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ABSTRACT

Lower extremity artery disease (LEAD) associates with amputations, mortality, and systemic atherosclerosis. The most extensive and severe form of LEAD, chronic limb-threatening ischemia (CLTI), associates with the highest rates of adverse events. CLTI is poorly understood due to its heterogenous nature and unpredictable progression. It is thus substantially underdiagnosed and undertreated. This thesis aimed to investigate in depth the clinical features, treatment, and prognosis of CLTI in patients.

The findings indicate that CLTI is an extensive arterial multi-site disease with severe crural involvement with typical associated risk factor profile. Ascertaining the patients with the highest risk of adverse events is challenging and current models have only modest predictive abilities. The information about distal atherosclerosis, the sex of patient, toe-brachial index (TBI) and toe pressure (TP) measurements could enhance the estimation. Despite the predominant location of atherosclerosis, TBI and TP are predictive of mortality. TBI and TP overcome the common problem of medial sclerosis and incompressible ankle arteries and therefore, they should be assessed together with ankle-brachial index (ABI). A surgical revascularization, if possible, should be chosen as it associates with better outcomes compared to an endovascular intervention. However, not all patients can be surgically revascularized; thus, endovascular revascularization or primary amputation may be the most appropriate treatment option in the long-term for such patients.

Senescence and diabetes mellitus are becoming more frequent as the main risk factors of LEAD, therefore a proportionate increase could be expected to occur for the number of CLTI patients and for the need of vascular care. This thesis demonstrates that clinical decision making is challenging in the treatment planning of CLTI. Risk factor modification, diagnostics, prognosis, and revascularizations are tools to combat the growing health burden of CLTI. However, amputation remains as the only realistic treatment for a significant proportion of CLTI patients.

KEYWORDS: lower extremity artery disease, chronic limb-threatening ischemia, revascularization, open bypass, endovascular, major amputation, ankle-brachial index, toe pressure, toe-brachial index

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TIIVISTELMÄ

Alaraajojen tukkiva valtimotauti (LEAD, lower extremity artery disease) on yhteydessä korkeaan kuolleisuuteen, amputaatioriskiin ja systeemiseen valtimonkovettumatautiin. Taudin vaikein muoto, krooninen raajaa uhkaava iskemia (CLTI, chronic limb-threatening ischemia) on erittäin huonoennusteinen sairaus. Oirekuvan moninaisuudesta ja arvaamattomasta taudinkulusta johtuen se on laajasti alidiagnosoitu, alihoidettu ja aliarvioitu sairaus. Tämän väitöskirjatyön tarkoituksena on syvällisemmin tutkia ja ymmärtää CLTI:n kliinisiä piirteitä, sairauden hoitoa ja ennustetta.

Tämä väitöskirjatyö osoittaa, että CLTI on yleensä laaja-alainen, erityisesti säärivaltimoita sairastuttava tauti ja sillä on tyypilliset riskitekijät. Riskipotilaiden tunnistaminen on haasteellista ja tarkempia työkaluja riskinarvioon tarvitaan. Vaikea säärivaltimoiden kovettumatauti, naissukupuoli, alentunut varvas-olkavarsi-indeksi (TBI) ja varvaspaine (TP) ovat yhteydessä huonoon ennusteeseen ja niiden lisäämistä riskinarviomalleihin voitaisiin harkita. TBI ja TP ovat kuolleisuuden ennustetekijöitä taudin pääasiallisesta sijainnista riippumatta. Nilkkavaltimoiden kompressoitumattomuuden vuoksi TBI ja TP antavat tietoa kuolemanriskistä ja niitä tulisi aktiivisesti hyödyntää riskinarviossa nilkka-olkavarsi-indeksin rinnalla. Aktiivista revaskularisaatiostrategiaa, erityisesti avokirurgisesti toteuttavaa, tulisi harkita leikkauskelpoisille potilaille. Huonokuntoisille potilaille suonensisäinen hoito tai amputaatio voivat kuitenkin olla ainoat mahdolliset hoitovaihtoehdot.

LEAD:n merkittävimmät riskitekijät, ikääntyneisyys ja diabetes yleistyvät väestössä ja samansuuntaisesti on odotettavissa, että CLTI-potilaiden määrä ja heidän tarvitsemansa hoidon tarve tulee lisääntymään. Tämä väitöstutkimus osoittaa, että CLTI-potilaiden riskinarvio on haasteellista. Riskitekijöiden hallinta, diagnostiikka, revaskularisaatiot ja oikeasuhtainen riskinarvio ovat työkaluja hillitsemään CLTI:n sairaustaakkaa. Edellä mainituista keinoista huolimatta amputaatio on edelleen ainoa realistinen hoitovaihtoehto merkittävälle osalle CLTI-potilaista.

