Invasive treatment for intermittent claudication
Clinical outcomes and cost-effectiveness

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To Cilla, Anna and Hjalmar
I. Abstract

Intermittent claudication (IC) is caused by obstructive arterial lesions and is characterized by effort-induced pain in the lower extremity, limiting walking distance, and reduced health-related quality of life (HRQoL). The prevalence of IC is increasing due to the ageing of the population, and the consequences of the economic effects are a global problem. The walking impairment can be reduced by exercise. Despite the paucity of evidence regarding long-term benefit and cost-effectiveness, invasive revascularization is also often performed.

We wanted to investigate whether invasive treatment for IC is safe with regard to procedure-related limb loss, whether it is cost-effective, and whether it has long-term clinical benefit compared to exercise only.

The Swedvasc registry was used to identify all revascularizations performed in Sweden for IC between 2008 and 2012. Amputations were captured using the National Patient Registry (Paper I). Cost-effectiveness was analyzed in two prospective randomized trials, the IRONIC trial and a randomized trial investigating stenting of the superficial femoral artery in IC (papers II, III, and IV). The long-term clinical effect was analyzed in the IRONIC trial (paper III).
We found a low rate of major amputations during the first year after revascularization for IC: 0.2% (Paper I). A liberal invasive treatment strategy was found to be more expensive than exercise advice only after two years of follow-up. Cost-effectiveness results were within the threshold of the Swedish national guidelines regarding willingness to pay (papers II and IV). Both the clinical benefit and the cost-effectiveness of a liberal invasive treatment strategy that were found after two years of follow-up was lost at five years (paper III).

In conclusion, invasive revascularization of patients with IC appears to be safe in terms of limb outcome within the first post-procedural year. A liberal invasive treatment strategy was cost-effective compared to exercise alone after two years of follow-up. No clinical benefit, nor cost-effectiveness compared to exercise remained after five years.

Future studies should aim at identifying IC subgroups that benefit the most from revascularization and exercise, respectively, in order to enhance the overall patient benefit from available treatment options.

Keywords: intermittent claudication, peripheral arterial disease, cost-effectiveness, invasive treatment, health-related quality of life
II. List of papers

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

I. Djerf H, Hellman J, Baubeta Fridh E, Andersson M, Nordanstig J, Falkenberg M.
   Low risk of procedure-related major amputation following revascularization for intermittent claudication – a population based study
   *Eur J Vasc Endovasc Surg. Published online: Dec 19, 2019.*

   Cost-effectiveness of revascularization in patients with intermittent claudication

III. Djerf H, Millinger J. Falkenberg M, Jivegård L, Svensson M and Nordanstig J.
    Absence of long-term benefit of revascularization in patients with intermittent claudication: five-year results from the IRONIC randomized controlled trial

IV. Djerf H, Svensson M, Nordanstig J, Gottsäter A, Falkenberg M, Lindgren H.
    Cost-effectiveness of primary stenting of the superficial femoral artery in patients with intermittent claudication: 2-year results of a randomized trial
    *Manuscript*
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<tr>
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<td>Ankle-Brachial Index</td>
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<td>BMT</td>
<td>Best Medical Therapy</td>
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<td>CEAC</td>
<td>Cost-Effectiveness Acceptability Curve</td>
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<td>CLTI</td>
<td>Chronic Limb-threatening ischemia</td>
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<td>EuroQol Five Dimensions</td>
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<td>HRQoL</td>
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1.1 What is intermittent claudication?

Intermittent claudication (IC) is caused by obstructive atherosclerotic lesions in the aorta or in the arteries distal to the aortic bifurcation. At rest, the blood flow to the lower extremity muscles is sufficient. However, due to an increased need for oxygen and nutrients in the muscles during exercise, the blood flow to the leg muscles increases. The arterial obstructions present in patients with IC then lead to an insufficient inflow of blood to the leg muscles, causing ischemic muscular pain that constrains the individual’s walking capacity. The pain is relieved by a short period of rest and returns when exercise is once again performed. Thus, the clinical definition of IC is: reproducible ischemic muscular pain in the lower extremity, induced by exercise and relieved with short periods of rest\(^1\).

The word claudication is derived from the Latin word “claudicare”, which means “to limp”. It comes from the name of the Roman emperor Claudius who could only walk short distances due to a limp. Although patients with IC do not limp, his name became the origin for the condition “Intermittent claudication”.

Introduction
1.2 Intermittent claudication is a manifestation of peripheral arterial disease

Intermittent claudication is the most common symptomatic manifestation of lower extremity arterial disease (LEAD), which is often referred to as peripheral arterial disease (PAD) even though the term “peripheral arterial diseases” also includes peripheral vessels that are not located in the lower extremities.

Most patients with PAD have no limb symptoms. This means that the arterial obstruction causes no symptoms at rest or during walking. The symptoms may, however, be masked due to other medical conditions.

Intermittent claudication is the most common clinical presentation of PAD. As mentioned earlier, the symptoms are reproducible ischemic muscular pain in the lower extremity, induced by exercise and relieved by short periods of rest.

The most severe form of PAD is chronic limb-threatening ischemia (CLTI), which is a limb-threatening condition due to inadequate blood flow and insufficient supply of oxygen and nutrients to lower extremity tissues at rest. The clinical symptoms of CLTI are extremity pain at rest and/or the development of ulcers or tissue gangrene. Patients with CLTI have a considerably higher risk of both amputation and mortality than patients with IC2.

The Rutherford and the Fontaine classifications are two classifications for PAD that are used in research. A formal assessment of IC according to the Rutherford classification requires a treadmill test, which is mostly not performed in clinical practice.

1.3 Effects of peripheral arterial disease and the natural history for the patient

Patients at any stage of PAD have been shown to have a significantly increased risk of cardiovascular events and premature death3.
For patients with IC, the mortality rate has been reported to be two and a half times that of an age-matched population. The increased cardiovascular risk and increased risk of mortality is the most important threat for patients with IC.

The impairment in walking function and the resulting reduction in health-related quality of life (HRQoL) constitutes the second problem for the patient with IC, even though most patients probably perceive this to be their key problem.

In contrast to the risk of CV events and death, the prognosis for the affected limb is relatively benign and loss of a limb is a rare outcome. Deterioration in IC occurs in 25% of the patients, and 13% may undergo a major amputation within five years. Another study found cumulative 10-year risks of developing ischemic rest pain and ischemic ulcer of 30% and 23%, respectively. Persistent smoking and diabetes may increase the risk of deterioration.

### 1.4 Prevalence of peripheral arterial disease and its impact in the world

Peripheral arterial disease affects over 200 million people and is increasing due to the ageing of the population.

The majority of people who are affected are asymptomatic regarding lower limb symptoms. Intermittent claudication, which is the most common symptomatic presentation, has a prevalence of almost 7% in individuals over 60 years of age and affects 20-40 million people worldwide.

Due to the growing number of people with PAD and the increasing costs associated with it, the consequences of IC for HRQoL and in economic terms constitute a global health problem.
1.5 Risk factors

The main cause of arterial obstruction is atherosclerosis (development of plaques inside the arteries). The word atherosclerosis is derived from the Greek words athere (meaning gruel) and skleros (meaning hard)\(^1\).

Intermittent claudication is a symptomatic presentation of atherosclerotic disease, so the general risk factors for development of atherosclerosis disease also apply to IC.

Smoking is one of the most prominent risk factors both for the development of IC and for deterioration of IC to CLTI\(^14\). Diabetes is also strongly associated with both incidence of IC and progression to CLTI\(^15,16\). Furthermore, hypertension and elevated cholesterol levels are also associated with the development of IC\(^17\).

Physical inactivity is an independent risk factor for cardiovascular and overall mortality\(^18\), and there is an association between risk factors for the metabolic syndrome and reduced peripheral circulation\(^19\). Patients with chronic kidney disease have an increased risk of developing PAD\(^20\).

Of the non-modifiable risk factors, age and non-white ethnicity have been found to be associated with an increased risk of PAD\(^21\). Women appear to be as affected as men\(^12\). People with low socioeconomic status tend to have a higher prevalence of IC, mostly due to exposure to other risk factors such as smoking\(^20\).

1.6 Anatomy

The arteries to the lower extremity consist of the aorta and the iliac vessels. Below the inguinal ligament, in the lower extremities, the vessels consist of the femoral arteries, the popliteal artery, the tibial arteries, and the peroneal artery. In the foot, the dorsalis pedis artery forms a foot arcade together with the posterior tibial artery.
1.7 Clinical diagnosis

Diagnosis of IC is done from clinical evaluation based on relevant patient history in combination with a physical examination.

The most common localization of the symptomatic presentation of muscle pain or fatigue is at the calf, but symptoms may also come from the thigh or buttocks. Intensification of exercise tempo such as climbing of stairs, walking uphill, or increased walking speed provokes symptoms more rapidly.

It is important to be aware of the possibility that other disease, which forces the patient to stop walking, may mask IC symptomatology. Examples of this would be cardiopulmonary diseases that impair the patient’s condition such as obstructive pulmonary disease or musculoskeletal or neurogenic diseases like spinal stenosis.

The physical examination includes an objective hemodynamic assessment of the peripheral perfusion using an ankle-brachial index (ABI). ABI is calculated by dividing the highest systolic blood pressure in the upper arms by the systolic blood pressure at ankle level. An index of 0.9-1.4 would be considered normal.

One should be aware that ABI at rest can be normal in patients with IC, and if there is any uncertainty about the diagnosis, a treadmill test can be performed. The treadmill test is a useful tool to distinguish IC from other conditions with similar symptomatology.

Treadmill testing enables the clinician to induce exercise stress and to measure the ABI before and after the exercise. The blood pressure at the ankle drops after exercise. A drop in ABI by more than 15-20% compared to the initial value verifies the diagnosis.

One should remember that for some patients (mainly those with diabetes or severe renal disease), the ABI may be falsely elevated. This is due to calcification of the arterial wall, which makes the blood vessel non-compressible. In these cases, additional testing is required for a PAD diagnosis.
Another possible origin of a false ABI would be if the patient has an arterial lesion in the subclavian or axillary artery, reducing the blood pressure to the arm.

Generally speaking, diagnosis of IC is based on clinical signs. Radiological imaging is mainly performed to plan a revascularization strategy.

