Peripheral Arterial Disease with focus on Intermittent Claudication. Outcome after Invasive Treatment

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Peripheral Arterial Disease with focus on Intermittent Claudication
Outcome of Invasive Treatment

HANS LINDGREN
CLINICAL VASCULAR RESEARCH | FACULTY OF MEDICINE | LUND UNIVERSITY 2016
Peripheral Arterial Disease with focus on Intermittent Claudication

Outcome of Invasive Treatment

Hans Lindgren, MD

LUND UNIVERSITY

DOCTORAL DISSERTATION
by due permission of the Faculty of Medicine, Lund University, Sweden.
To be defended at Helsingborg City Hall (Helsingborgs Rådhus). Friday the 22th of April 2016 at 1 pm.

Faculty opponent Lars Lönn, MD, PhD University of Copenhagen
Background and aims: Peripheral arterial disease (PAD) is common, affecting about 200 million individuals worldwide. Gender differences in treatment indication and results are debated. Incidence and results of invasive treatment of infrainguinal intermittent claudication (IC) in Sweden, as well as prevalence and impact of concomitant chronic widespread pain (CWP) in patients with PAD have not been established. The use of minimal invasive endovascular treatment is increasing, and there is a need to study results of primary stenting of infrainguinal IC, commonly caused by lesions in the superficial femoral artery (SFA), and to establish influence of concomitant CWP on treatment results.

Methods: Cohort study of 112 consecutive patients undergoing SFA stenting for IC and critical limb ischemia (CLI) analyzed 12 months after treatment (paper I). One year follow-up study of all 775 patients undergoing 843 infrainguinal procedures for IC during one year in Sweden (paper II). Analysis of 240 patients hospitalized for treatment of symptomatic PAD regarding health related quality of life (HRQoL) and concomitant CWP at baseline, and at 12 months after treatment (paper III). Prospective randomized study of 100 patients suffering from stable IC randomized to primary SFA stenting or continued best medical treatment (BMT) only, with HRQoL as primary, and ABI, walking distance, and influence of CWP on HRQoL analyzed after six months, as secondary outcome measures (paper IV).

Results: When undergoing SFA stenting women presented with more severe CLI and female gender was an independent risk factor for amputation. One year amputation-free survival was 67% (paper I). The Swedish annual incidence of invasive treatment of infrainguinal IC was 8.9/100,000 inhabitants, and treatment resulted in clinical improvement after 12 months in 73.2% of patients (paper II). CWP was twice as common in patients with PAD as in the general population, affecting 29% of patients scheduled for invasive treatment, and was associated with reduced HRQoL. Invasive treatment led to significant improvement of HRQoL in all patients, although to a lower level in patients with CLI and CWP than in patients with IC and without CWP at baseline (paper III). Primary stenting in patients with IC due to lesions in the SFA led to significant improvement in HRQoL, ankle-brachial index (ABI), and walking distance. In patients with concomitant CWP primary SFA stenting led to improvement in ABI and walking distance, but not in HRQoL (Paper IV).

Conclusion: Paper I revealed an increased risk of amputation in women, but successive studies did not indicate that invasive PAD treatment is less favourable for women. Invasive treatment of infrainguinal IC was frequently performed in Sweden, leading to improvement in three out of four patients. CWP was twice as common in patients with PAD as in the general population. Invasive treatment of PAD led to significant improvement of HRQoL in all patients, but to a lower level in patients with CWP. Primary stenting of SFA lesions in patients with IC led to significant improvement in HRQoL, ABI, and walking distance.
Peripheral Arterial Disease with focus on Intermittent Claudication

Outcome of Invasive Treatment

Hans Lindgren, MD
Emperor Claudius of Rome, version with stent in the superficial femoral artery.
Produced by Cecilia Lindgren

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Tryckt i Sverige av Media-Tryck, Lunds universitet
Lund 2016
To my beloved family

Lotta, Ulrika, Victor, and Cecilia
There is a crack in everything, that’s how the light gets in
Leonard Cohen
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The present thesis is based on the following papers, referred to by their Roman numerals and reprinted with consent from the respective publishers.


III. Lindgren H, Gottsäter A, Qvarfordt P, Bergman S. All cause chronic widespread pain is common in patients with symptomatic peripheral arterial disease and is associated with reduced health related quality of life. Submitted and revised

Abstract

Background and aims: Peripheral arterial disease (PAD) is common, affecting about 200 million individuals worldwide. Gender differences in treatment indication and results are debated. Incidence and results of invasive treatment of infrainguinal intermittent claudication (IC) in Sweden, as well as prevalence and impact of concomitant chronic widespread pain (CWP) in patients with PAD have not been established. The use of minimal invasive endovascular treatment is increasing, and there is a need to study results of primary stenting of infrainguinal IC, commonly caused by lesions in the superficial femoral artery (SFA), and to establish influence of concomitant CWP on treatment results.

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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ABI</td>
<td>Ankle-brachial index</td>
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<tr>
<td>BMS</td>
<td>Bare metal stent</td>
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<tr>
<td>BMT</td>
<td>Best medical treatment</td>
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<tr>
<td>BP</td>
<td>Blood pressure</td>
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<td>CLI</td>
<td>Critical limb ischemia</td>
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<td>CRP</td>
<td>Chronic regional pain</td>
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<td>CTA</td>
<td>Computerized tomography angiography</td>
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<td>CWP</td>
<td>Chronic widespread pain</td>
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<tr>
<td>EQ5D</td>
<td>European quality of life questionnaire, 5 dimensions</td>
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<tr>
<td>HRQoL</td>
<td>Health related quality of life</td>
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<tr>
<td>IC</td>
<td>Intermittent claudication</td>
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<tr>
<td>LDL</td>
<td>Low density protein</td>
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<tr>
<td>MRA</td>
<td>Magnetic resonance angiography</td>
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<tr>
<td>NCP</td>
<td>No chronic pain</td>
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<tr>
<td>PAD</td>
<td>Peripheral arterial disease</td>
</tr>
<tr>
<td>PTA</td>
<td>Percutaneous transluminal angioplasty</td>
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<tr>
<td>QoL</td>
<td>Quality of life</td>
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<tr>
<td>SET</td>
<td>Supervised exercise training</td>
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<tr>
<td>SF-36</td>
<td>Short-form -36</td>
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<tr>
<td>TASC</td>
<td>Trans atlantic inter-society consensus</td>
</tr>
<tr>
<td>TEA</td>
<td>Thrombendarterectomy</td>
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<tr>
<td>WIQ</td>
<td>Walking impairment questionnaire</td>
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Already in the beginning of my radiology training at Karlskrona Hospital back in the middle of the 80s, I realized that angiography and interventional radiology was what I wanted to work with. In fact it was, in combination with the “good world” created by my colleagues under guidance of my first clinical director Dr. Sven Hallqvist, the main reason for me to choose radiology as specialty. We were a couple of young registrars who wanted to work as much as possible with angiography, and I remember one of the more senior ones saying he was worried about our (not specifically mine) “barium education”, meaning that the gastrointestinal investigations were not of enough interest for us. Colonic barium investigations were very common in those days, and were like “bread and butter” for young radiologists in their beginning. Anyhow, I was very interested in angiography and did my first percutaneous transluminal angioplasty (PTA) of the superficial femoral artery (SFA) already after a few years of radiology training. We held a register of all interventions performed at the angiosuite, and I remember thinking that it would be interesting to analyze our results from PTA of the SFA but I turned the idea down, however, thinking it would be too hard with all the variety and complexity of the lesions in the SFA.

How little did I then know about what was to come in the future…

The idea of the studies in this thesis started in 2006 when I held a lecture in a workshop on SFA stenting and discussed with Dr Dierk Scheinert from Germany who was invited as a celebrity speaker. It was obvious that much progress had been made in stent development and that much could be achieved with stent treatment of the SFA and we expanded our indications for SFA stenting at Helsingborg Hospital a lot during the following years. In cases of critical limb ischemia (CLI) the indication was clear cut in most cases - but the question remained how to handle patients with intermittent claudication (IC), who in most cases was not considered for invasive treatment?

Why don’t we start a prospective randomized study on this?
Introduction

Peripheral arterial disease

Definition
Atherosclerosis is a degenerative disease affecting the arterial wall in which plaques (made of cholesterol, fatty substances, cellular waste products, calcium and fibrin) build up inside the arteries, leading to hardening and narrowing or occlusion of the vessel, and obstruction of blood flow in the vascular bed (1). Peripheral artery disease (PAD) refers to disease in vascular beds other than the coronary and intracranial arteries. This means that PAD in addition to lesions in the aorta with its branches, the iliac and the infrainguinal arteries of the leg including the arteries of the foot, technically includes atherosclerosis in the extracranial carotid arteries, the upper extremity arteries, and the renal and mesenteric circulation (2). This thesis is focused upon PAD affecting the arteries distal to the aortic bifurcation.

In clinical praxis PAD is, in addition to the presence of clinical signs and symptoms, diagnosed as ankle-brachial index (ABI; the ratio of the highest systolic blood pressure (BP) in the ankle divided by the systolic BP in the arm) < 0.9 (3). Normally, this value is between 0.9 and 1.3.

Epidemiology
Total PAD prevalence based on epidemiologic studies is in the range of 3% to 10%, increasing to 15% to 20% in persons over 70 years (4). The prevalence in a Swedish population based study on men and women between 60-90 years of age is 18% for any PAD, 11.1% for asymptomatic PAD, 8.8% for intermittent claudication (IC) and 1.2% for critical limb ischemia (CLI) (5).

Intermittent Claudication
Patients with IC experience muscle discomfort and pain in the lower limb, commonly localized to the calf, but it may also affect the thigh or buttocks, reproducibly produced by exercise and relieved by rest within 10 minutes. (Fontaine classification stage IIa-IIb) (6). Typical claudication occurs in up to one-third of all patients with PAD (4). The degree of disease severity is dependent on
the severity of the atherosclerotic lesions, patient’s lifestyle, and activity. In patients with comorbidities (such as congestive heart disease, severe pulmonary disease, and musculoskeletal disease) preventing activity levels producing leg ischemia, typical claudication symptoms may not occur.

Critical limb ischemia
CLI is a severe manifestation of PAD (Fontaine classification stage III-IV) (6) defined as ischemic rest pain, ulceration, and ultimately gangrene that can occur when the minimal nutritional requirements of skin, muscle, and nerves are not met. This end stage of PAD might in the worst case lead to limb loss, reported in 42% after one year when treated conservatively (7).

Gender differences
Data are conflicting on whether the PAD prevalence differs between men and women. More women than men have PAD according to some authors (8) others argue that men have more IC, but that the IC prevalence and its consequences may be underestimated in women (9). Women might therefore dominate both in IC and CLI prevalence (10). Female gender has also been reported to be associated to worse outcome after invasive treatment, due to various possible mechanisms such as postmenopausal hormonal effects (11) and smaller vessels (12).

Medical treatment
Indication for secondary prevention with best medical treatment (BMT) exists for all patients with atherosclerosis, including both patients with symptomatic and asymptomatic PAD in order to reduce their risk for future ischemic events. This treatment includes antiplatelet, lipid lowering, and antihypertensive drugs with treatment targets according to Swedish guidelines; LDL-cholesterol 1.8 mmol/l, BP 140/90 mmHg, and 140/85 mmHg in patients with diabetes mellitus (13), in addition to instructions about regular exercise and smoking cessation.

Invasive treatment
In addition to BMT, treatment options include minimally invasive endovascular treatments such as PTA with or without stenting, and surgical procedures such as thrombendarterectomy (TEA) with or without femoropopliteal bypass grafting. While there is little debate over the indication for invasive treatment of patients with CLI, the management of IC traditionally consists of risk factor modification and BMT with or without supervised exercise training (SET). When IC is caused by infrainguinal lesions invasive treatment is even more controversial, and international guidelines recommend that infrainguinal lesions in most cases should not be revascularized (4). This thesis deals with outcome after invasive treatment of PAD with focus on infrainguinal IC.
History of angiography

To track the development of angiography one has to go almost all the way back to the detection of X-rays by Wilhelm Conrad Röntgen in 1895 (14). The first imaging of a blood vessel was performed already in January 1986 by Haschek and Lindenthal who injected contrast material in an amputated hand (15). Early development of angiography and contrast material was based on studies on animals and cadavers. Arterial visualization with CT of the mummy of an Egyptian woman who lived already during the 18th dynasty (1550-1290 BC) (16) showing a calcification in the SFA (Figure 1), demonstrates that PAD existed already in ancient times.