AVAINSANAT: alaraajojen tukkiva valtimotauti, krooninen raajaa uhkaava iskemia, revaskularisaatio, ohitusleikkaus, endovaskulaarinen kirurgia, amputaatio, nilkka-olkavarsi-indeksi, varvaspaine, varvas-olkavarsi-indeksi

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Abbreviations

AAA	Abdominal aortic aneurysm
ABI	Ankle-brachial index
ACE	Angiotensin-converting enzyme
AKA	Above the knee amputation
AP	Ankle pressure
ATR	Angiotensin II receptor
AUC	Area under curve
BASIL	Bypass versus Angioplasty in Severe Ischemia of the Leg (study)
BEST-CLI	The Best Endovascular vs. Best Surgical Therapy in Patients with Critical limb Ischemia (study)
BKA	Below the knee amputation
BMI	Body mass index
CAD	Coronary artery disease
CFA	Common femoral artery
CI	Confidence interval
CIA	Common iliac artery
CIx	Crural index
CLI	Critical limb ischemia
CLTI	Chronic limb-threatening ischemia
COPART	The Cohorte de Patients Artériopathes (study)
COPD	Chronic pulmonary obstructive disease
CTA	Computed tomography angiography
CVD	Cerebrovascular disease
DM	Diabetes mellitus (both T1DM and T2DM)
DSA	Digital subtraction angiography
DUS	Duplex ultrasonography
EIA	External iliac artery
ESC	European Society of Cardiology
EUCLID	Examining Use of Ticagrelor in Peripheral Artery Disease (study)
FINNVASC	Finnish National Vascular Registry (registry)
GFR	Glomerular filtration rate

GLP-1	Glucagon-like peptide 1
GVG	Global Vascular Guidelines
HbA1c	Glycated hemoglobin A1c
HDL	High-density lipoprotein
HR	Hazard ratio
IC	Intermittent claudication
ICD-10	International Classification of Diseases 10th Revision
IQR	Interquartile range
IRONIC	Invasive Revascularization or Not in Intermittent Claudication (study)
IT-DM	Insulin treated diabetics
LDL	Low-density lipoprotein
LEAD	Lower extremity artery disease
MDAS	Most diseased arterial segment
MDAS AOI	Most diseased arterial segment (aortoiliac)
MDAS CR	Most diseased arterial segment (crural)
MDAS FP	Most diseased arterial segment (femoropopliteal)
MRA	Magnetic resonance angiography
NA	Not available
NIT-DM	Non-insulin treated diabetes
Non-CLTI	LEAD patients without CLTI
Non-DM	Non-diabetes
NREV	No history of revascularization
OR	Odds ratio
OSF	Official statistics of Finland (registry)
PAD	Peripheral artery disease
PREVENT III	Project of Ex-Vivo graft Engineering Transfection III (study)
PSCK9	Proprotein convertase subtilisin/kexin type 9
PTA	Percutaneous transluminal angioplasty
RCT	Randomized controlled trial
REV	History of revascularization
ROC	Receiver operating characteristic
RR	Risk ratio
SD	Standard deviation
SE	Standard error
SFA	Superficial femoral artery
SGLT2	Sodium glucose cotransporter 2
Swedvasc	Swedish Vascular Registry (registry)
TASC	Trans-Atlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease

TBI	Toe-brachial index
$TcPO_2$	Transcutaneous oxygen pressure
TIA	Transient ischemic attack
TP	Toe pressure
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
WIfI	Wound, Ischemia, and foot Infection (classification)

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Koivunen V, Juonala M, Venermo M, Laivuori M, Jalkanen J.M, Hakovirta, H.H. Toe Pressure and Toe Brachial Index are Predictive of Cardiovascular Mortality Regardless of the Most Diseased Arterial Segment in Symptomatic Lower-Extremity Artery Disease – A Retrospective Cohort Study. *PLOS one*, 2021; 16: 1-14; doi: 10.1371/journal.pone.0259122

II Koivunen V, Dabravolskaite V, Nikulainen V, Juonala M, Helmiö P, Hakovirta H.H. Major Lower Limb Amputations and Amputees in an Aging Population in Southwest Finland 2007-2017. *Clinical Interventions in Aging*, 2022; 17: 925-936; doi: 10.2147/CIA.S361547.

III Koivunen V, Juonala M, Mikkola K, Hakovirta H.H. Chronic Limb Threatening Ischemia and Diabetes Mellitus: The Severity of Tibial Atherosclerosis and Outcome after Infrapopliteal Revascularization. *Scandinavian Journal Surgery*, 2020, November; doi: 10.1177/1457496920968679.

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1 Introduction

Atherosclerosis is the main cause of coronary artery disease (CAD), cerebrovascular disease (CVD), and lower extremity artery disease (LEAD) (Ross, 1993). LEAD represents systemic atherosclerosis as approximately two-thirds of the patients present simultaneous CAD or CVD or a combination both (Cacoub et al., 2009). As advanced age and diabetes mellitus (DM), the main risk factors of LEAD, are becoming more common, the number of LEAD patients and their need of vascular care are expected to increase in a similar fashion (Danaei et al., 2011; Song et al., 2019).

The most common clinical presentation of LEAD is intermittent claudication (IC), which is characterized as pain and dysfunction while walking that eases upon rest (Kannel, 1996). The end-stage of LEAD is chronic limb-threatening ischemia (CLTI), which is a heterogeneous disease with various degrees of ischemia that complicates wound healing and associates with increased risk for limb loss (Conte et al., 2019). Ischemic rest pain, ulceration or gangrene are present for at least 2 weeks together with the objective evidence of arterial insufficiency (Conte et al., 2019). CLTI characterized as extensive, widespread atherosclerosis that simultaneously affects multiple vascular territories (Conte et al., 2019). It associates with the highest rates of major amputations, mortality and poor survival (Baubeta Fridh et al., 2017). If left untreated, one in every four CLTI patient dies or becomes an amputee within one year (Abu Dabrh et al., 2015).