1.8 Assessment of walking limitations and health-related quality of life in intermittent claudication

Objective assessment of walking capacity in patients with IC can be achieved in several ways. The most common way in clinical practice is to simply ask the patient about his/her walking capacity. This, however, is very unreliable and the assessment of distance is often inaccurate. In the study setting, the treadmill test is a widely adopted option and has been used for decades. It offers the possibility of grading the walking capacity. Several different protocols are in use, and the treadmill test can be varied both regarding speed and inclination.

Treadmill tests are not always available, however, and corridor-based tests have been developed that may better reflect the patient’s daily walking ability. One example is the six-minute walk distance test (6MWD), which encourages the patient to cover a distance of 100 feet (30.5 m) as many times as possible over 6 minutes. One should be aware that the results of 6MWD and the treadmill test may be different.

The objective measures of ABI and walking distance do not, however, correlate to daily functional status, mostly due to different needs of individual patients for walking capacity and to different lifestyles. To highlight the aspects of illness in individual patients, measures of health-related quality of life (HRQoL) are therefore used. When measuring HRQoL, both generic and disease-specific instruments can be used. A common strategy is to use both a generic and a condition-
specific instrument\textsuperscript{28}. One well-established generic HRQoL instrument is the medical outcomes study Short Form 36 (SF-36). It has often been used in IC patients and has been validated in Sweden\textsuperscript{29, 30}.

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). It also includes two summary measures, Physical Component Summary and Mental Component Summary. Possible domain scores range from 0 to 100 (where 100 denotes the best HRQoL).

Another measure is the EuroQoL Five-dimension questionnaire, which was developed by the EuroQoL group\textsuperscript{31}. It exists in versions with 3- and 5-scale steps. For patients with IC, it is mostly used for health-economic studies.

One disease-specific HRQoL instrument for patients with PAD is the Vascular Quality of Life questionnaire (VascuQoL), which was developed by Morgan et al.\textsuperscript{32} and is recommended for IC patients\textsuperscript{28, 33}. 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-stage response scale. It generates five domain scores and a total score ranging from one to seven (where seven is the best HRQoL).
The treatment of IC has two main objectives. The first objective is to reduce the risk of future cardiovascular events due to atherosclerosis and the second is to reduce lower limb symptoms. This necessitates a thorough approach including lifestyle changes, medical therapy, exercise, and – if needed – invasive treatment.

### 2.1 Reducing the risk of cardiovascular events

The first objective is to reduce the risk of future cardiovascular events. This requires lifestyle changes (smoking cessation, optimal diet, and increased physical activity) and pharmacological secondary preventive treatment. There have, however, been reports that a substantial number of patients do not receive risk factor treatment as recommended in guidelines.

Smoking cessation is important to reduce the risk of cardiovascular events and also to reduce the risk of deterioration of IC. Several studies have shown that statins provide improvements in the cardiovascular prognosis for patients with IC. As an extra benefit, statins have also been shown to improve pain-free and maximal walking distances in patients with IC. Anti-platelet therapy is recommended to reduce the risk of cardiovascular events in patients with PAD. All patients with PAD should have control of hypertension, and hypertensive patients should receive treatment to reduce cardiovascular events. Diabetes is associated with progression to CLTI and increased risk of cardiovascular events, and must be treated.
2.2 Reducing lower limb symptoms

The second objective is to improve HRQoL by reducing limb symptoms. Many of the strategies for reducing cardiovascular events contribute to the second goal of reducing lower limb symptoms. Thus, the first objective acts as a foundation for the second objective.

Lower limb symptoms can be alleviated by exercise therapy and by invasive treatment (revascularization)\(^6,38\). Regarding medications, statin has led to improved walking distances and is recommended in ESC guidelines\(^6\). Some other medications, mainly cilostazol, may have a positive effect on lower limb symptoms but have not been recommended in ESC guidelines.

2.2A Exercise

Exercise training is a cornerstone in the treatment of lower limb symptoms for IC. Supervised exercise therapy (SET) especially, where the patients receive training guidance from healthcare personnel in a healthcare facility, is often recommended as first-line treatment \(^6,39\). However, there is often no reimbursement for SET and it is not available to most patients\(^40\), in which case unsupervised exercise is recommended\(^6\). In addition, studies have mainly compared the efficacy for short periods of time\(^41\). Concerns have been raised regarding long-term adherence to SET, so it is uncertain whether the superior effects of SET compared to unsupervised exercise are maintained for long periods of time\(^42\).

A recent meta-analysis has also shown that home-based structured exercise therapy (HSET) – where patients perform the exercise at home but receive continuous feedback from healthcare personnel – may improve walking capacity\(^43\). The long-term effects of HSET still remain to be investigated.
2.2B Invasive treatment: general considerations
Invasive treatment can be performed by endovascular surgery or open surgery.

Endovascular surgery, a minimally invasive approach, is mostly conducted under local anaesthesia in an angio suite. A majority of the procedures performed for IC in Sweden are undertaken via the endovascular route. The approach is percutaneous, and by using the Seldinger technique an introducer is inserted into the vessel either with or without ultrasound guidance.

From the introducer, percutaneous transluminal angioplasty (PTA) of the atherosclerotic lesion can be performed with or without stenting of the artery.

Open surgery is performed in an operating theatre. In open surgery, the arteries explored are fully visible in the operational field by incision of the skin and by dissecting the target arteries free from the surrounding tissues. A minority of the IC procedures are performed by open surgery.

One example of open surgical technique is thrombendarctomy. For lower extremity arterial disease, this procedure is often performed in the common femoral artery. This method consists of opening the vessel and removing the atherosclerotic lesion, followed by suture or patch closure of the artery.

Another example is bypass surgery, where the surgeon bypasses the arterial occlusion with synthetic or autologous bypass material. The most commonly used autologous material is the great saphenous vein.
2.2C Invasive treatment: evidence

Invasive treatment is offered to patients to relieve lower limb symptoms\textsuperscript{6, 44}. Randomized studies comparing invasive treatment with exercise have often applied selective inclusion criterias, and there has been heterogeneity between the studies regarding the type of invasive modality performed, anatomical segments, type of concomitant exercise therapy, severity of IC, and primary endpoints – which has made it difficult to draw any general conclusions regarding invasive treatment. A few randomized studies (Nordanstig et al.\textsuperscript{45}, Gelin et al.\textsuperscript{46}, and the IRON-IC study\textsuperscript{47, 48}) have included both the aorto-iliac and femoro-popliteal segments and both endovascular and open surgery, when comparing an invasive strategy with a non-invasive strategy.

A number of randomized studies have shown some benefit of invasive treatment up to a year over exercise; for example, Gelin et al.\textsuperscript{46} found moderate benefits in walking capacity and HRQoL with open and endovascular treatment compared to SET\textsuperscript{49}, Lundgren et al. showed benefit of open vascular surgery compared to SET\textsuperscript{50}, and Fakhry et al.\textsuperscript{51} compared SET alone with combined endovascular treatment and SET, and found positive results regarding walking distances and HRQoL when invasive treatment was included. All studies included aorto-iliac and femoro-popliteal segments.

Superiority of invasive treatment compared to exercise in aorto-iliac and femoro-popliteal segments with two years of follow-up has been found in randomized studies by the IRONIC study\textsuperscript{48}, and by Greenhalgh et al., who showed some benefit of PTA as adjuvant treatment to SET in mild to moderate IC. Nylaende et al. also found some benefit of PTA over conservative treatment after two years\textsuperscript{52}.

In a study by Lindgren et al.\textsuperscript{53}, primary stenting of SFA in addition to exercise advice led to a durable increase in HRQoL after two years of follow-up compared to exercise advice alone.
However, several studies have not shown any benefit of invasive treatment compared to exercise.

Spronk et al. showed similar HRQoL results for endovascular treatment in aorto-iliac and femoro-popliteal segments and for supervised exercise after one year of follow-up.

Mazari et al. also showed comparable effects after one year of follow-up between three treatment arms, SET vs. PTA vs. SET and PTA together, for femoro-popliteal disease.

Whyman et al. did not find any benefit of PTA, in terms of HRQoL or walking capacity, at two-year follow-up.

Murphy et al. found similar effects of invasive treatment and exercise after 18 months when comparing between three treatment arms, stent treatment and BMT vs. SET and BMT vs. BMT alone, for moderate to severe claudication due to aorto-iliac lesions.

An earlier study by Nordanstig et al. showed no improvement in walking capacity after two years of follow-up after invasive treatment with endovascular or open surgery rather than exercise advice alone.

Furthermore, a systematic review by Malgor et al. showed benefits from both invasive treatment and exercise but the authors could not conclude that any particular treatment approach was superior.

A meta-analysis by Klaphake et al. could not distinguish any favourable effects in maximum walking distance or HRQoL when comparing endovascular treatment and SET with SET alone or endovascular treatment alone. In contrast to this, another meta-analysis from Saratsis et al. found benefits in terms of walking distance and HRQoL with combined treatment compared to PTA or SET alone after one year of follow-up.
In 2018, a Cochrane systematic review by Fakhry et al. summarizing the added effects of endovascular treatment found no significant benefit compared to SET, but the authors suggested that one should consider a combination of endovascular treatment and SET.

Thus, studies have mainly been performed with one- or two-year follow-up, and the results have varied regarding the benefit of invasive treatment.

Randomized studies by Fakhry and Mazari, with 7 years and 5 years of follow-up, respectively, have not been able to show any long-term superiority compared to SET\textsuperscript{59,60}. Fakhry et al., who compared SET and endovascular revascularization in both the iliac and femoro-popliteal segments, showed comparable effects after 7 years for SET and endovascular revascularization regarding quality of life and functional performance. Mazari et al., who compared PTA vs. SET vs. combined treatment for femoro-politeal disease found similar effects after 5 years in all three groups.

Thus, there have been no randomized studies demonstrating any benefits of invasive treatment over non-invasive treatment beyond the first two years.

When treating patients invasively, one must also consider the risk of complications. The most feared complication is the risk of amputation\textsuperscript{61}. One study found that an early revascularization strategy appeared to increase the long-term rate of amputation compared to patients initially treated with a non-invasive approach, at five-year follow-up\textsuperscript{62}.

Since endovascular treatment is constantly evolving, some vascular centres adopted new technical solutions during the course of this thesis work. One new solution is atherectomy, where the plaque is removed using endovascular techniques. However, one study showed high rates of amputation after one year\textsuperscript{63} and another study showed a high rate of
long-term adverse events with atherectomy compared to stent. One of the most prominent new solutions during the past decade have been the use of drug-coated stents and balloons that were developed to mitigate restenosis after endovascular treatment. However, in December 2018, Katsanos et al. presented a meta-analysis signalling an increased risk of death following the use of paclitaxel-coated devices. Further studies will hopefully provide evidence regarding whether this claim is or is not true.
3.1 Reasons for economic considerations

The costs of healthcare are increasing in Sweden and in many other western countries. In Sweden, the costs for PAD in 2005 were estimated to be more than a billion SEK, excluding costs for primary healthcare, municipal healthcare, and social services. Most of these costs were derived from in-patient treatment at hospitals.