The 1920s was an important decade for the development of angiography. In 1924 Brooks made the first visualization of an infrainguinal blood vessel (17), and in 1928 Edgar Moniz described the technique for cerebral angiography and its application in the diagnosis of cerebral lesions (18).

The first angiocardiography was described in 1937 by Ameuille (19). Imaging in different congenital heart diseases was described during the 1930s by Castallenos, Pereiras, and Garcia (20).

Visualization of the abdominal aorta, first described by Reynaldo Cid dos Santos in 1929, was performed by direct translumbar puncture of the aorta (21), a method mainly criticized for its invasive nature and risk of complications. The method did not gain much enthusiasm from start, due to both the reputation of complications and the lack of surgical methods to treat the diseases it could reveal. Not even Leriche, who reported the syndrome named after him (aortoiliac occlusive disease with the clinical triad of impotence, pelvis and thigh claudication, and absence of femoral pulses), strived for a more frequent use of lumbar angiography (22). It was not until 1947 when João Cid dos Santos (the son of Reynaldo Cid dos Santos) reported the first successful trombendarterectomy (23), that the translumbar angiography was appreciated for its real diagnostic value. Thereafter, aortic and peripheral angiography became necessary tools to guide physicians in many difficult operations (24).

During several years into the 1950s aortofemoral angiography was performed with translumbar puncture, or in case of infrainguinal angiography with contrast injection directly on the needle in the groin. To satisfy the need of more selective angiograms, Farina introduced aortic angiography with selective catheter placement after cut down to the common femoral artery (25).

It was not until one day in April 1952 when Sven-Ivar Seldinger (1921-1998) was, as described by himself, struck by “a severe attack of common sense” and realized how the three tools; the needle, the guidewire and the catheter could be used
together (Figure 2). The method was published in 1953 (26), but had been spread worldwide long before publication. This was one of the reasons why Sweden was in the frontline in angiographic development for many decades. “The Seldinger method” is a main contributing factor to the tremendous development in endovascular treatments and Sven-Ivar Seldinger is one of the world’s most cited physicians.

In modern clinical practice, noninvasive methods to visualize vessels and vascular diseases have been developed. They are Magnetic Resonance Angiography (MRA), CT Angiography (CTA) and duplex ultrasound. Even though having the disadvantages of being invasive and carry (by the use of iodinated contrast material) a risk of renal impairment, conventional angiography is still referred to as the reference angiographic method, with the great advantage of allowing endovascular treatment in the same session.

Figure 1. Sagittal reconstruction of CT scan of the SFA in the mummy of a woman living during the 18th dynasty (1550-1290 BC). Published with permission from the JAMA network.
Figure 2. The Seldinger technique. a=needle puncture, b=guidewire in, c= needle out, d=catheter on guidedwire, e=catheter further in, to the place of contrast injection, f=guidewire out, catheter ready for contrast injection. Published with permission from SAGE publications Ldt.
History of arterial stenting

The idea of stent treatment of an artery was developed as PTA occasionally led to suboptimal results due to mechanic recoil and intimal hyperplasia. Stents are expandable metal mesh tubes with superior patency than PTA alone when used in the coronary, renal, and iliac arteries (27).

Already in 1969 Dotter published an experimental study on the placement of expandable coils in the popliteal artery of a rabbit (28). Early experimental studies dealt with problems with biocompatibility, mechanical instability, and acute stent thrombosis (29). Many of these problems were solved with further development of stents; the remaining problems with arterial stenting are primarily intimal hyperplasia and stent fractures leading to restenosis and occlusion. There are two principally different stent designs; balloon-expandable (Figure 3) and self-expanding (Figure 4). In 1987 the first study on self-expanding stents in humans was published by Sigwart (30), shortly thereafter followed by Palmaz (31) and Strecker (32) describing results obtained with balloon-expandable stents. All these studies reported good results.

Further development led to devices with lower profile of both stent and delivery system, and a more optimal relation between stent flexibility and radial force. As the development of stents continued, the indication for endovascular stent treatment increased. This is reflected by changes in indications between the TransAtlantic Inter-Society Consensus (TASC) 2000 (33) and TASC 2007 (4) recommendations.

The indication for stenting has developed from secondary stenting in cases of suboptimal results with PTA to primary stenting in many vascular territories such as the iliac-and coronary arteries (27, 34), but what about infrainguinal vessels?

Figure 3. Balloon-expandable stent. Image from the Department of Interventional Radiology, Helsingborg Hospital, Sweden.
Endovascular treatment of the SFA

Femoropopliteal bypass surgery is associated with important complications (as wound infection) and prolonged hospital stay (35). The benefit for patients with IC has not been considered large enough to justify its risks (36) and the majority of infrainguinal IC cases are therefore treated by less invasive endovascular methods (37).

Due to anatomical reasons (movement of adjacent joints and fixation in the adductor canal) the SFA undergoes deformation; axial compression and extension, radial compression, bending and torsion (Figure 5) and shortens approximately 13% in the fetal compared to the supine position (38).
PTA has been widely used in the treatment of femoropopliteal disease for many years, but results have been suboptimal with very high restenosis rates with PTA alone in long SFA lesions. The presence of occlusion rather than stenosis, lesion length, and the severity of run-off vessel disease all contribute to poor results (39).
Several studies have investigated patency of balloon-expandable stents in the treatment of SFA lesions. These stents have low flexibility and a high risk of deformation when placed in the SFA, with suboptimal results and high restenosis rates, not better than PTA alone in long SFA lesions (40, 41).

Self-expanding nitinol stents, on the other hand, have higher flexibility and exert moderate to high radial force. Promising results have been obtained with placement of such stents in the SFA (42).

Stent treatment of the SFA is performed with guidewire and catheter recanalization of the lesion, followed by stent placement (Figures 6 a-b).

The SFA is however more subjected to stent fracture and restenosis than other vascular territories (43, 44) and even more pronounced in longer SFA lesions that requires longer, frequently overlapping stents (44), related to mechanical fatigue in the stents as a result of the complicated repetitive movement pattern mentioned above (Figures 5 and 7).

In treatment recommendations of infrainguinal lesions stent placement is still controversial; the role of primary or bailout stenting, and even the question whether to use stent at all are under debate (4). However, data on modern self-expanding nitinol bare metal stents (BMS) are now compiling in numerous prospective clinical trials showing efficacy both in terms of primary patency and safety of primary stenting of the SFA (45).
Figure 6. SFA stent treatment. a=guidewire across occlusive lesion. b=result with good blood flow after stent placement. Images from the Department of Interventional Radiology, Helsingborg Hospital, Sweden.
Figure 7. Nitinol stents in the SFA/popliteal artery in flexed knee position. Image from the Department of Interventional Radiology, Helsingborg Hospital, Sweden.
Chronic pain

In contrast to acute pain, chronic pain is in the literature often defined as pain with duration of at least 3 months (46). Several studies from Western Europe and the USA have shown that musculoskeletal pain is common in the general population, with a prevalence of 30–50% (47-49). In epidemiological studies, a distinction is often made with regard to the distribution of musculoskeletal pain; chronic regional pain (CRP) and chronic widespread pain (CWP) (46-48). Subjects with CWP can be identified as those reporting pain in two contralateral body quadrants (right or left and above or below the waist) and the axial skeleton (spine and anterior chest) for three months or more. Those reporting pain for at least three months, but not fulfilling the criteria for CWP are designated as having CRP. Subjects with no pain at all or with pain duration of less than three months are regarded as having no chronic pain (NCP). CRP is most common with a prevalence of 24%, whereas CWP occurs with a prevalence of 11% (47, 48).

Chronic musculoskeletal pain, and foremost CWP, has been shown to have other background factors than acute and more localized pain (50). CWP may reflect musculoskeletal disorders or other underlying organic diseases which are, however, reported only by a small proportion of CWP patients (51). Despite the possible lack of pathological findings, chronic musculoskeletal pain and especially CWP are known to have a negative impact on self-reported health, and also to be a common cause for visits in primary care (51-53). CWP is associated with increased risk for hospitalization due to serious medical conditions (54), increased cancer mortality (55) due to both a higher incidence of cancer and a reduced cancer survival (56), and worse outcome when patients are treated for other disorders such as rheumatic diseases (57). Some authors even consider chronic pain (especially CWP) as a disease entity in itself, partly explained by central sensitization of the nervous system (58, 59).

The risk of hospitalization due to cerebrovascular and ischemic heart disease (IHD) is significantly increased for both subjects with CRP and CWP. A nearly significant association between CWP and an increased mortality in cardiovascular disease has also been reported (60).

It is not known to what extent CWP is present in patients with PAD, or how it influences HRQoL before and after treatment in these patients.
Quality of Life

“Quality of life” (QoL) has become a general term used in a wide range of contexts, including the fields of international development, healthcare, politics and employment but confusion still exists about what it actually means.

Health Related Quality of Life

The word health means different things to different people, depending on the situation. The English word "health" comes from the old English word hale, meaning "wholeness, being whole, sound or well" (61).

The most famous modern definition of health was created during a Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19-22 June, 1946; “Health is a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity” (62).

The ultimate goal of health care is to maintain or improve the QoL of people. Health is an important determinant of a person’s QoL although it is not the only one. Other factors such as culture, religion, environment, education, and finance can also affect QoL, but are often beyond the scope of health care.

It is important not to mix up the concept of QoL in a more general sense with the term health related quality of life (HRQoL) used in medicine and clinical trials to describe dimensions of QoL influenced by diseases and possible to ameliorate with treatments (63). HRQoL is a multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning with important differences in aspects of HRQoL in different clinical situations (64).

HRQoL is the main concern of health care professionals and is an important health outcome indicator (65, 66).

Generic instruments

Assessment of HRQoL is achieved with the use of questionnaires that are either self-administered or conducted by an interviewer. Generic HRQoL instruments are broadly applicable to different health problems, and have the advantage of functioning as common assessment tools to compare HRQoL across several diseases. Several generic instruments exist as;

The short-form (SF)-36 health survey is one of the most commonly used HRQoL measures. It was developed as a short-form measure of functioning and well-being in the Medical Outcomes Study (67). It assesses eight domains; Physical Function (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Function (SF), Role Emotional (RE), and Mental Health (MH) (68).
Another common generic instrument is the European QoL questionnaire (EuroQoL) 5 dimensions (EQ5D); a standardized instrument for use as a measure of health outcome, and commonly used in different areas of medicine, developed by the EuroQol Research foundation. The name is derived from its methodology, which measures QoL in five dimensions, including mobility, self-care, usual activities, pain/discomfort and anxiety/depression (69).

The SF-36 and the EQ5D are the generic instruments used as main outcome measures in papers III and IV in this thesis.

**Disease specific instruments**

Compared to generic instruments disease-specific HRQoL instruments are designed to have better sensitivity in detecting clinically important changes that are related to a particular disease. Disease-specific HRQoL questionnaires for PAD were developed for evaluating the effectiveness of medical outcome and the success of treatment in patients with vascular disease, and are considered particularly important to examine well-being and function in IC patients (70).

Several disease specific instruments are available for PAD; The Claudication Scale (CLAU-S), the Peripheral Artery Occlusive Disease 86 questionnaire (PAVK-86), the Vascular Quality of Life questionnaire (VascuQoL), the peripheral Artery Questionnaire (PAQ), Sickness Impact Profile – Intermittent Claudication (SIPIC), the Intermittent Claudication Questionnaire (ICQ) and Walking Impairment Questionnaire (WIQ).

