studies. Because physical function and HRQoL have multiple determinants, no measure can cover all relevant areas. The psychometric properties of an outcome measures, i.e., the aspects of the measure that say how good the test or
measure is, are important (162). These aspects primarily include reliability, validity and responsiveness. Reliability refers to the measurement’s reproducibility, to what extent replicated measurements agree (163). Validity refers to the ability of the instrument in assessing what it is intended to measure (163). An instrument can be reliable even though it is not valid. On the other side, reliability is a prerequisite for validity. Yet, reliability is not sufficient for an instrument to be valid as it, in addition to being repeatable, has to provide meaningful information (164). Responsiveness is the degree to which the instrument is able to accurately detect a change when it has been a change in status (164), and is also referred to as sensitivity to change (164). Both reliability, validity and responsiveness are not constant characteristics of the measurement, however, it varies in relation to the conditions under which it is applied and to the population in which it is used (164). The known psychometric properties of each instrument are noted with the presentation of the instruments later in this chapter.

The outcome measurements used in this thesis are presented and categorised according to the ICF terminology presented in the introduction chapter (table 5). The domains of the HRQoL instruments, the SF-36 and the Claudication Scale (CLAU-S), were linked to the ICF structures according to the rules for linking the ICF and health status measurements that are based on a systematic and standardised approach and recommended in the literature (165, 166).

All measurements were taken during a single visit at baseline (prior to the planned PTA) and at three, six and 12 months after the PTA. Demographic information about age, gender, height, marital status, education, smoking status, medication, previous cardiovascular events and comorbidity were registered at baseline. Any changes in weight, body mass index (BMI), smoking status, medication, cardiovascular events and comorbidity were registered at the three, six and 12 months follow-up.
Table 5. Categorization of the outcomes used in papers I-III according to the International classification of function, disability and health framework

<table>
<thead>
<tr>
<th>ICF structures</th>
<th>Outcome measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body functions and structure</td>
<td>Height, weight, BMI</td>
</tr>
<tr>
<td></td>
<td>Blood flow: ABI, PVR</td>
</tr>
<tr>
<td></td>
<td>Biomarkers: Total cholesterol, HDL, LDL, triglycerides, HbA1c</td>
</tr>
<tr>
<td></td>
<td>HRQoL: SF-36 – Bodily pain, vitality, social function*, mental health;</td>
</tr>
<tr>
<td></td>
<td>CLAU-S – pain*, disease-specific anxiety*, psychological well-being</td>
</tr>
<tr>
<td>Activities and participation</td>
<td>Walking: 6MWT, MWD, PFWD, PRWD</td>
</tr>
<tr>
<td></td>
<td>HRQoL: SF-36 – Physical function, physical role, social function*, emotional role;</td>
</tr>
<tr>
<td></td>
<td>CLAU-S – Daily life, pain*, social life, disease-specific anxiety*</td>
</tr>
<tr>
<td>Environmental factors</td>
<td></td>
</tr>
<tr>
<td>Personal factors</td>
<td>Age, gender, marital status, education, smoking status, medication, comorbidity,</td>
</tr>
<tr>
<td></td>
<td>previous cardiovascular events</td>
</tr>
</tbody>
</table>

6MWT = Six Minute Walk Test; ABI = Ankle brachial index; BMI = Body Mass Index; CLAU-S = The Claudication Scale; HbA1c = Hemoglobin A1c; HDL = high-density lipoproteins; ICF = International classification of functioning, disability and health; LDL = low-density lipoproteins; PVR = pulse volume recording; MWD = maximum walking distance; PFWD = pain-free walking distance; PRWD = patient-reported walking distance; PVR = Pulse Volume Recording; SF-36 = Short form-36 questionnaire; *The domains contains items linked to two ICF structures based on (165, 166).

4.7.1 Physical function outcome measurements

The physical functioning measurements were grouped in measures of performed walking distance (4.7.1.1), blood flow (4.7.1.2) and biomarkers (4.7.1.3). Three physiotherapists blinded to the group assignment carried out the physical baseline tests and all the follow-up tests, and one physiologist who was blinded to the participants’ group assignment carried out the blood flow tests. Biomarkers was based on blood samples that were taken and analysed by employees at the hospital’s laboratory as routine samples. These employees had no further connection to the study.

4.7.1.1. Walking distance

Waking distance was measured via the standardised Six Minute Walk Test (6MWT), the MWD (also known as absolute claudication distance, ACD) and PFWD (also known as the initial claudication distance, ICD) on a treadmill. The patient-reported walking distance (PRWD) was obtained from the record of the patients’ last clinical visit prior to the PTA.
The 6MWT is an objective measure of functional exercise capacity that is well validated and has shown good reliability in this group of patients (167, 168). The test is simple, inexpensive and feasible in both clinical practice and research settings. The 6MWT was performed in a 30-metres pre-marked hospital corridor; the participants walked back and forth, and instructions and encouragements were given in accordance with the test’s guidelines (169). In this test, the walking speed was determined by the participants, and they were allowed to reduce or increase their pace or even make stops during the test if necessary.

MWD and PFWD were measured using a graded treadmill protocol; a constant speed of 3.2 km/h starting flat with no incline and then increasing 2% every two minutes up to 10% (170). Treadmill testing is a well-accepted means of testing walking distance within this patient group (25, 171) and has shown a very high reliability (172).

Information about the PRWD was, as previously mentioned, found in the clinical record from the last visit before the PTA. PRWD is often used in clinical assessment to guide therapeutic decisions; however, it is often used as a surrogate for more accurately measured walking distance because of a lack of time or available equipment (173, 174).

4.7.1.2. Blood flow

Blood flow velocity was measured using triplex ultrasound and indirectly via ABI and PVR.

The ABI is the ratio of the systolic blood pressure in the lower leg to the systolic blood pressure in the arm (2). The measurements were taken with the participants lying in a supine position. Blood pressure cuffs were placed on the arm and the leg and inflated, and pressure was measured using a handheld continuous wave Doppler ultrasound device. The ABI was then calculated by dividing the higher of the ankle-pressures (dorsalis pedis or posterior tibial arteries) by the higher of the brachial pressures (left or right). A normal ABI is defined as 1.0 – 1.4 (175). An ABI < 0.9 is considered abnormal and an indication of PAD. ABI > 1.3 may indicate incompressible arteries caused by mediasclerosis. Previously an ABI > 0.9 was considered normal; however, the range
between 0.90 and 0.99 is now considered borderline PAD because of the increased cardiovascular morbidity and mortality in this subgroup (2, 176). ABI is non-invasive and is regarded as a simple, low-cost and reliable measurement with a sensitivity of 79-95% and a specificity of 95-100% (171, 177). With calcified vessels, however, the ABI is not a reliable diagnostic tool, as it leads to incompressible or poorly compressible vessels, which are quite common in patients with diabetes mellitus and renal failure (175).

PVR is another indirect measure of the blood flow in the leg. It assesses the sum of all blood flowing to the examined limb, not just the flow in one specific blood vessel (178). PVR was measured with the participants lying in a supine position. A pressurised cuff on the leg compressed the veins but not the arteries, and the sensor in the cuffs felt for arterial pulsation without venous interference. The cuffs were connected to a plethysmograph (Stranden Macrolab, Norway), the pulse volumes were measured, and the contour and magnitude of the waves were tracked. A normal PVR is characterised by a rapid upstroke to a peak in the systole with a dicrotic notch that is followed by a descent during the diastole (176). A restricted blood flow is characterised by an indistinct upstroke, a flattened peak where the dicrotic notch has disappeared and a reduced amplitude of the PVR curve. With the most severe blood flow restrictions, the recording shows no waveform at all. In contrast to the ABI, PVR is independent of calcification in the arteries and is a suitable supplement in patients with incompressible vessels (178).

All of the participants were measured using triplex ultrasound (10 MHz transducers, Vivid E9, GE Vingmed Ultrasound, Horten) at baseline and during all follow-ups to monitor the blood flow velocity in the area of the treated lesions. Vascular ultrasound combines various modalities to study blood vessels and blood flow. In triplex ultrasound B-mode (brightness mode; a grey-scaled two-dimensional image of the vessel) and colour Doppler (different colours depending on the direction and speed of the flow) are combined with pulsed-wave Doppler (which shows direction and relative speed of the blood flow), hence the name “triplax” (179). Ultrasound, either duplex (B-mode and colour Doppler) or triplex, is considered a safe imaging modality with no known long-term side effects that rarely causes any discomfort to the patient (180); it is widely used.
in vascular assessment. Ultrasound is relatively inexpensive compared with other modes of investigation, such as CTA, DEXA or MRA imaging. However, it is operator-dependent, and a high level of skill and experience is needed to acquire good-quality images and make accurate diagnoses.

4.7.1.3 Biomarkers
Blood sampling of biomarkers was performed by bioengineers at the hospitals laboratory upon inclusion in the study and after 3, 6 and 12 months. Venous blood samples were taken after the blood flow measurements and before the treadmill test after overnight fasting. The samples were analysed for total cholesterol, high-density lipoproteins (HDL), low-density lipoprotein (LDL), triglycerides and haemoglobin A1c (HbA1c) via conventional routine methods at Oslo University Hospital, Aker.

4.7.2 Health-related quality of life instruments
The use of HRQoL instruments as an end-point in studies is recommended in TASC II, as it is important to see the impact of chronic diseases when they cannot be cured (37). HRQoL instruments can be generic or disease, domain or symptom specific (37). Generic instruments are applicable to a wide range of patient populations and can permit comparisons across populations, conditions and interventions. However, they can be less sensitive to change than specific instruments because they assess a broad range of domains. Specific instruments focus on areas of interest relevant to that specific disease, domain or symptom. However, this narrow focus does not allow for comparisons with other diseases and may also miss findings that are unexpected in a particular condition (116). The use of both generic and specific instruments can therefore be a solution to these limitations.

HRQoL was measured with a generic measurement, the SF-36, and a disease-specific instrument, the CLAU-S. The two questionnaires were self-completed by the participants.
4.7.2.1. SF-36

The SF-36 is designed to assess functional status, well-being and general perception of health (181). The SF-36 consists of 36 items grouped into eight multi-item conceptual domains: physical functioning, role limitation resulting from physical problems (physical role), role limitation resulting from emotional problems (emotional role), bodily pain, social functioning, mental health, vitality and general health perception. In addition, a physical component score and a mental component score can be calculated. The physical function, physical role and bodily pain domains contribute most to the scoring of the physical component score. The mental health, emotional role and social function domains contribute most to the scoring of the mental component score, and the vitality, general health and social function domains are correlated with both components.

