Physical activity and exercise in patients with intermittent claudication

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“If you can’t measure something, you can’t understand it. If you can’t understand it, you can’t control it. If you can’t control it,
you can’t improve it.”

H. James Harrington (1929-)

To Jakob, Moa and Clara

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ABSTRACT

Introduction. Supervised exercise is a guideline recommendation in patients with intermittent claudication (IC). As the availability of supervised exercise varies, interest has turned to the more accessible home-based exercise programmes. However, the reported effects of home-based exercise programmes are inconsistent and there are knowledge gaps in terms of studies evaluating effectiveness of both supervised and home-based exercise programmes over longer time periods as compared to unsupervised walk advice (WA) alone. There is also a need to evaluate health-related quality of life (HRQoL) and daily physical activity during an exercise intervention. Walk tests are important for the objective assessment of walking ability, but the measurement properties of the 6-minute walk test have scarcely been studied in IC.

The overall aim of this thesis was to evaluate the effectiveness of unsupervised WA alone or in combination with a hospital-based supervised exercise programme (SEP) or a home-based structured exercise programme (HSEP) on walking ability, muscle endurance, HRQoL, self-reported physical function and daily physical activity and to study the test-retest reliability and agreement of the 6-minute walk test in patients with IC.

Methods. Papers I-III originate from the SUNFIT trial (Supervised or UNsupervised exercise training For Intermittent claudication), a three-armed, multi-centre, randomised clinical trial including patients with IC. Papers I-III aimed to evaluate the effectiveness of an SEP, HSEP and WA on: I) walking ability and muscle endurance, II) generic (Short-Form 36 (SF-36) and disease-specific (Vascular Quality of life Questionnaire (VascuQoL) HRQoL and self-reported physical function and III) daily physical activity assessed with an accelerometer. Paper IV was a reliability and agreement study of the first 100 patients who enrolled the SUNFIT trial at Sahlgrenska University Hospital and performed the 6-minute walk test twice at baseline.

Main results. A total of 166 patients with IC (mean age: 72.1 (SD 7.4) years, 41% women) were included in Papers I-III. Paper I confirmed that an HSEP was non-inferior to an SEP, but that none of these interventions was significantly better than WA alone. In Paper II, no significant between-group differences were observed over time in generic HRQoL, while significant between-group differences were observed in disease-specific HRQoL in for example: at one-year in the domain Social (non-significant post hoc tests) and at six months in Summary score (favour SEP vs. WA) and in the domain Pain (favour SEP vs. both HSEP and WA). A significantly higher proportion of patients in the SEP reached the minimally important difference threshold for improvement in the VascuQoL Summary score at one year. Paper III showed no significant between-group differences at one year in any of the outcomes of accelerometer-measured physical activity. Paper IV demonstrated that the 6-minute walk test has excellent test-retest reliability, with a minimal detectable change at 46 m.

Conclusions. An HSEP was shown to be non-inferior to an SEP, but no significant differences were observed at one year between an HSEP, SEP and WA, in terms of the 6-minute walk test maximum and pain-free walking distance, muscle endurance or daily physical activity. In the VascuQoL, a few of the domains and Summary score reached a significant between-group differences over time and a significantly higher proportion of patients in the SEP reached the minimally important difference threshold for improvement in the VascuQoL Summary score at one year. This study is limited by low exercise adherence to the HSEP and SEP. As such, there is a need for future studies to assess the optimal exercise intervention to improve outcomes in this population. The 6-minute walk test has excellent test-retest reliability in patients with IC and can be recommended for use in clinical patient evaluation and as an important endpoint in clinical trials.

Keywords: accelerometry, Nordic walking, peripheral artery disease, quality of life, reproducibility of result, walk test

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SAMMANFATTNING PÅ SVENSKA

Bakgrund: Internationella riktlinjer rekommenderar handledd fysisk träning för patienter med claudicatio intermittents (CI). Eftersom tillgängligheten till denna träningsform är låg har intresset för att utvärdera de mer tillgängliga strukturerade hembaserade träningsprogrammen ökat. Dock är de rapporterade effekterna från studier på hembaserad fysisk träning inkonsekventa och det finns flera kunskapsluckor. Det saknas studier som utvärderar effekten av både handledd och hembaserad fysisk träning över längre tid samt som dessutom jämför de två träningsuppläggen med ytterligare en grupp, som enbart får råd om att gå ut och gå. Fler kunskapsluckor i samband med träning gäller behovet att utvärdera hälsorelaterad livskvalitet och daglig fysisk aktivitet. Dessutom, för att objektivt bedöma gångförmåga hos patienter med CI, är gångtest viktiga. Dock är mätegenskaperna hos sex-minuters gångtest dåligt studerade hos patienter med CI.
Det övergripande syftet med denna avhandling var att utvärdera effekterna av gångråd eller, gångråd i kombination med sjukhusbaserad handledd fysisk träning eller hembaserad strukturerad fysisk träning. De studerade utfallsmåtten var gångförmåga, muskeluthållighet, hälsorelaterad livskvalitet, patientrapporterad fysisk funktion och daglig fysisk aktivitet. Avhandlingen syftade även att studera test-retest reliabilitet och överensstämmelse hos sex-minuters gångtest för patienter med CI.

Metod: Delarbete I-III baseras på SUNFIT-studien (Supervised or UNsupervised exercise training For Intermittent claudicaTion), som var en trearmad, multicenter, randomiserad klinisk studie som inkluderade patienter med CI. Delarbete I-III syftade till att utvärdera effekterna av gångråd, gångråd + sjukhusbaserad handledd fysisk träning och gångråd + hembaserad strukturerad fysisk träning på: I) gångförmåga (sex-minuters gångtest) och muskeluthållighet, II) generisk (SF-36) och sjukdomsspecifik (VascuQoL) hälsorelaterad livskvalitet och patientrapporterad fysisk funktion och III) daglig fysisk aktivitet mätt med en accelerometer. Delarbete IV studerade test-retest reliabilitet hos sex-minuters gångtest genom att låta de första 100 patienterna som rekryterades till SUNFIT-studien vid Sahlgrenska Universitetssjukhuset, utföra 6-minuters gångtest två gånger vid baslinjen.

Resultat: Sammanlagt inkluderades 166 patienter med CI (medelålder: 72,1 (SD 7,4) år, 41% kvinnor) i SUNFIT-studien. De tre grupperna var lika vid baslinjen. Delarbete I bekräftade att hembaserad strukturerad fysisk träning inte var sämre än sjukhusbaserad handledd fysisk träning, men att ingen av dessa träningsinterventioner var signifikant bättre än gruppen som enbart fick gångråd. I delarbete II observerades inga signifikanta skillnader mellan de tre grupperna, avseende SF-36 eller patientrapporterad fysisk funktion. Signifikanta skillnader mellan grupperna observerades i VascuQoL. (VascuQoL består av fem domäner (aktivitet, smärta, emotionellt, social och symtom) samt en summerad poängskala.) Bland annat observerades signifikanta skillnader: vid ett år i social (dock var post-hoc testerna ickesignifikanta) samt vid sex månader i den summerade poängskalan (med fördel sjukhusbaserad handledd träning vs. gångråd) och i smärta (med fördel sjukhusbaserad handledd träning jämfört med både hembaserad strukturerad träning och gångråd). Delarbete III visade inga signifikanta skillnader mellan de tre grupperna i daglig fysisk aktivitet vid ett år. Delarbete IV visade att sex-minuters gångtestet har utmärkt test-retest reliabilitet och en minsta detekterbar förändring på 46 m.

Slutsats: Hembaserad strukturerad fysisk träning visade sig inte vara sämre än sjukhusbaserad handledd fysisk träning för patienter med CI. Det fanns inga signifikanta skillnader vid ett år mellan hembaserad strukturerad fysisk träning, sjukhusbaserad handledd fysisk träning eller gruppen som enbart fick gångråd, när det gäller maximal eller smärtfri gångsträcka vid sex-minuters gångtest, muskeluthållighet eller daglig fysisk aktivitet. I sjukdomsspecifik hälsorelaterad livskvalitet observerades en signifikant skillnad mellan grupperna hos några av domänerna och den summerade poängskalan över tid. Denna studie begränsas av låg följsamhet till de båda tränings-interventionerna och framtida studier behöver utvärdera vilken som är den optimala träningsmodellen för den här patientgruppen. Sex-minuters gångtest har utmärkt test-retest reliabilitet för patienter med CI och kan rekommenderas för att utvärdera gångsträcka både i klinik och som ett viktigt utfallsmått i kliniska studier.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Sandberg A, Bäck M, Cider Å, Jivegård L, Sigvant B, Wittboldt S, Nordanstig J. Effectiveness of supervised exercise, home-based exercise or walk advice strategies on walking performance and muscle endurance in patients with intermittent claudication (SUNFIT trial)-a randomized clinical trial. European Journal of Cardiovascular Nursing. *Accepted for publication August 2, 2022.*

II. Sandberg A, Bäck M, Cider Å, Jivegård L, Sigvant B, and Nordanstig J. Impact of walk advice alone or in combination with supervised or home-based structured exercise on patient-reported physical function and generic and disease-specific health-related quality of life in patients with intermittent claudication, a secondary analysis in a randomized clinical trial. *In manuscript*

III. Sandberg A, Nordanstig J, Cider Å, Jivegård L, Hagströmer M, Bäck M. The impact of walk advice and exercise strategies on daily physical activity in patients with intermittent claudication, a randomized clinical trial. *Submitted*

IV. Sandberg A, Cider Å, Jivegård L, Nordanstig J, Wittboldt S, Bäck M. Test-retest reliability, agreement, and minimal detectable change in the 6-minute walk test in patients with intermittent claudication. Journal of Vascular Surgery. 2020;71(1):197-203.

CONTENT

ABBREVIATIONS

6MWT	Six-Minute Walk Test
ABI	Ankle-Brachial Index
FITT-VP	Frequency, Intensity, Type, Time, Volume and Progression
IC	Intermittent Claudication
ICC	Intra-class Correlation Coefficient
HSEP	Home-Based Structured Exercise Programme
HRQoL	Health-Related Quality of Life
MDC	Minimal Detectable Change
PAD	Peripheral Artery Disease
PROM	Patient-Reported Outcome Measurements
PSFS	Patient-Specific Functional Scale
SEM	Standard Error of Measurement
SEP	Hospital-based Supervised Exercise Programme
SF-36	Short-Form 36
SUNFIT	Supervised or UNsupervised exercise training For Intermittent claudicaTion
VascuQoL	Vascular Quality of life Questionnaire
WA	Walk Advice
WIQ	Walking Impairment Questionnaire

DEFINITIONS IN SHORT

Agreement	The degree to which scores or ratings are identical (1)
Exercise	Physical activity that is planned, structured, repetitive, and purposive to improve or maintain components of physical fitness (2)
Exercise adherence	The extent to which a patient acts in accordance with the advised interval, exercise dose, and exercise dosing regimen (3)
Health-related quality of life	Can be described as a multidimensional concept that includes domains related to physical, mental, emotional, and social functioning and focuses on the impact that health status has on quality of life (4)
Home-based structured exercise	Self-directed exercise with guidance from a qualified healthcare provider (a physiotherapist in the Swedish setting), that takes place in a personal setting (5)
Intermittent claudication	Exertional calf pain that does not begin at rest, does not resolve during walking activity, but resolves within 10 minutes of rest (6)
Intraclass correlation coefficient	Reflects the average correlation between all possible ordering of pairs and varies from 0 to 1, where 1 corresponds to perfect reliability (7)
Minimal detectable change	The extent to which a significant change in an individual's status is reflected in the observed values of a test (8)
Non-inferiority trial	To evaluate a new treatment against an accepted and effective treatment with the goal of demonstrating that the new treatment is at least almost as good (not inferior) i.e. within a pre-determined acceptable non-inferiority margin (9)
Physical activity	Any bodily movement produced by skeletal muscles that results in energy expenditure (2)
Physical fitness	A set of attributes that people have or achieve which consists of skill-related and health-related fitness. Skill-related fitness includes: agility, balance, coordination,

	speed, power and reaction time. Health-related fitness includes: cardiorespiratory endurance, muscular endurance, muscular strength, body composition and flexibility (2)
Physical function	The capacity of an individual to carry out the physical activities of daily living. Physical function reflects motor function and control, physical fitness, and habitual physical activity (10)
Standard error of measurement	Describes the within-subject variability attributable to repeated measurements and is an indication of the precision of a score and is calculated with the confidence interval (11)
Structured exercise programme	Planned programme that provides individualised recommendations for type, frequency, intensity, and duration of exercise and recommendations for progression so that the body is consistently challenged to increase intensity as functional status improves over time. There are two types of structured exercise programme for patients with intermittent claudication: Supervised exercise and Home-based structured exercise (5)
Supervised exercise	Exercise directly supervised by a qualified healthcare provider (a physiotherapist in the Swedish setting), that takes place in hospital or at an outpatient facility (5)
Test-retest reliability	A method used to establish whether a test is capable of measuring a variable with consistency, meaning that repeated measurement should produce the same results when the testing conditions remain unchanged (8)

1 INTRODUCTION

The Latin word *claudicare,* means “to limp” and is the term from which claudication originates. The history of claudication began in 1831 and it was then primarily described in horses by a French veterinarian (12). In 1846, Brodie described classical claudication in humans (13). In 1858, the French neurologist Charcot introduced the term and diagnosis of *intermittent claudication* (IC) in patients (14). Intermittent claudication is the most common symptom in peripheral artery disease (PAD) and IC is consistently induced by exercise (usually walking) causing fatigue, discomfort, cramping, or pain of vascular origin in the muscles of the lower extremities (5) and thus limit walking ability in this patient population (15).

The early treatment recommendations in patients with IC included bedrest and the avoidance of physical activity (16). This approach had changed by 1966 when Larsen and Lassen (17) conducted the first exercise study in patients with IC. The exercise intervention consisted of six months of daily one-hour intermittent walking until maximum leg pain was experienced. The result showed positive effects on walking ability in the exercise group as compared with control treated with placebo tablets. In Sweden, one of the first hospital-based supervised exercise (SEP) studies was conducted in 1974 by Dahllöf et al. (18). Patients with IC were randomised to either an intervention that received an SEP or to control treated with placebo tablets. The exercise programme included dynamic leg exercise and was performed for 30 min, three times a week for six months. The exercise group showed increased walking ability as compared with control and the observed walking improvements correlated with metabolic activity of the skeletal muscle and not blood flow. Over the years, a great deal of research on the effects of exercise on IC limping symptoms has been conducted, resulting in strong evidence of the efficacy of SEP. Today, supervised exercise is regarded as a cornerstone in IC treatment and is a guideline recommendation for patients with IC for improving walking ability and physical function (5, 19).

1.1 ATHEROSCLEROSIS

Atherosclerosis is an endothelial systemic arterial disease that forms the common underlying pathophysiology for important cardiovascular health problems such as coronary artery disease, PAD and cerebrovascular/carotid artery disease (20). Briefly, deposits of lipid, inflammatory cells, fibrous elements and subsequent calcification within the vessel wall of large and medium-sized arteries lead to the progressive formation of atherosclerotic plaques that may in turn cause narrowing of the arterial lumen (21) hindering blood flow and ultimately leading to tissue ischaemia (22). Established atherosclerotic plaques may also become unstable, with the rupture of the fibrous cap and subsequent exposure of the underlying lipid-rich core, leading to the activation of the coagulation cascade. These unstable plaques may thus cause an acute arterial occlusion and are the underlying cause of severe cardiovascular complications such as myocardial infarction, ischaemic stroke, acute limb ischaemia and cardiovascular death. Cardiovascular diseases remain the worldwide leading cause of death (22, 23).

The progress of atherosclerosis is often slow, may affect several arterial beds and most people remain asymptomatic for years. The clinical presentation of atherosclerosis can be acute or chronic and differs depending on the affected vascular bed. When atherosclerosis affects the peripheral arteries, it can cause IC but also lower limb ulceration or even gangrene with a high risk of lower limb amputation (22).

There are several risk factors for developing atherosclerosis, they include an unhealthy diet, physical inactivity, dyslipidaemia, hyperglycaemia, hypertension, obesity, male gender, and age. Moreover, smoking is an independent and powerful risk factor for atherosclerosis. The chemical smoke components have high oxidative and inflammatory potentials that immediately cause damage to the endothelium and initiate an inflammatory response (21).