Objective peripheral pressure measurements are used to determine arterial insufficiency. The most widely used metric is ankle-brachial index (ABI), in which values $\leq$0.90 determines arterial insufficiency (Aboyans et al., 2018). However, calcification of the medial layer of the ankle arteries may cause misleadingly high ABI values, lessening the reliability of the measurement (Aboyans et al., 2018; Lanzer et al., 2014; Suominen et al., 2008) In these cases of medial calcification, toe-brachial index (TBI) <0.70 and toe pressure (TP) <60 mmHg indicate impaired arterial circulation as pedal arteries are rarely affected by medial sclerosis (Conte et al., 2019; Mills et al., 2014; Norgren et al., 2007). The anatomic distribution of the disease is typically assessed by using anatomic imaging, most commonly with digital

subtraction angiography (DSA), computed tomography angiography (CTA), or magnetic resonance angiography (MRA) (Cao et al., 2011).

Risk factor modification with smoking cessation, excercise, lipid, hypertension, glycemic and antitrombotic medication is the cornerstone of LEAD treatment (Aboyans et al., 2018; Anderson et al., 2013; M. J. Davies et al., 2018; Hamburg & Creager, 2017; Mach et al., 2020; Williams et al., 2018). However, in CLTI, these means of conservative treatment are often found to be inadequate and vascular reconstruction is needed due to the severe vascular impairment (Conte et al., 2019). Open bypass surgery is the traditional gold-standard revascularization procedure although within the last decades, less invasive endovascular methods have been introduced and largely adapted (Nikulainen et al., 2019; Norgren et al., 2007). This introduction of new technologies has enabled active revascularization for those who were hitherto unfit for invasive operations (Conte et al., 2019). In general, the choice of treatment is decided by the operating surgeon as no comprehensive consensus exists for the most appropriate treatment strategy.

The risk of amputation in LEAD patients is linearly associated with the severity of limb ischemia (Baubeta Fridh et al., 2017). In comparison, the risk of mortality is approximately 2-3.5 fold amongst patients without LEAD (Mueller et al., 2014). Compared to IC patients, CLTI associates with the highest adverse event rates and a worse survival for patients (Baubeta Fridh et al., 2017; van Haelst et al., 2018). The disease progression of CLTI is unpredictable and the risk estimation for patients with the highest risks for adverse events is challenging. As the current risk models have shown suboptimal predictive abilities, more accurate risk estimation tools are needed to recognize the patients at the highest risk of a poor outcome (Chung et al., 2014; Wijnand et al., 2020).

It is alarming that LEAD and especially CLTI patients have high risks of mortality and amputations and yet, both groups are significantly underestimated and undertreated. This thesis aimed to investigate in depth the clinical features, management, and survival of patients with CLTI to improve the decision making in the clinical practice.

2 Review of the Literature

2.1 Atherosclerosis

Atherosclerosis is a chronic arterial disease characterized by a developmental process of plaque formation (Herrington et al., 2016). These plaques are thickenings of the innermost layer of the artery, namely the intima, and they typically take years or even decades to develop (Ross, 1993). At the age of 65-69, the prevalence of cardiovascular disease has been estimated to be at least one in every five men and one in every ten women (Mittelmark et al., 1993). Clinically significant manifestations of atherosclerosis typically occur in premenopausal women 10 years later than they do in men (Mathur et al., 2015). However, the risk of extensive atherosclerosis significantly increases after menopause and the risk may indeed be higher in post-menopausal women than in men (Mathur et al., 2015). High levels of low-density lipoprotein cholesterol (LDL-cholesterol) and low high-density lipoprotein-cholesterol (HDL-cholesterol), smoking, diabetes mellitus (DM), hypertension, obesity, aging, and low physical activity are known risk factors of atherosclerosis (Rafieian-Kopaei et al., 2014). Worldwide, atherosclerosis and its clinical manifestations are one of the leading causes of mortality (Naghavi et al., 2015).

The normal intima thickens as a physical adaption to mechanical stress and does not obstruct the arterial lumen (Stary et al., 1992). Under numerous forms of insults, however, the process of atherosclerosis begins (Rafieian-Kopaei et al., 2014; Ross, 1993; Stary et al., 1994). At first, plaque formation is preceded by a fatty streak, a precursor of an atheroma that consists of a lipid-rich macrophages and T-cells that accumulate within the intima (Hansson, 2005; Stary et al., 1994). The lipids are phagocytised by the macrophages, namely the foam cells and if more lipids enter the intima than exit it, fatty streaks are formed (Rafieian-Kopaei et al., 2014). These fatty streaks can then either dissolve or progress to even more advanced atherosclerotic plaques (Hansson, 2005; Stary et al., 1995).

Foam cells and lipid accumulations form the lipid-rich core of the atheroma, which is then covered by a collagen-matrix and a cap of smooth-muscle cells (Hansson, 2005). Inflammation is a crucial part of both the initiation and progression of the atherosclerotic plaque formation (Hansson, 2005). As the plaques grow, they

cause disorganization of the intima, deform the artery, and further impede the arterial flow (Rafieian-Kopaei et al., 2014). Typically, these lesions gradually narrow the arterial lumen or form a local thrombosis (Hansson, 2005; Ross, 1993).

Atherosclerosis can simultaneously occur in multiple regions within the vasculature (Herrington et al., 2016). It is the main cause of the development of CAD, CVD, and can also cause atherosclerosis of the peripheral arteries, namely peripheral artery disease (PAD) (Ross, 1993). PAD is underrecognized, underdiagnosed and compared to these other atherosclerotic manifestations, greatly undertreated (Cacoub et al., 2009; Campia et al., 2019). Alarmingly, PAD patients have a higher risk for cardiovascular mortality and events than patients with CAD and CVD (Steg et al., 2007).