The WIQ was one of the first disease-specific questionnaires for assessing functional status in PAD patients and has been widely used (71). The WIQ assesses how limited patients are in walking defined distances at different speeds, and the degree of difficulty in climbing flights of stairs. Although the instrument lacks utility measures limiting its use in advanced QoL analysis, the WIQ provides information on the symptom-specific nature of the limitations in walking difficulty and can even detect impairment in PAD patients who are asymptomatic or having only mild symptoms (72). The questionnaire can be used in the clinical or research settings.

The WIQ is the disease specific instrument used as main outcome measure in papers III and IV in this thesis.

As generic measures are necessary to compare outcomes across different populations and disease-specific measures assess the special states of diagnostic groups, a simultaneous application of both instruments is considered superior to the use of a generic questionnaire only (73).
Aims of the thesis

Overall aim

The overall aim was to evaluate the effect of invasive treatment on clinical improvement and HRQoL in patients with lower limb PAD.

Specific aims

The more specific aims were;

To assess the outcome of treatment of the femoropopliteal segment with nitinol self-expanding stents in terms of amputation-free survival, with focus on gender differences in treatment indication and results (I).

To assess the nationwide incidence of invasive treatment of infrainguinal IC during one year in Sweden and treatment results in terms of clinical improvement (II).

To evaluate the prevalence of concomitant CWP and its influence on HRQoL in patients with symptomatic PAD scheduled for invasive treatment (III).

To assess the impact of primary stenting of the SFA on HRQoL, ABI, and walking distance in patients with stable IC (IV).

To assess the influence of concomitant CWP on HRQoL, ABI, and walking distance in primary stenting of the SFA in patients with stable IC (IV).
Background

Paper I

The role of stent treatment of infrainguinal lesions is controversial, as mentioned above. Women with cardiovascular disease run a risk of delayed diagnosis and have a poorer outcome after intervention than men (11), and female gender is associated with limb loss after infrainguinal endovascular treatment (74). Stent treatment is increasingly used in infrainguinal atherosclerotic occlusive disease, and outcome in terms of amputation-free survival with focus on gender differences has not been reported in detail.

The aim of this study was to assess the outcome of nitinol stent treatment of PAD in the femoropopliteal segment in a Swedish county hospital. In particular, we aimed to detect potential gender differences with respect to treatment indication and results.

Paper II

In spite of recommendations advocating conservative BMT (4), and the fact that the role of invasive treatment remains controversial, many patients with infrainguinal IC are treated with open and endovascular invasive methods (37). The incidence and one year results of such treatments in Sweden have not previously been reported.

The aim of this study was to evaluate one year incidence and results of all invasive procedures performed in Sweden on patients with infrainguinal IC.
Paper III

Invasive treatment with open surgical or endovascular revascularization is not always successful; for example it leads to improvement in 73.2% of patients invasively treated for infrainguinal IC (75). Concomitant medical disorders contribute to reduced HRQoL and hamper results of recanalization (76). CWP occurs with a prevalence of 11% in a general population (47, 48), and people with CWP report reduced HRQoL (51) and worse outcome when for instance treated for cancer and rheumatic diseases (55-57). It is not known to what extent CWP is present in patients with PAD or how it influences HRQoL in these patients.

The aim of this study was to evaluate the prevalence of concomitant CWP, and its influence on HRQoL in patients invasively treated for PAD.

Paper IV

Management of IC traditionally consists of risk factor modification and BMT with or without SET. Invasive treatment of infrainguinal IC is controversial and international guidelines recommend that infrainguinal lesions in most cases should not be revascularized (4). In spite of this, 8.9 per 100,000 inhabitants in Sweden underwent in 2009 invasive treatment of infrainguinal IC according to data in paper II (75). Results of endovascular treatment of the SFA are suboptimal with high restenosis rates after PTA alone on long lesions, but primary stenting with BMS is superior and frequently used, and its performance in terms of primary patency and safety has improved in recent years (45). CWP is common in the general population (47) and according to preliminary data in paper III even more in patients with PAD (77). Furthermore CWP is associated to reduced HRQoL (51, 77).

The main objective of this study was to assess the impact of primary SFA stenting with modern nitinol self-expanding BMS on HRQoL compared to continuing BMT only, in patients with stable IC due to SFA disease.

Secondary objectives were to study the results of primary SFA stenting on ABI and walking distance, and the influence of concomitant CWP on HRQoL, ABI, and walking distance.
Patients and methods

Overview of papers

Table 1. Overview of studies.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Design</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Register-based single center cohort study</td>
<td>112 SFA stented PAD patients</td>
</tr>
<tr>
<td>II</td>
<td>Register-based national cohort study</td>
<td>775 invasively treated patients with infrainguinal IC</td>
</tr>
<tr>
<td>III</td>
<td>Prospective multicenter study</td>
<td>240 patients hospitalized for invasive PAD treatment</td>
</tr>
<tr>
<td>IV</td>
<td>Prospective randomized multi center study</td>
<td>100 IC patients with SFA lesion randomized to stent or BMT only</td>
</tr>
</tbody>
</table>

**Paper I**

One hundred and twelve consecutive patients, 67 (60%) women, undergoing endovascular nitinol stent treatment of atherosclerotic lesions in the femoropopliteal segment causing IC or CLI were analysed concerning improvement in ABI, reinterventions, complications, amputation and survival rates up to 12 months after intervention. Risk factors for amputation, and death were analysed with multiple logistic regression.

**Paper II**

One year follow-up through the Swedish Vascular Registry (Swedvasc) of all 775 patients out of the Swedish population of 10 million inhabitants in whom 843 invasive infrainguinal procedures, 796 index procedures and 47 secondary procedures (open surgery, endovascular treatment or hybrid treatment) were performed for infrainguinal IC in 2009. Clinical outcome was calculated from patient reported leg function (unchanged, improved, deteriorated) and whether
amputation had been necessary or death had occurred. Patent reconstruction at one year was also counted as improvement.

**Paper III**

In 240 patients with planned invasive treatment of PAD, HRQoL and pain distribution were assessed with SF-36, EQ5D, WIQ, and a questionnaire concerning musculoskeletal pain (Appendix) before and 12 months after treatment. Based on a key question on the presence of chronic pain and a pain manikin with 18 predefined body regions (Figure 8) patients were identified having NCP, CRP or CWP. HRQoL was compared in patients with NCP, CRP, and CWP. SF-36 subscales PF, VT, and MH, representing important aspects of HRQoL (physical function, vitality, and mental health) were main outcome measures. Data on preoperative risk factors (diabetes mellitus, smoking, hypertension, renal function, BMI, history of stroke or myocardial infarction), clinical diagnosis (IC or CLI), self-reported walking distance, type of treatment (endovascular treatment, open surgery, or hybrid treatment) and treatment results were obtained from clinical records.
Figure 8. Pain manikin used in studies III-IV (47).
Paper IV

Prospective randomized study including 100 patients suffering from stable (i.e. > 6 months) IC (Fontaine II b) with walking capacity < 500 meters caused by SFA lesion (stenosis or occlusion). The target treatment segment was the full length of the SFA to the proximal limit of the popliteal artery not extending beyond approximately 3 cm above the patella on MRA or CTA, i.e. TASC II a-c lesions (4). A patent popliteal and at least one patent non-stenotic tibial run-off artery on the index side were required for inclusion in the study.

Patients were randomized to the stent or the control group on a 1:1 basis. Stratification was performed with regard to lesion length of less (short lesions) or more (long lesions) than 90 mm. Subjects in both groups received appropriate medication including antiplatelet, lipid lowering, and antihypertensive drugs with treatment targets according to Swedish guidelines, in addition to instructions about regular exercise. Smokers were actively advised to quit smoking, with help from a smoke cessation unit if needed.

Patients randomized to the stent group were treated with modern nitinol BMS designed for the SFA.

All patients were evaluated at a hospital out-patient visit at baseline and 6 months after inclusion. At this visit, primary (SF-36, EQ5D, WIQ questionnaires) (Appendix) and secondary (ABI, walking distance, and CWP) outcome measures were assessed.

Statistical methods

Papers I-IV. Data were reported as mean (SD). Student’s t-test and paired t-test were used to evaluate differences in continuous variables and the Chi2 test was used to evaluate differences in nominal variables between groups. Comparisons were based on two-sided tests, and results were considered statistically significant at p<0.05. Calculations were performed using SPSS 18.0, SPSS 20.0, and SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

Multiple logistic regressions analyses were performed with all factors found to be significantly associated to the depending variables in univariate analyses.

Paper III. Background factors found to be associated to HRQoL, the main outcome measure, in univariate analyses were assessed with multiple logistic regression analyses were the dependent variables (SF-36 domains PF, VT, MH, WIQ overall, and EQ5D) were dichotomized on the worse quartile.
Paper IV. The sample size was determined to study a clinically relevant difference between the two groups with regard to the primary outcome variable, HRQoL. With a significance level of 5% and with 50 patients in each group, a difference of 10 score in SF-36 domains PF and VT could be detected with a power of at least 80%.

Differences in continuous variables between groups were analyzed using the intention-to-treat (ITT) principle.

Methodological discussion

Parametric tests were used in group comparisons, although some continuous variables were skewed. Due to the sufficient number of participants in all groups, however, we considered that according to the central limit theorem (78), the use of parametric tests was justified. Also, additional control with non-parametric tests did not give any significant difference in outcome.

The numbers of comparisons made in the study increase the risk of rejecting a true null hypothesis, and therefore caution is necessary when interpreting the actual significance of p-values.

In subgroup analyses of treatment allocation and pain group affiliation (paper IV), there is a risk of beta errors due to small number of participants in each group, of particular interest in clinical relevant changes of outcome scores.

A response rate on 80% together with 95% subject’s compliance in completing surveys in paper III and IV was considered as satisfactory. Possible errors in registration of survey data are supposed to be random and therefore not introducing bias in analysis.
Ethics

Paper I. The study was approved by the Medical Ethics Committee at Lund University (Dnr. 2010/549) and was based on a quality follow-up registry in ordinary health care. In accordance with the ethical approval subjects had the opportunity to deny participation after public announcement.

Papers II-III. Informed consent was obtained in accordance with the ethical standards of the Helsinki Declaration of 1975, and the studies were approved by the Medical Ethics Committee at Lund University (Dnr. 2010/549).

Paper IV. The study was performed in accordance with the spirit of the Declaration of Helsinki and in agreement with the guidelines for conducting a clinical investigation as outlined in the ISO 14-155. Written informed consent was obtained from all patients. The study was registered in the Clinical Trials data base (Identifier: NCT01230229), and approved by the Medical Ethics Committee of Lund University (Dnr. 2009/478).
Results

Paper I

Mean (SD) age was 74.4 (10.8) years, 75.8 (11.8) in women and 72.5 (9.1) in men (P= 0.13). The clinical indication for endovascular treatment was CLI in 84 (75%) cases and IC in 28 (25%) cases. Women significantly more often presented with CLI (87% vs. 58 %; P=0.001), as shown by a significant gender difference in baseline tissue loss, 49 (73%) women and 18 (42%) men (P=0.001), and baseline mean (SD) ABI 0.33 (0.25) in women and 0.48 (0.25) in men (P=0.004; Table 2).
Table 2. Baseline data in 112 patients undergoing endovascular stent treatment in the femoropopliteal segment. Mean (SD) or n (%). P-values calculated between genders.

