Long-term results of invasive treatment of intermittent claudication and perioperative hemodynamic monitoring of the lower limb

Gunnarsson, Thordur Skuli

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THORDUR GUNNARSSON
DEPARTMENT OF CLINICAL SCIENCES MALMÖ | LUND UNIVERSITY

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Thordur Gunnarsson

LUND
UNIVERSITY

DOCTORAL DISSERTATION

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Title and subtitle: Long-term results of invasive treatment of infrainguinal intermittent claudication and perioperative hemodynamic monitoring of the lower limb.

Abstract:
Background and aims: Peripheral arterial disease (PAD) affects one in ten people over the age of 60 years. Long-term follow-up studies after invasive treatment of intermittent claudication (IC), which is the most common presentation of PAD are lacking in the field. As endovascular interventions have increased in the last decades, there is a need for evaluation of results regarding technical improvement, as well as for analysis of trends in operative modality in IC patients.

Methods: Retrospective cohort study of 775 patients revascularized in 2009. Eight years follow-up of data from Swedvasc, the Inpatient, and the Cause of death registries (paper I). Retrospective study of invasive treatment modality and sex differences of infrainguinal IC registered in Swedvasc between 2009 and 2022 (paper II). Multicentre randomized controlled trial of 100 patients comparing best medical treatment (BMT) and stent treatment, with health-related quality of life (HRQoL) as primary outcome and reintervention, amputation, and mortality as secondary outcomes after 36 and 60 months (paper III). Single-center prospective observational study on 21 patients with chronic limb threatening ischemia (CLTI), evaluating the feasibility of transcutaneous oximetry ($tcpO_2$) and systolic toe pressure (TP) monitoring during endovascular intervention. Continuous $TcpO_2$ measurements and TP measurements at start and finish of the endovascular revascularization, and follow-up measurement after 10 weeks (paper IV).

Results: The study cohort in paper I (n = 775) underwent a total of 486 new vascular interventions, and the yearly need for hospitalization was 79-99%. After 3, 5, and 8 years of follow-up major amputation and mortality rates were 2.7%, 3.9%, 6.7% and 10.2%, 20.0%, and 40.1% respectively. Diseases of the circulatory system was the most common cause of death, 42.4% (paper I). Modalities of invasive treatment of infrainguinal IC changed significantly between 2009 and 2022. The proportion of endovascular interventions increased from 56.9% to 69.7%, whereas open surgery decreased from 38.1% to 23.4%, bypass surgery decreased from 18.8% to 4.0%, and BMS treatment increased from 16.9% to 35.9%. Thrombendarterectomy (TEA) operations of the common femoral artery (CFA) remained unchanged. Women were more likely to undergo endovascular intervention and reintervention compared to men (paper II). Patients with IC due to SFA lesions randomized to stent treatment had significantly higher physical HRQoL after 36 months compared to those undergoing conservative treatment. No difference was seen between groups after 60 months (paper III). During endovascular revascularization in CLTI patients $tcpO_2$ decreased during the intervention, but increased at follow up ($p < .001$). TP increased significantly at the end of intervention ($p < .001$) and at follow up ($p < .001$) (paper IV).

Conclusions: Patients undergoing invasive treatment of infrainguinal IC have high morbidity, mortality, and need for hospitalization due to cardiovascular diseases. Endovascular interventions now constitute approximately 70% of all invasive treatments in this patient group, and women are more likely to undergo endovascular intervention. There is a positive effect of stent treatment compared to conservative treatment for patients with IC due to SFA lesions until 3 years, however, this effect is no longer measurable after 5 years. Periprocedural measurements of TP show promising results, however, the value of $tcpO_2$ monitoring during endovascular interventions seems limited.

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Thordur Gunnarsson

LUND
UNIVERSITY

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Faculty of Medicine
Department of Clinical Sciences Malmö

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To my beloved family,
Selma, Vigdís and Gunnar

Vits er þörf þeim er víða ratar.
Dælt er heima hvað.

He hath need of his withs who wanders wide.
Aught simple will serve at home.

Hávamál

Table of Contents

Original papers

The present thesis is based on the following papers, referred to by their Roman numerals and reprinted with the consent from the respective publishers.

I. Gunnarsson T, Gottsäter A, Bergman S, Troëng T, Lindgren H. Eight-year outcome after invasive treatment of infrainguinal intermittent claudication: A population-based analysis from the Swedish vascular registry (Swedvasc). SAGE Open Med 2020; 8:2050312120926782.

II. Gunnarsson T, Bergman S, Pärsson H, Gottsäter A, Lindgren H. Time trends and sex differences in invasive treatment of infrainguinal intermittent claudication in Sweden during 2009-2022, results from the Swedish Vascular Registry (Swedvasc). Eur J Vasc Endovasc Surg 2025 (in press).

III. Gunnarsson T, Bergman S, Pärsson H, Gottsäter A, Lindgren H. Long-term results of a randomized trial of stenting of the superficial femoral artery for intermittent claudication. Eur J Vasc Endovasc Surg 2023; 65:513-519.

IV. Gunnarsson T, Lindgren H, Gottsäter A, Pärsson H. Intraprocedural transcutaneous oxygen pressure and systolic toe pressure measurements during and after endovascular intervention in patients with chronic limb threatening ischemia. Eur J Vasc Endovasc Surg 2021; 62:583-589.

Abstract

Background and aims: Peripheral arterial disease (PAD) affects one in ten people over the age of 60 years. The most common presentation is intermittent claudication (IC) for which invasive treatment approach varies especially in infrainguinal disease. Long-term follow-up studies after interventions are lacking in the field. Endovascular interventions have increased in the last decades and there is need for evaluating results and tools to improve the technique as well as analyze the recent time trends in operative modality in IC patients.

Methods: Retrospective cohort study of 775 patients revascularized in 2009 for whom Swedvasc, Inpatient and Cause of death register data were collected and analyzed 8 years after revascularization (paper I). Retrospective study on changes in invasive treatment modality and sex differences of infrainguinal IC interventions registered in Swedvasc between 2009 and 2022 (paper II). Multicentre randomized controlled trial (RCT) in Sweden of 100 patients with IC due to arterial lesions in the superficial femoral artery (SFA). Patients were randomized to either best medical treatment (BMT) or stent treatment with health-related quality of life (HRQoL) as primary outcome and reintervention, amputation and mortality as secondary outcome after 36- and 60-months follow-up (paper III). Single-center prospective observational study on 21 patients with chronic limb threatening ischemia (CLTI) evaluating the feasibility of transcutaneous oximetry ($tcpO_2$) and systolic toe pressure (TP) monitoring during endovascular intervention. Continuous $TcpO_2$ measurements and TP measurements at start and completion of endovascular revascularization. Follow-up measurement after 10 weeks (paper IV).

Results: During the 8-year observational period (2010-2017), the study cohort (n = 775) underwent a total of 486 new vascular interventions (246 in index limb and 240 on contralateral limb) and the yearly need for hospitalization was 79-99%. Major amputation was 2.7%, 3.9%, and 6.7% after 3, 5, and 8 years respectively. Mortality was 10.2%, 20.0%, and 40.1% after 3, 5, and 8 years respectively. Cerebrovascular disease, ischemic heart disease, and other disease of the circulatory system was the most common cause of death, 42.4% (paper I). Invasive treatment of infrainguinal IC changed significantly in Sweden between 2009 and 2022. The proportion of endovascular interventions increased from 56.9% to 69.7%, open surgery decreased from 38.1% to 23.4%, bypass surgery decreased from 18.8% to 4.0%, and BMS treatment increased from 16.9% to 35.9%. Common femoral artery (CFA) thrombendarterectomy (TEA) operations remained unchanged, however.

Women were more likely to undergo endovascular intervention and reintervention compared to men. Men were more often treated with open surgery, OR 1.61 [95% CI 1.44 – 1.79] (paper II).

Patients with IC due to SFA lesions randomized to stent treatment had better physical HRQoL according to SF-36 (Role Physical and Physical Component Summary), and Walking Impairment Questionnaire (WIQ) after 36 months compared to those undergoing treatment alone. No difference was seen between groups after 60 months. Results might be affected by high crossover and loss of power due to loss of follow-up. No differences between groups were seen regarding amputation and mortality. (paper III). In patients with CLTI undergoing endovascular revascularization $tcpO_2$ decreased by 6.0 mmHg during the first part of the intervention, ($p < .001$) and did not recover to above baseline values after revascularization at the end of intervention. $TcpO_2$ increased by 14.7 mmHg at follow up ($p < .001$). TP increased by 13.0 mmHg during the intervention ($p < .001$) and by 30.0 mmHg at follow up ($p < .001$) compared to baseline (paper IV).

Conclusions: Patients undergoing invasive treatment of infrainguinal IC have high morbidity, mortality and need for hospitalization due to cardiovascular diseases. Endovascular interventions are now approximately 70% of all invasive treatment in this patient group, and women are more likely to undergo endovascular intervention compared to men. There is a positive effect on physical HRQoL of stent treatment compared to conservative treatment for patients with IC due to SFA lesions until 3 years, the effect is however not measurable after 5 years. Periprocedural measurements of TP show promising results, however, the value of $tcpO_2$ monitoring during endovascular interventions seems limited.

Abbreviations

ABI	Ankle brachial index
AFS	Amputation free survival
AP	Ankle pressure
ASA	Acetylsalicylic acid
BA	Brachial artery
BMS	Bare metal stent
BMT	Best medical treatment
BP	Bodily pain (SF-36 domain)
CAD	Coronary artery disease
CFA	Common femoral artery
CKD	Chronic kidney disease
CLTI	Chronic limb threatening ischemia
CVD	Cerebrovascular disease
CVI	Cerebrovascular incidence
DEB	Drug eluting balloon
DES	Drug eluting stent
DM	Diabetes mellitus
DP	Dorsalis pedis artery
DSA	Digital subtraction angiography
EQ-5D	EuroQol 5-dimensions
FP	Femoropopliteal
GLASS	Global limb anatomy staging system
HbA1c	Glycated hemoglobin
HBET	Home-based exercise training
HRQoL	Health related quality of life
IC	Intermittent claudication
IP	Infrapopliteal

IQR	Interquartile range
LD	Laser doppler
LDL	Low-density lipoprotein
MALE	Major adverse limb event
NO	Nitric Oxide
OS	Overall survival
PAD	Peripheral arterial disease
PCS	Physical component summary (SF-36)
PF	Physical function (SF-36)
PROM	Patient reported outcome measure
PTA	Percutaneous transluminal angioplasty
PVR	Pulse volume recording
QoL	Quality of life
RCT	Randomized controlled trial
SD	Standard deviation
SET	Supervised exercise training
SF-36	The Short-Form 36 health survey
SFA	Superficial femoral artery
TAP	Target artery pathway
TASC	Trans-Atlantic inter-society consensus
$TcpO_2$	Transcutaneous oxygen pressure
TEA	Thrombendarterectomy
TM	Transmetatarsal
TP	Systolic toe pressure
TPA	Tibialis posterior artery
TV	Target vessel
VascuQol-6	Vascular quality of life questionnaire - 6
WA	Walking advice
WIfI	Wound. Ischemia, foot infection classification
WIQ	Walking impairment questionnaire

Thesis at a glance

Paper	Aim	Method	Results
I. Eight-year outcome after invasive treatment for infrainguinal IC	Report new vascular interventions, hospitalization, mortality, and amputation	Retrospective cohort study: 775 patients revascularized in 2009. Data retrieved from Swedvasc, Inpatient, and Cause of death registries for 2010-2017.	486 new vascular interventions in 261 patients, 79-99% yearly need of hospitalization. Mortality: 10.2% (3 years), 20.0% (5 years), and 40.1% (8 years)
II. Time trends and sex differences in invasive treatment of infrainguinal IC during 2009-2022	Report changes in annual incidence, changes in invasive treatment modality and sex differences	Retrospective study of invasive treatment modality of infrainguinal IC registered in Swedvasc, 2009 – 2022, 13,322 registrations in 10,829 patients	Changes 2009 - 2022: No changes in incidence of treatment. Open surgery: 38.1 - 23.4% Endovascular intervention: 56.9 - 69.7% Bypass: 18.8 - 4.0% CFA TEA: 25.6 - 25.9% BMS: 16.9 - 35.9% Open surgery more common in men compared to women (OR 1.61)
III. Long term results of a RCT on stenting of the SFA for IC	Comparison of stenting vs BMT for IC due to SFA lesion	Multicentre RCT in Sweden. BMT (n=48) vs stent (n=52). 36- and 60-months follow-up. Primary outcome: HRQoL Secondary outcomes: reinterventions, amputation, and mortality	Physical SF-36 and WIQ better in stent group after 36 months, no differences after 60 months. No differences in amputation or mortality
IV. Intraprocedural $tcpO_2$ and TP measurements during and after endovascular intervention in CLTI patients	Evaluate changes in $tcpO_2$ and TP during endovascular intervention	Single-center prospective observational feasibility study. 21 patients with CLTI. Continous$TcpO_2$ measurements and TP measurements at start and finish of endovascular revascularization. Follow-up measurement after 10 weeks	In-line flow to foot at completion angiogram in all but 2 patients. $TcpO_2$ did not increase during the intervention, TP increased significantly at the end of intervention. Both $tcpO_2$ and TP increased at follow-up

Introduction

Peripheral arterial disease

Peripheral arterial disease (PAD) is a condition in which narrowing or occlusion of arteries causes reduced blood flow to the organ or extremity they supply. Arteries to the brain and heart are not included in this definition, as narrowing of these vessels are defined as cerebrovascular disease (CVD) and coronary artery disease (CAD), respectively. PAD is caused by atherosclerosis in the vast majority of cases. Other causes like vasculitis, peripheral artery aneurysms, popliteal entrapment, or undiagnosed past emboli account for approximately 5%[1] of the underlying pathology. Atherosclerosis is a systemic disease in which endothelial dysfunction causes accumulation of lipids in the intima, monocytes are recruited, and an inflammatory response causes fibrosis and plaque formation[2]. Subsequent plaque formation causes narrowing or stenosis of the artery, which can lead to deficient oxygen supply to the target organ or extremity. This thesis focuses on PAD in the lower extremities caused by atherosclerosis distal to the infrarenal aorta causing impaired blood flow, which is objectively measured by calculating the ratio between blood pressure in the brachial artery and ankle arteries, ankle brachial index (ABI). In clinical praxis lower extremity PAD presents as asymptomatic PAD, intermittent claudication (IC), or chronic limb threatening ischemia (CLTI). Asymptomatic PAD patients have objectively impaired perfusion to the legs, ABI $\leq$ 0.9 without lower extremity symptoms. Symptomatic PAD is classified as either IC, with ambulatory induced ischemic pain, or CLTI with ischemic pain at rest or ischemic ulcers.

Epidemiology and risk factors

Approximately 237 million people are affected by PAD worldwide[3]. The prevalence increases with age, and in Sweden PAD is present in approximately 18% of people between the ages of 60 and 90 years[4] of which 11% are asymptomatic, 7% have IC, and 1.2% have CLTI.

The risk factors for PAD are the same as for atherosclerosis in general; cigarette smoking, diabetes mellitus (DM), hypertension, renal insufficiency, hypercholesterolemia, and obesity[5].

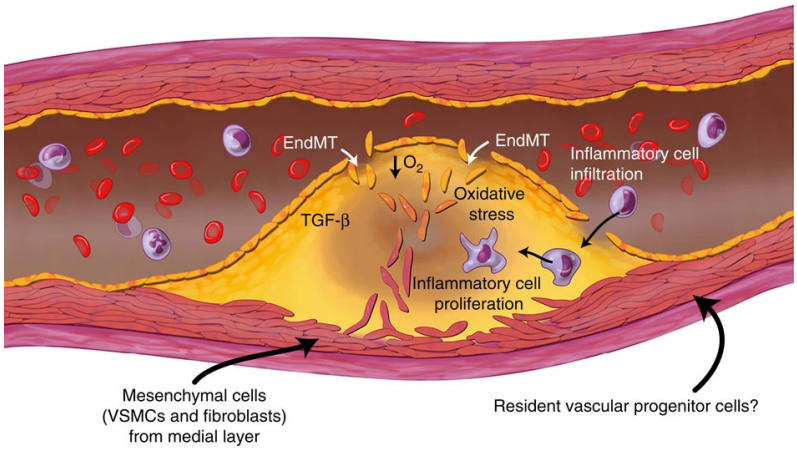

Figure 1 Schematic illustration of atherosclerotic plaque formation.
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Intermittent claudication

The most common form of symptomatic PAD is intermittent claudication (IC) presenting as exercise induced pain in the lower extremity, most commonly the calve muscles, which quickly subsides with rest[4]. This ischemic pain is due to the increased oxygen demand in muscles during walking or running which cannot be met due to a stenosis or occlusion in the arteries supplying the lower extremities[7]. When these symptoms are present and an ABI below 0.9 is established, a clinical diagnosis of IC can be made. IC is associated with a significant decrease in health-related quality of life (HRQoL)[8].

Chronic limb threatening ischemia

The most severe stage of PAD is chronic limb threatening ischemia (CLTI), in which the oxygen demand of the lower extremity is not met even at rest, causing ischemic rest pain and in more severe cases ischemic ulcers, tissue loss, and gangrene[9].

Best medical treatment (BMT)

Atherosclerosis is a systemic condition affecting all arteries of the body. It is essential to manage risk factors for atherosclerosis such as smoking, diet, and physical activity. Diabetes mellitus should be medically treated aiming for a HbA1c < 53mol/L[10]. Hypertension is treated with a blood pressure goal of 130/80 mmHg[5]. Anti-thrombotic treatment with single antiplatelet therapy with either clopidogrel or

aspirin is standard of care for all PAD patients. Recent trials have shown an additional risk reduction in cardiovascular and major adverse limb events (MALE) in patients receiving aspirin and low dose rivaroxaban, however there is a significant risk of GI bleeding[11, 12]. Lipid-lowering treatment is advocated to all PAD patients, including asymptomatic, with a treatment goal of LDL ≤ 1.4 mmol/L to reduce the subsequent risk of cardiovascular events, limb events, and disease progression[5, 13].

Invasive treatment

There are multiple options for invasive treatment of PAD with the objective to improve blood flow to the affected organ or limb. Open vascular surgery usually entails removal of atherosclerotic plaques (thrombendarterectomy) or creation of an alternative route for the blood past the occluded arterial segment (bypass). Endovascular interventions are carried out through percutaneous access to the arteries and catheter directed balloons to dilate stenosis or occlusions (PTA). Adjunctive techniques can be used to increase the patency of the PTA, most commonly by the placement of a metal mesh (stent)[14].

In some instances, both open and endovascular techniques are used simultaneously, which is referred to as hybrid intervention.

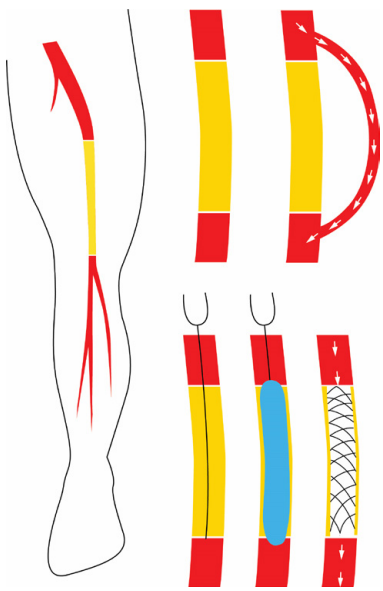

Figure 2. Invasive treatment of PAD.
Femoropopliteal bypass surgery with vein conduit and endovascular percutaneous angioplasty with ballon and stent treatment. Illustration by Selma Björk Kristjánsdóttir ©

Hemodynamic measurements in PAD

Ankle brachial index

Ankle brachial index measurement is the most used method for PAD diagnosis. The method was first described by Winsor in 1950[15]. The measurement is conducted with the patient in the supine position and the arterial pulse identified with a Doppler pen, a blood pressure cuff is inflated until the signal disappears and then deflated slowly until the Doppler signal reappears and the blood pressure is registered. This measurement is carried out bilaterally in the brachial artery (BA) and the ankle arteries, dorsalis pedis (DP) and tibialis posterior (TPA). The highest ankle pressure and the highest brachial pressure are thereafter used for calculation of the ABI.

$$A/B=I$$

ABI has a reported sensitivity and specificity for diagnosing PAD of 69-89% and 69-99% respectively, and the sensitivity and specificity is higher in suprapopliteal arterial disease and if the pre-test likelihood is high[16, 17]. ABI measurements are dependent on compressible tibial arteries for accuracy. Arterial medial calcification in the tibial arteries can cause a falsely high ABI > 1.4 due to incompressible tibial arteries. Medial calcification affects patients with diabetes mellitus (DM) and chronic kidney disease (CKD). In these cases, toe-pressure and transcutaneous oxygen pressure give a more accurate evaluation of the foot circulation[18].

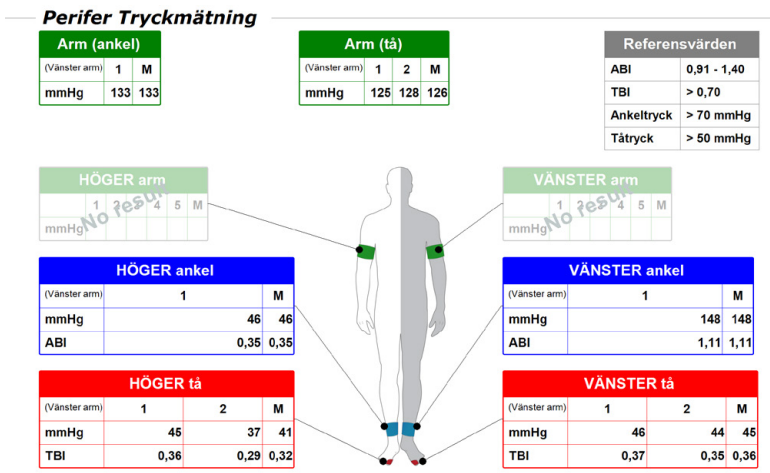

Figure 3.
Example of an ABI and TP measurement using Periflux 6000.