The SF-36 is the recommended generic instrument for patients with PAD (2) with regards to validity, reliability, and responsiveness (101, 182). The SF-36 is also the most widely used generic instrument in this group of patients (89). We used the standard (four-weeks recall) validated Norwegian Version 2.0. Missing responses in the HRQoL data were handled according to the SF-36 manual; missing responses were replaced by the subject’s mean sum for the other responses that constituted the relevant dimension score, provided that there were ≤ 50% missing responses within the dimension score (181). The SF-36 raw scores were coded and recalibrated following standard guidelines, and the items were then summed and transformed into the eight 0-100 scales, for which higher scores indicate better HRQoL. In addition, the SF-36 scores were compared with previously published population norms (183) adjusted for age and gender according to the method described by Hjermstad et al. (184).

4.7.2.2 CLAU-S

The CLAU-S (118) was first developed for use in pharmacological trials. It is one of the earliest disease-specific QoL instruments for intermittent claudication (144). It has mainly been used in research settings (185). The CLAU-S has five subscales: daily life, pain, social life, disease-specific anxiety and psychological well-being. Responses are given on four- or five-point Likert-type scales with the exceptions of one question, which rates pain intensity on a visual analogue scale graded from zero to ten. The CLAU-S raw
scores were coded, recalibrated, summed and transformed into five 0-100 scales, for which higher scores indicate better HRQoL. The CLAU-S is reported to be a valid, reliable measurement able to discriminate between patients with different disease states, but its sensitivity to change has not been reported (144). It is generally anticipated that disease-specific instruments show greater responsiveness than generic instruments do (144). The CLAU-S, however, has been shown to be better at detecting improvements in the patient's condition than it is at detecting deteriorations. For claudicants whose clinical condition remained stable, there was no change in scores, indicating that no placebo effect was associated with the analysis (144).

4.8 Statistical methods

4.8.1 Sample size calculation
Sample size calculation for the RCT reported in Paper II-III was performed based on the primary outcome, the 6MWT. According to Perera et al. (186), the number needed per group for a between-group comparison of a substantial meaningful change in the 6MWT (50 metres, standard deviation 50 metres) with 80% power is 13-20, and the number needed to determine a small clinically meaningful change for the 6MWT (20 metres, standard deviation 50 metres) is 71-115. These numbers are not based specifically on patients with intermittent claudication; however, the symptoms of these patients are quite comparable to those of the patients with mild to moderate mobility deficits who were included in the Perera study (186). We have calculated that with a significance level of 5% and a statistical power of 80%, we would need 22 patients in each group for a difference of 30 metres or greater to be statistically significant.

4.8.2 Analyses
The main statistical methods used in the three papers are presented below. All analyses were conducted on an intention-to-treat basis and involved all patients who were randomly assigned, regardless of their adherence. This method was used to avoid any bias associated with the loss, misallocation or non-adherence of participants; however, it might lead to an underestimation of the results (187). An alternative would have been per-protocol analysis, an analysis of the data of only the participants who adhered to the
protocol. In Paper II, missing data at three months were replaced by the participants’ baseline test values. In Paper III, a mixed model containing both fixed and random effects was used. This model uses existing data and is not influenced by missing data in the same way that other statistical models are.

The variables used in statistical analyses were described with median and range for skewed distributions or with the mean and standard deviation (SD) or the standard error of the mean (SEM) for normally distributed variables. Categorical variables were presented as proportions with percentages.

Comparisons between pairs of categorical variables were assessed with chi-square tests. Pairs of continuous variables with skewed distribution were compared with Mann-Whitney Wilcoxon test. For the correlation analysis, Spearman correlation coefficients were calculated. The strength of the correlations was interpreted according to Cohen’s criteria: 0.10 – 0.29 was small, 0.3 – 0.49 was medium, and 0.5 – 1 was large (188).

In Paper III, changes over time and differences between groups were analysed using mixed models for repeated measures, with group, time and the interaction between time and group modelled as fixed effects. The dependencies between time points were modelled using the diagonal covariance matrix.

All statistical analyses used the software program SPSS (Version 20.0. Statistical Package for Social Science, Chicago, USA). p-values ≤ 0.05 were considered statistically significant, and all tests were two-sided.

4.9 Ethical considerations

All work was conducted in accordance with the Declaration of Helsinki. The study is registered at ClinicalTrials.gov (NCT01109732) and was approved by the Regional Ethics Committee for Medical Research of the Eastern Health Region, Norway (2009/2192-1) and the Data Inspectorate at Oslo University Hospital. All of the participants were
informed and reassured that they had the option to withdrawn from the study without providing a reason at any time. All participants provided written informed consent.

The participants recruited into the study were potentially at risk because they were undergoing an invasive procedure. The study complied with the hospital’s handbook for invasive procedures. During the assessment and exercise intervention, special attention was given to participants who were potentially at risk of falling or other adverse advents. An emergency plan in cases of cardiac arrest or other severe events was developed and followed by all of the assessors and instructors in the exercise group. For the participants in the intervention group, instructions were given to gradually adjust to the exercise intensity to minimise the risk of overuse injuries or other adverse events.
5. Results

This chapter starts with a presentation of the study population (5.1) and its characteristics at baseline (5.2), followed by a summary of the main findings of Paper I-III (5.3 - 5.5). Concluding the chapter are the baseline results for HRQoL compared with an age- and gender-matched Norwegian population (5.6).

5.1 Study population

The analysis of Paper I is based on data from the baseline measurements of the RCT. Paper II presents data from the three-months follow-up with all participants still included. Paper III presents data through the 12-months follow-up. Further details about the flow of the participants are presented in Figure 2.
Figure 2. CONSORT flow chart of the study
5.2 Description of the participant characteristics at baseline

The most important demographic descriptions of the study participants are presented in table 6. A more comprehensive overview of the HRQoL at baseline measured by the SF-36 is provided in Chapter 5.6.

Table 6. Participant characteristics at baseline

<table>
<thead>
<tr>
<th></th>
<th>n=50</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (min-max) or % (n)</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>67 (49 - 83)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.3 (17.9 - 38.7)</td>
</tr>
<tr>
<td>Gender (men)</td>
<td>48 (24)</td>
</tr>
<tr>
<td>Marital status (married)</td>
<td>56 (28)</td>
</tr>
<tr>
<td>Years of school (&gt;9 years)</td>
<td>76 (38)</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
</tr>
<tr>
<td>Have never smoked</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Used to smoke</td>
<td>98 (49)</td>
</tr>
<tr>
<td>Currently smoke</td>
<td>40 (20)</td>
</tr>
<tr>
<td><strong>Current medication</strong></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>94 (47)</td>
</tr>
<tr>
<td>Platelet inhibitors</td>
<td>90 (45)</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>56 (28)</td>
</tr>
<tr>
<td><strong>Comorbidity</strong></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>14 (7)</td>
</tr>
<tr>
<td>COPD</td>
<td>6 (3)</td>
</tr>
<tr>
<td><strong>Previous cardiovascular events</strong></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>32 (16)</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Peripheral arterial surgery or endovascular treatment</td>
<td>18 (9)</td>
</tr>
</tbody>
</table>

*COPD = chronic obstructive pulmonary disease; TIA = transient ischemic attack*

5.3 Paper I

This paper presents a cross-sectional study of 50 patients selected to undergo PTA for intermittent claudication. Walking distance (6MWT and treadmill test), patient-reported walking distance (PRWD), and HRQoL (SF-36 and CLAU-S) were assessed.
The measured walking distance was markedly longer than the PRWD and correlated only with medium strength. The PRWD was significantly correlated with the 6MWT (rho = 0.47). The PRWD was not significantly correlated with the MWD or PFWD on a treadmill.

The associations between measures of walking distance and HRQoL domains were small to medium in strength. The measured walking distance on the 6MWT was significantly correlated with the SF-36 domains bodily pain (rho = 0.38) and emotional role (rho = 0.29). The MWD on a treadmill was significantly correlated with physical role (rho = 0.35) and bodily pain (rho = 0.35). The PFWD on the treadmill was correlated with the physical function (rho = 0.37), bodily pain (rho = 0.35), and vitality (rho = 0.35) domains. Each correlation was considered to be of medium strength. The 6MWT correlated significantly with the daily life domain of the CLAU-S (rho = 0.36). The MWD on a treadmill was significantly correlated with the daily life domain of the CLAU-S (rho = 0.47). The PFWD on the treadmill was correlated with the daily life domain of the CLAU-S (rho = 0.58). The other CLAU-S domains (pain, social life, disease-specific anxiety, and psychological well-being) were not significantly correlated with any of the measured walking distances. The PRWD was not significantly correlated with any of the SF-36 or CLAU-S domains.

There was a significant reduction in the SF-36 physical function, physical role and bodily pain domains and in the CLAU-S daily life domain in patients who had a walking distance lower than 200 metres compared with patients with a greater walking distance. For the other domains, no statistically significant differences were observed among patients with regards to the walking distance.

5.4 Paper II

Fifty patients who underwent PTA for intermittent claudication were included in the parallel group RCT. The participants were stratified according to the treatment site (aortoiliac or femoropopliteal) and randomised into the intervention or control group after the PTA. Both groups received the usual post-operative care. The intervention
group performed two sessions of hospital-based SET and one home-based exercise session per week for 12 weeks after PTA. The control group did not receive any additional follow-up regarding exercise. The outcomes were the 6MWT, the treadmill MWD, the treadmill PFWD, ABI, PVR of the leg and ultrasound scanning, and HRQoL was measured using the SF-36 and CLAU-S. All participants were assessed at the three-month follow-up.

In the intervention group, 26 of 29 patients (90%) completed the intervention, and 21 of the 26 (81%) patients completed more than 80% of the exercise sessions. The reasons for withdrawal were concomitant diseases that were not associated with PAD. No major adverse events associated with the prescribed intervention (exercise and activities) were observed.

All measures except for the SF-36 mental health domain showed statistically significant positive changes from baseline to three months for both groups (p<0.05). The median improvement from baseline to three months for the 6MWT was 66 metres for the intervention group and 45 metres for the control group. For the MWD, the median improvement was 251 metres for the intervention group and 93 metres for the control group. The median change from baseline on the ABI was similar for the two groups; however, for PVR, the intervention group had a 50% greater median change than the control group did. For HRQoL measured by the SF-36, the greatest changes were found in the domains of physical function, physical role, and bodily pain. On the disease-specific CLAU-S, the domains of daily life and pain showed greater changes from baseline than the domains of social life, disease-specific anxiety and psychological well-being, which had comparatively smaller changes. However, all of the variables except for pain showed a ceiling effect at three months (i.e., >20% have the highest possible score).

At three months, there was a statistical trend (p<0.10) (189) towards better results for the intervention group compared with the control group, but the differences were not statistically significant.
5.5 Paper III

This study continues to report the results of the 12 months of follow-up after the PTA. Fifty participants were included at baseline. Altogether, six participants underwent re-intervention after three months’ follow-up. Two participants withdrew during follow-up, after three and six months, respectively. One participant died before 12 months of follow-up.