The prognosis of atherosclerosis can be improved through primary and secondary prevention that include appropriate lifestyle changes and different pharmacotherapies that lower the risk of thrombotic complications and/or target the aforementioned modifiable risk factors (22).

1.2 PERIPHERAL ARTERY DISEASE AND INTERMITTENT CLAUDICATION

Definition

Peripheral artery disease is primarily caused by atherosclerotic stenosis or the occlusion of the arteries that supply the lower extremities (24). The severity of PAD ranges from being asymptomatic, to IC and at the most severe end of the clinical spectrum, chronic limb-threatening ischaemia with rest pain, ulcers and/or gangrene that may lead to lower limb amputation (25). The clinical stages of PAD can be classified using the Rutherford classification, presented in Table 1 (26). Importantly, while most individuals with PAD remain asymptomatic, IC is the most common and often the first clinical PAD symptom (24). Intermittent claudication is defined as exertional calf pain that does not begin at rest, does not resolve during walking activity, and resolves within 10 minutes of rest (6). Intermittent claudication can be unilateral or bilateral and occurs in the buttock, thighs or calves depending on the location of arterial obstruction (24), but the intensity of the symptoms may differ between patients who have a comparable level of disease progression (19). The severity of IC (Table 1) can be related to walking ability and can be further evaluated using a standardised treadmill walking test. Patients qualify as having severe claudication if they are unable to complete five minutes of treadmill walking, as a result of IC-related pain (26).

Table 1. The Rutherford classification of the clinical stages of PAD (26)

Category	Symptoms
0	Asymptomatic
1	Mild claudication
2	Moderate claudication
3	Severe claudication
4	Ischemic rest pain
5	Minor tissue loss
6	Major tissue loss

Prevalence

Peripheral artery disease is a major global health challenge and, in 2015, the prevalence of PAD was approximately 6 % (> 230 million), in people aged ≥ 25 years (27). An increasing trend in the prevalence of PAD is to be expected

in future decades, due to the continuing ageing process. In low- and middle-income countries, women run a statistically higher risk of developing PAD than men, but, in high-income countries, no significant gender difference in the prevalence of PAD is observed (27). In Sweden, the prevalence of PAD and IC among individuals aged 60 to 90 years was 18% and 7% respectively in 2007 (median age 71 years) (28). About a third of patients with PAD have symptoms of IC (5).

Pathogenesis

In PAD, complex mechanisms cause IC and involve reduced limb perfusion, systemic inflammation, vascular dysfunction, impaired angiogenesis, decreased microcirculatory flow and skeletal muscle dysfunction (29). One key mechanism of the walking limitation in IC is the reduced blood flow and oxygen delivery to the working muscle in the leg(s) that leads to muscle ischaemia while walking. In the longer term, the pathophysiological muscle responses lead to tissue damage, endothelial dysfunction and muscle metabolic abnormalities that further reduce exercise capacity (20). In response to the ischaemia, collateral arteries may expand to provide alternative blood flow around the affected artery. This early compensatory mechanism is known as arteriogenesis (30).

Co-morbidities and risk factors

Peripheral artery disease is associated with an increased risk of coronary and cerebrovascular disease morbidity and mortality (31). Advanced age, smoking (current and former), hypertension, diabetes mellitus, coronary heart disease, stroke, increasing waist circumference and high circulating levels of the inflammatory marker C-reactive protein (CRP) increase the risk of developing PAD (27). Smoking at least doubles the risk of developing PAD as compared with non-smokers (31) and there is a strong dose-response relationship between pack-years of smoking and the PAD risk (32). Smoking cessation is associated with lower rates of cardiovascular ischemic events, the risk of amputation and mortality in patients with PAD (5) and quit smoking may significantly improve walking distance in patients with IC (33). Additionally, it takes more than 20 years of smoking cessation to reduce the level of PAD risk to that of individuals (men) who have never smoked (32). Hypertension is strongly associated with PAD but the relative risk of developing PAD is less for hypertension than for smoking or diabetes (25). The strongest risk factors for IC are smoking, diabetes mellitus and advanced age (24). In patients with diabetes mellitus, the risk of IC is about twice as high compared with those without diabetes (25).

Diagnosis

According to PAD guidelines, the clinical assessment for PAD includes an evaluation of the patient's medical history, a review of leg symptom, and a physical examination that includes the palpation of lower extremity pulses and the inspection of legs and feet (5, 19). In addition, the main diagnostic test for PAD is the resting ankle-brachial index (ABI). The ABI is the ankle pressure in each leg divided by the brachial pressure. Patients with an ABI of ≤ 0.90 are diagnosed with PAD. Patients with an ABI on the borderline of 0.91-0.99 should undergo further ABI testing during exercise. Values of ≥ 1.40 are abnormally high and indicate that the arteries could not be compressed during measurements of ankle pressure due to media sclerosis (e.g. in diabetes mellitus and/or advanced chronic kidney disease) (5, 19). A treadmill test can also be used for objective functional assessment and to evaluate moderate stenosis (19). Different protocols can be applied and the test ends when the patient is unable to walk further because of maximum pain. This is the patient's maximum walking distance. A post-exercise ankle systolic blood pressure decrease of > 30mmHg or a postexercise ABI decrease of > 20% are diagnostic for PAD in the lower extremities (19). Moreover, patients with PAD who are considered for revascularisation, duplex ultrasound, computed tomography angiography (CTA), or magnetic resonance angiography (MRA) are recommended carefully to evaluate the location, extent and severity of the obstructive vascular lesion(s) (5, 19).

Treatment

The first-line treatment recommendations for patients with PAD, commonly referred to as "best medical treatment", include secondary preventive cardiovascular risk factor management, of both optimal pharmacological (lipid-lowering, antithrombotic, antihypertensive and antidiabetic drugs) and non-pharmacological treatment, such as smoking cessation, a healthy diet, weight loss and regular supervised exercise (19). Smoking cessation is an especially important component in IC care (5, 19) and patients who continue smoking should be advised to quit at every healthcare visit (5). In order to reach high smoking cession efficacy, co-ordinated interventions that include both non-pharmacological and pharmacological methods are recommended (5). Patients with IC that are reasonably adherent to best medical treatment but where the lower limb symptoms remain severely disabling, are potential candidates for a revascularisation procedure. A large majority of such invasive procedures are currently performed with minimally invasive endovascular techniques (i.e., "balloon dilatation"; with or without stent placement). Open procedures, such as surgical endarterectomy and lower limb bypass surgery, are reserved for patients with extensive atherosclerotic obstructions that are not suitable for endovascular treatment (5, 19).

1.3 PHYSIOTHERAPY

Physiotherapy is a clinical practice and science with movement as a central concept. The objective of physiotherapy is to promote health and reduce illness and suffering. Physiotherapy also aims to maintain or regain optimal movement and functional capacity and participation in the social life of people affected by illness or injury (34). Physiotherapists work in the health fields of promotion, prevention, treatment/intervention, and rehabilitation. By looking at physical, psychological, emotional and social wellbeing, physiotherapists help people enhance their quality of life (35). Physiotherapists can also play a significant role in patients with IC in prescribing exercise and promoting physical activity but within Swedish practice, exercise is underutilised in this patient population and only a few patients with IC are referred to a physiotherapist.

1.4 PHYSICAL ACTIVITY AND EXERCISE

Physical activity is any bodily movement produced by skeletal muscles that results in energy expenditure (2). Physical activity guidelines for the adult general population (including adults with chronic health conditions or disabilities) consist of 150-300 minutes weekly of moderate-intensity, or 75-150 minutes weekly of vigorous-intensity aerobic physical activity, or a combination thereof, for substantial health benefits (36). For additional health benefits, adults should also perform muscle-strengthening activities on at least two days a week. When adults with chronic conditions or disabilities are not able to comply with the guidelines of physical activity, they should engage in regular physical activity according to their abilities and avoid inactivity. The guidelines for physical activity include the suggestion that some physical activity is better than none and that adults should sit less and move more (36).

Exercise is a subset of physical activity that is planned, structured, repetitive, and purposive to improve or maintain the components of physical fitness (2). *Physical fitness* is a set of attributes that people have or achieve and it consists of skill-related and health-related fitness. *Skill-related fitness* includes agility, balance, coordination, speed, power and reaction time. *Health-related fitness* includes cardiorespiratory endurance, muscular endurance, muscular strength, body composition and flexibility (2). There are five general principles of exercise that can be applied to all forms of exercise (37), presented in Table 2.

Table 2. The general principles of exercise (37)

Individuality	The body's response to exercise is largely determined by heredity.
Specificity	Exercise adaptations are specific to the type, intensity and duration of exercise.
Reversibility	"Use it or lose it" if exercise is stopped, the improved performance will eventually be lost.
Progressive overload	It is necessary systematically to increase the demands on the body to promote continued improvement.
Variation	In order to maximise the effectiveness of exercise, aspects of volume and/or mode of the programme should be changed over time.

Prescribing exercise requires a basic knowledge of physiological responses to exercise, along with an understanding of the concepts and characteristics of physical activity. Six basic factors are involved when prescribing exercise: frequency, intensity, time or duration, type or mode, volume and progression and these are abbreviated to FITT-VP (37) and are presented in Table 3.

Table 3. Six basic factors when prescribing exercise

Factor	**Brief description**
Frequency	Exercise frequency is usually expressed as the number of exercise sessions a week (37).
Intensity	Exercise intensity can be monitored and expressed as absolute and relative intensity. *Absolute intensity* is the amount of energy expended during the exercise and is commonly expressed in kcal/min or the metabolic equivalent (MET). *Relative intensity* is determined based on an individual's maximum (peak) effort and can be prescribed as a percentage of maximum aerobic capacity (VO_2max), for example, or estimated using Borg's rating of perceived exertion (RPE) scale rate (37).
Time or duration	Described as weeks or months of exercise programme, days/week, exercise sessions/day, duration of exercise in minutes or hours (38).
Type or mode	For example *aerobic training* (continuous or interval) including cardiorespiratory endurance activities such as walking, running, cycling and swimming and *resistance training* (37).
Volume	Commonly described in MET-minutes or kcal expended per week and is related to exercise intensity, frequency and duration (37).
Progression	May involve changing one or several of the basic factors and must be individualised since the rate of progress is individually variable (37).

1.5 EXERCISE IN INTERMITTENT CLAUDICATION

Exercise recommendations
In the guidelines of the European Society of Cardiology (ESC) (19) and the American College of Cardiology/American Heart Association (ACC/AHA) (5), supervised exercise is recommended in patients with IC. When supervised exercise is not feasible or available, unsupervised exercise should be considered (5, 19). In addition to exercise being supervised or unsupervised, other modes of exercise, including cycling, upper body ergometry, and pain-free or low-intensity walking should be regarded as being beneficial to improve walking ability and physical function in patients with IC (5).

There are two types of structured exercise programmes in patients with IC: *supervised exercise programmes* (SEP) and *home-based structured exercise programmes* (HSEP). Both programmes are planned and provide individualised recommendations for the type, frequency, intensity, and duration of exercise and recommendations for exercise progression. As physical fitness improves over time, the exercise progression aims to ensure that the body is consistently challenged to increase exercise intensity and levels (5).

Supervised exercise programmes take place in a hospital or outpatient clinic and are supervised by a qualified healthcare provider (physiotherapist in the Swedish setting). Supervised exercise programmes for IC are recommended to be performed in sessions of 30-45 min, at least three times/week for at least 12 weeks. The exercise programme includes intermittent bouts of walking to moderate-to-maximum claudication, alternating with periods of rest. A warm-up and cool-down period starts and ends the SEP (5).

Home-based structured exercise programmes take place in a personal setting, in the patients' homes or in the community, and are self-directed with the guidance of a qualified healthcare provider (physiotherapist in the Swedish setting), who prescribes an exercise regimen similar to the supervised exercise programme. Instructions are given on how to maintain and progress the dose of the exercise programme and individual face-to-face meetings are arranged between patient and healthcare provider. Health coaching or the use of activity monitors are examples of techniques that may be incorporated for behavioural change (5).

Modes of exercise
The most extensively studied SEPs have used intermittent bouts of walking

exercise to moderate IC pain and are currently regarded as the most efficacious form of exercise to improve walking ability in patients with IC (16). Additionally, the majority of studies investigating SEP in IC involve treadmill walking exercise. Since the 1990s, treadmill-based SEP, evaluated with graded treadmill testing, have been shown to be persistently successful in increasing walking ability in patients with IC (4). For this reason, treadmill exercise can be regarded as the primary exercise modality in IC (39). Protocols of treadmill-based SEP comprise intermittent bouts of walking exercise to moderate to moderately-severe discomfort, followed by short periods of rest until the symptoms disappear (4). However, several more recent studies indicate that improvement can be achieved even without pain or mild pain (16).

In 2020, Jansen et al. (40), included ten RCTs in the Cochrane review that evaluated treadmill-based SEP versus other modes of exercise. The alternative modes of exercise were supervised and included lower-extremity resistance training, upper-arm ergometry, cycling, Nordic pole walking and combinations of walking and lower-extremity resistance training. Based on the low quality of evidence, no clear differences were observed between the alternative exercise modes and treadmill-based SEP, regarding maximum and pain-free walking distance, after twelve weeks of intervention, evaluated with treadmill testing (40).

Moreover, Nordic pole walking immediately enables patients with IC to walk further, with less leg pain, despite greater cardiopulmonary effort (41). It has been shown that in patients with IC who performed two treadmill tests, one including Nordic poles and one test of traditional treadmill walking, both the pain-free and maximum walking distance significantly improved, by 53 m and approximately 80 m respectively when using Nordic poles. Nordic pole walking is therefore suggested as a useful exercise strategy for improving cardiovascular fitness for patients with IC (41). Additionally, in a systematic review and meta-analysis of Nordic pole walking, Golledge et al.(42) included five clinical trials (n = 296 patients with PAD) and compared a wide range of control groups (including treadmill SEP, traditional walking or best medical treatment with no exercise). The main finding was that Nordic pole walking did not appear to have a significant benefit over treadmill SEP in improving walking ability. However, a significant improvement was found in home-based structured Nordic pole walking when compared with control receiving home-based traditional walking (42).

Exercise safety

The risk of complications during SEP is judged to be low in patients with IC (43). In a review, six cardiac events (including cardiac arrythmia, chest pain,

cardiac arrest and myocardial infarction) were reported during > 80,000 patient-hours of SEP (of mostly treadmill exercise), giving an event rate of one per 13,788 hours of SEP (43). Moreover, HSEP is also regarded as a safe exercise arrangement in patients with IC (44). A systematic review reported that the cardiac event rate during HSEP was one per 49,270 patient-hours of HSEP. The cardiac events in the systematic review included myocardial infarction, cardiac arrythmia and chest pain (44). One possible explanation of the low event rate in HSEP is that an HSEP is often performed at a self-selected pace (regardless of prescribed intensity) (44).

Exercise in earlier to current research on intermittent claudication
Over the years, a significant number of IC-exercise studies have been conducted worldwide, demonstrating benefits from exercise on walking distance (16). In 1994, Hiatt et al. (45) conducted the first three-armed exercise study of IC and compared three months of treadmill SEP, supervised resistance training and non-exercise control. At three months, the treadmill SEP group increased its treadmill maximum walking distance by 74 ± 58%, the supervised resistance training group by 36 ± 48% while no change was observed in the control group. After the first three months, patients in the treadmill SEP continued with the same exercise arrangement, patients in the supervised resistance training group started three months of treadmill SEP instead, and patients in the control group participated in a three-month combined programme of resistance and treadmill SEP. After three months of resistance training, the combined resistance and treadmill SEP group and treadmill SEP reported increases in treadmill maximum walking distance similar to those observed after three months of treadmill SEP alone. The authors concluded that six months of treadmill SEP should be regarded as an important treatment option in patients with IC (45).

Furthermore, several systematic reviews have been published on this topic over the years (40, 46-51). In 2017, Lane et al. (46) updated the Cochrane review "*Exercise for intermittent claudication*" and concluded that there is high-quality evidence in favour of SEP (including exercise programmes comprising walking, skipping, running, and home-based therapies) in terms of improving walking ability as compared with control (i.e. usual care, placebo or medication) (46).