Systolic toe-pressure

Systolic toe-pressure is a non-invasive measurement method most commonly performed on the great toe in patients with incompressible tibial arteries. The small arteries of the toes are not affected by medial calcification as the tibial arteries. A small cuff is placed around the base of the toe and blood flow is measured with laser-doppler (LD)[19]. The LD probe emits infra-red laser light (wavelength 780nm) which is reflected by moving erythrocytes at a 1.5 mm depth from the skin surface, and the LD signal is derived from the Doppler-shift of the laser light recorded by the probe. The cuff is inflated above the systolic blood pressure and then deflated until the return of Doppler signal in the same way as for ankle pressure. The TP is generally 20 mmHg lower than the AP and a TP above 65 mmHg is generally considered normal. TP above 30 mmHg has been shown to be beneficial for wound healing in diabetic patients[20].

Transcutaneous oxygen pressure

Transcutaneous oxygen pressure ($tcpO_2$) is a non-invasive measurement of the partial pressure of oxygen in the skin. A Clark electrode is placed on the skin at the region of interest and measures the partial pressure of oxygen diffusing through the skin. The sensor is heated to 44° C causing localized hyperemia facilitating oxygen diffusion[21]. A normal $tcpO_2$ is above 60 mmHg[22].

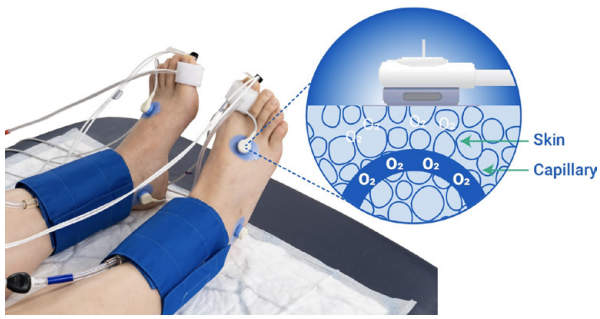

Figure 4.
$TcpO_2$ sensor measuring partial pressure of O_2 diffusing through the skin. The figure was reused with permission from Perimed AB ©.

Classification systems of PAD

The most widely adopted classification systems are the Fontaine[23] classification first presented in 1954 and the Rutherford [24] classification presented in 1986[25] and thereafter revised in 1997. Fontaine´s classification relies only on the clinical presentation while Rutherford´s includes hemodynamic measurements in the revised version from 1997.

Table 1. Fontaine classification[23]

Stage	
I	Asymptomatic
II	Mild claudication pain in limb
IIA	Claudication at distance > 200 m
IIB	Claudication at distance < 200 m
III	Rest pain, mostly in the feet
IV	Necrosis and/or gangrene of the limb

Table 2. Rutherford classification[24, 25]

Category	Clinical description	Objective criteria
0	Asymptomatic	Normal treadmill or reactive hyperemia test
1	Mild claudication	Completes treadmill exercise; AP after exercise > 50 mmHg but at least 20 mmHg lower than resting value
2	Moderate claudication	Between categories 1 and 3
3	Severe claudication	Cannot complete standard treadmill exercise, and AP after exercise is < 50 mmHg
4	Ischemic rest pain	Resting AP < 40 mmHg, flat or barely pulsatile ankle or metatarsal PVR; TP < 30 mmHg
5	Minor tissue loss – nonhealing ulcer, focal gangrene with diffuse pedal ischemia	Resting AP < 60 mmHg, ankle or metatarsal PVR flat or barely pulsatile; TP < 40 mmHg
6	Major tissue loss- extending above TM level, functional foot no longer salvageable	Same as category 5

Abbreviations: AP, ankle pressure; PVR, pulse volume recording; TM, trans metatarsal; TP, toe pressure.

Wound, Ischemia, foot infection (WIfI)

For CLTI patients these classification systems have been replaced by the WIfI classification, presented by the Society for Vascular Surgery in 2014 and used in modern practice[9].

Table 3. The WIfI classification system of PAD[26]

Component	Grade	Objective criteria		
Wound (W)	0	No ulcer (ischemic rest pain)		
	1	Small, shallow ulcer on distal leg or foot without gangrene		
	2	Deeper ulcer with exposed bone, joint or tendon ± gangrenous changes limited to toes		
	3	Extensive deep ulcer, full thickness heel ulcer ± calcaneal involvement ± extensive gangrene		
Ischemia (I)		ABI	Ankle pressure (mmHg)	Toe pressure or $TcpO_2$ (mmHg)
	0	≥ 0.8	>100	≥ 60
	1	0.60 – 0.79	70-100	40-59
	2	0.40 – 0.59	50-70	30 - 39
	3	≤ 0.39	< 50	< 30
Foot infection (fI)	0	No symtoms or signs of infection		
	1	Local infection involving only the skin/subcutaneous tissue	Infection present if ≥ 2 of the following: • Local swelling or induration • Erythema > 0.5 to ≤ 2.0 cm around ulcer • Local tenderness or pain • Local Warmth • Purulent discharge	
	2	Local infection involving deeper than skin/subcutaneous tissue		
	3	Systemic inflammatory response		

The WIfI classification system considers the extent of the foot wound, grade of ischemia, as well as potential foot infection. It can also be used to estimate the risk of amputation at 1 year in the absence of intervention, as well as the likelihood of benefit from revascularization [26].

a. Estimate risk of amputation at 1 year for each combination.

Stage 1: VL = very low, Stage 2: L = low, Stage 3: M = moderate, Stage 4: H = High.

	Ischemia – 0				Ischemia – 1				Ischemia – 2				Ischemia – 3			
W-0	VL	VL	L	M	VL	L	M	H	L	L	M	H	L	M	M	H
W-1	VL	VL	L	M	VL	L	M	H	L	M	H	H	M	M	H	H
W-2	L	L	M	H	M	M	H	H	M	H	H	H	H	H	H	H
W-3	M	M	H	H	H	H	H	H	H	H	H	H	H	H	H	H
	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3

b. Estimate likelihood of benefit of/requirement for revascularization

	Ischemia – 0				Ischemia – 1				Ischemia – 2				Ischemia – 3			
W-0	VL	VL	VL	VL	VL	L	L	M	L	L	M	M	M	H	H	H
W-1	VL	VL	VL	VL	L	M	M	M	M	H	H	H	H	H	H	H
W-2	VL	VL	VL	VL	M	M	H	H	H	H	H	H	H	H	H	H
W-3	VL	VL	VL	VL	M	M	M	H	H	H	H	H	H	H	H	H
	f-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3

Figure 5. The WIfI classification system of PAD[26]
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The Fontaine, Rutherford, and WIfI classifications are based on clinical presentation as well as measurements of hemodynamic consequences of the arterial lesion. The anatomic location and extent of these arterial lesions are graded in the Trans-Atlantic Society Consensus Document II (TASC II)[14] classification published 2007. The TASC II classification also gives recommendations on which treatment modality should be used for invasive treatment of the respective lesions (A-B; endovascular, C-D; open surgery).

Since the publication of TASC II in 2007 the endovascular technique has evolved and TASC II C-D aortoiliac lesions can be treated with endovascular technique with acceptable patency[27]. In 2019 the Global Vascular Guidelines writing group published the new Global Limb Anatomic Staging System (GLASS) classifications system for CLTI patients[9].

Table 4. The Trans-Atlantic inter-society consensus document II [14]
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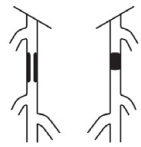
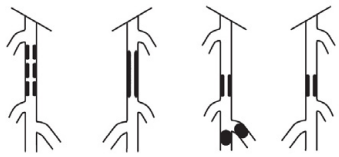
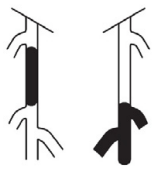
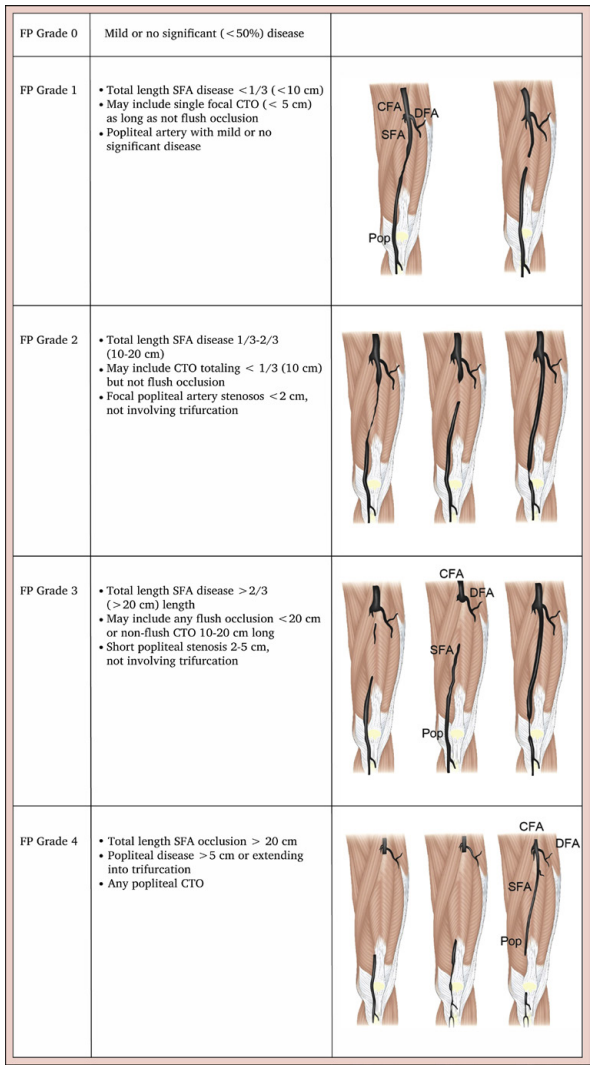
Femoropopliteal lesions TASC II a-d	
TASC A lesions • Single stenosis ≤ 10 cm in length • Single occlusion ≤ 5 cm in length	
TASC B lesions • Multiple lesions (stenoses or occlusions), each ≤ 5 cm) • Single stenosis or occlusion ≤ 15 cm not involving the infrageniculate popliteal artery • Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass • Heavily calcified occlusion of ≤ 5 cm in length • Single popliteal stenosis	
TASC C lesions • Multiple stenoses or occlusions totaling > 15 cm with or without heavy calcification • Recurrent stenoses or occlusions that need treatment after two endovascular interventions	
TASC D lesions • Chronic total occlusions of CFA or SFA (> 20 cm, involving the popliteal artery) • Chronig total occlusion of popliteal artery and proximal trifurcation vessels	

GLASS classification

The current CLTI guidelines[9] recommend the use of the WIfI and GLASS classifications together, where WIfI defines the clinical need for revascularization and GLASS stages I – III correlate with the expected immediate technical success and 1-year patency of endovascular intervention. This enables a recommendation on which revascularization modality to choose, given the patient is a candidate for both open and endovascular intervention.



Figere 7a. Femoropopliteal (FP) disease grading in Global Limb Anatomic Staging System (GLASS).

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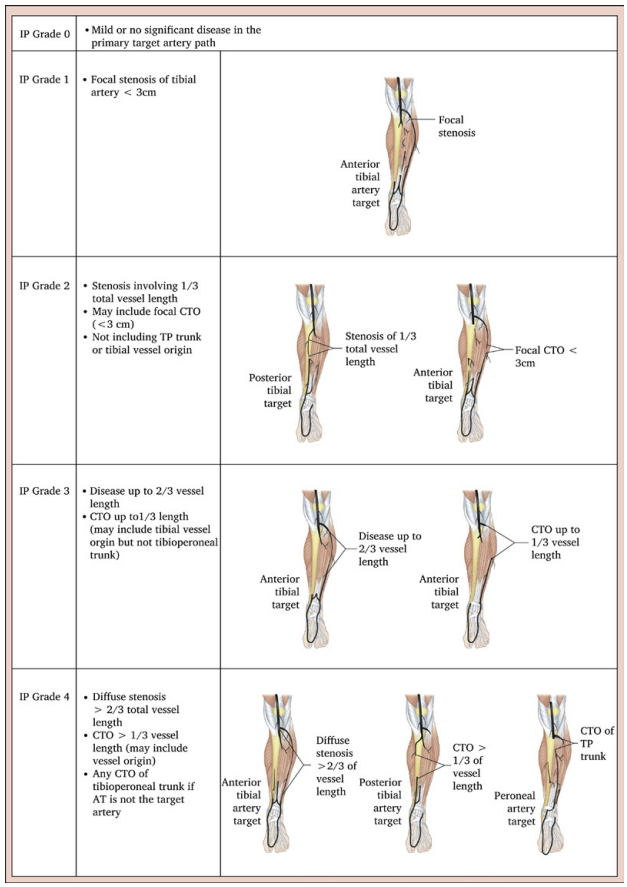

Figere 7b. Infrapopliteal (IP) disease grading in Global Limb Anatomic Staging System (GLASS).
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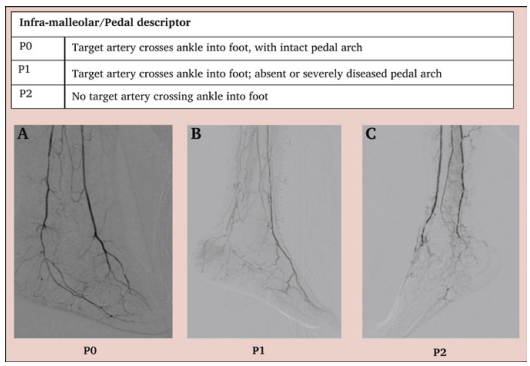
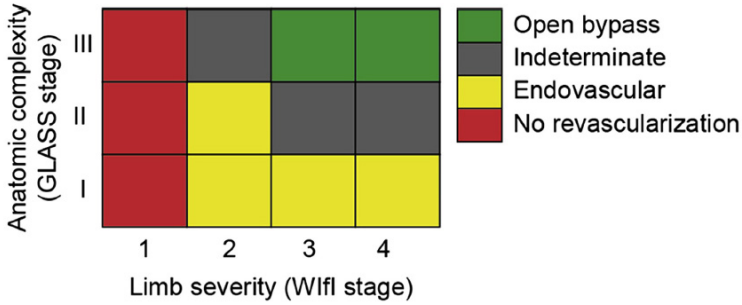


Figere 8. Inframalleolar or pedal disease grading in Global Limb Anatomic Staging System (GLASS).
The figure was reused by permission from Elsevier Inc © 2019[9].



Figere 9. Preferred initial revascularization strategy for infrainguinal disease in average risk patients with suitable autologous saphenous vein conduit for bypass.
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History of invasive treatment of PAD

History of open vascular surgery

Although studies of Egyptian mummies confirm that atherosclerosis has been prevalent for 3500 years[28], the history of surgical treatment for occlusive arterial disease is less than 100 years. Vascular surgery was mostly focused on the treatment of traumatic bleeding and aneurysmal disease by ligation or cautery by different means until 1886 when J.B Murphy performed the first femoral artery anastomosis on a patient with a gunshot wound; the damaged femoral artery was excised, and the proximal end was invaginated into the distal artery and then sutured[29]. The Frenchman Alexis Carrel established the modern technique of suturing blood vessels end-to-end with fine needles and suture material with a triangulation technique in 1902. Occlusive arterial disease did not come in focus until René Leriche described the obliteration of the terminal aorta in 1923, and described the symptoms caused by aortic occlusion which now bears his name[30]. Leriche advocated a resection of the distal aorta and common iliac arteries and a bilateral sympathectomy. The results of this procedure were not very successful. The first successful operation on PAD was a femoral thrombendarterectomy performed by the Portuguese João Cid Dos Santos in 1946. Endarterectomy of aortic occlusion was performed in 1948, and another big step forward for aortoiliac occlusive disease was made when the Frenchman Jaques Oudot performed a resection of the occluded aortoiliac section, replacing it with a homologous graft with end-to-end anastomosis in 1950[31]. The right iliac graft occluded six months later whereafter Oudot placed a crossover graft from the left to right external iliac artery creating the first extraanatomical bypass. The first long bypass of the femoral artery with a reversed saphenous vein was performed by the French surgeon Jean Kunlin in 1948[32]. The

first patient had previously had an arteriectomy of the superficial femoral artery, and exposure of the artery was difficult due to fibrotic tissue which caused Kunlin to perform an end-to-side anastomosis both proximally and distally and leaving the occluded artery. This method has since become the standard of open treatment of occlusive femoral artery disease.

History of endovascular intervention

The invention of angiography is a cornerstone of vascular surgery, serving initially as a diagnostic tool and then gradually taking over as the most common invasive treatment modality of atherosclerotic lesions. Only a few decades after Wilhem Konrad Rontgen discovered the X-rays in 1895[33], the first angiography was performed by Barney Brooks in 1923 depicting the infrainguinal arteries[34]. The first visualization of the abdominal aorta was performed by Reynaldo Cid dos Santos (the father of João Cid dos Santos) in 1929 by a trans lumbar puncture of the aorta. In April 1952 Sven-Ivar Seldinger invented the "Seldinger technique" using a needle, guidewire. and catheter to facilitate selective and catheterization of vessels[35]. Another pioneer in interventional radiology was Charles Theodore Dotter (1920-1985), who in 1964 was first to perform a percutaneous transluminal angioplasty (PTA) of a stenosis in the superficial femoral artery in an 82-year-old patient with gangrene[36]. Dotter dilated the stenosis with catheters with increasing diameters. Andreas Grüntzig (1939-1985) further developed the PTA technique in 1974, applying a catheter with an inflatable balloon at the tip to dilate a femoral artery stenosis[37] after which the first coronary artery PTA was performed in 1977. At this time another important step for the evolution of endovascular interventions was the invention of digital subtraction angiography (DSA) and angiographic "roadmap" by American physicist Charles Mistretta. These were pivotal tools for the evolution of endovascular interventions[38]. PTA of the coronary arteries gained popularity; however, shortcomings were noted as PTA could cause arterial dissection or elastic recoil causing acute occlusion of the artery. This problem was addressed with the development of stents, steel wire-mesh structures. The first coronary stent was implanted in a human by Ulrich Sigwart in 1986 [39].

The endovascular revolution

After Dotter performed the first femoral PTA in 1977 the technique was applied in selected cases only, but as data confirmed the safe application of the method the late 1980's the number of endovascular interventions in PAD patients increased significantly during the 1990's. Registrations of endovascular procedures before 1990 are sparse and comprised only 0.1 intervention per 100,000 inhabitants /year according to American data. This figure increased to approximately 5 per 100,000/year in 1995 and 58.0 per 100.000/year in 2000[40], suggesting that the

widespread use of endovascular interventions began in the late 90's. Reports on operative modality in acutely admitted PAD patients in the United States showed that 25% of patients were treated with endovascular intervention and 75% with open surgery in 1996, however, the ratio was 50/50 in 2004[41]. According to another report the proportion of endovascular interventions for PAD increased from 20% to 60%, and the proportion of bypass surgery declined from 67% to 31% between 1999 and 2007[42]. The increase in endovascular treatment was even larger for aortoiliac disease compared to for infrainguinal lesions[43]. As this increase in endovascular interventions for PAD has led some to speculate that open surgery might become obsolete in the future[44] it is relevant to clarify how the treatment incidence and the modalities used for infrainguinal arterial disease have changed during the last 15 years in Sweden.

Treatment of intermittent claudication

Patients with IC have a low risk of progression to CLTI and amputation[45, 46], but on the other hand they run a substantial cardiovascular risk[47] and have reduced health related quality of life (HRQoL)[48] compared to matched populations.

Non-invasive treatment

Cardiovascular risk reduction with BMT is the main initial treatment and the primary focus of treatment is improvement of HRQoL and not limb salvage as is the case in CLTI patients. This lowers the accepted risk of the selected treatment. The treatment options are exercise training, endovascular, or surgical revascularization. It is recommended that patients are first advised exercise training, which has a favorable risk profile compared to invasive treatments and can offer symptom relief[5]. Treatment should be offered in a stepwise manner; first exercise treatment, whereafter invasive treatment is reserved for patients who do not improve[5].

Exercise training for IC patients generally entails interval walking for 30-60 minutes at least 3 times a week for 3-6 months. Patients are recommended to walk as far as possible despite the pain. Exercise training can result in an increased nitric-oxide (NO) mediated vasodilatation and increased capillary density and improved peak oxygen uptake of the calve muscles[49].

Exercise therapies can differ, a few regimes have been scientifically evaluated. According to a Cochrane report patients receiving supervised exercise therapy (SET) had both a greater maximal and pain-free walking distance compared to home-based exercise therapy (HBET) or walking advice (WA). There was, however, no difference in HRQoL measures[50].

Invasive treatment

The decision to proceed with invasive treatment for the IC patient must be individualized. The patient should also be involved in the decision making process, as it is based on how debilitating the arterial disease is to the patient's lifestyle, and his or her willingness to accept the risks of complications associated with treatment. This varies depending on age and ambulatory status[51]; old frail individuals might accept a pain free walking distance of 50m, however a younger patient most likely will not. The treating physician must consider the patient´s individual risk profile and expected benefit, as well as the benign nature of IC regarding limb loss[52, 53].

Aorto-iliac segment

Invasive treatment of arterial lesions in the aorto-iliac segment provide symptom relief and has largely shifted to endovascular methods as stenting can provide a durable revascularization with > 90% patency after 5 years[54, 55].

