Intermittent claudication

Studies on clinical evaluation strategies and invasive treatment efficacy

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Cover illustration: Bust of Roman emperor Claudius (reworked from a bust of emperor Caligula), approximately 50 AD. It was found in the so-called Otricoli basilica in 1779, and now stands in the "Sala Rotonda" (Round Hall) in the Museo Pio-Clementino (Vatican Museums).

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"We look for medicine to be an orderly field of knowledge and procedure. But it is not. It is an imperfect science, an enterprise of constantly changing knowledge, uncertain information, fallible individuals, and at the same time lives on the line. There is science in what we do, yes, but also habit, intuition, and sometimes plain old guessing. The gap between what we know and what we aim for persists. And this gap complicates everything we do."

-Atul Gawande
Surgeon and journalist
Associate professor of surgery at Harvard Medical School

To Karolina, Louise and Annika

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ABSTRACT

Peripheral arterial disease is a common health problem that globally affects over 200 million individuals, and intermittent claudication (IC) is the most common symptomatic presentation. The leg symptoms in IC are provoked by walking exercise and can be alleviated by medical intervention, exercise training and invasive vascular interventions (revascularization). The quality of evidence for invasive treatment is low and the efficacy, in terms of patient-oriented endpoints (e.g. health-related quality of life, HRQoL, and walking capacity), remains to be established. Appropriate validated instruments for the evaluation of HRQoL in IC are scarce, and accurate clinical evaluation of walking capacity remains challenging. The main aim of this thesis was to investigate the efficacy of a primary invasive versus a primary non-invasive treatment strategy in IC patients receiving best medical treatment and a structured non-supervised exercise program. Secondary aims were to validate and develop HRQoL instruments in IC, and to study the ability of different walk tests to mirror free-living walking capacity and HRQoL.

The efficacy of revascularization was investigated in two randomized controlled trials (study I and V). A disease-specific HRQoL instrument (VascuQoL) was validated within a Swedish context in a prospective cohort study (study II), and the feasibility of a short version was explored (study III). The correlations of three clinically used walking capacity estimates with GPS-assessed "real-life" outdoors walking capacity and HRQoL were investigated in another cohort study.

We found that a primary invasive treatment strategy improved HRQoL (study I) and HRQoL and claudication distance (study V) during follow-up. Validity of the Swedish version of the VascuQoL was established (study II), and a promising short version (VascuQoL-6) could be developed (study III). The *six-minutes walk test* was shown to correlate closely to "real-life" outdoor walking capacity and HRQoL.

In conclusion, we established that a primary strategy of revascularization, when added to best medical treatment and structured non-supervised exercise training, improves quality of life and important aspects of walking capacity in patients with intermittent claudication. The Swedish version of the VascuQoL is valid in the assessment of HRQoL in IC and the VascuQoL-6 holds promise for practical use in routine clinical care. The *six-minutes walk test* could be recommended in the clinical evaluation strategy of IC patients.

Keywords: peripheral arterial disease, intermittent claudication, endovascular procedures, quality of life, exercise, revascularization, health-related quality of life, disease-specific instruments, walk test

POPULÄRVETENSKAPLIG SAMMANFATTNING (SUMMARY IN SWEDISH)

Aterosklerotisk kärlsjukdom i nedre extremiteten kan medföra en begränsning av blodflödet till den arbetande muskulaturen, vilket orsakar mjölksyrautveckling och smärtor i benen under gång – claudicatio intermittens, ”fönstertittarsjuka”. Bensymptomen vid claudicatio intermittens kan lindras av medicinska behandlingsinsatser och gångträning men även kärlkirurgiska ingrepp kan minska symptomen. Behandling med kärlkirurgiska metoder erbjuds i en ökande omfattning till patienter med claudicatio intermittens trots att det endast föreligger ett begränsat vetenskapligt stöd för invasiva behandlingsåtgärder. Risken för amputation är vid fönstertittarsjuka mycket liten och behandlingen av de gångrelaterade symptomen syftar i första hand till att förbättra livskvalitet och gångförmåga. Lämpliga validerade frågeformulär fokuserade på att mäta hälsorelaterad livskvalitet (HRQoL) vid claudicatio intermittens saknas i stor utsträckning i Sverige. Det föreligger heller ingen konsensus för hur gångfunktionsnedsättningen vid claudicatio intermittens bäst värderas i klinisk praxis. Den övergripande målsättningen med detta avhandlingsprojekt var att besvara frågorna:

1. Vilken är patientnyttan av invasiva, kärlkirurgiska behandlingsmetoder i tillägg till bästa medicinska terapi och gångträning hos relativt oselekterade patienter med claudicatio intermittens?

2. Hur skall patienter med claudicatio intermittens kliniskt värderas med avseende på hälsorelaterad livskvalitet och gångfunktion?

Den första forskningsfrågan studerades i två prospektiva randomiserade studier (n=201 respektive n=158) som båda, under olika tidsperioder, jämförde en primärt invasiv behandlingsstrategi mot en primärt non-invasiv behandlingsstrategi hos relativt oselekterade patienter med claudicatio intermittens. En primärt invasiv behandlingsstrategi visades förbättra hälsorelaterad livskvalitet (delarbete I) respektive hälsorelaterad livskvalitet och smärtfri gångsträcka (delarbete V) i jämförelse med en primärt non-invasiv behandlingsstrategi.

Den andra forskningsfrågan studerades i två prospektiva kohortstudier. I den första kohorten (n=200) validerades den svenska versionen av det sjukdomsspecifika livskvalitetsinstrumentet VascuQoL. Validiteten av frågeformuläret i en svensk kontext bekräftades med psykometriska metoder och instrumentet befanns mäta centrala aspekter av hälsorelaterad livskvalitet

vid benartärsjukdom. Förutsättningarna för en kortversion av instrumentet undersöktes, och en kortversion för möjlig användning i rutinsjukvård (VascuQoL-6) utvecklades med hjälp av psykometriska metoder, kognitiva intervjuer och Raschanalys.

I den andra kohorten (n=49) testades korrelationerna mellan tre olika sätt att värdera gångförmåga i kliniskt bruk vid claudicatio intermittens (patientrapporterad maximal gångsträcka, graderat gångmatteprov och så kallat *six-minutes walk test*) och verklig gångförmåga mätt utomhus med hjälp av en GPS-baserad smartphoneapplikation. Av de tre gångtesterna korrelerade *six-minutes walk test* starkast både till verklig gångförmåga utomhus och till hälsorelaterad livskvalitet, mätt med VascuQoL.

Sammanfattningsvis har detta avhandlingsprojekt visat, att en primärt invasiv behandlingsstrategi med kärlkirurgiska metoder förbättrar livskvalitet (efter ett och två år) och smärtfri gångsträcka (efter ett år) hos relativt oselekterade patienter med claudicatio intermittens som erhåller bästa medicinska terapi och gångträning. Validiteten av det sjukdomsspecifika livskvalitetsformuläret VascuQoL har bekräftats för svenska förhållanden, och en kortversion av instrumentet har utvecklats, som kan vara praktiskt möjlig att använda för att mäta hälsorelaterad livskvalitet vid claudicatio intermittens i klinisk rutinsjukvård. *Six-minutes walk test* korrelerar starkt till verklig gångförmåga mätt utomhus med GPS-metodik samt till hälsorelaterad livskvalitet, och kan rekommenderas för objektiv utvärdering av gångfunktion vid claudicatio intermittens i såväl klinisk praxis som i framtida interventionsstudier.

LIST OF PAPERS

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

I. Nordanstig J, Gelin J, Hensäter M, Taft C, Österberg K, Jivegård L.

Walking Performance and Health Related Quality of Life after Surgical or Endovascular Invasive versus Non-invasive Treatment for Intermittent Claudication – a Prospective Randomised Trial. *Eur J Vasc Endovasc Surg. 2011 Aug; 42(2): 220-7.*

II. Nordanstig J, Karlsson J, Pettersson M, Wann-Hansson C.

Psychometric properties of the disease-specific health-related quality of life instrument VascuQoL in a Swedish setting. *Health and Quality of Life Outcomes 2012, 10:45 doi: 10.1186/1477-7525-10-45.*

III. Nordanstig J, Wann-Hansson C, Karlsson J, Lundström M, Pettersson M, Morgan M.

Vascular Quality of Life Questionnaire-6 facilitates health-related quality of life assessment in peripheral arterial disease. *J Vasc Surg. 2014; 59: 700-7.*

IV. Nordanstig J, Broeren M, Hensäter M, Perlander A, Österberg K, Jivegård L.

Six-minutes walk test closely correlates to "real-life" outdoor walking capacity and quality of life in patients with intermittent claudication. *J Vasc Surg, in press.*

V. Nordanstig J, Taft C, Hensäter M, Perlander A, Österberg K,

Jivegård L.

Improved quality of life and claudication distance with a primary invasive, using TASC II principles, versus a primary non-invasive treatment strategy in claudicants – one-year results of the IRONIC trial. *Submitted.*

CONTENT

ABBREVIATIONS

ABI	Ankle-brachial index
BMT	Best medical treatment
CLI	Critical limb ischemia
GPS	Global positioning system
HRQoL	Health-related quality of life
IC	Intermittent claudication
ICD	Intermittent claudication distance (treadmill test)
INV	Invasive treatment
ISWT	Incremental shuttle walk test
MWD	Maximum walking distance (treadmill test)
MWP	Maximum walking performance (treadmill test)
NON	Non-invasive treatment
PAD	Peripheral arterial disease
PTA	Percutaneous transluminal angioplasty
QoL	Quality of life
RCT	Randomized controlled trial
SET	Supervised exercise training
SF-36	(Medical outcomes study) short form 36
SRM	Standardized response mean
SR-MWD	Self-reported maximum walking distance

SBU	Swedish council on technology assessment in health care
Swedvasc	Swedish national registry for vascular surgery
TASC II	Trans-atlantic society consensus document II
VascuQoL	Vascular quality of life questionnaire
WIQ	Walking impairment questionnaire
6MWD	Six-minutes walk distance test

1 INTRODUCTION

1.1 Historical background

The term "claudication" alludes to Tiberius Claudius Caesar Augustus Germanicus (Roman Emperor from 41 to 54 AD). Due to sickness in childhood, Claudius suffered from limp, and during walking, he could only walk for a short distance upon which he had to stop and stand for a moment before he could walk again. Claudication is therefore derived from the Latin verb *claudicare,* denoting to limp. It is generally believed, that Claudius disability in fact protected him from the (often lethal) intrigues within the Empire, because potential enemies did not consider him a menace. Ironically, intermittent claudication (IC) as a vascular disease entity does not at all protect the individual suffering from it. Conversely, beyond impairing functional status and quality of life, it confers a substantially increased risk for severe systemic vascular complications and premature death.

The observation that arterial obstruction could cause functional disability of an extremity was first made in veterinary medicine, when Bouley 1831 described the condition in a horse that had been drawing a cabriolet in the streets of Paris[1, 2]. A few years later, the first human observation was done by an physician named Barth[3] in 1835. During a post-mortem exam of a woman with a history of IC, Barth identified a distal aortic thrombosis associated with an atherosclerotic lesion. Charcot is otherwise often recognized for clearly defining and describing the syndrome of intermittent claudication (Bouley-Charcot syndrome) in humans and reported a similar observation. Charcot's patient suffered from IC due to an occlusion of the common iliac artery distal to a traumatic pseudo aneurysm, secondary to an earlier gunshot wound. However, in his report 1858[4], he cited Barth's observations made more than twenty years earlier.

It was Erb in 1898[5] that first associated the cause of pain in IC to a reduced muscle blood supply. It was also Erb that observed that IC was more common among smokers than non-smokers[6]. In 1922, Comroe demonstrated the disappearance of foot pulses in some IC patients during exercise, that returned on resting[7]. Comroe, attributing the symptoms in IC mainly to vasospasm, denominated the syndrome *paroxysmal angiospasm dolorosa*. However, in 1962 Thulesius demonstrated exercise-induced hyperaemia in a hind leg of a cat following ligation of the femoral artery[8], contravening the vasospasm theory. Instead, a theory of exercise-induced redistribution of blood from the working muscle in the affected limb due to vascular steal phenomenon was advocated[9, 10]. In the early 1970s, some attention was also given to the finding that IC patients had higher blood viscosity than age-

matched controls[11], and an inverse relation between walking capacity and blood viscosity was demonstrated[12], tentatively the result of compromised capillary passage of erythrocytes in skeletal muscle.

During the same time period, and following the introduction of heparin[13], reconstructive vascular surgery had also become feasible. In 1946, Dos Santos performed the first successful endarterectomy[14] and this achievement was soon to be followed by a successful autologous vein bypass by Kunlin 1948[15]. Eventually, reconstructive vascular surgery was also applied on claudicants[16]. Finally, when Dotter in 1964 reported the first successfully completed endovascular treatment of a superficial femoral artery occlusion, using a coaxial intravasal catheter to dilate the lesion[17], he pioneered the modern era of minimally invasive endovascular procedures, which has eventually become the mainstay technique for invasive procedures in IC.

In contemporary medicine, the pathophysiology of IC is largely attributed to the hemodynamic compromise, caused in turn by the severity and numbers of occlusive lesions in the peripheral circulation. A mismatch between oxygen supply and demand in the working muscle is thus created, resulting in anaerobic metabolism and lactic acid formation[18]. Moreover, intrinsic metabolic changes on the muscle cellular level has been demonstrated, including impaired energy utilization[19] and altered carnitine metabolism[20].

1.2 Epidemiology and natural history

Peripheral arterial disease (PAD) is a common health problem that globally affects over 200 million individuals. Attributable to the increasing life expectancy in the population, the prevalence has also increased substantially during the last decade, as the number of people living with PAD increased by nearly a quarter between 2000 and 2010[21]. Intermittent claudication is the most common symptomatic presentation in PAD, and roughly 20-40 million individuals in the world experience classic IC symptoms[21]. Earlier studies, performed over a decade ago, have estimated IC prevalence within primary care settings to approximately 10 % in older members of the population[22, 23]. A more recent population-based study in Sweden reported that almost a fifth of all elderly individuals (60-90 years) showed some stage of PAD, and that 6.8 % suffered from IC[24]. In that study, IC was equally common in men and women, while other studies have demonstrated a slight predominance of IC in male subjects[25, 26]. This may reflect an unusually high prevalence of IC among Swedish women. Interestingly, reverting to a worldwide perspective, PAD prevalence was recently shown to be consistently higher among men in high-income countries, while the opposite was true in low-income countries [21]. Non-white ethnicity also is associated with a high prevalence of PAD[27].

Related to the systemic nature of atherosclerosis, patients with any stage of PAD have an approximately threefold risk of cardiovascular death and major cardiovascular events compared to age- and gender matched controls[28, 29]. The mortality rate in IC has been reported to be two and a half times that of an age-matched general population and 2-4 % of IC patients experience non-fatal cardiovascular events annually[30, 31]; these findings represents the largest menace to IC patients.

By contrast, the prognosis with regard to the affected limb(s) is relatively benign in terms of risk for the development of limb-threatening ischemia. In a large long-term follow-up study by Aquino et. al., the cumulative 10-year risk for development of ischemic rest pain and ischemic ulcers were 30 % and 23 % respectively, and minor/major amputations occurred with a cumulative frequency of less than 10 %[32]. Hence, the leg symptoms in most IC patients do not ever deteriorate during the course of disease, although some important predictors, such as persistent heavy smoking and diabetes, may increase the risk for deterioration[33]. Limb loss thus constitutes a very rare outcome in IC.