In previous research, no walking benefits were reported in unsupervised go home and walk advice as compared with SEP (52). In a more recent RCT from 2013, McDermott et al. (53) evaluated six months of a home-based exercise programme including cognitive behavioural therapy and compared it with non-exercising control, in patients with PAD. They reported a significant increase

in walking distance of approximately 50 m in the six-minute walk test (6MWT) in the home-based exercise group as compared with control (53). In 2018, Hageman et al. (47) published the updated Cochrane review "*Supervised exercise therapy versus home-based exercise therapy versus walking advice for intermittent claudication*". This review included 21 RCTs that compared SEP (including regimens of both treadmill and traditional walking exercise), home-based walking exercise and walk advice. The review concluded that there was moderate to high-quality evidence of improvement in maximum walking distance/time in SEP compared with home-based walking exercise and walking advice alone (47).

Assessment of walking ability in exercise intervention studies
In exercise intervention studies in patients with IC, standardised treadmill walking test has traditionally been the most commonly used objective assessment of walking ability. The most frequently used corridor test is the 6MWT (4) but the measurements properties are poor investigated in patients with IC. As complements to the objective measurements, different questionnaires, such as the Walking Impairment Questionnaire (WIQ), have been used to evaluate walking ability in IC-exercise interventions (4).

Effects of exercise and physical mechanisms
The effects of walking exercise on lower extremity skeletal muscle in PAD remain unclear. More specifically, reduced myofibre size and muscle mass are seen in the calf muscles in PAD, but the effect of exercise on the calf muscles is unclear. Moreover, the levels of reactive oxygen species (ROS) are high and further associated with greater ischaemia in the lower extremities in PAD, but the effect of exercise on ROS is unclear. In addition, as compared with individuals without PAD, the mitochondrial function of the skeletal muscles in PAD is reduced and an earlier study of the effects of supervised walking exercise on improvements in mitochondrial oxidative capacity reported mixed results. Further, there is no evidence that exercise significantly increases capillary function in the gastrocnemius muscle in patients with PAD (54). Additionally, there are several *potential* mechanisms of the benefit of exercise, such as an expansion of existing collateral vessels, improved structure of myofibres, improved vasodilation of the microcirculation, improved skeletal muscle regeneration, and improved hemorheology (24, 54). However, if activities in daily life are compromised even with exercise intervention, revascularisation should be considered (5, 19).

To summarise, the current evidence suggests that SEP should be recommended to patients with IC. There is still a lack of evidence relating to HSEP and this creates a knowledge gap in this patient population.

1.6 ASSESSMENTS OF PHYSICAL ACTIVITY

Physical activity can be divided into four domains: leisure time, occupational, transportation and activities in the household/garden (55). In clinical and epidemiological research, physical activity can be measured using subjective/patient-reported and objective methods. Self-administered questionnaires, diaries and interviews are examples of patient-reported methods (56). Pedometers and accelerometers are examples of objective methods. One of the most commonly used methods in research is accelerometry-based sensors. Accelerometers are based on continuous and real-time measurement and sample body acceleration at a rate of 10–30 times/s in the three planes; vertical, anteroposterior and media-lateral. Accelerometers register the intensity and duration of the accelerations by converting the raw data using manufacturer- and model-specific algorithms into meaningful physical activity outcomes (57, 58), commonly expressed in energy expenditure units such as metabolic equivalents (METs), or in activity intensity categories, such as light, moderate and vigorous intensity physical activity (58). One limitation of accelerometers is that they are not able accurately to measure activities such as cycling, swimming or walking upstairs (58).

Furthermore, a daily step count and stepping cadence are other examples of outcomes from accelerometers. In healthy older adults, 30 minutes of daily moderate-to-vigorous physical activity accumulated in addition to usual daily activities are the equivalent of taking approximately 7,000-10,000 steps/day (59). Stepping cadence is an important variable because it can be used to estimate walking speed and the rate of energy expenditure. In older adults (aged 61-85 years), the cadence thresholds of 100, 110 and 120 steps/min are associated with 3, 4 and 5 METs, respectively (≥ 3 to 6 METs = moderate intensity) (60). Additionally, it is suggested that the fragmented walking pattern described in patients with IC, is reflected in accelerometer-assessed physical activity since individuals with IC had approximately 100 more walking events on average per upright event than those without IC (61).

Physical activity as outcome in exercise studies in patients with intermittent claudication

Assessments of physical activity have been used as a secondary outcome in previous IC studies comparing HSEP with control (53, 62). In 2011, Gardner et al. (63) conducted a three-armed RCT in which patients with IC were randomised to three months of treadmill-based SEP, HSEP or control (no exercise). The study included assessments of physical activity with step activity monitor. The authors concluded that three months of HSEP appear to be more efficacious in improving daily physical activity than SEP (63). In

2014, Gardner et al. (64) continued with a follow-up study, with a less frequently monitored HSEP intervention. The three study groups (n = 160) consisted of: treadmill-based SEP, home-based walking exercise (intermittent overground walking at a self-selected pace) and an attention-control group with light resistance training (64). The exercise interventions were evaluated after twelve weeks using the 6MWT and accelerometer-assessed daily physical activity, among other things. On average, patients in both exercise groups completed approximately 80% of the exercise sessions. At twelve weeks, the home-based walking exercise group significantly increased their 6MWT maximum walking distance by 45 m as compared with both the SEP group (15 m) and the attention-control group (4 m). No significant between-group differences were observed in terms of the daily step count at twelve weeks. The authors concluded that the HSEP improved the quality of walking, since the patients were able to walk more rapidly during the day, even though the daily step count did not increase (64).

In addition, earlier research indicates that improved pain-free and maximum walking distance after SEP does not necessarily lead to an increase in daily physical activity in patients with IC (65). Moreover, only a few RCTs have investigated the effect of concurrent IC-treatment options (SEP, HSEP, control/usual care, endovascular revascularisation) on daily physical activity and it remains unclear whether exercise interventions positively influence daily physical activity (66). The need for future exercise RCTs to include assessment of physical activity in patients with IC is also highlighted in systematic reviews (40, 47).

To summarise, there is a knowledge gap in terms of studies evaluating SEP and HSEP with assessments of physical activity with more than twelve weeks of intervention and a long-term follow-up.

1.7 ADHERENCE TO EXERCISE

Definition

According to the World Health Organisation (WHO), adherence is defined as "*the extent to which a person's behaviour taking medication, following a diet and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider*" (67). In medical literature, patients are regarded as adherent if they take 80% of their prescribed medication (68). Additionally, it is suggested that adherence to exercise is a more profound concept with deeper roots in the patients' behaviour and is more than just the percentage of attended sessions or the number of dropouts (69). Exercise adherence can be defined as "*the extent to which a patient acts in accordance with the advised interval, exercise dose and exercise dosing regimen*" (3); this definition was used in this thesis. Exercise adherence was further categorised into three different levels (3):

a) *Full adherence* was considered in patients participating in ≥ 80% of the scheduled exercise sessions at the recommended intensity according to Borg RPE rating and ≥ 30 minutes/session.

b) Partial adherence, patients attended ≥ 20% to < 80% of exercise sessions (irrespective of Borg RPE ratings).

c) *Non-adherence* was defined as attendance at < 20% of exercise sessions (irrespective of Borg RPE ratings).

Synonyms of adherence

In the literature, there are several definitions and synonyms of exercise adherence (70). An older term that is used is *compliance*, which is defined as "*the extent to which the patients' behaviour matches the prescriber's recommendations*" (68). When comparing adherence with compliance, compliance carries a negative and authoritative undertone of blaming the patients if their behaviour does not meet with healthcare professionals' recommendations (71). Moreover, exercise adherence can be confused with other terms such as *attendance* or *completion*. Attendance is the number or percentage of exercise sessions attended and could be regarded as a subset of adherence, as well as being an important measurement in exercise. Completion is defined as patients who are still attending the exercise intervention at follow-up and excludes patient withdrawal (70). For instance, full completion can be reported in a study, but adherence to the performed exercise is not reported and it is therefore possible that patients only completed the intervention period but

did not attend all the exercise sessions. On the other hand, full adherence can be reported in a study, but perhaps only half the patients completed the entire intervention. In both situations, exercise adherence can be falsely perceived due to a lack of clear reporting (72).

Factors affecting exercise adherence

According to the WHO, there are several factors simultaneously that affecting adherence to long-term therapies (67), see Table 4. These factors are reflected in a systematic review that identified a broad range of enablers and barriers to walking exercise in IC (73). Enablers were, for example, patient belief about the potential benefits of walking, perceived improvement, pain-coping strategies, goal setting and social/emotional/information support. Examples of barriers to walking were comorbidity and medical conditions, age (> 65 years), lack of IC-knowledge, walking limiting pain, lack of motivation and lack of specific walk advice. A review further concluded that patients with IC have different barriers to and enablers of walking exercise and that health-care needs to adopt a patient-centred approach (73).

Table 4. Factors affecting adherence (67)

Factors	**Examples**
Patient-related factors	Disease knowledge and beliefs, motivation, treatment expectations, resources, misunderstanding, stress
Disease characteristics	Symptom severity, degree of disability, co-morbidities
Health-care team and system-related factors	Weak capacity of the system to provide patient feedback, follow-up and education, for example. Overworked health-care providers. Lack of knowledge of managing chronic diseases in health care teams
Treatment-related factors	Direct treatment benefits, side-effects, treatment duration, frequent changes of prescriptions
Social and economic factors	Age, race

1.8 PATIENT-REPORTED OUTCOME MEASUREMENTS

Patient-reported outcome measurements (PROMs) can be described as an umbrella term for self-rating instruments that measure concepts of health status, health-related quality of life (HRQoL) and functional status in patients with different medical conditions, for example (74). PROMs include self-administered questionnaires and interviews and can be disease-specific or generic (75). PROMs can be applied in different contexts, such as in clinical trials for evaluating treatment effects and in clinical practice for screening and monitoring patients' symptoms, disabilities and in medical decision making (76).

Health, health status and quality of life
The WHO defines health as "*a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity*" (77). Health status is defined as the influence of disease on physical, emotional and social functioning (78). The WHO defines quality of life as "*individuals' perception of their position in life in the context of culture and value systems in which they live and in relation to their goals, expectations, standards and concerns*" (79).

Health-related quality of life (HRQoL)
There is no established definition of HRQoL (80). Treat-Jacobson et al. (4) describe HRQoL as "*a multidimensional concept that includes domains related to physical, mental, emotional, and social functioning and focuses on the impact that health status has on quality of life*". The HRQoL concept overlaps with health and quality of life and these three terms are often used interchangeably in the literature (80).

Patient-reported outcome measurements in research on intermittent claudication
Several different *disease-specific* PROMs are used in IC clinical research. PROMs used in assessments of HRQoL in IC include the Intermittent Claudication Questionnaire (ICQ) (81), the Peripheral Artery Questionnaire (PAQ) (82) and the Vascular Quality of Life (VascuQoL) (83). PROMs of assessments of functional status in IC include the Estimation of Ambulatory Capacity by History-Questionnaire (EACH-Q) (84) and the Walking Impairment Questionnaire (WIQ) (85). The most frequently assessed *generic* PROMs in IC research are the Short-Form 36 (SF-36) (86-88) and the EuroQoL-5D-3L (EQ-5D-3L) (89), with the SF-36 showing the most complete and positive evidence in favour of use in an IC population (90).

1.9 RATIONALE OF THIS THESIS

This thesis originates from the knowledge gaps that were discovered in a Health Technology Assessment, which was published as a systematic review in 2013 (48). In this systematic review, the effectiveness of HSEP was compared with SEP or unsupervised "go home and walk" advice in outcomes of walking ability and patient-reported disease-specific functional outcomes and HRQoL in patients with IC. The results indicated a lack of high-quality data on the efficacy of HSEP and the need for future well-designed RCTs in order to establish the optimal exercise components for patients with IC were suggested. Exercise programmes that lasts for > 12 weeks and also have a long-term follow-up were scarce (48). To move forward, it is important to determine whether SEP and HSEP have similar effects and if they are superior to a group receiving an unsupervised walk advice (WA) alone. An HSEP is less time consuming for patients as it does not require any traveling. If an HSEP is shown to be non-inferior to an SEP, it may be a treatment alternative, provided that both HSEP and SEP are superior to the WA group. Additionally, other systematic reviews signify the importance of future exercise RCTs including outcomes relating to HRQoL and physical activity (40, 47).

Moreover, in order objectively to evaluate walking ability in patients with IC, different standardised walk tests, such as the treadmill test and corridor walk test, are used in clinical research. Previous studies have shown that treadmill walking tests, may not accurately reflect walking distances in daily life (91) and that the 6MWT better correlates to outdoor walking ability in patients with IC (91-93). The measurement properties of the 6MWT have, however, scarcely been studied in IC.

To summarise the gaps of knowledge, studying exercise in both hospital- and home-based settings, with a third arm receiving the best medical treatment alone, with a more than three months of intervention period and a long-term follow-up at one year with additional clinically important endpoints of HRQoL, patient-reported physical function and physical activity in patients with IC, was needed. This was the foundation, when designing the SUNFIT trial (Supervised or UNsupervised exercise training For Intermittent claudication).

2 AIM OF THE THESIS

OVERALL AIM

The overall aim of this thesis was to evaluate the effectiveness of SEP, HSEP and WA on walking ability, muscle endurance, self-reported physical function, HRQoL and daily physical activity in patients with IC. The overall aim further included studying the test-retest reliability and agreement of the 6MWT in patients with IC.

The primary hypothesis of this thesis was that the effectiveness of HSEP is non-inferior to SEP. *The secondary hypothesis* was that both HSEP and SEP are superior to WA alone.

SPECIFIC AIMS

PAPER I: To evaluate the one-year effectiveness of six months of three treatment strategies: WA+SEP, WA+HSEP and WA only, in patients with IC, on walking ability, muscle endurance and patient-reported daily walking ability

PAPER II: To evaluate the one-year effectiveness of six months of three treatment strategies: WA+SEP, WA+HSEP and WA only, in patients with IC on patient-reported HRQoL and physical function

PAPER II: To evaluate the one-year effectiveness of six months of three treatment strategies: WA+SEP, WA+HSEP and WA only, in patients with IC on objectively assessed daily physical activity

PAPER IV: To evaluate the test-retest reliability, agreement, standard error of measurement (SEM) and minimal detectable change (MDC) of the 6MWT in patients with IC

3 MATERIAL AND METHODS

This thesis is based on the SUNFIT trial, a multicentre, three-armed randomised clinical trial in patients with IC. This trial was designed in 2014, in a co-operative project between vascular surgeons and physiotherapists at Sahlgrenska University Hospital, Södra Älvsborgs Hospital and Central Hospital of Karlstad. The study protocol, including Papers I-IV, was approved by the Regional Ethical Review Board in Gothenburg (entry no. 349-14) and amendment T789-16 and T254-17. The SUNFIT trial was registered in the ClinicalTrials.gov database, identification number: NCT02341716. An overview of the research design in the different papers is presented in Table 5.

Table 5. Overview of the research design in the different papers

	PAPER I	PAPER II	PAPER III	PAPER IV
Design	Randomised clinical trial			Reliability and agreement study
Study sample	All patients in SUNFIT (n = 166)			Subgroup of SUNFIT (n = 100)
Enrolment hospital	Sahlgrenska University Hospital, Södra Älvsborgs Hospital and Central Hospital of Karlstad			Sahlgrenska University Hospital
Enrolment period	September 2014 to February 2018			September 2014 and March 2017
Methods	6MWT, heel-rise test, chair stand test, WIQ	SF-36, PSFS, VascuQoL	Physical activity measured with activPAL3™	6MWT
Outcome assessments	At baseline, 3, 6, 12 months			Twice at baseline
Data analysis	Descriptive statistics. Intention-to-treat analysis. Parametric and non-parametric tests (as appropriate)			Descriptive statistics. ICC, SEM, SEM%, MDC

SUNFIT, supervised or unsupervised exercise training for intermittent claudication. 6MWT, six-minute walk test. Borg RPE, rating of perceived exertion. ICC, intraclass correlation coefficient. SEM, standard error of measurement. MDC, minimal detectable change. WIQ, walking impairment questionnaire. SF-36, short-form 36. PSFS, patient-specific functional scale. VascuQoL, vascular quality of life.

3.1 STUDY RECRUITMENT

Patients were referred from different primary care centres to the Vascular Surgery Outpatient Clinics at the Departments of Vascular Surgery at Sahlgrenska University Hospital, Södra Älvsborgs Hospital and Central Hospital of Karlstad, in Sweden, for evaluation regarding revascularisation. Figure 1 outlines the recruitment per hospital. The vascular surgeons asked patients to participate if eligible according to the following study criteria.