Common femoral artery

Stenosis or occlusion in the CFA or deep femoral artery can cause severe claudication, and treatment has historically entailed open thrombendarterectomy (TEA). Endovascular stenting of the CFA has not been utilized because of fear of stent fractures due to motion and bending of the hip and compromise of future arterial access sites needed for potential future endovascular treatments. Recent reports have shown no difference in 30-day mortality between the methods, primary patencies of 75% and 90% after 3 years for endovascular intervention and TEA, respectively. Wound infections are, however, significantly more common following TEA operation[56].

SFA and Popliteal Artery

The SFA remains a challenging area for endovascular treatment due to forces exerted on the artery during movement causing flexion, elongation and shortening, as well as radial and rotational forces. The early trials comparing PTA and balloon-expandable stents, which do not have high flexibility to accommodate the movement of the artery, did not show a long-term benefit over PTA[57-59]. The ballon-expandable stents had a higher initial success rate; however, they were also associated with higher rates of restenosis or thrombosis at 12 to 24 months follow-up. This problem was addressed with the more flexible self-expanding nitinol (nickel-titanium) stents, which improved patency at follow-up after 12 and 24 months according to the ABSOLUTE (2007) and RESILIENT (2010) trials [60, 61]. Problems with restenosis after PTA and in-stent restenosis remain after BMS treatment. This has led to the development of drug eluting ballons (DEB) and stents (DES) which are coated with an immunomodulating drug hypothesized to decrease the restenosis rate[62]. Recent randomized trials have shown favorable results for DEB compared to PTA[63, 64] however results have not been as clearly favorable for DES

compared to BMS[65, 66]. The Swedish multicentre randomized trial (Swedepad) evaluating both DEB and DES has completed inclusion, and results are expected to be reported soon. Most of these studies included both IC and CLTI patients, however, and follow-up was focused on patency and reinterventions, and not on HRQoL. A Cochrane review on BMS compared to PTA in the SFA published in 2014 could only report compiled results of studies in the field until 12-month follow-up, and concluded that future trials should focus on quality of life[67]. Even though stents have resolved the problem of early shortcomings of PTA treatment and improved patency, there is a lack of long-term follow-up studies on quality of life.

Whether open surgical bypass or endovascular intervention should be performed for SFA, and popliteal lesions has been highly debated. Endovascular treatment has increased in use over time and longer and more complex lesions are nowadays considered for treatment[14, 68]. Three major randomized trials have been conducted comparing bypass and endovascular intervention. BASIL-1 included 452 patients between 1999-2004 in the United Kingdom, with complete follow-up at 3 years and more than 54% follow-up at 5 years[69]. The trial did not show any difference in overall survival (OS) or amputation free survival (AFS), however in patients surviving past 2 years OS was better for the bypass group (HR 0.61 95% CI 0.50 – 0.75). Since the BASIL-1 trial endovascular techniques have been further developed and the more recent BEST-CLI and BASIL-2 trials were published in 2022 and 2023 respectively[70, 71]. The BEST-CLI trial randomized 1434 patients to either bypass with single segment GSV or endovascular intervention, with follow-up of 2.7 years. Primary outcome was a composite variable consisting of major adverse limb event (MALE), defined as amputation above ankle or a major index-limb reintervention, or death, which occurred in 42.6% and 57.4% ($p < .001$) in the bypass and endovascular groups respectively. Major index-limb reinterventions were the main cause of differences between the groups. The BASIL-2 trial randomized 345 patients to either bypass or endovascular treatment with a minimum of 2-year follow-up. The primary outcome was AFS, which occurred in 63% and 53% ($p = .037$) in the bypass and endovascular groups respectively. The reason for these divergent trial results is complex and further analysis of the trials are still being published, it should also be kept in mind that these three trials were conducted on patients with CLTI and not IC patients.

Infrapopliteal arteries

Invasive therapy in the tibial arteries is not recommended in IC patients, as it has poor patency and is uncertain whether it can adequately alleviate symptoms [5].

Sex differences in PAD

Sex related differences in PAD patients are not fully clarified, as women have historically been underrepresented in studies. Only 27% of patients enrolled in PAD studies are female according to a meta-analysis[72]. Epidemiological studies have shown equal prevalences of PAD in elderly women and men[4, 73], however, women generally present with PAD symptoms 5-10 years later in life compared to men, which might be due to the protective effect of estrogen on atherosclerosis in premenopausal women[74, 75]. Women also more often present atypical IC symptoms as tiredness, unsteadiness, and a reduced walking ability. Men, on the other hand, more often report severe leg pain and cramps[76]. Women also have a higher rate of CLTI and acute presentation at the initial diagnosis of PAD[4, 77], which might be caused by both patient´s and doctor´s delay due to atypical IC symptoms preceding progression to CLTI. Furthermore, men undergo invasive treatment more often than women. In European registry studies [78], only 23-46% of patients undergoing invasive treatment for PAD were women. Women are generally older and more frequently undergo endovascular interventions compared to men [78] for unknown reasons. They might perhaps more often be deemed unfit for surgery due to their more advanced age at presentation[75], but still Swedish data indicates lower rates of cardiovascular comorbidities in women with PAD compared to men [79]. Sex differences in the location of atherosclerotic lesions might also help explain why men are more often selected for open surgery. Few studies report arterial lesions characteristics in detail, however, Ortmann et al reported higher prevalence of femoropopliteal and multilevel disease in women admitted for CLTI[80].

Health Related Quality of Life in PAD

Quality of life (QoL) is the individual's perceived quality of everyday life which is affected by different external factors like climate, economic situation, work, and social environment. Health related quality of life (HRQoL) is the assessment of the perceived individual well-being affected by the person's health or lack thereof[81]. Not only physical factors affect HRQoL, mental and social aspects are also important factors. HRQoL is generally measured using patient reported outcome reports (PROMs) usually in the form of a questionnaire[82]. These PROMs are either generic, broadly applicable to different health problems, or disease specific, focusing on the main symptoms of a disease.

The short-form (SF)-36 health survey is the most commonly used generic PROM for HRQoL measurements in PAD patients[83]. SF-36 consists of 8 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)[84, 85].

Each domain is transformed into a 0-100 scale, and a score of 0 equals maximum disability whereas a score of 100 equals no disability.

The European QoL questionnaire (EuroQol) 5 dimensions (EQ-5D) is another generic questionnaire measuring HRQoL developed by the EuroQol Research foundation commonly used in PAD research[83] comprising five domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression[86].

The Walking impairment Questionnaire in a commonly used and validated disease specific PROMS for PAD disease[87-89]. The WIQ evaluates walking ability with focus on walking distance, walking speed, and the ability to climb stairs, and correlates well with the measures on a treadmill test[90].

The Vascular quality of Life Questionnaire (VascuQol)[91] was first published in 2001 and has since then been validated[92] and was first used in the BASIL trial[93]. The VascuQol aims to assess QoL in PAD patients regardless of disease severity and takes social and mental aspects of the effect of PAD into account whereas WIQ focuses on ambulatory ability. A short version of VascuQoL has been developed[94], VacuQoL-6 which is feasible for daily clinical use and registered in the Swedish Vacular Registry (Swedvasc).

SF-36, EQ-5D and WIQ are used as primary and secondary outcome measures, respectively, in paper III which started inclusion in 2010. Prior to 2010 PTA and primary stenting in the SFA had been compared in the ABSOLUTE trial[95], which reported higher SF-36 scores in primary stented patients in the "as treated" analysis at 12 months of follow-up and the RESILIENT trial[61] reported improved SF-8[96] (short version of SF-36) at 36 months of follow-up in both groups, however, no difference between groups. Endovascular intervention and conservative treatment (including SET) had been compared in the OBACT trial[97], reporting higher scores in SF-36 domains in the intervention group at 2-year follow-up, whereas Spronk et al.[98] reported increased SF-36 and VascuQol in both groups without significant difference between groups 12 months after randomization, and Greenhalgh et al[99] reported no difference in SF-36 at 24 months follow-up.

In summary, results from trials comparing conservative treatment and endovascular intervention were different and far from conclusive in 2010. Additionally, most trials included patients with both aortoiliac and infrainguinal disease and most patients received only PTA as endovascular treatment. Furthermore, follow-up at three years was only reported in one study (36). It was therefore relevant to assess long-term HRQoL results of stent treatment of the SFA compared to conservative treatment.

Swedvasc

The Swedish National Registry for Vascular Surgery, Swedvasc, is the registry in which all vascular operations and interventions in Sweden are registered. It was founded in 1987 and has nationwide coverage since 1994 as all Swedish Vascular clinics report both inpatient and outpatient procedures. Approximately 10.000-12.000 procedures are registered in Swedvasc each year[100].

The Swedvasc registration module for peripheral arterial interventions was updated in 2013 and 2014 with considerable changes. Previously, PAD patients with lesions in the aortoiliac segment were registered in the aorta module and patients with infrainguinal lesions in the infrainguinal PAD module. From 2014 and forward all PAD interventions (except for popliteal aneurysms) are registered in a common PAD module including both supra- and infrainguinal lesions.

External validation (completeness) of the Swedvasc registry has been studied and reported in 2008 and 2015[101, 102]. The external validity of the infrainguinal module in 2008 was 93%. The 2015 validation study only included the carotid and aorta registration modules, with an external validity of 100% and 98.8% respectively. Internal validity of the registry was 93-98% in these modules. Unfortunately, no external or internal validity studies have been published regarding the new PAD module in Swedvasc.

In paper II all registered procedures in Swedvasc of infrainguinal arterial lesions in IC patients between 2009 and 2022 are reported. During this period the infrainguinal module was used between 2009 and 2013 and the PAD module between 2014 and 2022.

Perioperative limb perfusion measurements

The goal of all revascularization procedures in PAD patients is to increase limb perfusion, which in turn alleviates walking or rest pains or facilitates wound healing. In open surgery this is usually done by flow measurement of the operated artery in the surgical wound and palpation of distal pulses. More extensive perfusion measurements of the limb are usually not feasible due to the need for a sterile environment in the operating room.

Endovascular procedures are performed with the aid of DSA rendering a two-dimensional arteriogram of the main arteries and larger branches. The pre and post revascularization angiograms during the intervention are visually compared by the treating physician, evaluating patency of the occluded vessel, improved vessel diameter, flow velocity, and decreased collateral flow[103]. This comparison is subjective, and objective techniques are seldom used. Another limitation of the DSA angiogram is the difficulty of visualizing an increase in the microcirculation of the foot, which is usually the desired effect, especially in CLTI patients. Generally, only the puncture site at the femoral artery needs to be sterile during endovascular interventions, which makes it possible to attach perfusion measurement tools on the foot during the procedure.

This has led to the search for an on-table tool to evaluate the effect of endovascular interventions on the microcirculation. Preferably such a tool would give instant feedback, be dynamic, not-interfering with the procedure and correlating with clinical outcome[104]. These features could help the treating physician in decision-making during the procedure. Many techniques have been or are being evaluated for this purpose: e.g. two-dimensional (2D) perfusion angiography[105-107], near-infrared spectroscopy [108], hyperspectral imaging[109], indocyanine green angiography[110, 111], single photo emission computed tomography[112], and injection of hydrogel sensors in the skin[113].

Systolic toe pressure and $tcpO_2$ are both non-invasive methods which are validated for predicting wound healing probability [20, 21, 114] in an ambulatory setting and are used for evaluating CLTI patients need for revascularization in current clinical praxis. The feasibility of periprocedural TP and $tcpO_2$ monitoring was evaluated in paper IV of this thesis.

Figure 10.
Perioprocedural setup of $tcpO_2$ and TP in the angiography suit. Photo © Thordur Gunnarsson

Figure 11.
Perioprocedural setup of $tcpO_2$ and TP in the angiography suit. Photo © Thordur Gunnarsson

Rational of the thesis

Intermittent claudication affects approximately one in fifteen elderly individuals. A stepwise treatment approach with BMT and SET is recommended for all patients, and invasive treatment is reserved for patients with debilitating disease. The indication for intervention is based on the effect of IC on the patient's quality of life. Despite this, the main outcome in PAD studies has been patency and limb salvage and most studies have compiled results from IC and CLTI patients. Invasive treatment of IC due to infrainguinal disease is especially debated due to concerns of long-term patency. There is a paucity in long-term follow-up studies after infrainguinal interventions focusing on morbidity and HRQoL in IC patients. This is especially important as the use of endovascular interventions for treatment of PAD has increased in the last decades, as the threshold for intervention might be considered lower due to the minimally invasive nature of this technique.

Although endovascular techniques and devices are constantly evolving, an objective on-table tool is needed to aid the treating physician in assessing the result of the intervention.

Aims of the thesis

Overall aims

To evaluate how the modalities of invasive treatment of infrainguinal IC have changed in Sweden since 2009, and to report long-term outcomes as well as evaluate hemodynamic monitoring with TP and $tcpO_2$ during endovascular intervention.

Specific aims

Paper I. To assess patient morbidity in the first 8 years after invasive treatment of infrainguinal IC.

Paper II. To analyze temporal changes in incidence and modalities of invasive treatment in Swedish patients with infrainguinal IC between 2009 and 2022.

Paper III. To compare the long-term effect on HRQoL of stenting or conservative treatment of patients with IC due to SFA lesions.

Paper IV. To establish whether TP or $tcpO_2$ can be used for hemodynamic monitoring during endovascular intervention in CLTI patients.

Patients and methods

Paper I

A retrospective cohort study of 755 patients treated for infrainguinal IC in Sweden in 2009 according to Swedvasc. Data was retrieved from Swedvasc, the Inpatient Register (IPR)[115] and the Cause of Death Register[116] from January 1st, 2010, to December 31st, 2017. Information was retrieved regarding new vascular interventions on index and contralateral limbs, duration and causes of hospitalization, mortality, causes of death, and major (thigh, lower leg, ankle joint, and Syme) lower limb amputation. Diagnoses in the IPR were classified according to the ICD-system [117] based on the primary discharge or cause of death diagnosis.

Paper II

A nationwide registry study on the incidence of invasive treatment, changes in treatment modality, patient characteristics, and sex differences in patients undergoing invasive treatment of infrainguinal IC in Sweden from 2009 to 2022. Data was retrieved from three different datasets in Swedvasc from 2009-2013 (old infrainguinal module), 2014-2017 (new PAD module), and 2018-2022 (new PAD module). Registrations with simultaneous supra- and infrainguinal intervention as well as all infrainguinal interventions were included. Datasets were merged for equivalent variables, but did not include Swedish Personal Identity Numbers (PIN). Instead, patients had an individual number in each dataset. Invasive treatment was classified as either open surgery, endovascular surgery, or hybrid intervention. Open procedures were classified as either common femoral artery TEA or bypass surgery. Endovascular interventions were classified as PTA (balloon angioplasty alone without other adjunctive treatment), BMS, DES, stent graft, or DEB.

Paper III

A multicentre randimomized controlled trial conducted at seven vascular clinics in Sweden (Helsingborg, Malmö, Kristianstad, Kalmar, Växjö, Örebro, and Eskilstuna) including 100 patients with stable (i.e. > 6 months) IC (Fontaine IIb) with walking capacity < 500m caused by de novo SFA lesions (stenosis or occlusion) graded as TASC II a-c. Popliteal lesions, defined as extending 3 cm above the patella on MRA or CTA were excluded. A patent popliteal artery and at least one patent non-stenotic tibial run-off artery were required for inclusion.

Eligible participants (n=310) were screened between 2010 and 2015. Included patients were randomized on a 1:1 basis to either primary stenting or BMT. Randomization was carried out by Spenshult Research and Development Centre with sealed envelopes containing group allocations. Stratification was performed with regard to lesion length being shorter or longer than 90 mm.

Both groups received pedometers and walking advice as well as appropriate antiplatelet, lipid lowering, and anti-hypertensive medication. Smokers were actively advised to quit smoking with help from a smoke cessation unit if needed.

All patients were evaluated at the hospital outpatient clinic, one, six, 12, and 24 months after randomization. Stents in the BMS group were assessed with duplex ultrasound. Indication for reintervention were classified as clinical deterioration (IC or CLTI) or duplex finding. HRQoL questionnaires (SF-36, EQ5D, WIQ) were sent to patients one, six, 12, 24, 36, and 60 months after randomization. Medical records were reviewed after 60 months, all invasive vascular treatments and amputations were recorded. Information on time and death were retrieved from the Cause of Death Registry[116].

Primary outcomes were SF-36 and EQ5D. Secondary outcomes comprised of WIQ, reinterventions on the included vessel defined as target vessel (TV), amputation, and death.

Paper IV

A prospective, observational, single center feasibility study including CLTI patients scheduled for infrainguinal endovascular intervention between March 2018 and December 2019. Patients with contralateral foot amputation or contralateral retrograde femoral puncture were excluded, as reference values could not be obtained or affected by contralateral arterial puncture. Twenty-nine patients were included. Medical history, Rutherford, and WIfI classifications were registered for all patients. GLASS grade for FP, IP, and IM arteries were determined retrospectively using the procedure angiogram. Blood pressure, oxygen saturation,

contrast media, oxygen, and NO administration were registered. Routine ABI was measured before intervention, 24 hours after, and at follow-up scheduled 8 weeks later.

TP and $tcpO_2$ were measured using Periflux 6000 Combined (Perimed AB Stockholm, Sweden). TP was measured using laser Doppler (LD). Peri-procedural TP was recorded before arterial puncture and directly after completion angiogram. $TcpO_2$ was measured bilaterally with two heated (44° C) electrodes on the dorsum of the foot in all patients prior to arterial puncture, continuously throughout the procedure, and at clinical follow-up. Electrode placement was photo documented to ensure same placement at follow-up. The timing of the first contrast injection and all balloon dilatations or stent deployments were registered during the procedures. As the continuous measurement of $tcpO_2$ registers a value every 64 ms, an average was calculated over one minute for the predetermined measurement points to increase measurement reliability. Five-minute averages prior to the first PTA and 10-minute average after the last PTA were also calculated.

At follow-up clinical outcome was also registered, and good clinical outcome was defined as wound healing or resolution of rest pain. All angiograms were analyzed by a senior vascular interventionist blinded to the $tcpO_2$ and TP results.

Statistical analysis

Continuous variables are presented as mean and standard deviation (SD) or median and interquartile range (IQR), depending on normal distribution assessed by a Shapiro-Wilk test. Independent samples t-test were used for comparison of normally distributed continuous variables (papers I - III). Paired t-test was used for intragroup comparison in paper III. Wilcoxon signed ranked test was used for comparing data lacking normal distributed (paper IV). Categorical variables are presented as numbers and percentage and statistical comparison calculated with chi-square test (papers I-III). P values were adjusted for multiple comparisons using the Bonferroni method (paper IV).

Power calculations were made with the PS Power and Sample Size program. In paper III, sample size was determined to study a clinically relevant difference between the two groups regarding the primary outcome variable (HRQoL). A clinically relevant difference in SD-36 score is 10 points. With a significance level of 5%, power of 80%, and 10% loss to follow-up or crossover during a 24-month period, the required sample size was 50 patients in each group. Differences between groups in paper III were analyzed using the intention to treat principle (ITT). In paper IV, a sample size of at least 15 patients was determined to detect a difference of 10 mmHg in $tcpO_2$ between measurements with a power of 80% assuming a SD

od 5 mmHg, with a significance of 5%. Sample size calculation was prospective and assumed normally distributed data, however the data were not normally distributed.

Amputation-free survival was assessed by the Kaplan-Meier survival analysis of time-to-event (first amputation or death) (paper I). Temporal changes during the study period in paper II were analysed with a linear regression model. Sex dependent odds ratio (OR) was calculated for each invasive treatment modality with a crude and a multivariate logistic regression model.

Calculations were performed using SPSS 18.0-28.0 (SpSS Inc. Chicago, IL, USA).

Ethics

As with all clinical studies, ethical aspects must be considered, and all studies were performed in accordance with the Declaration of Helsinki[118] and the guidelines for conduct of clinical investigation. Written consent was obtained from all patients in papers III and IV.

Paper I. The study was approved by the Ethics Committee at Lund University (2010/549 and 2017/1027). The Board of Health and Welfare only allowed analysis of data on hospitalization diagnoses, death, and causes of death on group level.

Paper II. The study was approved by the Ethics Committee at Lund University (2017/1027), and an extended data extraction was approved by the Swedish Ethical Review Authority (2022-06973-02).

Paper III. The study was approved by the Ethics Committee of Lund University (2009/478, 2013/822, and 2019/02641) and by the Swedish Ethical Review Authority (2021-01344). The study including prospective follow-up was registered in the ClinicalTrials.gov database (NCT01230229).

Paper IV. The study was approved by the Ethics Committee of Lund University (2016/924).

Results

Paper I

During the 8-year following invasive treatment of infrainguinal IC the 775 patients underwent 486 new vascular interventions, 246 on the index limb and 240 on the contralateral limb. Of the new vascular interventions 239 were due to IC and 226 to CLTI. The yearly incidence of a new vascular intervention was between 7 and 14% during the different years.

Patients in the cohort were admitted to hospital on 4662 different occasions, spending a total of 25,970 days in hospital. The annual need for hospitalization was 79-99% for surviving patients. The most common causes of hospitalization were CVD, CAD, and other diseases of the circulatory system, causing 47.5% of hospitalizations.

Major amputation was performed in 2.7%, 3.9%, and 6.7% after 3, 5, and 8 years respectively.

The cumulative mortality was 10.2%, 20.0%, and 40.1% after 3, 5, and 8 years respectively. CVD, CAD and other disorders of the circulatory system was the of death in 42.4% of patients and neoplasms 22.3% of patients.

Table 5. New vascular interventions and hospitalization during eight years (2010-2017) of follow-up in 775 Swedish patients after invasive infrainguinal treatment of intermittent claudication in 2009. Table 5 is a revised version of table 2 in paper II, with correction of percentages.