2.2 Lower extremity artery disease

PAD is a progressive, stenotizing and/or occlusive disease of all the large and medium-sized arteries except for the arteries that vascularize the heart and brain (Shu & Santulli, 2018). Most commonly PAD affects the arteries distal to the aorta and the lower limbs rather than the upper extremities (Shu & Santulli, 2018). The atherosclerotic process is the most common cause for PAD when the other causes, vasculitis, trauma, thromboembolism, popliteal entrapment, Buerger disease, and cystic adventitial disease, are rare (Farber & Eberhardt, 2016). This thesis concentrates on the PAD that is caused by atherosclerosis of the arteries of aortoiliac, femoropopliteal, and infrapopliteal arteries, namely, lower extremity artery disease (LEAD).

LEAD is associated with systemic atherosclerosis. Approximately two-thirds of patients have either CAD or CVD or a combination both (Cacoub et al., 2009). LEAD patients typically have an abundance of comorbidities, especially DM, hypertension, dyslipidemia, and a history of smoking (C. Diehm et al., 2004). The risk for having any coronary or cerebrovascular event is higher in patients with LEAD than in patients without it (C. Diehm et al., 2004).

2.2.1 Risk factors for LEAD

Smoking has been found to be the most contributing risk factor for LEAD (Fowkes et al., 2013). Smoking exposure, both active and passive, induces vasomotor dysfunction, atherogenesis, and thrombosis and therefore, is a significant promotor of accelerated atherosclerosis (Ambrose & Barua, 2004). When compared to the other manifestations of atherosclerosis, smoking appears to be associated with LEAD in particular (Criqui & Aboyans, 2015). The risk of LEAD is strongly dose-dependent as those smokers with the most pack-years of smoking have the highest

risks to develop LEAD (Joosten et al., 2012). Although current smoking associates with a higher incidence of LEAD than former smoking, the risk for LEAD does not return to baseline even after 20 years cessation (Joosten et al., 2012). Atherosclerosis-related structural vascular changes have been recognized as potential contributors to this elevated risk (Ding et al., 2019). Smoking especially associates with atherosclerosis in the proximal arteries of the lower extremities (N. Diehm et al., 2006).

The second strongest risk factor for LEAD is DM (Fowkes et al., 2013). DM is a complex metabolic disease, most distinctively characterized by elevated levels of blood glucose (Nathan, 1993). There are two main subtypes of DM. Type 1 DM (T1DM) is most commonly an autoimmune disease, defined by the destruction of insulin-producing pancreatic β-cells and an absolute insulin deficiency (American Diabetes Association, 2014). Type 2 DM (T2DM) on the other hand, is a heterogeneous disorder that presents varying degrees of insulin resistance and deficiency (American Diabetes Association, 2014). In this thesis, T1DM and T2DM are both referred as DM.

LEAD has been considered to be the main atherosclerotic complication of DM (Lange et al., 2004; Silbernagel et al., 2015). The duration of DM has been associated with the risk of developing LEAD in a stepwise fashion (Joosten et al., 2012). Diabetics typically have more severe arterial disease compared to non-diabetics, especially in the infrapopliteal arteries (Jude et al., 2001). This has been explained by diabetes-related hyperglycaemia, dyslipidemia, and insulin resistance that causes endothelium dysfunction and further, accelerated atherogenesis (Beckman et al., 2002). The diabetic population has been constantly growing both internationally and nationwide in Finland (L. Chen et al., 2012; Forssas et al., 2016). In Finland from 1994 to 2011, the number of diabetic patients have been reported to have increased by 135% (Forssas et al., 2016).

Advanced age is an independent risk factor for LEAD (Fowkes et al., 2013). Cellular senescence, characterized by decreased cell proliferation and apoptosis, DNA damage, epigenetic changes, and telomere dysfunction, promote the development of atherosclerosis (J. C. Wang & Bennett, 2012). It has been estimated that one in ten people over 70 years and one in six over 80 years have LEAD (Fowkes et al., 2013). Typically, increasing age associates with atherosclerosis in the arteries below-the-knee (N. Diehm et al., 2006).

The other common cardiovascular risk factors for atherosclerosis are independently associated with the development of LEAD. Elevated levels of LDL-cholesterol and low HDL-cholesterol have been associated with proximal LEAD (N. Diehm et al., 2006; Ness et al., 2000). A linear association between the duration of hypercholesterolemia and the incidence of LEAD similar to that found for smoking and DM has been observed (Joosten et al., 2012). In addition, hypertension is an

independent risk factor for LEAD and in contrast to other risk factors, it seems to affect the arteries in a nonuniform rather than a segment specific fashion (N. Diehm et al., 2006; Joosten et al., 2012).

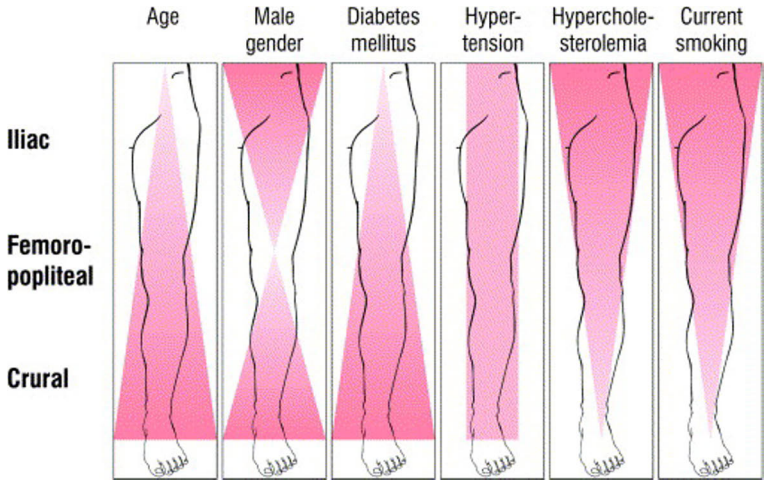


Figure 1. Known risk factors for LEAD according to the segmental distribution (N. Diehm et al., 2006). The red area and intensity depicts increased risk. Reproduced with the permission from Elsevier Ltd.