With the increasing number of patients with PAD, the economic impact on healthcare resources is expected to be substantial.

Since healthcare resources are limited, the use of economic evaluations in healthcare settings has increased considerably. Economic evaluations alongside clinical trials are an important resource to help decision makers when deciding which medical technologies should receive funding.
Economic analysis can be done from a payer/healthcare standpoint, where one only considers the cost to the healthcare provider, or from a broader perspective where one estimates the wider economic effects of the treatment on society.

It is important to remember that health-economic evaluations are meant to give support for decision making. The decision maker has many other aspects to consider that the evaluation itself may not have considered – considerations such as the severity of the disease and possible effects on society, if these have not been included in the analysis.

### 3.2 Assessment of the cost-effectiveness of invasive treatment for intermittent claudication

In a cost-effectiveness analysis, the treatment under study is compared with alternative course(s) of action that are clinically relevant. By considering both the resources used (the costs) and the clinical consequences of the treatments (the effects), one can perform a cost-effectiveness analysis.

**Assessing health-related quality of life in cost-effectiveness analysis**

There are different measures of health-related quality of life in economic analysis. One widely used measure is QALY (Quality-Adjusted Life Year). Another example is DALY (Disability-Adjusted Life Year). A recently proposed new alternative is Health Years in Total (HYT).

Different methods have been developed for evaluating health states and creating HRQoL instruments to be used in clinical studies for health-economic evaluations.

Evaluation of health states can be achieved by asking people to evaluate a health state that is described to them, or to ask them to evaluate their own state of health.
There are different views concerning the best way to evaluate health states.

Arguments favouring evaluations from the general public would be, for example, that tax payers are entitled to evaluate health states used in health-economic evaluations. Arguments favouring the argument that patients should evaluate the health states is that they have experience of the actual disease. It is important to know what preferences have been used when using a prescored HRQoL instrument, since the evaluations by patients differ from those of the general public69.

In cost-effectiveness analysis, we want to capture both the health aspect and the time aspect. QALY is a measure that combines both quality of life and quantity of life lived. One QALY can be viewed as one year lived in the best possible health state. It is often recommended as an effectiveness measure in health-economic evaluations70.

The quality of life component (qalyweight) is measured with an index where 1 is the best possible health state and 0 is assumed to be equivalent to death. Negative values are theoretically possible.

Three main direct methods have been used to produce QALY weights:

1. The first method, the rating scale, is often referred to as the visual analogue scale (VAS). In this method, the responders indicate where they would locate a specific health state on a ruler scale.

2. The standard gamble method makes people choose between different health state alternatives.

3. The third method, and the one used in our analysis, is the time trade-off (TTO) method. It was developed by Torrance in the 1970s and is often considered to be easier than the standard gamble method. It requires that people choose between different options of health states combined with a time preference. It aims at finding a point of indifference between time spent with a reduced health state compared to the time spent with a full health state71.
In applied cost-effectiveness studies, indirect prescored instruments are usually used to assess QALY weights. One of the most frequently used prescored instruments in health-economic evaluations is the EuroQol-5 dimensions (EQ-5D) instrument, developed by the EuroQol group. It contains five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. It exists in a three-level version and a five-level version. The original three-level value set was developed by Dolan by use of TTO responses from a sample of adults in the general population in England. Examples of other instruments used to create QALYs are SF-6D and HUI.

An advantage of QALYs is that they enable comparisons across all areas of healthcare.

A disadvantage with QALYs is that a gain in QALYs for a patient who has more severe illness might be worth much more than for a patient with less severe illness. QALYs may also discriminate against older people or people who already have a severe disease, since they have a shorter life expectancy and do not have the possibility of accumulating QALYs.

**Collection of cost data**
Cost data can be retrieved from different cost registries. The benefit of using hospitals’ cost systems is that it is possible to accumulate patient-specific use of resources and to capture the variations in costs between patients that exist in clinical praxis. Retrieval of cost data can be time- and resource-consuming. It is therefore important to determine how precise the costs need to be in a study. The most precise level can be referred to as “micro-costing”, which identifies each component of resource use (such as laboratory tests and drugs). It is easier to identify small cost components if the economic evaluation is undertaken alongside a prospective clinical study.
Comparative assessments in cost-effectiveness analysis
By comparing all the QALYs gained between treatments and the costs associated with the treatment, one can calculate the difference in cost per QALY and the result is referred to as the incremental cost-effectiveness ratio (ICER).

\[
\text{ICER} = \frac{(\text{Cost A} - \text{Cost B})}{(\text{Effect A} - \text{Effect B})}
\]
An illustrative way of graphically representing the results is the cost-effectiveness plane. The incremental effectiveness of the treatment versus the comparator is represented on the x-axis and the incremental cost versus the comparator is represented on the y-axis.

As can be seen in the cost-effectiveness plane, treatments in the north-west quadrant are less effective and more expensive, relative to the comparator, just as treatments are more effective and less expensive in the south-east quadrant. In these cases, the decision maker gets a clear result that is easy to act on. Often however, the incremental effectiveness and costs create a result that is situated in the north-east quadrant (where the treatment is more effective but costs more) or in the south-west quadrant (where the treatment is less costly but also less effective).
Under these circumstances, one has to decide if the health gain is worth the additional costs (or if the costs saving is worth the loss in health). The level of acceptance of how much money can be spent for a benefit in health varies depending on the country and the severity of the disease. This is often referred to as the maximum accepted level of public willingness to pay.

In Sweden, the National Board of Health and Welfare has set a threshold of 500,000 SEK/QALY to be considered expensive.

Guidelines according to the Swedish National Board of Health and Welfare\textsuperscript{74}.

\textbf{Table 1.}

<table>
<thead>
<tr>
<th>Classification</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Below 100,000 SEK/QALY</td>
</tr>
<tr>
<td>Moderate</td>
<td>100,000–499,999 SEK/QALY</td>
</tr>
<tr>
<td>High</td>
<td>500,000–1,000,000 SEK/QALY</td>
</tr>
<tr>
<td>Very high</td>
<td>Above 1,000,000 SEK/QALY</td>
</tr>
</tbody>
</table>

Unfortunately, it is not clear why these specific thresholds are recommended. Alternatively, the Swedish Dental and Pharmaceutical agency provides recommendations on which pharmacotherapies should receive public funding. An analysis of their recommendations has shown that for a relatively benign disease like IC, there is a higher acceptance limit of 700,000 SEK/QALY\textsuperscript{75}. 
Uncertainty in cost-effectiveness analysis

In all cost-effectiveness analyses alongside clinical trials, there will be uncertainties regarding the results.

The uncertainty of the data input in the study is called “parameter uncertainty”. The impact of this uncertainty of the result can be investigated by sensitivity analyses, in which the data parameters are varied. Sensitivity analysis with non-parametric bootstrapping means that new datasets are created with sampling with replacements from the original data, and a new result is obtained. This can, for example, be performed 1,000 times and we then get 1,000 different cost-effectiveness results. The result can be plotted in a cost-effectiveness plane (scatter plot), which is a good way to visually analyze the results.

Figure 2.
Scatterplot
The uncertainties when analyzing the results can also be expressed in relation to thresholds regarding willingness to pay for a QALY. By constructing a cost-effectiveness acceptability curve (CEAC), one can see the probability of a treatment being considered cost-effective at various thresholds. For example, at a willingness to pay of 500,000 SEK, we simply calculate how many of the bootstrap results are below this value. This process is then repeated for different threshold values.

**Figure 3.** Cost-effectiveness acceptability curve - CEAC
Dealing with missing data

Investigation whether missing data could have an important impact on the results of the cost-effectiveness analysis can be achieved in several ways. Imputation is a method that replaces missing values with estimated values. In multiple imputation (MI), data are drawn into repeated datasets from the original data to fill in the missing data\textsuperscript{76,77}.

The vehicle for cost-effectiveness analysis: trial-based vs. modelling based

Modelling analysis such as, for example, Markov modelling is a useful tool when effects or costs are expected to continue beyond the time limit of the cost-effectiveness analysis in a study. It is also useful when we lack long-term clinical data, when RCTs only capture a proportion of the patients treated in clinical reality, and when randomized trial are not possible for example for ethical reasons or due to unreasonable costs associated with implementation of a study.

Modelling analysis and cost-effectiveness analysis alongside RCTs can complement each other in providing evidence for decision making\textsuperscript{77}.

3.3 Economic evidence regarding invasive treatment for intermittent claudication

There have been few cost-effectiveness analyses alongside randomized trials in IC comparing invasive treatment against exercise. For one-year analysis comparing aorto-iliac and femoro-popliteal endovascular treatment against SET, Spronk et al.\textsuperscript{78} indicated that endovascular revascularization cost more than the accepted public willingness to pay when a threshold of €50,000 was used. Mazari (2013) compared PTA vs. SET vs. combined treatment for femoro-popliteal lesions and they concluded that SET provided similar gains in QALYs (compared to the other treatments), and being the least costly alternative SET was also the most cost-effective option\textsuperscript{79}. 
In the setting of a five-year horizon and by using Markov modelling approaches, Reynolds et al. compared stenting for aorto-iliac lesions with SET, and found that stenting had an ICER of $122,600 per QALY gained compared to SET\textsuperscript{80}. Van den Houten et al. compared endovascular revascularization with SET and found that invasive treatment had an additional cost of €91,600 per QALY gained compared to SET, and they concluded that SET was the most cost-effective option\textsuperscript{81}. An older study with Markov modelling, by de Vries et al., suggested that angioplasty had an acceptable cost of $38,000 per QALY gained compared to exercise alone, but that open bypass surgery had an additional cost of $311,000 per QALY gained compared to exercise\textsuperscript{82}.

As previously mentioned, SET is often not available and unsupervised exercise is often the non-invasive treatment option offered to patients. The few cost-effectiveness analyses alongside randomized studies have had SET as the non-invasive treatment option.