Inclusion criterion
Established mild to severe IC for > 6 months, confirmed to be of vascular origin, with an ABI of less than 0.9 or a post-exercise ABI drop of ≥ 30 %.

Exclusion criteria
- Previous revascularisation for IC performed within three months
- Revascularisation deemed necessary within twelve months by the vascular surgeon
- Cognitive dysfunction
- Inability to perform the 6MWT
- Inability to speak or understand the Swedish language

The vascular surgeon further informed the patients that, if they accepted participation in the trial, they would be randomised to one of three treatment strategies all of which were documented as effective for improving IC symptoms and walking ability and that the aim was to compare their effectiveness. Informed, written consent was obtained from all participants before entering the study.

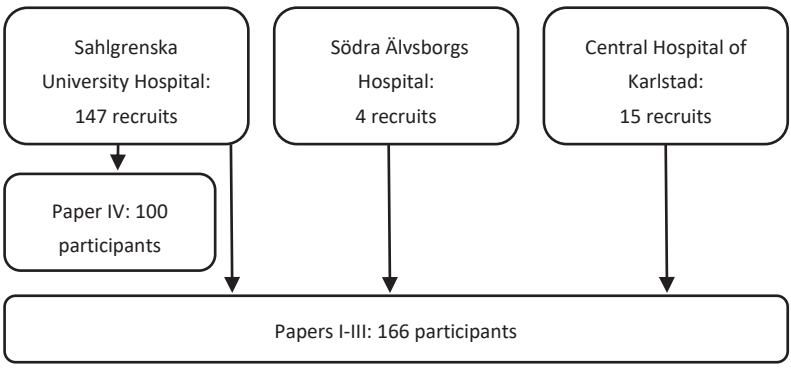

Figure 1. Overview of study recruitment, presented by hospital

3.1.1 RANDOMISATION PROCEDURE

Baseline characteristics were obtained by the vascular surgeons and the protocol included 16 variables with a known or assumed prognostic influence in IC, such as age, gender, ABI, IC-affected leg(s), smoking history and current smoking habit, patient-estimated walking distance on flat ground, patient-reported IC-related leg pain assessed with visual analogue scale (VAS) and the quality of the femoral and popliteal pulses (normal, reduced, absent). With the aim to minimising between-group differences at baseline, the 16 variables were used in the stratified, computerised randomisation procedure as described by Pocock and Simon (94). The randomisation was performed independently by research nurses at Sahlgrenska University Hospital . Randomised patients were then informed about their group allocation by the vascular surgeon.

3.1.2 WALK ADVICE STRATEGY

All randomised patients received the WA that comprised of *best medical treatment*, which included: verbal and written disease information from vascular surgeons about the anatomy and function of the circulatory system, IC causes, risk factors and symptoms. All smokers were advised to stop smoking and were offered contact with a dedicated smoking cessation unit. Pharmacological risk factor treatment (antiplatelet therapy, statins and optimised treatment of hypertension and diabetes) was instituted or enhanced for all patients according to international and local guidelines, unless contra-indicated.

The vascular surgeon gave all the patients the unsupervised WA; to perform limb symptom-induced Nordic pole walking for at least 30 minutes, three times weekly (Figure 2). The research nurses gave the patients free Nordic poles, individually adapted the pole length and instructed (verbally and in written) the patients how to use them.

Patients allocated to SEP and HSEP were further scheduled to visit the physiotherapist for exercise instructions, see Section 3.3 Interventions.

Figure 2. Nordic pole walking, photo by Anna Sandberg

3.1.3 STUDY PROCEDURE – PAPERS I-III

In the SUNFIT trial there were two teams of physiotherapists (A and B) at each hospital. Team A was blinded to patient group affiliation. All the patients were first scheduled to visit a physiotherapist in team A, as they were responsible for outcome assessments, at baseline and follow-up (Figure 3).

After at least eight days, patients allocated to SEP and HSEP were, further scheduled for an additional visit to a physiotherapist in team B. The eight-day time period between the visits was due to the accelerometer assessment.

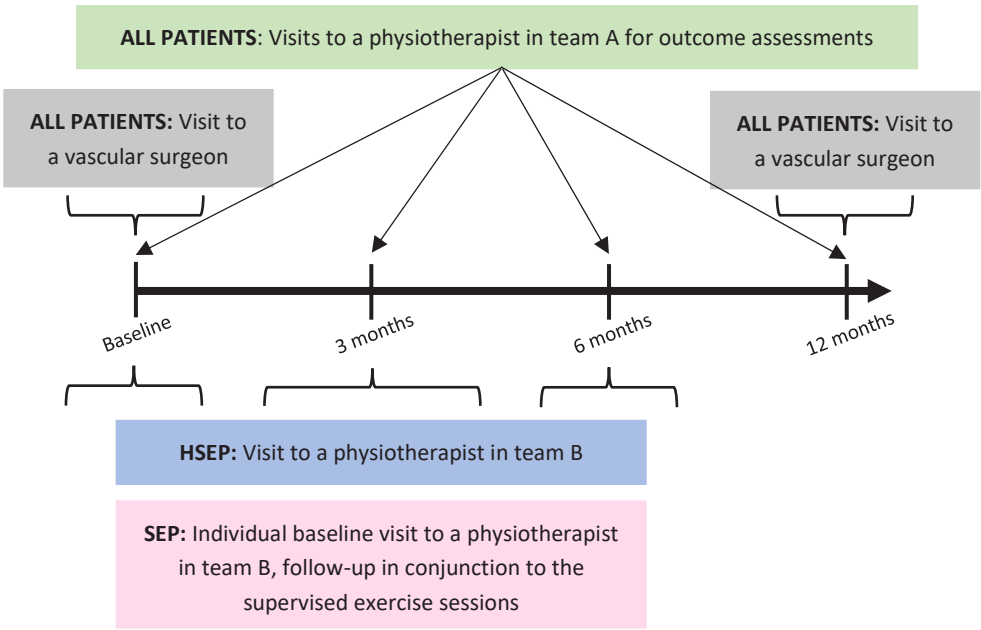

Figure 3. Overview of visit flow chart

One-year follow-up with the vascular surgeon

At the end of the study, patients were scheduled for a one-year follow-up with a vascular surgeon for assessments of ABI, Rutherford classification and questions about smoking habits, walking ability and symptoms of exacerbated ischaemia. Moreover, questions were asked about whether the patients had undergone revascularisation and had any requests for an additional IC investigation or intervention.

3.1.4 STUDY PROCEDURE – PAPER IV

In order to study the test-retest reliability, agreement and MDC of the 6MWT, a subgroup from the SUNFIT was included. This subgroup consisted of the first 100 patients at Sahlgrenska University Hospital who were instructed to perform the 6MWT *twice* at baseline. Patients rested seated for at least 30 minutes between the two tests. The reason for conducting both 6MWTs on the same visit was that the patients had a total of two to three visits at the hospital at baseline and the patient burden of a fourth visit was adjudged to be unreasonable. The same physiotherapist instructed both 6MWTs for each patient and, in total, four experienced physiotherapists conducted the 6MWTs in Paper IV.

3.2 OUTCOME MEASUREMENTS

In this thesis, different tests for measuring walking ability, both objectively and subjectively, were used. Moreover, measurements of leg muscle endurance, questionnaires on physical function and generic and disease-specific HRQoL were used. Physical activity was assessed with an accelerometer. Assessments of study outcomes were made at each hospital, at baseline and three, six and twelve months by a physiotherapist in team A (Table 6).

Table 6. Overview of outcome measurements in Papers I-IV

Outcome measurement	**Description**	**Used in Paper**
Six-minute walk test	Maximum walking distance Pain-free walking distance	I, IV I
Unilateral heel lift test	Endurance of the plantar flexors	I
Chair stand test	Strength and endurance of the leg muscle	I
Walking impairment questionnaire	Disease-specific, change in daily walking ability	I
Patient-specific functional scale	Physical function	II
Short-Form 36	Generic health-related quality of life	II
Vascular quality of life	Disease-specific health-related quality of life	II
Blood samples	Serum cholesterol, HbA1c (glycated haemoglobin), HDL (high-density lipoprotein), LDL (low-density lipoprotein) and serum triglycerides	I
Accelerometer activPAL3™	Daily physical activity: steps/day, time spent within a stepping cadence of ≥ 100 steps/min, time in upright position, number of transitions, number of sitting bouts spent in > 30min and > 60min duration	III

3.2.1 MEASUREMENT OF WALKING ABILITY AND MUSCLE ENDURANCE

Six-minute walk test (6MWT)
The 6MWT assesses the sub-maximum level of functional capacity where the patients walk at a self-paced intensity. The American Thoracic Society guidelines provide a 6MWT protocol (95) and this was used in the SUNFIT trial. Some adjustments to patients with IC were made to the protocol by adding measurements of pain-free walking distance and IC-related leg pain using the Borg category-ratio (CR-10) scale (96) and perceived exertion according to the Borg RPE scale (96). Patients were instructed to *walk as far as possible* during the six minutes and to make a sign (wave) when they first perceived the IC-related leg pain in order to assess the pain-free walking distance. Patients were informed that they were allowed to stop and rest during the test if needed. The timing continued during any pause and the number of pauses with time, distance, and duration were registered. Patients also rated their perceived IC-related leg pain during pause(s). The walking course was 30 m and two cones marked each end of it. During the test, the physiotherapist was close and gave standardised phrases of encouragement every minute: "*xx minute(s) have passed, good work*". The maximum and pain-free walking distance was recorded in metres. The distance covered was not revealed to the patient (95). This test was not previously evaluated for test-retest reliability in patients with IC.

Unilateral heel-lift test
A unilateral heel-lift test was used to measure the endurance of the plantar flexors. The heel lift was performed unilaterally with shoes on and at a 10° incline, with the standing leg straight and the other leg flexed. To assist balance, patients were permitted to apply fingertip support on the wall in front of them. A metronome set at 60 beats per minute provided a cadence of 30 heel lifts per minute. For each leg, the initial height of the heel lift was set using a wall-mounted stadiometer. The test was terminated when patients were no longer able to reach the headpiece, maintain the pace or flex the standing knee. The outcome score was the maximum number of correct heel lifts for each leg (97, 98). The unilateral heel-lift test has good test-retest reliability for healthy adults (97).

Chair stand test
The chair stand test was used to measure leg muscle strength and endurance. During 30 seconds, patients were instructed to stand up as many times as possible from a standard chair (43 cm) to a totally extended standing position with their arms folded across their chest. The recorded outcome was the

number of completed repetitions achieved in 30 seconds (99). This test has good test-retest reliability and validity for older adults (99).

3.2.2 PATIENT-REPORTED OUTCOME MEASUREMENTS

Walking Impairment Questionnaire (WIQ)
The WIQ is a disease-specific questionnaire for assessing walking ability and limiting symptoms of walking in patients with PAD and was first developed by Regensteiner et al. (85). The WIQ is brief, easy to complete and can be used in both daily practice and research (100). In the SUNFIT trial, a Swedish version of the revised WIQ prescribed by Sagar et al. (101) was used.
The WIQ contains 14 items, divided into three different subscales of walking distances (seven items), walking speed (four items) and the degree of difficulty climbing flights of stairs (three items). Each item can be graded from 0 (worst/inability) to 4 (best/without limitations). In the subscale of walking distance, the patients are asked to rate the degree of physical discomfort when walking a specific distance, ranging from walking indoors at home to 450 m (five blocks). In the subscale of walking speed, the patients are asked to rate the degree of physical exertion when walking a block (100 m) at a specific speed ranging from walking slowly to jogging. In the subscale of stair climbing, the patients are asked to rate the degree of physical exertion when climbing one to three flights of stairs (101). The WIQ is reliable and valid for measuring changes in daily walking ability in patients with IC and is suggested to be used as an alternative to the treadmill walking test when evaluating supervised exercise in patients with IC (102). In Paper II, for subscale calculation, each item response was first multiplied by a pre-specified weight and then added up and divided by the maximum possible score. Each subscale is ranges from 0-100, with higher scores indicating better walking ability. The overall score represents the average of all three subscales (101). The Swedish version does not contain the opportunity to answer “unable to do” or “Did not do for other reasons”.

Patient-Specific Functional Scale (PSFS)
The PSFS is a questionnaire assessing changes in physical function, applicable to a variety of health conditions (103-107). Patients nominate up to five physical activities which, due to their condition, they have difficulty performing. Patients rate the difficulty of each activity on a Likert scale, ranging from 0 (unable to perform) to 10 (able to perform the activity without difficulty) (104). In Paper II, patients were instructed to select up to three activities. The PSFS is reliable and valid when assessing physical function in older adults (108). In clinical research, the PSFS can be used to investigate group-level change over time, compare groups, or discriminate groups on the basis of physical function (109). In Paper II, for an overview, the patient-selected activities were categorisation in four domains of physical activity: 1) during leisure-time 2) related to work 3) in household/domestic/self-care and

4) for transportation (110). The score within each activity was presented, without further data processing.

HEALTH-RELATED QUALITY OF LIFE

Short-Form 36 (SF-36)

The SF-36 is a generic instrument that includes 36 items covering eight different domains of HRQoL: physical functioning (ten items), role physical (four items), bodily pain (two items), general health (five items), vitality (four items), social functioning (two items), role emotional (three items) and mental health (five items). The SF-36 is also presented with two summary components, physical component summary (PCS) and mental component summary (MCS). The SF-36 is reliable and valid for the general Swedish population (86-88). In Paper II we used the standard SF-36 scoring algorithms, each item score was coded, recalibrated, added, and transformed into a scale from 0-100, where a higher score indicates better health (111).

Vascular Quality of life Questionnaire (VascuQoL)

The VascuQoL is a disease-specific HRQoL questionnaire for evaluating treatment effects in patients with IC. Patients answer questions about the impact of their IC-related leg problems for the past two weeks. There are 25 items in the VascuQoL, sub-grouped into five domains: Pain (four items), Symptoms (four items), Activity (eight items), Emotional (seven items) and Social (two items) (83). The VascuQoL reflects the central aspects of HRQoL and is valid, reliable and responsive among patients with PAD within a Swedish context (112). In Paper II, no weighting of item responses was conducted in the VascuQoL. In each sub-group, the item responses were added up and divided by the respective total numbers of items. The VascuQoL Summary score is the average of all 25 item scores (83). As compared to baseline, the minimally important difference (MID) of the VascuQoL Summary score was, an increase of ≥ 0.87 for improvement and an increase of ≤ 0.23 for deterioration (113).

3.2.3 ADDITIONAL MEASUREMENTS

The laboratory tests were analysed by the laboratory at each hospital and included measurements of glycated haemoglobin (HbA1c), serum cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and serum triglycerides. These blood samples were chosen in order to assess the composition of the blood to evaluate the best medical treatment and also to study how both exercise interventions may affect these central risk markers.

3.2.4 PHYSICAL ACTIVITY

In this thesis, the activPAL3™ accelerometer (Physical Activity Logging (PAL) Technologies Ltd, Glasgow, United Kingdom) was used to study daily physical activity. By measuring the acceleration and by determining the orientation of the thigh, the activPAL3™ is capable of measuring body posture, body transitions, stepping and stepping cadence in patients with IC (61). The activPAL3™ is a reliable and valid accelerometer for identifying body posture and purposeful stepping in healthy adults (114).

In order to record seven days of measurement (the variation from all weekdays), patients wore the accelerometer (attached to the midline on the patient's right thigh) for nine days and then returned it by post to the Department of Physiotherapy at each hospital. Assessments of physical activity were made at baseline, and three, six and twelve months by the physiotherapist in team A.

Pre-defined decisions were made by the authors of the outcomes of physical activity that were of clinical interest in patients with IC. Six different outcomes in physical activity were chosen for study evaluation:

a) steps/day
b) time spent within a stepping cadence of ≥ 100 steps/min (approximately 4km/h, moderate intensity)
c) time spent in an upright position (standing still and stepping)
d) number of transitions (sitting to standing)
e) number of sitting bouts spent in > 30min duration
f) number of sitting bouts spent in > 60min duration

3.3 INTERVENTIONS

PAPERS I-III

Hospital-based supervised exercise programme (SEP)
At each hospital, patients in SEPs were scheduled for supervised exercise for six months, on Mondays, Wednesdays and Fridays, for approximately 50 min/session. The physiotherapist instructed and supervised the SEP as a patient group session. The exercise programme was performed to pre-recorded music. Over time, there were in average between three to seven patients in the exercise groups.