1.3 Risk factors

Representing a common manifestation of atherosclerotic disease, the risk factors for the development of IC are largely the same as for atherosclerotic diseases occurring in other vascular territories. Hereditary factors influence the atherosclerotic process, and smoking seems to be the most important risk factor both for development and progression of IC[34, 35]. Moreover, a relation between smoking exposure and ambulatory function in a dose-response manner has been demonstrated in IC[36]. Diabetes is also strongly associated to the development of IC symptoms[37] and the presence of diabetes predicts worse outcome[33]. Hypertension and elevated serum cholesterol represent other important contributing risk factors[38]. In fact, the presence of more components of the metabolic syndrome in IC imposes worse ambulatory function, health-related quality of life (HRQoL) and peripheral circulation compromise[39]. A substantial proportion of IC patients also have atherosclerotic lesions within other vascular territories[40-42], and such polyvascular involvement constitutes an independent predictor of mortality[43].

1.4 Clinical picture and diagnosis

The cardinal symptom in IC is pain in the affected limb(s) reproducibly provoked by exercise. Individuals with IC demonstrate a normal resting blood flow and are accordingly free of symptoms at rest. During exercise, the reduced arterial supply caused by the stenotic or occlusive vascular lesion(s) inhibits the required physiological increase in arterial perfusion, and consequently muscle pain is induced. The pain, most commonly localized to the calf but sometimes affecting the thigh or the buttocks, disappears rapidly (by definition within ten minutes) upon resting[6]. An increased work load, such as uphill or stair walking, induces IC symptoms more rapidly. Importantly, a substantial proportion of PAD patients, lacking the classical exercise-induced muscle discomfort, may experience a broad range of more non-characteristic leg symptoms (i.e. muscle fatigue, weakness, numbness or similar). Low activity levels and comorbid conditions that affect walking function may also obscure IC symptomatology, making the clinical findings less clear-cut[44].

The diagnosis of IC is made by a clinical evaluation, pairing the information from the medical history with the results from a vascular medical exam and an objective hemodynamic assessment using the ankle-brachial index (ABI). The ABI is normally calculated by dividing the systolic blood pressure at the ankle level with the blood pressure in the right forearm. A reduction in ABI $\leq$0.9 establishes the diagnosis of PAD. However, the resting ABI in IC may in fact be normal, and under these circumstances an exercise stress test may improve the diagnostic accuracy. By measuring the ABI before and after treadmill walking or a similar stress provocation, any hemodynamically significant vascular lesion can be unmasked due to the peripheral vasodilatation induced by exercise. The pressure drop is eventually detected by an accompanying reduction in the ABI immediately during recovery after the treadmill test, and a provoked gradient of 15-20 % establishes the PAD diagnosis[6]. In some patients though (preferentially in diabetes or severe renal disease) the ABI is not a reliable diagnostic tool. Due to severe peripheral arterial calcification the vessels could become non-compressible by the sphygmomanometer, imposing a falsely elevated ABI. These patients typically have an ABI $\geq$ 1.4, and additional non-invasive testing is then required for PAD diagnosis[6]. Moreover, the ABI measurement may be incorrect if the patient has associated obstructive lesions in the subclavian or axillary artery why it is important to measure the systemic blood pressure in both arms, and to use the highest achieved value at the arm level for the index calculation. Interestingly, a pressure gradient between the arms is another clinically useful marker of atherosclerosis and cardiovascular risk[45, 46].

2 ASSESSMENT OF WALKING CAPACITY IN INTERMITTENT CLAUDICATION

2.1 General considerations

Intermittent claudication entails a reduction in ambulatory function ranging from very mild symptoms to a severe impairment of walking capacity. In disabling cases, symptoms develop early during walking, and if the patient continues to walk increasing leg symptoms will necessitate a stop. Claudicants also demonstrate a reduced walking speed and step length[47] and show biomechanical alterations of joint movements at the hip- and ankle level as compared to healthy controls[48]. Moreover, the actual onset of IC pain acutely reduces walking speed both at preferred and rapid paces, and the onset of pain also induces a more asymmetrical gait pattern[49].

An objective assessment of walking capacity is important to guide decisions about the most appropriate treatment strategy with regard to the leg symptoms experienced by IC patients. In clinical practice, the most common way to assess ambulatory function is by simply asking the IC patient to report maximal walking distance on a flat surface (self-reported maximum walking distance, SR-MWD). However, this measure is notoriously unreliable, and highly inaccurate distance estimates have been reported both among claudicants[50] and vascular surgeons[51]. Even when considering more recent research, indicating that SR-MWD may not be as bad as previously claimed[52], a more objective assessment is usually recommended[6, 53]. The most widely adopted walk test is the treadmill test[54]. Other walking capacity estimates include different corridor-based tests[55] and self-reported symptom scores such as the Walking Impairment Questionnaire (WIQ)[56]. The development of new technologies also offers the possibility for *in vivo* measurement of free-living ambulatory function[57-59].

2.2 Treadmill testing

Treadmill exercise testing is still considered to represent the gold standard walk assessment in IC and has been used for decades in PAD[60]. The treadmill test, combined with pre- and post-exercise measurement of ABI, constitutes an important diagnostic tool that can confirm or exclude PAD as the likely cause in patients with unclear lower limb pain. The recorded walking capacity during treadmill testing is closely related to long-term prognosis (i.e. mortality rate and cardiovascular event rate) in patients with PAD[61]. Treadmill testing also offers a possibility to characterize and grade the walking impairment and several different test protocols are in clinical use.

The traditional test utilizes a constant speed and inclination. This test is typically set at a fixed value between 2-4 km/h and at a defined grade ranging from 0-12 %[54]. Originally adopted from cardiology[62], a graded treadmill protocol is also commonly used. This test is adjusted to a constant walking speed, and the workload is increased by a progressively elevating treadmill slope[63]. Yet other protocols use a progressive increment in speed[64] or a combination of increasing slope and speed (gradual ramp protocol)[65, 66].

The variables commonly recorded during treadmill testing include intermittent claudication distance (ICD) and maximum walking distance (MWD), where ICD implies the covered distance until the onset of IC symptoms and MWD implies the maximum possible covered distance. When comparing different protocols, a graded treadmill test has been shown to be more reliable and reproducible as compared to constant load protocols and is generally recommended as the preferred walk assessment in clinical trials[54, 67, 68]. One main disadvantage with the traditional, non-graded test is also that it may not provoke patients with less severe disease state to stop during the test.

One possible disadvantage of treadmill tests is, that they represent tightly regulated protocols, constituting a relatively artificial measure of walking capacity. In fact, the results of treadmill tests may not accurately reflect ambulatory function during daily life circumstances[55, 69, 70]. During treadmill testing, walking speed and incline are regulated by the protocol, limiting the possibilities for adaptive gait changes. By contrast, during free-living walking conditions the IC patient may functionally adjust more easily by an altered gait pattern.

Moreover, the variety of different treadmill protocols used in IC interventional trials makes comparisons of results between different studies difficult. In this context, disadvantages also include a gradual improvement of treadmill results over time with repeated testing, attributed to a “learning” effect. This phenomenon is especially pronounced when a constant load protocol is used. Hence, patient without active treatment generally improve treadmill performance during the course of a study, introducing a bias that may blur study results[68]. This is especially problematic when an intervention (whether surgical or medical) is tested versus a training program that includes regular treadmill exercise, i.e. when the outcome assessment also constitutes a component in the training program.

2.3 Corridor-based testing

In response to the limitations of treadmill testing as stated above, and also because treadmill test equipment may not be available or appropriate in every clinical setting, corridor-based walk tests has been developed. At least two tests have been utilized in IC, and both are originally developed for functional walking capacity assessment in chronic pulmonary disease[71, 72].

The six-minutes walk distance test (6MWD) is performed in a corridor or similar, where a distance of 30.5 meters (100 feet) is outlined with floor markings at each end. Subjects are instructed to walk from end to end attempting to cover as much distance as possible, and the total covered distance during the 6-minutes period is recorded[73].

During the incremental shuttle walk test (ISWT)[72], the test person is instructed to walk up and down a 10-metre distance, outlined by two cones, at increasing speeds as dictated by an audio signal. The patient is required to cover every shuttle before the audio signal and the test is terminated if the patient fails to complete one shuttle within the given time frame.

Although overwhelming evidence of utility within pulmonary medicine, the clinical experience with corridor-based testing in IC is still limited. However, available scientific work indicates a high reliability of the tests also in IC patients[74-76], and also a stronger correlation to free-living physical activity than treadmill testing[55].

2.4 Self-reported validated symptom scores

A variety of questionnaires have been developed to assess ambulatory function. The most widely used questionnaire among IC patients is the Walking Impairment Questionnaire (WIQ)[56, 77]. The WIQ is a potentially useful tool for the assessment of walking impairment in IC, providing a self-reported estimate of walking function in a less resource-intensive manner as compared to walk tests. The TASC II document states, that a "reduced function by questionnaire" has an equal decision value as "reduced treadmill performance"[6]. An important distinction however, is that the WIQ is merely a symptom score and not an assessment of HRQoL, which is described below.

Earlier research has demonstrated a fairly low correlation between the results of the WIQ and the measured results during treadmill testing[78] and thus the accuracy of the questionnaire has been questioned[79]. However more recent data, comparing WIQ results with community-based walking assessed with global positioning systems (GPS), suggest that WIQ may in fact provide a highly valid and accurate estimate of everyday ambulatory function[52, 70]. As with any extensive patient-reported measurement scale though, the relative

abundance of questions in the WIQ could render accurate patient completion challenging, reducing data quality[52, 79], and may prove too arduous in busy clinical settings. The validity of the WIQ also seems to be poorer in older age groups[80]. The recent development of a more simple symptom score, the Walking Estimated-Limitation Calculated by History questionnaire, may partially contravene these problems[81].

2.5 Walking activity monitoring

Every treatment strategy in IC should aim at reducing functional limitations by improving walking capacity during free-living activities in everyday life. It therefore seems reasonable to consider an assessment tool that measures this entity (i.e. free-living walking capacity). Following the introduction of different activity monitors that offer the possibility to measure activity and walking function *in vivo*, during daily life activities, such technologies are now evaluated among IC patients.

Pedometers are the simplest available technology, measuring the number of steps completed by the patient in a cumulative manner. With the addition of measured individual step length, the total covered distance can be measured. Pedometers have been validated in PAD individuals[57] and interesting results have been obtained in interventional clinical trials when using this technology as outcome measures[82-85].

Accelerometers measure vertical and horizontal acceleration and convert the recorded movements into an estimate of energy expenditure, mirroring activity level. Validity has been tested in PAD[57], and measurements with this technique have been used as additional endpoints in IC clinical studies[86]. Newer devices allow for differentiation of sedentary state (sitting or lying), standing and ambulation, making them a promising tool to precisely evaluate everyday physical activity in IC patients[59].

Walking activity monitoring by GPS has also recently been applied in IC patients[87], and has increased our understanding of walking pattern during outdoor walking activities[58]. An important limitation with GPS devices is that proper satellite coverage is a prerequisite for adequate measurements, why the technology is limited to outdoor walking assessments. A combination of GPS-assessments and accelerometer device measurements may prove even more powerful to detect walking activity during the full range of free-living activities[88].

Interestingly, both activity monitors and GPS systems are now incorporated in the latest generations of smartphones, making technology available at hand for a growing group of patients. The use of smartphone devices for remote

supervision of exercise programs has been tested within cardiac rehabilitation[89], and may offer similar possibilities to IC patients.

The main general drawback with all activity monitors is that special equipment is necessary. Proper use of the technologies also places additional demands on the patient, who must remain compliant with the monitoring procedures. Moreover, as compared to more traditional, well-established walk assessments (e.g. treadmill testing), further validation is needed and broad applicability for IC patients remains to be proven.

3 ASSESSMENT OF QUALITY OF LIFE IN INTERMITTENT CLAUDICATION

3.1 General considerations

The ultimate goal in IC is to improve health-related quality of life (HRQoL) by offering a treatment that improves ambulatory function in daily life. Consistent evidence shows that HRQoL is impaired in IC when compared to healthy controls[90-92]. On the individual level, the actual impact of IC symptoms on functional status largely depends on the specific life-style of the patient, and hence it is equally important to assess functional *limitations* in daily life. Clinical assessment in IC therefore requires a comprehensive approach including assessment of hemodynamic impairment and walking function, but also focusing on patient-reported outcome measures, such as HRQoL instruments[68, 93]. This is underscored by the fact that commonly used objective measures of circulatory compromise (i.e. ABI) correlate poorly to HRQoL in PAD[94]. HRQoL instruments thus offer a potential for health-care providers to evaluate the patient-specific burden of living with IC, which may help to guide selection of therapy. In routine clinical settings, the use of HRQoL measures sharpens evaluation of disease severity and functional status before and after treatment, and in clinical trials the use of HRQoL instruments as study endpoints seems logical given that HRQoL improvement is the ultimate treatment goal in any intervention for IC leg symptoms[95].

3.2 Development and validation of HRQoL instruments

Quality of life (QoL) is a broad and general multidimensional construct with different meanings under different circumstances that also imply different things for different people. In clinical medicine, the term *health-related quality of life* (HRQoL) is often used to highlight a focus on aspects of QoL that are affected by illness or handicap and are possible to influence by different medical interventions. Core components of HRQoL include several dimensions of living such as physical, emotional and social functioning and the definition of relevant aspects of HRQoL varies between diseases and clinical situations[96].

HRQoL is a *latent* variable, which means that it is unavailable for direct observation or measurement. HRQoL is therefore estimated by the use of indirect and subjective indicators or "items" (questions/assertions) asked to the patient in a questionnaire. A comprehensive description of all aspects of

the development and validation of HRQoL measurement scales is beyond the scope of this text. However, a few brief general aspects are important for the understanding of some of the methodology used in the thesis.

The development of HRQoL instruments follows a certain route and several guidelines describing steps in their development have been published[97]. One important issue is the intended target population. The development and testing of any useful HRQoL instrument should include every important subgroup of intended respondents and take into account the full range and degree of possible symptoms and QoL aspects affected by these symptoms. Ideally, a questionnaire should be brief but yet cover every relevant HRQoL aspect of the disease or disability of interest. During the initial construction phase of a new instrument, an exhaustive list of items and subscales considered relevant for the purpose are compiled. This process is purely qualitative in nature and achieved by a *literature search* (benchmarking any existing instrument that addresses similar or related areas) and by *individual and/or focus groups interviews*. The interviews should include patients (representative of intended target population) and specialists (health-care professionals or similar personnel working with the disease of interest). From the generated list, the most suitable items are selected for the provisional questionnaire. The items are ordered in relevant subscales (domains) supposedly reflecting different HRQoL aspects, and converted to clean-cut and easily responded questions. When designing the new questionnaire, it is important to include items that offer meaningful responses for all respondents, taking into account that HRQoL impact in life varies with disease severity and degree of symptoms experienced by the respondents. Furthermore, selected items should have the capacity to measure change over time and in response to treatment. It is most common that multi-items scales are used in HRQoL instruments, allowing for an increased measurement precision and a broader coverage of the latent variable(s); it is also considered to render the questionnaire more reliable when repeated assessments are performed[98].

The decision about rating scale and the number of response options for every item is a crucial component of the instrument. To differentiate between disease status and degree of functional impairment, several response options are needed while at the same time, the respondents have to be able to easily select the response option that applies to their individual HRQoL state in a non-arbitrary fashion[99].

The questionnaire-in-progress is pre-tested on smaller groups of patients to identify and solve potential linguistic and comprehension issues (ambiguous phrasing, difficult wording) and the proposed instrument is changed accordingly[100]. Thereafter, a larger “field-test” is generally performed in a

fully representative patient sample. The purpose of this is to provide sufficient data for the formal validation of the questionnaire.