Thus, in terms of cost-effectiveness studies alongside randomized studies, a comparison between the real-world alternatives (invasive treatment and unsupervised exercise) is lacking. Furthermore, there has been a lack of cost-effectiveness studies alongside randomized trials with a follow-up beyond one year for invasive revascularization vs. exercise treatment.
Aims

The aims of the work described in this thesis regarding invasive treatment of IC were as follows:

- To investigate the risk of major amputation attributable to lower limb revascularization for IC (Paper I).

- To investigate the cost-effectiveness of a liberal invasive strategy in addition to exercise therapy advise and best medical treatment compared to exercise therapy advice and best medical treatment only (Paper II, III and IV).

- To investigate the long-term clinical benefit of a liberal invasive strategy in addition to exercise therapy advice and best medical treatment compared to exercise therapy advice and best medical treatment only (Paper III).
Patients and methods

5.1 Ethics

All the studies in the thesis had ethical applications and approvals.

Study I. Regional Ethical Board, Gothenburg: Dnr 873-14
Studies II and III. Regional Ethical Board, Gothenburg: Dnr 501-09
Study IV. Regional Ethical Board, Lund: Dnr 2016/827

Ethical consideration.
One might consider it to be difficult to randomize people between invasive treatment and non-invasive treatment (papers II, III, and IV). Invasive treatment entails risks for the patient. However, it has been shown that patients with IC tend to take risks in order to receive help. Patients randomized to revascularization in a study may undergo the invasive procedure before the non-invasive approach has been adequately tested. In such instances, the revascularization – and the risks and costs entailed – may be unnecessary. On the other hand, one can argue that withholding invasive treatment from a patient who has been randomized to non-invasive treatment may unnecessarily prolong the patient’s lower limb symptoms and reduced HRQoL.
5.2 Patients and study design

The study designs of the four papers are summarized in Table 2.

Table 2.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Design</th>
<th>Patients</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper I</td>
<td>Retrospective national cohort study</td>
<td>n = 5,860</td>
<td>Major amputation</td>
</tr>
<tr>
<td></td>
<td>Data from the Swedvasc registry,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>the National Patient Registry, and medical</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>journals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paper II</td>
<td>Single-centre, randomized controlled trial</td>
<td>n = 158</td>
<td>Incremental cost-effectiveness</td>
</tr>
<tr>
<td></td>
<td>Invasive treatment vs. non-invasive treatment</td>
<td></td>
<td>ratio</td>
</tr>
<tr>
<td>Paper III</td>
<td>Single-centre, randomized controlled trial</td>
<td>n = 158</td>
<td>HRQoL</td>
</tr>
<tr>
<td></td>
<td>Invasive treatment vs. non-invasive treatment</td>
<td></td>
<td>Walking distance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Incremental cost-effectiveness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ratio</td>
</tr>
<tr>
<td>Paper IV</td>
<td>Randomized controlled multi-centre trial</td>
<td>n = 100</td>
<td>Incremental cost-effectiveness</td>
</tr>
<tr>
<td></td>
<td>Primary stenting of the superficial femoral</td>
<td></td>
<td>ratio</td>
</tr>
<tr>
<td></td>
<td>femoral artery vs. non-invasive treatment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5.3 Study I

This was a retrospective study with data from the Swedvasc registry and the National Patient Registry with complementary analysis of medical records.

The Swedvasc registry gathers data regarding vascular surgical procedures, i.e. both open and endovascular procedures, and follow-up data for a year. All vascular surgical centres report to the registry.

The National Patient Registry (NPR) has national coverage because it is mandatory for hospitals to report to this registry. It contains information regarding diagnoses and procedural codes including above-ankle amputation codes.

Patients aged 50 years or more who underwent revascularization for IC between May 2008 and December 2012 in Sweden were identified from the Swedvasc registry. The start of this study period was chosen in order to facilitate the extraction of data due to the fact that the dataset of Swedvasc was redesigned in May 2008. Since the NPR is updated once a year and the work began in 2015, the follow-up to 31 December 2013 was the maximum time duration that it was possible to receive available updates.

With a time limit of 31 December 2013 when extracting data from the NPR, all patients had one year of follow-up after invasive treatment. Data on major (i.e. above-ankle) amputations were extracted from the NPR and cross-matched with data from the Swedvasc registry.

In cases of uncertainty regarding amputation levels or laterality, the medical record was reviewed on site at the hospital.
In the next step, requests were made for medical records of patients with an invasive procedure and a subsequent ipsilateral amputation. In-depth analysis of the medical records was carried out at Sahlgrenska University Hospital.

The primary outcome, procedure-related major amputation, was defined as ipsilateral major amputation within one year after the revascularization procedure.
5.4 Studies II and III

The IRONIC trial (Invasive Revascularization or Not in Intermittent Claudication) was an open-label, prospective randomized trial comparing a liberal invasive treatment strategy with a non-invasive treatment strategy. It was performed at Sahlgrenska University Hospital.

Patients with established and stable (more than 6 months) mild-to-severe IC and duplex verified stenosis or occlusion in the aorto-iliac and/or femoro-popliteal segment were recruited at Sahlgrenska University Hospital. The patients were randomized either to invasive treatment in addition to best medical treatment and exercise therapy or to best medical treatment and exercise therapy alone.

Exclusion criteria were being aged > 80 years, having very severe or very mild IC, being unable to understand the instructions in Swedish, having more than one previously failed ipsilateral invasive treatment, and having ultrasound findings that indicated invasive treatment below the tibioperoneal trunk. The remaining patients who provided both verbal and written consent were enrolled.

After randomization, both study groups received medical management including secondary pharmacotherapy (anti-platelet and lipidlowering therapy) and a voluntary smoking cessation programme. Diabetes and hypertension were treated according to Swedish guidelines. All patients were offered cilostazol treatment. Both groups received verbal and written information on PAD, which also contained advice on exercise therapy sessions for at least 30 min at least three times a week.

For the invasive group, the Trans-Atlantic Society Consensus (TASC) II recommendations were practised and TASC II A-C had endovascular treatment and TASC D had open surgical treatment both for the aorto-iliac segment and the femoro-popliteal segment.

Both study groups had follow-up at 3, 6, 12, 24, and 60 months either by a vascular research nurse or a vascular surgeon. At follow-up, adherence to exercise advice was verified. Patients who underwent an invasive procedure had an additional follow-up after one month.
Costs were retrieved directly from the hospital’s cost-per-patient systems, which enabled cost comparisons between treatment arms. The following resource use items were identified: accumulated costs from the hospital’s cost-per-patient system concerning in-patient and out-patient visits. The costs for healthcare personnel comprised the full wage cost (included costs for social security). Patient-specific costs for primary and secondary surgical and endovascular procedures were identified based on the price per minute according to the hospital’s cost-per-patient system. Accumulated costs for postoperative care; costs of medications during surgery; and costs of anaesthetic procedures, further diagnostic procedures at the radiology department and the clinical physiology department, blood transfusions, and tests at the clinical chemistry and bacteriology laboratories, were retrieved.

To ensure the robustness of cost data, an economist with experience of the hospital’s cost-per-patient system manually cross-checked the economic system with the corresponding different clinical entries, procedures, and hospital stays.

The primary outcome measure for the study was change in HRQoL as assessed with the Short Form 36 (SF-36).

Supporting endpoints were changes in HRQoL measured with VasculQoL, a PAD-specific questionnaire, walking distances by treadmill testing, and a cost-effectiveness analysis from the EQ-5D-3L questionnaire.

For the cost-effectiveness analysis, the EQ-5D-3L questionnaire was used to calculate quality-adjusted life years (QALYs). In-patient and out-patient costs were obtained during follow-up and cost-effectiveness was assessed as the cost per QALY gained, expressed as the incremental cost-effectiveness ratio (ICER). The main cost-effectiveness analysis was performed from an ITT standpoint. Both costs and QALYs were calculated based on a three per cent annual discount rate. Regression analysis was used to adjust for the difference between groups in baseline QALY weight. The economic evaluation was performed from a payer/healthcare point of view.
5.5 Study IV

IC is commonly caused by lesions in the superficial femoral artery (SFA), and endovascular treatment is a frequently performed treatment strategy. Patients were enrolled in an open-label, controlled randomized multi-centre study involving seven hospitals in Sweden. Patients were randomized either to primary stenting and exercise advice and best medical treatment or to non-invasive treatment with exercise advice and best medical treatment alone.

Inclusion criteria were established and stable IC (more than 6 months), severity Fontaine IIB and walking capacity of less than 500 metres by the treadmill test and with a verified de novo or restenotic SFA stenosis or occlusion.

Exclusion criteria were age less than 18 years, no patent popliteal artery, less than one patent tibial artery, femoro-popliteal aneurysm, target artery diameter less than 4 mm, previous stent treatment in the femoro-popliteal artery, or reduced inflow to SFA. The lower boundary for the lesion had to be 3 cm above the patella. In addition, patients with earlier invasive treatment within three months of study inclusion, haemorrhagic stroke in the previous three months, earlier participation in any other clinical trial, or a life expectancy of less than two years were excluded.

After randomization, both study groups received medical treatment including secondary pharmacotherapy (anti-platelet and lipid lowering therapy) and a voluntary smoking cessation programme. Hypertension was treated according to Swedish guidelines. Stented patients were treated with dual anti-platelet for three months.

Both groups had follow-up at 1, 6, 12, and 24 months.

Costs for all patients treated in Skåne were obtained from the Region Skåne Healthcare Database (RSVD). The RSVD includes accumulated costs for in- and out-patient visits, including primary and secondary
revascularization procedures, anaesthetic procedures, postoperative care, drugs given during surgery and postoperative care, tests at the bacteriology and clinical chemistry laboratories, and diagnostic procedures at the clinical physiology and radiology departments. The costs for healthcare personnel comprised the full wage cost (included costs for social security).

To ensure the robustness of cost data, such data retrieved from RSVD were manually cross-checked with the corresponding medical records (procedures and in- and out-patient visits).

Cost data for the remaining patients (outside of Skåne) were not retrieved and were excluded from the analysis.

For the cost-effectiveness analysis, the EQ-5D-3L questionnaire was used to calculate QALYs.

The cost-effectiveness was assessed as the cost per QALY gained and expressed as the incremental cost-effectiveness ratio (ICER). The main cost-effectiveness analysis was performed from an ITT standpoint. Both costs and QALYs were calculated based on a three per cent annual discount rate\textsuperscript{85}. Regression analysis was used to adjust for the difference between groups in baseline QALY weight. The economic evaluation was performed from a payer/healthcare point of view. In occasional cases of loss of EQ-5D data, linear extrapolation was performed and the patient was included in the complete case analysis (CCA).