Year	Patients alive (n)	New vascular interventions (n [%])		New vascular intervention CLTI (n [%])	New vascular intervention IC (n [%])	New vascular interventions Indication not known (n [%])	Patients hospitalized (n [%])	Hospital days (n)	Hospital days per patient (median[range])
		Patients	Interventions						
2010	764	95 (12)	108 (14)	31 (4)	63 (8)	14 (2)	755 (99)	4196	3.0 (0-80)
2011	736	63 (9)	80 (11)	30 (4)	46 (6)	4 (1)	684 (93)	3830	3.5 (0-62)
2012	696	44 (6)	52 (7)	21 (3)	30 (4)	1 (0.1)	553 (79)	2900	3.0 (0-56)
2013	661	46 (7)	50 (8)	23 (4)	25 (4)	2 (0.3)	619 (94)	3475	3.0 (0–76)
2014	620	33 (5)	43 (7)	25 (4)	18 (3)	-	615 (99)	3392	3.0 (0-48)
2015	542	39 (7)	47 (9)	25 (5)	22 (4)	-	530 (98)	2932	3.0 (0-44)
2016	504	42 (8)	58 (12)	36 (7)	22 (4)	-	468 (93)	2446	3.0 (0-65)
2017	464	33 (7)	48 (10)	35 (8)	13 (3)	-	438 (94)	2799	4.0 (0-74)

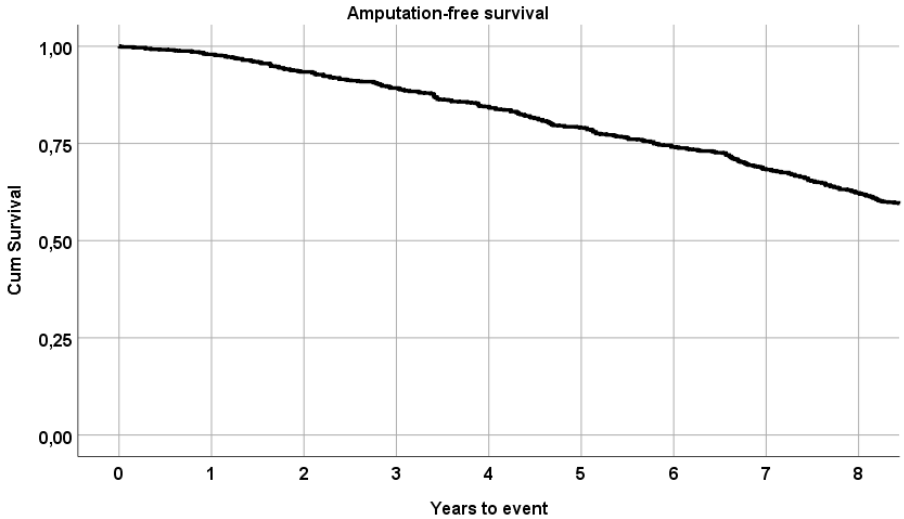

Figure 12.
Amputation free survival during eight years (2010-2017) of follow-up in 775 Swedish patients after invasive infrainguinal treatment of intermittent claudication in 2009.

Paper II

Incidence of invasive interventions 2009-2022

Between 2009-2022 a total of 13,322 invasive treatments were registered in 10,829 patients with IC due to infrainguinal lesions. The time trend for the yearly incidence of all invasive treatments did not show any statistical significance between 2009-2022, $p = 0.21$. The incidence of primary interventions was, however, 8.7 per 100,000 inhabitants in 2014 and decreased to 5.8 per 100,000 inhabitants in 2022, $p < .001$.

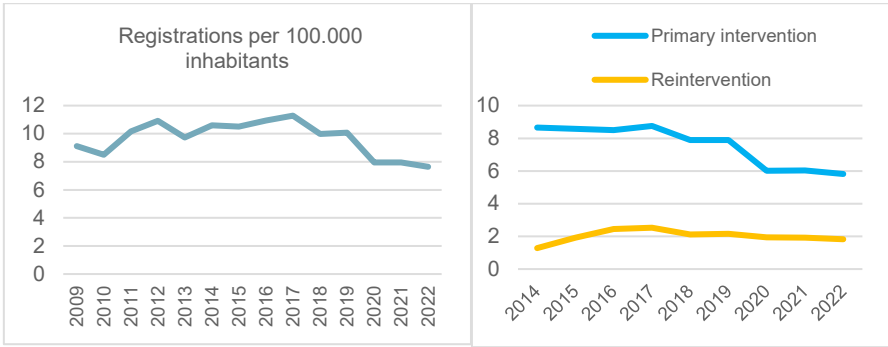

Figure 13. Registered infrainguinal interventions in Swedvasc 2009-2022 on patients treated for infrainguinal CI.

The observed dip in interventions between 2020 and 2022 due to the COVID pandemic led us to perform a sensitivity analysis excluding 2020-2022. There was a trend towards an increase in intervention incidence, p = .089, however, there was still a trend towards decreasing incidence of primary interventions, p = .069. The incidence of reinterventions was 1.3 per 100,000 inhabitants in 2014, and 1.8 per 100,000 inhabitants in 2022, p = .801 and p = .205 when excluding the COVID years 2020-2022 from the analysis.

Patient characteristics and risk factors 2009-2022

Comparison of the first and last study periods 2009-2013 and 2018-2022 revealed an increase in mean patient age from 71.6 (SD 9.5) years to 73.4 (SD 8.2) years, p < .001. The proportions of patients with hypertension increased from 74.3% to 86.5%, p < .001 and the proportion with diabetes increased from 26.9% to 34.0%, p < .001. The proportion of current smokers decreased from 12.7% to 8.6%, p < .001, whereas the proportion of invasively treated women increased significantly from 39.8% in 2009 to 43.4% in 2022, p = .033.

Table 6. Characteristics and risk factors for patients treated invasively for intermittent claudication due to infrainguinal arterial lesions according to the Swedvasc registry between 2009-2022. Comparing

	2009-2013		2018-2022	
	Mean/N	**SD/%**	**Mean/N**	**SD/%**
Patients	3789		3581	
Age (years)	71.6	9.5	73.4	8.2
Female	1589	41.9	1574	44.0
Hypertension	2815	74.3	3099	86.5
Diabetes	1018	26.9	1218	34.0
CKD	NA		436	12.3
Smoker	481	12.7	308	8.6
Prior smoking	2125	56.1	2469	68.7
Never smoked	574	15.2	513	14.3
Pulmonary disease	421	11.1	570	15.9
Cardiac risk	1244	32.8	1506	42.1
Prior CVI	346	9.1	359	10.0
ABI	0.58	0.23	0.62	0.26

CKD = chronic kidney disease, CVI = cerebrovascular incidence, ABI = ankle brachial index.

Invasive treatment modalities

The proportion of open surgery decreased from 38.1% in 2009 to 23.4% in 2022, $p < .001$. Endovascular and hybrid interventions increased from 56.9% to 69.7%, $p < .001$, and 4.8% to 7.0%, $p < .001$, respectively during the study period. The decrease in open surgery was due to the reduction in the proportion of bypass surgery, which decreased from 18.8% to 4.0%, $p < .001$.

Out of 587 bypasses 95 (8.0%) were distal, defined as distal anastomosis below the popliteal artery. Seventy percent (n = 66) of these were performed during the first half of the study period. The proportions of CFA TEA remained unchanged during the study period, 25.6% and 25.9% in 2009 and 2022 respectively, $p = .236$. Analysis of the different endovascular treatment modalities showed that the proportion of PTA decreased from 39.7% to 24.4%, $p = .003$, and BMS treatment increased from 16.9% to 35.9%, $p < .001$. DEB treatment was not registered in Swedvasc during 2009-2013 but comprised 6.1% of the interventions in 2014 and 11.1% in 2022, $p = .915$.

Table 7. Invasive treatment modalities registered in Swedvasc for patients treated for intermittent claudication due to infrainguinal arterial lesions during 2009 - 2022.

Operative modality N(%)	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
N	**852**	**800**	**964**	**1044**	**938**	**1033**	**1034**	**1093**	**1142**	**1020**	**1039**	**826**	**831**	**804**
Open surgery	325 (38.1)	291 (36.4)	310 (32.2)	337 (32.3)	322 (34.3)	285 (27.6)	287 (27.8)	315 (28.8)	296 (25.9)	282 (27.6)	270 (26.0)	190 (23.0)	187 (22.5)	188 (23.4)
Endovascular	485 (56.9)	477 (59.6)	615 (63.8)	672 (64.4)	562 (59.9)	689 (66.7)	689 (66.6)	716 (65.5)	778 (68.1)	679 (66.6)	683 (65.7)	574 (69.5)	588 (70.8)	560 (69.7)
Hybrid intervention	41 (4.8)	32 (4.0)	39 (4.0)	35 (3.4)	54 (5.8)	59 (5.7)	57 (5.5)	61 (5.6)	66 (5.8)	55 (5.4)	86 (8.3)	62 (7.5)	56 (6.7)	56 (7.0)
TEA	218 (25.6)	235 (29.4)	249 (25.8)	286 (27.4)	275 (29.3)	317 (30.7)	247 (23.9)	299 (27.4)	277(24.3)	277 (27.2)	293 (28.2)	205 (24.8)	205 (24.7)	208 (25.9)
Bypass	160 (18.8)	113 (14.1)	106 (11.0)	97 (9.3)	105 (11.2)	80 (7.7)	98 (9.5)	99 (9.1)	83 (7.3)	64 (6.3)	72 (6.9)	49 (5.9)	37 (4.5)	32 (4.0)
PTA	338 (39.7)	288 (36.0)	337 (35.0)	359 (34.4)	312 (33.3)	326 (34.8)	275 (26.6)	219 (20.0)	226 (19.8)	206 (20.2)	322 (31.0)	246 (29.8)	189 (22.7)	196 (24.4)
DEB	NA	NA	NA	NA	NA	63 (6.1)	120 (11.6)	154 (14.1)	167 (14.6)	140 (13.7)	30 (2.9)	62 (7.5)	100 (12.0)	89 (11.1)
BMS	144 (16.9)	155 (19.4)	255 (26.5)	264 (25.3)	214 (22.8)	317 (30.7)	322 (31.1)	337 (30.8)	359 (31.4)	323 (31.7)	317 (30.5)	244 (29.5)	296 (35.6)	289 (35.9)
DES	0 (0.0)	1 (0.1)	6 (0.6)	10 (1.0)	9 (1.0)	6 (0.6)	20 (1.9)	30 (2.7)	34 (3.0)	24 (2.4)	7 (0.7)	9 (1.1)	15 (1.8)	21 (2.6)
Stentgraft	17 (2.0)	32 (4.0)	34 (3.5)	42 (4.0)	28 (3.0)	28 (2.7)	21 (2.0)	36 (3.3)	25 (2.2)	42 (4.1)	39 (3.8)	38 (4.6)	33 (4.0)	32 (4.0)
Reintervention	NA	NA	NA	NA	NA	125 (12.3)	189 (18.3)	244 (22.3)	256 (22.4)	216 (21.2)	223 (21.5)	201 (24.3)	201 (24.2)	192 (23.9)

TEA = thrombendarterectomy of the common femoral artery, Bypass = bypass operation, PTA = percutaneous transluminal angioplasty alone with no other endovascular adjunctive technique, DEB = drug-eluting balloon angioplasty, BMS = bare metal stent, DES = drug-eluting stent.

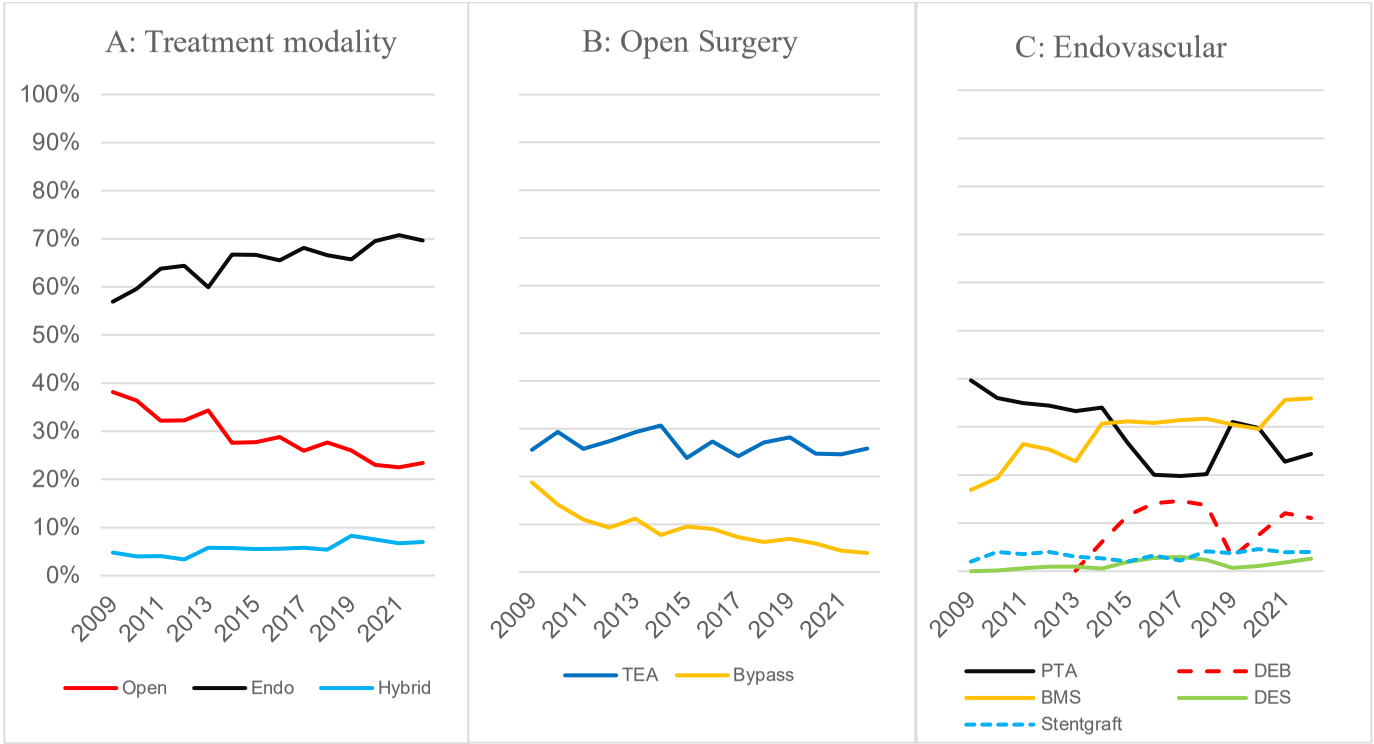

Figure 14. Invasive treatment modalities registered in Swedvasc for patients treated for intermittent claudication due to infrainguinal arterial lesions during 2009 - 2022.

Sex differences

A total of 5690 (42.7%) invasive treatments were performed on women during the study period. Women were significantly older, more commonly had a pulmonary disease, lower ABI, and a higher Rutherford classification at presentation compared to men. However, a higher proportion of men had diabetes, CKD, and cardiac disease. Men also more frequently received statin and anticoagulation treatment, whereas no difference in antiplatelet treatment therapy was noticed between sexes.

Open surgery was more often performed in men compared to women during the study period, 32.5% vs 24.0%, $p < .001$. CFA TEA was more often performed in men compared to women, 29.9% vs 21.7%, $p < .001$.

Endovascular treatment was significantly more often applied in women compared to men during the study period, 70.7% vs 61.6%, $p < .001$. PTA, on the other hand, was more frequently applied in women compared to men 32.2% vs 25.1%, $p < .001$. No sex differences were seen regarding the use of DEB, BMS, DES, or stent grafts. Significantly more interventions were registered as reinterventions in women compared to men, 22.3% and 20.2% respectively, $p = .018$.

Adjusting for all risk factors with significant differences, men were more likely to undergo open surgery, OR = 1.61 (95% CI 1.44 – 1.79), but less likely to undergo endovascular treatment OR = 0.62 (95% CI 0.56 – 0.69) and reintervention, OR = 0.77 (95% CI 0.68 – 0.87) than women.

Table 8. Characteristics and risk factors for patients treated invasively for intermittent claudication due to infrainguinal arterial lesions according to the Swedvasc registry between 2009-2022.

	Female	Male	P value
	N (%)	N (%)	
Procedures (N)	5690	7632	
Age (years)	73.48 (8.8)	71.23 (8.86)	<.001
Hypertension	4581 (80.5)	6191 (81.2)	.256
Diabetes	1422 (25.0)	2698 (35.4)	<.001
CKD*	366 (9.7)	619 (12.6)	<.001
Smoker	529 (9.3)	782 (10.3)	.0812
Prior smoking	3384 (59.5)	5109 (67.0)	<.001
Never smoked	1150 (20.2)	825 (10.8)	<.001
Pulmonary dis	874 (15.4)	895 (10.8)	<.001
Cardiac risk	1676 (29.5)	3354 (44.0)	<.001
Prior CVI	525 (9.2)	794 (10.4)	.072
ABI	0.58 (0.23)	0.62 (0.27)	<.001
Rutherford I	178 (4.7)	307 (6.2)	.002
Rutherford II	1147 (30.2)	1552 (31.3)	.292
Rutherford III	2471 (65.1)	3105 (62.6)	.014
Open Surgery	1367 (24.0)	2478 (32.5)	<.001
Endovascular	4020 (70.7)	4699 (61.6)	<.001
Hybrid operation	302 (5.3)	451 (5.9)	.137
TEA	1237 (21.7)	2280 (29.9)	<.001
Bypass	475 (8.3)	707 (9.3)	.066
PTA	1834 (32.2)	1911 (25.0)	<.001
DEB*	428 (11.3)	497 (10.0)	.057
BMS	1640 (28.8)	2183 (28.6)	.782
DES	79 (1.4)	111 (1.5)	.752
Stentgraft	196 (3.4)	246 (3.2)	.480
Reintervention*	845 (22.3)	1002 (20.2)	.018

CKD = chronic kidney disease, CVI = cerebrovascular incidence, ABI = ankle brachial index, TEA = thrombendarterectomy of the common femoral artery, Bypass = bypass operation, PTA = percutaneous transluminal angioplasty alone with no other endovascular adjunctive technique, DEB = drug-eluting balloon angioplasty, BMS = bare metal stent, DES = drug-eluting stent..* = data available between 2014-2022

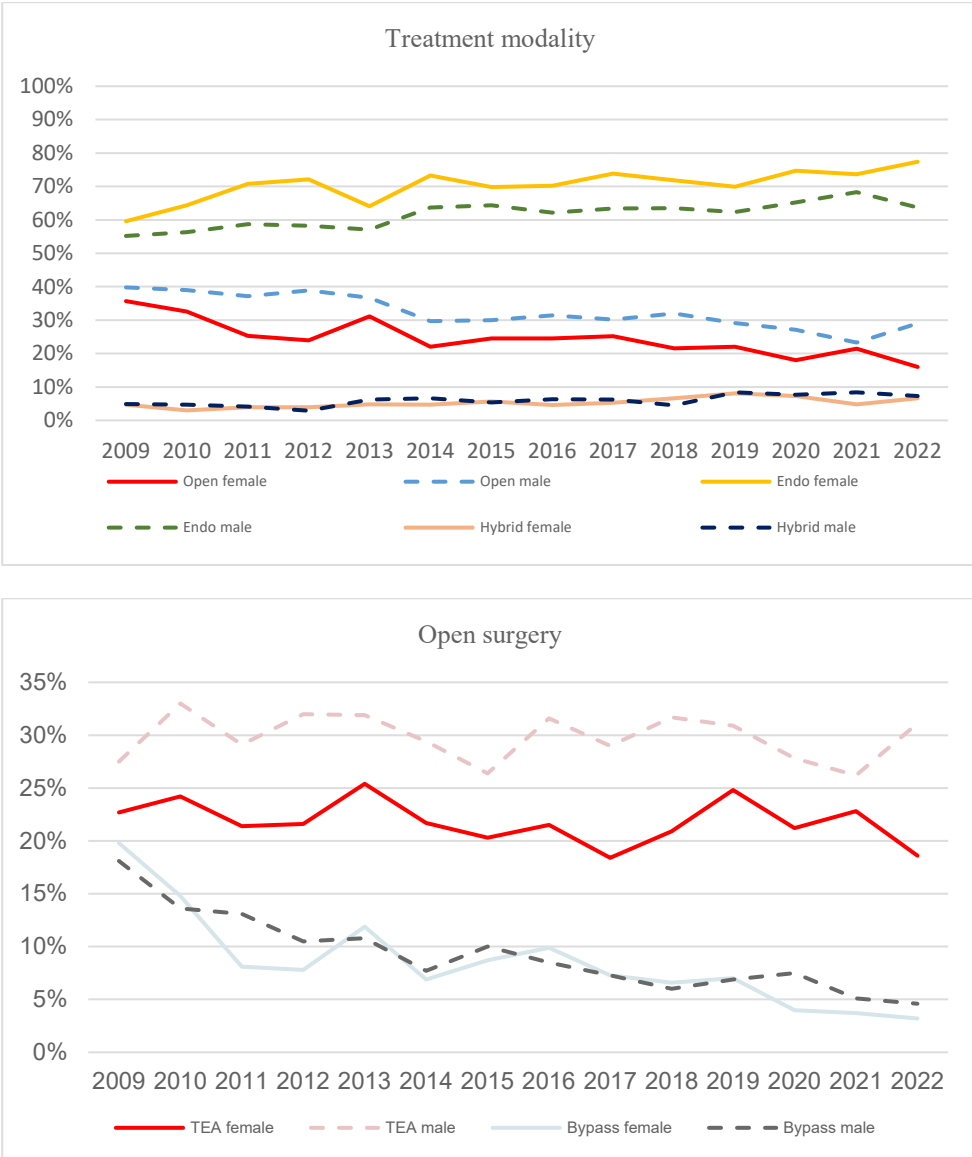

Figure 15. Sex differences in invasive treatment modalities registered in Swedvasc for patients treated for intermittent claudication due to infrainguinal arterial lesions during 2009 – 2022.