If needed, individual adjustments were made to the exercises (e.g. many patients had difficulties performing the lunge exercise). Patients were instructed to perform the exercises at a central intensity of 13-15 on Borg's RPE scale (96) and allowing ischaemic leg pain of up to 17 on Borgs RPE. The exercise progression was continuous and patients were continually reminded during the sessions to perform the exercise according to the intensity instructions. The content of the SEP is presented in the appendix section (Appendix). After six months of SEP, the patients were instructed to continue with the exercise programme at home (three times weekly), without supervision or feedback. Patients received the printed version of the HSEP.

Home-based structured exercise programme (HSEP)
The content, dose and progression of the HSEP were the same as for the SEP, but, for practical reasons, patients were instructed to perform the exercises for one minute (except the unilateral heel-lift exercise; 30 s/leg). The exercise programme was in printed format, with descriptive pictures and instructions from the physiotherapist on the baseline visit. No music was provided. Patients were instructed to perform the HSEP three times weekly, on self-selected weekdays. After six months of the HSEP, patients received the same information for continued exercise as patients in SEP. Both the SEP and HSEP was developed by an experienced physiotherapist in the research team.

Exercise logbooks
In order to assess exercise adherence, patients in the SEP and HSEP were given logbooks. Patients were instructed to self-register weekday, time/duration and an overall Borgs RPE rating of the performed exercise programme. At three and six months, the physiotherapist gave feedback on the performed exercise reported in the logbook, through dialogue with the patient. At three months, new logbooks for the coming three-month period were distributed. Patients were reminded/encouraged to return the logbooks but some logbooks were unfortunately missing.

Face-to-face visits
At three and six months, patients in the HSEP were scheduled for face-to-face visits to the physiotherapist. On this visit, exercise instructions and exercise programme were repeated, for quality of performance and patient comprehension of the exercises and progression.

Follow-up questions
Every two weeks during the first six months, the physiotherapist asked questions relating to exercise feedback in the SEP and HSEP. Question number four was an additional question was asked to patients in the HEP. This was made by telephone for patients in HSEP and conjunction with the exercise session in the SEP. The questions were as follows.

1. During the last two weeks, how many times have you performed the exercise programme according to the plan (i.e., 3 times weekly for 50 min and according to the Borg RPE scale recommendation)?

2. Would you recommend this exercise programme to a friend/someone you know with IC? (Ordinal scale: Absolutely not, probably not, maybe, probably, absolutely)

3. How do you perceive the level of exercise? (Ordinal scale: Easy, moderate, difficult).

4. Only to the patients in HSEP: What is the reason for not exercise according to the plan? (Other disease, other injury or pain, sick relative, travel, unmotivated, time, IC too burdensome, other personal reason).

3.4 DATA ANALYSIS

PAPER I

Walking Impairment Questionnaire

To compensate for missing responses in the WIQ, a data imputation approach was used as follows: within a patient, if the answer to one item was missing, the answer was imputed by the mean value of the patient's other answers per subscale. If the answer to > 1 item (per subscale) was missing, the subscale was removed and coded as missing.

PAPER II

Effect size

In the SF-36 and the VascuQoL, effect sizes were calculated by dividing the mean difference from baseline and the respective follow-up by the standard deviation (SD) at baseline. Cohen's criteria for interpreting effect size calculations were applied (small = 0.2 to < 0.5; moderate = 0.5 to < 0.8; large = > 0.8) (115).

PAPER III

Accelerometer-based physical activity

The data were downloaded from the device using the PAL Suite software (PAL Technologies Ltd, version 7, Glasgow, UK). The data from the activPAL3™ were systematically processed step by step, presented in Table 7.

Table 7. Step-by-step process of activPAL3™ outcome

1. The accelerometer data were processed to create event files using the aforementioned software program.
2. The event files were further processed with the PALbatch and CREA awake wear-time classification algorithm (PAL Technologies Ltd, 2020, PAL, PALbatch Software Suite, version 8.10.12.57, CREA version 1.2, Glasgow, UK). This process generated day-level variables.
3. In each nine-day recording, the first and last day were removed for each patient, in order to enable an evaluation of seven full days.
4. The exclusion of incorrect or unrepresentative data in the dataset by removing days with > 10 h non-wear time and patients with < four days of recording (per follow-up).
5. A visual inspection was made of the dataset in order to overview day-level variation within each patient.
6. All physical activity outcome measurements were calculated as average daily data during each monitoring period.

PAPER IV

Reliability

Reliable measurements obtain the same results when repeated, reliability is the stability of a measurement and the degree to which test scores differ is interpreted as measurement error (8). Measurement errors can be random or systemic. Random errors may occur by chance or from unpredictable factors such as motivation, simple mistakes, distraction or mechanical inaccuracy. Systemic errors are predictable and consistently over- or underestimate the true measurement score (8). For example, in a test of physical performance, individuals may perform better due to learning effect or less well due to fatigue (11).

Test-retest reliability

Assessments of test-retest reliability are used to determine whether a certain measurement is capable of measuring a variable with consistency. One sample of individuals performs two identical tests in conditions that are as unchanged as possible (8).

Agreement

Kotter et al. (1) define agreement as the degree to which scores or ratings are identical. There is a clear difference between the concepts of reliability and agreement. Agreement expects to maintain the relative order of the individuals in both tests as well as exactly the same result that each individual achieves on the two tests (116). A Bland-Altman plot is able to visualise agreement using the between-test difference plotted against the mean difference of the two test results for each test. For normally distributed data, the scatter should be evenly dispersed along the x-axis and the mean difference should be close to zero. For good repeatability, 95% of the difference should be less than two SD (limits of agreement) (117).

Intra-class correlation coefficient (ICC)

Reflecting both the degree of agreement and correlation between tests, the ICC is an index of reliability. There are several different forms of ICC, producing different results when applied to the same set of data. The ICC is a value ranging between 0 and 1, where 1 corresponds to perfect reliability (7). An ICC of > 0.90 is regarded as excellent reliability, 0.75 - 0.9 good, 0.5 - 0.75 moderate and < 0.5 poor reliability. As repeated tests are not randomised samples, the two-way mixed-effect model should be used. Absolute agreement should be selected in test-retest because the test is worthless if there is no agreement between the repeated measurements (7). In Paper IV, the ICC with an absolute-agreement, two-way mixed-effects single-measurement model was chosen, with the following equation (7):

$$\frac{MS_R - MS_E}{MS_R + (k-1)\,MS_E + \frac{k}{n}(MS_C - MS_E)}$$

MS_R = mean square of rows, MS_E = mean square for error, MS_C = mean square for columns, k = number of measurements, n = number of subjects.

Standard Error of Measurement (SEM)

The SEM describes the within-subject variability attributable to repeated measurements and is an indication of the precision of a score and provides an absolute index of reliability (11). Moreover, the SEM is an index that can be used to define the difference needed between separate measurements of a subject for the difference in the measurements to be considered real. The SEM is unaffected by inter-subject variability as compared to the ICC. The SEM has the same units as the measurement and is calculated with confidence intervals (CIs) for scores (11). In Paper IV, the following equation was used to calculate the SEM (11):

$$SEM = SD\sqrt{1 - ICC}$$

SD is the SD of the scores from all the individuals.

Minimal Detectable Change (MDC)

The MDC can be defined as the extent to which a significant change in an individual's status is reflected in the observed values of a test and is a statistical parameter based on the SEM (8). The MDC is calculated with a 95% CI (MDC_{95}). For all patients whose changes, when tested on multiple occasions, are ≥ the MDC, 95% of them would reflect a true change and not a difference within the measurement error. In Paper IV, the MDC was calculated using the following formula (11):

$$MDC = SEM \times 1{,}96 \times \sqrt{2}$$

3.5 STATISTICAL ANALYSIS

Sample size and power calculations for the SUNFIT trial (Papers I-III) were based on the reported meaningful change of 50 m in the 6MWT in patients with chronic obstructive pulmonary disease (118), as data for patients with IC was not available at that time. Moreover, a ±70 m SD, 80% power and a one-sided alpha level of 0.025 were chosen. With an assumed drop-out rate of 10% at one-year, 48 patients were needed in SEP and HSEP for the primary hypothesis testing. For the secondary hypothesis testing between the SEP, HSEP and WA, the sample size of 48 patients per group and 80% power enabled a between-group difference detection of 40 m. In total, 165 patients needed to be enrolled in the SUNFIT trial.

For the primary hypothesis, non-inferiority was shown if the upper boundary of the 95% CI for the observed between-group difference between the SEP and HSEP in the 6MWT maximum walking distance 0-12 months did not exceed 50 m (i.e. the non-inferiority margin).

Categorical data were presented as absolute and relative frequencies, whereas continuous data were presented as means and ±1 SD or 95% CI as appropriate, while ordinal data were presented as median, and minimum and maximum or interquartile range (IQR) values.

For between-group comparisons of the three groups, one-way analysis of variance (ANOVA) was used in normally distributed, continuous variables, while the Kruskal-Wallis test was used for non-normally distributed and ordinal data and x^2 was used and for binary data. Significant between-group results that were obtained by one-way ANOVA, Kruskal-Wallis test or x^2were further analysed with pairwise post hoc tests, adjusted by the Bonferroni correction for multiple tests. Additionally, in Paper I, mixed effects model regression analysis was performed in order to analyse the within- and between-subject variance longitudinally (unpublished material).

For within-group comparisons in normally distributed, continuous variables, a paired sample t-test was used , while the Wilcoxon's signed rank test was used for non-normally distributed and ordinal data. For all outcomes analyses (Papers I-IV), the full data set was used without imputation (except for the WIQ) and was undertaken on the initial treatment assignment (intention to treat).

In the per-protocol analyses with between-group comparisons of two groups, the Mann-Whitney U test was used.

The data were analysed using the Statistical Package for Social Sciences (SPSS) versions 24 and 25 (IBM, Armonk, NY, USA). Statistical significance was assumed at $p < 0.05$ in all four papers. An overview of the statistical methods used in this thesis is presented in Table 8.

Table 8. Statistical tests in Papers I-IV

Statistical test	**Paper I**	**Per-protocol (Paper I)**	**Paper II**	**Paper III**	**Paper IV**
Descriptive statistics					
Number (n) and percent	x	x	x	x	x
Mean (SD)	x	x	x	x	x
Median (IQR)	x		x		x
Intergroup comparisons					
Chi-square test	x			x	x
Mann-Whitney U test test		x			
One-way ANOVA	x			x	
Kruskal-Wallis test	x		x		
Intragroup comparisons					
Paired sample t-test	x			x	x
Wilcoxon's signed rank test	x				x
Estimate of magnitude of change					
Cohen's effect size			x		

3.6 ETHICAL CONSIDERATIONS

Prior to participating in the study, all the patients gave their written informed consent. The Regional Ethical Review Board in Gothenburg, approved the research protocol (DNR: 349-14 and amendment T789-16 and T254-17). The participants were allowed to withdraw from the study at any time, without stating a reason.

At the end of the study period, patients allocated to WA were offered an additional visit with the physiotherapist for exercise instruction and to receive the home-based structured exercise programme.

4 RESULTS

In the SUNFIT trial, 733 patients were assessed for eligibility according to the screening logs. Of these patients, 362 were adjudged to be eligible for the trial. In total, 166 patients (46% of the eligible patients) were included and randomised to the SEP, HSEP and WA (119). Paper IV included the first 100 patients enrolled at SU. No statistical differences were observed between the three groups at baseline. Table 9 outlines the baseline characteristics, presented by paper.

One patient in the HSEP and two patients in the SEP and WA respectively did not receive an allocated intervention. An additional nine patients withdrew during the course of the study and at one year, a further seven patients were lost to follow-up, leaving a total of 145 patients for the one-year analysis in Papers I and II. In Paper III, an additional six patients were not included in the one-year analysis due to missing activPAL data (n = 139).

In this thesis, the per-protocol analysis based on the patients regarded as fully adherent to the SEP and HSEP, on the 6MWT (maximum and pain-free walking distance), the chair stand test and the unilateral heel-rise test is presented in Section 4.1.3.

Table 9. Overview of baseline characteristics in Papers I-IV and the per-protocol analysis in Paper I

Variable	PAPERS I-III			Per-protocol (Paper I)		PAPER IV
	HSEP	SEP	WA	HSEP	SEP	N.A.
Number	56	54	56	9	14	100
Age, years	71.8 ±6.5	72.2 ±7.5	72.5 ±7.5	72.6 ±5.2	71.4 ±9.8	72 ±7.4
Sex, women	21 (37.5)	23 (42.6)	24 (42.9)	2 (22)	4 (29)	43 (43)
Rutherford classification:						
Mild	8 (14.3)	11 (20.4)	11 (19.6)	3 (33)	2 (14)	18 (18)
Moderate	34 (60.7)	33 (61.1)	35 (62.5)	6 (67)	11 (79)	62 (62)
Severe	14 (25.0)	10 (18.5)	10 (17.9)	0	1 (7)	20 (20)
Ankle-brachial index	0.66 ±0.27	0.64 ±0.18	0.67 ±0.21	0.68 ±0.15	0.67 ±0.23	0.62 ±0.20
Smoking:						
Never	4 (7.1)	5 (9.3)	6 (10.7)	0	2 (14)	10 (10)
Earlier	37 (66.1)	33 (61.1)	34 (60.7)	6 (67)	8 (57)	64 (64)
Yes	15 (26.8)	16 (29.6)	16 (28.6)	3 (33)	4 (29)	26 (26)
Diabetes mellitus	19 (33.9)	14 (25.9)	16 (28.6)	3 (33)	2 (14)	29 (29)
Heart disease*	18 (32.1)	18 (33.3)	17 (30.4)	2 (22)	5 (33)	29 (29)
Chronic obstructive pulmonary disease	8 (14.3)	8 (14.8)	7 (12.5)	0	2 (14)	13 (13)

Categorical variables are presented as the number (%). Continuous variables are presented as the mean and ± one standard deviation. N.A. not applicable. * Heart disease include diagnosis of chronic heart failure, stable angina pectoris and previous myocardial infarction.

4.1 PAPER I

The main finding in Paper I was that the HSEP was found to be non-inferior to the SEP, determined by the change from baseline to one year in the 6MWT maximum walking distance but no significant differences were observed at one year between these strategies and the group receiving WA alone.

In addition to the result published in Paper I, we also performed a mixed effects model regression analysis, in order to analyse the within- and between-subject variance longitudinally and these analyses are presented in Table 10 and Figures 4 and 5. The heel-lift test for the left leg indicates a similar result and is therefore not shown. Assumptions about the residuals were checked for and were satisfactorily fulfilled, except for some skewness in the normal distribution of heel-lift tests. In the model, with the interaction of group*time, no statistically significant difference was shown between the three groups; p-values are presented in Table 10.