During the 12-month follow-up, physical function measured as walking distance (6MWT, MWD and PFWD) showed a statistically significant difference between the two groups (p=0.005, p<0.001, p=0.014 for the 6MWT, the MWD and the PFWD, respectively). The intervention group showed a greater change in walking distance than the control group did.

Blood flow measured by the ABI and the PVR showed a statistical trend (p<0.10) (189) towards better results for the intervention group compared to the control group, but the results were not statistically significantly different between the two groups during the 12 months of follow-up (p=0.061 and p=0.077, respectively).

HRQoL, as measured using the SF-36 and CLAU-S, showed a statistically significant difference between the two groups during the 12 months of follow-up for the SF-36 domains physical function (p=0.018), bodily pain (p=0.007) and vitality (p=0.029), the physical component score (p=0.004), and the CLAU-S domain of pain (p=0.011). Regarding the daily life domain of the CLAU-S, there was a statistical trend towards a statistically significant difference (p=0.080) between the groups. The remaining domains of both the SF-36 and the CLAU-S showed no statistically significant difference between the groups during the follow-up. Regarding the CLAU-S results, most of the domains showed a ceiling effect during follow-up.
5.6 Supplementary results

The SF-36 scores for the sample were also compared to the previously published scores of an age- and gender-matched Norwegian population previously published (183). The SF-36 scores for the present study’s subjects showed that the HRQoL was impaired in all SF-36 domains except for physical role (table 7). The most pronounced differences were the domains measuring physical functioning and bodily pain.

Table 7. Short Form - 36 Questionnaire (SF-36) scores of the sample at baseline compared with the age- and gender-matched general population in Norway

<table>
<thead>
<tr>
<th></th>
<th>Median (IQR)</th>
<th>Mean (SD)</th>
<th>General Norwegian population *</th>
<th>Diff</th>
<th>% Diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>50 (21.3)</td>
<td>49.2 (15.4)</td>
<td>77.6</td>
<td>-27.6</td>
<td>-35.6</td>
</tr>
<tr>
<td>Physical role ‡</td>
<td>62.5 (37.5)</td>
<td>53.9 (24.8)</td>
<td>60.9</td>
<td>1.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>41 (19)</td>
<td>40.2 (16.3)</td>
<td>69.7</td>
<td>-28.7</td>
<td>-41.2</td>
</tr>
<tr>
<td>General health</td>
<td>57 (34.3)</td>
<td>57.1 (21.4)</td>
<td>69.6</td>
<td>-12.6</td>
<td>-18.1</td>
</tr>
<tr>
<td>Vitality</td>
<td>47.5 (15)</td>
<td>47.5 (14.6)</td>
<td>61.4</td>
<td>-13.9</td>
<td>-22.6</td>
</tr>
<tr>
<td>Social functioning ‡</td>
<td>75 (40)</td>
<td>75.5 (27.1)</td>
<td>86.6</td>
<td>-11.6</td>
<td>-13.4</td>
</tr>
<tr>
<td>Emotional role ‡</td>
<td>60 (33.3)</td>
<td>58.2 (20.1)</td>
<td>76.8</td>
<td>-16.8</td>
<td>-21.9</td>
</tr>
<tr>
<td>Mental health ‡</td>
<td>76 (76)</td>
<td>70.6 (14.9)</td>
<td>82.9</td>
<td>-6.9</td>
<td>-8.3</td>
</tr>
</tbody>
</table>

IQR = Interquartile range; Diff = difference. 0-100 scale, higher score reflect better health. SD = Standard Deviation. *Loge and Kaasa (1998)(183) n=2323. Mean score adjusted for age and gender. ‡ Not normally distributed.
6. Discussion

The discussion in this thesis it has been divided into three main parts. In the first part (6.1), the main results are discussed, reflecting the main focus of Papers I-III. The second part (6.2) discusses methodological considerations of the study and summarises the internal and external validity of the study. Lastly, the third part (6.3) discusses the overall relevance of the results.

6.1 Discussion of main results

6.1.1 Physical function
All measures of physical function showed statistically significant positive changes from baseline to three months for both groups. At three months, just after the termination of the SET for the intervention group, there was a statistical trend (p<0.10) (189) towards better results for the intervention group compared with the control group; however, the results were not statistically significant. During the 12-month follow-up, there was a statistically significant difference in physical function as measured by walking distance (6MWT, MWD and PFWD) between the two groups, with the intervention group performing better than the control group. Blood flow as measured by ABI and PVR showed a statistically significant increase compared with baseline and a statistical trend towards better results in the intervention group compared with the control group during the 12 months follow-up period.

Regarding the walking distance outcomes in our study compared with other relevant studies, we found a similar pattern of development and results in Mazari et al. (154), whose subjects showed statistically significantly better results at three months compared with baseline for all groups. The PTA+SET groups performed better than the PTA-alone and SET-alone did; however, the difference was not statistically significant between the groups. At 12 months, this initial advantageous effect of the PTA+SET group was not sustained in the study by Mazari (154). This finding differs from our study; we found a significantly statistically better effect for the PTA+SET group compared with the PTA-alone group during the 12-month follow-up. As Paper II notes, this disparity
might be explained by the use of different treadmill and exercise protocols. Our study had a treadmill protocol with a time-cap of 30 minutes (1600 metres), whereas Mazari et al. used a treadmill protocol of maximum five minutes (215 metres), which most likely did not allow sufficient time to reveal the expected progress of these participants after PTA. The exercise protocol in our study was a generic, not claudicant-specific, protocol, unlike the protocol of Mazari et al., which was claudicant specific. In addition, Mazari et al. did not report on the patients’ exercise after three months. We strongly urged the participants to perform further home-based exercise for another three months after the initial three months of hospital-based SET sessions.

Kruidenier et al. (153), who also investigated the effects of PTA+SET, however, showed a somewhat different pattern than both our study and that of Mazari et al. did. Kruidenier et al. reported a statistically significant difference between the groups at both the three- and six-month follow-up. Kruidenier et al.’s results for walking distance after SET+PTA were then maintained at the same level from the three- to the six-month follow-up, whereas our results improved from a lower result at three months to results at six months that were quite similar to those reported by Kruidenier et al. at that time point. Kruidenier et al., however, did no follow-up beyond six months, so whether the results were further sustained, improved or did declined are unknown.

Mazari et al. (154) and Kruidenier et al. (153) also measured blood flow using ABI and found different results. Mazari et al. measured ABI and found a significantly increase at follow-up in all three groups. There was a higher median result for the PTA-alone and PTA+SET groups compared with the SET-alone group, yet there were no differences between the PTA-alone and the PTA+SET groups. Increases in the ABI after PTA are expected, as noted in Chapter 2.3.2. Interestingly, the SET-alone group also showed a statistically significant improvement in ABI at the three-month follow-up, and this improvement was sustained at 12 months. This finding is different from those of the majority of studies on exercise in this patient group, which usually report no direct improvement in the ABI after exercise (85, 190, 191). Kruidenier et al. did not report ABI results at three months. At six months, they found an increase in ABI after PTA;
however, there was no significant difference between the PTA-alone and PTA+SET groups.

Unlike the two studies mentioned above, we found a statistical trend (p<0.10) toward a better outcome in the intervention group for both ABI and PVR compared with the control group during the 12 months of follow-up. The reasons for this disparity are not clear. It is not possible with our data to say whether this statistical trend could have yielded a statistically significant result with a larger sample size (a Type II error – declaring that a difference does not exist when in fact it does) (156), or if PTA+SET could produce previously undescribed changes in blood flow results.

6.1.2 Health-related quality of life
The results showed that the participants had lower HRQoL levels at baseline before the PTA compared with an age- and gender-matched Norwegian population. The improvements in measurements of function were accompanied by improvements in HRQoL. All domains of both the generic instrument (the SF-36) and the disease-specific instrument (the CLAU-S), except for the SF-36 domain of mental health, showed statistically significant positive changes from baseline to three months for both groups, but there was no statistically significant difference between the groups at three months. During the 12-month follow-up, however, the intervention group showed statistically significantly better results compared with the control group for the SF-36 domains physical function, bodily pain, vitality and the physical component score and for the CLAU-S domain of pain.

Although the present study was quite similar to the two previously mentioned studies by Kruidenier et al. (153) and Mazari et al. (154) with regards to the physical function results, the HRQoL results were not similar among the studies. Kruidenier et al. used the SF-36 and the EuroQoL-5D as HRQoL outcome measures and observed no difference in HRQoL between the PTA-alone and PTA+SET groups at three or six months. Mazari et al. used the SF-36 and VascuQoL as generic and disease-specific outcome measurements, respectively, and had a follow-up length of 12 months, as our study did. The changes Mazari et al. found were not the same across the different groups. In the PTA-alone
group, all SF-36 domains showed statistically significant improvements except for the domain of vitality. In the PTA+SET group, fewer domains showed statistically significant improvements from baseline; only the domains physical function, bodily pain and social function did. The SET-alone group showed statistically significant improvements from baseline in the physical function, emotional role and mental health domains; however, intergroup comparisons did not show any differences between the three groups at 12 months on any of the SF-36 domains or on the VascuQoL.

Reasons for the disparity in HRQoL results between these studies and the present study are not as obvious as the reasons for the disparities in physical function. It may be that the greater improvement in walking distance that was found after twelve months in the present study might affect the patient’s experience to such an extent that it influences the HRQoL results and makes a difference that was not observed in the previously mentioned studies. Some authors have suggested that improvements in HRQoL may occur more slowly than improvements in functional ability (75, 170), and this might explain why these results became clearer at the 12-month follow-up than with earlier results. This difference in the timing of improvements might also explain why Kruidenier et al. (153) did not find any differences in HRQoL at the six-month follow-up. In contrast, Mazari et al. (154) also followed patients for 12 months, but, found no difference in HRQoL results after 12 months that favoured any of the treatment groups. The relationship between physical activity and HRQoL is discussed further in Chapter 6.1.3.