5.6 Statistics

Data management and statistical analysis were done using Microsoft Excel version 16.16.18; SPSS version 25.0 (IBM Corp., Armonk, NY); and Stata version 15.1 (StataCorp, College Station, TX).

Descriptive statistics for baseline data were presented as mean ± standard deviation (SD). Student’s t-test was used for two-group comparisons of means, and Fisher’s exact test or Chi-square test was used for dichotomous variables.
Regarding HRQoL outcomes (paper III), Student t-tests were used for inter-group comparisons of normally distributed continuous variables and the Mann-Whitney U-test was used for skewed distributions. The size of HRQoL change (effect size) was derived from the difference in mean values between baseline and follow-up divided by the SD at baseline. Cohen criteria for clarifying effect size were used (small, 0.2–0.5; moderate, 0.5–0.8; and large, over 0.8) Significance was assumed at p < 0.05.

In our studies, the basis of the HRQoL outcomes and also of the cost-effectiveness outcome was the intention-to-treat (ITT) analysis (Papers II, III, and IV). In this analysis, the data were analyzed based on the initial treatment allocation regardless of whether the patient received the allocated treatment during the study period.

In Study II, we also performed an “as treated” analysis where the data were analyzed based on the actual treatment that was given to the patient (regardless of which allocation group he/she belonged to) (Paper II). In Paper III, we performed a complementary per-protocol analysis, which only analyzed the patients who had received the allocated treatment.

In the cost-effectiveness analysis, QALYs and costs were treated as continuous variables and differences in means between treatment groups were analyzed. Sampling uncertainty was evaluated using non-parametric bootstrapping with 1,000 bootstrap resamples.

Where there were missing QALY weight data, we used multiple imputation (MI) methods (Papers III and IV).
Results

6.1 Study I

Altogether, 5,860 patients were revascularized for IC between May 2008 and December 2012. Of these, we found that 5,748 patients had not suffered any major amputation after cross-checking with data from the NPR and limited medical record reviews at participating vascular centres in cases of uncertainty.

For three additional patients, there was uncertainty regarding the laterality of the amputation in the NPR, and the medical records could not be obtained. For the remaining 109 patients who had suffered a major amputation after revascularization for IC, in-depth medical chart analysis was performed regarding the primary outcome, which was defined as major amputation within the first post-procedural year.

The chart analysis showed that 51 patients had been revascularized for CLTI, two had been revascularized for indications other than PAD, two had had no or minor amputation, one had not been revascularized, 17 had duplicate registrations, and 17 had had an amputation more than one year after revascularization. Only nine patients had undergone amputation within a year after invasive treatment for IC, giving an amputation rate of 0.2% (9/5,860).
The nine patients who had been amputated within the first post-procedural year had had different invasive IC procedures: three endovascular procedures, three hybrid procedures, and three open surgical bypasses. The majority (eight of the nine patients) had undergone procedures involving the femoro-popliteal segment whereas only one patient had a solely iliac procedure. Eight of the nine patients had onset of new symptoms within 2 months, and data on new symptoms could not be obtained for one patient.

All the patients received one or several re-interventions. Amputations were performed three to ten months after the index revascularization procedure.
Table 3.
Baseline characteristics of all patients who underwent invasive treatment for intermittent claudication (2008–2012) and for the patients with major amputation following revascularization

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Revascularized IC (n = 5,860)</th>
<th>Amputated after &lt; 1 year (n = 9)</th>
<th>Amputated after &gt; 1 year (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>3,196 (55%)</td>
<td>7 (78%)</td>
<td>18 (67%)</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>70 (50–96)</td>
<td>70 (65–82)</td>
<td>68 (52–85)</td>
</tr>
<tr>
<td>INVASCIVE METHOD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endovascular therapy</td>
<td>4,676 (80%)</td>
<td>3 (33%)</td>
<td>19 (70%)</td>
</tr>
<tr>
<td>Open surgery</td>
<td>1,033 (17%)</td>
<td>3 (33%)</td>
<td>8 (30%)</td>
</tr>
<tr>
<td>Hybrid surgery</td>
<td>151 (3%)</td>
<td>3 (33%)</td>
<td>0</td>
</tr>
<tr>
<td>SMOKING</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>355</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Former</td>
<td>1,604</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>456</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Missing data</td>
<td>3,445</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Time to onset of new symptoms</td>
<td>NA</td>
<td>1 day to 2 months (1 not known)</td>
<td>1 day to 23 months (12 not known)</td>
</tr>
<tr>
<td>Time to major amputation, months</td>
<td>NA</td>
<td>3–10 (1 not known)</td>
<td>14–61</td>
</tr>
</tbody>
</table>

NA = Not Applicable

In the group who underwent amputation after more than one year after revascularization, two out of the 27 had had instant failure of the index procedure with immediate re-intervention, and underwent amputation after 14 and 18 months.

The risk of procedure-related major amputation one year after revascularization for IC was small, but existing.
6.2 Study II

From March 2010 to November 2012, 464 patients aged less than 80 years were admitted to the vascular surgery out-patient clinic for suspected intermittent claudication and screened for inclusion, whereas 338 patients had a confirmed diagnosis of IC. 65 patients had very mild symptoms and/or severe comorbidity. 52 patients had very severe symptoms and invasive treatment was considered mandatory (main criteria: according to protocol, inability to work).

One patient weighed more than 120 kg (which was the maximum weight for the treadmill), 2 patients had had two or more failed ipsilateral vascular interventions, and 13 patients did not speak Swedish. After applying the inclusion and exclusion criteria, 205 were still eligible for the trial. One patient was excluded due to the need for revascularization below the tibio-peroneal trunk and 48 patients declined participation in the study. The remaining 158 patients were included. Thus, 77% of all eligible patients were included (47% of all patients with established intermittent claudication referred to the out-patient ward).
Figure 6.
Flow chart of enrolment in the Invasive Revascularization or Not in Intermittent Claudication (IRONIC) trial.

Enrolment

464 patients < 80 years admitted to the vascular surgery outpatient clinic for suspected intermittent claudication

338 patients < 80 years with intermittent claudication

221 patients

205 eligible patients

158 subjects with intermittent claudication randomized

Other diagnosis n=126 (not intermittent claudication)

Very mild symptoms and/or severe comorbidity n=65

Very severe symptoms, invasive treatment considered mandatory n=52

Weight >120 kg n=1

Two or more failed ipsilateral vascular interventions n=2

Not swedish speaking n=13

Need for open revascularization below tibioperoneal trunk n=1

No consent n=46
### Table 4.
Baseline demographic data and risk factor profiles, by treatment group

<table>
<thead>
<tr>
<th></th>
<th>Invasive group (n = 79)</th>
<th>Non-invasive group (n = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years*</td>
<td>68(7)</td>
<td>68(6)</td>
</tr>
<tr>
<td>Sex ratio (M : F)</td>
<td>41 : 38</td>
<td>42 : 37</td>
</tr>
<tr>
<td>Smoking habits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>24 (30)</td>
<td>22 (28)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>22 (28)</td>
<td>32 (40)</td>
</tr>
<tr>
<td>Never smoked</td>
<td>33 (42)</td>
<td>25 (32)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (18)</td>
<td>16 (20)</td>
</tr>
<tr>
<td>BMI, kg/m²*</td>
<td>26 (5)</td>
<td>26 (4)</td>
</tr>
<tr>
<td>Duration of symptoms, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1</td>
<td>17 (22)</td>
<td>10 (13)</td>
</tr>
<tr>
<td>1–2</td>
<td>20 (25)</td>
<td>39 (49)</td>
</tr>
<tr>
<td>&gt; 2</td>
<td>42 (53)</td>
<td>30 (38)</td>
</tr>
<tr>
<td>Ankle: brachial pressure index*</td>
<td>0.73 (0.17)</td>
<td>0.74 (0.14)</td>
</tr>
<tr>
<td>Femoral pulse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>41 (52)</td>
<td>44 (56)</td>
</tr>
<tr>
<td>Reduced</td>
<td>23 (29)</td>
<td>21 (27)</td>
</tr>
<tr>
<td>Absent</td>
<td>15 (19)</td>
<td>14 (18)</td>
</tr>
<tr>
<td>Lesions on duplex ultrasonography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aorto-iliac</td>
<td>32 (41)</td>
<td>30 (38)</td>
</tr>
<tr>
<td>Femoro-popliteal</td>
<td>63 (80)</td>
<td>62 (78)</td>
</tr>
<tr>
<td>Infra-popliteal</td>
<td>2 (3)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Intermittent claudication treadmill distance, m*</td>
<td>78 (59)</td>
<td>87 (60)</td>
</tr>
<tr>
<td>Maximal treadmill distance, m*</td>
<td>189 (106)</td>
<td>194 (103)</td>
</tr>
<tr>
<td>Serum haemoglobin, g/l*</td>
<td>135 (13)</td>
<td>137 (13)</td>
</tr>
<tr>
<td>Serum cholesterol, mmol/l*</td>
<td>4.9 (1.1)</td>
<td>4.7 (1.2)</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/l*</td>
<td>1.5 (1.0)</td>
<td>1.5 (1.0)</td>
</tr>
<tr>
<td>Serum creatinine, mmol/l*</td>
<td>81 (26)</td>
<td>89 (30)</td>
</tr>
<tr>
<td>Kidney failure (serum creatinine &gt; 170 mmol/l)</td>
<td>3 (4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>7 (9)</td>
<td>10 (13)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>12 (15)</td>
<td>10 (13)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>7 (9)</td>
<td>9 (11)</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>10 (13)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Type of index procedure (70 patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aorto-iliac, endovascular</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Aorto-iliac, open</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Femoro-popliteal, endovascular</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Femoro-popliteal, open</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Infra-popliteal, endovascular</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Infra-popliteal, open</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Values in parentheses are percentages unless otherwise indicated.
*Values are mean (SD).
Of the 158 patients, 79 were randomized to each group. In the invasive group, 70 of the 79 patients received invasive treatment. Thirteen of the 70 patients needed and received 22 re-interventions. In the non-invasive group, 6 out of 79 underwent invasive procedure due to worsening of symptoms.

Follow-up analysis included 71 patients in the revascularization group and 68 patients in the non-invasive group.

The invasive treatment strategy had an improved HRQoL compared to the non-invasive strategy after two years of follow-up, with a mean gain in QALY of 0.16 per patient.

The mean cost per patient was more than four times higher in the revascularization group, with a cost difference of €6,379. The incremental cost-effectiveness ratio (ICER) was €42,881 per QALY in an ITT analysis.

