Chronic Limb-Threatening Ischaemia

Prognosis after intervention

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“Öppenheten för livet ger en blixtlik insikt i andras livssituation. Ett krav: att från känslostinget driva problemet till en klart fattad intellektuell gestaltning – och handla därefter.”

Dag Hammarskjöld

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ABSTRACT

Introduction: Lower-extremity arterial disease (LEAD) is a major health problem worldwide. Chronic limb-threatening ischaemia (CLTI) is the most severe manifestation of LEAD. Open or endovascular recanalization is recommended for most patients with CLTI. The aim of this thesis has been to investigate the impact of comorbidities, medications, gender, preoperative symptoms, and revascularized arterial segment on outcome after revascularization in terms of amputation or death and to investigate whether it is possible to make a correct preoperative assessment of infrapopliteal lesions in CLTI patients using the TransAtlantic Inter-society Consensus (TASC) II classification on magnetic resonance angiography (MRA).

Methods: All patients who were revascularized for intermittent claudication (IC, n = 6,272) and CLTI (n = 10,617) from May 2008 to May 2013 in Sweden were assembled in a database. Patients were identified using the Swedvasc register and the data was complemented with mandatory national healthcare registers. In addition, medical records of 1,366 patients were reviewed to safeguard accuracy on ipsilateral amputation. Descriptive statistics, Cox regression models with hazard ratios (HRs), and Kaplan-Meier curves were used in Papers I–III. In Paper IV, 68 preoperative MRAs and perioperative digital subtraction angiographies (DSAs) were evaluated using the infrapopliteal TASC II criteria. Visual grading characteristics (VGC) analysis and Krippendorff's α were used for analysis of differences and agreement between modalities and observers.

Results: CLTI patients had different preoperative comorbidities than IC patients. The risk of amputation following revascularization for CLTI was particularly high during the first 6 months. Mortality was high in all revascularized LEAD patients. Renal insufficiency, diabetes, heart failure, atrial fibrillation, male gender and presence of tissue loss, were found to be independently associated with increased risk of amputation after revascularization for CLTI. Conversely, medication with low-dose acetylsalicylic acid and statins were associated with improved limb salvage and survival. No systematic difference was detected between MRA and DSA in grading of infrapopliteal lesions. Agreement between observers in preoperative assessment of infrapopliteal TASC II class was poor, mainly due to a variable choice of intended target vessel between observers. A suggested novel infrapopliteal aggregated lesion severity score (IALSS), based on evaluation of all four infrapopliteal arteries, had better inter-observer agreement.

Conclusions: CLTI and IC affects different patient populations. Mortality is substantial in both. Amputation rate is particularly high in the first 6 months following revascularization for CLTI and associated with well-defined risk factors, most markedly renal insufficiency, diabetes, and tissue loss. Statins and platelet inhibitors should be considered for all patients with LEAD. Infrapopliteal TASC II grading can be done using MRA, but the required choice of a target vessel is a concern. An alternative score, independent of intended target vessel, may provide a more reproducible tool for assessment of infrapopliteal disease severity.

Keywords: Amputation, arterial occlusive disease, atherosclerosis, comorbidity, magnetic resonance angiography, mortality, peripheral arterial disease.

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SAMMANFATTNING PÅ SVENSKA

Introduktion: Benartärsjukdom (LEAD) är globalt ett stort hälsoproblem. Symptomatisk LEAD delas in i claudicatio intermittens (IC), vardagligt benämnt som fönstertittarsjuka, och kritisk ischemi (CLTI) som är den svåraste formen av LEAD. För de flesta patienter med CLTI rekommenderas öppen eller endovaskulär revaskularisering. Målet med den här avhandlingen har varit att studera hur samsjuklighet, läkemedel, kön, preoperativa symptom samt revaskulariserat kärlsegment påverkar utfallet avseende amputation och död efter ett revaskulariseringsingrepp samt om det är möjligt att göra en korrekt preoperativ bedömning av kärlförändringar nedom knäledsnivå (infrapopliteal) hos CLTI patienter genom att på magnetresonansangiografi (MRA)-bilder använda ”TransAtlantic Inter-society Consensus (TASC) II” klassifikationen.

Metod: Alla, i Sverige, revaskulariserade patienter för IC (n = 6272) och CLTI (n = 10617) mellan maj 2008 till maj 2013 samlades in i en databas. Patienterna identifierades genom det nationella kvalitetsregistret för kärlkirurgi, Swedvasc, och samkördes med högkvalitativa, obligatoriska svenska nationella sjukvårdsregister. Utöver detta granskades patientjournaler hos 1366 patienter för att säkerställa tillförlitliga data kring amputation. För arbete I-III användes deskriptiv statistik, Cox-regressionsmodeller med hasardkvoter (HR) och Kaplan-Meier kurvor. I arbete IV, granskades 68 preoperativa MRA undersökningar samt 68 peroperativa digital subtraktionsangiografier (DSA) med avseende på TASC II klassifikationen. ”Visual grading characteristics” (VGC) analys och Krippendorffs α användes för analys av skillnaderna och samstämmigheten mellan modaliteter och observatörer.

Resultat: CLTI patienter har annan preoperativ samsjuklighet jämfört IC patienter. Risken för amputation efter ett revaskulariseringsingrepp för CLTI är speciellt hög de första 6 månaderna postoperativt. Mortaliteten är hög hos patienter som revaskulariserats för PAD. Njursvikt, diabetes, hjärtsvikt, förmaksflimmer, manligt kön och förekomsten av bensår var faktorer som enskilt var associerade med en ökad risk för amputation efter revaskularisering för CLTI. Omvänt, medicinering med lågdos acetylsalicylsyra och statiner var associerat med minskad amputationsrisk och förbättrad överlevnad. Ingen systematisk skillnad påvisades mellan MRA och DSA i graderingen av kärlförändringar nedom knäledsnivå. Samstämmigheten mellan observatörer i preoperativ bedömning av infrapopliteal TASC II klassifikation var medioker, företrädesvis pga skillnad i val av målkärl för en revaskularisering. Ett föreslaget nytt sammanvägt infrapoplitealt kärllesionsscore (IALSS), som baserats på evalueringen av alla fyra infrapopliteala artärer, hade bättre samstämmighet mellan observatörer.

Slutsats: CLTI och IC drabbar olika patientpopulationer. Dödligheten är påtaglig i båda grupperna. Amputationsfrekvensen är speciellt hög det första halvåret efter ett revaskulariseringsingrepp och associerat med väldefinierade riskfaktorer där de mest framträdande är njursvikt, diabetes och bensår. Statiner och trombocythämmare bör övervägas hos alla patienter med PAD. Infrapopliteal TASC II gradering kan göras med MRA, men kravet att välja ett målkärl är problematiskt. Ett alternativt score, oberoende av ett tänkt målkärl, skulle kunna vara ett mer reproducerbart verktyg i bedömningen av infrapopliteal sjukdomsgrad.

LIST OF PAPERS

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

I. Baubeta Fridh E, Andersson M, Thuresson M, Sigvant B, Kragsterman B, Johansson S, Hasvold P, Falkenberg M, Nordanstig J.
Amputation Rates, Mortality, and Pre-operative Comorbidities in Patients Revascularised for Intermittent Claudication or Critical Limb Ischaemia: A Population Based Study.
European Journal of Vascular and Endovascular Surgery, 2017;54(4):480-486.

II. Baubeta Fridh E, Andersson M, Thuresson M, Sigvant B, Kragsterman B, Johansson S, Hasvold P, Nordanstig J, Falkenberg, M.
Impact of Comorbidity, Medication, and Gender on Amputation Rate Following Revascularisation for Chronic Limb Threatening Ischaemia.
European Journal of Vascular and Endovascular Surgery, 2018;56(5):681-688.

III. Baubeta Fridh E, Andersson M, Thuresson M, Nordanstig J, Falkenberg M.
Impact of Preoperative Symptoms and Revascularized Arterial Segment in Patients With Chronic Limb-Threatening Ischemia.
Vascular and Endovascular Surgery, 2019 Mar 17, doi: 10.1177/1538574419834765.

IV. Baubeta Fridh E, Ludwigs K, Svalkvist A, Andersson M, Nordanstig J, Falkenberg M, Johnsson ÅA.
Comparison of magnetic resonance angiography and digital subtraction angiography for assessment of infrapopliteal arterial occlusive lesions, with evaluation based on the TASC II classification and on an aggregated lesion severity score.
Manuscript.

CONTENTS

ABBREVIATIONS

2D	Two-dimensional
3D	Three-dimensional
ABI	Ankle-Brachial Index
AFS	Amputation-free survival
AI	Aorto-iliacal
ATA	Anterior tibial artery
ATC	Anatomical Therapeutic Chemical classification
ATP	Posterior tibial artery
AUC	Area under the curve
BASIL	Bypass versus Angioplasty in Severe Limb Ischaemia
BMI	Body mass index
CBCT	Cone-beam computed tomography
CI	Confidence interval
CLI	Critical limb ischaemia, see CLTI
CLTI	Chronic limb-threatening ischaemia
CT	Computed tomography
CTA	Computed tomographic angiography
DSA	Digital subtraction angiography
ESC	European Society of Cardiology
ESVS	European Society for Vascular Surgery
FA	Fibular artery
FINNVASC	National vascular registry in Finland
FP	Femoro-popliteal
GLASS	Global Anatomic Staging System
HR	Hazard ratio
IALSS	Infrapopliteal aggregated lesion severity score

IC	Intermittent claudication
ICD-10	The International Classification of Diseases, 10th revision
IP	Infrapopliteal
LDASA	Low-dose acitylsalicylic acid
LEAD	Lower-extremity arterial disease
MIP	Maximum-intensity projection
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
NPR	National Patient Register
PACS	Picture archiving and communication system
PAD	Peripheral arterial disease
PREVENT III	Project of Ex-vivo graft Engeneering by Transfection III
PTA	Percutaneous transluminal angioplasty
RF	Radio-frequency
SD	Standard deviation
SLI	Severe limb ischaemia
Swedvasc	The Swedish National Registry for Vascular Surgery
T	Tesla
TASC	TransAtlantic Inter-Society Consensus
TFT	Tibio-fibular trunk
TIA	Transient ischaemic attack
TOF	Time of flight
VGC	Visual grading characteristics
WIfI	Wound Ischaemia and foot Infection classification

1 INTRODUCTION

Atherosclerosis is a multifactorial disease, and historically has the involvement of high plasma concentrations of cholesterol been regarded as one of the main risk factors. The knowledge of atherosclerosis has evolved and is nowadays seen as being a multifactorial disease.[1] Cholesterol is connected to the vessel wall inflammatory process important in the formation of atherosclerotic plaques.[2] Inflammation is now regarded as one of the main contributors in the atherosclerotic evolvement.[3, 4] Atherosclerotic lesions are formed by vessel wall injury and inflammation, which leads to vessel wall plaque formation, fat deposition, and calcifications leading to varying degrees of stenosis or occlusion.