The process of validation uses different quantitative psychometric methods (psychometrics is the field of science concerned with the theory and technique of psychological measurement) and should establish *validity*, *reliability, sensitivity and responsiveness* of the HRQoL questionnaire. *Validity* concerns the accuracy with which the instrument measures the latent variable and *reliability* regards the ability for stable measurement at interval time-points. *Sensitivity* implies the ability to differentiate and grade HRQoL status in respondents with different disability, while *responsiveness* means the ability to detect change. The theoretical framework underpinning the psychometric models applied when testing these entities is often denominated *classical test theory*[101].

In recent years, increased attention has been given to models that use *item response theory*, including the Rasch model[102]. This approach offers an alternative method to develop and test a questionnaire, using a model that explores the difficulty and discriminative properties of every item. The Rasch model is a complicated psychometric model, and an exhaustive explanation of the underlying assumptions and the mathematic framework constituting the basis for the model is beyond the scope of this text. However, when the Rasch model is employed, the objective is to obtain data that fit to the model[103]. The rationale for this perspective is that the Rasch model embodies requirements that must be met in order to obtain proper measurements.

In essence, the probability of a specified response is modelled as a function of person ability and item difficulty in the Rasch model. The Rasch model in this way conceptualizes the measurement scale like a ruler. Firstly, items are located along the measurement scale according to their difficulty. This part of the process of scaling is often referred to as item *calibration.* Subjects responding to the items can also be located on the same measurement scale and are located according to their ability. The higher a person's ability relative to the difficulty of an item, the higher the probability of a successful response on that item. When a person's location on the latent trait that is being measured (e.g. HRQoL in PAD) is equal to the difficulty of the item, there is by definition a 0.5 probability of a successful response in the Rasch model. If the data do fit the model adequately for the purpose, then the Rasch analysis also linearizes the total score, which is bounded by 0 and the maximum score on the items, into measurements (log-odds units or “logits”), rendering data available for analysis with parametric statistical techniques.

The Rasch model provides information about how well different items function to describe a capability or trait. It is ideal for testing the properties of

existing multi-item scales and allows for the development of shortened versions of existing measurement instruments[104].

Any HRQoL instrument intended for use in a new country has to be rigorously translated and linguistically validated[105]. Following this, a thorough validation in a new national patient sample is also recommended before use in research and clinical routine. The latter is appropriate because the performance of the instrument may be sensitive to culture- and other country-specific context differences[106].

3.3 Generic health-related quality of life instruments

Generic instruments are intended for general use and are applicable in wider populations, irrespective of disease or treatment. Due to their general nature, generic instruments allow for comparisons between patients with various diseases and also between patients and the general population. Inherent in this design, generic instruments may not be sensitive enough to reveal smaller, but clinically important changes, because they do not focus on the specific problems experienced by a certain group of patients[107]. One well-established generic HRQoL instrument is the Medical Outcomes Study Short Form 36 (SF-36). It includes 36 items covering different aspects of HRQoL, generating eight different domain scores (PF= physical functioning; RP= role physical; BP= bodily pain; GH= general health; VT= vitality; RE = role emotional; SF= social functioning and MH= mental health). Results may also be presented in two summary measures, Physical Component Summary (PCS) and Mental Component Summary (MCS). Possible domain scores range between 0-100, where 100 represents best possible HRQoL. The questionnaire has been validated in Sweden[108, 109] and has been used exhaustively among IC patients[110-113]. The SF-36 may also be used for cost-utility analysis within healthcare.

3.4 Disease-specific health-related quality of life instruments

Disease-specific HRQoL instruments are designed to focus on the specific problems and issues related to a certain disease. The driving force for the development of disease-specific instruments was mainly that generic instruments often proved insensitive to detect differences in clinical interventional trials[114, 115]. When using HRQoL as a clinical endpoint in IC studies, disease-specific HRQoL instruments may be especially important because IC patients are often affected not only by leg ischemia but often also

by several associated comorbidities that may negatively influence HRQoL even after a successful vascular procedure. Vascular Quality of Life Questionnaire (VascuQoL), developed by Morgan et. al. in 2001[116] is an example of a disease-specific HRQoL instrument intended for use in PAD. The instrument has been translated to several languages[117] and is endorsed as one of the preferred disease-specific questionnaires for HRQoL measurement in IC patients[118, 119]. It consists of 25 items, subdivided into five domains: activities (eight items), symptoms (four items), pain (four items), emotional (seven items) and social (two items). Each question has a seven-point response scale. An overall total score and five domain scores are generated, ranging from one (worst HRQoL) to seven (best HRQoL). Recently, with respect to clinical change, the *minimal important difference* has been established for the VascuQoL in patients with critical limb ischemia[120]. The *minimal important difference* represents the smallest change in health status (e.g. as identified by a HRQoL questionnaire) that a patient would identify as important[121].

For research purposes it is generally recommended to use a combination of a generic- and a disease-specific HRQoL instrument. The former allows for comparisons with other diagnoses and the general population and the latter adds sensitivity to detect clinical change in response to different treatment algorithms[119].

4 TREATMENT OF INTERMITTENT CLAUDICATION

4.1 General considerations

The treatment algorithm in intermittent claudication relies on a two-armed strategy. The first component concerns reduction of the risk for major vascular complications (cardio- and cerebrovascular) attributable to atherosclerotic disease, and the second component concerns the management of the claudication symptoms. This requires a comprehensive approach using a combination of risk factor modification efforts, medical therapy, exercise training and, sometimes, revascularization[122]. Moreover, adjunctive measures such as brief psychological intervention may be important in encouraging IC patients to change their behaviour towards increased walking activity[83, 84].

4.2 Risk factor modification and medical therapy

Medical treatment strategies in IC are usually targeted against systemic atherosclerosis and risk factor modification. However, despite well-established recommendations, commonly recognized risk factors may not be optimally treated in IC[123].

Smoking cessation is probably the most cost-effective way of reducing the risk for cardiovascular events and stroke in IC, and may include nicotine replacement therapy and partial nicotine antagonists[124].

Antiplatelet therapy in the form of aspirin reduces serious cardiovascular events and stroke in IC[125] and is recommended in the medical management of symptomatic PAD[6, 126, 127]. Clopidogrel constitutes an effective alternative[128, 129], that also may be used in patients intolerant to aspirin[127]. Even the combination of aspirin and clopidogrel may be considered in selected high-risk cases[130], but the small to moderately increased effect of dual antiplatelet therapy might be counterbalanced by an increased risk of bleeding complications[131].

The use of statins is widely recommended in symptomatic PAD and has been showed to reduce cardiovascular events during long-term follow-up irrespective of baseline s-cholesterol level[132]. The prescription of statins to nearly every patient with PAD is thus recommended in the recent UK National Institute for Health and Clinical Excellence guideline for the

management of PAD[129]. Furthermore, statin therapy may also improve walking capacity in IC[133-135].

All IC patients with elevated blood pressure should receive antihypertensive treatment to reduce risk of major vascular complications. In the Trans-Atlantic Society Consensus (TASC II) document, angiotensin-converting enzyme (ACE) inhibitors or thiazide diuretics are considered as appropriate first-line antihypertensive treatment options[6]. The ACE inhibitor ramipril, compared to placebo, was recently shown to substantially improve maximum treadmill walking distance in IC after two years in subjects with a baseline systemic blood pressure <160/90[136], and might thus be preferred as antihypertensive agent among IC patients. However, close initial monitoring of renal function is mandatory, as a large proportion of PAD patients have coexistent renal artery stenotic disease[122] and in such patients ACE inhibition may induce renal failure.

Improvements in diabetic metabolic control have been shown to coincide with reduced disease progression in cardiovascular disease[137] but corresponding studies in PAD are lacking. However, extrapolating results from other vascular districts, several PAD guidelines advocate aggressive metabolic control in diabetics with PAD[6, 138].

There are also a few vasoactive drugs specifically designated to improve walking function in IC. These include cilostazol, naftidrofuryl oxalate[139] and pentoxifylline[140]. The only available drug approved by the Swedish Medical Products Agency is cilostazol, a phosphodiesterase III inhibitor. Although the mechanism of action for cilostazol is not fully understood, the effect in IC has been attributed to its cyclic adenosine monophosphate-mediated vasodilating properties and its reversible inhibition of platelet aggregation[141]. The positive effect of cilostazol on walking function in IC has been demonstrated in several studies[142, 143], with consequent improvement in HRQoL[144]. A Cochrane review from 2008, based on eight RCTs, concluded that cilostazol improves ICD, MWD and HRQoL in IC patients. A health technology assessment by the Swedish Council on Technology Assessment in Health Care (SBU) made similar conclusions regarding walking improvement, but questions were raised regarding cost-effectiveness and the lack of long-term follow-up data[145]. In a recent systematic review comparing the efficacy of different vasoactive drugs, both cilostazol and naftidrofuryl oxalate were found to be effective treatments for IC[146]. In that study, naftidrofuryl oxalate was considered to be the more effective of the two drugs, however, no long-term safety data is available for naftidrofuryl oxalate. The long-term safety of cilostazol was tested in the CASTLE study[147]. In this study, all cause mortality, cardiovascular mortality and serious bleeding events were similar as compared to placebo[147] although the study was actually underpowered to detect a small adverse impact, due to a

lower event rate than expected with regard to the primary end point (all-cause mortality). Interestingly, cilostazol has been shown to mitigate intimal hyperplasia[148] and thereby also theoretically offers the potential to improve the results of invasive procedures in IC[149, 150].

4.3 Exercise training

Because of the muscle pain brought on by exercise, individuals with PAD often avoid physical activity. This may lead to additional functional decline and reduced health-related quality of life[95]. Extensive scientific evidence has established the benefit of walking exercise in improving walking capacity in IC, why exercise therapy is recommended to all IC patients as a part of standard care[151]. Supervised exercise training programs (SET), conducted in physiotherapy departments, have been shown to further improve walking distance when compared to non-supervised exercise/standard care[152], and also to enhance the effect of revascularization when used as an adjunctive treatment[153]. However, compliance with SETs is generally low in IC[154, 155] and SETs are currently not available to the majority of IC patients[156]. Moreover, the long-term efficacy of SETs remains to be proven[129, 152]. To overcome some of these shortcomings, interest has turned to home-based exercise programs and there is some preliminary evidence that this approach may improve short-term walking capacity and HRQoL in IC[157, 158] as compared to unsupervised exercise/standard care. More recent advances within physiotherapy also offer several alternative training modalities in IC including Nordic pole walk exercise, leg-and arm ergometry and resistance training[159].

Exercise therapy might also have the potential to reduce the long-term risk for major vascular complications, although little is known about the magnitude and details of such potential effects in IC. Improved serum lipid profiles have been demonstrated in IC patients participating in exercise training[85, 160] and a recent study reported improved surrogate variables for endothelial function and vascular repair mechanisms imposed by a SET program[161].

4.4 Revascularization

Although exercise therapy still constitutes the mainstay for the treatment of leg symptoms in IC, an increasing number of patients are currently offered revascularization. According to the Swedish National Registry for Vascular Surgery (Swedvasc), 1824 invasive treatments were undertaken 2012 due to IC in Sweden and the absolute numbers have successively incremented every year since 2009[162]. This development may partly be driven by the current broad availability and marketing of minimally invasive revascularization

techniques and the increasing trend of using endovascular treatment options in IC[163]. This is also supported by data from the Swedvasc reporting that 90 % of the aortoiliac lesions and 63 % of the femoropopliteal lesions were treated by endovascular means in IC patients in 2012[162].

However, the evidence for justifying the use of vascular surgical treatment options in IC still has low or very low quality[129]. In their health technology assessment report, SBU recommended that future research should focus on establishing whether revascularization is an effective treatment option of leg symptoms when compared to non-invasive therapies in IC[164]. The Institute of Medicine of the National Academies ranked this research question among the top fifty American health challenges[165]. Large differences in studied patient populations, heterogeneity of comparators/control groups, differences with regard to severity of lesions in the vascular segment(s) studied, and the large variety of applied revascularization strategies all hamper the possibility to draw general conclusions from the existing evidence[164]. Moreover, the results reported from published trials are partly contradictory (outlined below) with regard to the perceived benefits of revascularization.

In a study by Whyman et. al, percutaneous transluminal angioplasty (PTA) of short femoropopliteal lesions did not confer any benefit in terms of walking capacity or HRQoL two years after the procedure when added to medical treatment alone[166]. Perkins et. al. investigated the effect, in terms of treadmill walking capacity, of PTA as compared to a supervised exercise program. Their study included patients with stable, unilateral IC and vascular lesions appropriate for endovascular intervention. In this study, PTA proved inferior to a supervised exercise program during short-term follow-up. With regard to long term follow-up data (a scarce commodity in existing IC interventional trials), equivalent treatment results were demonstrated for the two treatment groups[167].

More recently, a sustainable benefit from PTA has been demonstrated both in the aortoiliac- and the femoropopliteal segments with regard to walking capacity and HRQoL two years after the intervention, when added to exercise training and medical therapy[168, 169]. In 2008, Spronk et al. compared endovascular therapy of single-level aortoiliac- or femoropopliteal lesions suitable for angioplasty with a hospital-based SET programme and found no difference regarding ambulatory function or HRQoL after 12 months. Moreover, SET was found to be the most cost-effective option[170]. In the CLEVER study, Murphy et. al. compared the results of primary stent treatment + best medical therapy (BMT) in the aortoiliac segment vs. SET + BMS vs. BMT alone[85]. After six months, both the stent- and the SET groups showed a benefit in treadmill walking performance and HRQoL as compared to BMT alone. Interestingly, cilostazol treatment was included in BMT in all treatment groups in this trial. When comparing the stent- and the SET groups

head-to-head in the CLEVER trial, treadmill-walking capacity was somewhat better in the SET group (although the confidence interval for the advantage was wide and included zero), while HRQoL was significantly better in the stent group. In the CLEVER trial, the SET program was provided for six months and included treadmill sessions three times a week why a "learning effect" (se section 2.2) in the SET group may have introduced a bias possibly explaining these contradicting findings. Long-term follow-up in the trial is still ongoing.

As compared with PTA alone, primary stent placement in the aortoiliac segment has recently been shown to increase technical success and reduce major procedural complications[171].

Mazari et. al. recently compared the efficacy of PTA, SET and PTA + SET in a three-armed study of IC patients with femoropopliteal lesions. At 12-month follow-up, all studied treatment options were found to be equally effective in improving walking distances and HRQoL[172], however, SET was found to be the most cost-effective treatment option[173].

The Sahlgrenska Academy has contributed significantly to this field of research. In 1988, Lundgren et. al. demonstrated a substantial advantage with reconstructive open vascular surgery compared to SET in terms of walking performance after a mean follow-up of 13 months. Surgery however entailed more complications[174]. Gelin et. al. in 2001 compared open or endovascular revascularization versus SET versus a control group without active treatment. In this study, revascularization was shown to moderately increase walking capacity[155] and HRQoL at one-year follow-up[175]. Interestingly, in this study, SET did not entail any benefit in walking capacity as compared to a training advice alone, and compliance to the SET program was only 59 % when analysed at one year.

Although revascularization strategies in IC have uncertain merits and also confer risks for procedure-related and systemic vascular complications[176], some authors recommend revascularization of IC patients with synchronous coronary heart disease unable to participate in indicated cardiac rehabilitation programs due to leg symptoms. The purpose of revascularization in this setting is to enable participation, with the ultimate goal of preventing future cardiac events[177]. Preliminary data also indicate that revascularization might reduce the occurrence of future major cardiovascular events in IC patients[178].