This was within the accepted threshold according to Swedish National Guidelines, but above that in the UK National Institute for Health and Care Excellence guidelines.

In a complete case, “as treated” analysis, the cost difference was higher with a difference of €7,973 and with a higher mean in QALY of 0.19, giving an ICER of €42,704, which was very similar to the ICER from the ITT analysis.
Table 5.
Cost comparison between Invasive and Non-invasive group

<table>
<thead>
<tr>
<th></th>
<th>Invasive group</th>
<th>Non-invasive group</th>
<th>Difference</th>
<th>Mean cost per patient, €</th>
<th>Mean QALYs per patient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ITT</td>
<td>As treated</td>
<td>ITT</td>
<td>As treated</td>
<td></td>
</tr>
<tr>
<td>Mean cost per patient</td>
<td>8,280</td>
<td>(6,421, 10,339)</td>
<td>1,901</td>
<td>(732, 3,071)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9,201</td>
<td>(7585, 10,816)</td>
<td>1,228</td>
<td>(−319, 2,775)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6,379</td>
<td>(4,229, 8,728)*</td>
<td>7,973</td>
<td>(5,739, 10,206)</td>
<td></td>
</tr>
<tr>
<td>Mean QALYs per patient</td>
<td>1.41</td>
<td>(1.29, 1.46)</td>
<td>1.25</td>
<td>(1.17, 1.34)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.24</td>
<td>(1.18, 1.31)</td>
<td>0.16</td>
<td>(0.06, 0.24)*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.19</td>
<td>(0.09, 0.28)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost-effectiveness</td>
<td>42,881</td>
<td>42,704</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ratio, € per QALY</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values in parentheses are 95% confidence intervals. QALY, quality-adjusted life year; ITT, intention-to-treat; *P < 0.010, †P < 0.001 (t-test).
Uncertainty analysis was performed and expressed as a cost-effectiveness acceptability curve showing the probability of invasive treatment being cost-effective relative to non-invasive treatment at different thresholds of willingness to pay.

**Figure 7.**
Cost-effectiveness acceptability curve (intention-to-treat analysis).
6.3 Study III

At five-year follow-up, 13 deaths in the invasive group and seven in the non-invasive group had occurred. Three patients in each group had progression to CLTI and one patient in the non-invasive group had a major amputation after unsuccessful revascularization procedures.

Invasive procedures during the five-year study period

In the invasive group, 72 of the 79 patients had an invasive treatment during the five-year study period. Of the patients who were not treated invasively, six had improved while waiting for revascularization and one patient had a non-significant stenosis on digital subtraction angiography.

Twenty-two patients required more than one invasive treatment. In total, the invasive group had 114 procedures, of which 82 were endovascular, two were hybrid, and 30 were open vascular procedures.

In the non-invasive group, 20 of the 79 patients had invasive treatment during the five-year study period. Seven patients required more than one procedure. Altogether, 33 procedures were performed, of which 17 were endovascular, three were hybrid, and 13 were open vascular procedures.
Assessed for eligibility (n = 338)

- Excluded (n = 180)
  - Did not meet inclusion criteria (n = 134)
  - Declined participation (n = 46)

Randomized (n = 158)

- Allocated to non-invasive group (n = 79)
  - Underwent revascularization (n = 20)
    - > 1 procedure (n = 7)
    - 1 procedure (n = 13)
  - 1 procedure (n = 13)

- Allocated to invasive group (n = 79)
  - Underwent revascularization (n = 72)
    - > 1 procedure (n = 22)
    - 1 procedure (n = 50)

Lost to follow up of HRQoL endpoint (n = 21)
- Death (n = 13)
  - Severe cardiac disease (n = 7)
  - Cancer (n = 3)
  - Stroke (n = 1)
  - Cause not verified (n = 2)
- Withdraw consent (n = 3)
- Moved (n = 1)
- Kidney failure (n = 1)
- Stroke (n = 1)
- Cancer (n = 1)
- Heart failure (n = 1)

Additional loss to follow-up for treadmill testing
- Withdraw consent (n = 15)
- Cancer (n = 1)

Follow-up 5-year

- Lost to follow up of HRQoL endpoint (n = 21)
  - Death (n = 7)
    - Severe cardiac disease (n = 2)
    - Sepsis (n = 1)
    - Cause not verified (n = 2)
    - Cancer (n = 2)
    - Stroke (n = 1)
  - Withdraw consent (n = 7)
  - Amputation (n = 1)
  - Moved (n = 2)
  - Stroke (n = 1)
  - Hip fracture (n = 1)
  - Cancer (n = 1)
  - Heart failure (n = 1)

Additional loss to follow-up for treadmill testing
- Withdraw consent (n = 9)

Analysis

- Analyzed primary endpoint HRQoL (n = 58)
- Analyzed treadmill testing (n = 42)

Analysis

- Analyzed primary endpoint HRQoL (n = 58)
- Analyzed treadmill testing (n = 49)
Primary outcome
For the primary outcome, HRQoL data were available for 116 patients (73% of all study patients and 84% of all patients who were alive) at five-year follow-up (Figure 1).

The mean follow-up time was 5.2 years (range 4.8–6.1). The major reason for non-participation was death (n = 20).

Concerning changes between the groups compared to baseline, no differences were observed for the SF-36 sum and domain scores, except for the SF-36 “role emotional” domain score, which had a greater improvement in the non-revascularization group both in the ITT analysis and the per-protocol analysis.

Regarding changes within the groups compared to baseline, both groups improved on the SF-36 physical component summary (p < 0.05) and on several domain scores:

Invasive group: physical functioning, p < 0.05, and bodily pain, p < 0.01;

Non-invasive group: physical functioning, p < 0.01, bodily pain, p <0.01, and role emotional, p < 0.01).

In both groups, however, all the effects sizes for domain and summary scores were trivial, small, or moderate.

Supporting outcomes
In congruence with the SF-36 results, no significant inter-group differences for VascuQoL changes were observed (n = 116). The results here were also consistent between the ITT analysis and the per-protocol analysis.
Spider plot illustrating HRQoL outcomes in intent-to-treat analysis, presented as effect sizes (ES) calculated between baseline and 60 months. Cohen's criteria for ES: 0.0-0.2=trivial; 0.2-0.5=small; 0.5-0.8=moderate; >0.8=large.

All differences between invasive + exercise vs exercise patients were non-significant except for SF-36 Role emotional domain score with a p-value at 0.013 (Mann-Whitney U). Data was available and analyzed for 116 patients.
Figure 10. Per protocol analysis

Spider plot illustrating HRQoL outcomes in per-protocol analysis, presented as effect sizes (ES) calculated between baseline and 60 months. Cohen’s criteria for ES: 0.0-0.2=trivial; 0.2-0.5=small; 0.5-0.8=moderate; >0.8=large.

All differences between invasive + exercise vs exercise patients were non-significant except for SF-36 Role emotional domain score with a p-value at 0.017 (Mann-Whitney U). Data was available and analyzed for 98 patients.
**Walking capacity**

Regarding walking capacity, the treadmill test showed no significant inter-group differences in change between baseline to five-year follow-up for ICD, or in MWD.

Regarding changes within the groups, both groups improved significantly in ICD but no significant improvement in MWD was observed. The invasive group had a (non-significant) deterioration in MWD. There was an additional loss of patients in the treadmill test, and data were available for 91 patients.

**Figure 11.**
Change in walking capacity.

![Figure 11](image-url)

Change in walking capacity measured on a graded treadmill, from baseline to five-year follow-up. ICD, intermittent claudication distance; MWD, maximum walking distance.
Cost-effectiveness analysis
Cost-effectiveness analysis was performed on an ITT basis for the complete cases including deaths (n = 130).

The changes in health status assessed with QALYs and adjusted for difference in baseline gave a non-significant difference of −0.10 for the invasive group. The cost in the complete case analysis was almost double for the invasive group, with a difference of $6,133.

Thus, the invasive treatment was dominated (more expensive and worse health outcome).

In the multiple imputation analysis, the mean gain in QALYs for the invasive group was 0.001 with a cost difference of $5,849, which gave a cost-effectiveness result of $5,503,448 per QALY.

Thus, the MI analysis gave an ICER where invasive treatment was not cost-effective compared to non-invasive treatment, irrespective of which willingness-to-pay threshold applied.
<table>
<thead>
<tr>
<th></th>
<th>Complete case analysis including deaths (n = 130)</th>
<th>Full sample results based on multiple imputation (n = 158)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-invasive group</strong></td>
<td><strong>Cost per patient</strong></td>
<td><strong>Cost per patient</strong></td>
</tr>
<tr>
<td></td>
<td><strong>(95% CI)</strong></td>
<td><strong>(95% CI)</strong></td>
</tr>
<tr>
<td></td>
<td>6,965</td>
<td>13,098</td>
</tr>
<tr>
<td></td>
<td>(2,975–10,955)</td>
<td>(9,713–16,482)</td>
</tr>
<tr>
<td></td>
<td>3.04</td>
<td>2.88</td>
</tr>
<tr>
<td></td>
<td>(2.81–3.26)</td>
<td>(2.59–3.16)</td>
</tr>
<tr>
<td><strong>Invasive group</strong></td>
<td><strong>Cost per patient</strong></td>
<td><strong>Cost per patient</strong></td>
</tr>
<tr>
<td></td>
<td><strong>(95% CI)</strong></td>
<td><strong>(95% CI)</strong></td>
</tr>
<tr>
<td></td>
<td>13,098</td>
<td>5,849</td>
</tr>
<tr>
<td></td>
<td>(9,713–16,482)</td>
<td>(1,202–10,496)</td>
</tr>
<tr>
<td></td>
<td>2.88</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>(2.59–3.16)</td>
<td>(~0.32 to 0.32)</td>
</tr>
<tr>
<td><strong>Difference</strong></td>
<td><strong>6,133 (972–11,292)</strong></td>
<td><strong>5,849 (1,202–10,496)</strong></td>
</tr>
<tr>
<td></td>
<td>-0.10* (~−0.45 to 0.25)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>ICER</strong></td>
<td><strong>Invasive treatment dominated</strong></td>
<td><strong>$5,503,448 per QALY</strong></td>
</tr>
<tr>
<td></td>
<td><strong>incremental cost-effectiveness ratio.</strong></td>
<td><strong>(more expensive and worse health outcome)</strong></td>
</tr>
</tbody>
</table>

* Due to adjustment for the difference in baseline QALY weight (lower for invasive group), the difference in the CCA analysis results is a slightly different outcome compared to the difference in raw values. In the full sample, estimates of the difference between groups were based on multiple imputed QALYs (the combined result was based on Rubin’s rules).
Uncertainty analysis was performed with non-parametric bootstrapping (1,000 bootstraps). The results are shown in both a cost-effectiveness scatter plot and a cost-effectiveness acceptability curve based on the multiple imputation analysis.