The differences between the two groups in both physical function and HRQoL increases after three months follow-up were only trends at best (Paper II). We do not have quantitative data on the intervention groups adherence to exercise after three months, nor do we have that information for the control group. However, the maintained or increased results for both physical function and HRQoL may indicate that the exercise behaviour that led to the initial results at three months were maintained even after the cessation of the hospital-based SET. The effect of exercise will diminish if the exercise is not continued (192, 193), so continued improvement in physical function and HRQoL might indicate that the exercise frequency and habits were maintained. The participants in the intervention group may have incorporated new or better exercise and physical
activity habits into their daily routine during the SET period and continued these habits for the following months. The participants may also have felt more secure in terms of the activities they could and should do safely after receiving supervision for the first months; they may also have felt and observed the effects of their efforts and been inspired to continue. Previous studies on exercise adherence in patients with intermittent claudication, on the other hand, have reported low adherence to exercise, especially without supervision (78, 194). However, this effect was shown in patients with intermittent claudication who experience pain when exercising, which might explain why their adherence is lower compared with patients who have undergone PTA. In the present study, which included patients after PTA, the initially poor blood flow is improved; this improvement might have strengthened patients’ adherence to exercise, which might in turn have led to improvements in physical function and HRQoL. It may have been that PTA has paved the way for the effects of exercise by diminishing the patient’s blood-flow limitations. This possibility is consistent with our assumption in Chapter 2.6 about the effect of the combination of PTA and exercise. However, this is only a possible explanation, as we do not have data to verify the patients’ adherence.

6.1.3 Associations between physical function and health-related quality of life

The association between physical function (in this case, walking distance) and HRQoL in the present study at baseline was small to medium in strength. This finding is in accordance with previous studies that report that the relationship between physical activity and HRQoL is multifactorial and not caused by a single mechanism (195, 196). The strength of the relationship could be influenced by both mediating mechanisms, such as physiological (increased fitness and strength) and psychological factors (self-efficacy), and moderating mechanisms, such as participants or group characteristics (physiological and psychological health status, personality) and the characteristics of the exercise protocol (197). In contrast, this association could also be reciprocal, as HRQoL also influences participation in physical activity (196). The reported association was measured when the participants were experiencing pain when walking, i.e., before the PTA which prevented many of them from exercising on a regular basis (76). The strongest statistically significant association was found between the daily life domain of the disease-specific HRQoL measure CLAU-S and PFWD (rho = 0.58), followed by the
association between the CLAU-S and MWD (rho = 0.47). All other statistically significant associations between measures of walking distance and HRQoL were less than rho = 0.38. Previous studies (listed in Chapter 2.5) have reported both lower and higher correlations between walking distance and HRQoL. The best correlations have been observed in the physical domains of HRQoL, a finding that was confirmed in the present study as well. These differences may be expected because longer walking distances could reflect less severely affected physical function and pain (124, 135). However, these differences also indicate that walking distance, although an important factor for maintaining physical independence in activities of daily life, is in fact only one of the many factors that influence HRQoL, and likewise, HRQoL is one of many factors that influence physical function (196).

To the best of our knowledge at the time Paper I was written, no differentiation of results based on walking distance and the Fontaine stage classification system has been reported. There was a significant difference in the SF-36 domains physical function, physical role and bodily pain and the CLAU-S daily life domain. Patients whose walking distance was below the cut-off of 200 m had lower HRQoL scores in the mentioned domains compared with patients with a walking distance greater than 200 metres. This might not be unexpected for the same reasons that were mentioned in the preceding paragraph about the physical domains. However, for the remaining domains (mainly those constituting the mental component score of the SF-36), no statistically significant differences were observed based on the walking distance. This lack of difference might be of further additional interest, even though obvious and explanatory reasons are more difficult to uncover. Patients with intermittent claudication are asked about their walking distance and undergo walking distance assessments. It is nevertheless, important to note that walking distance does not always reflect how the patients feel or how the disease affects their HRQoL (198), which could be one possible explanation for the physical and mental domains’ differing relationship with walking distance. A patient could feel very limited in what they want to do or to be even though their walking distance is longer than the minimum that is considered long enough to allow independence in activities of daily life (72, 73). This matter will also support the
argument that HRQoL is influenced by elements other than walking distance, as even patients with the longest walking distances report reduced HRQoL (135, 198).

The walking distance results prior to the PTA in this sample showed a wide range of distances (Paper I). These patients were nevertheless all selected to undergo PTA based on a total evaluation of their walking distance and how it affected their life and lifestyle. There is no consensus regarding a “cut-off” walking distance that indicates when endovascular treatment is the best option compared with exercise and medical therapy (2). If the walking distance were the only criterion on which a treatment decision was based, many of the patients in the present study would most likely not have met the criterion, as they had relative long walking distances compared with many patients with intermittent claudication. In contrast, the frequency of PTA is increasing as an alternative to both surgery and conservative treatment (2, 59). Although PTA’s complications are few, it is known that invasive treatments are associated with risks, and re-occlusions may require open surgery at earlier stages (199). Patients might be qualified to assess the risk involved in invasive treatment and might view this option as an easy, quick and good solution to an extensive problem.

With this in mind, the low to medium strength of the association between walking distance and HRQoL and the difference in the Fontaine stage classification should be considered to emphasise the importance of evaluating more than walking distance for patients with intermittent claudication, as the current guidelines recommend (2, 25). Assessing HRQoL in patients with PAD has been recommended in previous studies, already in 1996 (139) and research and clinical practice guidelines; however, many clinical practices do not include a standardised HRQoL assessment and therefore do not obtain a thorough picture of the patient’s state (4). The present results also emphasise the importance of considering all aspects or domains of HRQoL, not only the physical aspects of HRQoL, that are most frequently explored and reported in the literature on HRQoL and intermittent claudication (123). Although specific limits or cut-off values for walking distance, HRQoL and other appropriate aspects could be a feasible treatment guide for the physician, the patient and possibly even society in terms of better standardisation and predictability of costs, it is not possible to establish such values. Yet,
as much information as possible from different aspects and sources can provide good guidance for treatment decisions.

6.2 Methodological considerations

6.2.1 Internal and external validity

Internal and external validity are important terms related to the degree to which inferences can be drawn from a study. Internal validity is the degree to which a study is free from bias or systematic errors (200), and it is commonly argued that internal validity is a prerequisite for external validity (201). The use of randomisation and blinding can achieve a fair comparison of the treatments studied. If the experiment is properly conducted, any observed difference should occur either because there actually is a real difference in the treatment effect or by coincidence and not because of systematic differences between the treatment groups beyond the different treatments they received (202). By these means, a study will have a high internal validity. The probability that coincidence has led to a wrong conclusion about the effect is controlled by the p-value (203).

External validity is the degree to which the results can be generalised to populations or groups that did not participate in the study; it is associated with the inclusion and exclusion criteria (200, 204), and threats to the external validity will compromise this degree of confidence. Considerations about internal and external validity are based on judgment and knowledge of the specific subject matter and methodology in general (200). Issues related to both internal and external validity is further discussed in this chapter and then summarized at the end.

6.2.1.1 Design

In Paper I, a cross-sectional design was used. This design is appropriate for describing a sample at one point in time or investigating associations between chosen variables; therefore, it provides an alternative to the case-control or cohort approaches (156). This design does not suffer from as many difficulties as other designs; however, an
observational study cannot establish a cause-and-effect relationship between exposure and outcome.

In Paper II and III, an RCT design was applied. An RCT is considered the top of the experimental study hierarchy – the gold-standard design – for assessing the efficacy of one treatment compared with no treatment, a different treatment or a placebo treatment (164, 205). No other study designs can minimise or balance the effects of known and unknown confounding factors that could influence the outcomes; an RCT can control such factors through random allocation (i.e., participants are assigned to one of the study groups by chance alone (156)), the concealment of allocation (the non-disclosure of the method that generated the sequence that ensured random allocation (200)) and possibly blinding (202). Regardless of the superiority of the RCT design, there are still possibilities for introducing bias (202). Bias, defined as systematic deviations of the results, inferences from the truth, or processes leading to such deviation (200), can be introduced and found in any stage of the research process, including planning, conduct, analysis, interpretation and reporting, and might result in either the underestimation or overestimation of the effects of an intervention (202). A single RCT cannot yield conclusive answers alone, and it is important to view the results of an individual trial in the context of other relevant studies and sources of information (164, 202).

6.2.1.2 Sample and sample-size
The participants in the present study had already been chosen to undergo PTA because they had undergone previous medical and exercise treatments without achieving the desired effects. Therefore, exercise therapy alone was not a treatment option any longer. The consequence of this is that our results are not quite comparable to the many studies on exercise therapy alone or exercise therapy compared to PTA; they are only comparable to studies of PTA alone or PTA in combination with exercise. Furthermore, we chose to exclude patients who had had previous PTA on the same leg in the past two years to avoid the interference of previous treatment results. However, it is quite common for this group of patients to undergo a re-intervention if the first treatment is unsuccessful. With strict inclusion and exclusion criteria to control these known biases,
the study sample can become very narrow, making it difficult or impossible to generalise the results to the entire intermittent claudication patient population, hence affecting the external validity. Concerns about this issue and other related methodological issues were also recently addressed in an editorial by Abbott (206), who saw the consequence of such issues to be a need for many more studies to thoroughly cover the full spectrum of PAD patients.

Because of changes in the hospital structure during inclusion, the inclusion rate was lower than expected, resulting in fewer participants than had been planned for at the end of the scheduled inclusion period. It was not feasible to extend the inclusion period further because of limited time and economic resources. Nevertheless, many of the variables did reach a clinically relevant and statistically significant level (see further discussion in Chapter 6.3). However, for the variables that did not reveal any differences between the groups, the possibility of a Type II error (156) cannot be ruled out, as the sample size was lower than the estimated. The sample size was also too low to permit level-specific (aortoiliac and femoropopliteal) analyses with sufficient precision in the estimates. This would have refined the specificity of the results and illuminated possible differences resulting from the treatment level. Nonetheless, because the participants were stratified based on treatment-level, the possible biases of overestimating or underestimating the results were reduced.

6.2.1.3 Outcome measurements
Historically, health outcomes relevant for assessment have emerged from purely mortality and disease-control to also include other aspects related to disease and disability (164). There is a wide range of health outcomes available for assessment, and there is an even wider range of outcome measurements to choose from (162). This wide range of measurement, and with that a heterogeneous use of instruments has resulted in difficulties comparing results across studies.

We chose the 6MWT as our primary outcome measure. The 6MWT has the advantage of being a corridor-based test that is more representative of walking in daily life and is stronger associated with physical activity levels during daily life compared to treadmill
walking in patients with intermittent claudication, especially by being self-paced and allowing stops (167). In contrast, because the test is self-paced and allows stops, it does not a measure either exact MWD or PFWD if the participants do stop and then continue within the six minutes. Being self-paced the test has a potential for motivational factors to largely influence on performance (207). Yet, by strictly following the test’s guidelines for encouragement, as was done in the present study, this potential bias is reduced.