The term peripheral arterial disease (PAD) refers to atherosclerotic manifestations outside the heart and brain. The most importantly recognized risk factors for the evolvement of PAD is cigarette smoking, diabetes, hypertension, and dyslipidemia.[5] PAD most commonly affects the lower limbs—so-called lower-extremity arterial disease (LEAD). Symptoms vary depending on the degree of atherosclerotic plaques—from asymptomatic to symptomatic—and symptomatic LEAD falls into two main categories: intermittent claudication (IC) and chronic limb-threatening ischaemia (CLTI). LEAD, both symptomatic and asymptomatic, is associated with an increased cardiovascular morbidity and mortality.[6] The prevalence of LEAD has increased in the last few decades, partly because of the increase in life expectancy but also due to increased exposure to risk factors for PAD, so also younger individuals are affected.[7, 8] LEAD is one of the most common atherosclerotic morbidities globally, only surpassed by coronary artery disease and cerebrovascular disease.[9] In those who are over 60 years old in Sweden, the prevalence of LEAD has been estimated to be as high as 20%, making it one of the major health problems.[10] Even though LEAD affects a large number of individuals, the knowledge of LEAD in the general population is low.[11]

1.1 LOWER EXTREMITY ARTERIAL DISEASE

Atherosclerotic lesions impair the blood flow to the extremity, resulting in ischaemic symptoms of varying degrees. Depending on the extent and location of the arterial lesions, the symptoms differ on a broad spectrum from being asymptomatic to having severe pain and tissue loss. Symptomatic disease is classified as either IC or CLTI.

Typical symptoms of IC are exercise-induced pain from the lower extremity, most commonly from the calves, with relief when the patient is at rest. By definition, CLTI symptoms have to include the presence of pain when at rest and/or ischaemic wounds. There are many classifications for LEAD but the two most widely used are the Rutherford classification, where IC is classified as 1–3 and CLTI as 4–6, and the Fontaine classification, where IC corresponds to IIA and IIB whereas CLTI is defined as being class III or IV.[12, 13] The Rutherford and Fontaine classifications as presented in the ESC guidelines are summarized in Table 1.

Table 1: The Rutherford and Fontaine classifications

Fontaine classification				***Rutherford classification***		
Stage		*Symptoms*		*Grade*	*Category*	*Symptoms*
I		Asymptomatic	←→	0	0	Asymptomatic
II	IIa	Non-disabling intermittent claudication	←→	I	1	Mild claudication
				I	2	Moderate claudication
	IIb	Disabling intermittent claudication		I	3	Severe claudication
III		Ischaemic rest pain	←→	II	4	Ischaemic rest pain
IV		Ulceration or gangrene	←→	III	5	Minor tissue loss
				III	6	Major tissue loss

1.2 DIAGNOSIS

The ankle-brachial index (ABI) is the easiest method to diagnose LEAD. Brachial blood pressure is measured in both arms (to avoid errors due to upper extremity occlusive disease), and in both the dorsalis pedis artery and posterior tibial artery. The highest of these pressures is then divided by the highest arm pressure. An ABI of 1 is normal and lower values, <0.9, are consistent with higher severity of LEAD. The exception is the presence of severely calcified uncompressible crural arteries, which will give falsely high ABI values.

Digital subtraction angiography (DSA) is seen as the reference method for arterial imaging. It is an invasive technique using radiation, where a catheter is placed into the artery to inject contrast medium. Mainly due to its invasiveness, DSA is usually not the primary imaging modality for diagnostic purposes. Typical angiographic images are two-dimensional (2D), but many modern imaging machines have the ability to obtain rotational, three-dimensional (3D), images by means of cone-beam computed tomography (CBCT). Iodinated contrast agents are mostly used, but DSA can use carbon dioxide as the contrast medium, e.g. in patients with impaired renal function.

Duplex ultrasound is a non-invasive imaging technique that uses a combination of blood flow acquisition with pulsed Doppler spectral analysis and the anatomic information from colour Doppler and/or B-mode. The interpretation of the images is based on both the anatomic information (presence of stenosis etc.) and the flow information (increased/decreased flow velocity and pulse curves) from the test.[14]

Computed tomographic angiography (CTA) uses radiation, and the X-ray tube and the detector rotate around the patient, while the patient slides through the gantry of the CT. This gives thin-sliced trans-axial images that can be used as an image volume to produce 3D reconstructions. This technique results in a higher dose of radiation than conventional X-ray.[15] The contrast enhancement is normally obtained with iodinated contrast agents. In comparison to MRA, CTA has the benefit of often being more immediately available, partly due to lower cost and relatively fast image acquisition with shorter scan times, with higher spatial resolution.[16]

Magnetic resonance angiography (MRA) produces images by polarizing protons through a large external magnetic field, normally 1.5 Tesla (T) or 3T, which is modified by applying oscillating magnetic fields, known as radio-frequency fields (RF). The signals produced by the protons are then detected by a receiver coil. MRA images can be obtained both as 2D and as 3D dimensional data. The ability to produce images without ionizing radiation is one of the advantages over CTA. Further, angiography with magnetic resonance imaging can be obtained without contrast enhancement, usually through time-of-flight (TOF) imaging. The blood is visualized by magnetizing protons in the blood in one slice that will move with the blood flow to the region of interest, thereby creating a greater signal than the surrounding tissue in the region of interest. Potential downsides of TOF angiography are artifacts due to flow velocity, and direction, which might be a problem in, for example, tortuous or horizontally oriented vessels. Over the last few years, improvements have been made to non-contrast MRA techniques.[16] However, in clinical practice, for diagnosis of LEAD, contrast-enhanced MRA is still normally preferred. Gadolinium-based contrast agents are used due to the paramagnetic properties of this element.[17] Gadolinium-based contrast agents are safer in patients with renal insufficiency compared to iodinated contrast agents, as normally used in CTA. MRA can also produce time-resolved images, which add a functional assessment to the images.[16]

Arterial lesions can be graded using the Transatlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) classification.[18] This classification was originally introduced in 2007, but initially it did not include the infrapopliteal segments. In 2015, the TASC II classification was extended to include the infrapopliteal segments.[19] The classification is based on the anatomical location, the characteristics of the lesion, and—in the infrapopliteal segment—the target vessel of an intended revascularization procedure. Lower-extremity vascular lesions are classified on a scale as either A, B, C, or D with increasingly severe vascular lesions. In the infrapopliteal segment a TASC A lesion corresponds to a focal short (≤ 5 cm) stenosis. Lesions graded TASC C and D includes multiple stenosis or occlusions with longer lesion lengths (≥ 10 cm).

1.3 MEDICAL TREATMENT

The first priority in treatment of patients with LEAD is controlling cardiovascular risk factors. Smoking cessation is one of the mainstays in reducing atherosclerotic risk. Smoking imposes worse outcome after revascularization procedures.[20] In addition, a healthy diet, weight loss, and physical activity are recommended.[21]

Physical activity reduces the cardiovascular risk mainly by reducing blood pressure and inflammatory processes.[22] In IC patients, physical activity plays an especially important role in improving symptoms, partly by stimulating angio-neogenesis.[23] An increased level of physical activity is also associated with a decreased risk in mortality and cardiovascular morbidity in patients with LEAD.[24]

As primary prevention, the positive effect of low-dose acetylsalicylic acid (LDASA) is ambiguous in a general population since the positive effects not clearly compensate the increased risk of bleeding.[25] In symptomatic PAD patients the use of anti-platelet therapy, such as LDASA, has been shown to reduce the risk of myocardial infarction and stroke.[26] LEAD patients are therefore usually prescribed LDASA. Also, treatment of hyperlipidaemia, hypertension, diabetes, and other risk factors is recommended in current guidelines.[21] Even though there has been an increase over time, a large proportion of PAD patients are still under-treated in regard of cardiovascular preventive medication.[27] In a more recent Swedish study only 45% of CLTI patients and 65% of IC patients were offered best medical treatment (defined as patients concomitantly being treated with statins in combination with antiplatelet or anticoagulant therapy) preoperatively.[28]

1.4 REVASCULARIZATION

In patients with intermittent claudication, the first line of treatment has the aim of targeting cardiovascular risk factors, and promote angio-neogenesis, by interventions in lifestyle factors and pharmacological treatment. In IC patients with more severe symptoms and in most CLTI patients, some kind of revascularization procedure is recommended.[21] Revascularization can be performed either as open surgery or as an endovascular intervention.

The most common open surgical procedures for LEAD are femoral thrombendarterectomy, where a local plaque is removed through an arteriotomy, usually in the common femoral artery, and by-pass surgery either with an autologous saphenous vein or with a prosthetic graft.

Endovascular procedures are usually performed through an access in the common femoral artery in the groin. Under fluoroscopic guidance, guide-wires and catheters are then used to reach the stenotic or occluded segment where a percutaneous transluminal angioplasty (PTA) balloon or stent is inserted to dilate the vascular lesion. During endovascular procedures, diagnostic images are normally obtained using DSA technique for guidance and for completion control.

Which technique is used depends on patient characteristics (age, comorbidities, the extent of wounds or infection) and lesion characteristics (lesion length, stenosis versus occlusion, proximal versus distal lesion, the number and quality of patent run-off vessels). The BASIL-trial was a randomized controlled trial comparing open surgery by-pass to endovascular revascularization in patients with severe limb ischaemia (SLI, equal to CLTI).[29] In the endpoint amputation-free survival (AFS) no difference was seen between the methods in the one and three-year follow up. However, for patients living beyond two years from randomization, survival rates were better for patients randomized to by-pass surgery. A majority of infrainguinal revascularizations are today performed by an endovascular technique, as shown in Paper I.

It is still not clear which infrapopliteal vessel to choose when performing a revascularization procedure. The angiosome concept, initially described in 1987, gives an anatomic description of the vascular territories in the leg and foot, defined as angiosomes.[30, 31] In a recent meta-analysis, the authors concluded that the existing data is of low quality, but there seems to be a preferable effect of direct (revascularization of the vessel corresponding to the affected vascular territory) versus indirect revascularization.[32] These results are in line with the recommendations in the current European guidelines.[21] The number of patent vessels also appears to be of importance for limb salvage rates, where more than one patent vessel after a revascularization procedure is preferable.[33, 34] It is still an ongoing debate whether the positive outcomes, seen in multi-vessel recanalizations, is the effect of increased probability for revascularizing the correct angiosome, or if the multi-vessel revascularization itself is the reason for improved.[35]

1.5 AMPUTATION

In patients not suitable for a revascularization procedure or when the revascularization procedure is unsuccessful in giving a sufficient blood flow to the affected limb, a lower extremity amputation is an alternative. Amputation is one of the oldest surgical procedures and is often successful in achieving pain relief in patients with severe ischaemia. It is also a useful tool for controlling an infection affecting the limb.[36] The most commonly performed amputations are in toes and foot, i.e. one or several affected toes, transmetatarsal, Lisfranc's, or Chopart's joint. These amputation levels all have in common that more or less of the foot is intact lending variable ambulatory support. In more advanced ischaemia or when the blood flow is compromised to the foot or lower leg, an amputation at higher levels can be performed. These are most commonly performed transtibial, through the knee, transfemoral, and hip disarticulation. Depending on amputation level—with better ambulatory prognosis in more distally performed amputation—different types of prosthesis are available for ambulatory patients.[37] Major amputations, i.e. transtibial and above are associated with high mortality rates, both in short and long term.[38] Proximal amputations have been found to have an association with higher mortality rates.[39, 40]

1.6 WHICH PATIENTS SHOULD BE REVASCULARIZED, AND WHEN?

What patient to revascularize and when depends on the clinical picture. A patient presenting with severe symptoms of LEAD, especially with rest pain and/or tissue loss, will be evaluated using some kind of imaging technique such as MRA. If the MRA shows vascular lesions that would explain the patient's symptoms, a revascularization procedure is probably justified. In clinical praxis, the time frame concerning when to intervene will mainly depend on the patient's symptoms. However, the current guidelines give little support regarding risk stratification between rest pain and/or tissue loss.[21]

Clinical experience guides physicians in prognosing patients with LEAD. The most severe outcomes for the patient are amputation and death. Amputation and mortality rates after a revascularization procedure have decreased over the years in LEAD patients, but these outcomes still remain a considerable risk.[41-43]

There have been numerous attempts to produce risk stratification scores over the years, of which some are summarized in Table 2. Patients with CLTI are a complex group to study, and this diversity is shown in the numerous different grading systems available. The risk scores cover various aspects of the symptomatology, different time spans, and different outcome measures. Further knowledge on the relative impact of individual risk factors, such as comorbidities, preoperative symptoms, and the anatomic location is warranted and requested.[44]

It is therefore of importance to gain a better understanding of the impact of comorbidities and preoperative symptoms on the kinds of outcomes that can be expected after intervention for chronic limb-threatening ischaemia.