<table>
<thead>
<tr>
<th></th>
<th>Men (n=45)</th>
<th>Women (n=67)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankle brachial index</td>
<td>0.48 (0.25)</td>
<td>0.33 (0.25)</td>
<td>0.004</td>
</tr>
<tr>
<td>Age (years)</td>
<td>72.5 (9.1)</td>
<td>75.8 (11.8)</td>
<td>0.13</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>17(38)</td>
<td>17(25)</td>
<td>0.16</td>
</tr>
<tr>
<td>Ulcer</td>
<td>18(42)</td>
<td>49(73)</td>
<td>0.001</td>
</tr>
<tr>
<td>Preserved walking capacity</td>
<td>42(93)</td>
<td>53(81)</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Active or former smoker</td>
<td>36(80)</td>
<td>44(66)</td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>6(13)</td>
<td>22(33)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3(7)</td>
<td>1(2)</td>
<td></td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td></td>
<td></td>
<td>0.75</td>
</tr>
<tr>
<td>&lt; 1 month</td>
<td>5(11)</td>
<td>8(12)</td>
<td></td>
</tr>
<tr>
<td>1-3 months</td>
<td>12(27)</td>
<td>17(25)</td>
<td></td>
</tr>
<tr>
<td>3-12 months</td>
<td>14(31)</td>
<td>24(36)</td>
<td></td>
</tr>
<tr>
<td>&gt; 12 months</td>
<td>5(11)</td>
<td>3(5)</td>
<td></td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>19(42)</td>
<td>9(13)</td>
<td>0.001</td>
</tr>
<tr>
<td>Critical limb ischemia</td>
<td>26(58)</td>
<td>58(87)</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of runoff vessels</td>
<td></td>
<td></td>
<td>0.42</td>
</tr>
<tr>
<td>0</td>
<td>0(0)</td>
<td>3(5)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>19(42)</td>
<td>29(43)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>16(36)</td>
<td>18(27)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>10(22)</td>
<td>17(25)</td>
<td></td>
</tr>
<tr>
<td>Arcade in the foot complete</td>
<td>41(98)</td>
<td>52(90)</td>
<td>0.12</td>
</tr>
<tr>
<td>No vessels in the foot arcade</td>
<td>1(2)</td>
<td>6(10)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Lesion length mean (SD) was 12.2 (8.7) cm. The lesion was stenotic (i.e. > 50 % lumen diameter reduction) in 50 (45%) cases, and occlusive in 62 (55%) cases. There was no significant gender difference concerning run-off vessel status, whereas women tended to have longer lesions (13.3 cm vs. 10.6 cm; P=0.11), and tended to be treated with additional below the knee interventions more often (43% vs. 29%; P=0.12). Eighteen minor and 5 major procedure-related complications occurred, two of which were followed by amputation.
Within the 12 month follow-up period 27 patients with CLI died, 19 (28%) women and 8 (18%) men (P=0.20). No deaths were related to IC or procedural complication. The 30 day mortality rate was 4/112 (4%); two men and two women with a mean age of 71.5 years.

Sixteen patients, 14 (22%) women and 2 (4%) men (P=0.01), with CLI underwent amputation; in this group limb salvage rate was 82%.

Vessel diameter was not assessed, but no technical procedural factors such as lesion length, occlusion vs. stenosis, type of stenting (primary or secondary), number of stents implanted, lesion passage (intraluminal or subintimal), lowest stent margin, stent brand, or run-off vessel status influenced the risk of subsequent amputation when tested in multivariate models. Women with additional below the knee interventions ran an increased risk of amputation (OR 7.1; 95% CI 1.8-28.8; P=0.006) compared to women undergoing endovascular intervention in the SFA alone. Stent patency could be assumed before amputation in 13 cases, whereas stent occlusion was confirmed in one case and information was lacking in the remaining two cases.

After 12 months ABI mean (SD) had improved in both genders, from 0.40 (0.26) at baseline to 0.86 (0.22) after 12 months, (P<0.001).

The overall amputation-free survival at 12 months was 67%, significantly higher (P=0.03) in men (80%) than in women (58%; Figure 9).

![Figure 9. Kaplan-Meier plot of amputation-free survival in 45 men and 67 women undergoing endovascular stent treatment in the femoropopliteal segment.](image-url)
After adjustment for age, diabetes mellitus and smoking, female gender was an independent risk factor for amputation (OR 9.0; 95% CI 1.1-76.5; P=0.045), but not for death (OR 2.1; 95% CI 0.7-6.2; P=0.18).

**Paper II**

Out of a total of 3304 invasive procedures on patients with chronic PAD performed in Sweden in 2009 and registered in the Swedvasc database, 843 were invasive infrainguinal procedures performed on 775 patients with IC (Figure 10). This corresponds to a treatment incidence of 8.9/100,000 inhabitants per year. Among the patients 304 (39.2%) were women and 471 (60.8%) men. Mean (SD) age was 70.4 (9.6) years, 72.6 (8.4) in women and 69.7 (10.1) in men.

![Flow chart of invasive infrainguinal procedures](image)

**Figure 10.** Flow chart of 843 invasive infrainguinal procedures performed in all 775 Swedish patients undergoing invasive infrainguinal treatment of intermittent claudication in 2009.
Improvement at one year was seen in 567 (73.2%) patients, 225 (77.6%) in the open surgery group, 320 (71.6%) in the endovascular treatment group, and 22 (57.9%) in the hybrid treatment group (P=0.046). No significant difference was found between the open surgery and endovascular treatment groups, together comprising 737/775 patients (Table 3; P=0.350). Hybrid treatment gave significantly worse results. Fifty-seven (7.3%) patients reported unchanged limb function, and 32 (4.1%) patients reported deterioration.


<table>
<thead>
<tr>
<th></th>
<th>Open</th>
<th>Endovascular</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>225 (77.6)</td>
<td>320 (71.5)</td>
<td>545 (73.9)</td>
</tr>
<tr>
<td>Unchanged</td>
<td>16 (5.5)</td>
<td>37 (8.3)</td>
<td>53 (7.2)</td>
</tr>
<tr>
<td>Deteriorated</td>
<td>7 (2.4)</td>
<td>21 (4.9)</td>
<td>28 (3.8)</td>
</tr>
<tr>
<td>Living amputated</td>
<td>2 (0.7)</td>
<td>3 (0.7)</td>
<td>5 (0.7)</td>
</tr>
<tr>
<td>Dead</td>
<td>8 (2.7)</td>
<td>11 (2.5)</td>
<td>19 (2.6)</td>
</tr>
<tr>
<td>Amputated and dead</td>
<td>2 (0.7)</td>
<td>1 (0.2)</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Missing data</td>
<td>30 (10.3)</td>
<td>54 (12.1)</td>
<td>84 (10.8)</td>
</tr>
</tbody>
</table>

Within 30 days two patients died and one patient was amputated. Within one year 10 patients underwent 11 amputations (1.4%); 5 (1.7%) in the open surgery group, 3(0.6%) in the endovascular treatment group, and two patients (7.5%) in the hybrid treatment group; one patient underwent bilateral amputation (P=0.07). Twenty-two patients died; 10 (3.4%) in open surgery group, 12 (2.7%) in the endovascular treatment group, and none in the hybrid treatment group (P=0.465).

Neither the type of institution (tertiary center or county hospital), nor patient characteristics (age, sex, hypertension, diabetic mellitus, renal impairment, cardiovascular risk, cerebrovascular risk, smoking, or distal landing zone) influenced improvement rate after one year in multiple regression analysis (data not shown).
Among 240 patients scheduled for invasive treatment of symptomatic PAD (IC 77% and CLI 23%) baseline prevalences were 10% for NCP, 61% for CRP and 29% for CWP, without significant (P=0.153) differences between patients with IC or CLI. CWP was significantly more common in women (36 %) than in men (24 %; P=0.035), whereas there was no gender difference for CRP (56 vs 64 %; P=0.244). At baseline patients with CWP reported lower HRQoL scores than those with NCP (Figure 11), and patients with CLI reported lower HRQoL scores than those with IC (Figure 12). In 25 (10.5%) of scheduled cases no invasive treatment was performed. Treatment regimen was endovascular in 170 (79.0%), open surgical in 26 (12.1 %), and hybrid treatment (TEA + iliac stenting) in 19 (8.8%) patients, with no significant difference in treatment strategy between the IC and CLI groups (P=0.317; Table 4). Invasive treatment of PAD led to a significant improvement of HRQoL after twelve months regardless of baseline pain group affiliation, but patients with CWP at baseline still reported significantly lower scores in all outcome measures (except SF-36 domain PF) than patients with NCP at baseline (Figure 11). Twelve months after treatment patients with IC at baseline improved significantly in all HRQoL scores, whereas patients with CLI at baseline improved in WIQ overall and EQ5D but still to significantly lower scores than patients with IC at baseline (Figure 12).

When analyzing data taking all SF-36 domains in consideration treatment led to significant improvement also in the SF-36 domains RP, BP, SF, and RE in patients with CWP at baseline (Figure 13), and in all HRQoL measures in patients with IC and SF-36 domains BP and SF in patients with CLI at baseline (Figure 14, data not presented in paper III).

In the whole study group any improvement was seen in 70-85% of patients (Figure 15), details and percentages of IC patients with any improvement are shown in Figure 16 (data not presented in paper III). In 32 (13.3%) patients with endovascular SFA treatment significant improvement was seen in most HRQoL outcomes in patients with IC, while no significant improvement was seen in patients with CLI (Figure 17, data not presented in paper III).

In multivariable logistic regression analyses the presence of CWP at baseline was found to predict worse outcomes in different important aspects of HRQoL, controlled for CLI, age, gender, and baseline value of the actual HRQoL domain. CLI also predicted worse outcome in all HRQoL measures except SF-36 domain MH (Table 5).
Figure 11. Health related quality of life (HRQoL) before and 12 months after treatment in patients in different pain groups. Mean values.

NCP= no chronic pain, CWP=chronic widespread pain, PF = SF-36 domain physical function, VT = SF-36 domain vitality, MH = SF-36 domain mental health (68). EQ5D= EuroQoL 5-dimensions (69). SN= Swedish norm for ages 70-74 years. (79, 80), WIQ = Walking Impairment Questionnaire (71). SF-36 and WIQ 0-100, EQ5D 0-1, shown as % of 1.

a=p<0.05, b=p=<0.001 for differences between patients with NCP and CWP at baseline.  
c=p<0.05, e=p<0.01 for differences between patients with NCP and CWP 12 months after treatment.  
e=p<0.05, f=p<0.01 for differences between baseline and 12 months after treatment in patients with NCP.  
g=p<0.01, h=p<0.001 for differences between baseline and 12 months after treatment in patients with CWP.
Figure 12. Health related quality of life (HRQoL) before and 12 months after treatment of peripheral arterial disease (PAD) in patients with intermittent claudication (IC) and critical limb ischemia (CLI). Mean values.