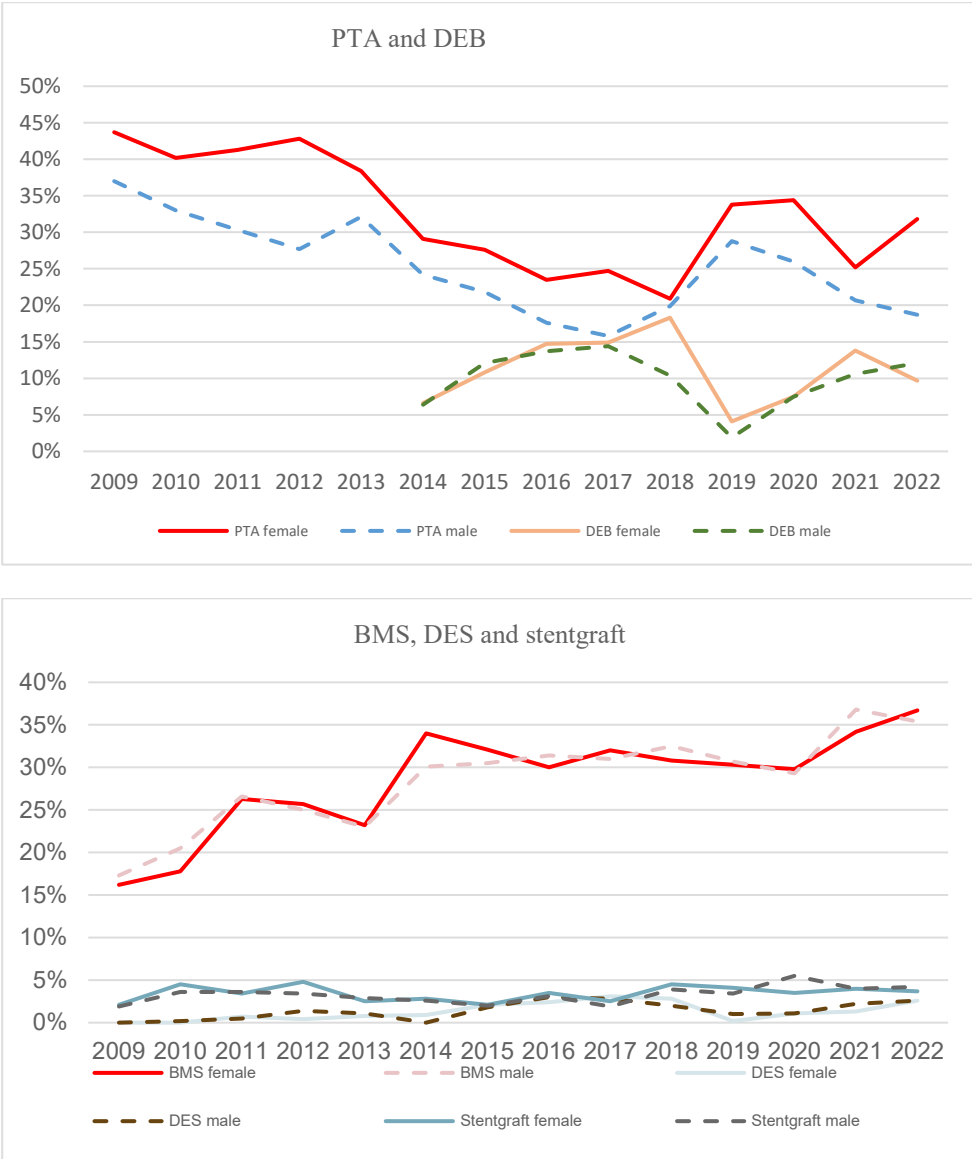

Figure 16. Sex differences in invasive treatment modalities registered in Swedvasc for patients treated for intermittent claudication due to infrainguinal arterial lesions during 2009 – 2022.

Table 9. Invasive treatment modalities registered in Swedvasc for patients treated for intermittent claudication due to infrainguinal arterial lesions between 2009 and 2022. Results of logistic regression analyses on the effect of male sex on operative modality.

Operative modality	Odds Ratio [95% CI] crude analysis	p value	Odds Ratio [95% CI] multivariate analysis	p value
	N = 13322		N = 7712	
Open surgery	1.47 [1.36 – 1.59]	<.001	1.61 [1.44 – 1.79]	<.001
Endovascular	0.69 [0.64 – 0.74]	<.001	0.62 [0.56 – 0.69]	<.001
Hybrid operation	1.10 [0.95 – 1.29]	.197	1.19 [0.98 – 1.44]	.075
TEA	1.56 [1.44 – 1.69]	<.001	1.64 [1.47 – 1.83]	<.001
Bypass	1.02 [0.91 – 1.16]	.706	1.20 [1.00 – 1.45]	.051
PTA	0.71 [0.66 – 0.77]	<.001	0.61 [0.54 – 0.68]	<.001
DEB	0.87 [0.76 – 1.00]	.056	0.76 [0.65 – 0.89]	<.001
BMS	1.01 [0.94 – 1.09]	.795	1.06 [0.96 – 1.17]	.273
DES	1.02 [0.76 – 1.36]	.908	0.90 [0.72 – 1.45]	.898
Stentgraft	0.92 [0.76 – 1.11]	.390	0.87 [0.75 – 1.27]	.867
Reintervention	0.87 [0.78 – 0.96]	.008	0.77 [0.68 – 0.87]	<.001

Crude analysis = logistic regression model adjusting for sex and age. Multivariate analysis = logistic regression model adjusting for all confounders with significant sex differences, TEA = thrombendarterectomy of the common femoral artery, Bypass = bypass operation, PTA = percutaneous transluminal angioplasty alone with no other endovascular adjunctive technique, DEB = drug-eluting balloon angioplasty, BMS = bare metal stent, DES = drug-eluting stent.

Paper III

Forty-eight patients were randomized to the stent group and 52 to the control group. HRQoL questionnaires were answered at both 36 and 60 months by 63 patients. Twenty-five patients did not return the questionnaires, and 12 patients died during 60-month follow-up. Relevant hospital files were reviewed for all randomized patients.

During follow-up 14 patients in the control group underwent stent treatment of the included SFA lesion, after a median of 19 (IQR 13-41) months from randomization.

Baseline patient characteristics, HRQoL, and risk factors did not differ between groups, except that lesions were longer in the stent group.

Table 10. Baseline demographic data and lesion characteristics in 100 patients with intermittent claudication randomized to primary stenting or best medical treatment only (control group). Mean (SD) or n (%). The table is a modified version of previously published trial results, Lindgren et al[119]

	Stent (n=45)	Control (n=49)	P value
Age (years)	71.3 (5.3)	69.8 (5.8)	.184
Sex			
Male	22	28	.540
Female	23	21	
ABI	0.58 (.12)	0.63 (.17)	.129
Walking distance (m)	178 (87.3)	210 (107.4)	.114
Duration of IC (months)	30 (29.3)	41 (48.3)	.179
Lesion length (mm)	145 (91)	103 (97)	.021
Occlusion (n)	31	36	.654
Stenosis (n)	14	13	NS
Degree of stenosis (%)	81.7 (16.3)	91.5 (3.1)	.065
No crural vessels (n)	2.5 (0.6)	2.3 (0.7)	.219

ABI = ankle brachial index, IC = intermittent claudication.

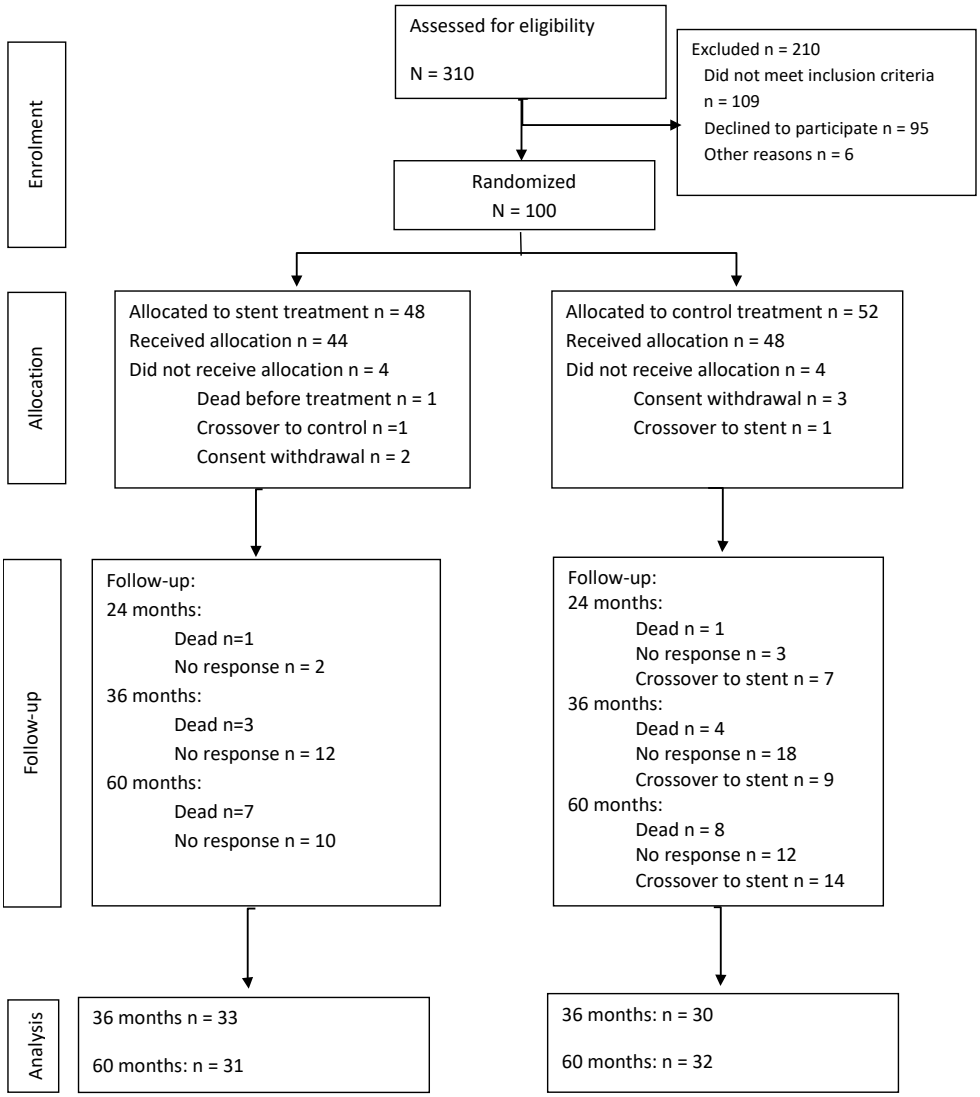

Figure 17. Study Consort diagram. Death and crossover to stent are presented as cumulative numbers during the study period.

Primary outcome at 36 and 60 months

Intergroup comparison at 36 months showed significantly better scores in SF-36 RP, p = .023 and PCS, p = .032, in the stent group compared with the control group. SF-36 scores in other domains did not differ significantly between groups at 36 months. After 60 months, there was no longer any significant difference between groups in SF-36 score. EQ5D showed no significant difference between groups after 36, p = .52 or 60 months, p = .051.

Intragroup comparison at 36 months showed significantly improved scores in the stent group in SF-36 domains PF, p = .012, RP, p = .013, BP, p = .007, and PCS, p = .016. SF-36 scores in domain BP were still significantly improved in the stent group (p = .044) at 60 months. No SF-36 domain or EQ5D were significantly improved in the control group at 36 and 60 months.

Secondary outcome at 36 and 60 months

WIQ scores were significantly better in the stent group compared to the control group after 36 months, p = .029, but not after 60 months, p = .40. After 36 months the intragroup comparison showed improved WIQ scores in the stent group, p = .007, but not in the control group, p = .097. After 60 months intragroup comparison showed significant improvement in both the stent, p = .024, and the control group, p = .005.

Seventeen reinterventions were performed on the included SFA in the stent group 17 (eight due to worsening IC, two had progression to CLTI, and seven had significant restenosis). Six reinterventions were performed in the 14 patients in the control group that underwent stenting during the study period, 10 due to disabling IC and 4 due to progression to CLTI.

Two patients underwent major amputation, one in each group. Five-year mortality was 14.6% and 15.4% (p = .99) in the stent and control group, respectively. The most common cause of death was ischemic heart disease, and no deaths were related to TV reinterventions.

Table 11. Baseline, 36- and 60-month levels of primary (SF-36 and EQ5D) and secondary (WIQ) outcome variables in 100 patients with intermittent claudication randomized to primary stenting or best medical treatment only. Mean (SD), p-values comparing groups.

	Baseline			36 mo			60 mo		
	Stent (n = 45)	Control (n = 49)	p	Stent (n = 33)	Control (n = 30*)	p	Stent (n = 31)	Control (n = 32*)	P
PF	43 (17)	43 (17)	.972	60 (23)	48 (24)	.065	52 (26)	54 (26)	.730
RP	41 (39)	43 (41)	.731	62 (40)	38 (38)	.023	38 (40)	44 (42)	.570
BP	40 (17)	38 (17)	.734	55 (26)	48 (23)	.258	51 (25)	49 (27)	.702
GH	54 (17)	52 (20)	.867	59 (22)	51 (20)	.166	55 (23)	50 (25)	.411
VT	49 (22)	50 (23)	.686	58 (25)	51 (25)	.253	56 (22)	51 (25)	.432
SF	74 (23)	72 (30)	.648	83 (23)	81 (26)	.859	76 (25)	73 (26)	.723
RE	54 (44)	58 (44)	.801	70 (36)	52 (47)	.096	52 (45)	58 (45)	.574
MH	72 (21)	72 (24)	.861	79 (20)	75 (25)	.503	78 (20)	73 (21)	.421
PCS	31 (8)	31 (7)	.912	38 (11)	33 (8)	.032	34 (11)	32 (11)	.961
MCS	48 (12)	49 (14)	.646	50 (10)	49 (13)	.691	48 (12)	47 (12)	.747
EQ5D	0.56 (0.27)	0.46 (0.31)	.121	0.63 (0.27)	0.58 (0.31)	.523	0.64 (0.23)	0.59 (0.32)	.508
WIQ	40 (18)	35 (18)	.175	62 (27)	46 (27)	.029	56 (27)	50 (24)	.404

PF = Physical Function, RP = Role Physical, BP = Bodily Pain, GH = General Health, VT = Vitality, SF = Social Function, RE = Role Emotional, MH = Mental Health, PCS = Physical Component Summary, MCS = Mental Component Summary, WIQ = walking impairment questionnaire. * At the 36 and 60 month follow ups, six and eight patients, respectively, in the control group had undergone stenting of the included target vessel.

Table 12. Intragroup comparison of mean change in primary (SF-36 and EQ5D) and secondary (WIQ) outcome variables in 100 patients with intermittent claudication randomized to primary stenting or best medical treatment only after 36- and 60-months. P-values compared to baseline. SF-36 domains with non-significant results are not reported in the table.

	Stent group 0 vs 36 mo (n = 33)		Control group 0 vs 36 mo (n = 30*)		Stent group 0 vs 60 mo (n = 31)		Control group 0 vs 60 mo (n = 32*)	
	Mean change (95% CI)	P	Mean change (95% CI)	P	Mean change (95% CI)	P	Mean change (95% CI)	P
PF	11.1 (2.7- 19.5)	.012	1.6 (-7.1 - 10.4)	.704	6.9 (-1.7 – 15.4)	.112	7.3 (-1.7 – 16.3)	.110
RP	13.7 (3.2 - 24.3)	.013	-9.5 (-24.8 - 5.8)	.216	-4.6 (-18.6 – 9.3)	.503	1.1 (-12.4 – 14.7)	.868
BP	13.0 (3.7 - 22.3)	.007	6.6 (-2.4 - 15.6)	.145	10.2 (0.3 – 20.0)	.044	8.7 (-0.9 – 18.2)	.074
PCS	4.1 (0.8 - 7.4)	.016	-0.7 (-3.7 - 2.3)	.654	1.0 (-3.0 – 5.1)	.609	2.3 (-1.6 – 6.2)	.236
MCS	1.2 (-3.5 - 5.9)	.604	0.36 (-4.2 - 4.9)	.871	0.1 (-5.6 – 5.8)	.977	-1.5 (-6.0 – 3.0)	.505
EQ5D	0.05 (-0.07 - 0.16)	.396	0.10 (-0.03 - 0.23)	.114	0.07 (-0.06 – 0.20)	.265	0.11 (-0.0.1 – 0.23)	.780
WIQ	15.2 (4.5 - 25.9)	.007	7.9 (-1.5 - 17.4)	.097	13.5 (1.9 – 25.2)	.025	13.3 (4.7 – 22.2)	.005

PF = Physical Function, RP = Role Physical, BP = Bodily Pain, GH = General Health, VT = Vitality, SF = Social Function, RE = Role Emotional, MH = Mental Health, PCS = Physical Component Summary, MCS = Mental Component Summary, WIQ = walking impairment questionnaire. * At the 36 and 60 month follow ups, six and eight patients, respectively, in the control group had undergone stenting of the included target vessel.

Table 13. Results of sensitivity analysis, excluding crossover patients from control group after 36 and 60 months are presented in the table. Mean (SD), p-values comparing groups.

	36 months excl. crossover			60 months excl. crossover		
	Stent (n=33)	Control (n=25)	P	Stent (n = 31)	Control (n = 24)	P
PF	60 (23)	46 (23)	.024	52 (26)	49 (26)	.742
RP	62 (41)	36 (38)	.018	38 (40)	44 (42)	.609
BP	55 (27)	44 (20)	.099	51 (25)	46 (26)	.452
GH	59 (22)	50 (20)	.059	55 (23)	50 (24)	.447
VT	58 (25)	50 (25)	.106	56 (22)	51 (23)	.462
SF	83 (23)	80 (26)	.376	76 (25)	70 (26)	.437
RE	70 (36)	48 (46)	.025	52 (45)	56 (46)	.696
MH	79 (20)	74 (26)	.187	78 (21)	73 (21)	.202
PCS	38 (11)	32 (8)	.014	34 (11)	33 (11)	.362
MCS	50 (10)	49 (13)	.322	48 (12)	47 (13)	.325
EQ5D	.63 (.27)	.55(.32)	.159	.64 (.23)	.61 (.27)	.349
WIQ	62 (27)	42 (22)	.003	56 (27)	47 (23)	.111

PF = Physical Function, RP = Role Physical, BP = Bodily Pain, GH = General Health, VT = Vitality, SF = Social Function, RE = Role Emotional, MH = Mental Health, PCS = Physical Component Summary, MCS = Mental Component Summary, WIQ = walking impairment questionnaire.

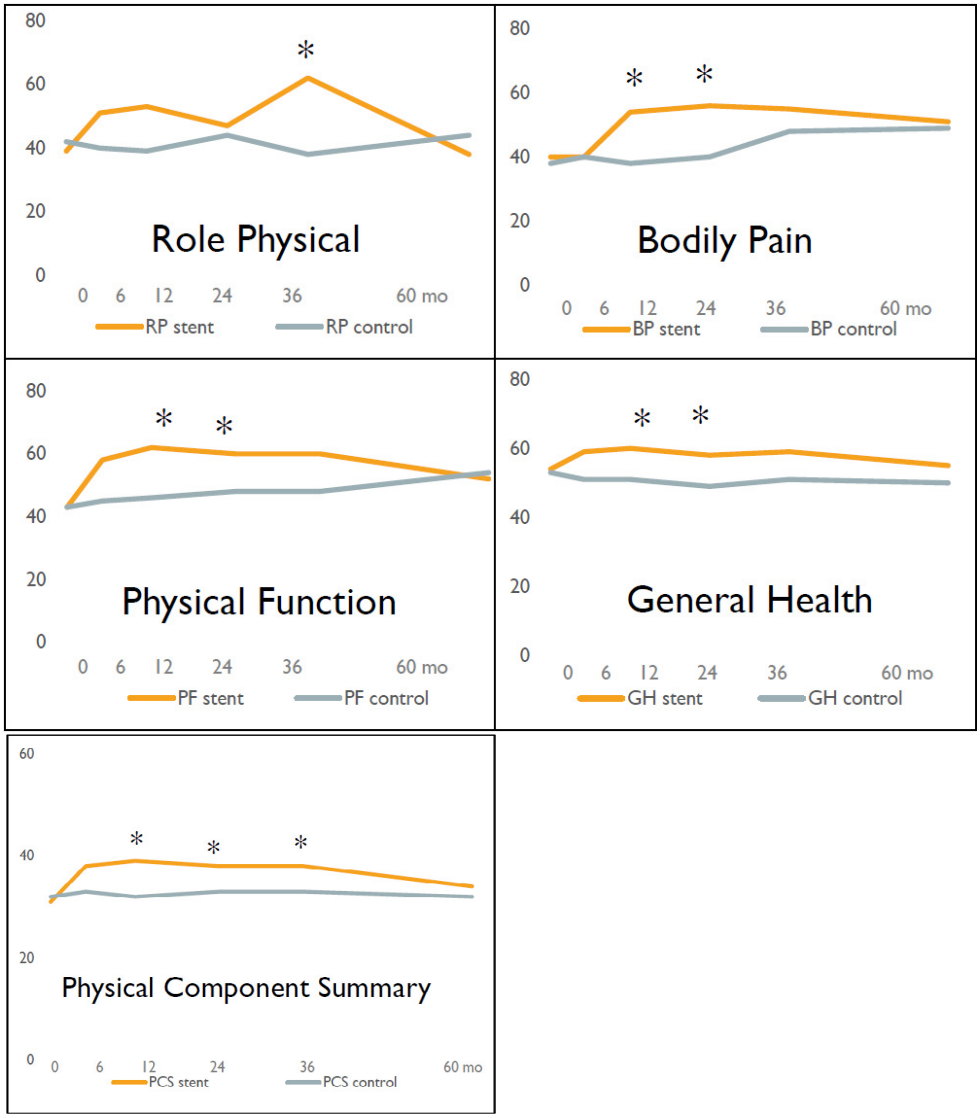

Figure 18. Diagram of physical SF-36 domains outcome in 100 patients with intermittent claudication randomized to primary stenting or best medical treatment only of SFA lesions.
* $p < .05$

Paper IV

Twentynine patients were included, of which 4 were excluded due to endovascular failure and proceeded to surgical bypass, one because of $tcpO_2$ electrode calibration failure, one because of an incorrect pre-operative diagnosis, one was lost to follow up, and one had bypass surgery for stent occlusion before follow up. Twenty-one patients completed the study and are included in the final analysis

Patients completing the study had a median age of 77 years (IQR 73.8 – 81.3), WIfI classification stage 3 (IQR 2.0-3.8), FP GLASS grade 3 (IQR 1-4), and IP GLASS grade 2 (IQR 0-3). Eight patients had ischemic rest pain (Rutherford class IV) and 13 had minor tissue loss (Rutherford class V). Median ABI was 0.40 (IQR 0.32 – 0.50) and median TP and $tcpO_2$ were 25.0 mmHg (16.0-35.0) and 28.1 mmHg (10.8-39.6) respectively.