2.2.2 Prevalence of LEAD

In 2015, it was estimated that over 237 million people globally suffer from LEAD (Song et al., 2019). As the main risk factors, advanced age and DM, are becoming more frequent, the number of LEAD patients is constantly increasing (Danaei et al., 2011; Song et al., 2019). Between 2000 and 2010, the number of LEAD patients increased by nearly a quarter (Fowkes et al., 2013). The rapid growth of LEAD has been particularly marked in the elderly people aged over 80 years (Fowkes et al., 2013). LEAD is not an isolated problem of Western countries as in in low and middle-income countries, the prevalence of LEAD is increasing rapidly (Fowkes et al., 2013; Song et al., 2019). Therefore, this already large burden on healthcare is continuously growing in all nations worldwide, creating a global threat to public health (Fowkes et al., 2013; Song et al., 2019). Interestingly, the prevalence of LEAD in women in low and middle income countries has been reported to be greater compared to high income countries, which is contrary to that found for men (Fowkes et al., 2013).

2.2.3 Diagnosis of LEAD

The diagnosis of LEAD consists of the assessment of clinical symptoms, physical examination, and the evaluation of the vascular impairment, most routinely done with non-invasive peripheral pressure measurements (Aboyans et al., 2018). When invasive treatment is considered, the precise anatomic distribution is typically assessed using the scanning modalities, such digital subtraction angiography (DSA), computed tomography angiography (CTA), or magnetic resonance angiography (MRA)(Cao et al., 2011).

2.2.3.1 Clinical classifications of LEAD

2.2.3.1.1 Classifications systems of LEAD

The Fontaine classification was the first comprehensive classification system for LEAD and it was introduced in 1954 (Fontaine et al., 1954). The clinical picture is categorized into one of the five classes according to the clinical symptoms (Fontaine et al., 1954). Another widely adapted system, the Rutherford classification, was introduced in 1986 and then revised in 1997 (Rutherford et al., 1986, 1997). Based on the symptoms, clinical findings and objective peripheral pressure criteria, the Rutherford system classifies LEAD into categories 0 to 6 (Rutherford et al., 1986, 1997). Both the aforementioned classification systems have been and are still extensively used in studies investigating LEAD (Hardman et al., 2014). Fontaine and Rutherford classifications are presented in Table 1.

Table 1. Fontaine and Rutherford classifications of LEAD. Obtained from the study of Fontaine et al. and Rutherford et al. and which was modified (Fontaine et al., 1954; Rutherford et al., 1986, 1997)

FONTAINE		**GRADE**	**CLINICAL SYMPTOMS**	**OBJECTIVE CRITERIA**
		I	Asymptomatic	Was solely based on symptoms and did not include hemodynamc measurements.
		IIA	Mild claudication	
		IIB	Moderate-severe claudication	
		III	Ischemic rest pain	
		IV	Necrosis and/or gangrene	
	GRADE	**CATEGORY**	**CLINICAL SYMPTOMS**	**OBJECTIVE CRITERIA**
RUTHERFORD	0	0	Asymptomatic	Normal treadmill/reactive hyperemia test
		1	Mild claudication	AP post-excercise >50 mmHg but ≥20 mmHg lower than rest value
	I	2	Moderate claudication	Between 1-3
		3	Severe claudication	Cannot complete treadmill, AP <50 mmHg post-exercise
	II	4	Ischemic rest pain	AP <40 mmHg, TP <30 mmHg, abnormal ankle or metatarsal pulse volume recording
	III	5	Minor tissue loss	AP <60 mmHg, TP <40 mmHg, abnormal ankle or metatarsal pulse volume recording
		6	Major tissue loss	Same as 5

AP, ankle pressure; TP, toe pressure. Minor tissue loss includes non-healing ulcers and/or focal gangrene with pedal ischemia. In major tissue loss, severe ischemic ulcers and/or gangrene have progressed beyond the trans-metatarsal level.

2.2.3.1.2 Asymptomatic LEAD

It has been estimated that the majority of LEAD patients are asymptomatic. In one study, nearly 90% of patients with ABI <0.90 had no LEAD related claudication (Blanes et al., 2009). The asymptomatic patients manifest LEAD by ankle-brachial index (ABI) <0.9 or absent pulse palpations (Aboyans et al., 2018). A subgroup of these asymptomatic patients have severe LEAD and the lack of symptoms can be caused by sensory neuropathy and concurrent comorbid conditions that limit physical activity (Aboyans et al., 2018). Asymptomatic LEAD patients have an increased risk of cardiovascular morbidity and mortality despite being symptom free (Behroozian & Beckman, 2021).