**Figure 12.**
Cost-effectiveness plane based on multiple imputation. Each dot represents one bootstrapped result (in total, 1000).

**Figure 13.**
Cost-effectiveness acceptability curve based on multiple imputation.
6.4 Study IV

From 2010 to 2015, 310 patients were assessed for eligibility and 100 patients were enrolled in the study. An intention-to-treat, complete case analysis was performed for the patients with sufficiently answered EQ-5D data and complete cost data (n = 65: stent group, n = 36, control group, n = 29). One EQ-5D response was missing for 14 of the 65 patients (stent, 5, control, 9) and linear extrapolation was performed in these cases. A table with baseline characteristics of these patients was drawn up.

Table 7.
Baseline demographic data and lesion characteristics (by treatment group) for the patients in the complete case analysis (n = 65).

<table>
<thead>
<tr>
<th>Region Skåne (n = 65)</th>
<th>Stent (SD)</th>
<th>Control (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>70.8(5.3)</td>
<td>70.5(4.8)</td>
<td>0.79</td>
</tr>
<tr>
<td>Male</td>
<td>15</td>
<td>16</td>
<td>0.324</td>
</tr>
<tr>
<td>Female</td>
<td>21</td>
<td>13</td>
<td>0.427</td>
</tr>
<tr>
<td>ABI</td>
<td>0.60(0.12)</td>
<td>0.62(0.18)</td>
<td>0.263</td>
</tr>
<tr>
<td>WD</td>
<td>167(88)</td>
<td>192(96)</td>
<td>0.608</td>
</tr>
<tr>
<td>Duration IC (months)</td>
<td>29(29)</td>
<td>34(44)</td>
<td>0.066</td>
</tr>
<tr>
<td>Smoking, active</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Smoking, former</td>
<td>21</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Smoking, never</td>
<td>11</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>2.5(0.9)</td>
<td>2.5(0.7)</td>
<td>0.962</td>
</tr>
<tr>
<td>B-gluc</td>
<td>7.3(3.0)</td>
<td>6.1(1.2)</td>
<td>0.098</td>
</tr>
<tr>
<td>BP syst</td>
<td>154(22)</td>
<td>145(23)</td>
<td>0.182</td>
</tr>
<tr>
<td>BP diast</td>
<td>80(11)</td>
<td>78(8)</td>
<td>0.347</td>
</tr>
<tr>
<td>Creatinine</td>
<td>86(25)</td>
<td>83(19)</td>
<td>0.686</td>
</tr>
<tr>
<td>Lesion length</td>
<td>144(94)</td>
<td>96(100)</td>
<td>0.05</td>
</tr>
<tr>
<td>Occl</td>
<td>23</td>
<td>21</td>
<td>0.382</td>
</tr>
<tr>
<td>Stenosis</td>
<td>12</td>
<td>8</td>
<td>0.382</td>
</tr>
<tr>
<td>Degree of stenosis</td>
<td>95.2(10)</td>
<td>97.4(4)</td>
<td>0.291</td>
</tr>
<tr>
<td>No. crural vessels</td>
<td>2.4(0.6)</td>
<td>2.5(0.7)</td>
<td>0.982</td>
</tr>
</tbody>
</table>

Mean (SD) or n (%).
B, blood; BP, blood pressure; IC, intermittent claudication; LDL, low-density protein; ABI, ankle-pressure index.
The mean gain in QALYs was 0.24 for the invasive group compared to the non-invasive group, after adjustment for the difference in baseline QALY weight.

The cost was three times higher in the invasive group, with a mean difference of SEK 81,216, resulting in an ICER of 332,112 SEK/QALY.

To investigate the effects of missing QALY weight data, an additional intention-to-treat, multiple imputation analysis was performed for the patients with complete cost data. In this analysis, two patients were excluded due to the total absence of EQ-5D responses. In this MI analysis (n = 75: stent, 40, control, 35) where the missing QALY weight was imputed, the difference between the invasive group and the non-invasive group was higher, with a mean QALY per patient of 0.3999. In the MI analysis, the difference in cost was SEK 87,700. This resulted in a lower ICER with a value of 219,357 SEK per QALY.

**Table 8.**
Costs of stent treatment + exercise advice compared to exercise advice alone

<table>
<thead>
<tr>
<th></th>
<th>Mean cost per patient (SEK)</th>
<th>Mean QALYs per patient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ITT CCA (n = 65)</td>
<td>ITT Multiple imputation (n = 75)</td>
</tr>
<tr>
<td>Stent treatment + exercise advice</td>
<td>115,757 (92,439, 139,075)</td>
<td>1.31 (1.18, 1.44)</td>
</tr>
<tr>
<td>Exercise advice alone</td>
<td>34,541 (22,889, 46,193)</td>
<td>0.97 (0.78, 1.17)</td>
</tr>
<tr>
<td>Difference</td>
<td>81,216 (53,653, 108,779)</td>
<td>87,700 (61,430, 113,971)</td>
</tr>
<tr>
<td></td>
<td>0.24* (0.05, 0.43)</td>
<td>0.40* (0.03, 0.77)</td>
</tr>
</tbody>
</table>

Cost-effectiveness ratio (SEK per QALY)  

<table>
<thead>
<tr>
<th></th>
<th>ITT CCA (n = 65)</th>
<th>ITT Multiple imputation (n = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>332,112</td>
<td>219,357</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% confidence intervals. ITT, intention-to-treat; CCA, complete case analysis. *Due to adjustment for the difference in baseline QALY weight, the outcome for the difference in mean QALYs was slightly different from the difference in raw values.
Uncertainty analysis was performed with non-parametric bootstrapping (1,000 bootstraps) for a complete case, ITT analysis. The results were expressed in a cost-effectiveness plane where they were mainly centred in the northeast quadrant, whereby invasive treatment was more expensive but also provided a better health outcome compared to non-invasive treatment. The results was also expressed in a CEAC to show the probability of being cost-effective at different thresholds regarding willingness to pay for QALY.

**Figure 14.**
Cost-effectiveness plane based on intention to treat analysis in the complete case analysis (n=65). Each dot represents one bootstrapped result (in total, 1000).

**Figure 15.**
Cost-effectiveness acceptability curve based on intention to treat analysis in the complete case analysis (n=65).
7.1 Study I

This retrospective cohort study included IC patients who were treated invasively between 2008 and 2012. To our knowledge, no major changes in technological treatment approaches for these patients have been adopted since 2012.

Large registries are suitable for capturing rare but important events, such as major amputation after a revascularization procedure for IC. In-depth analysis of the medical records of the amputated patients did, however, reveal a sizeable number of misclassifications concerning the reported revascularization indication in the Swedvasc registry. If patients are wrongly classified throughout the entire register, this could possibly affect the results of this study, and also of all other studies that use similar data from this registry. In clinical reality, patient symptomatology can make it difficult to clearly distinguish between very severe IC and CLTI, which may explain some of the misclassifications. There have been evaluations of the Swedvasc registry. Troeng et al. investigated the external validity only, however, and not whether the specific indications for the bypasses were correct; similarly, Venermo et al. validated only the external and internal validity for the carotid and aortic registrational work flows.
The definition of a major amputation potentially attributable to a procedure is difficult, since a patient might deteriorate to CLTI due to rapidly progressing atherosclerosis – especially if the patient is non-compliant regarding advice about lifestyle changes such as medication and cessation of smoking. Thus, a reasonable arbitrary line was set, within one year after the procedure.

We believe that the one-year time point chosen during follow-up is relevant in this particular context, as it was likely to capture patients that had been amputated due to short- or medium-term complications of the surgical intervention. By limiting the primary follow-up time point to one year, but still reporting events during a median follow-up period of 3.9 years, we aimed to discriminate between possible procedure-related limb complications and events that occurred due to progression of the atherosclerotic disease.

**7.2 Studies II, III, and IV**

Randomized controlled trials (RCTs) constitute a key source of a high level of evidence. However, they have some limitations. One of the major problems is the generalizability. In the IRONIC study, 77% of all eligible patients were included and 47% of all patients with confirmed intermittent claudication who were referred to the vascular out-patient ward were randomized in the study.

Of the patients who were excluded, 65 had very mild symptoms and/or severe comorbidity whereas 52 had very severe IC, as compared to 158 patients in the whole study. Thus, on the one hand, we were missing the possible increase in health-related quality of life that invasive treatment might provide for the 52 patients with very severe IC, but on the other hand, also the unnecessary revascularization procedures, with the risks entailed, that the patients with very mild IC would have been omitted to.

In Study IV, patients were recruited between 2010 and 2015 from seven hospitals. Considering the long accrual period and the large number of hospitals involved, probably only a small proportion of patients admit-
ted to the vascular open ward with intermittent claudication, caused by a lesion in the SFA, were assessed for the study. This may have impaired the generalizability of the study.

Comparing the patients included in studies II and III with all the patients revascularized for IC in Sweden between 2008 and 2012 (n = 5,860) in Study I, there were no major differences regarding age or gender.

There were more active smokers in the IRONIC study than in the cohort in Study I, but since there were data missing for the majority of patients regarding smoking status in Paper I, we do not know the real proportion of active smokers in that cohort.

The majority of index procedures were endovascular in the IRONIC study (76 %), as in study I (80%).

Comparing Papers III and IV with the data by Kumakura et al., who investigated 1,107 patients with de novo IC, there was similarity in age and smoking habits. Sixty per cent in this cohort were male.

The potential problem of generalizability in RCTs also applies to the cost-effectiveness analysis. We chose to conduct the cost-effectiveness analysis from a healthcare point of view. We then might have missed possible effects on and benefits to productivity. Considering that one of the exclusion criteria in the IRONIC study was very severe IC, which in most cases precluded the patients from working, these patients were already excluded in the analysis. In Study IV, this was not a direct exclusion criterion, but it is unlikely that many patients with difficulties in working due to IC would have been included in the study.

Thus, one must emphasize that the cost-effectiveness results in these studies are not applicable from a societal standpoint, where invasive treatment possibly enables patients to return to work.