IC = intermittent claudication, CLI = critical limb ischemia, PF = SF-36 domain physical function, VT = SF-36 domain vitality, MH = SF-36 domain mental health (68). EQ5D = EuroQoL 5-dimensions (69). SN = Swedish norm for ages 70-74 years. (79, 80), WIQ = Walking Impairment Questionnaire (71). SF-36 and WIQ 0-100, EQ5D 0-1, shown as % of 1.

a = p<0.05, b = p<0.01 for differences between patients with IC and CLI at baseline,
c = p<0.01, d = p<0.001 for differences between patients with IC and CLI 12 months after treatment.
e = p<0.05, f = p<0.001 for differences between baseline and 12 months after treatment in patients with IC.
g = p<0.05, h = p<0.01, for differences between baseline and 12 months after treatment in patients with CLI.
Table 4. Treatment modalities in 215 patients with peripheral arterial disease (PAD).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iliac stent</td>
<td>95</td>
<td>44.2</td>
</tr>
<tr>
<td>Iliac + SFA endovascular</td>
<td>6</td>
<td>2.8</td>
</tr>
<tr>
<td>SFA endovascular</td>
<td>32</td>
<td>14.9</td>
</tr>
<tr>
<td>SFA + BTK endovascular</td>
<td>17</td>
<td>7.9</td>
</tr>
<tr>
<td>BTK endovascular</td>
<td>20</td>
<td>9.3</td>
</tr>
<tr>
<td>Femoral TEA</td>
<td>20</td>
<td>9.3</td>
</tr>
<tr>
<td>Femorodistal bypass</td>
<td>6</td>
<td>2.8</td>
</tr>
<tr>
<td>Femoral TEA + iliac stent</td>
<td>19</td>
<td>8.8</td>
</tr>
</tbody>
</table>

SFA=superficial femoral artery, BTK=below the knee, TEA=thrombendarterectomy

Figure 13. Mean improvement in HRQoL between results 12 months after treatment and baseline in patients treated for PAD with regard to pain group affiliation

NCP= no chronic pain, CRP= chronic regional pain, CWP=chronic widespread pain, PF= SF-36 domain physical function, RP= SF-36 domain role physical, BP= SF-36 domain bodily pain, GH= SF-36 domain general health, VT = SF-36 domain vitality, SF= SF-36 domain social function, RE= SF-36 domain role emotional, MH = SF-36 domain mental health (68). EQ5D= EuroQoL 5-dimensions (69). WIQ = Walking Impairment Questionnaire (71). SF-36 and WIQ 0-100, EQ5D 0-1, shown as % of 1.

a=p<0.05, b=p<0.01 for differences between baseline and 12 months after treatment in patients with NCP.
c=p<0.01, d=p<0.001 for differences between baseline and 12 months after treatment in patients with CRP.
e=p<0.05, f=p<0.01 for differences between baseline and 12 months after treatment in patients with CWP.
g=p<0.001 for differences between baseline and 12 months after treatment in patients with CWP.
Figure 14. Mean improvement in HRQoL between results 12 months after treatment and baseline in patients treated for PAD with regard to clinical diagnosis at baseline

IC = intermittent claudication, CLI = critical limb ischemia, PF = SF-36 domain physical function, RP = SF-36 domain role physical, BP = SF-36 domain bodily pain, GH = SF-36 domain general health, VT = SF-36 domain vitality, SF = SF-36 domain social function, RE = SF-36 domain role emotional, MH = SF-36 domain mental health (68). EQ5D = EuroQoL 5-dimensions (69). WIQ = Walking Impairment Questionnaire (71). SF-36 and WIQ 0-100, EQ5D 0-1, shown as % of 1.

a = p<0.01, b = p<0.001 for differences between baseline and 12 months after treatment in patients with IC. c = p<0.05, d = p<0.001 for differences between baseline and 12 months after treatment in patients with CLI.
Figure 15. Percentage of patients with any improvement in health related quality of life (HRQoL) 12 months after treatment in patients with PAD (all pain and treatment groups).

PF = SF-36 domain physical function, VT = SF-36 domain vitality, MH = SF-36 domain mental health (68). EQ5D= EuroQoL 5-dimensions (69). WIQ = Walking Impairment Questionnaire (71). SF-36 and WIQ 0-100, EQ5D 0-1, shown as % of 1.
Figure 16. Percentage of patients with any improvement in health related quality of life (HRQoL) 12 months after treatment in patients with IC.

PF = SF-36 domain physical function, RP = SF-36 domain role physical, BP = SF-36 domain bodily pain, GH = SF-36 domain general health, VT = SF-36 domain vitality, SF = SF-36 domain social function, RE = SF-36 domain role emotional, MH = SF-36 domain mental health (68). EQ5D = EuroQoL 5-dimensions (69). WIQ = Walking Impairment Questionnaire (71). SF-36 and WIQ 0-100, EQ5D 0-1, shown as % of 1.
Figure 17. Mean change in outcome in 32 patients with endovascular SFA treatment. (IC=22), (CLI=10)

IC= intermittent claudication, CLI= critical limb ischemia, PF= SF-36 domain physical function, RP= SF-36 domain role physical, BP= SF-36 domain bodily pain, GH= SF-36 domain general health, VT= SF-36 domain vitality, SF= SF-36 domain social function, RE= SF-36 domain role emotional, MH = SF-36 domain mental health (68). EQ5D= EuroQoL 5-dimensions (69). WIQ = Walking Impairment Questionnaire (71). SF-36 and WIQ 0-100, EQ5D 0-1, shown as % of 1.

a=p<0.05, b=p<0.01 for differences between baseline and 12 months after treatment in patients with IC.
Table 5. Multivariable logistic regression analyses with Odds Ratios (OR) and 95% confidence intervals (CI) for reporting the worse quartile of health related quality of life (HRQoL) 12 months after treatment of peripheral arterial disease (PAD) with respect to presence of chronic pain, age, sex, and diagnosis (intermittent claudication [IC] and critical limb ischemia [CLI]) at baseline.

<table>
<thead>
<tr>
<th></th>
<th>PF OR (95% CI)</th>
<th>VT OR (95% CI)</th>
<th>MH OR (95% CI)</th>
<th>WIQ overall OR (95% CI)</th>
<th>EQ5D OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Women</td>
<td>1.0 (0.4-2.5)</td>
<td>0.9 (0.4-2.0)</td>
<td>0.9 (0.4-2.1)</td>
<td>1.8 (0.8-4.4)</td>
<td>1.0 (0.4-2.2)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>1.1 (1.0-1.1)</td>
<td>1.1 (1.0-1.1)</td>
<td>1.0 (1.0-1.1)</td>
<td>1.1 (1.0-1.1)</td>
<td>1.1 (1.0-1.1)</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IC</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CLI</td>
<td>7.8 (2.9-21.3)</td>
<td>4.0 (1.5-10.9)</td>
<td>1.6 (0.6-4.6)</td>
<td>3.3 (1.1-9.5)</td>
<td>3.0 (1.1-7.8)</td>
</tr>
<tr>
<td><strong>Pain-group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCP/CRP</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CWP</td>
<td>2.8 (1.1-7.3)</td>
<td>3.0 (1.2-7.2)</td>
<td>2.3 (0.9-5.8)</td>
<td>1.9 (0.7-4.7)</td>
<td>1.4 (0.5-3.4)</td>
</tr>
</tbody>
</table>

NCP=no chronic pain, CRP=chronic regional pain, CWP=chronic widespread pain. PF=SF-36 domain Physical Function, VT= SF-36 domain Vitality, MH= SF-36 domain Mental Health (68), EQ5D= EuroQoL 5-dimensions (69), WIQ overall=Walking impairment questionnaire overall result (71). Outcomes were also controlled for their value at baseline.
Paper IV

At baseline, the stent and control groups were well matched concerning background variables such as age, sex, smoking habits, BP, LDL-cholesterol, duration of IC (Table 6) and lesion characteristics (Table 7). Furthermore, no significant differences existed between groups at baseline in SF-36, EQ-5D, or WIQ scores (Table 8).

Table 6. Baseline data in patients with intermittent claudication (IC) caused by lesions in the superficial femoral artery (SFA) treated with primary stenting (stent, n=45) or best medical treatment only (control, n=49). Mean (SD) or (n).

<table>
<thead>
<tr>
<th></th>
<th>Stent (n=45)</th>
<th>Control (n=49)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.3 (5.3)</td>
<td>69.8 (5.8)</td>
<td>0.184</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n)</td>
<td>22</td>
<td>28</td>
<td>0.540</td>
</tr>
<tr>
<td>Female (n)</td>
<td>23</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>ABI</td>
<td>0.58 (0.12)</td>
<td>0.63 (0.17)</td>
<td>0.129</td>
</tr>
<tr>
<td>Walking distance (meters)</td>
<td>178 (87)</td>
<td>210 (107)</td>
<td>0.114</td>
</tr>
<tr>
<td>Duration of IC (months)</td>
<td>30 (29)</td>
<td>41 (48)</td>
<td>0.179</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current (n)</td>
<td>7</td>
<td>11</td>
<td>0.125</td>
</tr>
<tr>
<td>Former (n)</td>
<td>26</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Never (n)</td>
<td>12</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>2.75 (1.1)</td>
<td>2.55 (.9)</td>
<td>0.374</td>
</tr>
<tr>
<td>B-glucose (mmol/l)</td>
<td>7.0 (2.8)</td>
<td>6.3 (2.1)</td>
<td>0.207</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>155 (21)</td>
<td>150 (21)</td>
<td>0.282</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>80 (11)</td>
<td>79 (9)</td>
<td>0.831</td>
</tr>
<tr>
<td>S-creatinine (µmol/l)</td>
<td>84 (24)</td>
<td>82 (22)</td>
<td>0.653</td>
</tr>
</tbody>
</table>
Table 7. Characteristic of lesions in the superficial femoral artery (SFA) in patients treated with primary stenting (stent, n=45) or best medical treatment only (control, n=49) at baseline (Mean [SD] or n [%]).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Stent (n=45)</th>
<th>Control (n=49)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion length (mm)</td>
<td>145 (91)</td>
<td>103 (97)</td>
<td>0.021</td>
</tr>
<tr>
<td>Occlusion (n[%])</td>
<td>30 (69)</td>
<td>36 (73)</td>
<td>0.654</td>
</tr>
<tr>
<td>Stenosis (n[%])</td>
<td>14 (31)</td>
<td>13 (27)</td>
<td>0.654</td>
</tr>
<tr>
<td>Degree of stenosis (%)</td>
<td>81.7 (16.3)</td>
<td>91.5 (3.1)</td>
<td>0.065</td>
</tr>
<tr>
<td>Number of crural vessels</td>
<td>2.5 (.5)</td>
<td>2.3 (.7)</td>
<td>0.219</td>
</tr>
</tbody>
</table>

Table 8. Baseline levels of HRQoL scores in patients with intermittent claudication (IC) treated with primary stenting (stent, n=45) or best medical treatment only (control, n=49). Mean (SD)

<table>
<thead>
<tr>
<th>Item</th>
<th>Stent</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF</td>
<td>43 (17)</td>
<td>43 (17)</td>
<td>0.972</td>
</tr>
<tr>
<td>RP</td>
<td>39 (38)</td>
<td>42 (41)</td>
<td>0.731</td>
</tr>
<tr>
<td>BP</td>
<td>39 (18)</td>
<td>38 (17)</td>
<td>0.734</td>
</tr>
<tr>
<td>GH</td>
<td>54 (18)</td>
<td>53 (20)</td>
<td>0.867</td>
</tr>
<tr>
<td>VT</td>
<td>48 (22)</td>
<td>50 (23)</td>
<td>0.686</td>
</tr>
<tr>
<td>SF</td>
<td>74 (22)</td>
<td>72 (30)</td>
<td>0.648</td>
</tr>
<tr>
<td>RE</td>
<td>54 (44)</td>
<td>57 (44)</td>
<td>0.801</td>
</tr>
<tr>
<td>MH</td>
<td>72 (20)</td>
<td>72 (24)</td>
<td>0.861</td>
</tr>
<tr>
<td>EQ5D</td>
<td>0.56 (0.27)</td>
<td>0.47 (0.31)</td>
<td>0.121</td>
</tr>
<tr>
<td>WIQ</td>
<td>40 (18)</td>
<td>35 (18)</td>
<td>0.175</td>
</tr>
</tbody>
</table>

PF= SF-36 domain physical function, RP= SF-36 domain role physical, BP= SF-36 domain bodily pain, GH= SF-36 domain general health, VT = SF-36 domain vitality, SF= SF-36 domain social function, RE = SF-36 domain role emotional, MH = SF-36 domain mental health (68). EQ5D=EuroQoL 5-dimensions (69). WIQ = Walking Impairment Questionnaire (71). SF-36 and WIQ 0-100, EQ5D 0-1, shown as % of 1.
Study enrolment is shown in Figure 18, and flow of randomized patients in Figure 19.

Figure 18. Flow of enrollment in the trial reported in paper IV.
No serious adverse events (SAE) occurred during the invasive treatment; all lesions were successfully recanalized and treated without any bailout procedure.

After 6 months, patients in the stent group reported significant HRQoL improvements in SF-36 domains PF, BP, VT, SF, and WIQ, and nearly significant improvement in EQ5D (p = 0.062), whereas all HRQoL variables were unchanged in the control group (Table 9). ABI and walking distance improved significantly in both groups, but significantly more in the stent group. Patients in the stent group without CWP at baseline improved in SF-36 domains PF, BP, VT, WIQ, ABI, and walking distance, whereas patients in the stent group with CWP at baseline improved in ABI and walking distance while their HRQoL scores remained statistically unchanged. Patients in the control group without CWP at baseline improved in EQ5D, WIQ, ABI and walking distance, whereas patients in the control group with CWP at baseline showed unchanged scores in all outcome measures (Table 10 and Figure 20-22).
In on treatment analysis SF-36 domain RP and EQ5D improved significantly after primary stenting in addition to the effects noted in the ITT analysis, and for patients with concomitant CWP at baseline primary stenting led to significant improvement in SF-36 domains PF and VT, in addition to ABI and walking distance.