The "Achilles heel" of all vascular interventions in PAD is restenosis of the treated vascular segment imposed by neo-intimal hyperplasia[179]. New technological advancements in the endovascular "tool-kit", aimed at enhancing the beneficial effects of angioplasty and counteracting the development of restenosis, are continuously made available by the medical

device industry. In a recent meta-analysis of adjunctive techniques for use during endovascular treatment of infrainguinal PAD, drug-eluting stents and drug-coated balloons appeared to be promising technologies worth of further study. Although data from this meta-analysis has to be interpreted with caution given the small and heterogeneous patient samples, the predominant use of composite and surrogate endpoints and the heterogeneity of performed interventions, these techniques may hold a potential to further improve the results of revascularization in the near future[180].

5 AIMS OF THE THESIS

- To test the hypothesis that a primary invasive treatment strategy (surgical or endovascular revascularization) improves health-related quality of life and walking distance more than a primary non-invasive strategy in relatively unselected patients with intermittent claudication, receiving best medical treatment and structured (non-supervised) exercise therapy.

- To test the hypothesis that the translated version of the PAD-specific health-related quality of life instrument VascuQoL is valid in a Swedish setting, allowing for consequent use as endpoint in IC interventional trials.

- To test the hypothesis that it would be possible to develop a short yet efficient version of the VascuQoL, for practical use in clinical routine scenarios.

- To test the hypothesis that a corridor-based walk test indoors closely correlates to "real-life" outdoor walking capacity and health-related quality of life.

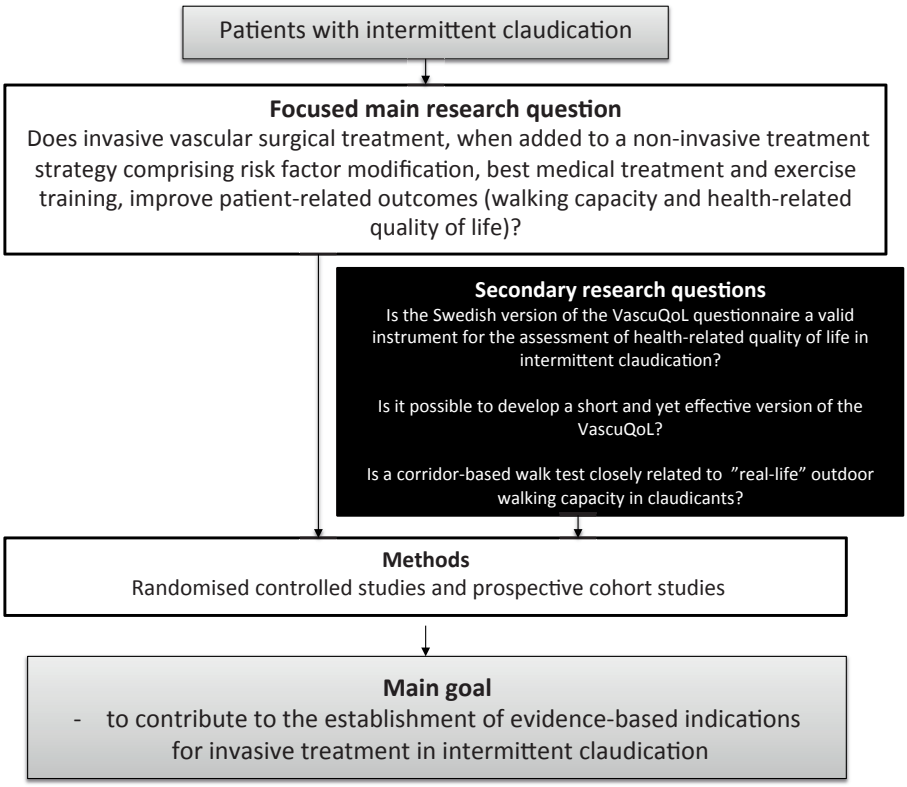

Figure 1. Focused research question and secondary research questions for the thesis project.

6 PATIENTS AND METHODS

	Study design	Participants	Intervention	Comparison	Primary outcome
Paper I	Randomized controlled trial	IC patients, n=201	Revascularization + BMT	BMT	MWP after 2 years
Paper II/III	Observational prospective cohort study	PAD patients, IC, n=129 CLI, n=71	N/A	N/A	N/A
Paper IV	Observational prospective cohort study	IC patients, n=49	N/A	N/A	N/A
Paper V	Randomized controlled trial	IC patients, n=158	Revascularization + BMT	BMT	HRQoL after 1 year

Table 1: Overview of studies included in the thesis. IC=intermittent claudication; CLI=critical limb ischemia; BMT=best medical treatment; MWP=maximum walking performance; HRQoL=health-related quality of life; N/A=non applicable.

6.1 Study populations, general design, follow-up and outcome

A summary of study designs for the trials included in this thesis is provided in table 1.

6.1.1 Study I

In this prospective randomized controlled study, we tested the hypothesis that a primary invasive treatment strategy (surgical or endovascular revascularization) improves health-related quality of life and walking distance more than a primary non-invasive strategy in relatively unselected patients with intermittent claudication, receiving best medical treatment and structured (non-supervised) exercise therapy. All referred patients with supposed IC symptoms were screened for inclusion. Every patient ≤85 years with established IC and stable symptoms were considered for inclusion. Patients with two or more previously occluded ipsilateral vascular reconstructions were excluded, as were cases with very severe symptoms where invasive treatment was considered mandatory (main criteria according to protocol: inability to work because of IC; subcritical ischemia with

occasional rest pain; infrarenal aortic thrombosis). Included patients underwent duplex ultrasound of the aortoiliac- and femoropopliteal segments, and in the presence of a significant vascular lesion consenting individuals were randomised in the study. Randomisation was performed using a computerized minimisation procedure[181] based on fifteen variables with presumed prognostic importance and 201 IC patients were subsequently randomised to primary invasive (INV, n=100) or non-invasive (NON, n=101) treatment during a seven-years period ending in January 2002. Both groups received identical (non-supervised) training advice, risk-factor management and medical intervention for secondary prevention. All patients were followed for two years and primary endpoint was maximum graded treadmill walking performance (MWP) calculated based on speed, slope and body weight and expressed in watts (W). Secondary outcomes included HRQoL, assessed with SF-36.

6.1.2 Study II and III

In these two studies, we first tested the hypothesis that that the Swedish version of the PAD-specific health-related quality of life instrument VascuQoL is valid in a Swedish setting. Following this, the hypothesis that it would be possible to develop a short and yet effective version of the VascuQoL was tested. A prospective cohort of 200 patients with established PAD diagnosis was consecutively recruited from the vascular centres at two university hospitals (Malmö and Gothenburg). Out of the 200 patients, 129 had IC and 71 had critical limb ischemia (CLI). All patients independently completed the Swedish VascuQoL and the SF-36 questionnaires at the vascular outpatient clinic. At one of the vascular centres, 127 of the participating patients also completed both questionnaires (administered by mail) six months after a vascular intervention. ABI was measured using a non-directional pen Doppler and a standard blood pressure cuff. Information regarding prospectively defined cardiovascular risk factors was collected from the medical records.

In study II, construct validity of the VascuQoL was investigated with psychometric methods and face validity was assessed by a group of Swedish PAD experts (n=5).

In study III, a combined strategy of psychometric testing, using the same dataset as in study II, and individual cognitive interviews (IC patients, Rutherford stage 3, n=15) were used for the selection and reduction of items. Rasch analysis[102] was used to assess and revise the proposed short version with regard to rating scale, discriminative properties, item-fit and targeting. The Rasch model was also used to test unidimensionality and signs of differential item functioning of the short version. In addition, criterion validity of the developed short version (VascuQoL-6) was further assessed in a group of IC patients (n=21), correlating the results of the VascuQoL-6 with

the measured walking distances during a 40-minutes GPS-monitored outdoor test walk.

6.1.3 Study IV

In this study, we tested the hypothesis that a corridor-based walk test indoors closely (CI for r>0.5) correlates to "real-life" outdoor walking capacity and health-related quality of life. In a prospective observational cohort study setting, patients with established IC without any other activity-limiting medical condition and of age ≤85 years were eligible. Exclusion criteria were inability to understand Swedish language, thromboembolic aetiology and weight >120 kilograms. After written informed consent, forty-nine patients were recruited from the vascular surgical outpatient clinic. Self-reported maximum walking distance (SR-MWD) was recorded in every patient and all patients completed the VascuQoL questionnaire. All patients underwent a graded treadmill test and maximum walking distance on the treadmill was recorded (MWD). In addition, every patient performed the *six-minute walk test* (6MWD). "Real life" outdoor walking capacity was assessed during a 40-minutes outdoor test walk using a smartphone GPS-application (Walkmeter®, version 10.0.3, Abvio Inc.); the total covered distance during the test walk was recorded and used as "real-life" walking capacity. Precision of the measurements captured by the smartphone application was established by repeated measurements (n=22) on a 400 m track-and-field arena. Associations between the different walk estimates and "real-life" walking capacity and HRQoL respectively were investigated by correlation analysis.

6.1.4 Study V

In this prospective randomized controlled study, we tested the hypothesis that a primary invasive treatment strategy (surgical or endovascular revascularization) improves health-related quality of life and walking distance more than a primary non-invasive strategy in relatively unselected patients with intermittent claudication, receiving current and updated best medical treatment and structured (non-supervised) exercise therapy. A senior vascular surgeon screened all patients ≤ 80 years, referred to the vascular surgical outpatient clinic because of suspected IC symptoms, for inclusion in the study. Of individuals with confirmed IC diagnosis, patients with very mild symptoms and patients with so severe symptoms that invasive treatment was considered mandatory (main criteria according to protocol: inability to work due to IC; subcritical ischemia with occasional rest pain; infrarenal aortic thrombosis) were excluded. Patients with a weight >120 kilograms (maximum possible load on treadmill) were also excluded, as were patients with two or more previously failed ipsilateral vascular interventions. In addition, patients with inability to understand the Swedish language (Swedish versions of HRQoL assessments were used) were excluded. The remaining

patients were included, and underwent duplex ultrasound of the aortoiliac and femoropopliteal arterial segments. Finally, patients that after duplex ultrasound assessment required open surgical revascularization below the tibioperoneal trunk were excluded. The remaining patients, giving informed consent, were subsequently randomised. Computerized minimisation[181], based on nine variables with presumed prognostic importance, was used for group allocation and 158 patients were subsequently randomized to invasive (INV, n=79) or non-invasive (NON, n=79) primary treatment during a three years period ending in December 2012. Both groups received identical (non-supervised) training advice and current risk-factor management and medical intervention for secondary prevention. Patients randomized to revascularization were treated according to the recommendations in the TASC II document[182] and all patients were followed for one year. Primary endpoint was HRQoL, assessed with VascuQoL and SF-36, and secondary outcomes included graded treadmill testing. To further assess HRQoL outcomes, SF-36 data from an age- and gender matched sample (n=158) retrieved from the Swedish general population (Swedish SF-36 normative database[183]) were compared with the SF-36 scores at twelve months in the INV and NON group respectively.

6.1.5 Aggregated analysis (study I and V)

An outcome analysis was performed of endpoints available in both studies (MWD and MWP at 12 months), pooling data from study I with the corresponding outcome data from study V.

6.2 Psychometric and statistical methods

Statistical analysis was mainly performed using SPSS version 17.0 - 20.0 (SPSS Inc., Chicago, IL, USA). The multitrait/multi-item scaling analysis (study II) was performed using MAP-R for Windows, version 1.0 and the factor analysis (study III) was performed in the SAS/STAT® statistical software package. The Rasch model calculations (study III) were made in the Winsteps 3.70.2 program (Chicago, Illinois).

6.2.1 Study I and V

The intent-to-treat principle was applied and included all randomised patients. For intergroup comparisons of the primary and secondary endpoints, the Student's t-test was used for normally distributed continuous values and the Mann-Whitney U test for data with skewed distributions. The Mann-Whitney U test was consistently used to assess intergroup differences in all HRQoL parameters. The magnitude of change in HRQoL was estimated using effect size calculations (*ES*=difference in mean values between

baseline and one year divided by the standard deviation at baseline). Cohen's criteria for interpreting ES were applied (small=0.2-0.5, moderate=0.5-0.8, large>0.8)[184]. Results are presented as means (SD) or median (range) values for continuous variables and percentages for categorical variables. Significance was assumed at $p < 0.05$.

6.2.2 Study II

The latent construct of the VascuQoL was tested by correlation analysis versus corresponding SF-36 subscales, using Pearson correlation coefficient. Multitrait/multi-item scaling analysis was used to test item-scale convergent and divergent validity and reliability was assessed by Cronbach's alpha calculations. Cronbach's alpha is a measure of internal reliability, or consistency, i.e. how closely related a set of items is as a group. A Cronbach's alpha value of ≥ 0.7 is generally considered acceptable for group data, while 0.9 is recommended for individual assessment[185]. Sensitivity was evaluated by testing the ability of the VascuQoL to discriminate individuals with IC from critical limb ischemia patients, using the non-parametric Mann-Whitney U test. Standardized response mean (SRM) was used for responsiveness testing and was calculated for each domain of VascuQoL, SF-36 and ABI (SRM = mean difference in score after vascular intervention as compared to baseline, divided by the standard deviation of the difference). Cohen's criteria for interpreting effect sizes were applied (small=0.2-0.5, moderate=0.5-0.8, large>0.8)[184].

6.2.3 Study III

For item selection and reduction from VascuQoL-25 we applied the following criteria:

1. *Correlation analysis criteria* (item- versus total score, corrected for overlap), choosing the items that correlate most strongly with the total score of VascuQoL-25, using Pearson correlation coefficient.
2. *Exploratory factor analysis criteria*: choosing the items with the strongest factor loading in a single factor model for all 25 variables.
3. *Disease burden criteria*: choosing the items where respondents report most problems/limitations.
4. *Responsiveness criteria*: choosing items that change most after treatment.
5. *Content criteria*: selecting at least one item from every domain of VascuQoL-25.

Cronbach's alpha was used to assess internal consistency of the short version. Sensitivity was evaluated by testing the ability of VascuQoL-6 to

discriminate between patients with intermittent claudication and critical limb ischemia, using the Mann-Whitney U test.

VascuQoL-6 responses were thereafter organized into a Rasch measurement model (cf. section 3.2) with the aim of creating a latent variable of disability caused by peripheral vascular disease on a single linear scale. Rasch analysis tests the following psychometric properties of the questionnaire:

1. *Rating scale*. This test investigates whether the category thresholds are ordered. VascuQol-25 uses seven response categories, and so there are six thresholds between the response probabilities.
2. *Ability to discriminate different levels of person ability*. This is a reliability test, which results in two quantities: person separation and separation reliability. The separation reliability coefficient represents the precision of the item measures[104].
3. *Item fit statistics*. Each item should conduce to a picture of the respondent's ability in a predictable way. Two fit statistics are generated in the analysis: infit and outfit mean square. Both these fit statistics should have a value of 1, with suggested limits of 0.7 and 1.3[186].
4. *Targeting precision of the instrument to the studied population*. Ideally, the ability of the patients and the difficulty of the questions should centre on the same mean. There should be meaningful items for the more able patients as well as for the less able patients[187].
5. *Unidimensionality.* This signifies that the items in the instrument measure one and the same underlying trait. Unidimensionality is necessary to create and use a summary score[188].
6. *Differential item functioning*. This test evaluates whether a specific group of patients (e.g. divided by gender, co-morbidity, disease status, etc.) responds differently to an individual item despite similar levels of the underlying trait being measured. DIF can cause misfitting of the data to the Rasch model. In our analysis, testing for DIF was performed between groups differing by age and gender.