2.2.3.1.3 Intermittent claudication

The most common symptom of LEAD is intermittent claudication (IC). It is characterized as pain and dysfunction in walking that is alleviated in minutes by rest (Kannel, 1996). The risk of mortality for patients with IC is higher compared to the general population, i.e. the risk of cardiovascular mortality has been estimated to be at least 2-fold at 1- and 5 -years (van Haelst et al., 2018). A frequent cause of IC is atherosclerosis in the proximal arteries of the lower limb (Aboyans et al., 2018).

2.2.3.1.4 Critical limb ischemia and chronic limb-threatening ischemia

The term critical limb ischemia (CLI) was first established in 1982 in International Vascular Symposium (Bell et al., 1982). According to the definition, CLI was described as rest pain with ankle pressures (AP) <40 mmHg or ulcers/gangrene with AP <60 (Bell et al., 1982). Although these criteria were the first to describe patients with severe limb ischemia, they have been criticized for being too narrow to detect patients at the risk of limb loss (Conte et al., 2019; Thompson et al., 1993).

The definition of CLI has evolved continuously over the years. In the Second European Consensus in 1991, CLI was defined as rest pain for at least two weeks with AP ≤50 mmHg or toe pressure (TP) ≤30 mmHg or ulcers/gangrene with AP ≤50 mmHg or TP ≤30 mmHg (Second European Consensus, 1991). However, this definition has been criticized for having cut-off values that were considered to be too low (Conte et al., 2019). In 2000, the Trans-Atlantic Inter-Society Consensus (TASC) redefined the criteria of CLI (TASC I) and again in 2007 (TASC II)(Dormandy & Rutherford, 2000; Norgren et al., 2007). According to the latest TASC II guidelines, for patients with ischemic rest pain, AP <50 or TP <30 was indicative of CLI, whereas for patients with ulcers/gangrene, AP< 70 mmHg or TP <50 mmHg indicate CLI (Norgren et al., 2007). Similar to previous definitions, TASC II criteria had its weaknesses. For example, the authors acknowledge the lack

of uniform consensus on the hemodynamic criteria of CLI (Norgren et al., 2007). As demonstrated, the definition of CLI has considerably changed since 1982, which exemplifies the challenges of CLI diagnosis and indicate how creating strict diagnostic criteria is extremely difficult (Azuma, 2018; Conte et al., 2019; Novo et al., 2004).

Precise diagnostic criteria is crucial to understand fully the features, treatment, and prognosis of severe limb ischemia (Fagrell, 1992). However, it is evident that not all patients meet the criteria although they present varying stages of clinical ischemia and a significant risk for limb loss. To characterize further this diverse group of patients, the term chronic limb-threatening ischemia (CLTI) was introduced in both European Society of Cardiology (ESC) 2017 guidelines in 2018 and the Global Vascular Guidelines (GVG) in 2019 (Aboyans et al., 2018; Conte et al., 2019). The definition consisted of the same clinical features together with the presence of documented atherosclerotic LEAD, while also acknowledging that severe ischemia is not the sole cause of limb loss (Conte et al., 2019). According to the latest definition, CLTI is a heterogeneous disease with various degrees of ischemia that complicates wound healing and associates with increased risk for limb loss (Conte et al., 2019). Ischemic rest pain, ulceration or gangrene are present for at least 2 weeks together with the objective evidence of arterial insufficiency (Conte et al., 2019). The presence of wound and infection also associate with increased risk of amputation. Specific cut-off values were diagnostic of CLI, but the new guidelines suggest not to rely solely on certain thresholds for CLTI.

In the past, smoking had been the main risk factor of severe ischemia whereas today a significant proportion of the overall risk are due to diabetics with ulcers, neuropathy, and infection (Aboyans et al., 2018; Conte et al., 2019; Mills et al., 2014). WIfl classification system (wound, ischemia, and foot infection), has been developed to describe both severity of CLTI and risk of limb loss (Mills et al., 2014). WIfl acknowledges all the three risk factors, the presence and extent of wounds, the state of ischemia measured by ABI, AP, or TP/ transcutaneous oxygen pressure ($TcPO_2$) and also possible infection (Mills et al., 2014). It has been proposed that the term CLTI should be preferred when referring to advanced limb ischemia instead of CLI. Henceforward in this thesis, the term CLTI is used to for both CLI and CLTI, according to these current guidelines (Aboyans et al., 2018; Conte et al., 2019).

CLTI represent the most advanced form of LEAD (Farber & Eberhardt, 2016). According to the most widely adapted LEAD classifications, CLTI represents categories Rutherford 4-6 and Fontaine III and IV classes (Fontaine et al., 1954; Rutherford et al., 1986, 1997). CLTI should be differentiated from acute limb ischemia, which is a different disease entity as it is an acute limb-threatening event caused by thrombosis or thromboembolism (Novo et al., 2004). Furthermore, CLTI is characterized as extensive, widespread atherosclerosis that simultaneously affects

multiple vascular territories, although it is predominant in the crural arteries (Conte et al., 2019; Farber & Eberhardt, 2016). Extensive lesions in all three major crural arteries are common especially in patients with DM and CLTI (Faglia et al., 2006).

CLTI patients have the highest rates of amputation, mortality and frequency of cardiovascular morbidity compared to their counterparts with IC (Baubeta Fridh et al., 2017). Hypertension, DM, coronary artery disease, myocardial infarction, atrial fibrillation, ischemic stroke, chronic obstructive pulmonary disease (COPD), and chronic renal insufficiency are prevalent comorbidities within CLTI (Baubeta Fridh et al., 2017; Novo et al., 2004).