Stent treatment was used for 13 femoropopliteal lesions in 13 patients and in infrapopliteal lesions in one patient, PTA were used in femoropopliteal lesions in 4 patients and in infrapopliteal lesions in 9 patients. In 19 patients the completion angiogram showed in-line flow to the foot.

The $tcpO_2$ and TP measurements did not interfere with the intervention or peri-interventional care or cause any clinical complications. $TcpO_2$ electrodes did not interfere with the interpretation of foot angiograms.

The median time to follow up was 10 weeks (range 8-13 weeks), and all but one patient had a good clinical outcome at this stage.

$TcpO_2$ outcome

Baseline (before arterial puncture) $tcpO_2$ for the study group was 24.4 mmHg (IQR 10.8 - 39.6), and results are presented as changes from baseline. The tcpO2 decreased significantly -6.0 mmHg (IQR -11.3 - -4.1; $p < .001$), from before arterial puncture to five-minute average before PTA. At the end of the intervention the tcpO2 did not rise above the baseline value, – 4.8 mmHg (IQR -17.4 – 1.3; $p = .16$). However, there was a significant increase in the tcpO2 by 14.7 mmHg (IQR 5.0 – 33.6; $p < .001$) at follow-up. The $tcpO_2$ values in the reference foot were unchanged during the intervention and at follow-up, median change of 1.2 mmHg (IQR -4.1 – 8.6; $p = .38$), and 2.4 mmHg (IQR -8.7 – 15.6; $p = .34$) respectively.

Systolic toe pressure outcome

Median baseline TP value of the index foot was 25.0 mmHg (IQR 16.0 – 34.0), and this value increased significantly during the intervention by 13.0 mmHg (7.0 – 48.5; $p < .001$).

Table 14. Vascular lesion anatomical classification (GLASS), endovascular treatment option and angiographic results for each study patient.

Patient id	WIfI	GLASS FP	Treatment	GLASS IP	TAP	Treatment	GLASS IM	Successful revascularisation
1	2	2	PTA	4	PTA	PTA	P1	Yes
2	3	1	Stent	3	ATA	PTA	P1	Yes
3	3	0	None	4	PA	PTA	P2	Yes
4	NA	0	None	3	PTA	PTA	P1	Yes
5	4	1	Stent	3	PA	PTA	P1	Yes
6	3	4	Stent	4	ATA	Stent	P1	Yes
7	2	4	Stent	4	PTA	PTA	P1	Yes
8	3	0	None	2	PA	PTA	P2	No
9	4	3	Stent	0	PTA	None	P1	Yes
10	NA	4	Stent	0	PA	None	P2	Yes
11	2	3	Stent	0	PTA	None	P0	Yes
12	3	4	Stent	0	PTA	None	P1	Yes
13	2	3	PTA	2	ATA	None	P1	Yes
14	4	4	Stent	4	ATA	None	P1	Yes
15	4	1	None	3	ATA	PTA	P1	No
16	2	3	PTA	0	ATA	None	P1	Yes
17	2	2	Stent	0	ATA	None	P1	Yes
18	2	4	Stent	0	ATA	None	P1	Yes
29	1	3	PTA	0	ATA	None	NA	Yes
20	3	2	Stent	0	PTA	None	P1	Yes
21	4	2	Stent	4	ATA	PTA	P0	Yes

Wound, Ischaemia and foot Infection, FP = femoropopliteal, IP = infrapopliteal, TAP = target artery pathway, IM = inframalleolar (P0 = target artery crosses ankle into foot, with intact pedal arch, P1 = target artery crosses ankle into foot, absent or severely diseased pedal arch; P2 = no target artery crossing ankle into foot), POBA = plain old balloon angioplasty, PTA = posterior tibial artery, ATA = anterior tibial artery, PA = peroneal artery, NA = not available. Successful revascularisation = inline flow to the foot.

Table 15. Toe pressure (TP) and transcutaneous oxygen pressure ($tcpO_2$) results and clinical outcome for each study patient.

Patient id	Toe Pressure (mmHg)			$TcpO_2$ (mmHg)			Clinical outcome
	Baseline	End	Follow-up	Baseline	End	Follow-up	
1	35	52	57	43.3	37	50.3	WH
2	30	41	63	38.0	19.5	62.7	WH
3	20	29	39	24.4	14.6	29	WH
4	66	82	83	48.6	32.4	48.4	WH
5	45	64	73	38.4	28.2	49.3	WH
6	20	29	50	31.8	36	50.2	Pain resolved
7	33	47	82	11.1	14.3	60.7	WH
8	30	43	63	45.6	24.5	49.2	WH
9	16	23	83	7.9	19.3	61.7	Pain resolved
10	16	23	41	4.8	21.4	42.2	Pain resolved
11	20	39	72	7.8	39.8	48.8	Pain resolved
12	10	14	48	20.3	18	44.3	Pain resolved
13	42	60	38	56.8	22.5	60.1	WH
14	25	48	63	32.9	32.2	38.2	WH
15	13	16	38	14.2	9.4	26.7	Not improved
16	30	34	57	52.3	2.8	43.9	Pain resolved
17	7	30	57	5.1	0.3	19.7	Pain resolved
18	25	37	73	11.5	8.3	26.5	Pain resolved
29	74	105	125	34.9	10	47.6	Pain resolved
20	31	23	55	10.4	1.4	40.2	WH
21	10	27	36	10.9	7.1	77.2	WH

WH = wound healing

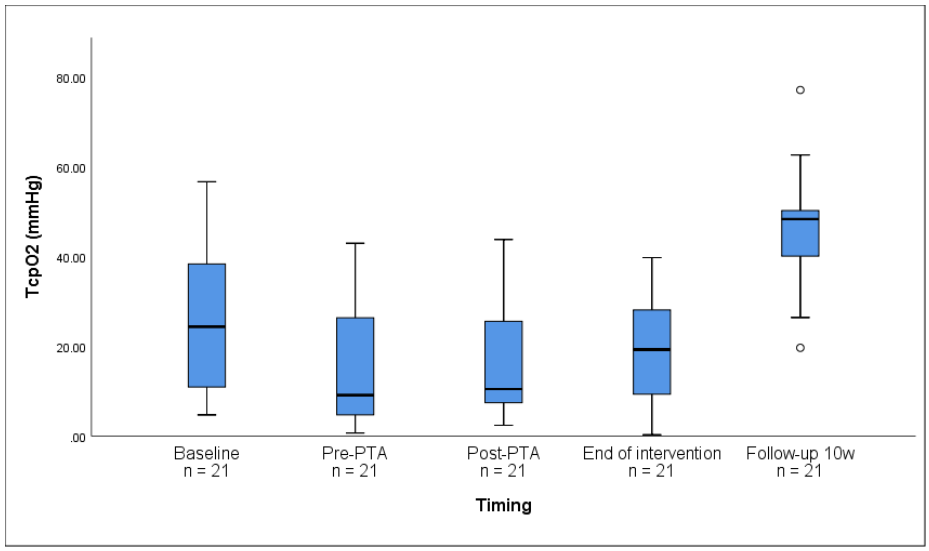

Figure 19. Median transcutaneous oxygen pressure, $tcpO_2$, during endovascular intervention and at follow-up 10 weeks later.

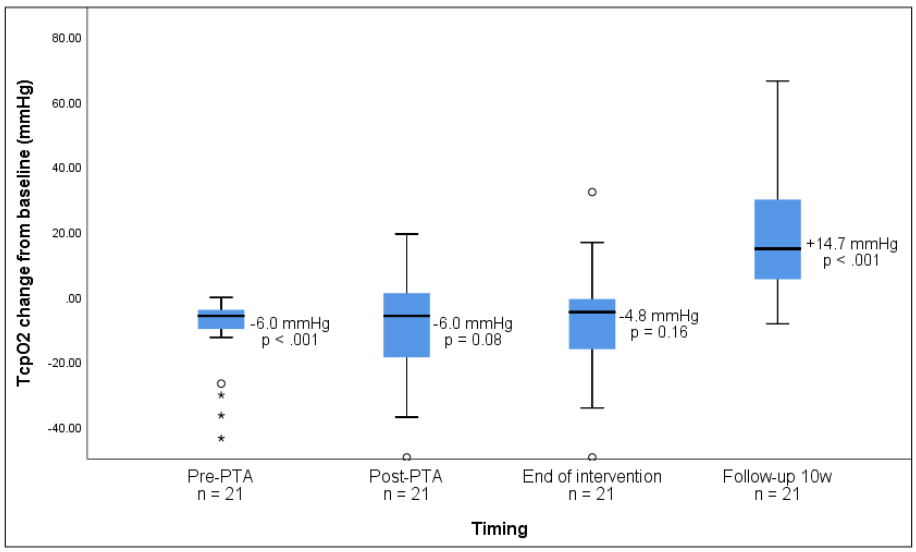

Figure 20. Median change in transcutaneous oxygen pressure, $tcpO_2$, from baseline (before arterial puncture), at specific time points during endovascular intervention and at follow-up 10 weeks later.

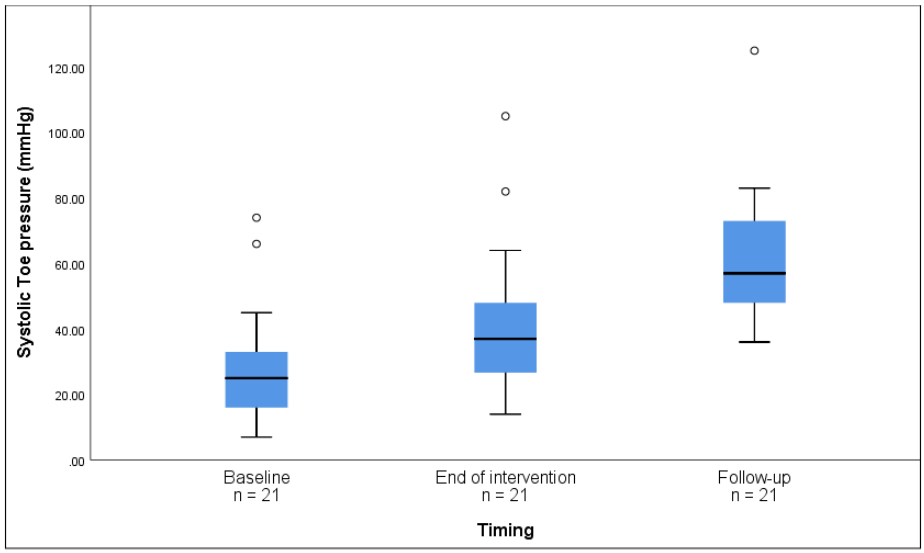

Figure 21. Median systolic toe pressure at baseline (before arterial puncture), end of endovascular intervention and at follow-up 10 weeks later.

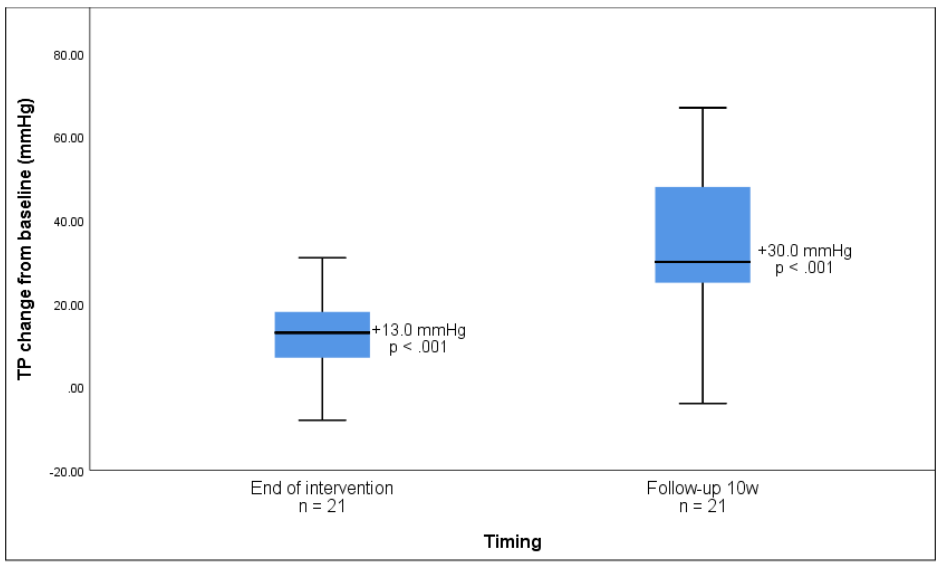

Figure 22. Median change in systolic toe pressure, TP, from baseline (before arterial puncture) to end of endovascular intervention and at follow-up 10 weeks later.

Discussion

In this thesis long-term outcome of invasive treatment of infrainguinal IC has been studied in two papers; paper I focusing on the fate of infrainguinal IC patients eight years after invasive treatment, and paper III reporting HRQoL three and five years after either conservative treatment or SFA stenting. The changes in invasive treatment modality in Sweden between 2009 and 2022 are reported in paper II, whereas paper IV evaluates the feasibility of $tcpO_2$ and TP measurements as on-table decision making tools during endovascular intervention.

Invasive treatment of infrainguinal IC

There is great variation in the incidence of invasive treatment of IC between countries and even between vascular clinics in Sweden[78, 120, 121]. The reason for this is probably that the decision to offer invasive treatment is based on the patients' subjective symptoms and expectations on walking ability. The most important factors in decision making are the individual risk profile of the patient and the expected improvement in quality of life. The risk of periprocedural complications for an endovascular intervention is lower compared to open surgery[122], tipping the risk/benefit scales towards more endovascular interventions. For this to be acceptable the benefits of endovascular treatment must be long lasting, however. Patency of endovascular interventions on aortoiliac lesions are as high as 90% at 5 years[54, 55], whereas patency of endovascular interventions of the SFA are 30-50% at 5 years[123-126]. Infrainguinal endovascular interventions in IC patients are therefore more controversial compared to interventions at the aortoiliac level.

IC patients have a high risk of CV disease and mortality. A Swedish observational study reported 50% mortality in 8 years[47] in an unselected cohort. Paper I reports an 8-year mortality of 40% in patients after invasive treatment, this difference might reflect the selection of younger and healthier patients for intervention. Patients with IC have a lower HRQoL compared to a healthy reference population[8], and paper I offers valuable insights into the underlying causes. The annual need for hospitalization of between 79-99% in surviving subjects, and the fact that the study cohort spent no less than a total of 25,970 days in hospital. Furthermore, one in three patients needed another vascular intervention during the 8 years.

Paper III reports the long-term results of the RCT, which reported significant improvement in HRQoL after 12 and 24 months[119, 127]. The HRQoL results after 36 and 60 months reported in paper III still showed a positive effect of stenting after 36 months, although not to the same degree as after 12 and 24 months. On the other hand, no difference was measurable between groups after 60 months. Another important outcome of the study was that progression to CLTI, or amputation was the same in both groups. This is in line with other Swedish reports on patients undergoing invasive treatment for IC[53], although an increased risk for amputation has been reported in IC patients undergoing early revascularization compared to initial conservative treatment[128].

Most studies on invasive treatment of IC only include 2-year follow-up after intervention[67]. The IRONIC trial (113, 114) included patients from Gothenburg 2012-2014 and followed them for 5 years. The trial included both patients with supra- and infrainguinal lesions undergoing both open and endovascular treatment[129, 130]. The IRONIC trial also reported a significant benefit of physical QoL (SF-36) 12 and 24 months after randomization, however, this effect was no longer measurable after 5 years. Even though the trial had 25% crossover to revascularization in the conservative group, per protocol analysis did not show any significant difference either. There was no difference in progression to CLTI, amputation, or mortality.

The ERASE trial, a multicentre RCT conducted in the Netherlands compared SET with a combination of invasive treatment and SET[131, 132]. All interventions on supra- and infrainguinal lesions were performed endovascularly. Both maximum walking distance and HRQoL were significantly better at 12-month follow-up in invasively treated patients. There was no longer any significant difference between groups after 5 years, however, although both groups had increased their maximum walking distance by 1000 meters and increased their physical HRQoL according to SF-36. The fact that approximately 50% of patients randomized to SET underwent an endovascular revascularization during the follow-up period makes the comparison of SET and combination therapy unreliable. No per protocol analysis was reported. However, the rates of progression to CLTI, amputation, and mortality were not higher in the invasive treatment group

The results of our RCT trial, IRONIC, and the ERASE study show that invasive treatment does not increase progression to CLTI, risk of amputation, or death. The benefit of revascularization is clear and significant until 2 years after treatment, and to some degree still present after 3 years (paper III). Five years is a long time for patients with IC, during which many factors can affect their health. One in five will be dead, most patients are annually admitted to hospital for various diseases, and 20-50% of patients initially treated conservatively will have undergone invasive treatment. This makes the comparison between treatments after 5 years difficult. However, these trials give vital information for the treating physician when discussing treatment options with their IC patients. An increased HRQoL for 2-3

years might be of great value and interest for this elderly IC patient and helps the patient make an informed decision regarding invasive treatment.

Time-trends in invasive treatment of IC

Endovascular interventions in IC patients increased threefold in the United States between 1999 and 2007[42]. Another American study conducted between 2011 and 2022 reports initial increase of interventions from 2011 to 2014[133], followed by a sharp decline 2020-2022. International guidelines have since 2007 gradually increased the emphasis on conservative treatment. According to the Inter-Society Consensus document in 2007, exercise therapy was not regarded necessary before endovascular intervention[14], whereas the 2011 ESC Guidelines stated that advances in endovascular treatment have prompted more liberal indications for invasive treatment by physicians[134]. Both the 2017 and 2024 ESVS Guidelines put even more emphasis on initial conservative treatment with exercise training[5, 68].

Paper II in this thesis showed a trend towards increasing rates of invasive treatment between 2009 and 2017, followed by a sharp decline in 2020 - 2022. Our study, however, reports both open and endovascular interventions in infrainguinal IC patients. The COVID-19 pandemic is likely the cause for the decline in invasive treatment of IC between 2020 and 2022, as healthcare resources were limited and conditions like IC were not prioritized[135]. Therefore, we cannot draw any firm conclusions from the results of paper II regarding whether rates of invasive treatment is increasing or not. It will be interesting to see if the decrease in invasive treatment of IC observed during the pandemic was transient or not.

The time-trends in the choice of treatment modality (paper II) are quite clear, showing that endovascular interventions increased, and bypass surgery decreased during the study period. The proportion of IC patients receiving bypass surgery decreased from 18% in 2009 to 4.4% in 2022. For comparison, bypass surgery is applied in 20-30% of CLTI patients in the USA[136]. The most likely reason for the difference in treatment between IC and CLTI patients is that patients undergoing bypass surgery have a higher rate of cardiovascular, infectious, and wound complications, and a longer hospital stay compared to those undergoing endovascular interventions[137]. This might not be accepted for a benign condition like IC. As the main focus of trials comparing bypass versus endovascular surgery today is on CLTI patients, it is unlikely that bypass surgery will return to previous numbers in the IC population. Unlike bypass surgery, the incidence of TEA of the CFA did not decrease in IC patients from 2009 to 2022, reflecting that stenting of the CFA has not yet become a common method in Sweden.

Endovascular interventions in infrainguinal IC increased in Sweden between 2009 and 2022, which is not surprising. The type of endovascular modality used also

changed significantly. BMS treatment increased significantly, and endovascular interventions featuring only PTA without adjunctive endovascular treatment decreased. In 2022 BMS were used in approximately 50% of all endovascular interventions of infrainguinal IC, compared to PTA only in 35% of cases. As the latest ESVS guidelines advocate a more restrictive use of stents[5], it will be interesting to see if this trend continues

Paper II also depicts the start, pause, and restart of the Swedepad 2 trial, which started inclusion in December 2014 and finished in 2023. The proportion of IC patients receiving DEB and DES was 17.6% of all infrainguinal interventions in 2017. However, in December 2018 the trial stopped recruiting patients after Katsanos et al. published a meta-analysis showing increased mortality in patients treated with paclitaxel-coated angioplasty ballons[138]. As a consequence of this, drug eluting devices were only used in 3.6% of registrations in 2019 (paper II). After an interim analysis of the Swedepad population showing-no increased mortality in the paclitaxel group[139], Swedepad restarted recruitment of patients in March 2020, resulting in a rapid recovery of the use of DEB and DES treatment to 13.8% in 2021.