Table 10. The p-values (type III) from the mixed effects model regression analysis

Intention-to-treat analysis (n = 158)		**Maximum walking distance**	**Pain-free walking distance**	**Heel-lift test, right leg**	**Heel-lift test, left leg**	**Chair stand test**
Model		p-value	p-value	p-value	p-value	p-value
Interaction model	Group	0.507	0.932	0.657	0.551	0.004
	Time	0.172	<0.001	<0.001	<0.001	0.001
	Group*Time	0.984	0.159	0.959	0.849	0.857
Without interaction	Group	0.528	0.948	0.667	0.408	0.006
	Time	0.171	<0.001	<0.001	<0.001	0.001

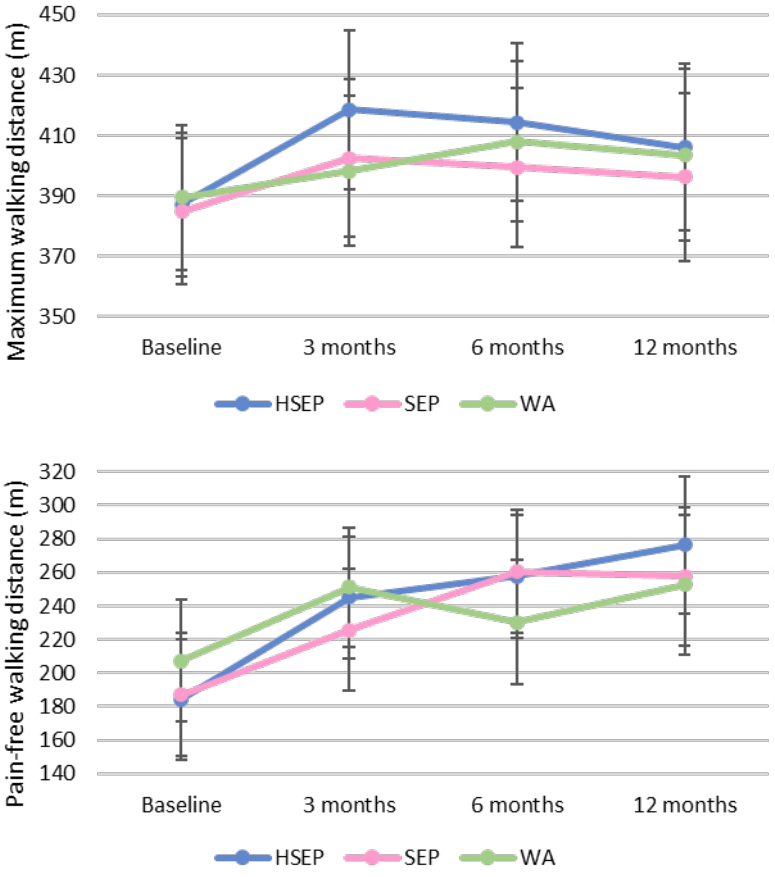

Figure 4. Results from the mixed effects model regression analysis. 6MWT maximum walking distance and 6MWT pain-free walking distance. Note that the Y-axis scales do not start at zero.

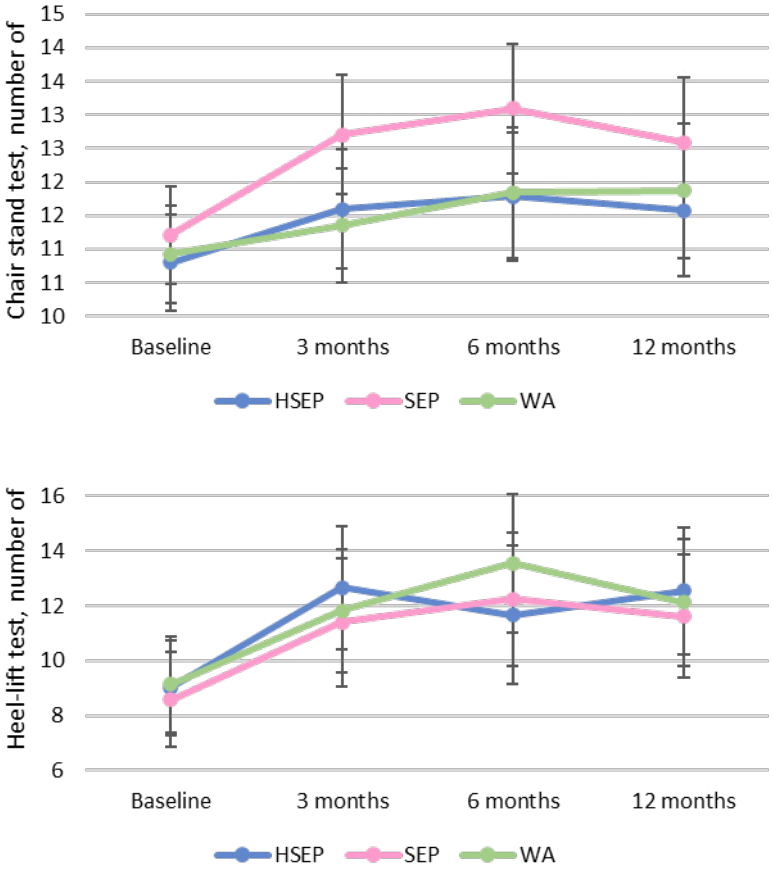

Figure 5. Results from the mixed effects model regression analysis. Chair stand test and heel-lift test (right leg). Note that the Y-axis scales do not start at zero.

4.1.1 ADHERENCE TO EXERCISE

Adherence to the HSEP and SEP was pre-defined and calculated from the self-reported logbooks and, in the case of the SEP, also from attendance registration (Figure 6).

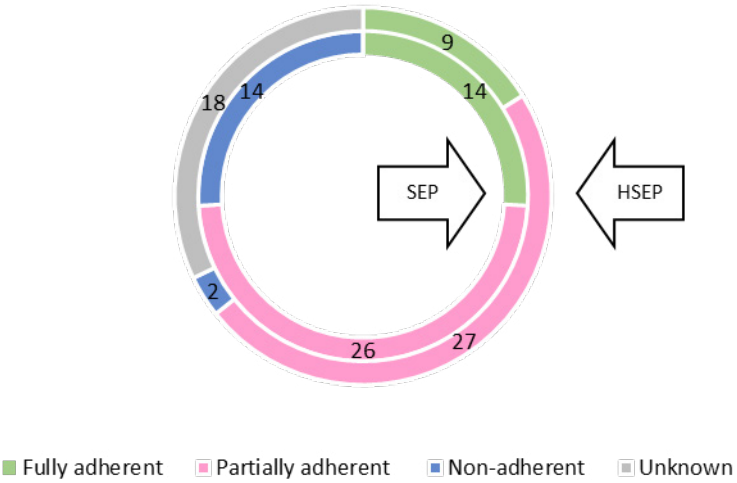

Figure 6. Number of patients, presented by level of adherence. The outer circle represents the HSEP and the inner circle represents the SEP. The reason for "unknown" is no return of logbook.

4.1.2 EXERCISE FOLLOW-UP QUESTIONS

In total, there were 571 registered follow-up responses to the questions in the HSEP and 531 in the SEP. As presented in Figure 7, most patients reported the perceived level of the exercise programmes as moderate or difficult and most patients would recommend the exercise programme, if they had a friend with IC. On 84 occasions, patients in the HSEP reported reasons for not having performed the exercise programme and reasons of other disease, injury or pain were reported in the majority of the cases (57%; Figure 8).

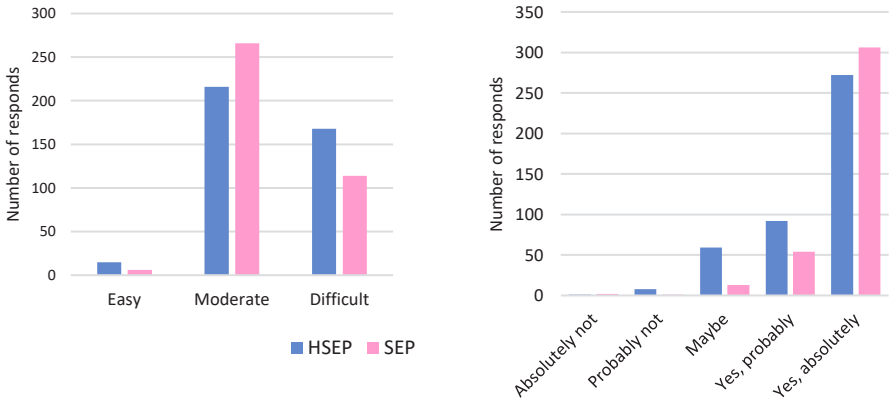

Figure 7. Patient-reported perceived severity of exercise programme and if they would recommend the exercise programme to other patients with IC

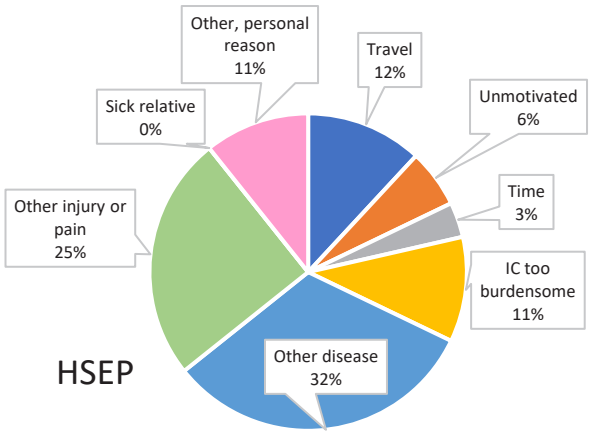

Figure 8. Patient-reported reasons for not exercising in the HSEP

4.1.3 PER-PROTOCOL ANALYSIS

Patients regarded as being fully adherent to the exercise programmes in the HSEP (n = 9) and SEP (n = 14) were analysed in a per-protocol analysis (Table 11). Baseline characteristics are presented in Table 9. Due to the small number of patients (n = 23) and the similar patterns of results, the per-protocol analysis was not published in Paper I.

At one-year, the mean difference in the 6MWT maximum walking distance in the SEP was -11.8 m (67.2), while it was 4.8m (26.4) in the HSEP. The mean difference between the SEP and HSEP at one-year in the 6MWT maximum walking distance was -16.6 m with 95% CI: -65.7 m to 32.6 m. Moreover, no significant between-group results were observed over time, except for a change in heel-rise right leg at 0-12 months, in favour of the HSEP.

Table 11. Outcomes for the 6MWT and muscle endurance tests presented by group and over time, per-protocol analysis

Outcome	Group	Baseline	3 months	6 months	12 months	p value
6MWT, maximum walking distance, m	HSEP	427.56 (73.7)	428.56 (66.4)	414.89 (86.3)	432.33 (85.2)	0.557[a]
	SEP	423.79 (56.2)	431.00 (65.9)	426.00 (69.3)	412.00 (109.0)	
6MWT, pain-free walking distance, m	HSEP	260.89 (125.8)	310.33 (114.0)	291.00 (105.5)	345.56 (186.6)	0.926[a]
	SEP	218.00 (132.3)	228.07 (107.4)	259.50 (115.9)	284.14 (155.4)	
Chair stand test	HSEP	11.4 (2.7)	12.2 (2.4)	12.3 (2.4)	11.8 (4.2)	0.096[a]
	SEP	11 (1.7)	12.8 (2.5)	13.9 (3.6)	13.3 (3.7)	
Heel-rise test (right leg)	HSEP	13 (6.9)	19.9 (10.5)	15.8 (7)	17.7 (6.2)	0.046[a]
	SEP	10.4 (8)	12.1 (9.2)	13.1 (10.6)	11.5 (8.5)	
Heel-rise test (left leg)	HSEP	12.7 (6.4)	17 (6.5)	14.8 (8.1)	16 (5.7)	0.877[a]
	SEP	8.6 (6.5)	10.9 (6.8)	13.5 (9.9)	11.2 (8.5)	

Continuous variables are presented as the mean and standard deviation. [a] Between-group comparisons of the difference 0-12 months using a Mann-Whitney U test.

4.1.4 ONE-YEAR VISIT TO VASCULAR SURGEON

In total, 149 patients attended the one-year follow-up visit to a vascular surgeon (Table 12). During the study period, eight patients underwent lower limb revascularisation (HSEP n=4, SEP n=4).

Table 12. One-year visit to the vascular surgeon, presented by group

Outcome	**HSEP (n = 51)**	**SEP (n = 50)**	**WA (n = 48)**
Rutherford classification: mild	25 (45)	25 (46)	24 (43)
moderate / severe claudication	19 (34) / 2 (4)	21 (39) / 4 (7)	18 (32) / 6 (11)
ABI, mean (SD)	0.67 (0.23)	0.67 (0.20)	0.66 (0.19)
Smoking, No / yes	33 (59) / 18 (32)	36 (67) / 12 (22)	38 (68) / 10 (18)
Patients have achieved their own exercise goal: No / partly	11 (20) / 20 (36)	10 (19) / 16 (30)	19 (34) / 15 (27)
Yes	19 (33)	22 (41)	14 (25)
Subjectively estimated IC-related leg pain (VAS) – mm, mean (SD)	39 (24)	44 (22)	47 (25)
Subjectively estimated walking distance – m, median (min-max)	800 (75-5000)	600 (10-5000)	400 (15-10 000)
Change in walking ability: a lot worse to worse / unchanged	7 (13) / 9 (16)	10 (19) / 12 (22)	13 (23) / 10 (18)
Better to a lot better	35 (63)	28 (52)	25 (45)
Limiting walking ability: IC-pain	41 (73)	41 (76)	37 (66)
Chest pain / dyspnoea	1 (2) / 2 (4)	0 / 3 (6)	0 / 5 (9)
Fatigue / other	1 (2) / 6 (11)	1 (2) / 4 (7)	1 (2) / 4 (7)
Patient request investigation for invasive therapy: No / Yes	36 (64) / 14 (25)	34 (63) / 15 (28)	35 (63) / 13 (23)
Patient request for other IC-therapy: No	39 (70)	28 (52)	24 (43)
Yes, exercise / Yes, other*	10 (18) / 2 (4)	14 (26) / 8 (15)	15 (27) / 8 (14)

Categorical variables are presented as the number (%). Continuous variables are presented as the mean and one standard deviation (SD) or as median and min-max. VAS; visual analogue scale.* E.g. invasive treatment or Pletal.

4.2 PAPER II

A summary of the main findings relating to generic and disease-specific HRQoL and physical function in Paper II follows.

The SF-36
No significant between-group differences were detected at any of the follow-ups for the SF-36. The non-significant change from baseline to one year in the SF-36 PCS was 3.3 (7.4) in the HSEP, 3.4 (7.9) in the SEP and 2.4 (8.0) in WA (p = .720).

The VascuQoL
Over time, five significant between-group differences were observed in the VascuQoL, presented in Figure 9.

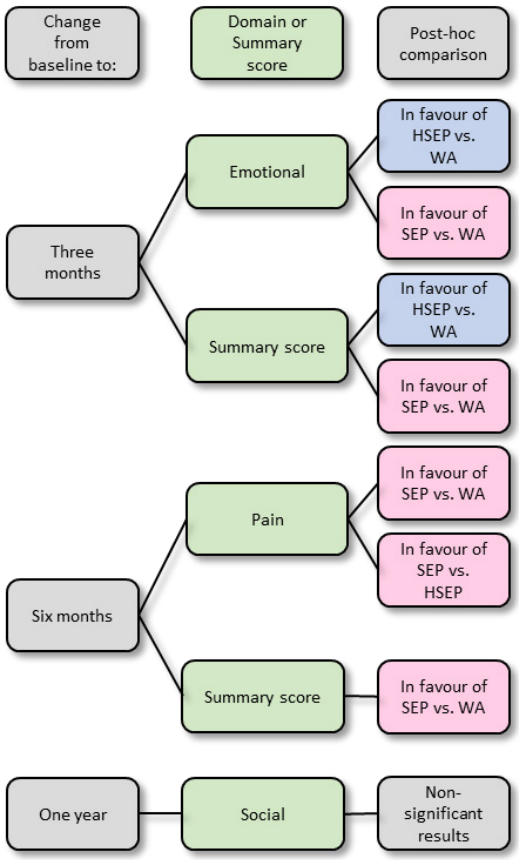

Figure 9. The significant between-group results observed in the VascuQoL and the post-hoc comparison, presented by follow-up.

Moreover, a significant result (p = .007) was observed in the VascuQoL Summary score at one year, when comparing the between-groups proportions of patients reaching of the MID thresholds for improvement, unchanged and deterioration. The post-hoc analysis showed that a significant higher proportion of patients in SEP reached the MID for improvement (p < .001). The proportion of patients reaching the MID for improvement was 42% in the SEP, 22% in the HSEP and 10% in WA.

Effect size

The calculated effect sizes in the SF-36 and the VascuQoL were mostly small.

The PSFS

In the PSFS, patients chose three physical activities they had difficulty performing due to their condition. In all three patient-selected activities, an activity related to walking was the most commonly nominated activity. No significant intergroup differences were detected between the three groups at any of the follow-ups for the PSFS.

4.3 PAPER III

The main finding in Paper III relating to physical activity can be summarised as the significant between-group differences that were observed.

- In the outcome of *time spent within a stepping cadence of ≥ 100 steps/min,* a significant between-group difference was observed at three months and the post-hoc comparisons indicated that this was in favour of the HSEP as compared with WA (p = .006).

- In the outcome of *number of sitting bouts of > 60-min duration,* a significant between-group difference was observed at six months and the post-hoc comparisons indicated that WA spent less time sitting as compared with the SEP (p = .010).

No statistically significant between-group differences were observed in the HSEP, SEP and WA at any follow-up in the outcomes of steps/day, time spent in an upright position, number of transitions and number of sitting bouts spent in >30-min duration. Figure 10 shows the non-significant result of steps/day at baseline and follow-up.