Table 2: A selection of present risk stratification systems.

	FINNVASC[45]	*PREVENT III*[46]	*BASIL*[47]
Patient group	CLTI	CLTI	SLI
Variables	1 point each for: Diabetes Gangrene Coronary artery disease Urgent operation	Dialysis (4 points) Tissue loss (3 points) Age > 75 years (2 points) Coronary artery disease (1 point)	Tissue loss BMI Creatinine Bollinger score Age Smoking Coronary artery disease Ankle pressure
Output method	Stratified by sum of points (1-4 points)	Low risk (≤3 points) Medium risk (4-7 points) High risk (≥8 points)	Calculated by a model available online[48]
Predicted outcome	30 day mortality and limb loss	1 year AFS	2 year survival

BMI = Body mass index, AFS = Amputation-free survival, CLTI = Chronic limb-threatening ischaemia, SLI = Severe limb ischaemia.

2 AIMS

The aim of this thesis work was to compare characteristics of revascularized patients with chronic limb-threatening ischaemia (CLTI) and those of patients with intermittent claudication (IC); to find factors that affect the outcome in terms of amputation and mortality after interventions for chronic limb-threatening ischaemia (CLTI); and to evaluate whether infrapopliteal CLTI can be assessed using preoperative MRA.

More specific, the aims were:

- to determine differences in preoperative comorbidities in revascularized IC and CLTI patients (Paper I);
- to determine the risk of amputation and mortality in patients who have been revascularized for IC and CLTI (Paper I);
- to evaluate the impact of comorbidities, medication, and gender on amputation rate and mortality after revascularization for CLTI (Paper II);
- to determine the impact of preoperative symptoms (i.e. rest pain and/or tissue loss) and the level of revascularization on the risk of amputation and mortality (Paper III);
- to compare infrapopliteal TASC II classification as assessed by preoperative MRA and TASC II grading by the reference method DSA (Paper IV);
- to explore an alternative score for summation of disease severity in all infrapopliteal vessels (Paper IV).

3 MATERIALS AND METHODS

The original cohort used in this thesis consisted of all Swedish patients who were revascularized for lower-limb PAD between May 2008 and May 2013. Altogether, we identified 16,889 patients using the Swedish National Quality Register for Vascular Surgery (Swedvasc).

In Paper I, the patients were analyzed in two subgroups: IC (n = 6,272) and CLTI (n = 10,617). In Papers II and III, we performed subgroup analysis of patients with CLTI. Paper IV differed methodologically, and this cohort contained a (somewhat extended) small subgroup of patients treated with an isolated infrapopliteal revascularization performed at Sahlgrenska University Hospital in Gothenburg between 2008 and 2016. The structure of the four papers is illustrated in Figure 1.

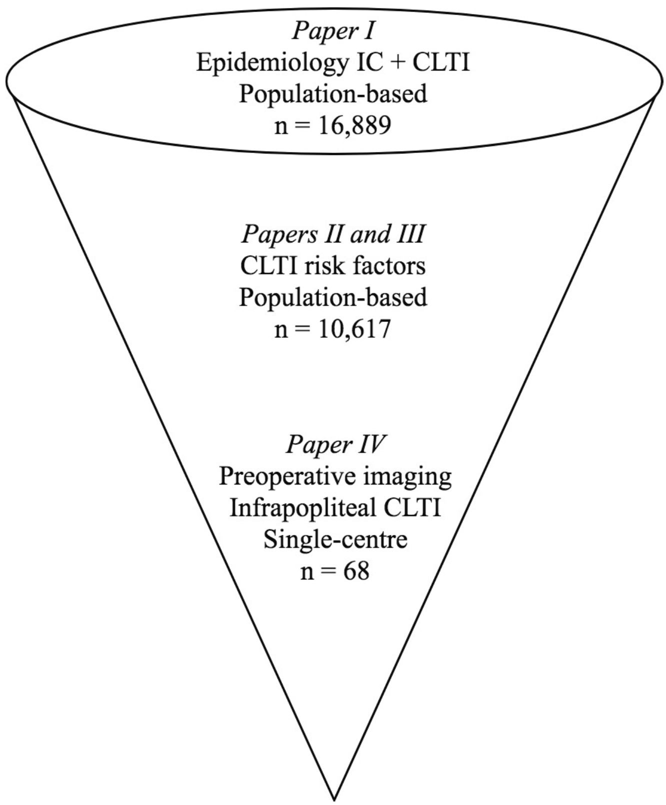


Figure 1: Schematic presentation of the four papers included in this thesis.

All patients included were ≥ 50 years of age. The age limit was set to lower the risk of including revascularization procedures performed for reasons other than atherosclerosis. All of the patients had undergone lower limb revascularization by either open surgical or endovascular techniques for symptomatic LEAD. Each patient is only included once in our studies, even though some had additional subsequent revascularizations. Additional revascularizations during the study period were not analyzed, even though performed in the other leg. One patient in our cohort corresponds to one limb.

Ethics

The studies in this thesis were approved by the Regional Ethical Review Board of the University of Gothenburg, Sweden (reference numbers 873-14, T084-16, 220-17, and T1060-17).

3.1 DATA SOURCES

Epidemiological data were collected from national and mandatory healthcare registries, which are presented in more detail below. We concentrated on two hard endpoints, amputation and death. To ensure that we had as accurate data as possible for the amputation endpoint, a large number of patient medical records were reviewed. A flow chart showing data collection in Papers I–III is given in Figure 2.

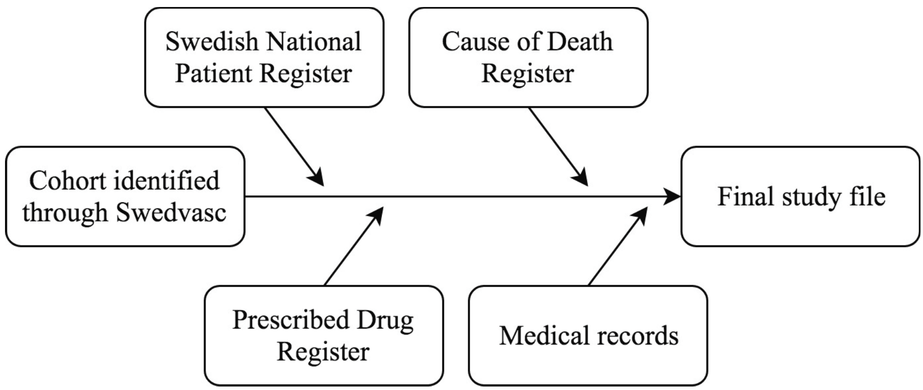


Figure 2: Flow chart for data collection, Papers I–III.

The Swedish National Registry for Vascular Surgery, Swedvasc (Papers I–IV)

Swedvasc started in 1987 and reached full coverage of all Swedish centres performing vascular surgery in 1994.[49, 50] Every year, around 12,000 procedures are registered in Swedvasc, about 3,000 of which are primary lower-limb PAD procedures. Validation studies have repeatedly found that Swedvasc has a high degree of accuracy.[51, 52] Data on the revascularization procedure, i.e. date, indication, and revascularization method, was retrieved from Swedvasc.

THE NATIONAL PATIENT REGISTER (PAPERS I–III)

The NPR started in 1964 and is mandatory for all county council caregivers in Sweden. The register is supervised by the National Board of Health and Welfare and covers over 99% of all hospital discharges. Information on hospital stays, diagnosis, and operations is included in the register. Since 1997, the International Classification of Diseases, 10th revision (ICD-10) has been used for coding of diagnoses. Since 2007, it has been mandatory to report operations performed (such as amputations) to the NPR using a national Swedish coding system where all health interventions have a specific code, based on the type of intervention and the anatomical location.

Information on comorbidities and amputations were received through the NPR. Comorbidities included the time period from 1997 to the index date (date of revascularization). Amputation procedures were searched until December 31, 2013.

CAUSE OF DEATH REGISTER (PAPERS I–III)

The Cause of Death Register is also supervised by the National Board of Health and Welfare. All deaths of Swedish citizens in Sweden and abroad have been registered in this register since 1961, and coverage the event of death is close to 100%. Data in the Cause of Death Register, in combination with the NPR, have previously been found to have high accuracy regarding other patient populations with cardiovascular disease.[53]

THE PRESCRIBED DRUG REGISTER (PAPERS I–III)

This register has been active since 2005, and, because it is mandatory, it contains almost 100% of all the drugs dispensed in Swedish pharmacies. The register is kept by the National Board of Health and Welfare and drugs are classified according to the anatomical therapeutic chemical (ATC) classification system.[54]

Only dispensed drugs from the pharmacy were included in the analysis. Prescribed medications that were not collected by the patient were not included. Dispensed drugs from four months before the index procedure until the day of revascularization were included in the analysis with the exception for low-dose acetylsalicylic acid (LDASA) and statins, as these drugs are often initiated during the same hospital admission as the CLTI revascularization procedure.[28] For these latter drugs, the time period for analysis included four months before and one month after the revascularization.

Medical records (Papers I–III)

In order to ensure that there were as accurate data as possible on amputations, the individual medical records of patients who were registered as having had amputation in the NPR, but where there was missing information on this in Swedvasc were examined. In Swedvasc, follow-up is kept to a maximum of one year and information beyond one year was retrieved from the NPR. The review was performed in the medical charts, at the treating hospital. Altogether, the medical records of 1,366 patients throughout Sweden were reviewed.

Imaging material (Paper IV)

Magnetic resonance images (MRIs) from patients who were revascularized infrapopliteally between 2008 and 2016 at Sahlgrenska University Hospital were obtained from the hospital picture archiving and communication system (PACS). The examinations were enhanced with gadolinium-based contrast and had been carried out on 1.5 T magnetic resonance systems using standard clinical protocols (for further details, see Paper IV). The images were presented as static 3D maximum-intensity projections (MIP) and/or dynamic MIP series.