The prevalence of CLTI has been estimated to be approximately 1% amongst the general population and 11 % of the LEAD population (Nehler et al., 2014). Advanced age, smoking, and DM have been acknowledged to be the most important risk factors for the disease progression to CLTI, which occurs in 5-10% of all LEAD patients within a 5-year period (Farber & Eberhardt, 2016; Howard et al., 2015; Norgren et al., 2007; Novo et al., 2004). Additionally, both hypercholesterolemia and hypertriglyceridemia propagate the atherosclerotic process further to CLTI (M. G. Davies, 2012; Smith et al., 1996). Furthermore, it has been estimated that the rapid increases of the elderly and diabetic populations are likely to result in a proportionate increase in the CLTI population (Farber & Eberhardt, 2016).

2.2.3.2 Peripheral pressure measurements

Non-invasive peripheral blood pressure measurements are a convenient and practical way to evaluate the arterial sufficiency in the lower limb (Aboyans et al., 2018). They can therefore be easily applied to everyday practice to confirm the diagnosis of LEAD.

2.2.3.2.1 Ankle-brachial index

Ankle-brachial index (ABI) is the principal non-invasive parameter used for LEAD after clinical examination and it should be systematically measured in all patients suspected of LEAD (Aboyans et al., 2018). The relevance of ABI in LEAD patients is indisputable and it is an economical and advantageous way to investigate arterial sufficiency in a limb (Higashi et al., 2019; Marston et al., 2006; McDermott, 1999; Sikkink et al., 1997).

To obtain ABI, the highest systolic AP is divided the by the highest systolic brachial pressure (Aboyans et al., 2018). The patient is first positioned in the supine position and then, a pneumatic, inflatable cuff is placed above the ankle joint (Chaudru et al., 2016). The systolic blood pressure of the posterior tibial, anterior tibial, or dorsalis pedis artery are measured (Aboyans et al., 2018). The cuff is

inflated until the Doppler probe flow signal ceases and then slowly deflated until it appears again (Chaudru et al., 2016). Both limbs are evaluated separately if LEAD is clinically suspected (Aboyans et al., 2018). A normal ABI lies within the range of 1.00 – 1.40 (Aboyans et al., 2018). Abnormal ABI values are <0.90 and >1.40 whereas an ABI within 0.90 – 1.00 is considered borderline (Aboyans et al., 2018).

Calcification of the medial layer stiffens the arterial wall, decreases the vessel wall elasticity, which make arteries incompressible and causes abnormally elevated ABI values typically above the 1.30-1.40 (Aboyans et al., 2018; Lanzer et al., 2014; Suominen et al., 2008). This calcification process is called medial sclerosis (Mönckeberg's medial sclerosis) and should be distinguished from intimal calcification, which is caused by atherosclerotic plaque formation and leads to luminal obstruction of the arteries (Ho & Shanahan, 2016; Rocha-Singh et al., 2014). Medial sclerosis and elevated ABI are commonly seen in the elderly, diabetics, and patients with chronic renal impairment (Ho & Shanahan, 2016). Patients with elevated ABI should be considered to have LEAD as well (Aboyans et al., 2008). Compared to decreased ABI, however, the incompressible ankle arteries and thus elevated ABI has been associated with even higher mortality rates and poorer survival (Laivuori et al., 2021).

2.2.3.2.2 Toe-brachial index and toe pressure

When ABI is abnormally high and incompressible ankle arteries are suspected, TBI and TP are recommended for more accurate estimation of arterial sufficiency (Conte et al., 2019). As the pedal arteries are rarely affected by medial sclerosis, the use of TP and TBI overcomes the problem of medial sclerosis of ankle arteries (Conte et al., 2019). According to the current TASC II, GVG guidelines, and WIfl classification, TP <60 mmHg and TBI <0.70 indicate impaired arterial circulation (Conte et al., 2019; Mills et al., 2014; Norgren et al., 2007).

To assess TP, patient's feet are first pre-warmed to minimize the effect of local vasoconstriction and then the patients are positioned in the supine position (Bonham, 2006). Subsequently, an appropriately sized pneumatic cuff is wrapped around the big toe (Conte et al., 2019). Similar to that for ABI measurement, the cuff is first inflated and then slowly deflated until the arterial signal of the Doppler flow detector or photoplethysmography device appears again (Conte et al., 2019). To obtain TBI, the highest measured systolic TP is then divided by the highest brachial systolic pressure, as described for ABI measurements (Andras & Ferket, 2014).

The current guidelines recommend the use of TP and TBI in cases with elevated ABI and suspected incompressible arteries (Aboyans et al., 2018). Interestingly, there is a significant group of patients with normal or near normal ABIs but whom have decreased TBI and TP. For example, in one study, low TBI combined with

normal ABI characterized approximately one-fifth of patients with suspected LEAD (Høyer et al., 2019). Patients with normal or near normal ABIs often have similar baseline comorbidities and poor survival compared to those with abnormally low ABI (Høyer et al., 2019; Laivuori et al., 2021). It has been suggested that when ABI is the only measured parameter, there plausibly remains a large group of patients without LEAD diagnosis and risk estimation (Høyer et al., 2019). Although some studies recommend that TBI and TP should be assessed together with ABI for all patients with confirmed or suspected LEAD (Høyer et al., 2019; Laivuori et al., 2021), only a limited number of studies exist that compare all these three parameters together. In Table 2., all the three parameters are introduced and compared with each other.