Sex differences

Women comprised a minority of patients in paper II, even though studies have reported equal prevalence of IC in both men and women in the Scandinavian population[4, 140]. These findings are in line with previous studies on invasive treatment [77, 78], and might reflect that women more often present with atypical IC symptoms compared to men[76]. During the study period the proportion of women increased from 39.8% in 2009 to 43.4% in 2022, which might reflect either an increased incidence among women or an increased awareness of atypical IC symptoms in women. In paper II women were more often treated with endovascular intervention compared to men, which is in line with previous reports[78]. Some authors speculate that this difference is due to women presenting at a more advanced age, having more advanced vascular disease, smaller vessels, and worse surgical outcome[77]. However, the multivariable analysis adjusting for age and other risk factors in paper II showed an OR of 1.61 for men to undergo open surgery compared to women. This difference was mainly due to significantly more TEA operations of the CFA in men compared to women, and not to more bypass surgery in men as one might think given that the saphenous vein is more often available for bypass surgery in men compared to women [141]. To our knowledge CFA lesions are not more frequent in men, however, Ortmann et al reported that femoropopliteal lesions, without specifying CFA, superficial femoral artery (SFA) or popliteal location, were more common in women with CLTI(30), and reports on TASC II classification and anatomical location in an endovascular material have not shown any sex differences[77].

On table hemodynamic observation

The feasibility of TP and $tcpO_2$ measurements during endovascular intervention in CLTI patients was studied in paper IV. The study showed that these measurements did not interfere with the endovascular intervention, affect the interpretation of the foot angiogram, or compromise safety. We also found that TP increased significantly at the end of the intervention, whereas $tcpO_2$ values did not.

$TcpO_2$ values dropped during the pre-revascularization phase of the intervention and then started to rise slowly after revascularization. There was no significant increase above baseline at the end of the intervention, however, even though the angiogram was considered satisfactory. The patients improved clinically at follow-up 10 weeks later, when $tcpO_2$ values had increased significantly. A decrease in $tcpO_2$ levels during endovascular procedures has been reported by Wildgruber et al. who measured $tcpO_2$ in 15 patients undergoing diagnostic angiography and 45 patients subjected to endovascular revascularization. $TcpO_2$ values dropped in both groups during the intervention, however, the $tcpO_2$ values started to recover 24 hours after the intervention in the revascularization group without reaching baseline values[142]. Pardo et al. reported similar findings in 40 patients undergoing endovascular revascularization, with a decrease in $tcpO_2$ after the administration of contrast medium and inflation of PTA balloons. The study reported a rise in $tcpO_2$ values after PTA above baseline values, however, without specifying at what time point these measurements were made[143]. These studies as well as paper IV all show the same pattern of a decline in $tcpO_2$ values during the pre-revascularization phase of an endovascular intervention and a slow increase in $tcpO_2$ after revascularization. The time when the $tcpO_2$ value can be expected to have increased above baseline values is, however, not known. Studies have measured different intervals after procedures from 24h to 8 weeks, reporting a gradual increase of the $tcpO_2$ until reaching maximum levels at 6 weeks after revascularization[142-144]. This makes $tcpO_2$ measurements unsuitable as an on-table tool during endovascular interventions, as the response is not fast and dynamic. The reason for the decrease in $tcpO_2$ values during endovascular intervention and diagnostic angiography is unknown. It could be the results of decreased blood caused by vasospasm due to intravascular catheterization or reduced vessel lumen due to introducer sheath insertion. Microcirculatory disturbances due to contrast media have also been suggested. In vitro studies have shown decreased nitric oxide levels and increased levels of reactive oxygen species in the endothelium after exposure for contrast medium[145, 146]. The correlation between the $tcpO_2$ at the end of intervention and clinical outcome was poor, as $tcpO_2$ decreased in 16 of 21 patients during the intervention and all but one improved clinically at follow up.

Systolic TP was measured at the start and end of the endovascular intervention. TP had already then increased significantly (+13.0 mmHg) and thereafter increased even further (+ 30.0 mmHg) during follow-up. It would have been interesting to

measure TP during the endovascular intervention, however, we refrained from such measurements as we suspected that the inflation of the toe cuff could make patients move their foot involuntary. It is vital for the patient to lie still during the endovascular treatment, especially in treatment of infrapopliteal lesions which was often the case. Intraoperative TP measurements were not included in the study protocol.

Both TP and $tcpO_2$ can predict wound healing according to studies in an ambulatory setting. Most patients in these studies have diabetic foot ulcers. No clear cut-off value for predicting wound healing has been established, however, for both $tcpO_2$ and TP a value below 20 mmHg is associated with non-healing and a value above 30 mmHg correlates quite well with ulcer healing[20, 21, 147, 148]. No studies with measurements of systolic TP in patients in the angiography suite have been conducted, and common practice is to measure ABI or TP after intervention and at a clinical follow-up several weeks later.

The discrepancy between intraprocedural TP and $tcpO_2$ in paper IV might reflect the different nature of these measurement techniques. $TcpO_2$ is the partial pressure of oxygen diffusing from red blood cells in cutaneous capillaries through interstitial space and surrounding skin cells. Part of the oxygen supplies skin cell metabolism, whereas the rest diffuses through the skin, which might be negatively affected by the endovascular procedure. However, laser doppler (LD) technique detecting the Doppler shift of infrared laser light undergoing reflection by moving particles is used to measure TP. These moving particles are mainly erythrocytes, enabling an indirect measurement of arterial blood flow which might not be negatively affected to the same degree by the endovascular procedure.

The study suggests that $tcpO_2$ measurements react too slowly for on-table use, however, the results on TP measurements warrant further investigation in the intraoperative setting.

Methodological discussion

The methods used in the papers of this thesis are quite diverse, ranging from a retrospective registry cohort study (paper I) focusing on the fate of infrainguinal IC patients 8 years after invasive treatment, a cross-sectional study (paper II) analysing the invasive treatment modality of infrainguinal IC patients in Sweden performed each year between 2009 and 2022 focusing on temporal changes and sex differences, a multi-centre RCT (paper III) on a very specific treatment option for IC patients, SFA stenting, focusing on HRQoL, and a pilot study (paper IV) trying to evaluate the feasibility of $tcpO_2$ and TP measurements during endovascular intervention as on-table decision making tools. This methodological diversity constitutes a strength of the thesis, as papers I-III have analysed different aspects of

invasive treatment of infrainguinal IC. Nevertheless, many methodological limitations are present in all studies. Paper IV is the odd one out, studying the utility of $tcpO_2$ and TP during interventions in CLTI patients and not IC patients.

Registry studies (paper I-II)

All registry study results suffer from risk of information bias depending on the quality and completeness of the information registered in each registry. The patients registered in Swedvasc have been selected by clinically active physicians and surgeons causing a certain selection bias but representing real world data. The study cohort in paper I consisted of all patients treated invasively for infrainguinal IC in Sweden in 2009. At that time the old infrainguinal module, which has been reported to have a high external validity[101], was still in use. In paper II data was collected from Swedvasc from 2009 to 2022, however, and a new PAD module was introduced in 2014 with new variables. Both supra- and infrainguinal interventions were registered, and a new option to define an intervention as reintervention had been introduced. It is highly likely that a learning curve was needed for the Swedish clinicians registering the interventions in the new module. Unfortunately, no external validation has been performed on the new PAD module, but the registry performs annual checks of internal validity with random sample controls. In the initial study plan for paper II, the study period was shorter (2010-2017), which would have enabled analysis of 4 years before and 4 years after the change of PAD module in Swedvasc. Such a design would have been prone to bias due to new registration module, and the main outcome might have reflected the changes in registrations and not real-world data. Extension of the study period to 2009 – 2022 minimised this effect on the results. In the initial study plan for paper II, 30 day and 1 year amputation and mortality rates were included as outcomes. However, there were high percentages of missing data especially after 1 year, making it unreliable. Information from the Cause of death and Inpatient registries would have been needed to obtain reliable data [115, 116]. These registers were used in paper I for 8-year follow-up after invasive treatment. A limitation of this data is, however, that both registerers delivered unidentified data for the 2009 cohort. This drawback enabled only group analysis, and long-time outcome coupled with different operative method was not possible.

In paper II Swedvasc data was retrieved in three separate datasets, 2009-2013, 2014-2017, and 2018-2022. Ethical approval did not include Swedish personal identification number (PIN); however, each patient had an identification within each dataset. This caused an overestimation of the number of patients undergoing invasive treatment, however, the total number of interventions was correct.

Randomized controlled trial (paper III)

The planning phase of the RCT was done prior to this doctoral thesis, with patient inclusion between 2010-2015. In those years many studies had shown superior patency with primary stenting of the SFA compared to PTA with provisional stenting. This was also implemented in the ESC 2011 guidelines recommending primary stenting of the femoropopliteal segment[134]. Long-term studies have illustrated comparable results with primary or PTA with provisional stenting[149], and the 2024 ESVS guidelines for treatment of the femoropopliteal segment in patients with IC do not recommend primary stenting over PTA with provisional stenting[5]. It is therefore possible that the trial would have been differently designed if conducted today with the intervention group consisting of PTA (with optional DEB) and provisional stenting (with optional DES). The control group would also probably been differently designed, with more emphasis on SET, which was not available in Sweden during the study inclusion. It is, however, interesting to notice that the use of BMS increased significantly in treatment of infrainguinal IC between 2009 and 2022 according to Swedvasc data, whereas PTA declined, and drug-eluting technologies comprised only a minority of cases (paper II). This illustrates the fast evolution of the endovascular field, and that scientific research has a hard time keeping up with product development and clinical practice, which do not always walk hand in hand.

The RCT was conducted at seven different vascular clinics in Sweden, but most patients were included in Helsingborg. It can be a weakness of a trial to be conducted at too many locations with each location including few patients, making it difficult to adhere to a strict protocol. It is, however, more likely that it constitutes a strength if the trial is multicentre as it makes the results more generalizable. The trial was designed to detect a difference of 10 points in SF-36 outcomes at 24 months with an expected loss to follow-up of 10%. After 36 months 9 of 52 (17%) patients in the control group had undergone stent treatment, and after 60 months this number had increased to 14 of 52 (26%) which negatively impacted the analysis of the results. This might in some way explain the loss of difference between the groups at 60 months. The trial results were analysed using the intention to treat method as recommended for RCTs, to keep the balance in the groups by randomisation. During the course of a trial patients might either drop out or undergo different other treatments, and per protocol analysis might therefore enable better understanding of the true effect of the treatment. This however causes a certain bias, e.g. patients who deteriorate in their IC symptoms during a trial are more prone to crossover to stent treatment reducing the difference between groups (assuming a positive effect of stents). In a per protocol analysis patients who crossover due to deterioration leave the control group and are analysed in the stent group, creating a selection of patients in the control group with high HRQoL without stent treatment. This is however also important information. Continued conservative treatment with exercise and BMT in patients with acceptable symptoms who did not need invasive treatment creates a

subgroup of IC patients which according to the results of paper III, can have equal HRQoL after 5 years as patients undergoing invasive treatment. The trial was also subject to non-responder and survival response bias, as subjects most likely to have a low HRQoL due to comorbidities pass away. Mortality rates were equal in both groups, however, so this is unlikely to have affected the results significantly.

HRQoL

There are some pitfalls in analysing HRQoL data with regards to clinically relevant difference of HRQoL scores between groups. For SF-36 the relevant levels are generally thought to be approximately 5 points for the composite values and 10 points for each of the 8 domains or a 30% increase[150, 151]. Larger trials with many included patients might report a statistically significant difference between groups, even if this difference might not be clinically relevant. In paper III some results suggest clinically significant or nearly significant differences without enough statistical power, e.g. PF after 36 months. It is important that both clinical and statistical significance is met when interpreting HRQoL data.

Pilot study (paper IV)

Paper IV was an experimental pilot study examining the feasibility of $tcpO_2$ and TP measurements during endovascular intervention in CLTI patients. Planning of the study introduced many methodological difficulties and dilemmas. Firstly, IC patients most likely have an almost normal $tcpO_2$ at rest, and therefore only CLTI patients were recruited. $TcpO_2$ is affected by the patient's arterial blood oxygen saturation and therefore a reference value is essential to identify $tcpO_2$ changes due to systemic changes. Many studies use a chest electrode[152]; however, this is not feasible during an endovascular intervention, and the contralateral foot was therefore chosen for reference value. Contralateral retrograde arterial access was therefore excluded as not to interfere with the reference value of the contralateral limb. These narrow inclusion criteria and the fact that only one investigator (TG) initially included patients and conducted the interventions caused a slow and non-consecutive inclusion rate. A research nurse was thereafter recruited to the study, which made it possible to recruit more patients. Another challenge was to select the relevant timepoints for measurement during the interventions. These needed to be defined beforehand and included in the study protocol (see protocol in appendix). $TcpO_2$ was measured every 64 ms, so choosing only one reading might not have been representative. Different averages over 1, 5 or 10 minutes were chosen according to similar studies in the field[143]. Electrode placement was also photo documented to ensure same placement at follow-up. In this kind of pilot trials endless methodological decisions must be made, which might end up affecting the results. The reproducibility of similar results of studies conducted of different groups at different clinics is therefore a strong indicator of a true effect[142, 143].

Conclusion

Patients undergoing invasive treatment for infrainguinal IC have considerable morbidity in the following 8 years. One in three patients needs a new vascular intervention, 79-99% of patients will need hospitalization annually, and 40% of patients will have passed away with vascular disease being the most common cause of death. (I)

The incidence of invasive treatment of IC in Sweden has not changed significantly between 2009 and 2022. Endovascular interventions have increased proportionally, and bypass surgery has decreased. The proportion of CFA TEA operations has not changed between 2009 and 2022. Stent treatment has increased and PTA without other adjunctive treatment decreased. Women more often undergo endovascular intervention compared to men, and the main gender difference was observed regarding the proportion of CFA TEA operations. (II)

In patients with IC caused by SFA lesions, primary stenting conferred a benefit in physical HRQoL compared to BMT until up to 36 months from treatment. However, these benefits were no longer detectable at 60 months. (III)

TcpO2 and TP measurements are safe and feasible non-invasive techniques for hemodynamic monitoring during endovascular interventions. TP showed a response during endovascular intervention and might potentially be a useful indicator of adequate blood-flow for wound healing during intervention, whereas the additional value of tcpO2 monitoring during an intervention seems limited.

Future perspectives

There are many areas in need of further research regarding invasive treatment of infrainguinal IC. New endovascular modalities like DEB and DES show promising results in increasing patency in treatment of femoropopliteal lesions. A trial comparing conservative treatment and DEB with provisional stenting, in which both groups would receive SET, would be of interest.

Larger studies on intraprocedural TP measurements are needed to verify the results of paper IV. TP measurements during the interventions need to be analyzed more in depth. With more study participants it might be possible to identify a TP value during or directly after the interventions correlating well with a good clinical outcome.

Studies on the discrepancy in invasive treatment modalities used in men and women are warranted. Women receive open surgery to a lesser extent, mainly due to the lower number of TEA operations compared to men. Are there really differences in anatomical distribution of atherosclerotic lesions between genders?

Future studies on the annual incidence of invasive treatment of IC in Sweden are needed to evaluate whether the decrease in invasive treatment observed in 2020-2022 represents only a transient phenomenon due to the COVID pandemic.

Populärvetenskaplig sammanfattning på svenska

Fönstertittarsjuka

Perifer kärlsjukdom orsakas av åderförkalkning i benens artärer som leder till nedsatt blodflöde. Syrebrist i muskler vid gång ger upphov till obehag och smärta (fönstertittarsjuka) som är huvudämnet i denna avhandling. I allvarligare fall av perifer kärlsjukdom råder även syrebrist i vila och orsakar vilovärk, sår eller kallbrand (kritisk syrebrist). Diagnosen ställer man med att räkna ut kvoten mellan blodtrycket i armen och i kärlen vid fotleden (ankeln), ankelbrachial index (ABI). Fönstertittarsjuka orsakar nedsatt livskvalité jämfört med hos friska jämnåriga individer och alla patienter bör behandlas med medicin (blodfettsänkande och blodförtunnande samt i förekommande fall behandling av blodtrycksförhöjning och diabetes) och rekommenderas rökstopp. Gångträning bör även erbjudas alla med fönstertittarsjuka. Denna behandling nämns konservativ behandling. Perifer kärlsjukdom kan även behandlas invasivt med både öppen kirurgi och endovaskulära metoder. Antalet endovaskulära ingrepp har ökat mycket sedan början av 90 talet. Internationella riktlinjer förespråkar att alla patienter med fönstertittarsjuka bör behandlas konservativt initialt, och att endast de patienter som inte förbättras och fortsatt har en mycket nedsatt livskvalité skall erbjudas invasiv behandling. Invasiv behandling av kärlen nedom ljumsken (infrainguinalt) är något kontroversiell men görs ändå hos många patienter i Sverige. Det är brist på vetenskapliga studier om hur det går för patienterna på lång sikt och trots att studier har visat på att fönstertittarsjukdom är lika vanligt hos svenska män och kvinnor över 60 år så utgör i tidigare rapporter män majoriteten av de patienter som får invasiv behandling.

Hemodynamisk övervakning under endovaskulära ingrepp

Cirkulationen till nedre extremiteten värderas med ABI mätning i flesta fall, men hos patienter med svår kärlsjukdom och diabetes kan denna mätning vara opålitlig

pga svårt förkalkade underbenskärl. I dessa fall är tåtrycksmätning och transkutan syrgastension (tcpO2) mer pålitliga metoder. Tåtryck mäter man som ”vanligt” blodtryck med en blodtrycksmanschett på stortån, och tcpO2 mäter man med elektroder på huden som mäter syrgastensionen i huden. Båda dessa mätmetoder kan förutspå sårläkning hos patienter med fotsår pga kritisk syrebrist. Endovaskulära ingrepp görs med hjälp av röntgengenomlysning och kontrastinjektion i kärlen för att visualisera behandlingens resultat och kallas angiografi. Bedömningen av angiografibilderna görs av operatör och är ett subjektivt ögonmått om blodflödet är förbättrat eller inte. Det finns därför ett behov av en objektiv mätmetod av cirkulationen som kan användas under endovaskulär behandling.

Avhandlingens målsättning

Att studera sjuklighet hos patienter med fönstertittarsjuka under 8 år efter genomgången invasiv behandling av kärlsjukdom nedom ljumske.

Att studera ändringar i invasiv behandling av infrainguinal fönstertittarsjuka i Sverige under åren 2009–2022.

Att jämföra livskvalité hos patienter med infrainguinal fönstertittarsjuka 3 och 5 år efter endovaskulär behandling med stent i lårbensartären (SFA) med patienter med samma tillstånd som behandlades konservativt.

Att utvärdera om tåtrycksmätning och transkutan syrgastension är lämpliga som hemodynamiska mätmetoder under endovaskulär behandling av benartärsjukdom.

Avhandlingens metod och resultat

År 2009 genomgick 775 patienter invasiv behandling av infrainguinal fönstertittarsjuka i Sverige. Information om dessa patienter från svenska kärlkirurgiska registret (Swedvasc), Patientregistret och Dödsregistret samlades in för åren 2010 till 2017. Studien visade att av 775 patienter behövde 261 genomgå en ny invasiv behandling under dessa 8 år efter ingreppet. Nästan alla patienter, 79–99%, blev inlagda årligen på sjukhus där den vanligaste orsaken var kärlsjukdom. Efter 8 år hade 40% av patienterna gått bort och 6,7% genomgått amputation.

För utvärdering av eventuella ändringar i indikationerna för invasiv behandling i Sverige samlades in data från Swedvasc gällande alla infrainguinala invasiva ingrepp under perioden 2009 – 2022. Studien visade att incidencen av ingrepp var oförändrad under dessa år. Andelen ingrepp som görs med öppen kirurgi minskade

från 38,1% till 23,4% medan andelen endovaskulära ingrepp ökade från 56,9% till 69,7% under tidsperioden. Detta orsakas framför allt av minskning av andelen bypassoperationer, 18,8% till 4,0%. Studien visar även att kvinnor utgjorde ungefär 42% av alla patienterna och att endovaskulär behandling var vanligare hos kvinnor (70% mot 61%) jämfört med män som oftare genomgick öppen kirurgi (32% mot 24%).

Patienter med fönstertittarsjuka pga åderförkalkning i SFA hade lottats till antingen konservativ behandling (52 patienter) eller stentbehandling (48 patienter) under åren 2010–2015 vid sju sjukhus i södra Sverige, och resultat från uppföljning både ett och två år senare har publicerats tidigare. I denna avhandling har livskvalitetsformulär, patientjournaler och data från dödsorsaksregistret samlats in 3 och 5 år efter studiestart. Studien visar att patienterna som fick stentbehandling hade en förbättrad fysisk livskvalité 3 år från studiestart jämfört med patienter som behandlats konservativt, men denna skillnad var borta vid 5 års uppföljning. Ingen skillnad förelåg mellan patientgrupperna gällande dödlighet eller amputation.

Tåtryck och transkutana syrgastensionsmätningar under endovaskulär behandling av benartärsjukdom utvärderades genom mätningar på 21 patienter med kritisk syrebrist under behandlingen. Transkutan syrgastensionsmätning utfördes kontinuerligt under hela ingreppet medan tåtryck mättes vid start och avslut med patienten fortfarande på bordet. Vid återbesök 10 veckor senare gjordes samma mätningar på patienterna. Studien visade att tåtrycket, men däremot ej transkutan syrgastension steg direkt efter ingreppet. Avseende båda mätmetoder förelåg högre värden vid återbesöket efter 10 veckor.