Digital subtraction angiographies (DSAs) were also obtained from the local PACS. These images were captured during the endovascular revascularization procedures.

Figure 3 shows the data collection process leading to the final analyzed cohort.

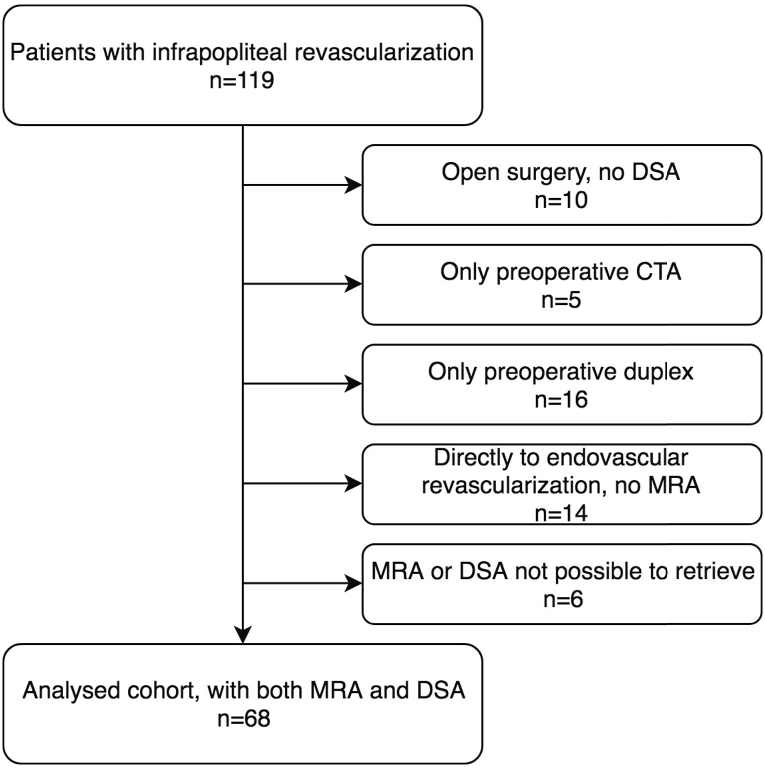


Figure 3: Flow chart on the cohort identified, and exclusions that led to the final cohort.

3.2 OUTCOME AND EVALUATION

AMPUTATIONS (PAPERS I–III)

We defined the outcome amputation as an amputation performed above the ankle. Patients undergoing minor amputations (toe, metatarsal, or forefoot) were not included in the analysis. Time to amputation was defined as the time elapsed between the index date and the first ipsilateral amputation. Possible amputations were identified through the NPR. Using operation codes, we identified amputations performed above the ankle using NFQ09 (hip exarticulation), NFQ19 (transfemoral amputation), NGQ09 (knee exarticulation), and NGQ19 (transtibial amputation). In most cases, codes of laterality of amputation performed and the exact amputation date were not present in the register. In these cases, we reviewed the medical records of the patients to obtain precise information on laterality and the date of amputation.

MORTALITY (PAPERS I-III)

Mortality was defined as all-cause mortality that occurred during the study period, i.e. death from any reason, not necessarily as a direct result of LEAD or the performed revascularization procedure. For Paper I and II mortality was included until December 31, 2013 and for Paper III until May 13, 2015.

IMAGE EVALUATION (PAPER IV)

Image evaluation was done using ViewDEX software, which is a dedicated in-house-developed image viewer for research and optimization tasks in medical imaging.[55-57] ViewDEX allowed us to present the images to the observers in random order and anonymized. It also permitted us to ask specific questions about the characteristics of the lesions and the image quality.

TASC II AND IALSS (PAPER IV)

Image evaluation was done according to the TASC II classification. Four observers participated in the study. Observer 1 and 2 evaluated the full set of MRAs and DSAs twice each, starting with MRA. Observer 3 evaluated one set of MRAs and observer 4 evaluated one set of DSAs. Thus, each study was reviewed by three observers for inter-observer analysis and twice by two observers for intra-observer analysis. The observer was asked to assess each infrapopliteal vessel according to TASC II as if this vessel were to be the target vessel. After this procedure was performed, the observer was asked to make a selection of his or her preferred target vessel, depending on the image and own clinical experience, and to make a TASC II classification depending on the chosen target vessel.

One of our hypotheses was that the choice of infrapopliteal target vessel, as required by the TASC II classification, would differ between observers, and also that more than one vessel could act as target vessel in some cases. For these reasons, we created an infrapopliteal aggregated lesion severity score (IALSS) based on the infrapopliteal TASC II class. In order to calculate the additive effect of lesions in several infrapopliteal arteries, the TASC II class of each vessel was translated into an integer (0–4). A vessel without lesions was scored as 0. A type A lesion was scored as 1, a type B lesion was scored as 2, and so on. Combining the points from the TASC II class of each vessel, gave a scale between 0 and 15, i.e. a maximum of 3 points for tibiofibular trunk, due to its limited length, and 4 points to each of the three other infrapopliteal vessels.

STATISTICS

For Papers I–III, only the first revascularization procedure performed during the study period was included in the analysis. If a patient had repeated revascularizations or deteriorated from IC to CLTI during the study period, that patient was analyzed on the basis of the initial category. For descriptive statistics, mean ± SD, median with range, and absolute and relative frequencies were used. Differences between groups were analyzed using the χ^2 and Mann-Whitney U tests. Preoperative comorbidities were presented as age-adjusted frequencies, where we used a direct adjustment for age. For multivariable-adjusted analysis of time to amputation, death, and the combined endpoint of amputation or death, Cox proportional hazards models were used in a three-step procedure. First, univariable models included each covariate separately. Each covariate with a p-value < 0.05 in the univariate model was then inserted into the multivariable regression analysis. In the third step, an optimal model was defined with the minimum Akaike information criteria value by using a stepwise selection of covariates. Results from the Cox regression models are presented as hazard ratios (HRs). Kaplan-Meier curves were used for graphical presentation of cumulative incidence. In Paper III a competing-risk analysis was performed on the risk of amputation with the risk of death taken into account. For patients who were registered in the NPR as having had amputation but where there were remaining uncertainties about the exact date or laterality of the amputation performed, even after review of the medical records, the data were censored at the time of registration in the NPR. We also performed a sensitivity analysis in which these patients were regarded as having had an amputation.

In Paper IV, visual grading characteristics (VGC) analysis[58, 59] was used for evaluation of TASC II using MRA and DSA. VGC analysis gives an area under the curve (AUC_{VGC}), describing the degree of separation between the two datasets. An AUC_{VGC} of 0.5 indicates equality between two datasets. Krippendorff's α[60] was used to estimate inter- and intra-observer agreement, where lower α values correspond to a weaker agreement. As a rough rule of thumb, a Krippendorff's α value ≥ 0.67 can be considered to be acceptable.

3.3 QUALITY OF DATA

As a reader of this thesis, it may be difficult to get an overall impression of the data, as many registers and medical records were used. Data quality is important regarding how to interpret results and how to draw conclusions. Data merging was done based on the unique Swedish personal identification number. The cohort was identified through the Swedvasc register, which has shown an accuracy of > 95% in validation studies.[51, 52] The mandatory NPR, the Prescribed Drug Register, and the Cause of Death Register cover > 99% of all hospital admissions in Sweden, > 99% of all prescribed drugs in Sweden, and > 99% of all deaths of Swedish citizens that occur in Sweden and abroad. Amputation codes were searched in the NPR using the ICD-10 coding system. In total, 2,394 patients in our total cohort of 16,889 (14.2%) had an amputation registered in the NPR. In cases where the code for laterality or the exact date was missing, we reviewed the medical records on site. Altogether, the medical records of 1,366 patients were reviewed. After this procedure was completed, we were still not able to obtain full amputation data on 232 remaining patients (12 of 119 patients with IC (10.1%) and 220 of 2,275 patients with CLTI (9.7%)) and these patients were censored at the time of amputation registered in the NPR. To determine how the remaining uncertainties might possibly affect our results, we performed a sensitivity analysis whereby patients for whom there was some degree of uncertainty were considered to have an event. This changed the results only marginally.

4 RESULTS AND COMMENTS

Altogether, we analyzed 16,889 patients where 6,272 (37%) were revascularized for IC and 10,617 (63%) were revascularized for CLTI. The follow-up time ranged from 0 to 6.6 years, with a median of 3.1 years. For IC patients the median follow-up time was longer, 3.8 years, whereas for CLTI patients it was 2.7 years. In both groups, endovascular procedures were performed more commonly than open surgery, and 79.8% of revascularization procedures in IC and 75.6% in CLTI were endovascular.

Baseline demographics and comorbidities are presented in Table 3.

Age-adjusted preoperative comorbidities showed approximately twice the prevalence of diabetes, ischaemic stroke, heart failure, and atrial fibrillation in CLTI patients compared to IC patients. The prevalence of renal insufficiency was almost threefold greater and the prevalence of dementia was almost fivefold greater in CLTI patients than in IC patients.

On the other hand, we found no significant difference between groups in the prevalence of angina pectoris, transient ischaemic attacks (TIAs), or cancer.

Table 3. Baseline demographics and age-adjusted comorbidity rates for patients with intermittent claudication (IC) and patients with chronic limb-threatening ischaemia (CLTI) at admission for revascularization

	IC (n = 6,272)	**CLTI** (n = 10,617)	**p-value***
Demographics**			
Gender, n (%)			
Women	2,858 (45.6%)	5,390 (50.8%)	< 0.001
Men	3,414 (54.4%)	5,227 (49.2%)	< 0.001
Age, years			
Mean (SD)	70.0 (8.4)	76.8 (9.6)	< 0.001
Median (range)	70 (50–96)	78 (50–103)	
Comorbidity, n (%)***			
Hypertension	5,208 (83.0%)	9,024 (85.0%)	0.001
Angina pectoris	1,786 (28.5%)	2,936 (27.7%)	0.257
Myocardial infarction	939 (15.0%)	2114 (19.9%)	< 0.001
Heart failure	801 (12.8%)	2944 (27.7%)	< 0.001
Atrial fibrillation	892 (14.2%)	2564 (24.2%)	< 0.001
Ischaemic stroke	522 (8.3%)	1548 (14.6%)	< 0.001
TIA	393 (6.3%)	708 (6.7%)	0.321
Diabetes mellitus	1,630 (26.0%)	5,010 (47.2%)	< 0.001
Chronic obstructive pulmonary disease	706 (11.3%)	1,476 (13.9%)	< 0.001
Chronic renal insufficiency	154 (2.5%)	713 (6.7%)	< 0.001
Aortic aneurysm	395 (6.3%)	436 (4.1%)	< 0.001
Arterial embolism and thrombosis	56 (0.9%)	131 (1.2%)	0.049
Cancer	1,267 (20.2%)	2,068 (19.5%)	0.263
Dementia	33 (0.5%)	279 (2.6%)	< 0.001

** p-value for differences between IC and CLI patients.*
*** Data from the Swedvasc Registry.*
**** Data from the Swedish National Patient Register (NPR).*
SD, standard deviation; TIA, transient ischaemic attack.