Both women (46%) and men improved significantly in primary outcome measures after stent treatment, although improvement in certain physically oriented domains was greater in men (Figure 23, data not shown in paper IV), female gender did not predict worse outcome in any primary outcome measure in multiple logistic regression analyses (data not shown).
Table 9. Changes between baseline and six months in primary and secondary outcome measures in patients with intermittent claudication (IC) treated with primary stenting (stent, n=45) or best medical treatment only (control, n=49).

<table>
<thead>
<tr>
<th></th>
<th>Stent group</th>
<th>Control group</th>
<th>Stent group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean difference of improvement (95%CI)</strong></td>
<td></td>
<td>P</td>
<td>Meanc change (95%CI)</td>
<td>P</td>
</tr>
<tr>
<td><strong>PF</strong></td>
<td>12.8</td>
<td>3.9-21.6</td>
<td>0.005</td>
<td>13.9</td>
</tr>
<tr>
<td><strong>RP</strong></td>
<td>13.1</td>
<td>-3.6-30.0</td>
<td>0.123</td>
<td>9.2</td>
</tr>
<tr>
<td><strong>BP</strong></td>
<td>9.9</td>
<td>-0.4-20.2</td>
<td>0.059</td>
<td>11.8</td>
</tr>
<tr>
<td><strong>GH</strong></td>
<td>8.1</td>
<td>1.5-14.8</td>
<td>0.018</td>
<td>4.9</td>
</tr>
<tr>
<td><strong>VT</strong></td>
<td>9.5</td>
<td>-0.3-19.2</td>
<td>0.056</td>
<td>9.6</td>
</tr>
<tr>
<td><strong>SF</strong></td>
<td>8.0</td>
<td>-2.3-18.3</td>
<td>0.126</td>
<td>9.0</td>
</tr>
<tr>
<td><strong>RE</strong></td>
<td>20.2</td>
<td>0.8-39.7</td>
<td>0.041</td>
<td>14.9</td>
</tr>
<tr>
<td><strong>MH</strong></td>
<td>7.0</td>
<td>-0.7-14.7</td>
<td>0.075</td>
<td>5.6</td>
</tr>
<tr>
<td><strong>EQ5D</strong></td>
<td>0.04</td>
<td>-0.1-0.2</td>
<td>0.544</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>WIQ</strong></td>
<td>11.3</td>
<td>0.2-22.3</td>
<td>0.046</td>
<td>16.8</td>
</tr>
<tr>
<td><strong>ABI</strong></td>
<td>0.19</td>
<td>0.1-0.3</td>
<td>&lt;0.001</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>WD</strong></td>
<td>354</td>
<td>222-484</td>
<td>&lt;0.001</td>
<td>420</td>
</tr>
</tbody>
</table>

PF = SF-36 domain physical function, RP = SF-36 domain role physical, BP = SF-36 domain bodily pain, GH = SF-36 domain general health, VT = SF-36 domain vitality, SF = SF-36 domain social function, RE = SF-36 domain role emotional, MH = SF-36 domain mental health (68). EQ5D = EuroQoL 5-dimensions (69). WIQ = Walking Impairment Questionnaire (71). SF-36 and WIQ 0-100, EQ5D 0-1, shown as % of 1.
Table 10. Changes between baseline and six months in primary and secondary outcome measures in patients with intermittent claudication (IC) treated with primary stenting (stent, n=45) or best medical treatment only (control, n=49) with regard to CWP at baseline.

<table>
<thead>
<tr>
<th></th>
<th>Stent Group No CWP</th>
<th>Stent Group CWP</th>
<th>Control Group No CWP</th>
<th>Control Group CWP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean change (95%CI)</td>
<td>P</td>
<td>Mean change (95%CI)</td>
<td>P</td>
</tr>
<tr>
<td>PF</td>
<td>19.1 (7.2-30.9)</td>
<td>0.003</td>
<td>8.6 (1.5-18.8)</td>
<td>0.090</td>
</tr>
<tr>
<td>RP</td>
<td>5.3 (-11.5-22.1)</td>
<td>0.520</td>
<td>13.1 (2.6-28.9)</td>
<td>0.096</td>
</tr>
<tr>
<td>BP</td>
<td>19.3 (7.6-30.9)</td>
<td>0.003</td>
<td>4.0 (10.7-18.7)</td>
<td>0.573</td>
</tr>
<tr>
<td>GH</td>
<td>5.6 (-2.4-13.5)</td>
<td>0.157</td>
<td>4.3 (4.2-12.7)</td>
<td>0.301</td>
</tr>
<tr>
<td>VT</td>
<td>12.0 (-0.1-24.1)</td>
<td>0.052</td>
<td>7.2 (-3.5-17.8)</td>
<td>0.173</td>
</tr>
<tr>
<td>SF</td>
<td>10.1 (-1.5-21.7)</td>
<td>0.084</td>
<td>7.9 (-3.1-18.9)</td>
<td>0.150</td>
</tr>
<tr>
<td>RE</td>
<td>12.2 (-6.4-40.0)</td>
<td>0.185</td>
<td>17.6 (-10.3-45.5)</td>
<td>0.201</td>
</tr>
<tr>
<td>MH</td>
<td>7.6 (-2.5-17.7)</td>
<td>0.133</td>
<td>3.5 (-5.9-12.9)</td>
<td>0.442</td>
</tr>
<tr>
<td>EQ5D</td>
<td>0.17 (-0.1-0.4)</td>
<td>0.078</td>
<td>0.05 (-0.1-0.2)</td>
<td>0.485</td>
</tr>
<tr>
<td>WIQ</td>
<td>21.1 (9.4-32.8)</td>
<td>0.001</td>
<td>11.4 (-5.2-28.3)</td>
<td>0.172</td>
</tr>
<tr>
<td>ABI</td>
<td>0.32 (0.2-0.4)</td>
<td>&lt;0.001</td>
<td>0.22 (0.1-0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WD</td>
<td>463 (293-633)</td>
<td>&lt;0.001</td>
<td>332 (164-500)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

PF= SF-36 domain physical function, RP= SF-36 domain role physical, BP= SF-36 domain bodily pain, GH= SF-36 domain general health, VT= SF-36 domain vitality, SF= SF-36 domain social function, RE= SF-36 domain role emotional, MH = SF-36 domain mental health (68). EQ5D= EuroQoL 5-dimensions (69). WIQ = Walking Impairment Questionnaire (71). SF-36 and WIQ 0-100, EQ5D 0-1, shown as % of 1.
Figure 20. Changes between baseline and six months in SF-36 domain PF in patients with intermittent claudication (IC) treated with primary stenting (stent, n=45) or best medical treatment only (control, n=49) with regard to chronic widespread pain (CWP) at baseline.

Figure 21. Changes between baseline and six months in EQ5D in patients with intermittent claudication (IC) treated with primary stenting (stent, n=45) or best medical treatment only (control, n=49) with regard to chronic widespread pain (CWP) at baseline.
Figure 22. Changes between baseline and six months in Walking Impairment Questionnaire =WIQ in patients with intermittent claudication (IC) treated with primary stenting (stent, n=45) or best medical treatment only (control, n=49) with regard to chronic widespread pain (CWP) at baseline.
Figure. 23. Improvement in women (n=22) and men (n=26) with IC 6 months after primary SFA stent treatment

PF= SF-36 domain physical function, RP= SF-36 domain role physical, BP= SF-36 domain bodily pain, GH= SF-36 domain general health, VT = SF-36 domain vitality, SF= SF-36 domain social function, RE= SF-36 domain role emotional, MH = SF-36 domain mental health (68). EQ5D=EuroQoL 5-dimensions (69). WIQ = Walking Impairment Questionnaire (71). SF-36 and WIQ 0-100, EQ5D 0-1, shown as % of 1.

a=p<0.05 for significant improvement after stent treatment in women with IC at baseline.
b=p<0.05, c=p<0.01 for significant improvement after stent treatment in men with IC at baseline.
Discussion

Invasive treatment of PAD in women (I-IV)

Paper I showed that women more frequently than men suffered from CLI and that female gender was an independent risk factor for amputation, when controlled for age, diabetes mellitus and smoking.

The poorer outcome in women in paper I might have several reasons as e.g. delayed PAD diagnosis (11), gender differences in the quality of medical treatment (81), or more narrow vessels in women (12). Although paper I was not designed to detect these factors and vessel diameter was not assessed, none of them or other technical factors could be found to influence the outcome.

The higher proportion of CLI in women at presentation might be due to different perception of PAD symptoms in genders, with women more often accepting walking difficulties like IC as a part of normal ageing, but being unable to neglect symptoms of CLI (9).

These results from paper I were not corroborated in papers II-IV, where female gender did not predict worse treatment outcome in multiple logistic regression analyses. In paper IV some of the more physically oriented outcomes (SF-36 domains PF, BP, and WIQ) showed greater and more clinically relevant improvement in men. This might be explained by more women having CWP, but the study is too small and underpowered to draw firm conclusion on this. Excellent ABI improvement and favourable limb salvage rate with stent treatment of SFA lesions were reported in paper I, and no clear evidence indicating that SFA-stent treatment should be less technically suitable for women could be demonstrated. However, the results from paper I together with results previously reported on cardiovascular disease (11, 82) raise concerns about the efficacy and ability of the health care system to adequately appreciate symptoms of PAD in women.
Invasive treatment of infrainguinal IC (I-IV)

Although recommendations advocate conservative BMT (4), and the role of invasive treatment remains controversial, we report an annual treatment incidence of 8.9 per 100,000 subjects with infrainguinal IC in Sweden in paper II. This figure is in the upper part of the interval reported by Vascunet (83), analyzing 32,084 cases of infrainguinal bypass surgery in nine countries. The treatment incidence per 100,000 individuals varied between 2.3 and 24.6, out of which 15.7% to 40.8% were performed on IC patients, corresponding to a median treatment incidence of 2/100,000.

In paper II improvement at one year was reported by 73.2% of patients invasively treated for infrainguinal IC. Comparison with the rather benign natural course of the disease with only 1% to 3% of patients with IC ever requiring major amputation over a 5-year period, and 50% of patients with IC becoming symptom free during 5 years' follow-up (84), challenges the rationale of invasive treatment in patients with IC at all.

Invasive treatment of IC is however supported by data from paper III demonstrating any improvement of all HRQoL scores in 70-90% of patients (Figure 16). Furthermore, subanalysis of IC patients in paper III that underwent endovascular SFA treatment showed significant improvement in most HRQoL outcome measures one year after treatment (Figure 17).

Also when investigating invasive treatment of infrainguinal IC in a randomized controlled setting (paper IV), comparing primary stenting with continued BMT only in patients with stable IC due to lesions in the SFA, the rationale of invasive treatment was further supported. Patients in the stent group reported significant improvement in all primary outcome measures, whereas only small and statistically insignificant changes occurred in the control group. Improvements in ABI and walking distance were also of a much larger magnitude and of clinical relevance in the stent group; with significant between-group differences in improvement of these parameters. Previous studies with mixed patient materials, studying both supra- and infrainguinal lesions and different interventional techniques (85) corroborate our findings in paper IV that invasive treatment of IC leads to significant improvement in HRQoL. Paper IV presents six month data, but further follow-up is planned for 12 and 24 months concerning all data, and up to 60 months concerning HRQoL data. These results will be influenced by the patency of the implanted nitinol BMS. It is interesting that studies on drug eluting devices have shown promising results (86) regarding patency. In Sweden such devices are still quite scarcely used in clinical practice, however, due to lack of stable evidence of superiority and for economic reasons. This has prompted the initiation of a national prospective trial in which eligible patients with
infrainguinal disease are now randomized between drug eluting or non-drug eluting devices (87).