Avhandlingens slutsatser:

- Patienter med infraiguinal fönstertittarsjuka som kräver ingrepp har stor övrig sjuklighet. Var tredje behöver ytterligare kärlintervention, nästan alla behöver läggas in på sjukhus årligen och 4 av 10 har avlidit under 8 år.
- Andelen endovaskulära ingrepp för infrainguinal fönstertittarsjuka har ökat under åren 2009–2022 i Sverige, och endovaskulär behandling är vanligare hos kvinnor än män.
- Stentbehandling av SFA kan jämfört med konservativ behandling ge förbättrad livskvalité under upp till 3 år efter behandlingen, medan ingen skillnad är mätbar efter 5 år.
- Tåtryck stiger direkt efter endovaskulär kärlintervention och skulle eventuellt kunna användas som ett utvärderingsverktyg under ingrepp, medan transkutan syrgastension inte är användbart i detta syfte.

Samantekt á Íslensku

Heltiganga

Útæðasjúkdómur af völdum æðakalkana (atherosclerosis) í slagæðum ganglima veldur skertu blóðflæði til fóta. Birtingamynd þess skiptist í heiltigöngu (claudicatio intermittens), þegar ekki er unnt að anna aukinni súrefnisþörf vöðva í árynslu sem veldur blóðþurrðarverk í vöðvum, og langvinna tvísýna blóðþurrð (chronic limb-treatening ischemia) þegar blóðþurrð er viðvarandi og sem veldur blóðþurrðarverk í fæti í hvíld og í verstu tilvikum sáramyndun og drepi.

Heltiganga veldur verulega skertum lífsgæðum og ber að meðhöndla alla með blóðflöguhemjandi og blóðfitulækkandi lyfjum ásamt reyklausum lífstíl og ráðleggingum um gönguæfingar. Blóðþrýstingslækkandi og sykursýkislyfjum er bætt við sé þess þörf. Lyfjameðferð og gönguæfingar nefnast íhaldsmeðferð (conservative treatment). Einng er hægt að beita ífarandi meðferð, hvort heldur opnum skurðaðgerðum eða innæðaaðgerðum (endovascular intervention) þar sem innæðaaðgerðum hefur fjölgað verulega frá upphafi tíunda áratugar síðustu aldar.

Samkvæmt alþjóðlegum ráðleggingum er fyrsta meðferð við heltigöngu íhaldsmeðferð og einungis þeim sjúklingum sem ekki skána og hafa enn mjög skert lífsgæði boðin ífarandi meðferð. Deilt er um réttmæti þess að framkvæma ífarandi inngrip á slagæðum neðan nára hjá sjúklingum með heltigöngu þó slíkt sé algengt í Svíþjóð og skortur á vísindalegum rannsóknum um afdrif þessara sjúklinga til lengri tíma.

Blóðflæðimælingar í innæðaðagerðum

Mat á blóðflæði til ganglima er vanalega gert með blóðþrýstingsmælingu í upphandlegg og ökkla og reiknað ökklaupphandleggshlutfall (ÖHH) (ankla-brachial index). Sú mæling getur reynst röng hjá sjúklingum með sykursýki eða mjög kalkaðar æðar neðan hnés og þá eru táþrýstimæling (systolic toe pressure) og hlutþrýstingur súrefnis í húð (trancutaneous oxygen pressure) næmari mæliaðferðir. Táþrýstingur er mældur með því að setja blóðþrýstimæli á stórutá og hlutþrýstingur súrefnis í húð er mældur með rafskautum sem eru límd við húðina. Þessar aðgerðir

geta báðar spáð fyrir um sáragróanda hjá sjúklingum með fótasár vegna langvinnrar tvísýnnar blóðþurrðar. Innæðaaðgerðir eru framkvæmdar með skuggaefnisindælingu í slagæð og æðamyndatæku með hjálp röntgen gegnumlýsingu. Sá sem framkvæmir innæðaaðgerðina leggur huglægt mat á árangur inngripsins út frá myndrannsókn fyrir og eftir inngripið en þörf er á mæliaðferð sem veitir hlutlægt mat á blóðrás við innæðaaðgerð.

Tilgangur rannsóknanna var að:

I. Meta sjúkleika (morbidity) hjá sjúklingum sem hafa farið í æðainngrip neðan nára vegna heltigöngu.
II. Meta breytingar á æðainngripum neðan nára vegna heltigöngu í Svíþjóð á tímabilinu 2009 til 2022.
III. Bera saman lífsgæði sjúklinga með heltigöngu vegna æðakölkunar í grunnu lærisslagæð (superficial femoral artery) meðhöndlað með íhaldsmeðferð eða innæðaaðgerð með stoðneti (stent).
IV. Meta möguleika á að nýta mælingu á táþrýsting eða hlutþrýsting súrefnis í húð sem hlutlæga blóðflæðimæli aðferð í innæðaaðgerðum.

Aðferðir og niðurstöður rannsóknanna:

Í fyrstu rannsókn var öllum sjúklingum sem höfðu farið í æðainngrip í Svíþjóð árið 2009 á slagæðum neðan nára vegna heltigöngu fylgt eftir í 8 ár með því að sækja gögn frá sænska æðaaðgerða gagnasafninu (Swedvasc), vistunarskrá heilbrigðistofnanna í Svíþjóð (Patientregistret) og dánarmeinaskrá Svíþjóðar (Dödsorsaksregistret). Niðurstöður rannsóknarinnar eru að af 775 sjúklingum þurfti 261 sjúklingur að fara í aðra æðainngrip á tímabilinu. Nánast allir sjúklingarnir, 79-99%, þurftu árlega að leggjast inn á sjúkrahús og var algengasta innlagnarástæðan æðasjúkdómar. Átta árum eftir aðgerð höfðu 40% af sjúklingunum látist og 6,7% gengist undir aflimun.

Í annari rannsókn voru sótt gögn í Swedvasc fyrir sjúklinga sem höfðu farið í æðainngrip á slagæðum neðan nára vegna heltigöngu á árunum 2009 til 2022. Rannsóknin sýndi að nýgengi aðgerða hélst stöðugt tímabilinu. Hlutfall opinna skurðaðgerða minkaði úr 38,1% í 23,4% en hlutfall innæðaaðgerða jókst úr 56,9% í 69,7%. Fækkun hjáveituaðgerða úr 18,8% í 4,0% er helsta ástæðan fyrir þessu. Um 42% sjúklinga sem gengust undir æðainngrip voru konur og var innæðaðgerð frekar beitt hjá konum (70%) en hjá mönnum (61%). Opinni skurðaðgerð var beitt í 32% tilfella hjá körlum en aðeins 24% tilfella hjá konum.

Í þriðju rannsókninni var sjúklingum með heltigöngu vegna æðakalkana i grunnu lærisslagæðinni meðhöndlaðir annað hvort með íhaldsmeðferð (52 sjúklingar) eða stoðnetsmeðferð með innæðaaðgerð (48 sjúklingar). Val á meðferð var slembivalin. Sjúklingunum var fylgt eftir með spurningalistum um lífsgæði, sjúkraskrár skoðaðar og dánarmeinaskrá Svíþjóðar skoðuð 5 árum eftir upphaf meðferðar. Niðurstöðurnar sýndu að þeir sjúklingar sem fengu stoðnetsmeðferð með innæðaaðgerð voru með betri líkamleg lífsgæði miðað við íhaldsmeðferðar hópinn eftir 3 ár en enginn munur var á hópum eftir 5 ár. Það munaði engu í lifun og aflimunum hjá hópunum tveimum.

Í fjórðu rannsókninni var táþrýstingur og hlutþrýstingur súrefnis í húð mældur á fæti á meðan innæðaaðgerð var framkvæmd á 21 sjúklingi með tvísýna blóðþurrð. Hlutþrýstingur súrefnis í húð var mældur samfellt á meðan aðgerðinni stóð en táþrýstingur var mældur í upphafi og í lokin. Mælingar voru endurteknar í endurkomutíma 10 vikum seinna. Niðurstöðurnar sýndu að táþrýstingurinn hækkaði strax að lokinni heppnaðrar innæðaaðgerðar en ekki hlutþrýstingur súrefnis í húðinni. Báðar mæliaðferðir höfðu hækkað 10 vikum síðar.

Ályktanir ritgerðar

- Sjúklingar með heltigöngu sem fara í æðainngrip neðan nára hafa töluverða þörf á frekari æðaaðgerðum og árlegri spítalavistun ásamt dánartíðni upp á 40% á 8 árum.
- Hlutfall innæðaaðgerða neðan nára vegni heltigöngu hefur aukist í Svíþjóð og er algengari meðal kvenna en karla.
- Sjúklingar með heltigöngu vegna æðakölkunar í grunnu lærisslagæðinni sem hljóta stoðnetsmeðferð njóta aukinnar lífsgæði miðað við þá sem fá eingöngu íhaldsmeðferð eftir 3 ár en ekki greinist munur eftir 5 ár.
- Táþrýstingur hækkar strax eftir innæðaaðgerð og gæti mögulega nýst sem aðferð til að meta blóðflæði á meðan innæðaaðgerð er framkvæmd en mæling hlutþrýstings súrefnis í húð virðist ekki nothæf till þess.

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Appendix

Appendix 1

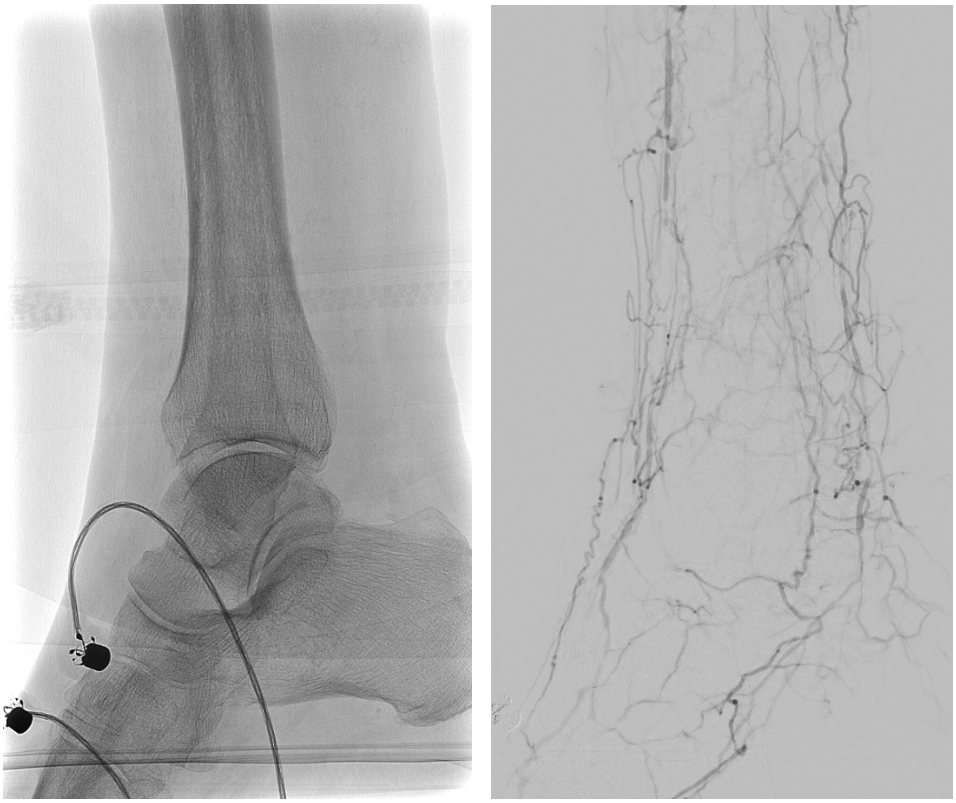


Image 23. Example of procedural images of the foot of a study participant in paper IV. X-ray image (left) and DSU (right) illustrates that electrodes do not affect the angiogram.

Appendix 2

Studieprotokoll för TcpO2 pilotstudie på angiolab Helsingborg

Studieansvariga: Thordur Gunnarsson ST läkare, Hans Lindgren ÖL kärlkirurgen, Håkan Pärsson ÖL kärlkirurgen och Lena Toft forskningssköterska.

Inkluderade pat: Kritisk benischemi pga sjukdom i artärer distalt om iliaca externa där man har bedömt endovaskulär åtgärd som bästa behandlings alternativ. Reoperation på tidigare endovaskulärt patienter ingår ej. Pat amputerade på andra benet ingår ej pga referens mätning på andra foten är nödvändig.

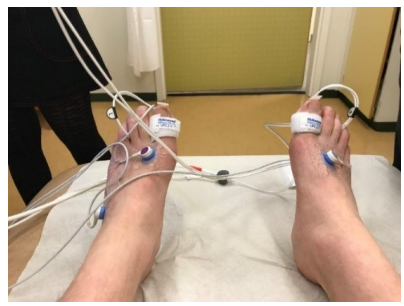
Pat får sedvanliga förberedelser enligt Helsingborgs PM för angiografi.

Inskrivning: Medgivande formulär ☐

Pre-op ABI Hö _____ Vä_____

På angiolab kopplas de upp till Periflux 6000 med tåtrycksmätare och transkutansyrgastensionsmätare, $tcpO_2$ elektrod. Ring Lena Toft forskningssköterska som sköter uppkoppling av patienter, tel 61570 eller Thordur 61527 (070-2613966).

TcpO2 elektrod placering:



- Två elektroder på aktuell behandlingsfot. Elektrod 1 placeras på fotryggen mellan metatarsus 1 och 2. Om det föreligger sår här placeras elektroden så distalt som möjligt nära såret. Elektrod 2 placeras mer proximalt och lateralt ungefär vid basen av metatarsus 5.
- En elektrod som referens på andra foten. Placeras som elektrod 1 på behandlingsfot.
- Vid placering skal man undvika att lägga elektrod direkt ovan på ben och ytliga vener. Det är även bra att tejpa runt kanten av elektroden för att minska risk på läckage.
- Elektrodplacering fotodokumenteras med kamera ☐

Studieprotokoll för TcpO2 pilotstudie på angiolab Helsingborg

Studieansvariga: Thordur Gunnarsson ST läkare, Hans Lindgren ÖL kärlkirurgen, Håkan Pärsson ÖL kärlkirurgen och Lena Toft forskningssköterska.

Mätningar:

BT_____ SpO_2_____ med _____ O_2

Före punktion tas en tåtrycksmätning ☐ och baslinje för $tcpO_2$ ☐ registrerar apparaten själv när kurvan har stabiliserat sig.

Endovaskulärt ingrepp utförs sedan på sedvanligt sätt och operatör är blindad för $tcpO_2$ värden.

Under ingreppet registreras $tcpO_2$ kontinuerligt. För att kunna tolka kurvan i efterhand registreras vissa moment under angiografin. Detta görs med att skapa en flagga i programmet som markör på tcpO2 kurvan. Vid denna flagga kan man skriva kommentar t ex ”PTA SFA”.

Flagga skal sättas när:

1 Punktion

2 Introducer är på plats ☐

3 Rekanalisering med ledare

4 PTA eller stentning utförs (registrera när ballong är insuflerad/desuflerad) ☐

5 Innan man drar introducer ☐

6 Ingreppet är slutfört (registrera om det är femostop) ☐

En tåtrycksmätning ☐ skal även göras när ingreppet är slutfört.

Vid återbesök 6-8 Veckor

1 Mäta ABI och TBI på Periflux 6000 ☐

2 Kolla elektrodplacering vid interventionen (foto) ☐

3 Placera elektroder som vid intervention och fotodokumentera☐

4 Sätt på maskinen och notera baseline-värdet bilateralt efter cirka 20 minuters sängläge☐

5 Notera tcpO2 baseline värde bilateralt☐

6 Tag bort elektroder och stäng av maskinen☐

Appendix 3

SF-36

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**)

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

SF-36

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 **tid** Du normalt ägnat åt arbetet	Ja ☐	Nej ☐
b. **Uträttat 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 ängslan)? Med arbete avses både arbete utanför hemmet och hushållssysslor. (Sätt ett kryss vid Ja eller Nej för varje fråga)

a. Skurit ned på den **tid** Du normalt ägnat åt arbetet	Ja ☐	Nej ☐
b. **Uträttat 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 (innefattar både arbete utanför hemmet och hushållssysslor)? (Sätt kryss i en ruta)

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

SF-36

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)

	Hela tiden	Största delen av tiden	En hel del av tiden	En del av tiden	Lite av tiden	Inget av tiden
a. Har Du känt Dig riktigt pigg och stark?	☐	☐	☐	☐	☐	☐
b. Har Du känt Dig mycket nervös?	☐	☐	☐	☐	☐	☐
c. Har Du känt Dig så nedstämd att ingenting kunnat muntra upp Dig?	☐	☐	☐	☐	☐	☐
d. Har Du känt Dig lugn och harmonisk?	☐	☐	☐	☐	☐	☐
e. Har Du känt Dig full av energi?	☐	☐	☐	☐	☐	☐
f. Har Du känt Dig dyster och ledsen?	☐	☐	☐	☐	☐	☐
g. Har Du känt Dig utsliten?	☐	☐	☐	☐	☐	☐
h. Har Du känt Dig glad och lycklig?	☐	☐	☐	☐	☐	☐
i. Har Du känt Dig trött?	☐	☐	☐	☐	☐	☐

SF-36

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)

- Hela tiden ☐
- Största delen av tiden ☐
- En del av tiden ☐
- Lite av tiden ☐
- Inget av tiden ☐

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)

	Stämmer precis	Stämmer ganska bra	Osäker	Stämmer inte särskilt bra	Stämmer inte alls
a. Jag verkar ha lättare att bli sjuk än andra människor.	☐	☐	☐	☐	☐
b. Jag är lika frisk som vem som helst av dem jag känner.	☐	☐	☐	☐	☐
c. Jag tror min hälsa kommer att bli sämre.	☐	☐	☐	☐	☐
d. Min hälsa är utmärkt.	☐	☐	☐	☐	☐

EQ5D

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 påklädning ☐
- 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

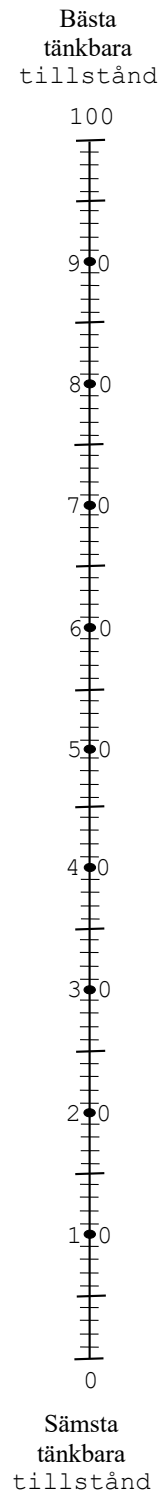
- Jag är inte orolig eller nedstämd ☐
- Jag är orolig eller nedstämd i viss utsträckning ☐
- Jag är i högsta grad orolig eller nedstämd ☐

EQ5D

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.

Ditt nuvarande hälsotillstånd



WIQ

Nu följer frågor angående Dina upplevelser av gångproblem. Även om Du inte har några problem med att gå är det viktigt att frågorna besvaras.

19. Gångproblem: Följande frågor rör orsakerna till att Du haft gångsvårigheter. Med svårigheter menar vi hur svårt det var eller hur mycket fysisk ansträngning som krävdes för att gå pga vart och ett av problemen. Under den senaste veckan, hur svårt var det att gå pga av följande?

	Inte Alls	Lite	Något	Mycket	Väldigt mycket	Ej tillämpligt
a. Smärta, värk eller kramp i vaderna eller skinkorna?	☐	☐	☐	☐	☐	☐
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 jämn mark utan att stanna eller vila för vart och ett av de följande avstånden?

	Inte Alls	Lite	Något	Mycket	Kan inte	Ej tillämpligt
a. Gå omkring inomhus, som t.ex hemma?	☐	☐	☐	☐	☐	☐
b. Gå 20 meter?	☐	☐	☐	☐	☐	☐
c. Gå 50 meter?	☐	☐	☐	☐	☐	☐
d. Gå 100 meter?	☐	☐	☐	☐	☐	☐
e. Gå 200 meter?	☐	☐	☐	☐	☐	☐
f. Gå 300 meter?	☐	☐	☐	☐	☐	☐
g. Gå 500 meter?	☐	☐	☐	☐	☐	☐

WIQ

21. Gånghastighet: Under senaste veckan, hur svårt var det för Dig att gå motsvarande 100 meter på jämn mark vid var och en av följande hastigheter utan att stanna?

	Inte Alls	Lite	Något	Mycket	Kan inte	Ej tillämpligt
a. Gå 100 meter långsamt?	☐	☐	☐	☐	☐	☐
b. Gå 100 meter vid medelhastighet?	☐	☐	☐	☐	☐	☐
c. Gå 100 meter snabbt?	☐	☐	☐	☐	☐	☐
c. Springa eller jogga 100 meter?	☐	☐	☐	☐	☐	☐

22. Gå i trappor: Under den senaste veckan, hur svårt var det för dig att gå i trappor utan att stanna eller vila?

	Inte Alls	Lite	Något	Mycket	Kan inte	Ej tillämpligt
a. Gå en trappa upp?	☐	☐	☐	☐	☐	☐
b. Gå två trappor upp?	☐	☐	☐	☐	☐	☐
c. Gå tre trappor upp?	☐	☐	☐	☐	☐	☐

Tack för Din medverkan!

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THORDUR GUNNARSSON was born in Reykjavik, Iceland in 1986. He received his medical degree from the University of Iceland in 2012 and moved to Helsingborg in 2016 and completed specialization in general surgery in 2019. He has since done his vascular surgery specialty training at Helsingborg Hospital and Vascular Center Malmö alongside working on the research projects in this thesis.

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