At three, six and 12 months follow-up we saw a greater improvement for both groups and a greater difference between the groups from baseline to follow-up in the treadmill test compared to the 6MWT. An important factor with regards to this discrepancy is the different time caps of the two outcome measures. The time-cap of the treadmill test was 30 minutes whereas in the 6MWT the time-cap was, as the name indicates, six minutes. Six minutes are most likely not enough time to discover a possible difference between the groups as the expected progress of the PTA alone is also great (91). Although the participants can walk as fast as they want in the 6MWT, whereas in the treadmill test there is a set pace of 3.2 km/h, there is a certain speed when it is easier to start running than to continue walking (208). The treadmill test has the advantage of being performed in a tightly controlled setting with controlled speed and grade which allow direct comparison between participants (209). However, it has been associated with balance problems and anxiety in older patient populations (210, 211). Treadmill walking has also been associated with a learning effect (170), but this might be a more influential bias when an intervention also include treadmill walking which the present study did not encompass. Another disadvantage of treadmill testing in intermittent claudication is that a clinically meaningful change in walking performance is not defined as it is for the 6MWT (55). Thus, the combination of a corridor-based test and a treadmill test will be complementary and might provide advantages in assessing PAD patients treated with PTA (167).

PRWD is in the literature reported to be different from performance-based clinically measured walking distance (212). These types of data are conceptually different as self-report data are related to the concept of disability because they reflect subjective performance within a socio-cultural context, and assessment by an external observer is
closer to objective functional limitations (213). In addition, it is stated that performance-based tests are more robust than self-reported measures in terms of validity, reliability and sensitivity to change (214, 215). Thus, tests based on self-reported functioning and actual performance are assumed to complement each other (216-218). The validity of PRWD is also discussed. The information of the PRWD is often recorded in the medical chart without further verification, however, only moderate correlation between PRWD and measured distance both on a treadmill and in a corridor has been reported (212, 219). In the present study, PRWD was obtained through the patients’ medical chart. There were no standardised instructions on how to report this distance. The obtainment of this outcome could therefore have been better controlled and standardised if the assessor in charge of the physical tests had asked the participants directly. However, as mentioned, estimating a walking distance has been shown difficult in both patients and other health workers. PRWD, if to be included, should therefore be complemented by performance-based data on walking distance to obtain a more accurate picture of the walking ability of the participants.

As all interesting outcomes are impossible to measure due to time, resources and ethics, choosing the appropriate amount of outcomes and the right outcome measures is important, however difficult. On the other side, whether measuring walking distance, blood flow and blood values are representative of physical function as a whole might be discussed. A feasible alternative to expand the measurement of physical function could have been to use a set of measurements composed especially for such, like the Senior Fitness Test by Rikli and Jones (220). The Senior Fitness Test is a test battery of six different tests measuring the underlying physical parameters associated with functional ability, and identifies whether an older adult may be at risk for loss of functional ability (220). This could have expanded our view of physical function to also include strength, balance and flexibility. It could also have made it possible to compare these patients further with other older people and other patient populations who are tested by the SFT. However, choosing a limited numbers of outcome measurements, walking distance and blood flow were chosen as it is stated to be the main symptom and reason of loss of function in patients with intermittent claudication (2).
For measuring HRQoL it is recommended to use both a generic and a disease-specific instrument (133). As a generic instrument, the SF-36 was a clear choice as it is found to be the most appropriate generic instrument for this patient group with regard to validity, reliability and responsiveness (101, 144). Among disease-specific instruments the CLAU-S was chosen even though the choice was not as obvious. Few disease-specific instruments have been translated into Norwegian and tested extensively with regard to its psychometric properties. The CLAU-S has a good validity (144), however, its sensitivity has not been reported. A great portion of the CLAU-S domains showed a ceiling effect at the three follow-ups, and one domain even at baseline, which then further will exclude the possibility of capturing a potential further improvement of the HRQoL in these participants. This resulted in a quite limited utilisation of the disease-specific instrument in this project.

6.2.1.4 Intervention

The Norwegian Ulleval Model is described in the literature (159). It was developed as a cardiac rehabilitation program that emphasised improvement of physical capacity, body awareness and emotional well-being (159), and was slightly modified to this patient group. It is not previously described used in a PAD patient population in specific. Many exercise therapy programs for PAD are claudicant specific, which means that they focus specifically on walking in intervals, often on a treadmill (2, 86). Many patients have previous to the PTA treatment been hindered from doing much exercise because of pain from the lower extremities when exercising (47). The consequence of this, as noted in Chapter 2.3, is lower physical fitness in general which often include reduced endurance, strength and balance. However, after PTA the initial most limiting factor resulting in reduced walking ability should be diminished as the narrowed or occluded area in the vessel is dilated. In that sense, an exercise program focusing mainly on endurance, strength and mobility is very appropriate. Its good feasibility in that sense might result in better availability and utilisation of exercise therapy as several patients groups as well as healthy people can benefit from the same exercise program. On the other side, the Norwegian Ulleval model requires the skills and knowledge of a professional instructor to conduct and monitor the participants (159). Yet, even though this is a supervised
program, its components are quite simple so it is possible to adapt them for home-based exercise if desired.

As previously mentioned in chapter 2.2.6.1, SET has been found more effective than non-supervised exercise for patients with intermittent claudication. Whether this is the same for patients after PTA is not yet investigated. However, as the control group was strongly encouraged to engage in exercise after the PTA, one of the main differences between the two groups was the known amount of supervision in the intervention group. One of the suggested explanations for the benefit of supervision have been a generally assumed higher energy level of the performance with supervision, which might lead to an increase of the general physical condition (221). The results of the present study showed that the group with a known level of supervision reached better results than the control group where the amount of supervision is unknown.

The control-group of our study received no SET after PTA beyond encouragement to engage in any exercise organised by themselves, however to which degree or whether supervised or not was not monitored. This is currently the standard treatment at our hospital with regards to exercise, hence, they were not deprived any standard treatment. Whether this study had an active control or a no-contact control group might be discussed. An active control group is one in which the participants engage in some activity or tasks during the intervention period, yet it is not necessarily matched in terms of for example frequency or intensity (222) (223). A no-contact or no-treatment control group, on the other side, are assessed with the same tests at baseline and every follow-up, but with no further contact with the project coordinator or other persons involved in the study in the meantime (223). Regarding exercise in general, the control group may have been an active group that engaged in exercise on their own initiative; however, because we have no data to this effect, the control group may be defined as a no-contact control group. To reduce this bias we could have monitored the exercise level of the control group as well as was done by following the adherence of the intervention group in terms of registering the attendance in groups. Activity monitors like step-counters and similar devices could also have been used.
The effect of being under observation, called the Hawthorne effect, may alter the results of the way a patient behaves (224). In the present study, the aim was to study the effect of SET after PTA, which resulted in difference in time of attention between the two groups as only one group received SET. The intervention group was all together given more attention in time and treatment compared to the control group. The effect of this divergence in attention could have been reduced by giving the control group another exercise intervention or by other means like regularly follow-up, and thereby having an active control group. This bias of attention can therefore not be ruled out when analysing the results.

6.2.1.5 Summary of internal and external validity
Factors relevant to internal and external validity have now been discussed. The strengths of the study with regards to relevant elements of internal validity are the proper randomisation, stratification based on treatment level, blinding of the assessors, good adherence of the participants in the intervention group and use of relevant and valid outcomes measurements. Other elements like the lack of activity registration of the control group after discharge from hospital, the registration method of PRWD and the ceiling effect of the disease-specific HRQoL instrument CLAU-S will, however, influence and challenge the internal validity. The eligible participants for this study were already selected to undergo PTA for intermittent claudication. Consequently, the results of this study will not be externally valid to all patients with intermittent claudication; however, because the use of PTA for intermittent claudication is increasingly common, the number of patients this might relate to will also increase.

6.3 Relevance of results

In addition to why and what to measure, the question as to whether improvements in any of the measured variables are not only statistically significant, but also clinically relevant, is important, yet could be difficult to answer. The concept of minimally important difference, first defined and described by Jaesche in 1989 (225), has been established to better express clinically important and significant relevance (226). It attempts to define the smallest change in the measured outcome that constitutes an
important and meaningful change for the patient (225) which might differ from the statistically significant change and difference. Estimations of minimally important difference is based on anchor-based (compared with another relevant measure) or distribution-based (with focus on statistical characteristics of the variability of the sample) approach, and the present recommendation in the calculation of minimally important difference is to use multiple approaches (161, 227).

The 6MWT, which was used as the primary outcome of this study, has previously been explored with regards to which change or difference that yields clinical relevance in several patient populations (186). This is not done specifically for PAD-patients in general or in patients with intermittent claudication. However, it has been done in older adults with mild to moderate mobility deficits which could be used as a comparable group (186). For this group 50 metres was suggested to be a substantial clinical relevant change, and 20 metres as a small clinical relevant change. During the 12 months of follow-up, the mean change from baseline to 12 months in the 6MWT was 97 metres and 65 metres for the intervention group and the control group, respectively. These changes from baseline are therefore most likely clinically relevant changes for both groups.

A clinically relevant change in walking distance is not defined for treadmill walking as it is for the 6MWT (55). Some suggestions have been proposed as mentioned previously in chapter 2.3.2. As the changes from baseline to 12 months in the treadmill measures were even greater than in the 6MWT with a mean change of approximately 430 metres and 275 metres for the intervention groups and the control group in MWD, respectively, and a mean change of 567 metres and 402 metres for the intervention groups and the control group in PFWD, respectively. These mean changes are more than 100% increase from baseline, which exceed the different value of possible clinical relevance suggested. This does strengthens the picture of the clinical relevance in walking distance of this intervention. The difference between the two groups with regards to clinical relevance from baseline to 12 months follow-up was approximately 150 metres and 160 metres for the MWD and the PFWD, respectively. As the baseline results for PFWD were shorter than for the MWD, the clinical relevance of an almost similar difference between the
groups is most likely greater in for the PFWD as a change of 160 metres is a greater partial than approximately 150 metres in the MWD. However, because no minimally important difference is defined for treadmill walking in intermittent claudication or for the expected change after PTA, further assumptions will be arbitrary.

The ABI is not particularly relevant to the patient, but for diagnostic purposes, it is an important measure because the diagnosis of PAD is based on a specific value or drop in the index (175). As such it is a measure of the PAD disease related to diagnosis and also prospects for survival (175). ABI is, as mentioned in chapter 2.3.2, influenced by PTA, but less by physical exercise. In this study, we have reported statistical trends of change also in the ABI and PVR as a consequence of the combined treatment with PTA and SET which are different to previously reported results. The ABI index is still most likely not clinically relevant for the patients as a number, and as seen not strongly correlated with either measures of physical function or HRQoL. Nevertheless, it might be interesting to continue further research of possible changes in the ABI after the combined treatment of PTA and SET to verify or falsify its effect on the ABI and also the PVR and possibly its noteworthy influence on prospects of survival.