Standardized response mean (SRM), based on the calculated Rasch person scores, was used for responsiveness testing of the VascuQoL-6. Correlations between VascuQoL scores and outdoor walking capacity during the outdoor test walk was explored using nonparametric measures of statistical dependence (Spearman rho).

6.2.4 Study IV

For continuous variables, means and standard deviations or medians and ranges were calculated, and for categorical variables percentages were calculated. The relationships between the different clinical walk assessments

(SR-MWD, MWD and 6MWD) and outdoor walking capacity and HRQoL respectively were explored using nonparametric correlation analysis (Spearman rho). With regard to the accuracy of the smartphone GPS application, test-retest reliability was assessed by analysing the coefficient of variation (CV) and the proportion of observations within ± 10 % from the known distance. Significance was assumed at $p < 0.05$.

7 RESULTS

7.1 Study I

Baseline data were nearly identical in the two groups (table 2); the flow of randomised patients in the study is given in figure 2. Baseline MWP was 66 (25) and 67 (24) W in the invasive- and non-invasive groups respectively. HRQoL at baseline were similar in both groups and was impaired for all SF-36 domains as compared to age- and gender-matched population data (figure 3). In the INV group, 80 % received invasive treatment after a median time of 14 (3-72; interquartile range =17) weeks. Open surgical revascularization was performed in 53 % of the cases and 47 % were treated endovascularly. Seven patients (4 %) died (INV: n=1; NON: n=6, n.s. between groups) during the two years but no amputations were performed. The attendance rate at 24 months was 86 % in the INV versus 71 % in the NON group (figure 2).

With regard to the primary endpoint, the change in MWP at 2 years in the INV versus the NON group failed to reach significance (p=0.104, figure 4). Two SF-36 physical subscales, Bodily Pain ($p<0.01$) and Role Physical ($p<0.05$) improved significantly more in the INV- versus the NON group.

	Invasive group (n=100)	Non-invasive group (n=101)
Age, years (range)	68 (41-84)	68 (44-84)
Gender male/female, %	62/38	64/36
Smoking habits, %, yes/ex-smoker/no	41/32/27	42/33/25
Diabetes mellitus, %	16	18
Body Mass Index (BMI)	26 (3.8)	26 (3.4)
Duration of symptoms, <1y/1-2 y/>2y, patients	1/48/51	0/47/54
Systolic blood pressure, mmHg	162 (23)	158 (27)
Ankle pressure, most symptomatic side, mmHg	94 (27)	94 (31)
Ankle-brachial index	0.59 (0.17)	0.60 (0.19)
Femoral pulse (symptomatic side), normal/reduced/absent, %	56/29/15	63/24/14
Maximal treadmill performance (W, watts)	66 (24)	67 (24)
S-hemoglobin (g/l)	144 (14)	144 (13)
S-cholesterol (mmol/l)	6.0 (1.3)	6.2 (1.3)
S-triglycerides (mmol/l)	2.1 (1.2)	2.3 (2.7)
S-Creatinine (μmol/l)	104 (27)	107 (27)

Table 2. Baseline demographic data and risk factors used in the computerized minimization procedure, presented according to treatment group. Values are given as mean (SD) when applicable.

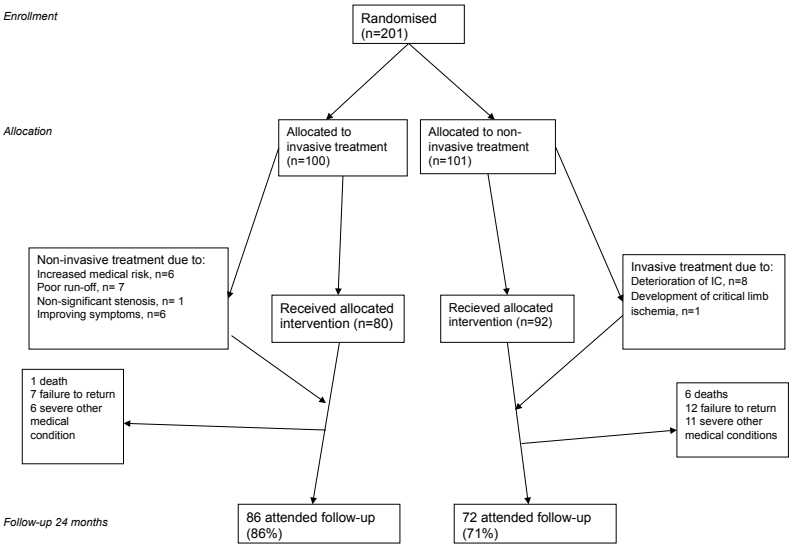

Figure 2. Diagram showing flow of randomized patients through trial.

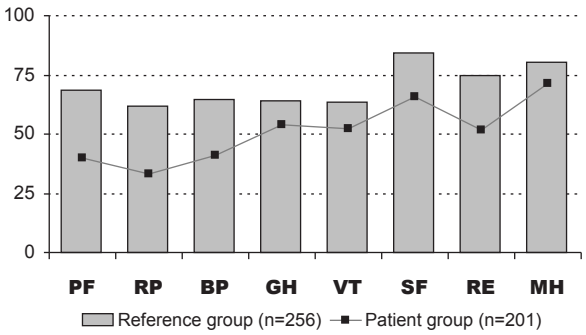

Figure 3. Health related quality of life (HRQoL), assessed with SF-36 in study population at baseline, as compared to age and gender matched population data (reference group).

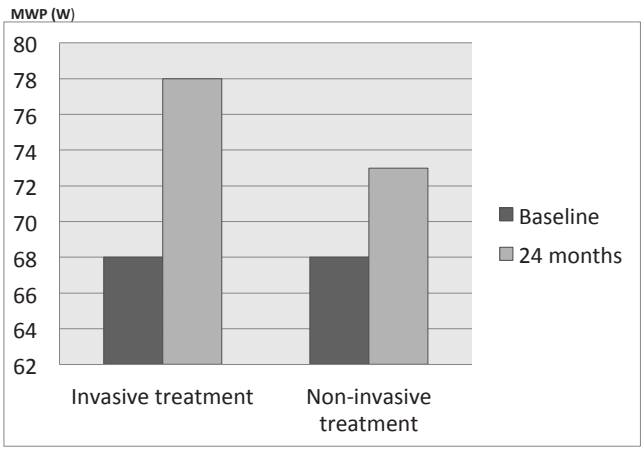

Figure 4. Results regarding maximal walking performance (MWP) in the INV versus the NON group, from baseline to 24 months (p=0.104 for the intergroup difference of MWP change).

7.2 Study II

Baseline demographic data and risk factors are shown in table 3. Missing data was low and in the final dataset, 183 out of the 200 patients (92 %) had complete HRQoL registrations and all patients had computable scales (using the half-scale method). All five PAD experts agreed that VascuQoL covers central aspects of PAD disease. Questions were raised about the relevance of the seven-point response option and a reduction of possible response options was suggested.

Demographics and risk factors in patient population

Age, mean (SD)	**70 (9) y**
Gender (male/female; %)	**57/43**
Regulary smoking (current or in the last five years), %	**49**
Previous TIA or stroke, %	**10**
Diabetes, %	**29**
Hyperlipidemia, %	**11**
Angina pectoris/previous myocardial infarction, %	**43**
Chronic pulmonary disease, %	**13**
Kidney disease (s-creatinine >150 mmol/l), %	**10**
Ankle-brachial –index, mean (SD)	**0.70 (0.18)**

Table 3. Demographics and risk factors in patient population, n=200.

Correlation analysis showed significant correlations between several SF-36 subscales and VascuQoL domain scores. The strongest correlations were noted between VascuQoL *activity* subscale and SF-36 *physical functioning* subscale (PF) (r=0,69; p<0.01) and between VascuQoL *emotional* subscale and SF-36 *mental health* subscale (MH) (r=0,68, p<0.01). Also, the VascuQoL *pain* subscale correlated strongly with SF-36 *bodily pain*, as did VascuQoL *total* score and SF-36 *physical component summary*, pcs.

Multitrait/multi-item scaling analysis results are summarized in table 4. Item-scale correlations indicated satisfactory convergent validity (i.e. whether different measures that theoretically should be related, are in fact related) for the subscales *pain*, *social* and *emotional*. The *activity* subscale performed generally well while the *symptoms* subscale showed a relatively poor convergent validity. With regard to discriminant validity (i.e. whether measurements that are supposed to be unrelated are in fact unrelated), the subscales *activity* and *emotional* performed well but the subscales *pain*, *social* and *symptoms* were shown to have relatively poor discriminant validity.

Multitrait/multi-item scaling tests					
	Item-scale convergent validity		**Item-scale discriminant validity**		**Scaling fulfilment**
	Range of r	**Criterion 1**	**Range of r**	**Criterion 2**	
Scale	Item-scale correlations[a]	% of item-scale correlations ≥ 0.40[b]	Correlation with other scales[c]	Number of items higher[d]	Number of items that meet both criteria 1 and 2[e]
Activity	0.25-0.71	88	0.04-0.70	7/8	7/8
Pain	0.51-0.66	100	0.38-0.66	2/4	2/4
Emotional	0.59-0.76	100	0.42-0.64	5/7	5/7
Social	0.55-0.55	100	0.48-0.70	0/2	0/2
Symptom	0.3-0.55	50	0.29-0.63	0/4	0/4

Table 4. Summary of results of multitrait/multi-item scaling tests of the Swedish VascuQoL questionnaire.

[a]Pearson correlations between items and hypothesized scale (corrected for overlap).

[b]Number of item-scale correlations that meet the minimum standard for convergent validity (r≥ 0.40)/total numbers of correlations.

[c]Pearson correlations between items and competing scales.

[d]Correlations higher between items and hypothesized scale in comparison with all other scales.

[e]Items in each scale that meet criteria for both item-scale convergent (Criterion 1) and discriminant (Criterion 2) validity.

For the VascuQoL *total* score, Cronbach's alpha was 0.94 and for the subscales, alpha values were acceptable (alpha ≥ 0.7), except for the *symptom* subscale that had a somewhat weak alpha value (0.64).

Proportions of patients scoring at the lowest possible scale level (floor effect) were marginal for all subscales (≤2.5 %). Ceiling effects (proportion of patients scoring at the highest possible scale level) were also negligible, although 6.5% of the patients scored at the maximum scale level of the social subscale.

VascuQoL total and all domain scores were shown to discriminate significantly ($p<0.001$) between patients with intermittent claudication and critical limb ischemia. All but one (*social* scale) of the VascuQoL subscales demonstrated a standardized response mean (SRM) value over 0.8, indicating excellent responsiveness. In comparison with SRM for the different SF-36 scores and ABI, VascuQoL performed better.

7.3 Study III

This study utilized data from the same patient population as in study II (table 3).

7.3.1 Psychometric selection of VascuQoL items

The results of the psychometric analysis are summarized in table 5. The item-total correlation analysis shows the strength of association between each of the 25 VascuQoL items and the total VascuQoL-25 score. The outcome of the item-total correlation analysis was similar to the item-factor pattern obtained from factor analysis. However, the disease burden and responsiveness criteria uncovered a somewhat different item structure. The analysis of disease burden identified in which areas the respondents report most problems/limitations in HRQoL. Responsiveness assessment showed items that are most sensitive to changes in HRQoL after treatment. The intention was to select items that performed well according to all selection criteria. However, as the aim was to construct a short-form instrument that would perform well for both the description of disease severity and as an outcome measure after vascular intervention, we attached greater importance on items that were most effective according to disease burden and responsiveness criteria. Also, as walking limitations are of great concern for most PAD patients, two items from the activity domain were chosen, and one item from the remaining four domains (*symptoms*, *pain*, *social* and *emotional* subscales), resulting in six items for the short version of the instrument, VascuQoL-6. The selection of two items from the activity domain was also supported by factor analysis, which revealed that four of the five highest loading items were from the activity domain, table 5.

Item-total correlation analysis		Exploratory factor analysis		Disease burden		Responsiveness	
Pearson correlations (r) between the 25 items and the total VasquQoL-25 score (corrected for overlap).[1]		Factor correlations are presented. Results of a single factor model including all 25 items.[2]		Mean item score before treatment. A lower mean value indicates more health problems/limitations (range 1-7).		Change in item score after treatment. A larger mean change indicates greater improvement.	
Activity 16	0.74	Activity 16	76	Activity 4	2.15	**Activity 18**	**1.92**
Social 6	0.72	Activity 22	76	Pain 1	2.20	Pain 1	1.91
Activity 22	0.71	Social 6	72	**Activity 18**	**2.58**	**Emotional 12**	**1.91**
Emotional 25	0.69	Activity 14	72	**Emotional 12**	**2.69**	**Pain 20**	**1.76**
Activity 14	0.69	**Activity 18**	**71**	**Symptoms 5**	**2.74**	Activity 4	1.74
Emotional 12	**0.68**	**Social 15**	**71**	**Pain 20**	**2.79**	**Activity 10**	**1.60**
Emotional 11	0.67	**Emotional 12**	**70**	**Activity 10**	**3.10**	**Symptoms 5**	**1.59**
Social 15	**0.66**	Emotional 11	70	**Social 15**	3.32	Symptoms 8	1.50
Pain20	**0.66**	Emotional 25	69	Activity 14	3.33	Emotional 19	1.48
Symptoms 5	**0.66**	**Pain 20**	**68**	Activity 22	3.37	Pain 7	1.46
Activity 18	**0.65**	**Symptoms 5**	**67**	Symptoms 8	3.53	**Social 15**	1.40
Emotional 21	0.65	Emotional 19	67	Emotional 19	3.71	Activity 22	1.34
Emotional 19	0.65	**Activity 10**	**65**	Pain 7	3.93	Emotional 25	1.31
Pain 13	0.63	Emotional 21	65	Emotional 25	4.03	Symptoms 3	1.17
Pain 7	0.63	Symptoms 8	62	Symptoms 3	4.20	Activity 14	1.17
Symptoms 8	0.62	Pain 7	61	Activity 16	4.20	Activity 16	1.17
Activity 10	**0.62**	Activity 4	61	Pain 13	4.35	Emotional 11	1.03
Emotional 2	0.60	Pain 13	61	Emotional 11	4.37	Emotional 23	0.99
Emotional 23	0.60	Emotional 2	59	Social 6	4.58	Social 6	0.94
Activity 4	0.57	Emotional 23	58	Emotional 2	4.61	Pain 13	0.94
Pain 1	0.51	Pain 1	53	Emotional 21	4.92	Symptoms 17	0.93
Symptoms 17	0.49	Symptoms 17	48	Emotional 23	4.74	Emotional 2	0.83
Symptoms 3	0.42	Symptoms 3	41	Symptoms 17	5.21	Emotional 21	0.82
Activity 9[3]	0.16	Activity 9	24	Activity 9	1.73	Activity 9	1.60
Activity 24[3]	0.57	Activity 24	58	Activity 24	4.71	Activity 24	1.26

Table 5. Summary of psychometric analysis of VascuQoL-25 items according to four criteria: item-total correlation analysis, exploratory factor analysis, disease burden and responsiveness. Items are labelled according to the health domain they represent in VasuQoL-25. Item numbers correspond to the placement in VascuQoL-25 (cf. Appendix section). The six items selected for the VascuQoL-6 are in bold font.