The mean age at baseline for study patients was 68 in the IRONIC study, and 71 (stent group) and 70 (control group) in Study IV.
Using RCTs for cost-effectiveness analysis has the disadvantage of a limited follow-up, such as the two-year limit in Papers II and IV. In a clinical study setting, this is often considered to be a long-term follow-up but from a health-economic point of view this may be considered to be a short time frame. Effects of the treatments may extend beyond the time limit of the study, and the costs associated with each treatment may continue. Thus, one must interpret the results from such studies with caution regarding the real-world effects. It is worth mentioning that when Paper II was published, it was the cost-effectiveness analysis (comparing invasive treatment and non-invasive treatment for IC) alongside a randomized trial with the longest follow-up to be performed. Thus, this paper added further knowledge to the field.

A negative aspect of having a longer follow-up time may be the increased risk of missing data. In elderly patient populations, as in the studies in this thesis, death will be a factor that affects the results during longer-term follow-up. The higher number of deaths in the invasive group than in the non-invasive group (13 vs. 7) did of course affect the economic analysis. When calculating an ICER in a CCA analysis without deceased patients, invasive treatment was no longer dominated but invasive treatment was still not cost-effective at any willingness-to-pay threshold applied.

The IRONIC study used in Papers II and III was powered for two-year follow-up and an additional loss of patients at five years may have affected the results in Study III. It is not clear why the results were different from those in earlier reports, which showed a significant benefit from invasive treatment compared to non-invasive treatment. As expressed in Paper III, the reason may have been loss of patency for invasive treatments during the follow-up, which might have contributed to the loss of benefit. The index procedures were guided by the TASC II recommendations, and choice of technique was strictly regulated. In retrospect, the possible improvement in operative technique that could have been considered for the index procedures might have been primary stenting of the femoro-popliteal segment instead of angioplasty alone.
However, superior long-term patency of primary stenting compared to angioplasty is yet to be proven.

One might consider that necessary lifestyle changes would not be put into practice if an early invasive treatment reduced the patient’s motivation to undertake such changes. Other reasons for the loss of benefit could be that other concurrent diseases affecting walking capacity and HRQoL might have developed during the study. As with the clinical results, the cost-effectiveness results changed between two- and five-year follow-up. When comparing between invasive treatment and non-invasive treatment in an RCT, one might expect that the costs for the invasive treatment group could be found at the beginning of the study. However, in the IRONIC trial, the invasive group still continued to undergo more invasive interventions that generated costs even later on. One reflection from a clinical point of view is that it may be difficult to deny the patient a second procedure if the first one fails or if the benefit of the procedure starts to fade. With the number of procedures persisting and a loss in HRQoL at five years, the invasive treatment strategy was not found to be a cost-effective option.

At baseline in the IRONIC study, there were no significant inter-group differences in the SF-36 or in the Vascular Quality of Life questionnaire (VascuQoL). There was a slight – although not significant – difference between treatment arms regarding EQ-5D at baseline. EQ-5D at follow-up showed trends similar to the results for SF-36. In Study II, the adjustment for difference in baseline QALY weight was not described in the paper.

In Study IV, there was also a non-significant difference in EQ-5D at baseline in the complete case analysis (p = 0.11). No significant inter-group differences in the SF-36 were found at baseline.

For the cost-effectiveness analysis in Papers II and III, we also assessed the outcome with SF-6D (which is derived from SF-36) and found no major differences from the results with EQ-5D.
In Study IV, there were also greater costs (about 50% increase) at two-year follow-up, both for the non-invasive group and for the non-invasive group, compared to the IRONIC study in Paper II. This difference can be partly explained by the study setting in the IRONIC trial, with follow-up visits by a nurse, whereas the patients had follow-up visits by doctors in Study IV.

The RSVD system in Paper IV is not as precise as the cost-per-patient system used in the IRONIC trial. The cost-per-patient system in the IRONIC study enabled diagnostic procedures and costs for each operative procedure to be pinpointed to an individual patient whereas the RSVD system cannot pinpoint each diagnostic procedure or a price per minute for the procedures. It is based on a system where the accumulated costs for each economic section (e.g. the open ward) are divided by the calculated production for that economic section. The patient’s diagnosis will thereafter render a specific cost for each out-patient or in-patient entry.

Health-economic evaluations that extract costs from hospital registries are always dependent on the costs that have been apportioned for each item. When registries change over time, the allocation of costs for different items can change, affecting the results.

Compared to the multi-centre study in Paper IV, the IRONIC study (Papers II and III) was a single-centre study and the operative results in this study were therefore dependent on the operative expertise at one single hospital. The Vascular Department at Sahlgrenska University Hospital is a large vascular centre that is well acquainted with both open surgical and endovascular treatment.

When performing an RCT, the optimal arrangement is to conceal the real treatment from both the healthcare personnel and the patients. This is difficult to accomplish when comparing a surgical intervention with conservative management, and one must consider that a placebo effect would be introduced with invasive treatment, at least for the initial follow-up. To this end, the results from the double-blinded randomized controlled ORBITA study, where patients with stable angina
pectoris were randomized to either percutaneous coronary intervention or a placebo intervention, highlight this problem. In this study, there was no significant difference in exercise time between PCI and the placebo intervention.

For the non-invasively treated patients in the IRONIC study, enrolling patients in a study with a more rigorous follow-up scheme compared to the real clinical situation might give the study participants increased motivation compared to patients in a real-world clinic, a feature that may introduce bias. However, as the same follow-up scheme was provided in both treatment arms, the effect of this phenomenon would be expected to be limited.

In clinical trials, it is difficult to include all possible comparative treatments.

Regarding patient benefit and cost-effectiveness of invasive and non-invasive treatment, the studies in Papers II, III, and IV all compared invasive treatment with the most common non-invasive treatment used, which was exercise advice. Other treatment arms would also have been possible, for example a more intense home-based structured exercise programme or a hospital-based supervised exercise programme, but such treatment arms were not included in any of the studies. It remains unclear whether the benefit of invasive treatment in Studies II and IV would still yield results that would be below the willingness-to-pay threshold according to Swedish national guidelines, if the non-invasive comparative option had been a supervised or home-based exercise programme. In the setting of a shorter follow-up period, Markov modelling by Bermingham et al. indicated that SET was a more cost-effective option than unsupervised exercise.

Supervised or home-based exercise programmes are interesting alternatives, both as separate alternatives and as adjuncts to invasive treatment, to improve long-term HRQoL and also as long-term cost-effective treatment options. One must, however, take into account the costs
associated with the development and maintenance of a hospital-based supervised exercise programme or a home-based exercise programme.

One word of caution when interpreting results from studies with SET: some studies allow patients allocated to SET to perform the exercise on the treadmill, and then use treadmill testing as endpoint. Since there is a well-known “learning effect” with exercise performance on treadmills, there is bias that might blur the result\textsuperscript{56, 91, 92}. 
Invasive treatment for IC had a low but real risk of major amputation within the first post-procedural year.

A liberal invasive treatment strategy for IC increased costs after two years of follow-up, but since HRQoL also increased, the cost-effectiveness results were within the acceptable threshold according to the Swedish national guidelines regarding willingness to pay.

The clinical benefit of a liberal revascularization strategy observed at two years was lost at five years, and in the long term was not a cost-effective option compared to exercise alone.
The main consideration when dealing with patients with IC is that the clinician has a patient presenting with a peripheral problem while the factors that have developed this disease have also led to an increased risk of a major cardiovascular event and a higher mortality risk relative to the general population. The patients are not often aware of this aspect. Thus, the treatment of the localized peripheral disease must always be combined with treatment of the increased risk of cardiovascular events, and we must make the patient aware of the necessary changes in lifestyle that are needed.

Today, invasive procedures are an established method for reducing lower limb symptoms in IC.

The randomized studies in this thesis were all front-line research investigating clinical outcomes and cost-effectiveness with two and five years of follow-up. However, more studies are needed to clearly define the role of invasive treatments in reducing lower limb symptoms.

From a cost-effectiveness point of view, it is interesting if the availability of a home-based or supervised exercise programme can reduce the number of invasive procedures in the long term.
In the five-year follow-up by Mazari60, the adding of SET to endovascular therapy reduced the number of re-interventions in the long term, which might be beneficial from a cost-effectiveness standpoint.

More long-term studies are also needed to investigate the optimal exercise programme that may provide long-term compliance and long-lasting benefit for IC patients.

Future studies might consider having the option of physical activity as an extra measure. One meta-analysis concluded that structured exercise programmes increased physical activity in the short term (and endovascular procedures did not), which could possibly lead to additional benefits regarding the risk of cardiovascular events18, 93.

Invasive treatment is constantly developing, and new endovascular technology might provide better long-term patency for IC procedures. More precise targeting of patients might be possible in the future, with more advanced imaging to select which patients are likely to develop restenosis after invasive procedures94.

Overall, further studies, preferably large randomized multi-centre studies, are needed to determine when to choose invasive treatment instead of non-invasive treatment, and to provide information on which procedures can provide long-lasting benefit in HRQoL and at a cost that is acceptable to the healthcare provider.
Populärvetenskaplig sammanfattning på svenska

Claudicatio intermittens, även kallad fönstertittarsjuka, orsakas av otillräcklig blodtillförsel till benens muskler på grund av arterosklerotiska förträngningar. Vid ansträngning leder detta till mjölksyrautveckling och smärtor i benen som i sin tur resulterar i nedsatt gångförmåga och livskvalitet. Dessa bensymtom kan lindras både av gångträning och operationer.

Resursåtgången för denna grupp förväntas öka på grund av en åldrande befolkning. Långtidseffekten och kostnadseffektivitet av operativ behandling är dock bristfälligt studerad.

Den övergripande målsättningen med detta avhandlingsprojekt var att undersöka kliniska resultat och kostnadseffektivitet för operativ behandling vid claudicatio intermittens jämfört med gångträning.

Den mest fruktade komplikationen vid operation för claudicatio intermittens är att operationen misslyckas och att blodflödet till benet istället försämras, vilket i värsta fall kan leda till amputation. Vi fann att denna risk var låg men att den trots allt existerade och varje beslut om operativ behandling måste därför noggrant övervägas.

Efter två års uppföljning var operativ behandling dyrare jämfört med gångträning, men på en acceptabel kostnadsnivå jämfört med nationella svenska riktlinjer.

På lång sikt (fem års uppföljning), såg vi dock att den tidigare observerade nyttan vid två år, med operativ behandling (jämfört med enbart gångträning), inte längre kunde påvisas. Operativ behandling var inte heller ett kostnadseffektivt alternativ jämfört med gångträning efter fem års uppföljning.
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