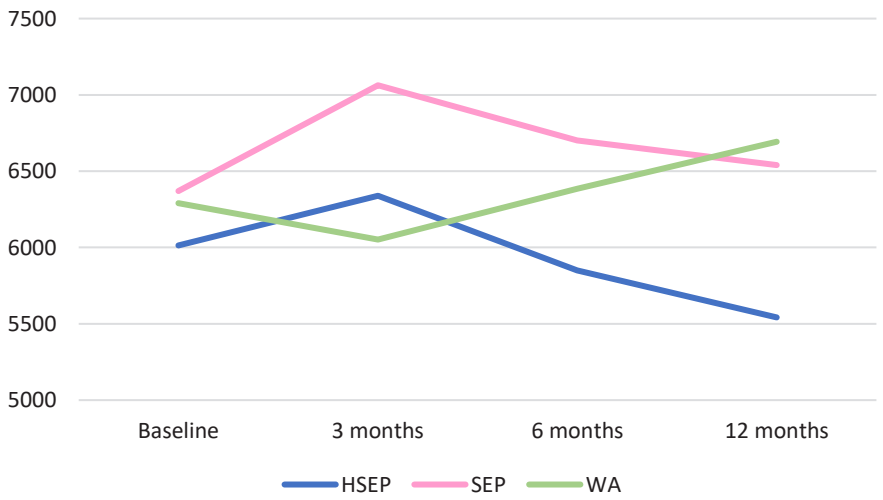

Figure 10. The non-significant result for steps/day, presented by group at baseline and at follow-up. The Y-axis represents the number of steps and starts with 5,000 steps

4.4 PAPER IV

In the test-retest reliability and agreement study of the 6MWT, the maximum walking distance was a mean of 397.9 m (80.2) at the first test and 397.7 m (83.9) at the second test (n = 100). Having finished the 6MWTs, patients rated their perceived exertion according to the Borg RPE scale at a median value of 13 (min-max: 6-17) at the end of first test and 13 (min-max: 6-19) at the end of second test. The outcomes for test-retest reliability are presented in Table 13.

Table 13. Results for the test-retest reliability of the 6MWT

Variable	
Intraclass correlation coefficient	0.95, 95% CI: 0.94 to 0.97
Standard error of measurement	16.6 m, 95% CI: 14.6 to 19.3
Standard error of measurement %	4.2%
Minimal detectable change	46 m

5 DISCUSSION

This thesis aimed to evaluate the effectiveness of SEP, HSEP and WA on walking ability, muscle endurance, self-reported physical function and HRQoL, and daily physical activity in patients with IC. An additional aim was to study the test-retest reliability and agreement of the 6MWT in patients with IC. All four papers originate from the SUNFIT trial.

5.1 Hospital-based supervised exercise vs. home-based structured exercise

Paper I confirms that a home-based structured exercise programme was non-inferior to a hospital-based supervised exercise programme. This is an important result, as the question of whether or not HSEP has comparable clinical effectiveness compared with SEP has long been the focus of debate. Previously published RCTs demonstrate inconsistent results for HSEP and this has contributed to uncertainty regarding the benefits of HSEP in patients with PAD (120). In guidelines, HSEP should be considered as an alternative, when SEP is not available, to improve walking ability and physical function (5, 19).

In Papers I-III, the settings of SEP and HSEP differed for the first six months. The SEP required attendance at the hospital, three times weekly on specific weekdays and times, while HSEP could be performed at home on self-selected days and times. There are many suggested advantages to exercising in a home-based setting; for example patients do not need to travel to the facility to participate and this is also positive for patients living in rural areas with limited access to health care and exercise facilities or for those without access to SEP. Home-based structured exercise programmes are likely to be less costly compared with SEP that requires supervision and facilities (120).

In Paper I, both exercise groups made significant within-group improvements in the 6MWT pain-free walking distance and in the muscle endurance at three, six and twelve months. The HSEP also made within-group improvements in the 6MWT maximum walking distance at all follow-ups while this only applied to SEP at three months. The comparable within-group results may be explained by the similarity in the exercise programmes. Furthermore, when comparing the HSEP in the SUNFIT trial and other exercise studies in IC, the content of our HSEP is probably unique. In previous IC studies, home-based exercise programmes include *structured advice on walking*, with a heterogeneous toolbox of additional behavioural components such as exercise monitoring, patient education, technological coaching, feedback and goal setting. In addition, only a few home-based studies have included exercise programmes with different content than walking (47).

Moreover, earlier exercise studies of IC often compare treadmill-based SEP and HSEP, i.e. structured walking advice and report significant results at three months in treadmill walking distance in favour of SEP compared with HSEP (47). However, the phenomenon “exercise on the outcome measurement” can partly explain the large effect of SEP as it means that treadmill exercise facilitates familiarity with treadmill walking (121). When comparing results

from treadmill-based SEP evaluated with a 6MWT instead, treadmill-based SEP was shown to be less effective (122). Importantly, the outcomes of walking distance obtained by treadmill walking or a 6MWT cannot be used interchangeably in patients with PAD (121).

5.2 Nordic pole walking

The results from Paper I indicates that giving patients with IC standardised walking advice along with free Nordic poles may help to increase the pain-free walking distance, as all three groups made significant within-group improvements in the 6MWT pain-free walking distance and in the muscle endurance over time. In the author's experience, many of the study patients expressed positive surprise at being able to walk further immediately with Nordic poles as compared with walking without them. In addition, previously research by Spafford et al. (123) shows that, when evaluating Nordic pole walking with a modified corridor shuttle walking test (to walk as quickly as possible and for as long as possible on a 50-m figure-of-eight circuit), patients with IC directly increase their median maximum walking distance by 141 m when walking with poles as compared with walking without them (123).

In Papers I-III, the extent to which the patients actually used the Nordic poles or adhered to the WA is unknown. The reason for this was the intention to keep the WA group unsupervised and adding assessments of adherence to the WA could have contributed to the impression of being supervised. In addition, as shown in Paper III, WA was the only group, as compared with HSEP and SEP, with a within-group increase at one year in terms of steps per day (non-significant result between the groups). It could be hypothesised that this is a result of the Nordic pole walk advice. Furthermore, in a study of patients with IC by Oakley et al. (124), which compared Nordic pole walking with control (advice on traditional walking), both to be performed for 30 min, three times weekly. Good adherence to Nordic pole walking was found at one year, as 98% of the patients in the Nordic pole walking group were still walking with poles as compared with 74% in the control group of traditional walking. The Nordic pole walking group significantly improved both walking distance and speed as compared with control (124).

5.3 The six-minute walk test

In this thesis, the American Thoracic Society protocol of the 6MWT (95) was modified to suit patients with IC, by adding assessments of pain-free walking distance, for example, something that is of clinical interest in this patient population. Assessments of saturation and ratings of dyspnoea were removed from the protocol since these outcomes were adjudged to be non-significant within an IC population.

In previous IC-exercise studies, several different 6MWT protocols were used and there is no consensus on in which 6MWT protocol should be used. Furthermore, the most commonly used 6MWT protocol is the Montgomery protocol developed by Montgomery and Gardner for patients with PAD and IC (125). It is followed by the American Thoracic Society protocol (95). The results from Paper IV contribute important knowledge relating to the 6MWT measurement properties and conclude that the 6MWT can be recommended for evaluating walking distance in interventions in patients with IC (126).

Furthermore, at least two previous reliability studies of the 6MWT and patients with IC have been published (125, 127). In the study by da Cunha-Filho et al. (127), patients were instructed to walk as *fast* as possible on a 60 m quadrangular course with verbal encouragement every minute (127). Montgomery et al. (125) used the Montgomery protocol with non-standardised phrases given every second minute. Both studies present results of the ICC that indicate high reliability for the 6MWT in patients with IC. However, none of the studies has calculated the standard error of measurement or the minimal detectable change of the 6MWT or evaluated agreement (125, 127).

The estimated values of the standard error of measurement or the minimal detectable change for the 6MWT presented in Paper IV, can be used by physiotherapists as significant thresholds for identifying changes from the 6MWT distance beyond those expected from measurement error and individual variability in patients with IC (126). The minimal detectable change is an important value, as the observed change (improvement and deterioration) in a measurement after an intervention can be used to demonstrate the effectiveness of the intervention (128). When applying the minimal detectable change of 46 m to the one-year results in Paper I, at total of 27 patients increased their 6MWT maximum walking distance by > 46 m as compared with baseline (HSEP n = 8, SEP n = 10, WA n = 9), indicating that 95 % of them would reflect a true change.

Moreover, there are a number for synonyms of the minimal detectable change (MDC), such as the minimal detectable difference, the smallest real difference, the smallest detectable change or the reliability change index (128). Additionally, another concept is *the minimal clinically important difference* (MCID) that can be defined as "*the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side-effects and excessive cost, a change in the patient's management*" (129). As compared with the MDC, the MCID is an aspect of the validity and responsiveness of an instrument (128). Importantly, a test cannot be used to detect a change when its measurement error is larger than the change we want to be able to detect (116). For example, Gardner et al. (130) reported that a moderate MCID was 33 m following supervised and home-based exercise programmes in patients with PAD (130). That MCID of 33 m is smaller than the MDC of 46 m reported in Paper IV. In situations where the MCID is smaller than the MDC, changes as large as the MCID may be important for patients, but they cannot be distinguished from measurement error (131).

5.4 Methodological considerations

External validity
In the SUNFIT trial, we included 46% of the eligible patients. Most patients who declined to participate in this study did so because they were reluctant to be randomised to the SEP group which required attendance at the hospital three times a week for six months. In addition, it can be speculated that patients with greater interest in their health agreed to participate in this exercise study and this might cause selection bias. The fact that our patients were referred to a vascular surgeon for evaluation regarding revascularisation, is important to keep in mind when generalise our results. Our results are probably transferable to similar patient populations, whereas generalisation to other patient populations with IC may be less certain. The fact that this study was conducted in Sweden, a high income country with a health care system that is tax-funded, should be considered when generalising the study results to other countries with different situations.

Exercise adherence
In the SUNFIT trial, we used exercise logbooks and for SEP, also attendance registration at hospital, to assess exercise adherence. In the HSEP, 18 patients did not return their logbooks and the exercise adherence of those patients is thus unknown. Moreover, both subjective and objective methods can be used to assess exercise adherence. Physical activity questionnaires and patient-reported diaries are examples of subjective methods while objective methods include recordings from accelerometers, for example (3). In a hospital-based setting, adherence can be directly monitored by healthcare professionals. In a home-based setting, there are different options for monitoring exercise, such as regular visits to healthcare professionals or remotely, by telephone or online (3). Overall, self-reported exercise diaries are the tool that is most widely used to measure exercise adherence (132). In patients with complex regional pain syndrome, using an exercise diary may increase adherence to home-based exercise programmes but the patients tend to overestimate the performed exercise by approximately 10% as compared with patients not receiving an diary (133). In patients with IC, the extent in which patients may overestimate the performed exercise in HSEPs is unknown. Additionally, within a clinical trial, exercise adherence is likely to be better than during the ordinary course of healthcare (133).

In Papers I-III, adherence to the SEP and HSEP was low and this was first revealed after the study period, when analysing the group-level data from the exercise logbooks. As most patients did not perform the prescribed dose of exercise, this can be viewed as an Achilles heel of the SUNFIT trial. Prior IC

research has shown that exercise programmes with a longer duration and less exercise variety tend to be those with the lowest levels of adherence (134). In the SUNFIT trial, the most reported reasons for not exercising in HSEP, were due to other diseases, injuries or pain. In the SEP, reasons for not attending the exercise sessions were not systemically logged and they are probably multifaceted. In addition, according to prior research, lack of motivation was the most common reason for not completing an SEP, followed by reasons of co-morbidity in patients with IC (72, 134).

What about the *layout design* of the exercise programme? In the SUNFIT trial, the HSEP was printed on paper with descriptive text and pictures or photos of each exercise. There were 40 exercises in total (10 pages), but some of the exercises were recurrent. Patients in the SEP received the same printed version at the end of the six-month period. Layout versions other than printed paper may have advantages in future exercise design. For example, a film or a smartphone application may facilitate understanding and improve the quality of exercise as well as adherence.

Patient-reported outcome measurements
In Papers II and IV, four different PROMs were used to study HRQoL and physical function, including both generic and disease-specific PROMs. It is suggested that the VascuQoL is one of the most appropriate disease-specific HRQoL PROMs to use in patients with IC (135). In the development of the VascuQoL, both patients and experts within the field were involved, confirming items of relevance for patients with IC (135). However, prior studies point out that many different PROMs are used in IC-research (90, 136). In 2022, an attempt to reach consensus of which PROM to use in IC-treatment was made (137). An expert panel, consisting of both international vascular specialists and patient representatives, identified the VascuQoL-6 (items) as the preferred PROM, with twelve additional items of interest to use in IC treatment. Smoking, the impact of IC on walking impairment and exercise and patient satisfaction and experienced improvement from treatment, are examples of the twelve additional items of interest (137).

In Paper IV and the Patient-Specific Functional Scale (PSFS), the patient-selected activities (that they had difficulty performing) consisted primarily of transport-related activities, such as walking and walking up stairs and hills. This may indicate an important finding in the PSFS and the fact that IC is associated with walking ability, as this was reflected in the patient-selected activities. To the best of my knowledge, this is the first time the PSFS has been used in patients with IC.

Pros and cons of objectively assessed physical activity

The SUNFIT trial used the activPAL3™ accelerometer objectively to assess physical activity. This device is easy to administer and practical for use in the home environment. It allows continuous assessment and patients do not have to remove the accelerometer while showering or sleeping, for example. Moreover, issues of integrity and privacy are important when gathering technology-based information. Patients might be concerned that the activPAL3™ is able to determine the activity that has been performed and they may also feel that they are being observed and recorded. In Paper III, user acceptance was found to be high and only two patients declined to wear the accelerometer. However, there were several other reasons for not collecting the activPAL3™ data in Paper III, for example, the activPAL3™ was broken, fell off or had low battery power and, in addition, three of the accelerometers were lost in the post.

As compared with pedometers, activity watches or bracelets or smart phone applications of physical activity, for example, patients wearing an activPAL3™ do not receive any feedback and are unable to interact with the accelerometer. In addition, as compared with self-reported physical activity, accelerometers are more reliable when it comes to recalling the frequency, duration and intensity of physical activity. Self-reported physical activity is often overestimated in older adults, thus affecting the validity of these measurements (138). At present, no device for simultaneously assessing the frequency, duration, intensity and type of physical activity exits and this also applies to each of the domains (leisure time, occupational, transportation and activities in the household/garden) (58).

In Paper III, the outcome time spent sitting was evaluated but we did not use the term "*sedentary behaviour"*, as sedentary behaviour is defined as any waking behaviour characterised by an energy expenditure of ≤ 1.5 metabolic equivalents of task (MET) in a sitting or reclining posture (139). The activPAL3™ only provides information of the body posture (i.e. sitting/lying) and not information on MET. Therefore, time spent sitting/lying is not compliant with the definition of sedentary behaviour (140). Additionally other accelerometers, such as the ActiGraph (ActiGraph LCC, Pensacola, FL, USA), estimate "sedentary behaviour" exclusively based on energy expenditure, and not body posture. Maybe future accelerometers will have the ability to measure both body posture and METs. However, it is important to use the appropriate term when using accelerometers in research and not imply to study sedentary behaviour when you don't.

5.5 Statistical considerations

Non-inferiority design and choice of margin
Traditional RCTs evaluate whether one intervention is superior to another. The null hypothesis for these studies is that the two interventions have the same effect. Rejection of the null hypothesis indicates that the treatment effects are different, determined by a statistically significant p value, for example. Non-inferiority-designed trials evaluate whether a novel intervention is not unacceptably less effective than the standard intervention. The non-inferiority approach is often used when examining secondary advantages of the novel intervention, such as patient accessibility, better compliance, safety or lower cost (9). In the SUNFIT trial, the SEP was regarded as the standard intervention and the HSEP as the novel intervention.

Moreover, the conclusion from a non-inferiority trial depends on the value from the chosen *non-inferiority margin* (Δ). This value is determined by the researchers' judgement and represents the maximum acceptable difference that is clinically acceptable and further assumes that a difference larger than this would matter in practice (128). Further, the choice of Δ influences the sample size calculation. A larger Δ require a smaller sample size and vice versa (141).