1. Corrected for overlap means that the value of the test item is subtracted from the total VascuQoL-25 score.

2. One factor accounted for 74.4% of the variance.

3. Items 9 and 24 were excluded because of suboptimal item construction.

The correlation between VascuQoL-25 and VascuQoL-6 was r=0.88 (before intervention), r=0.96 (after intervention) and r=0.91 (difference), p<0.001. Cronbach's alpha for VascuQoL-6 was 0.85 before and 0.94 after intervention, indicating good internal consistency. VascuQoL-6 significantly differentiated individuals with intermittent claudication from critical limb ischemia patients (p<0.001).

7.3.2 Cognitive interviews

Every item of the VascuQoL-25 was considered comprehensible by the responders. Items 2, 11, 17, 21, and 23 (se Appendix section) were considered least relevant in relation to the disease and were not considered for the short version. Most responders (14 of 15) commented on the abundance of response options, and suggested that three to four response options should be used. Of the proposed items for the short version, the participants considered all of the selected items as highly relevant for PAD disease.

7.3.3 Rasch analysis

Rasch analysis demonstrated disordered category thresholds. The categories for the six chosen items were therefore reduced from 7 (VascuQoL-25) to 4 (VascuQoL-6), which gave ordered thresholds (illustrated with item 20 in figure 5). Person separation for VascuQoL-6 was 2.23 and separation reliability coefficient was 0.83, indicating high precision. Item fit was good with "infit" between 0.85 – 1.23 and "outfit" between 0.79 – 1.12. Targeting showed that the degree of difficulty of the items matched the ability of the responders as item mean was 0 logits and person mean 0.09 logits. Evidence of unidimensionality was shown by analysis of residuals, demonstrating that the variance explained by the measures was comparable for empirical calculation (62.7%) and by the model (62.5%). The VascuQol-6 was free of differential item functioning (<0.5 logits) by sex and age. Standardized response mean, calculated on the person scores achieved from Rasch analysis, was 1,15 for the short version, which indicates excellent responsiveness.

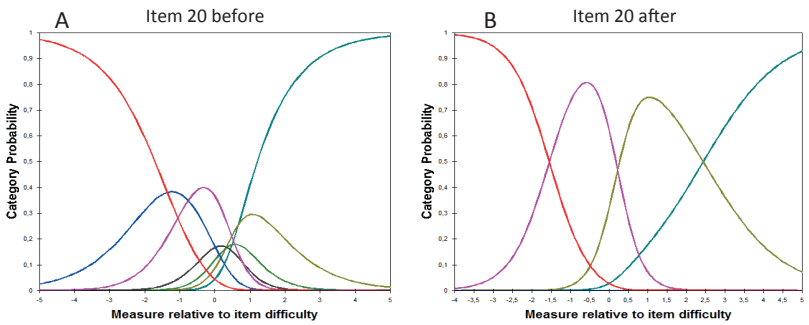

Figure 5. Example of category thresholds for item 20 in VascuQol-25 before collapsing categories (A) and for the same item in VascuQol-6 after collapsing categories (B).

7.3.4 GPS-monitored outdoor test walk

Both VascuQoL-25 and VascuQoL-6 correlated strongly with the total covered walking distance during the test walk. Spearman rank correlation coefficient was r= 0.78; p<0.01 for VascuQoL-25 and r=0.72; p<0.01 for VascuQoL-6, figure 6.

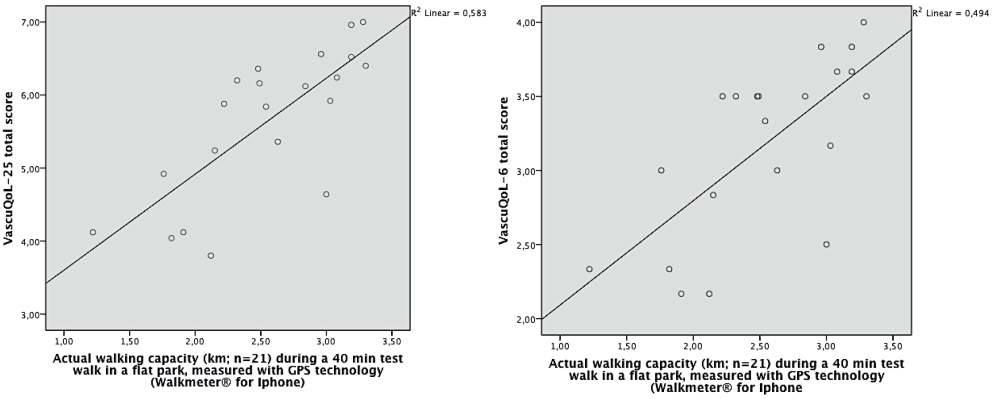

Figure 6. Correlation scatterplots for the correlations between VascuQoL-25 and VascuQoL-6 versus the total covered distance during the 40 min test walk.

The finally developed VascuQoL-6 instrument is provided in the Appendix section.

7.4 Study IV

During the 22 consecutive pilot tests of the smartphone GPS-application on the 400 meters track-and-field arena, adequate recordings were captured during 100 % of the walks. The coefficient of variation for the 22 consecutive test walks was 3.1 % (CI 2.4-4.5 %) and the median captured walk distance during the test walks was 415 (390-450). Out of all recordings, 96 % were at 400 m ± 10 %.

Demographic data and risk factors in the study population are provided in table 6. Median (range) outdoor walking distance during the 40 minutes outdoor test walk was 2495 (1110-3300) m.

Median (range) SR-MWD was 200 (25-1000) m, MWD on graded treadmill was 175 (58-507) m and median walking distance during 6MWD was 399 (183-523) m.

Demographics and risk factors in study population, n=49	
Age (mean + SD, years)	70 ± 6
Gender (male/female), %	49/51
Smoking habits	
Current smoker, %	29
Previous smoker, %	41
Non-smoker, %	30
Hypertension, %	76
Diabetes, %	8
Coronary disease/heart failure, %	27
Cerebrovascular disease, %	10
Pulmonary disease, %	18
Rutherford classification	
Category 1 (mild IC), %	43
Category 2 (moderate IC), %	37
Category 3 (severe IC), %	20
Lowest ankle-brachial index (mean + SD)	0.6 ± 0.2

Table 6. Baseline demographic data and risk factors in the studied population.

The associations between outdoor walking capacity and the different clinical walk assessments are given in figure 7. SR-MWD correlated moderately to outdoor walking capacity ($r=0.56$, CI 0.33-0.73, $p<0.001$) while MWD correlated strongly to outdoor walking capacity ($r=0.65$, CI 0.45-0.79, $p<0.001$). The 6MWD test showed the strongest correlation to the outdoor walking capacity ($r=0.78$, CI 0.64-0.87, $p<0.001$).

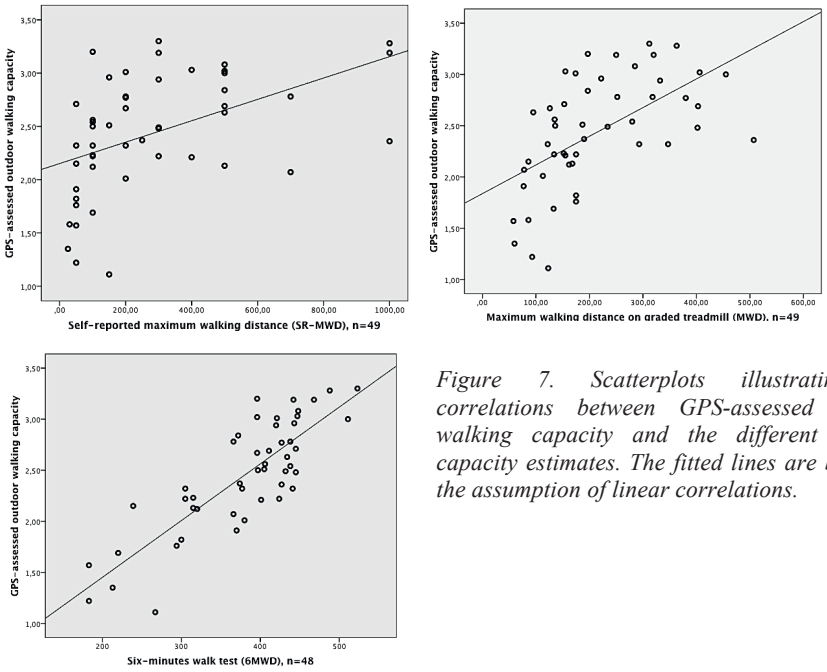

Figure 7. Scatterplots illustrating the correlations between GPS-assessed outdoor walking capacity and the different walking capacity estimates. The fitted lines are based on the assumption of linear correlations.

The correlation patterns between the different walk assessments and the VascuQoL are shown in table 7. Among the different walk tests, the 6MWD correlated most strongly with the VascuQoL, as 6MWD showed moderate correlations with the VascuQoL sum score and all of the domain scores. The treadmill performance (MWD) correlated moderately to the VascuQoL sum score and to two of the VascuQoL domain scores (*activity* and *pain*). SR-MWD showed moderate correlation to the VascuQoL sum score and to only one of the domain scores (*activity*).

	VascuQoL Activity score	VascuQoL Symptom score	VascuQoL Pain score	VascuQoL Emotional score	VascuQoL Social score	VascuQoL Total sum score
SR-MWD	0.40*	0.30	0.32	0.24	0.23	0.37*
MWD	0.37*	0.23	0.40*	0.27	0.20	0.34*
6MWD	0.57**	0.38*	0.52**	0.39*	0.38*	0.53**

*Table 7. Correlation pattern (Spearman ρ (rho)) between the different walk tests and the VascuQoL total and domain scores. SR-MWD=patient-reported walking distance; MWD=maximum walking distance during graded treadmill test; 6MWD=six minutes walk test. *=p<0.05; **=p<0.01.*

7.5 Study V

Between 2010 and 2012, 464 patients ≤ 80 years were screened for inclusion in the study and of these, IC diagnosis was established in 338 cases. When applying the predefined inclusion- and exclusion criteria, 205 were eligible for the trial and of these, 158 (77 % of eligible; 47 % of all patients with IC) were randomised in the trial. Demographic data at baseline showed no significant differences between groups (table 8). The enrollment in the study is shown in figure 8, and the flow of randomised patients is given in figure 9.

	Invasive group (n=79)	**Non-invasive group (n=79)**
Age, years	68 (7)	68 (6)
Gender male/female, %	52/48	53/47
Smoking habits, %, yes/ex-smoker/no	30/28/42	28/40/32
Diabetes mellitus, %	18	20
Body Mass Index	26(5)	26(4)
Duration of symptoms, <1y/1-2 y/>2y, %	22/25/53	13/49/38
Ankle-brachial index	0.73(0.17)	0.74(0.14)
Femoral pulse normal/reduced/absent, %	52/29/19	56/27/18
Intermittent claudication treadmill distance, m	78 (59)	87 (60)
Maximal treadmill distance, m	189(106)	194(103)
S-hemoglobin, g/l	135(13)	137(13)
S-cholesterol, mmol/l	4.9(1.1)	4.7(1.2)
S-triglycerides, mmol/l	1.5(1.0)	1.5(1.0)
S-creatinine, μmol/l	81(26)	89(30)
Kidney failure (s-creatinine >170 μmol/l), %	4	1
Angina pectoris, %	9	13
Previous myocardial infarction, %	15	13
Cerebrovascular disease, %	9	11
Chronic pulmonary disease, %	13	6

Table 8. Baseline demographic data and risk factors according to treatment group. Values are given as means (SD) where applicable. For all variables, no statistically significant differences between groups were noted. Variables used in the computerized minimization procedure are shown in bold font.

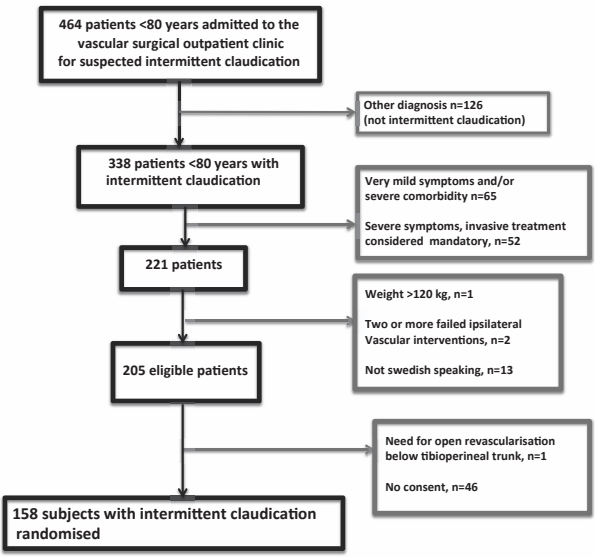

Figure 8. Flowchart of enrollment in the IRONIC trial.

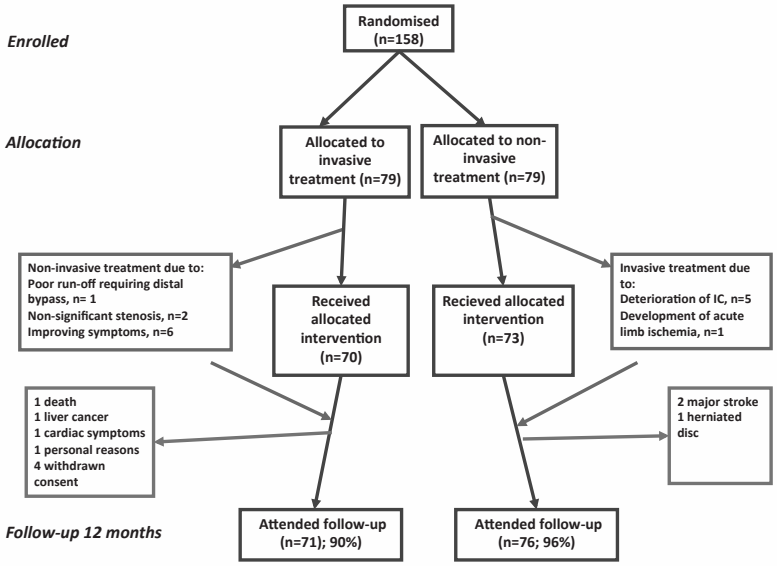

Figure 9. Flow of randomised patients in the IRONIC trial.

In the INV group, 52 of 70 patients (73 %) were treated by an endovascular approach. During follow-up, 13 INV patients underwent 21 re-interventions. Eight of these procedures were performed in a new vascular segment, ipsi- or contralateral, due to persistent symptoms, as allowed in the study protocol. Nine of the procedures (performed in four patients) were indicated to maintain primary patency and four of the procedures (of which three were undertaken in one patient where secondary patency could not be maintained) were indicated to establish secondary patency.

At 12 months (after correcting for multiple comparisons using the Bonferroni-Holm method[189]), SF-36 physical component summary ($p<0.001$) and two SF-36 physical subscales (PF and BP) improved significantly more in the INV versus the NON group. VascuQoL total score and three out of five domain scores were significantly improved in the INV versus the NON group (figure 10). When comparing SF-36 scores in an age- and gender matched sample from the general population (Swedish SF-36 normative database, n=158) with the corresponding scores at twelve months in the INV and NON groups, no differences were found for the INV group regarding any SF-36 variable, whereas all but one (RP) of the SF-36 subscales were significantly lower in the NON group (figure 11).