COMMENTS

The purpose of this section is to shed some light on differences between patients who are revascularized for IC and those who are revascularized for CLTI in terms of age, gender, and comorbidities. Even though the data on comorbidities are age-adjusted, there are differences between the patient groups with greater morbidity in CLTI patients, mainly from an increased prevalence of diabetes, ischaemic stroke, heart failure, atrial fibrillation, renal insufficiency, and dementia. This can be explained to some extent by a higher threshold for surgical interventions in IC patients than in CLTI patients. It could also reflect an inherent difference between the two groups, which might also be part of the relatively rare progression from IC to CLTI.[18, 61] Interestingly, no difference in the prevalence of angina pectoris or TIA was found, which can probably be explained by the fact that, even though they do not have as severe symptoms in the lower extremity as CLTI patients, IC patients still suffer from severe atherosclerosis that affects other organs, resulting in as frequent manifestation of these comorbidities as in CLTI patients. Interestingly, the prevalence of abdominal aortic aneurysm was higher in patients revascularized for IC than in patients revascularized for CLTI. One explanation for this could be the different comorbidity panorama with a lower prevalence of diabetes in the IC group. As diabetes, or the diabetes medications, probably have a protective effect against aortic aneurysm, this at least in part, could be the explanation to our finding.[62]

4.1 CLTI AND THE RISK OF AMPUTATION

Patients with CLTI have a high risk of amputation, both in absolute numbers and in comparison to IC patients. There was a high risk of amputation mainly within the first 6 months after revascularization, as 12% of CLTI patients and 0.3% of those registered as IC patients underwent amputation after 6 months. Amputation rates in CLTI patients level out after approximately one year (14.8% amputated) and remain at around 2% per year. Amputation rates in those registered as IC patients are linear over time, at around 0.4% per year. Differences in amputation rates are presented in Table 4 and are shown as Kaplan-Meier curves in Figure 4.

A Cox regression analysis revealed factors associated with the risk of amputation.

Increased amputation risk was seen in male patients (hazard ratio [HR] 1.20, 95% CI 1.09–1.33) and patients with renal insufficiency (HR 1.57, 95% CI 1.32–1.87), diabetes (HR 1.45, 95% CI 1.32–1.60), heart failure (HR 1.17, 95% CI 1.05–1.31), and atrial fibrillation (HR 1.15, 95% CI 1.03–1.29).

Table 4. Cumulative incidence of ipsilateral amputation in patients revascularized for intermittent claudication (IC) or chronic limb-threatening ischaemia (CLTI). Data are presented as percentage (95% CI)

	IC	**CLTI**
6 months	0.3 (0.2–0.4)	12.0 (11.3–12.6)
12 months	0.5 (0.3–0.7)	14.8 (14.1–15.5)
24 months	0.9 (0.7–1.2)	17.2 (16.4–17.9)
36 months	1.2 (0.9–1.5)	18.6 (17.7–19.4)

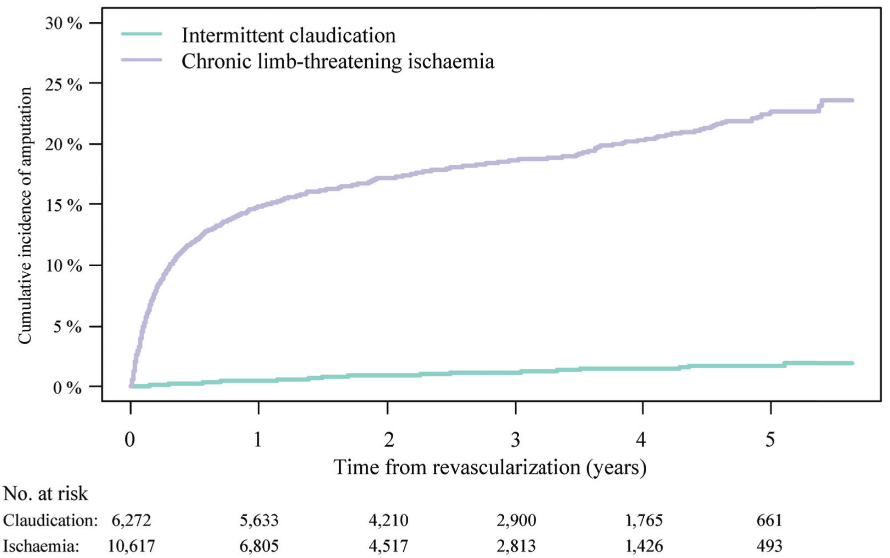


Figure 4. Kaplan-Meier curves of cumulative incidence of amputation for intermittent claudication (IC) patients and chronic limb-threatening ischaemia (CLTI) patients

The type of CLTI symptoms, i.e. rest pain, tissue loss, or a combination of rest pain and tissue loss, plays an important role in the risk of amputation. The latter groups were observed to have the highest risk. In comparison, patients with tissue loss alone had an observed HR of 0.72 (95% CI 0.64–0.82) and those with rest pain alone had an observed HR of 0.37 (95% CI 0.31–0.43). Kaplan-Meier curves showing the cumulative incidence of amputation for the three groups are presented in Figure 5.

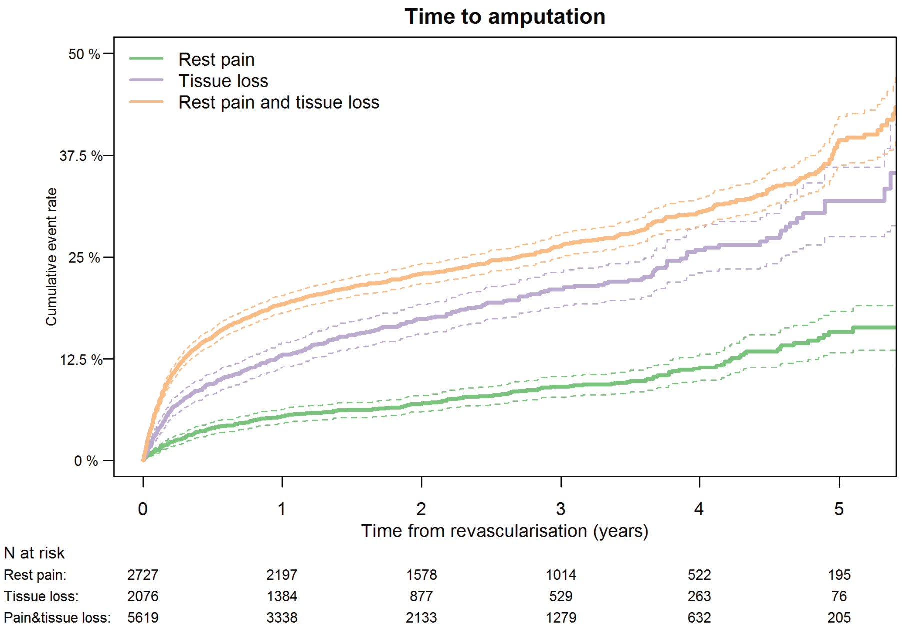


Figure 5: Cumulative incidence of amputation in CLTI patients, stratified by preoperative symptoms. Dashed lines indicate the 95% confidence intervals.

To determine how the mortality in CLTI patients affected the risk of a major amputation, a competing-risk model was created, as presented in Figure 6. This model showed that the main adverse events that occurred after revascularization were amputations, but over time mortality played an increasing role affecting the risk of amputation.

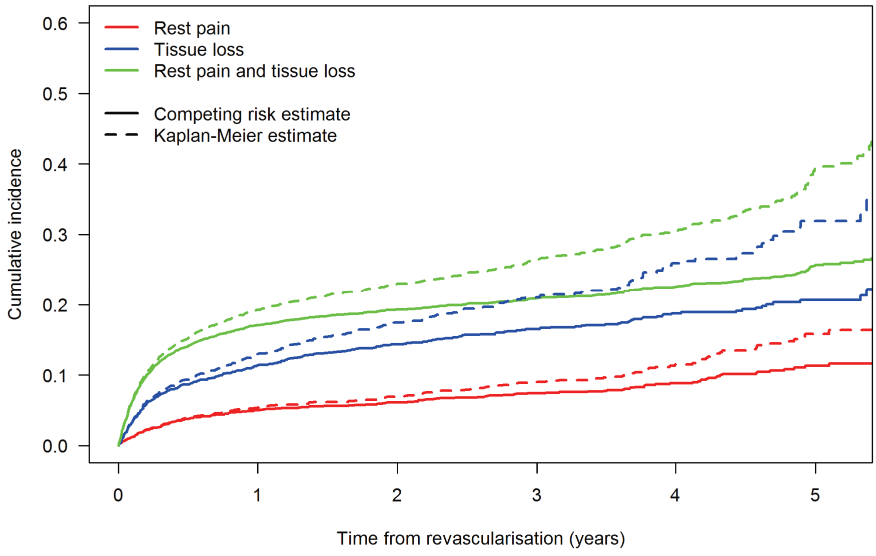


Figure 6: Comparison of competing-risk estimate and Kaplan-Meier curves of the risk of major amputation in CLTI patients, stratified by preoperative symptoms.

The Cox regression model revealed that there was no difference in risk when comparing the method of revascularization: open versus endovascular (HR 0.99, 95% CI 0.88–1.11); nor was there a difference in amputation risk when analyzing the level of revascularization: femoropopliteal versus aortoiliacal (AI) revascularization (HR 0.87, 95% CI 0.74–1.02) and infrapopliteal versus AI (HR 1.04, 95% CI 0.84–1.28).

Some factors were also associated with a decrease in risk. In the Cox regression model, LDASA (HR 0.77, 95% CI 0.69–0.87) and statins (HR 0.71, 95% CI 0.64–0.78) had such an association.

COMMENTS

CLTI patients have a high risk of amputation. The risk is especially high in the first 6 months after revascularization; thereafter, the curve flattens out and the risk stabilizes at around 2% per year. This may be due to a number of causes; obviously the revascularization procedure itself aims to resolve the ischaemic problem. For some patients, the revascularization procedure is not successful and the patients become candidates for amputation. In the cases with a successful revascularization procedure, the patient's symptoms have improved and the risk of amputation decreases. This might also be an effect of more revascularizations over time being performed in patients with more comorbidities, thus making them more vulnerable.[42] A theory based on our results would be that the high initial amputation rates might also be due to a temporarily more critical phase in the patient's longstanding chronic ischaemia. This condition, often described as "acute-on-chronic", might be triggered by numerous factors, for example, a recent traumatic wound, thrombosis or embolus in chronically diseased leg arteries, the time required for development of collaterals, infection, neuropathy, and aggravated heart failure—giving a cascade of deteriorating symptoms that would lead to a more acute need for revascularization and also an increased risk of amputation. When these factors are optimally treated and at stable levels, the patient reverts to having an annual risk of around 2%. This suggests that it may not be only the chronic and stable lesions of the lower-limb arteries that contribute to patient symptoms in CLTI, but also some kind of acute, temporal aggravation. Our results might also indicate that such a temporary deterioration plays a more important role than has generally been believed.