As opposed to the walking distance measured by the 6MWT where a clinical relevant change and difference is defined for many groups of patients, the interpretation of scores on HRQoL questionnaires is hampered by the lack of a definition as to what amount of change or difference in scores between groups constitutes a clinically relevant change or difference (161). As far as we know, the only study that has reviewed this in the PAD population is a recently published study in patients with critical limb ischemia who completed the disease-specific instrument VascuQoL before and six months after treatment (161). It is therefore difficult to state whether the change we have observed in the HRQoL instruments of this study is clinically relevant in addition to its statistically significance in some of the domains. Fayers and Machin emphasise in their book on QoL that patients will consider change in domains differently, yet, that a possible rule of tomb, based on studies on a variety of scales, changes of between 5% and 10% are perceived by the patients and held by them as clinically relevant (37). Based on this statement, the present study has then seen clinical relevant changes (more than
5 %) from baseline during 12 months of follow-up in all of the SF-36 domains but mental health in addition to the daily life and pain domain of CLAU-S. The difference between the groups is of lesser extent compared to the measured walking distance.
7. Conclusion and future perspectives

7.1 Conclusion
The overall aim of this thesis was to investigate the associations between physical function and HRQoL in patients selected to undergo PTA, and describe and evaluate the effect of SET after PTA on physical function and HRQoL in patients with intermittent claudication. Based on the three articles included in this thesis, the following conclusions can be drawn:

- The associations between measures of walking distance and domains of HRQoL were small to medium in strength (paper I).
- There was a significant difference in some HRQoL domains between those patients who were able to walk less than 200 m and those who walked more than 200 m (paper I).
- SET after PTA in patients with intermittent claudication led to a greater improvement in walking distance after three months for the intervention group than for the control group, which had PTA alone. These improvements are considered clinically relevant for this patient group, yet not statistically significant (paper II).
- SET after PTA in patients with intermittent claudication yielded statistically significantly better results during 12 months’ follow-up on walking distance and the physical components of HRQoL compared to PTA alone. These improvements were clinically relevant to the participants (paper III).
- There was a trend towards better results for indirect measures of blood flow in the intervention group compared to the control group during the 12 months of follow-up (paper III).

7.2 Future perspectives
The present findings are a contribution to the evidence-based knowledge of efficient treatment for intermittent claudication, particularly the emerging data on the effect of the combined treatment of SET followed by PTA. However, the results are based on a small sample size and further sub analysis of possible differences according to the level
of treatment was not possible to perform. In addition, this is only the third published study on the effect of PTA+SET, in which all have given variable results even though some results are in the same direction. Hence, this intervention should be explored further, however, with greater sample-size, possibly as a multicentre study. Neither of the existing studies reported follow-up results for longer than 12 months; hence, longer-term follow-up is of great importance.

Of the three most frequently mentioned treatment goals for patients with intermittent claudication; to prevent future cardiovascular events and related mortality, to improve functional status and to improve HRQoL, improved HRQoL is getting increased attention as the most important treatment goal and measured outcome. Intermittent claudication is neither life-threatening nor limb-threatening in itself, but it has a considerable impact on the lives of PAD patients. In this study, as in the majority of previous studies of the effect of treatment in patients with intermittent claudication, HRQoL was a secondary outcome. Future studies should strongly consider HRQoL as a primary outcome. However, it is suggested to possibly use a better and more suitable disease-specific HRQoL instrument than the CLAU-S, based on the present experience of a ceiling effect after PTA.

For increased evidence-based knowledge about the effect of this intervention and its clinical relevance, priority should be given to establishing the minimally clinical important values for the most frequently used outcome measurements. There is also a need for additional studies to evaluate the cost-benefit of an interventions that include additional supervised exercise after PTA.
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Twelve-Months Follow-up of Supervised Exercise after Percutaneous Transluminal Angioplasty for Intermittent Claudication: A Randomised Clinical Trial

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Abstract: The aim of this study was to explore the effects during 12 months follow-up of 12 weeks of supervised exercise therapy (SET) after percutaneous transluminal angioplasty (PTA) compared to PTA alone on physical function, limb hemodynamics and health-related quality of life (HRQoL) in patients with intermittent claudication. Fifty patients were randomised to an intervention or a control group. Both groups received usual post-operative care and follow-up measurements at three, six and 12 months after PTA. The intervention group performed 12 weeks of SET after PTA. The control group did not receive any additional follow-up regarding exercise. During the 12 months’ follow-up, the members of the intervention group had significantly better walking distance than the control group. The intervention group had a significantly higher HRQoL score in the physical component
score of the SF-36, and the domains of physical function, bodily pain and vitality. For limb hemodynamics, there was a non-significant trend towards better results in the intervention group compared to the control group. Conclusion: SET after PTA yielded statistically significantly better results for walking distance and HRQoL in the intervention group than the control group during the 12 months of follow-up.

Keywords: exercise; PTA; intermittent claudication; follow-up; randomised clinical trial

1. Introduction

Peripheral arterial disease (PAD) is a condition where atherosclerotic plaques build up in the arteries. With time, the size of the plaque might increase and narrow the lumen of the arteries, consequently limiting the blood flow distal to the affected arterial segment. This flow limitation may cause pain during activity, which is relieved with rest. These symptoms are called intermittent claudication, and they affect approximately 30% of the patients with PAD. PAD itself is present in approximately 20% of people older than 65 years and it increases with age [1]. Because of its high prevalence, high rate of nonfatal cardiovascular ischemic events, high risk of mortality and reduction of quality of life the consequences of PAD are significant [2]. The treatment aim of PAD is to reduce symptoms, improve quality of life and physical function, and prevent further progression and complications. Treatment strategies include lifestyle changes like smoking cessation, exercise, medication and, if necessary, revascularisation, either endovascular or by surgery [1,3,4].

As there is no definitive cure for PAD, prevention of further progression of the disease is of great importance. Previous research and clinical experience have identified several effective treatment options [5–8]. However, the best treatment in terms of costs, the intensity and frequency of the intervention, and the length of health professionals’ involvement is not known [9]. The scarce knowledge on enabling patients to be independent and master their own everyday lives including management of a life-long disease, are also important factors as to why research is still needed in this field [10].

Authors have suggested the relatively new treatment option of supervised exercise training (SET) after percutaneous transluminal angioplasty (PTA) as an important topic for future research [11–13]. The possible advantage of adding SET after PTA is the twofold focus on locally increased blood flow during activity in the treated area and the general effects of exercise, which also influence general risk factor development for further manifestation of cardiovascular disease. However, little is known about the effects of SET after PTA for PAD, particularly for longer-term follow-up. To our knowledge, only two studies on SET following PTA have previously been reported [14,15]. Mazari et al. [15] used a three-month training intervention, and reported statistically significant improvements in walking distance at three months for all the studied treatment arms (PTA alone, SET alone and PTA+SET) with the PTA+SET group performing better than either treatment alone. At 12 months of follow-up, this advantage was not sustained. For HRQoL, statistically significant improvements were reported throughout the 12-month follow-up, though with no difference between the three treatment arms. Kruidenier et al. [14] used a six-month training intervention, but no further follow-up beyond the end of the intervention was
reported. They found an increased walking distance with additional SET after PTA after six months compared to PTA alone. However, no additional improvement in HRQoL was observed.

Thus, the aims of this study were to explore the effects during one year of 12 weeks of SET (not claudicant specific) after PTA and to compare them with those of PTA alone on physical function, limb hemodynamics and HRQoL in patients with severe claudication. We hypothesised that the group offered SET after PTA would have better results in terms of a positive effect on physical function as well as HRQoL and limb hemodynamics.

2. Methods

2.1. Study Design

The study was a blinded, prospective, randomised clinical trial with parallel group design. It followed the Consolidated Standards of Reporting Trials (CONSORT) statement criteria for reporting clinical trials [16].

2.2. Sample and Sample Size Calculation

Recruitment, interventions and data collection were performed at Oslo University Hospital Aker, Oslo, Norway, between March 2010 and June 2013. Patients eligible for participation in this study were patients selected to undergo PTA due to intermittent claudication (Fontaine stage II) after best medical treatment had failed. Best medical treatment consisted of an urgent request of smoking cessation, appropriate medication for lowering lipids and for diabetes mellitus and hypertension if present, and most important, strongly advise to start or continue exercise. A further requirement was availability to return for hospital-based exercise twice weekly for three months. The exclusion criteria were previous PTA on the same leg during the previous two years, a present unsuccessful attempt at PTA, asymptomatic PAD (Fontaine stage I), critical limb ischemia (Fontaine stage III or IV) and reduced walking ability caused by factors other than PAD (i.e., orthopaedic problems, spinal stenosis, angina pectoris or dyspnoea). The lesions were determined by clinical examination, ABI and ultrasound triplex as a part of the assessment by the vascular specialist. If indication for further investigations, the participants were referred to MRA (or CTA if MRA was contraindicated) to better estimate the options for possible endovascular treatment.

Sample size calculation was performed based on the primary outcome Six-Minute Walk Test (6MWT). According to Perera et al. [17] the number needed per group with 80% power for a between-group comparison of a substantial meaningful change in the 6MWT (50 m, standard deviation 50 m) is 13–20, and of a small clinically meaningful change for the 6MWT (20 m, standard deviation 50 m) is 71–115. These numbers are not based specifically on patients with intermittent claudication, however the symptoms of the latter are quite comparable to mild to moderate mobility deficits. We have calculated that with significant level of 5% and keeping statistical power of 80%, we would need 22 patients in each group so that a difference of 30 m or larger would be statistically significantly different from 50 m (a known threshold).
2.3. Ethical Considerations

Approval was obtained from the regional research ethics committee, and written informed consent was obtained from each participant. The study was performed according to the Helsinki Declaration and is registered at ClinicalTrials.gov (NCT01109732).

2.4. Randomisation and Blinding

The participants were stratified according to the treatment site (aortoiliac or femoropopliteal) and randomised into the intervention or control group (ratio 3:2) after the PTA. The ratio 3:2 was chosen with regards to the intervention group’s more demanding effort and therefore possibly a greater drop-out rate in this group. A computer-generated block-randomised list was used together with consecutively numbered and sealed envelopes. The administrative staff prepared the sealed envelopes in advance, and the block size and randomisation list were inaccessible to the project coordinator (E.B.), who enrolled the patients and assigned them to the groups. The assessors were blinded to the group assignment.

2.5. PTA and Post-Operative Care

PTA was performed by a vascular interventional radiologist in accordance with the hospital’s guidelines. Access was gained through puncture of the common femoral artery; retrograde for treatment of lesions in the aortoiliac segment and antegrade for treatment of lesions in the femoropopliteal segment. A six French sheath was introduced. Lesions in iliac arteries were all treated with stents primarily. In femoropopliteal lesions we preformed balloon angioplasty, and implanted stent only in case of flow-limiting dissection or significant residual stenosis. Both groups received post-operative care in agreement with the ward’s usual procedures and were discharged either the same day or on the first post-operative day. The discharging doctor and the responsible nurse gave general advice on the importance of exercise, smoking cessation and diet.