**Invasive treatment of (infrainguinal) CLI (I, III)**

In paper I the clinical indication for SFA stenting was CLI in 84 (75%) cases. As mentioned above, women were significantly more often treated for CLI (87% vs. 58 %; P = 0.001). Amputations were in 12 of the 16 cases performed on patients with very severe CLI with ulceration or gangrene already at baseline. Stent patency could be assumed before amputation in 13 cases, whereas stent occlusion was confirmed in one case and information was lacking in the remaining two cases. These facts indicate that the need for amputation might have reflected a failure to reverse an already severe ischemic damage rather than loss of patency of the endovascularly treated segments. This has previously been reported to be the most common cause of limb loss after invasive treatment (88).

Although none of the papers in this thesis were primarily aimed to investigate results after invasive treatment of CLI, data from paper III show that CLI (together with CWP) was associated with different aspects of reduced HRQoL at baseline and even if patients with CLI improved significantly after invasive treatment in WIQ overall and EQ5D they still reported significantly lower scores than patients with IC, and did not improve in any SF-36 domain. However only a minority (33%) of these patients were treated infrainguinally.

CLI patients were significantly older than patients with IC (paper III), had a mortality of 24%, and an amputation-free survival of 67% (paper I) reflecting the fact that CLI patients typically are old and fragile.

**Invasive treatment of PAD patients with CWP (III-IV)**

The prevalence of CWP among patients with PAD was two times higher than in the general population. We found prevalence of 29% in paper III and 35.5 % in paper IV compared to 11 % in the general population (47, 48). The presence of CWP at baseline was associated with reduced HRQoL, but treatment led to significantly better HRQoL for all patients regardless of pain group affiliation at baseline. When, in addition to results presented in paper III, taking all SF-36 domains in consideration treatment led to significant improvement also in SF-36 domains RP, BP, SF and RE in patients with CWP (Figure 13) but HRQoL was
still after treatment on a significantly lower level than in patients without CWP at baseline (paper III).

Patients with CWP experience, as previously reported, worse outcome when treated for numerous medical disorders such as cancer and rheumatic diseases (55-57). CWP was found to have a large impact on HRQoL in patients with PAD as shown in papers III and IV, and stent treatment of patients with CWP showed improvement only in ABI and walking distance and not in HRQoL (paper IV). This subanalysis of results in paper IV should however, be interpreted with caution due to risk of beta errors. Only when analysing “on treatment results” in paper IV, the results from paper III were corroborated and patients with CWP at baseline improved significantly in HRQoL (SF-36 domains PF and VT) after primary SFA stenting. In fact patients in the control group without CWP improved in several HRQoL outcomes (EQ5D and WIQ), suggesting that the presence of CWP have a more negative impact on HRQoL than not to perform SFA stenting. Patients in the control group with CWP did not improve in any outcome measure at all, indicating that withholding invasive treatment of PAD patients with CWP leaves them without any amelioration at all.

Treatment of PAD in patients with CWP seems important also with respect to HRQoL and we suggest evaluating if CWP is present, when communicating with the patient, evaluating disease severity, in decision making on invasive treatment, and in follow-up of treatment results.

.  

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Summary

Although the high proportion of CLI in women at presentation and the significant predominance of women being amputated after SFA treatment in paper I was not confirmed by poorer outcome in women in paper II-IV it raised concerns about the ability of the health care system to adequately appreciate symptoms of PAD in women.

The incidence of invasive treatment of infrainguinal IC in Sweden was 8.9 per 100,000/year, with improvement in 73.2% of patients. Sub analysis of patients with IC in paper III, and analysis of primary stenting of SFA in patients with IC in a randomized controlled setting in paper IV, showed significant improvement of HRQoL by invasive treatment.

Patients with infrainguinal CLI are often old and at an increased risk of limb loss. Invasive treatment led to 67% amputation-free survival and could significantly improve EQ5D and WIQ overall (but to lower levels than in patients with IC).

The prevalence of CWP among patients with PAD was two times higher than in the general population and CWP was associated with reduced HRQoL. Treatment of PAD led to significant improvement of HRQoL (albeit to a lower level than in patients without CWP).

Primary stenting of lesions in the SFA led to significant improvement in HRQoL, ABI and walking distance in patients with IC. Stent treatment of patients with concomitant CWP led to improvement of ABI and walking distance but not of HRQoL, they actually had worse HRQoL than patients without CWP in the control group.

Invasive treatment of PAD patients with CWP seems important with respect to HRQoL as withholding treatment of PAD patients suffering from concomitant CWP left them without any amelioration at all.
Conclusions

Treatment of the femoropopliteal segment with nitinol self-expanding stents led to 67% amputation-free survival. Women had more severe CLI at treatment and female gender was an independent risk factor for amputation. (I)

Invasive treatment of infrainguinal IC was frequently performed in Sweden with an annual treatment incidence of 8.9/100,000 inhabitants. Treatment resulted in clinical improvement in 73.2% of patients after 12 months. (II)

CWP, with a prevalence of 29%, was twice as common in patients with PAD as in the general population and associated with reduced HRQoL. Invasive treatment of PAD led to significant improvement of HRQoL (although to a lower level than in patients without CWP). (III)

Primary stenting of lesions in the SFA led to significant improvement in HRQoL, ABI, and walking distance in patients with stable IC. (IV)

Primary stenting of lesions in the SFA in patients with stable IC and concomitant CWP did not improve HRQoL, but did improve ABI and walking distance. (IV)
Future perspectives

Several areas for future research and development in the field of invasive treatment of PAD and its relation to CWP can be identified.

1. The future treatment incidence and what are the results of infrainguinal IC in Sweden over time.
2. Long-time results in terms of influence on HRQoL of primary stenting of lesions in the SFA in patients with IC have not yet been established.
3. The influence of CWP on invasive treatment of IC in a large cohort has not been investigated.
4. Further research on the relation between painful disorders, as PAD, and CWP to establish whether the painful disorder triggers the development of CWP or if people with CWP are more prone to develop other diseases such as PAD.
5. The cost-effectiveness of primary stenting in patients with IC due to SFA lesions remains to be established.
6. Potential effects of devices eluting anti-proliferative drugs, (drug eluting stents [DES], and drug eluting balloons [DEB]) upon intimal hyperplasia and in-stent restenosis are currently being investigated.
Perifer kärlsjukdom

Olika sjukdomsgrader – olika behandling?
Vid perifer kärlsjukdom begränsas blodflödet till benen, vilket i den lindrigaste formen ger upphov till obehag och smärta vid gång som ger vika i vila – claudicatio intermittens (s.k. fönstertittarsjuka). I allvarligare fall är blodflödet så nedsatt att det ger upphov till ilovårk, sår och i värsta fall kallbrand (vävnadsdöd) – kritisk ischämi (kritisk syrebrist). Vid kritisk ischämi, som obehandlad innebär en risk för amputation på ca 42% inom ett år, är det i de flesta fall inte svårt att fatta beslut om operativ behandling. Vid fönstertittarsjuka däremot, där risken för amputation är mycket liten, och behandlingen i första hand syftar till att förbättra patientens livskvalitet och gångförmåga saknas stabilt vetenskapligt stöd för operativ behandling.

Hur behandlas fönstertittarsjuka?
Behandling vid fönstertittarsjuka är enligt både svenska och internationella riktlinjer i första hand medicinsk i form av reglering av blodtryck, blodfetter, gångträning och rökstopp. Trots dessa riktlinjer behandlas fönstertittarsjuka med både öppen bypass operation (då en ny förbinder läggs som leder blodet förbi förträngningen) och endovaskulär metod (då man via ett litet stick i ljumsken vidgar blodkärlet från insidan med en ballong och möjligen även placerar ett stent/kärlnät) i stor omfattning. Indikationen för invasiv behandling (med öppen operation eller endovaskulär metod) av fönstertittarsjuka är speciellt omdiskuterad ifall kärlförträngningen sitter nedom ljumsken (infrainguinalt), eftersom riskerna vid sådan behandling är större och resultaten sämre än om förträngningarna sitter högre upp.
Hur är behandlingsresultaten vid fönstertittarsjuka?

Invasiv behandling av fönstertittarsjuka ger inte alltid den förväntade förbättringen i form av hälsorelaterad livskvalitet (engelsk förkortning; HRQoL), gångsträcka och ABI (förhållandet mellan ankelblodtryck och armblodtryck) då andra sjukdomar, såsom hjärt- och lungsjukdom och sjukdomar i rörelseorganen som exempelvis långvarig generaliserad smärta (på engelska chronic widespread pain, förkortas; CWP) också kan påverka gångförmåga och hälsorelaterad livskvalitet.

Avhandlingens målsättning

Målsättningen med det här avhandlingsprojektet har varit att utvärdera resultat av invasiv behandling (öppen operation eller endovaskulär behandling) av perifer kärlsjukdom (nedom stora kroppspulsåderns delning), speciellt avseende;

- Effekten av invasiv behandling av kärlsjukdom i lårbensartären, med speciell hänsyn till eventuella könsskillnader.
- Förekomst och resultat av invasiv behandling av infrainguinal (nedom ljumsken) fönstertittarsjuka i Sverige.
- Samtidig förekomst av långvarig generaliserad smärta och dess påverkan på hälsorelaterad livskvalitet hos patienter med perifer kärlsjukdom.
- Effekten av stentbehandling av kärlsjukdom i lårbensartären vid fönstertittarsjuka på hälsorelaterad livskvalitet, och eventuell påverkan på behandlingseffekten av samtidig långvarig generaliserad smärta.

Avhandlingens metod och resultat

För att utvärdera resultaten av behandling av perifer kärlsjukdom i lårbensartären utvärderades i en återblickande studie vid Helsingborg lasarett resultaten vid stentbehandling av 112 patienter. Studien visade att stentbehandling av lårbensartären fungerade väl men att kvinnor vid behandlingen hade mer uttalad kritisk ischemi (kritisk syrebrist) och blev inom ett års uppföljning amputerade i större utsträckning än män.

För att utreda förekomst och resultat av invasiv behandling av fönstertittarsjuka nedom ljumsken utvärderades alla 775 patienter som under ett år enligt det svenska kärlregistret Swedvasc genomgått sådan behandling. C:a 73 förbättrades.

För att undersöka samtidig förekomst av långvarig generaliserad smärta och dess påverkan på hälsorelaterad livskvalitet studerades 240 patienter som lades in i Malmö och Helsingborg för invasiv behandling (med öppen operation eller endovaskulär behandling) av perifer kärlsjukdom i en framåtblickande studie.
Långvarig generaliserad smärta förekom c:a dubbelt så ofta hos dessa patienter som i befolkningen i övrigt. Förekomsten av långvarig generaliserad smärta påverkade den hälsorelaterade livskvaliteten negativt, men behandling av kärlsjukdomen ledde till förbättrat hälsorelaterad livskvalitet hos alla patienter, även de med långvarig generaliserad smärta (fast till en lägre nivå än hos dem som inte hade långvarig generaliserad smärta).

Påverkan av stentbehandling hos patienter med fönstertittarsjuka till följd av åderförkalkning i SFA studerades i en framåtblickande studie vid 7 svenska sjukhus (Eskilstuna, Helsingborg, Kalmar, Kristianstad, Malmö, Örebro och Växjö) där 100 patienter slumpmässigt fördelades mellan stent och konservativ behandling. Stentbehandling visade sig förbättra hälsorelaterad livskvalitet, ABI och gångsträcka medan endast småre och mindre relevanta förändringar i dessa parametrar sågs hos de patienter som inte stentbehandlades. Vid samtidig förekomst av långvarig generaliserad smärta förbättrade stentbehandlingen bara ABI och gångsträcka men inte hälsorelaterad livskvalitet.