High mortality rates in these patients are problematic when studying amputation rates, as patients that die are no longer at risk of having an amputation. In a real-world setup, as we intend to study, both outcomes affect the actual risk of having an event.[63] The Cox regression models estimate cause-specific hazards and are not affected by mortality events, but cumulative incidence based on Kaplan-Meier curves might be overestimated in the presence of competing risks. We, therefore, performed a competing-risk analysis, which showed that over time mortality plays an increasing role in the risk of amputation, making standard Kaplan-Meier curves overestimate amputation rates. Thus, the long-term risk of amputation is probably somewhat lower than presented in our Kaplan-Meier curves. This idea is supported in other recent work.[64] This is an interesting finding since amputation rates stabilize at a relatively low level after the first 6–12 months. Our findings might indicate that this risk, post the acute phase, is even lower.

In patients with CLTI, the amputation risk varies considerably depending on the preoperative symptoms. A patient with rest pain and tissue loss has an almost threefold higher risk of amputation than a patient with rest pain alone. These results are in line with both historical studies, by Taylor et al., and contemporary studies, by Mustapha et al., indicating that CLTI should be stratified into the presenting symptoms rather than being treated as one single entity.[65, 66] Our work confirms that these results are valid, but probably more importantly, giving estimate numbers on the relative risk connected to presenting symptoms. In Paper III, the difference between the presenting symptoms was larger than in the results reported by Mustapha et al., and more in line with those of Taylor et al. However, this may reflect a difference in reporting standards rather than a real difference in outcome. Furthermore, the Wound, Ischemia, and foot Infection (WIfI) classification also heighten the importance of CLTI symptoms, where wound, ischaemia, and foot infection are all taken into account.[67] The type of revascularization—open or endovascular—and the level of revascularization had no influence on the risk of amputation, which is consistent with the results of other contemporary studies.[66, 68]

Male patients have worse outcome than female patients in our study, which contradicts more historical studies but is more in line with contemporary work in this field.[69-71]

The nature of comorbidities and the kinds of medications the patient takes have an influence on the risk of amputation. Renal insufficiency, for example, is associated with a > 50% increase in risk of amputation and diabetes an increase in risk of just under 50%. On the other hand, if patients are being treated with statins or LDASA, a decrease in risk can be seen (by 29% and 23%, respectively). The protective effect of statin therapy has been elusive in studies of LEAD. In unselected LEAD populations, an association with reduced risk of amputation has been found.[72, 73] In CLTI patients, it has been difficult to show statistically significant associations between statin use and a reduced risk of amputation.[74, 75] In the randomized BASIL trial, statins were excluded from the prediction model due to low prescription rates in the randomized patients[29]. As many patients are being prescribed secondary preventive drugs such as statins and LDASA during their hospital stay for revascularization[28], we chose to include patients who were prescribed these drugs for 30 days after revascularization. This, in combination with our large cohort, made it possible to analyze the effect of statins and LDASA and obtain statistically significant results.

It has previously been shown that LDASA can have a limb-protective effect after bypass.[76] The findings of our study indicate that this effect might also be applicable to endovascular revascularizations. Even though guidelines strongly recommend the prescription of statins and LDASA in this patient group[21], a study in a similar cohort revealed that only 45% of CLTI patients are prescribed a combination of statins and an anti-platelet drug, such as LDASA, or anti-coagulant.[28] The results from this thesis justify further efforts to improve the use of preventive medication in this patient group.

4.2 CLTI AND THE RISK OF DYING

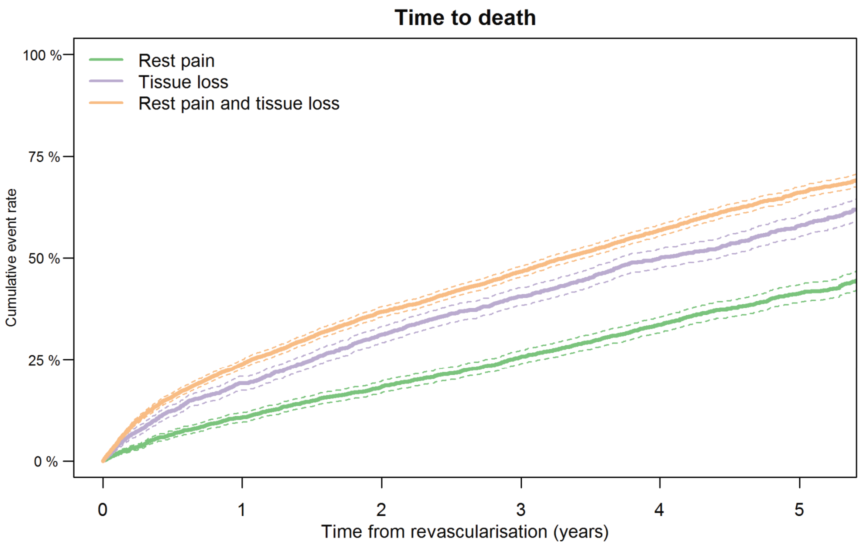
Regarding mortality, we found that CLTI patients had much higher mortality rates than IC patients, as one-year mortality after revascularization was 20.5% in CLTI patients and 3.4% in IC patients. Data on mortality are presented in Table 5.

Table 5. Cumulative incidence of mortality for intermittent claudication (IC) patients and chronic limb-threatening ischaemia (CLTI) patients. Data are presented as percentage (95% CI)

	IC	**CLTI**
6 months	1.6 (1.3–2.0)	13.5 (12.8–14.1)
12 months	3.4 (2.9–3.8)	20.5 (19.7–21.3)
24 months	7.5 (6.8–8.2)	31.7 (30.8–32.6)
36 months	12.0 (11.1–13.0)	41.4 (40.3–42.4)

Among comorbidities, renal insufficiency (HR 2.28, 95% CI 2.06–2.52) and heart failure (HR 1.90, 95% CI 1.79–2.01) were found to be associated with the highest increase in the risk of death. Diabetes (HR 1.16, 95% CI 1.09–1.23) and previous myocardial infarction (HR 1.20, 95% CI 1.12–1.28) had a lower impact on mortality risk.

Preoperative symptoms also play a role in the risk of death. The multivariable analysis of rest pain only versus the addition of tissue loss gave an HR of 0.59 (95% CI 0.54–0.63) and tissue loss only versus the addition of rest pain gave an HR of 0.87 (95% CI 0.81–0.94). This is presented graphically with Kaplan-Meier curves in Figure 7.



N at risk

Rest pain:	2727	2435	2230	1631	1102	632
Tissue loss:	2076	1679	1429	964	585	338
Pain&tissue loss:	5619	4277	3551	2434	1485	770

Figure 7: Cumulative incidence for mortality. Dashed lines indicate 95% confidence intervals.

The type of revascularization procedure did not change the risk of dying; endovascular versus open surgery gave an HR of 1.06 (95% CI 0.99–1.14). Proximal revascularizations, in the aortoiliacal (AI) segment were associated with higher mortality rates compared to infrainguinal procedures. Femoropopliteal versus AI revascularization revealed a decrease in risk (HR 0.73, 95% CI 0.67–0.79). Infrapopliteal versus AI revascularization gave an HR of 0.70 (95% CI 0.62–0.80).

Comments

The risk of death in a population is not easy to calculate, as it depends on a large number of factors and varies with time. However, according to the governmental Statistics Sweden[77], for individuals in Sweden aged 70 and 77 years, respectively (the mean ages of the patient groups IC and CLTI in our cohort), the expected annual risk of death in 2012 was 1.9% for men and 1.2% for women aged 70 years and 4.1% for men and 2.6% for women aged 77 years. In comparison to the outcome in our cohort, where IC patients had a one-year risk of death of 3.4% and CLTI patients had a mortality of 13.5% in 6 months, 20.5% in one year, and 41.4% in three years, we conclude that mortality is high in both groups, especially in CLTI patients, which is also supported by a more recent publication.[78] In fact, mortality rates are worse in CLTI patients than in patients with heart failure, stroke, and most cancers.[66]

A CLTI patient presenting with rest pain alone has almost half the risk of dying compared to a patient with both rest pain and tissue loss. This is interesting, since CLTI is described as one entity in European guidelines.[21] Our results are in line with previous and contemporary work in this field.[65, 66, 71]

We found an association between more proximal revascularizations and an increased mortality rate. Furthermore, we found an association between the revascularization level and the level of amputation. The amputation itself appears to be associated with an increased mortality risk.[66] A recent Danish study analyzing level of amputation and the risk of mortality found that more proximal amputations were associated with a higher risk of death.[39] In our work, we did not find higher amputation rates following proximal revascularizations—rather the opposite, even though these associations disappeared when we adjusted for comorbidities. A more proximal revascularization might rather be a surrogate measure of a more widespread atherosclerotic disease. These patients undergo proximal revascularizations, thus making a more proximal amputation a more lethal one, even though it may not be the amputation itself that causes the mortality. The specific causes of death in this subgroup of patients would therefore be interesting to study in future research.

No difference in mortality rate was seen when we compared open surgery to endovascular technique. Since the comparison between revascularization techniques was not one of our aims, one should be careful when drawing conclusions from this result. Similar results came out of another recent observational study.[66] However, it is interesting to note that the randomized

BASIL trial initially reported that there was no difference between revascularization techniques, but for patients who were alive after two years they found an increased overall survival in patients who underwent by-pass surgery.[79] The explanation for this is not fully known, and the authors discussed whether this could be an effect of more closely detailed follow-up programmes for by-pass surgery than for angioplasty.

4.3 CLTI AND AMPUTATION-FREE SURVIVAL

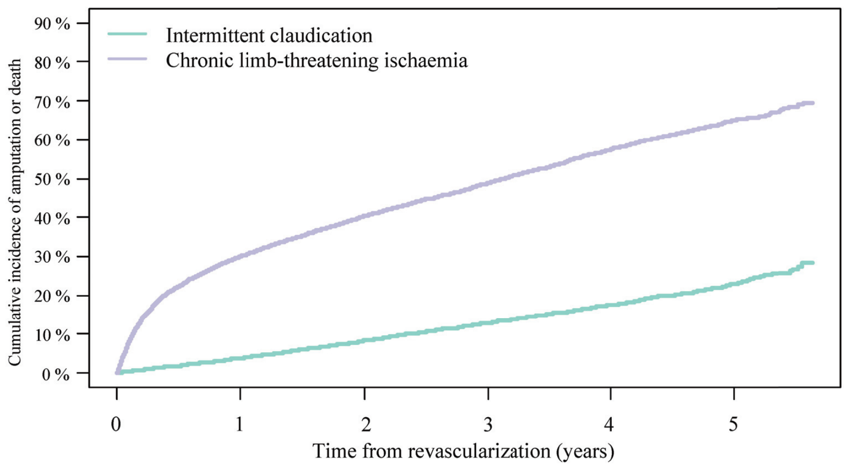
In the analysis of "adverse event" (i.e. amputation or mortality), a difference was seen between IC and CLTI patients. In 6 months, 1.9% of IC patients (95% CI 1.6–2.3) and 22.2% of CLTI patients (95% CI 21.4–23.0) had either undergone amputation or had died. The corresponding numbers after 36 months were 12.9% (95% CI 12.0–13.9) for IC and 48.8% (95% CI 47.7–49.8) for CLTI. The cumulative incidence of amputation or death for IC and CLTI patients is presented in Table 6 and shown graphically in Kaplan-Meier curves in Figure 8.