2.6. Intervention

The intervention group received hospital-based SET two days per week for 12 weeks. In addition, the participants conducted one home-based exercise session every week. After the period of hospital-based SET, the participants conducted three home-based exercise sessions every week for an additional 12 weeks.

The SET was based on The Norwegian Ulleval Model [18], a modified cardiac rehabilitation program, and was slightly adjusted to be applicable to this patient group. Each SET session lasted for 60 min and consisted of warm-up exercises, three high-intensity intervals (each lasting for five to ten minutes), two moderate-intensity intervals (each lasting for five to ten minutes) and cool-down exercises, including stretching. The exercises were simple aerobic dance movements and walking, and involved the use of both upper and lower extremities. During walking the participants walked alternating in a circle in the gym, in the corridor or stair climbing. The instructor walked the opposite direction within the circle or close by in the corridor and the stairs to monitor the participants. The exercise intensity was adjusted using the Borg scale of perceived exertion [19] and the beats per minute of the music [18]. During the high-intensity exercises, the participants were motivated to
gradually increase their exercise intensity towards 15–17 on the Borg scale, and during the exercise sessions, the patients informed the instructor of their Borg Scale ratings. The participants also used this scale to monitor the home-based exercise session each week. No extra equipment was required for this program. Each session had between two and twelve participants. The control group did not receive any additional follow-up regarding exercise beyond general advice on the importance of exercise at discharge.

2.7. Assessments at Baseline and Follow-ups

All measurements were taken during a single visit at baseline (prior to the planned PTA) and three, six and 12 months after the PTA.

The primary outcome was a standardised Six-Minute Walk Test (6MWT). The 6MWT was performed in a 30 m pre-marked hospital corridor, and instructions and encouragements were given in accordance with the test’s guidelines [20]. This test is well validated in PAD patients and has shown good reliability in this patient group [21,22].

Secondary outcomes were measurement of physical function, limb hemodynamics and HRQoL. The physical function measurements were pain-free walking distance (PFWD) and maximal walking distance (MWD) on a treadmill (graded protocol, 3.2 km/h constant speed, starting with a 0% incline that increased 2% every two minutes up to 10%) [23]. Treadmill testing is a well-accepted means of testing walking distance for this patient group [4,24] and has shown very high reliability [25]. Limb hemodynamics were measured using the ankle-brachial-index (ABI) (ankle-pressure/arm-pressure) by doppler and pulse volume recording (PVR) on the leg by a pressurized cuff on the leg connected to a plethysmograph (Stranden macrolab, Oslo, Norway). In addition, all participants were measured by triplex ultrasound at baseline and all follow-ups. HRQoL was measured with a generic instrument, the Short Form 36 (SF-36) [26], as well as a disease-specific instrument, the Claudication Scale (CLAU-S) [27]. The SF-36 has previously been used in numerous PAD studies and is recommended as one of the most appropriate generic instruments for this patient group with regard to validity, reliability and responsiveness [28,29]. The eight domains on the SF-36 are physical function, physical role, bodily pain, general health, vitality, social function, emotional role and mental health. The SF-36 raw scores were coded and recalibrated following standard guidelines [26], and the items were then summed and transformed into the eight scales ranging from 0 to 100 (higher scores indicate better quality of life). CLAU-S is a valid instrument [30] and has five subscales: daily life, pain, social life, disease-specific anxiety and psychological well-being. The CLAU-S raw scores were also coded, recalibrated, summed and transformed into the five scales ranging from 0–100 (higher scores indicate better quality of life).

2.8. Statistical Analysis

Continuous data in the tables are described with mean and standard deviation or standard error of the mean (SEM) when normally distributed or with median and range when having a skewed distribution. Categorical variables are presented as numbers and percentages. Crude differences between pairs of categorical variables were assessed with Chi-square tests and with Mann-Whitney Wilcoxon test for continuous variables. Changes over time and differences between groups were analysed using mixed models for repeated measures with group, time and the interaction between time and group being modelled as fixed effects. The dependencies between time points were modelled using
diagonal covariance matrix. \( p \)-values \( \leq 0.05 \) were considered statistically significant and all tests were two-sided. All analyses were conducted using SPSS 20.0 (SPSS Corporation, Chicago, IL, USA).

3. Results

Of the 118 patients potentially eligible for the study, 50 participants were included. Participants who did not meet the inclusion criteria were excluded. The main exclusion reasons were work-related obligations, previous PTA during the previous two years, reduced walking ability due to other factors than PAD and lack of interest to participate in the study. Figure 1 shows the flow of participants through the study. Altogether, six participants underwent re-intervention after three months’ follow-up. Two participants withdrew during follow-up, after three and six months, respectively. One participant died before 12 months follow-up. There were no statistically significant differences between genders at baseline regarding the variables connected to the main outcome. The general participant characteristics are shown in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Participant characteristics at baseline.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention group (n = 29)</strong></td>
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<tr>
<td>Mean</td>
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<tr>
<td>%</td>
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<tr>
<td><strong>Demographics</strong></td>
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<tr>
<td>Age (years)</td>
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<td>Body mass index (kg/m²)</td>
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<td>Gender (men)</td>
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<td>Marital status (married)</td>
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<tr>
<td>Years of school (&gt;9 years)</td>
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<td><strong>Blood status</strong></td>
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<tr>
<td>Total cholesterol (mmol/L)</td>
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<td>HDL (^1) (mmol/L)</td>
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<td>LDL (^1) (mmol/L)</td>
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<tr>
<td>Triglycerides (mmol/L)</td>
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<td>HbA1c (^1) (%)</td>
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<tr>
<td><strong>Smoking status</strong></td>
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<tr>
<td>Have never smoked</td>
</tr>
<tr>
<td>Used to smoke</td>
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<tr>
<td>Currently smoke</td>
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<tr>
<td><strong>Current medication</strong></td>
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<td>Statins</td>
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<td>Anticoagulants</td>
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<td>Hypertension</td>
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<td>Diabetes</td>
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<tr>
<td>COPD</td>
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<tr>
<td><strong>Previous cardiovascular events</strong></td>
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<td>Myocardial infarction</td>
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<tr>
<td>Stroke/TIA (^1)</td>
</tr>
<tr>
<td>Peripheral arterial surgery or endovascular treatment</td>
</tr>
</tbody>
</table>

\(^1\) HDL = high-density lipoproteins; LDL = low-density lipoproteins; HbA1c = hemoglobin A1c; COPD = chronic obstructive pulmonary disease; TIA = transient ischemic attack.
Figure 1. CONSORT flow chart of the study.

Assessed for eligibility (n=128)

Excluded (n=68)
- Not meeting inclusion criteria: 41
- Declined to participate: 27

Baseline testing and PTA (n=50)

Aortoiliac lesions (n=25)

Intervention group (n=15)
- Hospital-based SET
  - Received allocated intervention (n=14)
  - Did not receive allocated intervention (n=1)
  - Lost to 3 months follow-up (n=0)
  - 3 months follow-up (n=15)
  - Lost to 6 months follow-up (n=0)
  - 6 months follow-up (n=15)
  - Lost to 12 months follow-up (n=0)
  - 12 months follow-up (n=15)

Control group (n=10)
- Standard care without SET
  - Received allocated intervention (n=10)
  - Lost to 3 months follow-up (n=0)
  - 3 months follow-up (n=10)
  - Lost to 6 months follow-up (n=0)
  - 6 months follow-up (n=10)
  - Lost to 12 months follow-up (n=1)
  - 12 months follow-up (n=9)

Intervention group (n=14)
- Hospital-based SET
  - Received allocated intervention (n=12)
  - Did not receive allocated intervention (n=2)
  - Lost to 3 months follow-up (n=0)
  - 3 months follow-up (n=14)
  - Lost to 6 months follow-up (n=4)
  - Retreated with PTA: 4
  - 6 months follow-up (n=10)
  - Lost to 12 months follow-up (n=2)
  - Dead: 1
  - 12 months follow-up (n=10)

Control group (n=11)
- Standard care without SET
  - Received allocated intervention (n=11)
  - Lost to 3 months follow-up (n=0)
  - 3 months follow-up (n=11)
  - Lost to 6 months follow-up (n=3)
  - Retreated with PTA: 2
  - 6 months follow-up (n=8)
  - Lost to 12 months follow-up (n=0)
  - 12 months follow-up (n=8)
3.1. Physical Function

Physical function measured by walking distance (6MWT, MWD and PFWD) showed a statistically significant difference between the two groups at the 12-month follow-up ($p = 0.005$, $p < 0.001$, $p = 0.014$, respectively). The intervention group showed a greater change in walking distance than the control group (Table S1 and Figure 2). In the 6MWT, both groups achieved a statistically significant increase in walking distance at three months’ follow-up. The intervention group continued to increase in walking distance up to 12 months’ follow-up, while the control group showed a decrease in walking distance from three to six months and then maintained this level at 12 months. For the MWD and PFWD, the progress followed the same pattern in both groups: an increase up to six months and maintaining the same level from six to 12 months. When analysed as percentage mean change from baseline to 12 months, the mean change of 6MWD was 23% and 15% in the intervention group and the control group, respectively. For the MWD the percentage mean change from baseline was 107% in the intervention group and 96% in the control group, and for the PFWD the percentage mean change from baseline was 346% in the intervention group and 293% in the control group.

Figure 2. Walking distance. Values are mean, error bars indicate ±SEM. m = metres.
3.2. Limb Hemodynamics

Regarding the limb hemodynamics, as measured by the ABI and PVR, both groups significantly increased from baseline to three months, which was expected due to the nature of the endovascular treatment. For both the ABI and the PVR, there was a statistical trend ($p < 0.10$) towards better results in the intervention group compared to the control group, but the results were not statistically significantly different between the two groups during the 12 months of follow-up ($p = 0.061$ and $p = 0.077$, respectively) (Figure 3).

Figure 3. Limb hemodynamics. Values are mean, error bars indicate ±SEM. mm = millimetres.

3.3. HRQoL

HRQoL measured using SF-36 showed a statistically significant difference between the two groups during the 12 months of follow-up for the domains physical function ($p = 0.018$), bodily pain ($p = 0.007$) and vitality ($p = 0.029$) (Figure 4). The same was true of the SF-36 physical component score ($p = 0.004$) (Figure 5), in contrast to the lack of a statistically significant difference in the SF-36 mental component score ($p = 0.513$). The domains that had statistically significant differences between the groups were also the ones with the lowest scores at baseline. The remaining domains showed no statistically significant difference between the groups during the follow-up.
Figure 4. SF-36 domain scores. A score of 0 represents the worst possible health, and 100 represents the best possible health. SF-36 = Short Form-36 Health Survey. Values are mean, error bars indicate ±SEM.