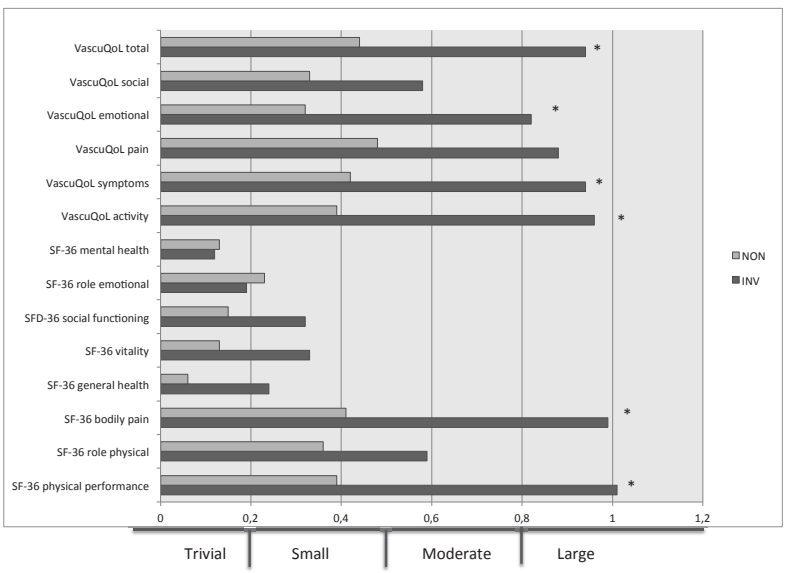

*Figure 10. SF-36 and VascuQoL subscale effect sizes (ES) calculated between baseline and 12 months for INV and NON patients. Cohen's criteria for ES: 0.0-0.2=trivial; 0.2-0.5=small; 0.5-0.8=moderate; >0.8=large. * $p<0.01$ between treatment groups.*

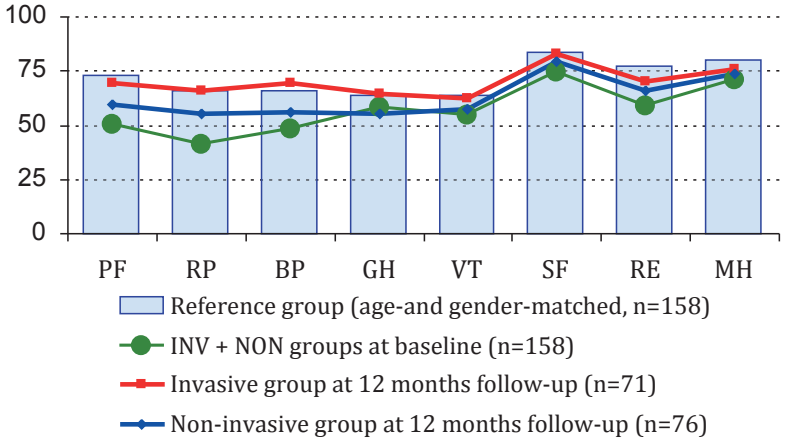

Figure 11: Status at 12 months with regard to the different SF-36 domain scores in INV-versus NON group, as compared to an age- and gender-matched reference population, retrieved from the general population in Sweden (Swedish SF-36 normative database). (PF=physical functioning; RP=role physical; BP=bodily pain; GH=general health; VT= vitality; RE=role emotional; SF=social functioning and MH=mental health).

The ICD on treadmill improved in the INV as compared to the NON group (+124 (196) m vs. +50 (99) m, p=0.003). The improvement in MWD did not differ between treatment groups (INV +59 (156) m vs. NON +30 (92) m, p=0.170).

During follow-up, one patient in the INV group died (due to myocardial infarction, six months after the vascular surgical procedure). No amputations were performed during follow-up. Two INV- and one NON patient suffered procedure-related complications.

7.6 Aggregated analysis, study I and V

Twelve months results of maximum treadmill walking distance (MWD) and performance (MWP) are summarized in table 9. The results from study I and V was pooled, rendering 306 individuals available for analysis. In this aggregated analysis, neither MWD (p=0.055) nor MWP (p=0.204) reached significance.

	Maximum walking distance (MWD)		Maximum walking performance (MWP)	
	INV	NON	INV	NON
Study I	+32 (13-50) m	+12 (-7-30) m	+8 (1-14) W	+3 (-2-7) W
Study V	+59 (22-96) m	+30 (9-51) m	+10 (5-14) W	+8 (4-12) W

Table 9. Summary of maximum treadmill results (MWD and MWP) at twelve months from study I and V. Values represent mean values (95% confidence interval).

8 DISCUSSION

8.1 Revascularization in intermittent claudication

In this thesis, the efficacy of a primary revascularisation strategy in intermittent claudication, when added to risk factor modification, medical therapy and non-supervised exercise training, was investigated in two fairly large randomised controlled trials. These studies are important as revascularization is increasingly applied to IC patients, in our country approaching 2000 procedures yearly, despite the surprisingly low quality of evidence for a patient benefit from such procedures. Partially conflicting results of invasive treatment efficacy have been reported previously (se section 4.4), and the actually achieved patient benefits with revascularization are uncertain[85, 166, 168-170, 172]. Also, there is a weak rationale for a generalisation of existing evidence to the majority of IC patients. The latter is highlighted by the fact that the lion's share of current existing trials have used highly selective inclusion criteria, including only subgroups of patients with vascular lesions of a certain severity and length, located in specific vascular regions, and with suitable anatomy for endovascular procedures. Moreover, there is significant heterogeneity with regard to patients, medical interventions and exercise programs used in the published studies, restricting possibilities to draw firm general conclusions. In addition, recent important developments in both invasive and medical interventions underscore the need for new well-designed clinical trials as a basis for evidence-based guidelines for revascularization in IC. As all existing treatment modalities in IC are currently rapidly evolving, the study of the optimal treatment strategy for claudicants represents a "moving target" in modern medicine. Recent important developments of available treatment options were also the main driving force for the conduct of study V, in which we aimed to fill the evidence-gap as identified by both the Institute of Medicine of the National Academies in the United States[165] and the by the Swedish Council on Technology Assessment in Health Care[164], in a currently relevant medical context.

Our study design, in both randomised trials presented in this thesis, differs from most recently published trials within this research area, and addresses a somewhat different research question. Our main research focus was extracted from the common clinical scenario where a vascular surgeon at the outpatient clinic is faced with a patient with established life-style limiting IC, seeking consultation for revascularization, and was formulated in the question – *"Does invasive vascular surgical treatment, when added to a non-invasive treatment strategy comprising risk factor modification, best medical*

treatment and exercise training, improve patient-related outcomes (walking capacity and health-related quality of life)?". We therefore aimed for a pragmatic study design that allowed for the inclusion of fairly unselected IC patients, only excluding patients with either very mild or very severe symptoms. Inclusion was admissible irrespective of the severity, numbers and distribution of the vascular lesion(s) and necessary revascularisation technique. In this way, we included a substantial proportion of patients from (by far) the most common group of IC patients seeking medical advice from a vascular surgeon, and where the efficacy of revascularization remains to be firmly established. We therefore opine, that our results may allow for a generalization to a large proportion of IC patients.

In this patient group, we consistently showed that a primary strategy of revascularization (endovascular or surgical) significantly improved important aspects of HRQoL when added to medical intervention and exercise training. In study I, HRQoL represented a secondary endpoint but the results were confirmed and enhanced in study V, where HRQoL constituted the primary endpoint. The effects were generally moderate to large and were not restricted to HRQoL components of activity but also included pain- and emotional aspects. Thus, invasive treatment entailed improved physical function, less pain and improved emotional status. In fact, the HRQoL status in invasively treated patients at twelve months was similar to that of an age- and gender-matched sample of individuals retrieved from the general population (figure 11). Invasive treatment also substantially (+124 vs. +50 m, $p<0.003$) improved the pain-free walking distance on a graded treadmill test at one year (study V). This difference may possibly translate to substantially longer walking distances on flat ground during free-living activities, as indicated by the more pronounced increase in self-reported walking distances (median +500 m vs. + 100 m, $p<0.001$ in INV vs. NON patients). In both studies, hemodynamic measurements of peripheral circulatory compromise improved more in INV versus NON patients.

Interestingly, neither of the studies (nor the aggregated analysis of the pooled data at twelve months in study I and V) could demonstrate a significant effect with regard to maximum treadmill walking capacity, although the per-protocol analysis in study I supported an effect with marginal significance. The negative results noted in the aggregated analysis in the combined patient sample (n=306) from study I and V data also lends support to the notion that the reason could not fully be explained by a type 2 error, although there was a strong trend towards significance for MWD with $p=0.055$ in this aggregated analysis. In study I, the reasons for termination of the treadmill test was recorded, and we made the observation that invasive treatment significantly reduced claudication pain as a reason to stop during treadmill testing, compared to non-invasive treatment, while not significantly improving

maximal walking performance. These findings raised a secondary research question, further explored in study IV, and discussed below (section 8.3).

The demonstrated benefits of revascularisation have to be weighed against the risk for procedure-related complications. We recognize that the sample sizes in both our randomized studies do not allow firm conclusions with regard to the risk of procedure-related adverse events or rare complications. However, in both of our studies, complications were generally few and benign in subjects undergoing revascularisation. No amputations were undertaken during follow-up (totalling 463 followed patient-years, figure 2 and 9) in either study and mortality was unrelated to vascular procedures and equally distributed in treatment groups in both trials. Mortality was also substantially lower (8 deaths during 560 known patient-years, i.e. rendering an annual mortality rate of 1.4 %) than previously reported in claudicants[30]. This interesting finding might indicate that previously reported mortality rates do not longer apply to claudicants that receive modern medical management, which has improved markedly over the last decade[190]. It is generally believed that, in the era of minimally invasive endovascular interventions performed under local anaesthesia, the risks of serious adverse events and systemic complications are also currently low during revascularisation. Recently, we indeed also showed a low risk for severe systemic vascular complications during infrainguinal endovascular treatment in a nationwide setting, analysing outcomes from more than 9000 endovascular procedures[176].

A crucial point whenever implementing a new intervention or expanding the indication for an existing treatment modality is cost-effectiveness. This is especially important in a medical condition such as IC, because the leg symptoms very rarely pose a threat for limb loss, and medical intervention with exercise training could substantially reduce symptoms. Indeed, existing data supports that supervised exercise training programs are more cost-effective as compared to endovascular revascularization[170, 173] and may also reduce the numbers of patients ever requiring revascularization[191]. Such a strategy also accordingly would limit the numbers at risk of suffering complications from invasive treatment. It is important to emphasize though, that these preliminary conclusions are applicable in settings where hospital-based supervised training programs are offered, a modality that is broadly unavailable to IC patients in our country and in most parts of Europe[156]. This fact is also one of the main reasons why we chose a structured but non-supervised training program in our studies, i.e. we aimed at mirroring the most common current clinical practise. Longer follow-up and health economy assessments of the patients in study V will provide further information concerning the definite role for primary invasive treatment in unselected IC patients.

Important limitations to consider is that our results do not apply to IC patients with either very mild or very severe symptoms, as we did not study these subgroups. However, patients with mild non-limiting symptoms in general respond well to medical intervention and walk exercise why revascularization rarely are considered in clinical practise[192]. The opposite is true for claudicants with very grave symptoms that physically prohibits even basic functions in everyday life and in these cases revascularization is often considered mandatory. Another limitation with our chosen design (at the same time representing one of the largest strengths) is that we have not studied the specific results of invasive treatment e.g. in selected vascular segments, in lesions of a certain length/severity, or in terms of different applied techniques for revascularization. In certain selected IC subgroups, the effect of revascularization could be different, and may in fact be larger, than in our unselected sample and the identification of such subgroups constitute an important topic for future research. Finally, we did not use a supervised exercise program in any of the studies and it could be argued that a supervised program more effectively alleviate IC symptoms as compared to a non-supervised program[152]. However, as stated above (section 4.3), SETs are currently unavailable to most IC patients, patient compliance in SET programs is questionable and the long-term benefit of SET also remains unproven. In both our randomized studies, we used structured exercise recommendations (i.e. thorough verbal and written information delivered by experienced vascular surgeons) and this approach may be more effective than the more simple "go home and walk" advice.

8.2 Evaluation of health-related quality of life

A major effort was also made to validate and develop patient-reported outcome measures for peripheral arterial disease. The reason for this was that a secondary research question was raised when we designed study V, in which we aimed to use HRQoL as the primary endpoint: - *"How should health-related quality of life in intermittent claudication be evaluated?"*

As described above (section 3.4), a combined use of a generic- and a disease-specific HRQoL instrument[115] for clinical outcome measurement is usually recommended, and we identified a lack of modern disease-specific instruments for the assessment of HRQoL in PAD in Sweden. The VascuQoL was often recommended in international literature[115, 118] and this questionnaire had been translated and linguistically validated in Swedish[193]. We therefore went forward with a validation study of the VascuQoL with the aim of establishing validity in a Swedish context.

In short, we found that the VascuQoL proved valid when testing the questionnaire in a prospective cohort of 200 patients with established peripheral arterial disease. Multitrait/multi-item scaling analysis indicated good convergent and divergent validity although we identified some scaling errors. Responsiveness to clinical change was excellent, as all but one (*social* scale) of the VascuQoL subscales showed a standardized response mean value over 0.8, and in this respect, VascuQoL performed better than the SF-36. However, we found that certain items in the questionnaire had a sub-optimal design and could be possible to remove without loss of information. In addition, the *social* subscale proved somewhat weak. This scale only contains two items and these items showed a suboptimal correlation structure. Therefore, this subscale should ideally be strengthened by the addition of a few items in future versions of the instrument. Important future work also includes establishment of the level of *minimal important difference* of the VascuQoL for IC patients, using patient-based anchors[120]. The *minimal important difference* represents the smallest change in health status that a patient would identify as important. The *minimal important difference* hence could be used as a tool to define clinically important changes (rather than statistically significant changes), and is important also when designing future trials using HRQoL as endpoint.

During the validation study we found that the original VascuQoL questionnaire, including 25 items, was difficult to complete for certain patients, preferentially older patients with critical limb ischemia. The time frame needed for patients to complete the instrument also seemed too long (mean 9.6 minutes[194]) to be really practical for the integration in routine clinical care. These observations led to the idea of a short version of the VascuQoL and the possibilities for this were investigated. By using a combination of classical psychometric methods, cognitive interviews and Rasch analysis, we were able to reduce and revise the instrument to only six items while preserving a lot of information, as illustrated by the high correlations found between the scores of the original- and the short version and the remaining high association with the GPS-monitored outdoor test walk. However, it is important to emphasize that this new short version needs to be further tested, confirming validity in a new patient sample.

It is of crucial importance to integrate patient-centered endpoints in the clinical care of vascular patients. Such measurements offer important and new information about the vascular patient that could be used in the follow-up of different treatment strategies and possibly also as an evaluation tool for patient selection to certain treatments. HRQoL status should represent one of the most important endpoints to assess in IC, as the main aim of every treatment focused on improving leg symptoms ultimately is to achieve an HRQoL improvement. Moreover, new medical and vascular surgical treatment options are continuously and rapidly introduced in PAD, due to

technological advancements. The efficacy of these interventions needs to be scientifically investigated and in this context, valid HRQoL instruments could play an important role. Our work so far has resulted in a validated Swedish questionnaire (VascuQoL) with main intended use in PAD research. A promising short version (VascuQoL-6) for the assessment of HRQoL in routine medical settings has also been added to the clinical vascular armament. The mean time taken for patients to complete the VascuQoL-6 (mean 1.4 minutes, reported in study III) should allow for convenient use even in busy clinical scenarios.