Avhandlingens slutsatser

• Stentning i lårbensartären ger goda resultat, men kvinnor hade en ökad risk för amputation pga. mer uttalad kärlsjukdom redan innan behandling.
• Invasiv behandling av fönstertittarsjuka nedom ljuvmken är vanlig i Sverige och ger förbättring hos 3 av 4 patienter.
• Långvarig generaliserad smärta är dubbelt så vanligt hos kärlsjuka patienter som befolkningen i övrig. Smärtnä förbättrar livskvaliteten men invasiv behandling av kärlsjukdomen förbättrar den.
• Stentbehandling av lårbensartären hos patienter med fönstertittarsjuka ger (till skillnad mot konservativ behandling) förbättrad hälsorelaterad livskvalitet, ABI och gångsträcka. Vid samtidig långvarig generaliserad smärta förbättras inte livskvaliteten, men däremot ABI och gångsträcka.
I would like to express my sincere gratitude to all colleagues and friends who have contributed to, and supported me in my work with this thesis in different ways:

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Appendix

Livskvalitet vid perifer kärlsjukdom

Enkät:

Datum: _______________________

Namn: _______________________

Personnummer: [__] - [__]
Först kommer frågor om hur Du ser på Din hälsa. Informationen skall hjälpa till att följa hur Du mår och fungerar i Ditt dagliga liv. Besvara frågorna genom att sätta kryss i rutan för det alternativ som Du tycker stämmer bäst in på Dig. Om Du är osäker, kryssa ändå för det alternativ som känns riktigast.

1. I allmänhet, skulle Du vilja säga att Din hälsa är:

   (Sätt kryss i en ruta)
   - Utmärkt
   - Mycket god
   - God
   - Någorlunda
   - Dålig

2. Jämfört med för ett år sedan, hur skulle Du vilja bedöma Ditt allmänna hälsotillstånd nu? (Sätt kryss i en ruta)

   - Mycket bättre nu än för 1 år sedan
   - Något bättre nu än för 1 år sedan
   - Ungefär det samma
   - Något sämre nu än för 1 år sedan
   - Mycket sämre nu än för 1 år sedan

3. De följande frågorna handlar om aktiviteter som Du kan tänkas utföra under en vanlig dag. Är Du på grund av Ditt hälsotillstånd begränsad i dessa aktiviteter nu? Om så är fallet, hur mycket? (Sätt ett kryss för ett alternativ på varje rad)

   a. Ansträngande aktiviteter, som att springa, lyfta tunga saker, delta i ansträngande sporter.
   b. Måttligt ansträngande aktiviteter, som att flytta ett bord, dammsuga, skogspromenader eller trädgårdsarbete.
   c. Lyfta eller bära matkassar
   d. Gå uppför flera trappor
   e. Gå uppför en trappa
   f. Böja Dig eller gå ner på knä
   g. Gå mer än två kilometer
   h. Gå några hundra meter
   i. Gå hundra meter
   j. Bada eller klä på Dig

   Ja, mycket begränsad  Ja, lite begränsad  Nej, inte alls begränsad

1
4. Under **de senaste fyra veckorna**, har Du haft något av följande problem i det arbete Du normalt utför, **som en följd av Ditt kroppsliga hälsotillstånd?**

Med arbete avses både arbete utanför hemmet och hushållssysslor. (Sätt ett kryss vid Ja eller Nej för varje fråga)

   a. Skurit ned på den **tijd** Du normalt ägnat åt arbetet  
      Ja ☐  Nej ☐
   b. **Uträttad mindre** än Du skulle önskat  
      Ja ☐  Nej ☐
   c. Har ej kunnat utföra **vissa arbetsuppgifter**  
      Ja ☐  Nej ☐
   d. Haft **svårigheter** att utföra arbete  
      Ja ☐  Nej ☐

   (t.ex. genom att det krävde extra ansträngning)

5. Under **de senaste fyra veckorna**, har Du haft något av följande problem i det arbete Du normalt utför, **som en följd av känslomässiga problem** (t.ex. nedstämdhet eller ångslan)? Med arbete avses både arbete utanför hemmet och hushållssysslor. (Sätt ett kryss vid Ja eller Nej för varje fråga)

   a. Skurit ned på den **tijd** Du normalt ägnat åt arbetet  
      Ja ☐  Nej ☐
   b. **Uträttad mindre** än Du skulle önskat  
      Ja ☐  Nej ☐
   c. Inte utfört arbetet så **noggrant** som vanligt  
      Ja ☐  Nej ☐

6. Under **de senaste fyra veckorna**, i vilken utsträckning har Ditt kroppsliga hälsotillstånd eller Dina känslomässiga problem stört Ditt vanliga umgänge med anhöriga, vänner, grannar eller andra? (Sätt kryss i en ruta)

   Inte alls ☐  Lite ☐  Måttligt ☐  Mycket ☐  Väldigt mycket ☐

7. Hur mycket **värk eller smärta** har Du haft under de **senaste fyra veckorna**? (Sätt kryss i en ruta)

   Ingen ☐  Mycket lätt ☐  Lätt ☐  Måttlig ☐  Svår ☐  Mycket svår ☐

8. Under **de senaste fyra veckorna**, i vilken utsträckning har **värken eller smärtan** stört Ditt normala arbete (innehåller både arbete utanför hemmet och hushållssysslor)? (Sätt kryss i en ruta)

   Inte alls ☐  Lite ☐  Måttligt ☐  Mycket ☐  Väldigt mycket ☐
9. Frågorna här handlar om hur Du haft det under de **senaste fyra veckorna**. Ange för varje fråga det svarsalternativ som bäst beskriver hur Du har känt Dig. Hur stor del av tiden under de **senaste fyra veckorna**...
(Sätt ett kryss för ett alternativ på varje rad)

<table>
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<th>Hela tiden</th>
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<tr>
<td>a. Har Du känt Dig riktigt pigg och stark?</td>
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<td>b. Har Du känt Dig mycket nervös?</td>
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<td>c. Har Du känt Dig så nedstämd att ingenting kunnat mantra upp Dig?</td>
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<td>d. Har Du känt Dig lugn och harmonisk?</td>
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<td>e. Har Du känt Dig full av energi?</td>
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<td>f. Har Du känt Dig dyster och ledsen?</td>
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<td>g. Har Du känt Dig utsлит?</td>
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<td>h. Har Du känt Dig glad och lycklig?</td>
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<tr>
<td>i. Har Du känt Dig trött?</td>
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</tbody>
</table>
10. Under de senaste fyra veckorna, har Ditt kroppsliga hälsotillstånd eller Dina känslomässiga problem stört Dina möjligheter att umgås (t.ex. hälsa på släkt, vänner etc.)? (Sätt kryss i en ruta)

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11. Välj det svarsalternativ som bäst beskriver hur mycket vart och ett av följande påståenden stämmer eller inte stämmer in på Dig. (Sätt ett kryss för ett alternativ på varje rad)

<table>
<thead>
<tr>
<th></th>
<th>Stämmer precis</th>
<th>Stämmer ganska bra</th>
<th>Osäker</th>
<th>Stämmer inte särskilt bra</th>
<th>Stämmer inte alls</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Jag verkar ha lättare att bli sjuk än andra människor.</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>b. Jag är lika frisk som vem som helst av dem jag känner.</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>c. Jag tror min hälsa kommer att bli sämre.</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>d. Min hälsa är utmärkt.</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>
12. Har Du under de senaste 12 månaderna haft värk eller smärta som varat mer än 3 månader? 
- Ja ☐
- Nej ☐
- Vet ej ☐


   a. Bröstkorgens framsida ☐
   b. Nacke ☐
   c. Vä Skuldra/Överarm ☐
   d. Hö Skuldra/Överarm ☐
   e. Vä Armbåge/Underarm ☐
   f. Hö Armbåge/Underarm ☐
   g. Bröstrygg ☐
   h. Ländrygg/Korsrygg ☐
   i. Vä Hand/Handled ☐
   j. Hö Hand/Handled ☐
   k. Vä Skinka ☐
   l. Hö Skinka ☐
   m. Vä Höft/Lår ☐
   n. Hö Höft/Lår ☐
   o. Vä knä ☐
   p. Hö knä ☐
   q. Vä Underben/Fot ☐
   r. Hö Underben/Fot ☐
Nu följer ytterligare frågor om Ditt hälsotillstånd. Även om Du upplever att vissa frågor känns upprepade så är det väsentligt att Du svara på alla.

Markera, genom att kryssa i en ruta i varje nedanstående grupp, vilket påstående som bäst beskriver Ditt hälsotillstånd i dag.

14. Rörlighet
   Jag går utan svårigheter
   Jag kan gå men med viss svårighet
   Jag är sängliggande

15. Hygien
   Jag behöver ingen hjälp med min dagliga hygien, mat eller påklädnad
   Jag har vissa problem att tvätta eller klä mig själv
   Jag kan inte tvätta eller klä mig själv

16. Huvudsakliga aktiviteter (t.ex arbete, studier, hushållssysslor, familje- och fritidsaktiviteter)
   Jag klarar av mina huvudsakliga aktiviteter
   Jag har vissa problem med att klara av mina huvudsakliga aktiviteter
   Jag klarar inte av mina huvudsakliga aktiviteter

17. Smärtor/besvär
   Jag har varken smärtor eller besvär
   Jag har måttliga smärtor eller besvär
   Jag har svåra smärtor eller besvär

18. Oro/nedstämdhet
   Jag är inte orolig eller nedstämd
   Jag är orolig eller nedstämd i viss utsträckning
   Jag är i högsta grad orolig eller nedstämd
Till hjälp för att avgöra hur bra eller dåligt ett hälsotillstånd är, finns den termometer-liknande skalan till höger.

På denna har Ditt bästa tänkbara hälsotillstånd markerats med 100 och Ditt sämsta tänkbara hälsotillstånd med 0.

Vi vill att Du på denna skala markerar hur bra eller dåligt Ditt hälsotillstånd är, som Du själv bedömer det. Gör detta genom att dra en linje från nedanstående ruta till den punkt på skalan som markerar hur bra eller dåligt Ditt nuvarande hälsotillstånd är.
Nu följer frågor angående Dina upplevelser av gångproblem. Även om Du inte har några problem med att gå är det viktigt att frågorna besvaras.


   a. Smärta, värk eller kramp i vaderna eller skinkorna?  
      | Inte | Alls | Lite | Något | Mycket | Väldigt | Ej | mycket | tillämpligt |
   b. Smärta, stelhet eller värk i lederna (fotlederna, knäna eller höfterna)?  
   c. Svaghet i det ena eller båda benen?  
   d. Smärta eller obehag i bröstet?  
   e. Andfåddhet?  
   f. Hjärtklappning?  
   g. Övriga problem? (ange nedan)  

Övriga problem: 

20. Gångavstånd: Under den senaste veckan, hur svårt var det att gå på järnväg mark utan att stanna eller vila för vart och ett av de följande avstånden?

   a. Gå omkring inomhus, som t ex hemma?  
      | Inte | Alls | Lite | Något | Mycket | Kan | inte | Ej | tillämpligt |
   b. Gå 20 meter?  
   c. Gå 50 meter?  
   d. Gå 100 meter?  
   e. Gå 200 meter?  
   f. Gå 300 meter?  
   g. Gå 500 meter?
21. Gånghästighet: Under senaste veckan, hur svårt var det för Dig att gå motsvarande 100 meter på järnmärk vid var och en av följande hastigheter utan att stanna?

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<tbody>
<tr>
<td>a. Gå 100 meter långsamt?</td>
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<td>b. Gå 100 meter vid medelhastighet?</td>
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<td>c. Gå 100 meter snabbt?</td>
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<td>c. Springa eller jogga 100 meter?</td>
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22. Gå i trappor: Under den senaste veckan, hur svårt var det för Dig att gå i trappor utan att stanna eller vila?

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<tbody>
<tr>
<td>a. Gå en trappa upp?</td>
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<tr>
<td>b. Gå två trappor upp?</td>
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<td>c. Gå tre trappor upp?</td>
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Tack för Din medverkan!
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