Figure 5. SF-36 component scores. A score of 0 represents the worst possible health, and 100 represents the best possible health. SF-36 = Short Form-36 Health Survey. Values are mean, error bars indicate ±SEM.
The pain score of CLAU-S was statistically significantly different between the two groups during the 12 months of follow-up ($p = 0.011$). Regarding the daily life domain, there was a statistical trend ($p < 0.01$) towards a statistically significant difference ($p = 0.080$). The remaining three domains (social life, disease specific anxiety and psychological well-being) did not show any significant difference during the 12 months of follow-up ($p = 0.141–0.443$) (Figure 6). Regarding the results of the CLAU-S, most domains showed a ceiling effect (>20% scored the highest possible score) [31] at follow-up. The exceptions were the domains pain at three months, daily life at 12 months and psychological well-being at three, six and 12 months. The social life domain showed a ceiling effect at baseline and all three follow-ups.

**Figure 6.** CLAU-S domain scores. A score of 0 represents the worst possible health, and 100 represents the best possible health. CLAU-S = the Claudication Scale. Values are mean, error bars indicate ±SEM.
3.4. Medication and Adverse Events

There were only minor changes of medication during follow-up. No major adverse events associated with the prescribed follow-up were observed.

4. Discussion

The main finding in the present study was significantly better walking distance in the intervention group than for the control group during the 12 months of the study. With regards to HRQoL, the intervention group had a significantly better score in the physical component of the SF-36, which also mirrors their significantly better results of the physical function, bodily pain and vitality domains. For limb hemodynamics, there was a trend towards better results in the intervention group compared to the control group; however, the results were not statistically significantly different between the two groups during the 12 months of follow-up.

A statistically significant improvement from baseline has been reported for walking distance, limb hemodynamics and HRQoL at three months follow-up for the present study population, with no statistically significant difference between the two groups [32]. From three to 12 months, the differences for most of the outcomes increased between the groups. At three months, it might be reasonable to think that both groups were strongly influenced by the initial known effect of PTA, more than any additional effect of SET. However, from three months onwards, as the differences increased, the hypothesised effects of SET after PTA seemed to come to pass, and this effect remained even at 12 months. Differences in HRQoL seem to develop later after exercise interventions compared to other outcomes, specifically more physical outcomes such as walking distance and limb hemodynamics [33,34]. In the present study the inter-group differences in HRQoL were greater after three months than at three months, but even so, HRQoL showed less improvement than walking distance and limb hemodynamics.

Determining clinical significance is difficult for patients with intermittent claudication as the disease impact their HRQoL differently. However, a study on older adults with mild to moderate mobility deficits [17] has a suggested recommendation for a substantial clinical meaningful change for the 6MWT of 50 m and a small clinical meaningful change for the 6MWT of 20 m. These numbers are not based specifically on patients with intermittent claudication, however the symptoms of the latter are quite comparable to mild to moderate mobility deficits. In the present study the mean change from baseline to 12 months of the 6MWT were 97m and 65m for the intervention group and the control group, respectively, and therefore most likely clinically significant for both groups. In addition, the mean changes from baseline to 12 months in the treadmill measures of walking distance were even greater, which strengthens the picture of the clinical significance of this intervention. When analysed with regards to percentage change, the mean change from baseline to 12 months was about 100% for both MWD and PFWD in both groups. Unfortunately, no minimal clinically important difference of change for neither maximal- nor pain-free walking distance on treadmill has been established for patients with intermittent claudication [35] so clear comparisons were not possible.

The present study’s results differ somewhat from Mazari et al. [15] and Kruidenier et al. [14]. Mazari et al. found PTA+SET to be more effective at three months’ follow-up than PTA or SET alone, but this effect was not sustained at 12 months. Possible explanations for this disparity between the
studies might be the use of different treadmills and exercise protocols. The present study had a treadmill protocol with a time-cap of 30 minutes (1,600 m), whereas Mazari et al. used a treadmill protocol of a maximum of five minutes (215 m), which most likely did not cover the expected progress of these participants after PTA. The exercise protocol in the present study was a generic, not claudicant-specific, protocol, unlike the protocol of Mazari, which was claudicant specific. In addition, Mazari et al. did not report on the patients’ exercise after three months. We strongly encouraged the participants to perform further home-based exercise for another three months after the three months of hospital-based SET sessions.

Kruidenier et al. reported better results at three months’ follow-up compared to the present study. The good results for walking distance after SET+PTA were maintained at six months’ follow-up, but they did no further follow-up beyond six months, so whether the results were sustained is unknown. Compared to the present study, the development from baseline to three months was different, but the results were quite similar at six months. Kruidenier et al. observed no difference in HRQoL between the groups at three or six months. In contrast, we observed significant differences between the groups with regards to three domains and the physical component score during the 12 months of follow-up. The exercise protocol of Kruidenier et al. was claudicant specific such as that of Mazari et al. The exercise intervention in Kruidenier et al. was community-based, as opposed to the present exercise intervention, which was hospital-based. The community-based setting, however, might be a more realistic option than a hospital-based intervention because, for instance, transportation costs may be reduced.

We want to point out one specific result in the present study; the possible increased results of the intervention after cessation of the hospital-based SET. Participants in the intervention group increased particularly their walking distance, and they maintained and even somewhat improved their limb-hemodynamics parameters. In terms of HRQoL, we also observed the same trend. Limited data exist on how to maintain an achieved exercise behaviour, and, the most efficient means of action are inconclusive [10]. Potential reasons for the results of the present study may be that participants in the intervention group incorporated new or better habits of exercise and physical activity into their daily life routine during the first three months and continued, as they were encourage to do for the next three months in particular. They may also have felt more secure with regards to activities they could and should do safely by supervision they received during the first three months [36]. In addition, they may have felt and observed the effect of the effort they put into the exercise over the weeks that the intervention lasted and become inspired to continue. The exercises of the intervention were deliberately simple and easy to transfer to other settings for further usage.

Our study has limitations that need to be addressed. A great portion of the CLAU-S domains showed a ceiling effect early in the follow-up, and one domain even did at baseline, and this outcome measure did not capture the possible progress of the HRQoL in these participants. The exercise intervention was hospital-based, which may limit its generalisability. The sample size was small, however, the majority of our results reached the level of statistical significance. Due to limited sample size we have not had acceptable statistical power to do separate analysis based on treatment level with sufficient precision in the estimate. Therefore, we chose to stratify the participants by the level of the obstruction before randomization into the two groups to be sure that the groups were as similar as possible at baseline. The results of this study do not elucidate the potential difference in the effect of
SET after PTA at the aortoiliac- or femoropopliteal level. Our results may therefore be viewed as preliminary with regards to this issue, and should be focused on in future studies. The strength of our study is its design and its inclusion of the trajectories of several measures of physical function, HRQoL and limb hemodynamics.

5. Conclusions

In this study, SET after PTA for intermittent claudication yielded statistically significantly better results during 12 months’ follow-up on walking distance and the more physical components of HRQoL compared to PTA alone. In addition, there was a trend towards better results for limb-hemodynamics in the intervention group. These findings are an important contribution to the evidence-based knowledge of efficient treatment for intermittent claudication, particularly the emerging data on the effect of offering SET after PTA. However, this is based on a small sample size and therefore our results should be interpreted with caution and confirmed in future research. Future research should also include longer follow-up to be able to observe more long term benefits of SET. In addition, we recommend including health-economic analyses to plan the appropriate treatments and evaluate treatment efficacy, as limited economic means is a restricting factor for health services in general, and for non-life-threatening conditions in particular.

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Conflicts of Interest

The authors report no conflicts of interests.

References


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**Twelve-Months Follow-up of Supervised Exercise after Percutaneous Transluminal Angioplasty for Intermittent Claudication: A Randomised Clinical Trial**

Table S1. Observed baseline and follow-up measurements.

<table>
<thead>
<tr>
<th>Physical function</th>
<th>Sample size</th>
<th>Mean value at baseline (95% CI)</th>
<th>Mean value at 3 months (95% CI)</th>
<th>Mean value at 6 months (95% CI)</th>
<th>Mean value at 12 months (95% CI)</th>
<th>Mean change: 12 months minus baseline (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>6 MWT (m)</em></td>
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<td></td>
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<tr>
<td>Intervention group</td>
<td>28</td>
<td>412 (375.7–448.3)</td>
<td>492.4 (460.6–524.2)</td>
<td>502.1 (468.9–535.4)</td>
<td>513.7 (482.9–544.5)</td>
<td>96.8 (68–125.7)</td>
</tr>
<tr>
<td>Control group</td>
<td>21</td>
<td>407.2 (362.5–453)</td>
<td>480.2 (445.1–515.2)</td>
<td>456.3 (406.8–505.8)</td>
<td>458.1 (407.8–508.3)</td>
<td>64.2 (20.1–108.4)</td>
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<tr>
<td><em>MWD treadmill (m)</em></td>
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<td></td>
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<tr>
<td>Intervention group</td>
<td>26</td>
<td>398.6 (289.3–507.8)</td>
<td>657.5 (499.2–815.8)</td>
<td>831.8 (604.3–1059.3)</td>
<td>876 (654.9–1097.1)</td>
<td>429.5 (233.7–625.4)</td>
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<tr>
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<td>21</td>
<td>284.6 (191.5–377.6)</td>
<td>445.5 (330.8–560.1)</td>
<td>513.1 (368.7–657.5)</td>
<td>516.9 (324.5–709.4)</td>
<td>274.7 (116.6–432.9)</td>
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<td><em>PFWD treadmill (m)</em></td>
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<td>163.5 (113–214)</td>
<td>480.2 (242.5–717.9)</td>
<td>698.4 (355.8–1041)</td>
<td>705.9 (475.8–936)</td>
<td>566.7 (344.3–789)</td>
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<td>20</td>
<td>137.3 (77.5–197.1)</td>
<td>250.6 (61–440.3)</td>
<td>476.9 (297.4–656.4)</td>
<td>460.9 (223.8–698)</td>
<td>402.3 (168.4–636.2)</td>
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<td><em>Limb hemodynamics</em></td>
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<td><em>Ankle Brachial Index (%)</em></td>
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<tr>
<td>Intervention group</td>
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<td>58.9 (53.2–64.6)</td>
<td>92 (85.7–98.2)</td>
<td>93.3 (87.8–98.9)</td>
<td>91.9 (85.8–97.9)</td>
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<td>57.2 (50–64.3)</td>
<td>89.6 (81.9–97.2)</td>
<td>87.3 (76.7–97.7)</td>
<td>84.9 (74.7–95)</td>
<td>29.8 (20.4–39.2)</td>
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<td><em>Pulse Volume Registration (mm)</em></td>
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<td>10.1 (9–11.1)</td>
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<tr>
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<td>20</td>
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