Table 6. Cumulative incidence of ipsilateral amputation or death in intermittent claudication (IC) patients and chronic limb-threatening ischaemia (CLTI) patients. Data are presented as percentage (95% CI)

	IC	**CLTI**
6 months	1.9 (1.6–2.3)	22.2 (21.4–23.0)
12 months	3.9 (3.4–4.3)	30.1 (29.2–30.9)
24 months	8.3 (7.6–9.0)	40.3 (39.3–41.3)
36 months	12.9 (12.0–13.9)	48.8 (47.7–49.8)

The Cox regression model identified risk factors for an increased risk of amputation or death: male gender (HR 1.25, 95% CI 1.18–1.32), renal insufficiency (HR 1.94, 95% CI 1.75–2.14), and heart failure (HR 1.50, 95% CI 1.40–1.60) were the factors associated with the largest increase in risk.

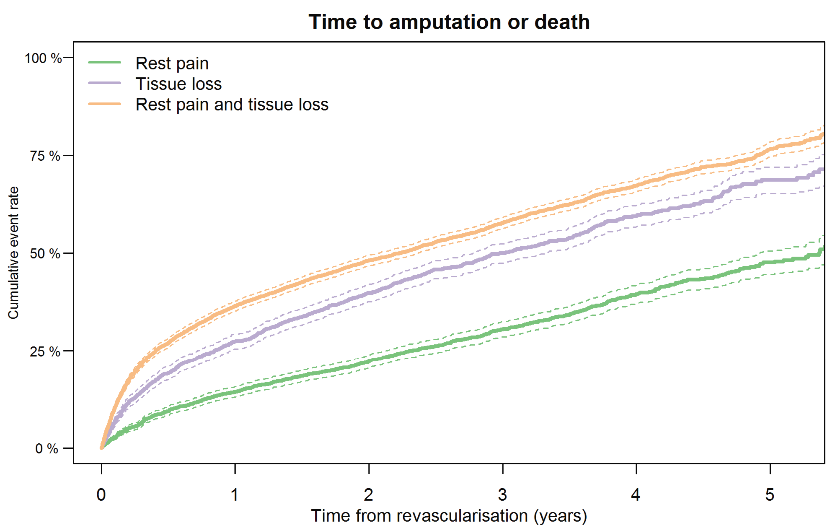
Preoperative symptoms play an important role in the risk of amputation or death. Rest pain only compared to both rest pain and tissue loss gave an HR of 0.51 (95% CI 0.47–0.55) and tissue loss alone compared to rest pain and tissue loss gave an HR of 0.80 (95% CI 0.75–0.87). Figure 9 shows Kaplan-Meier curves of cumulative incidence of amputation or death.



No. at risk

Claudication:	6,272	5,633	4,211	2,900	1,765	661
Ischaemia:	10,617	6,885	4,588	2,862	1,452	501

Figure 8. Cumulative incidence of "amputation or death" in revascularized intermittent claudication and chronic limb-threatening ischaemia patients.



N at risk

Rest pain:	2727	2197	1578	1014	522	195
Tissue loss:	2076	1384	877	529	263	76
Pain&tissue loss:	5619	3338	2133	1279	632	205

Figure 9: Cumulative incidence for the combined endpoint "amputation or death". Dashed lines indicate 95% confidence intervals.

No difference was seen between open surgery and endovascular revascularization (HR 1.04, 95% CI 0.97–1.12). A more distal revascularization was associated with a reduced risk (femoropopliteal versus aortoiliacal (AI): HR 0.79, 95% CI 0.72–0.86; and infrapopliteal versus AI: HR 0.80, 95% CI 0.70–0.91).

On the protective side, statins (HR 0.69, 95% CI 0.65–0.73) and low-dose ASA (HR 0.82, 95% CI 0.77–0.88) were associated with a decrease in risk.

COMMENTS

The combined endpoint of amputation or death—which is more often reported in this research field as amputation-free survival (AFS)—reflects the two outcomes already discussed. However, AFS is an important outcome to consider, as it reflects the overall risk of a poor outcome for the patient.

The risk of an adverse event is high both for IC patients and CLTI patients. An increased risk of an adverse cardiovascular event or death is in fact increased solely by the presence of a lowered ABI. However, the more severe the ischaemia is, the more the risk increases.[6] These facts have clearly been confirmed by the results in this thesis. Further, while the main risk lies in mortality for IC patients, CLTI patients have high amputation rates and high mortality rates. After 6 months, one quarter—and after three years, one half—of the CLTI patients have either had amputation or have died.

In this revascularized cohort, there was an even distribution of woman and men, but the revascularized women were significantly older than the men. When we adjusted for age in the Cox regression model, an increase in the risk of amputation and death among the men was seen. As discussed previously in this thesis, historically research suggested a worse outcome among women than in men.[69] However, more contemporary research, and also the findings in this thesis, indicate that revascularized men with CLTI have an increased risk of a poor outcome.[70, 71] Even though women seem to have a better result in terms of amputation and death, differences between the genders are still present, and there are indications that the symptomatology differs between men and women, that interventions performed might differ, and that women more often suffers from complications after revascularization procedures.[80]

Renal insufficiency has previously been identified as a risk factor for amputation or death in patients with diabetes.[81, 82] Furthermore, dependence on dialysis has also been identified as a risk factor.[71] In our cohort renal insufficiency, independently of dialysis or diabetes, was associated with twice the risk of amputation or death. It was also found to be the most important risk factor for both amputation and "amputation or death".

Patients with rest pain and tissue loss had twice the risk of amputation or death compared to patients with rest pain alone. This highlights the fact that CLTI, regardless of symptoms, is not one entity. This is in line with the WIfI recommendations and has shown in previous research.[67, 71]

There was a correlation between revascularization level and the risk of amputation or death, in that a more proximal revascularization was associated with an increased risk.

Pharmacological treatment with statins and low-dose aspirin was associated with a 31% and 18% decrease (respectively) in the combined endpoint amputation or death. Risk reductions in line with our results have previously been observed on mortality in PAD patients.[83] In other populations—with an increased risk of cardiovascular events—similar risk reduction levels have been shown for vascular mortality and morbidity, and that these results also seem to remain over time.[84]

4.4 INFRAPOPLITEAL CLTI AND PREOPERATIVE IMAGING

In the fourth paper, a total of 68 preoperative MRAs and DSAs of the infrapopliteal arterial segment were included. All analyses were based on examinations that were assessed as having good diagnostic quality by the observers. Table 7 shows descriptive statistics on the number of examinations with sufficient diagnostic quality and the distribution of assessed TASC II class.

No systematic differences were found when comparing MRA and DSA for assessment of infrapopliteal TASC II class, with an AUC_{VGC} of 0.48 ($p = 0.58$). Also, in analysis of reader confidence in a given TASC II class, we found no significant difference between the modalities ($AUC_{VGC} = 0.51$; $p = 0.87$).

When we performed inter-observer analysis based on TASC II classification, we found that there was a statistically significant difference between all three observer pairs (AUC_{VGC} = 0.70, 0.71, and 0.80; all $p \leq 0.01$) on 51 MRAs with diagnostic quality. The corresponding figures from DSA gave significant differences for two pairs (AUC_{VGC} 0.63 and 0.63; $p \leq 0.01$ for both) and no significant difference for one ($AUC_{VGC} = 0.55$; $p = 380$).

Regarding the choice of target vessel, the inter-observer agreement for the three observers using MRA (n = 51) and DSA (n = 61) was low, with a Krippendorff's α-value of 0.19 (95% CI 0.01–0.36) for MRA and 0.41 (95% CI 0.24–0.56) for DSA. We also compared the target vessel chosen on MRA with the vessel that was eventually actually revascularized, with Krippendorff's α-values of −0.02, 0.14, and 0.39 individually for the three observers. Inter-observer agreement between three observers for infrapopliteal TASC II based on preoperative MRA (n = 51) was low (Krippendorff's α = 0.13, 95% CI −0.07 to 0.31).

When we applied the TASC II lesion criteria to each of the four crural vessels, not only the target vessel, Krippendorff's α showed fair values (0.57–0.79) for one observer between modalities (Table 8a). For the same modality, inter- and intra-observer agreement had good Krippendorff's α-values (> 0.67) with few exceptions (Table 8b and 8c).

Inter-observer agreement for the infrapopliteal aggregated lesion severity score, IALSS, was analyzed using Krippendorff's α and showed high α-values (between 0.76 and 0.80) for both modalities. Table 9 shows inter-observer agreement regarding the choice of target vessel along with inter-observer and modality comparison for IALSS. Intra-observer agreement between modalities gave fair Krippendorff's α-values: 0.68 (95% CI 0.53–0.79, n = 56) for observer 1 and 0.65 (95% CI 0.45–0.81, n = 48) for observer 2, which was better than the formal TASC II classification.

Table 7: Distribution of TASC II classes according to modality and identity of observer.

		Examinations assessed	*Good diagnostic quality (%)*	*Assessed TASC II class, n (%)*				
				0	*A*	*B*	*C*	*D*
Observer 1	MRA	68	62 (91.2)	0 (0.0)	5 (8.1)	11 (17.7)	36 (58.1)	10 (16.1)
Observer 2	MRA	68	52 (76.5)	1 (1.9)	16 (30.8)	25 (48.1)	10 (19.2)	0 (0.0)
Observer 3	MRA	68	64 (94.1)	0 (0.0)	15 (23.4)	25 (39.1)	23 (35.9)	1 (1.6)
Observer 1	DSA	68	62 (91.2)	0 (0.0)	11 (17.7)	14 (22.6)	30 (48.4)	7 (11.3)
Observer 2	DSA	68	62 (91.2)	0 (0.0)	14 (22.6)	28 (45.2)	16 (25.8)	4 (6.4)
Observer 4	DSA	68	65 (95.6)	1 (1.5)	18 (27.7)	32 (49.2)	13 (20.0)	1 (1.5)

Table 8a-c: Krippendorff's α (with 95% confidence interval, CI) for assessed TASC II grade according to vessel. TFT, tibiofibular trunk; ATA, anterior tibial artery; ATP, posterior tibial artery; FA, fibular artery.