8.3 Clinical assessment of walking capacity

The objective assessment of walking capacity in IC patients is not straightforward and different clinically used tests have different advantages and shortcomings; good specific arguments could be made for the majority of existing tests[54, 59, 74, 75, 87]. An ideal test of walking capacity in intermittent claudication should be easily and rapidly performed, have high reproducibility, be able to firmly categorize and grade patients with different walking capacity and also accurately reflect the walking function as experienced by the patient during everyday life. During the course of this thesis project, partly in response to observations that were done in study I with regard to the graded treadmill test traditionally used in our department, a secondary research question was raised: *"Is a simple corridor-based walk test closely related to "real-life" outdoor walking capacity?"*

In study I we made the observation that, although not improving maximum walking performance at follow-up, invasive treatment significantly reduced imperative IC symptoms as the reason to terminate the treadmill test. Instead, the test was increasingly terminated due to general fatigue, angina or similar causes. And although invasive treatment did not confer any significant benefit with regard to maximum walking performance during treadmill testing, important aspects of HRQoL were significantly improved by invasive treatment. The graded treadmill test set-up in our department, using successive increases in slope and speed during the course of the test, has the advantage of a high reproducibility and it also forces every tested patient to eventually stop, regardless of symptom severity. But the result of the test is a measure of maximum walking capacity and as such; it also measures maximum physiological reserve. Therefore, it may not accurately reflect the walking function and limitations perceived by claudicants during free-living walking conditions and it may not be an optimal endpoint for the assessment of walking function in claudicants. We therefore hypothesized that treadmill performance, and in particular maximum treadmill performance, may not accurately reflect walking capacity of claudicants during everyday life. This was the main reason why we designed study IV, in which we explored the associations of different clinically used walk

assessments with "real-life" outdoor walking capacity. The latter was defined as the total covered distance during a 40 minutes outdoor walk, and was assessed with GPS. As compared to previous authors[58, 87], we also simplified the GPS-recording of walking distance during an outdoor walk by testing the precision of a commonly available GPS-based smartphone walking application. We pragmatically considered the GPS measurement to represent a "gold standard" because it measures real-time walking, and we used a walk time of 40 minutes, as it is likely that this time frame is sufficient to provoke IC symptoms. We then investigated the correlation between this "gold standard" measure and some commonly used clinical walking capacity estimates (the self-reported maximum walking distance, the maximum walking distance on a graded treadmill test and the six-minutes walk test). We found that the six-minutes walk test correlated most closely to "real-life" outdoor walking capacity. The six-minutes walk test was also most closely correlated to HRQoL, assessed with the VascuQoL. The six-minutes walk test is easy and rapid to perform and demands practically no extra equipment or resources. Validity of the six-minutes walk test have been proven in other areas of medicine[195], test-retest reliability of the test is generally good and strong evidence supports responsiveness to clinical change in similar medical settings[196].

We therefore propose that the six-minutes walk test should be integrated in the routine clinical evaluation of IC patients, as an adjunct or even an alternative to treadmill testing. The main rationale for this implementation is the close correlation to aspects that intuitively are important to IC patients, i.e. "real-life" walking capacity and quality of life. The test may also represent a relevant endpoint in future clinical trials in IC.

8.4 Management strategies in intermittent claudication

In an optimized management strategy in intermittent claudication, several aspects have to be considered. First and foremost, it is paramount that every intervention considered relies on balanced scientific evidence, as obtained from systematic reviews and health technology assessments. And, as discussed above, it is important to scrutinize if existing evidence for an intervention is applicable for IC patients in general, or only apply to certain defined subgroups. Since the main purpose of treating leg symptoms in IC is to improve quality of life, the conceivable benefit of any medical or surgical intervention have to be weighed against costs and potential side-effects and attendant risks brought on by the procedure. And even if serious procedure-related complications are likely to be rare in the era of endovascular

intervention, whenever occurring they may be devastating to the patient[176]. Furthermore, it is important to remember that the long-term benefit of invasive vascular interventions currently is restricted by the inherent risk of restenosis[179]. The mostly benign course of the disease with regard to the leg symptoms[30] also has to be taken into account and communicated to the patient. Finally, the expectations and resources of the individual patient seeking advice are also crucial to consider when designating a tailored approach for the individual IC patient.

In IC, basic measures (risk factor modification, basic medication and exercise) can mitigate leg symptoms sufficiently in many patients. Also, vasoactive drugs targeted at improving leg symptoms in IC may contribute to symptom relief[143]. Therefore, even though our randomized studies showed that a primary invasive treatment strategy could be beneficial for a large proportion of claudicants, a staged management algorithm seems most reasonable to suggest, reducing the numbers at risk for suffering procedure-related complications during invasive procedures and reducing societal costs (figure 12). If medical interventions and properly administered exercise training as outlined below fail to sufficiently alleviate leg symptoms, revascularization constitute a valid option that could be offered to the patient as a second-line treatment. A more precise targeting of subgroups in which revascularization entails most benefits constitutes an important field for further research.

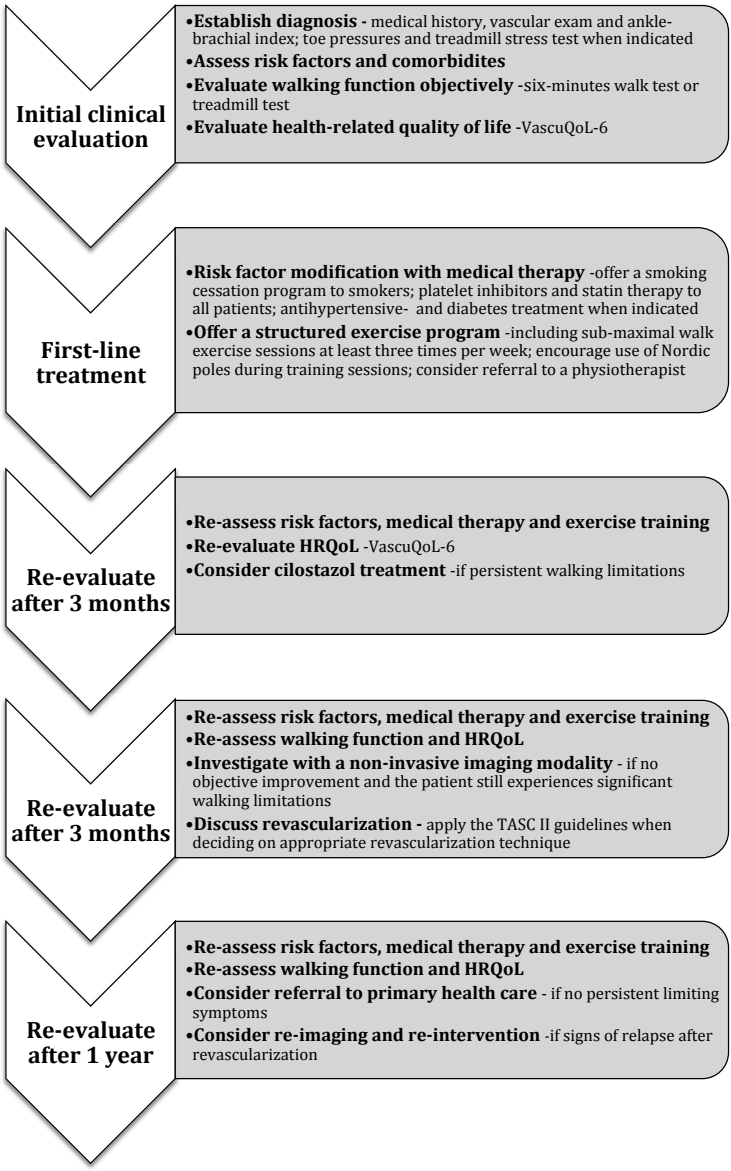

Figure 12. Suggested clinical management strategy in intermittent claudication.

9 CONCLUSIONS

- ✓ A primary invasive treatment strategy (surgical or endo-vascular revascularization) improves health-related quality of life and pain-free walking distance more than a primary non-invasive strategy in relatively unselected patients with intermittent claudication, receiving best medical treatment and structured (non-supervised) exercise therapy.

- ✓ The Swedish version of the disease-specific health-related quality of life instrument VascuQoL is valid and measures core aspects of health-related quality of life in patients with peripheral arterial disease.

- ✓ The VascuQoL-6, a short version of the VascuQoL, proved possible to develop and constitutes a new simplified tool to assess health-related quality of life among patients with peripheral arterial disease in routine clinical scenarios.

- ✓ The six-minutes walk test closely correlates to "real-life" walking capacity and health-related quality of life, and could therefore be used to objectively define walking capacity in intermittent claudication.

10 FUTURE PERSPECTIVES

There are several areas in which further research can guide improvement in the clinical care of patients with intermittent claudication, and some important topics to consider for future research are listed below:

What is the cost-effectiveness and long-term benefit of a primary revascularization strategy in patients with intermittent claudication, when compared to a primary non-invasive treatment strategy?

Which subgroups of patients with intermittent claudication benefit most from revascularization, and which subgroups do not?

What is the long-term efficacy and cost-effectiveness of different exercise training programs (different supervised programs versus non-supervised programs) in intermittent claudication?

Could new technical advancements (i.e. drug-elution devices, biodegradable stents or other adjuncts to endovascular procedures) improve long-term efficacy of revascularization in claudicants, in terms of patient-related endpoints?

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13 APPENDIX

VascuQoL-25 questionnaire[1]

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Instructions: These questions ask you how you have been affected by poor circulation to your legs over the last two weeks.
You will be asked about the symptoms you have had, the way that your activities have been affected and how you have been feeling.
Please read each bit of the answer and then tick the one that applies best to you.
If you are unsure about how to answer a question, please give the best answer you can. There is no right or wrong answer. Please answer every question. Thank you.

1. In the last two weeks I have had pain in the leg (or foot) when walking ……

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

2. In the last two weeks I have been worried that I might injure my leg ……

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

3. In the last two weeks cold feet have given me ……

1. A very great deal of discomfort or distress
2. A great deal of discomfort or distress
3. A good deal of discomfort or distress
4. A moderate amount of discomfort or distress
5. Some discomfort or distress
6. Very little discomfort or distress
7. No discomfort or distress

4. In the last two weeks, because of the poor circulation to my legs, my ability to take exercise or to play any sports has been …..

1. Totally limited, couldn't exercise at all
2. Extremely limited
3. Very limited
4. Moderately limited
5. A little limited
6. Only very slightly limited
7. Not at all limited

5. In the last two weeks my legs have felt tired or weak …

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

6. In the last two weeks, because of the poor circulation to my legs, I have been restricted in spending time with my friends or relatives …

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

7. In the last two weeks I have had pain in the foot (or leg) after going to bed at night….

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

8. In the last two weeks pins and needles or numbness in my leg (or foot) have caused me ….

1. A very great deal of discomfort or distress
2. A great deal of discomfort or distress
3. A good deal of discomfort or distress
4. A moderate amount of discomfort or distress
5. Some discomfort or distress
6. Very little discomfort or distress
7. No discomfort or distress

9. In the last two weeks the distance I can walk has improved …

1. Not at all (tick this if distance is unchanged or has decreased)
2. A little
3. Somewhat
4. Moderately
5. A good deal
6. A great deal
7. A very great deal

10. In the last two weeks, because of the poor circulation to my legs, my ability to walk has been….

1. Totally limited, couldn't walk at all
2. Extremely limited
3. Very limited
4. Moderately limited
5. A little limited
6. Only very slightly limited
7. Not at all limited

11. In the last two weeks being (or becoming) housebound has been a concern of mine …..

1. A very great deal
2. A great deal
3. A good deal
4. Moderately
5. Somewhat
6. A little
7. Not at all

12. In the last two weeks I have been concerned about having poor circulation to my legs …..

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

13. In the last two weeks I have had pain in the foot (or leg) when I am at rest …..

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

14. In the last two weeks, because of the poor circulation to my legs, my ability to climb stairs has been …..

1. Totally limited, couldn't climb stairs at all
2. Extremely limited
3. Very limited
4. Moderately limited
5. A little limited
6. Only very slightly limited
7. Not at all limited

15. In the last two weeks, because of the poor circulation to my legs, my ability to take part in social activities has been …..

1. Totally limited, couldn't socialise at all
2. Extremely limited
3. Very limited
4. Moderately limited
5. A little limited
6. Only very slightly limited
7. Not at all limited

16. In the last two weeks, because of the poor circulation to my legs, my ability to perform routine household work has been …..

1. Totally limited, couldn't perform housework at all
2. Extremely limited
3. Very limited
4. Moderately limited
5. A little limited
6. Only very slightly limited
7. Not at all limited

17. In the last two weeks ulcers in the leg (or foot) have given me pain or distress…..

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time (tick this if you do not have leg ulcers)

18. Because of poor circulation to my legs, the overall range of activities that I would have liked to do in the last two weeks has been …..

1. Severely limited – most activities not done
2. Very limited
3. Moderately limited – several activities not done
4. Slightly limited
5. Very slightly limited – very few activities not done
6. Hardly limited at all
7. Not limited at all – have done all the activities that I wanted to

19. In the last two weeks the poor circulation to the legs have made me feel frustrated …..

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

20. In the last two weeks when I do get pain in my leg (or foot) it has given me ….

1. A very great deal of discomfort or distress
2. A great deal of discomfort or distress
3. A good deal of discomfort or distress
4. A moderate amount of discomfort or distress
5. Some discomfort or distress
6. Very little discomfort or distress
7. No discomfort or distress

21. In the last two weeks I have felt guilty about relying on friends or relatives …..

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

22. In the last two weeks, because of the poor circulation to my legs, my ability to go shopping or carry bags has been …..

1. Totally limited, couldn't go shopping at all
2. Extremely limited
3. Very limited
4. Moderately limited
5. A little limited
6. Only very slightly limited
7. Not at all limited

23. In the last two weeks I have worried I might be in danger of losing a part of my leg or foot

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

24. In the last two weeks the distance I can walk has become less …..

1. A very great deal
2. A great deal
3. A good deal
4. Moderately
5. Somewhat
6. A little
7. Not at all – tick if distance is unchanged or has increased

25. In the last two weeks I have been depressed about the poor circulation to my legs…..

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

VascuQoL-6 questionnaire

VASCUQOL-6

1 *Because of the poor circulation in my legs, the range of activities that I would have liked to do in the past two weeks has been....*

1 ☐ Severely limited – most activities not done
2 ☐ Moderately limited – several activities not done
3 ☐ Very slightly limited – very few activities not done
4 ☐ Not limited at all – have done all the activities that I wanted to

2 *During the past two weeks, my legs felt tired or weak....*

1 ☐ All of the time
2 ☐ Some of the time
3 ☐ A little of the time
4 ☐ None of the time

3 *During the past two weeks, because of the poor circulation in my legs, my ability to walk has been....*

1 ☐ Totally limited, couldn't walk at all
2 ☐ Very limited
3 ☐ A little limited
4 ☐ Not at all limited

4 *During the past two weeks, I have been concerned about having poor circulation in my legs....*

1 ☐ All of the time
2 ☐ Some of the time
3 ☐ A little of the time
4 ☐ None of the time

5 *During the past two weeks, because of the poor circulation in my legs, my ability to participate in social activities has been....*

1 ☐ Totally limited, couldn't socialize at all
2 ☐ Very limited
3 ☐ A little limited
4 ☐ Not at all limited

6 *During the past two weeks, when I have had pain in the leg (or foot) it has given me...*

1 ☐ A great deal of discomfort or distress
2 ☐ A moderate amount of discomfort or distress
3 ☐ Very little discomfort or distress
4 ☐ No discomfort or distress

Each question is scored 1-4. When using the VQ6, the sum of each individual question score is used to generate a 'Total' Quality of Life Score. A higher value indicates better health status.