The intention-to-treat principle (ITT) includes all participants and means that data are compared on the basis of random treatment allocation, regardless of drop-out or adherence to the interventions. The ITT protects from potential bias if drop-outs are related to group assignment and maintains the baseline between-group balance achieved by randomisation (128). In a per-protocol analysis, only participants who are sufficiently adherent to the study protocol are included (128), i.e., in our case, the patients who were fully adherent to the SEP and HSEP respectively. The recommended approach for non-inferiority trials is to perform both ITT and per-protocol analyses and to conclude non-inferiority if both analyses produce the same result (141). The results in Paper I indicate that non-inferiority was reached by both the ITT and the per-protocol analysis as none of the upper 95% CI exceeded the 50 m non-inferiority Δ.

In 2014, when designing the SUNFIT trial, the Δ of 50 m was a rounding down from the 54 m that was considered to be the minimal important change in the 6MWT for patients with chronic obstructive pulmonary disease (118), as studies of IC were not available. Since then, studies of minimal clinically important differences (MCID) or a meaningful change in the 6MWT maximum walking distance in patients with PAD have been published (130, 142). A moderate MCID was reported to be 33 m, following supervised and home-based exercise programmes (130), while, in another study approximately 8 m

and 20 m respectively represented a small and large meaningful change in the 6MWT maximum walking distance, (no intervention) (142). All these aforementioned distances are smaller than the 50 m that we have chosen for Δ. If we should have decided to use a smaller Δ, it would have required a larger sample size. However, from a clinical perspective, it can be discussed whether an estimated change in the 6MWT of 8 to 33 m is really significant for the patient with IC. Furthermore, these estimated values can be compared with the results from a meta-analysis, in patients with coronary artery disease undergoing cardiac rehabilitation, that reported the estimated changes in the 6MWT after cardiac rehabilitation was 60.4 m (95% CI: 54.57 to 66.30 m) (143).

5.6 How to design the optimal exercise programme in intermittent claudication

The goal of exercise in patients with IC is to improve walking ability, HRQoL and physical activity and there are several parameters of interest when designing an exercise programme.

Firstly, the *setting*, where do the patients prefer to exercise? At home or at a hospital/outpatient clinic? One future approach may be to test a combination of exercise at an outpatient clinic and at home. It may be to intensify the supervision in the beginning of the exercise period and thereafter move over to more home-based structured exercise or a combination of both settings over the week.

Secondly, what about a more *person-centred exercise approach*? Person-centred care is based on the individual's experiences related to their life situation, including experiences of health and disease or injury (144). The focus in person-centred care is to build relationships between the patient and the healthcare provider in order to encourage the patient to play an active role in healthcare and treatment (144). Patients with IC have different barriers and enablers to exercise and, further, different preferences and expectations of their IC treatment (73). A person-centred approach with individualised exercise may increase patients' engagement in and adherence to exercise (145). An additional area of research is the recent study by Sinninge et al. (146) that evaluated how "personalised outcomes forecasts" (i.e. individual estimates of patients' maximum walking distance, shown to the patients by the physiotherapist) were used by physiotherapists in IC exercise. The results showed that personalised outcomes forecasts could be used to motivate patients, to set realistic exercise goals and to achieve goals, as well as explaining the exercise plans to patients. The authors suggest that the use of personalised outcomes forecasts by physiotherapists might contribute to a more person-centred care approach (146).

Thirdly, what about IC-related *leg pain* during exercise? Guidelines recommend that exercise should be performed at moderate-to-maximum IC-pain (5). Additionally, it is suggested that leg pain is one of the main reasons or possibly fears for patients with IC when it comes to attending an exercise programme (145). A better understanding of the patients' beliefs in relation to IC pain is recommended to improve the outcomes of exercise (147). In addition, only a few studies have evaluated exercise at different levels of perceived leg pain during exercise in patients with IC (148). For example, in an RCT, Novaković et al. (149) evaluated exercise at moderate pain, pain-free

exercise (both in treadmill walking) and control. The result showed an equivalent improvement in walking ability after both exercise programmes. Further, the authors imply that the exercise at moderate pain may improve the vascular function to a greater extent, but this study is limited by the small sample size (149). To summarise, it is unclear which level of IC pain is optimal for improving walking ability (148).

Fourthly, there is a need to improve *exercise adherence.* Within an SEP and HSEP, personal, behavioural and environmental barriers to exercise may need to be addressed in order to promote and maintain exercise (73). In patients with chronic disease and older adults, several different components are suggested for increasing exercise adherence (69). These components include patient education, related to the diagnosis and the risks and benefits of the exercise programme, and goal-setting so that patients can have realistic expectations. Support from and communication with a multidisciplinary team and giving the patient an active role in self-management and empowerment in relation to the exercise set-up were other components of importance (69). Moreover, one of the latest focal points in HSEP are studies that also include *mobile health interventions using wearable activity trackers* that provide feedback, guidance and reminders of physical activity, for example (150). A recent systematic review and meta-analysis from Kim et al. (150) included six RCTs that applied Mobile Health-Based Exercise Interventions (mHealth) in HSEP in patients with PAD. The mHealth interventions included wearable activity trackers (some of them were interactive), daily activity goal-setting and regular feedback from health-care professionals. The controls received walk advice, light resistance training or no intervention, for example. After twelve weeks of intervention, the mHealth group showed significant improvements in both treadmill-assessed pain-free and maximum walking and 6MWT distance as compared with control. No significant improvement in quality of life was reported in the mHealth group. The authors conclude that an HSEP with mHealth appears to maintain high exercise adherence in patients with PAD during the study period. However, the exercise adherence was only reported by two of the included RCTs (> 80% in both studies) (150).

Fifthly, *maintaining exercise* after ending a study is important. Patients with IC are recommended lifelong maintenance at least twice a week (4) and healthcare providers should further help the patients in the transition to the long-term maintenance of exercise, in the home or in a community-based setting (39). Moreover, in a recent multicentre RCT, patients with PAD (n = 190) were randomised to three months of a home-based walking exercise behavioural change intervention or usual care (151). The intervention was provided by physiotherapists and aimed to enable patients to continue their

walking exercise independently after the final follow-up. The patients received two 60-min in-person visits and two 20-min telephone sessions, a pedometer and a handbook (included an exercise diary, with individualised goal setting, progress monitoring, problem-solving, and action planning worksheets). At three months, a significant between-group result of 16.7 m was found in the 6MWT in favour of the exercise group as compared with control. In addition, adherence to the four intervention sessions was assessed but not for the actual performed walking. The study also presented results in the 6MWT up to six months, but these results were only presented in a per-protocol analysis, due to a large loss to follow-up (151). This indicates that maintaining exercise after an intervention may be difficult in this patient population.

Sixthly, what about *high-intensity exercise*? In 2019, Pymer et al. (152) conducted a systematic review of high-intensity interval training (HIIT) in patients with IC. The HIIT was defined as an interval approach conducted at 85% or greater peak heart rate (i.e. ≥80% maximum exercise capacity or peak oxygen uptake or a rating of perceived exertion of ≥15) and the HIIT was compared with control groups. The interventions lasted from six weeks to six months. All the included studies showed significant improvements in walking distance in HIIT as compared with control. Based on limited evidence (owing to the heterogeneity of the interventions and the small sample sizes in the included studies), the review provides initial evidence and suggests that an HIIT is able to improve walking distances and exercise capacity and also potentially improve quality of life in patients with IC. In addition, the HIIT was shown to be tolerable and acceptable in patients with IC, as the reported exercise adherence was generally > 90% and this was reported in the majority of studies (152).

5.7 National and international perspectives of exercise and the role of physiotherapists

As importantly highlighted by international guidelines, patients with PAD are less likely to receive the best medical treatment (including exercise) as compared with patients with other forms of cardiovascular disease, including coronary artery disease (5). In Europe, evidence indicates that SEPs are not always available or accessible to patients with IC (153). There are several suggested reasons why SEP is not offered to all patients with IC (154). Firstly, there is the economic aspect; is SEP covered by healthcare systems? Both the healthcare settings and the degree of financial coverage for SEP in IC are different in different countries.

In the United Kingdom, for example, only one third of the total vascular centres (n = 78) were able to offer SEP in 2022 to patients with IC and, of those, only four offered SEP that was fully compliant with current guidelines. Lack of resources and low patient adherence were, for example, reported reasons for not offering SEP (155). Another example is Denmark and in 2019, SEP was still a largely underutilised tool in the management of patients with IC. Only 10% of vascular surgeons referred patients with IC to SEP to improve walking distance and only a few of the public rehabilitation departments and none of the hospitals had a specific rehabilitation programme designed for this patient population (156). To the best of my knowledge, studies examining in which extent patients with IC receive SEP in Sweden, are not conducted.

Outside Europe, in the United States for example, it was decided in 2017 that SEP should be included and covered by the Centres for Medicare & Medicaid Services for patients with IC (157). However, during the first 19 months after approval of medical coverage, only 1.3% of the patients that were diagnosed with IC were enrolled in SEP (158). Additionally, only 5% of the patients that enrolled in SEP completed all 36 exercise sessions (158). Moreover, in a survey conducted in 2020 in the United States, approximately half the respondents, including vascular surgeons, vascular medicine physicians and cardiologists, reported that no SEP were available at their clinic (159).

Moreover, another question is to whom the vascular surgeons should refer patients for exercise? The role of physiotherapists within IC treatment differs around the world. In the United States, for example, physiotherapists are not included in the list of non-physician practitioners (physician assistants and nurse practitioners/clinical nurse specialists) and they may therefore *"participate as qualified auxiliary personnel who may be able to deliver the SEP*" (i.e. SEP covered by the Centres for Medicare & Medicaid Services)

(157). In Europe, vascular surgeons imply that the majority of SEPs in their countries were managed by physiotherapists (160). In the Netherlands and Sweden, for example, physiotherapists are the profession who prescribe exercise. In the Netherlands, through the nationwide network "the ClaudicatioNet", physiotherapists have come a long way on developing and implementing SEP for patients with IC (154). Up to 90% of the patients with IC in the Netherlands were prescribed SEP in 2011-2015 (161).

5.8 Clinical implications

The finding in this thesis that the HSEP was shown to be non-inferior to the SEP increases the knowledge of the effectiveness of exercise in different settings in patients with IC.

Patients with IC did not increase their daily physical activity when they were enrolled in an exercise study.

The estimated values of the standard error of measurement or the minimal detectable change for the 6MWT presented in Paper IV can be used by physiotherapists as significant thresholds for identifying changes from the 6MWT distance beyond those expected from measurement error and individual variability in patients with IC.

It is sufficient for a patient with IC to perform one 6MWT, on each test occasion.

6 CONCLUSION

- A home-based structured exercise programme was shown to be non-inferior to a hospital-based supervised exercise programme in patients with intermittent claudication.

- No significant differences were observed at one year between the home-based structured exercise programme, hospital-based supervised exercise programme and walk advice groups, in any of the study outcomes, including walking ability, muscle endurance, daily physical activity or patient-reported outcome measurements of physical function and health-related quality of life, except in the VascuQoL, where a few of the domains and the Summary score reached significant between-group differences over time. A significantly higher proportion of the patients in the hospital-based supervised exercise group reached threshold for the minimally important difference for improvement in the VascuQoL Summary score at one year.

- The concept of the home-based structured exercise programme and the hospital-based supervised exercise programme in this study only attracted a few patients to be fully adherent to the prescribed exercise. In fact, the observed low exercise adherence to home-based structured exercise programme and hospital-based supervised exercise programme limits the conclusions that can be drawn when evaluating the effectiveness of the two exercise programmes.

- The six-minute walk test has excellent test-retest reliability in patients with intermittent claudication and can be recommended for use in patient evaluation and clinical trials. For the individual, a change in maximum walking distance of > 46 m after an intervention would be required to be 95% confident that the change is significant.

7 FUTURE PERSPECTIVES

It remains to be seen in future studies whether an individualised exercise intervention with documented higher exercise adherence may further improve outcomes in this patient population.

Future research should continue to further develop and evaluate different modes and settings of exercise in patients with IC and in the extent work with implementation of exercise programmes in IC in the healthcare system.

An important focus of research should be on elaborating on factors that increase daily physical activity in exercise-intervention studies in patients with IC.

Future studies should aim to identify methods for increasing exercise adherence in this patient population. Future exercise studies should systematically log, continuously monitor and carefully report patients' adherence to exercise interventions.

Research is needed about strategies to maintaining exercise after having finished supervised or structured exercise programme.

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APPENDIX

This is a simplified version of the hospital-based supervised exercise programme, with instructions to the physiotherapist.

Låt 1 Louise Hoffsten: Only the dead fish follow the stream Tid: 3.02 Låtpuls: 60/120 bpm Stående	Gång på stället + rita cirklar med armbågarna Höga knäuppdrag möt med hand motsatt knä Gå på stället och simma med armarna framåt och bakåt…. Gå två steg åt sidan och sedan tillbaka igen. Möt armbåge mot motsatt knä, 12 stycken åt vardera håll
Låt 2 Tomas Ledin: Genom ett regnigt Europa. Tid: 3.36 Låtpuls: 96 bpm Stående	Gång i ring på tå, tå, häl, häl Gång i sidled, först ena hållet sedan andra hållet (steg-ihop med händer på höfter) Gå och korsa med benen (variera på linje eller med långa kliv) Gång i ring tå, tå, häl, häl
Låt 3 Justin Timberlake: Not a bad thing Tid: 4.27 Låtpuls: 81 bpm Stående	Tåhävningar bilateral med höftflexion, cirka 18st Dutta med foten framåt, växla mellan vänster och höger Twist (sida/sida), raka ben, fötter ihop Knäböj med benstäck, cirka 16st Twist (som ovan) Utfallsteg, växla ben efter varje ca 16st Dutta med foten (som ovan)
Låt 4 Den svenska björnstammen: Svalkar vinden Tid: 3.09 Låtpuls: 92 bpm Jogging- och gångvarianter	Långsam jogging rulla foten framåt, små steg. Gång i ring tå, tå, häl, häl Hoppsasteg ena hållet …. andra hållet (mkt fötter i golvet, nästa släpa foten) Gå och markera med hand ned mot golvet på vart 4:e – 8:e steg
Låt 5 Robert Broberg: Vatten Tid: 2.13 Låtpuls: 84 bpm Stående – handstöd mot t ex vägg	8st + 8st: Tåhävning- unilateral med rakt knä 20st: Tåhävning bilateral med raka knän 8st + 8st: (1) Böj knä- (2) gå upp på tå Slutet: Unilateral knäböj

Låt 6 Per Myrberg, Leppe Sundevall: Alla snubbar vill ju vara katt Tid: 5.55 Låtpuls: 84 bpm Gång och joggingvarianter	Jogga på stället. Spring 8 steg fram och 8 steg bakåt Twist Armkrok spring runt ett par varv och byt sedan håll (ej vid yrsel). Knälyft möt med motsatt hand
Låt 7 Melissa Horn och Lars Winnerbäck: Som jag hade dig förut Tid: 3.44 Låtpuls: 60 bpm Sittande	Tåhävning, sätt tryck på knäna Häl och knä ihop vik fotbladet in och ut Fotpromenad tå och häl… Rakt ben lyft, länge + små lyft (vinkla foten olika)
Låt 8 Bo Kaspers orkester: Semester Tid: 2.13 Låtpuls: 84 bpm Sittande	Res upp till stående, variera tempo Kombinationsövning = raka ben framåt -> raka ben isär -> in isär -> ihop (hålla i sig)
Låt 9 Bjørn Eidsvåg och Lisa Nilsson: Mysteriet Deg Tid: 4.00 Låtpuls: 84 bpm Sittande	Tåhävning, sätt tryck på knäna Häl och knä ihop vik fotbladet in och ut Fotpromenad tå och häl… Rakt ben lyft
Låt 10 Ricky Martin: She bangs Tid: 4.42 Låtpuls: 134 bpm Gång och joggingvarianter	Kicka ben och arm fram- åt sidor och bakåt samt möt med hand Gång/Joggning fram- och baklänges Gång i ring tå, tå, häl, häl Twist
Låt 11 Björn J:son Lind: Brusa högre lilla å Nedvarvning Tid: 5.07	Nedvarvning, gå med armrörelser Stretching av vader, quadriceps, höftadduktorer, hamstrings och petoraler och triceps

BPM; beats per minute.