Table 8a:

	n	*TFT*	*ATA*	*ATP*	*FA*
Modality comparison					
DSA – MRA: observer 1	56	0.57 (0.37–0.74)	0.60 (0.42–0.75)	0.63 (0.47–0.77)	0.75 (0.64–0.84)
DSA – MRA: observer 2	48	0.71 (0.55–0.85)	0.65 (0.52–0.78)	0.79 (0.65–0.90)	0.71 (0.54–0.85)

Table 8b:

	n	*TFT*	*ATA*	*ATP*	*FA*
Inter-observer agreement					
MRA: observer 1, observer 2, and observer 3	51	0.67 (0.57–0.77)	0.75 (0.68–0.82)	0.77 (0.69–0.84)	0.77 (0.69–0.84)
DSA: observer 1, observer 2, and observer 4	61	0.83 (0.76–0.89)	0.67 (0.59–0.74)	0.73 (0.67–0.79)	0.77 (0.70–0.83)

Table 8c:

	n	*TFT*	*ATA*	*ATP*	*FA*
Intra-observer agreement					
MRA: observer 1	61	0.72 (0.55–0.86)	0.74 (0.63–0.85)	0.71 (0.60–0.82)	0.85 (0.78–0.91)
MRA: observer 2	47	0.32 (−0.08 to 0.66)	0.43 (0.13–0.67)	0.68 (0.48–0.83)	0.79 (0.62–0.91)
DSA: observer 1	62	0.83 (0.71–0.92)	0.72 (0.57–0.85)	0.78 (0.68–0.88)	0.82 (0.70–0.92)
DSA: observer 2	60	0.89 (0.81–0.96)	0.85 (0.75–0.93)	0.83 (0.73–0.90)	0.86 (0.74–0.95)

COMMENTS

We did not find any statistically significant systematic differences in infrapopliteal TASC II classification based on MRA compared to DSA, which is in line with previous research in this field.[85] However, there was a lack of consensus in the assessment of TASC II grade. This was due to poor agreement between observers regarding the choice of target vessel. The agreement about which target vessel to choose was actually close to chance, possibly making the TASC II classification, which requires choice of a target vessel, less suitable for prediction models. On the other hand, when the target vessel was already defined the agreement between observers for each artery using the infrapopliteal TASC II lesion criteria was better. We used the sums of the TASC II classifications of all four infrapopliteal vessels to calculate and test a novel infrapopliteal aggregated lesion severity score (IALSS). The IALSS had better inter- and intra-observer agreement, making it more useful for making preoperative prognoses.

As described above, one concern in using the TASC II classification for infrapopliteal preoperative imaging for prognostic use is that the classification relies on the choice of a target vessel. In Paper IV, we saw that in around one third of all infrapopliteal endovascular revascularizations, more than one vessel had had intervention. A recent, small prospective randomized, study showed that revascularization of more than one infrapopliteal vessel might be beneficial, at least in terms of wound healing.[34] Even though an ongoing debate, whether to focus on one direct target vessel or as many vessels as possible, the field probably evolves against a multiple infrapopliteal vessels recanalization, especially in an era with increasing endovascular procedures.[35, 86] This evolvement will probably increase the importance of prognostic classifications in giving a complete evaluation of the lower leg. The TASC II classification is not the only classification where this might be a problem. The Bollinger classification, for example, uses a numerical range for grading each infrapopliteal vessel independently of the intended target vessel.[87] However, like the TASC II classification, the combined evaluation of all infrapopliteal vessels—to get an overall picture of the infrapopliteal segment—must be done outside the classification. Also, the infrapopliteal module of the upcoming Global Anatomic Staging System (GLASS)[88] will depend on an intended target vessel, with the same potential drawbacks in terms of prognostication and comparisons between methods as with the TASC II classification.

Table 9: Krippendorff's α (with 95% confidence interval, CI) for inter-observer agreement regarding A.) target vessel and B.) infrapopliteal aggregated lesion severity score (IALSS). Modality comparison for IALSS.

A.) **Target vessel**		
Inter-observer agreement	**n**	**α**
MRA: observer 1, observer 2, and observer 3	51	0.19 (0.01–0.36)

B.) **IALSS**		
Inter-observer agreement		
MRA: observer 1, observer 2, and observer 3	51	0.76 (0.71–0.82)
DSA: observer 1, observer 2, and observer 4	61	0.80 (0.75–0.85)
Modality comparison		
DSA – MRA observer 1	56	0.68 (0.53–0.79)
DSA – MRA observer 2	48	0.65 (0.45–0.81)

5 SUMMARY

Risk of amputation

In this thesis, I found a high amputation and mortality rate in CLTI patients, not only relative to the general population but also in comparison to patients with lower-extremity PAD with less severe symptoms, i.e. patients with IC.

The highest risk of amputation occurred within the first 6 months after a revascularization procedure, where 12% of revascularized CLTI patients were undergoing amputation.

The most important risk factor for amputation was the presence of tissue loss. A patient with rest pain and tissue loss had an almost threefold increase in the risk of amputation compared to a patient with rest pain alone. Renal insufficiency and diabetes were the second most important risk factors, as they increased the risk of amputation by around 50%. Male patients had a worse prognosis than female patients.

Treatment with statins and LDASA had a limb-protective effect.

Mortality

Mortality was also substantial, and within the first year following a revascularization procedure 20.5% of CLTI patients died. After three years, around 50% of revascularized patients will have had an adverse event, i.e. an amputation or death.

Three factors were identified as being most important in the mortality risk of these patients. Renal insufficiency, heart failure, and the presence of rest pain in combination with tissue loss doubled the risk of death. Other factors with risk increase of mortality were male gender and aortoiliacal revascularization.

The risk of an adverse event overall, i.e. AFS, of course reflects the underlying risks of amputation and death. However, some factors turns out to be more important for this combined end-point, as renal insufficiency and the combination of rest pain and tissue loss stand out as having a doubled risk.

Also in this combined endpoint, treatment with statins and LDASA had an association with lower risk of amputation and death.

PREOPERATIVE IMAGING

In our evaluation of preoperative diagnostic imaging, we were able to conclude that MRA can be used for infrapopliteal vascular lesions. However, the TASC II classification in its present form, where the evaluation is dependent of the choice of a target vessel, may not be suitable for prognostic purposes preoperatively. When we removed the requirement for choosing a target vessel, the inter-observer agreement increased. We therefore developed the infrapopliteal aggregated lesion severity score (IALSS), using the sum of evaluation of all four infrapopliteal vessels. The IALSS had good inter-observer and intra-observer agreement.

STRENGTHS AND LIMITATIONS

The large heterogeneity—in terms of symptoms, comorbidities, medications etc.—and the relative impact of these factors makes LEAD patients difficult to study. This is reflected in a diversity of classification and grading systems that have been suggested over the years. The main strength of the cohort studied in this thesis is that it represents very close to the whole Swedish population, with very few missing data concerning the actual endpoints studied.

The epidemiological part of this thesis (Paper I-III) is based on highly valid national medical registers and includes a large number of patients. We also made an effort to obtain data that were as accurate as possible—with as little missing data as possible—by reviewing a large number of individual medical records of patients. The data used is recorded at all the hospitals that perform vascular surgery in Sweden, so the results should be generalizable.

It must be emphasized that only revascularized patients were included in the studies, thus introducing selection bias. We have not determined whether these results are applicable to patients who have not been revascularized.

Mortality, one of our main outcomes, has an accuracy of > 99% as the population registry is automatically updated and includes all Swedish citizens who die in Sweden or abroad. Amputation, our second main outcome, had slightly less than 10% missing data, despite our extensive effort to minimize uncertainties. To gain a better picture of what this meant for our results, we performed a sensitivity analysis treating uncertain amputations as events, which changed the results only marginally.

On the other hand, we have not been able to confirm all registrations done on all patients, and there is a risk of data inaccuracies—especially in revascularizations with poor outcome. Lifestyle variables are known to have lower reporting numbers, and the amount of data missing, e.g. for smoking habits, is substantial.

The fourth paper was based on a much smaller subset of patients, all of whom were revascularized at Sahlgrenska University Hospital in Gothenburg. The main strength of this paper is the structured reviewing process with random image order and observers kept blind regarding patient characteristics as well as their own and other observers assessment. Also, we not only analyzed variability for the index method, but also for the reference method.

Since the data were retrospective, the images used were originally produced for diagnostic or revascularization purposes outwith the study. We therefore had to evaluate the diagnostic quality of the studies included using only those with sufficient diagnostic quality.

6 CONCLUSIONS

- Revascularized CLTI patients had a different comorbidity pattern from that of IC patients, with a doubled prevalence of diabetes, ischaemic stroke, heart failure, and atrial fibrillation; an almost tripled prevalence of renal failure; and a fivefold increased prevalence of dementia.
- After a revascularization for CLTI, the risk of amputation was particularly high during the first 6 months. IC patients are rarely amputated. Both IC and CLTI patients had a substantial mortality following revascularization.
- Among the comorbidities, renal insufficiency was the strongest independent risk factor for both amputation and "amputation or death", followed by diabetes and heart failure, in patients revascularized for CLTI. Men with CLTI had a higher risk of amputation than women. Secondary preventive medication with statins and LDASA was associated with improved limb salvage.
- Patients with CLTI presenting with both rest pain and tissue loss had a threefold increased risk of amputation and twice the mortality risk compared to patients who presented with rest pain alone. Distal revascularizations had a higher amputation rate, which could be explained by differences in preoperative comorbidities. Proximal revascularizations, in the aortoiliac arteries, were associated with higher mortality compared to infrainguinal revascularizations.
- Infrapopliteal TASC II classification can be performed using preoperative MRA, but the inter-observer variability in choosing the target vessel is a major concern and affects agreement with DSA results.
- The variability in choosing the target vessel also affects the reproducibility, which may make an aggregated lesion severity score (IALSS) more useful in evaluation of disease severity.

7 FUTURE PERSPECTIVES

We still have some way to go in our understanding of postoperative risk in these patients. There are several risk scores available aimed at stratification of CLTI patients into different risk groups. The risk scores covers different aspects of the symptomatology, different time spans, and different outcome measures. Patients with CLTI are a complex group to study and this diversity is shown in the numerous different grading systems available.

The most commonly used clinical classification system, Fontaine and Rutherford, stratifies LEAD patients into IC patients and CLTI patients based on walking distance, pain, and tissue loss. In Paper IV, we used the infrapopliteal TASC II classification for grading of lesions by distribution and anatomical localization. This revealed agreement between observers in how to assess arterial lesions but without consensus on which vessel to revascularize. This is an issue in prognosis making, pointing at the need for an anatomical classification of infrapopliteal arterial segments without the need for the choice of a specific vessel at the preoperative stage. We suggested the IALSS, but a future prognostic scoring system could as well be another one. For the IALSS, further studies are still needed to evaluate the impact of each and every vessel and to set adequate scoring levels. We also plan to compare the capability of the infrapopliteal TASC II classification with the suggested IALSS in predicting limb outcome in terms of amputation following infrapopliteal revascularization for CLTI using random order blinded MRA evaluations on a larger cohort of patients.

The FINNVASC score included the risk factors diabetes, coronary artery disease, foot gangrene, and urgent operation, and pointed out associations between these factors and adverse postoperative outcomes.[45] In the WIfI classification, the CLTI symptoms are risk stratified according to the presence of wounds (ulcer or tissue loss), ischaemia (based on ABI or other blood pressure measurements), and signs of infection.[67] A more recent attempt to risk stratify patients, by using grade of functioning, is the use of the frailty concept, whereby patients with a higher degree of frailty, i.e. impaired everyday functionality, also have a higher overall risk of death and lower amputation-free survival.[89] These risk stratification methods highlight the complexity of this patient group, and also the importance of gaining knowledge regarding what factors predict outcome after revascularization in CLTI patients. Our results do not contradict these previous scores, but rather lend support to many of them. What we have also added is further knowledge regarding the relative impact of specific risk factors.

Since our cohort was selected from already revascularized patients, there is an inherent risk of selection bias—making it difficult to draw further conclusions about the causality between the studied risk factors and outcome in patients who do not undergo a revascularization. Our data, however, could be used for future prospective studies aimed at developing new and more precise prognostic methods. In addition, we plan to investigate if computational algorithms, generated in the context of machine learning, can be applied to our large database to create a prediction tool for outcome in patients evaluated for revascularization due to CLTI.[90]

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