Table 2. Comparisons of ABI, TBI, and TP. Sensitivity and specificity are reported to detect ≥50% stenosis as diagnosis of LEAD by ABI, TBI and TP, modified from studies (Herraiz-Adillo et al., 2020; Tehan et al., 2017) Note; no studies exist that compare the diagnostic accuracy between the three parameters altogether (Cao et al., 2011).

METHOD	ABI	TBI	TP
TECHNIQUE	Systolic AP by systolic brachial pressure	Systolic TP divided by systolic brachial pressure	Systolic TP
TRESHOLD FOR ISCHEMIA	≤0.90	<0.70	<60 mmHg
ADVANTAGES	Good availability, simple, inexpensive	Simple, inexpensive, useful in small arteries and medial sclerosis	Simple, inexpensive, useful in small arteries and medial sclerosis
LIMITATIONS	Unreliable in medial sclerosis, does not localize disease	Lack of standardization, technically more challenging than ABI, not available in primary care, does not localize disease	Lack of standardization, technically more challenging than ABI, not available in primary care, does not localize disease
SENSITIVITY	61% (95% CI 55-69%)	81% (95% CI 70-94%)	DM: 74% (95% CI 64-81) Non-DM:67% (95% CI 59-74%
SPECIFICITY	92% (95% CI 89-95%)	77% (95% CI 66-90%)	DM:72 % (95% CI 59-84%) Non-DM:71% (95% CI 58-83%)

ABI, ankle-brachial index; TBI, toe-brachial index; TP, toe pressure; DM, diabetes mellitus; CI, confidence interval.

2.2.3.3 Diagnostic imaging and LEAD

The anatomic extent of LEAD can be assessed with imaging (Cao et al., 2011). In general, this is performed prior to invasive treatment to decide on the most appropriate treatment modality (Cao et al., 2011). The entire vasculature of the symptomatic extremity is commonly visualized with DSA, CTA, and MRA (Aboyans et al., 2018; Cao et al., 2011). Nevertheless, the diagnostic imaging should always be considered in conjunction with the patient's symptoms and hemodynamic tests, especially prior to invasive treatment (Aboyans et al., 2018).

2.2.3.3.1 DSA, CTA, and MRA

DSA is the accepted gold-standard of vascular imaging modality for LEAD patients and the procedure-of-choice in many vascular centers (Cao et al., 2011). It provides an easily interpretable two-dimensional full view depicting the area from infrarenal aorta to the pedal arteries and if eligible, endovascular revascularization can be performed during the imaging procedure (Novo et al., 2004). DSA is a precise method to estimate lesions within the crural segment (Cao et al., 2011; Conte et al., 2019). Limitations of DSA are radiation exposure, nephrotoxicity, and possible contrast-medium allergies (Cao et al., 2011). In addition, catheterisation complications, both intra-arterial and puncture site, should also be kept in mind (Cao et al., 2011).

CTA is a method that is becoming increasingly popular due to advances in imaging technology (Cao et al., 2011). No radiation is used for MRA imaging unlike for DSA and CTA (Conte et al., 2019). Both good specificity and sensitivity have been reported with CTA and MRA (Cao et al., 2011; Menke & Larsen, 2010; Met et al., 2009). In some vascular centers duplex ultrasound (DUS) is the method-of-choice to obtain information on arterial flow and haemodynamics of the limb (Cao et al., 2011; Conte et al., 2019). DUS should be performed together with ABI and it is mainly used to confirm the presence of LEAD lesions or possible autologous bypass reservoir (Aboyans et al., 2018; Cao et al., 2011). All the imaging modalities, DSA, CTA, MRA, and DUS are compared in Table 3.

Table 3. Comparisons between DSA, CTA, MRA, and DUS to identify ≥50% stenosis or occlusion in LEAD patients. Modified from the studies of Cao et al, Menke and Larsen, Met el al., and Visser and Hunink. Note; no up-to date data exists for sensitivity and specificity of DSA since DSA is often chosen as reference modality. (Cao et al., 2011; Menke & Larsen, 2010; Met et al., 2009; Visser & Hunink, 2000)

METHOD	DSA	CTA	MRA	DUS
TECHNIQUE	Radiopaque iodinated contrast medium and a sequence of x-ray images provide a two-dimensional view of the vasculature	Radiopaque iodinated contrast medium and highspeed CT scanners provide three-dimensional illustration of the vasculature	A powerful magnetic field with or without contrast medium provides a three-dimensional illustration of the vasculature	Non-invasive, measures peak systolic velocity and ratios within or behind the obstruction, turbulence, and pulsatility
ADVANTAGES	Superior in crural region, endovascular revascularization can be performed during imaging	Quick, allows the evaluation of previously stented arteries	The most specific anatomic visualisation compared to other methods	Provides information of disease localization, conduit reservoir, and efficacy after revascularization
LIMITATIONS	A risk of contrast-induced nephropathy, allergy, and catheterization complications	May overestimate stenosis especially in the crural segment, radiation, risk of contrast-induced nephropathy and allergy	May overestimate stenosis, calcified lesions and prior metal implants may mimic arterial occlusion	Limited accuracy in crural segment, operator dependent
SENSITIVITY	Reference	95% (95% CI 92-97%)	95% (95% CI 92-96%) [a]	88% (95% CI 84-91%)
SPECIFICITY	Reference	96% (95% CI 93-97%)	96% (95% CI 94-97%) [a]	95% (95% CI 93-96%)
CONTRAINDICATIONS	Severe renal insufficiency[b], contrast medium allergy	Severe renal insufficiency[b], contrast medium allergy	Relative; in-body metal,pacemakers, neurostimulation, defibrillators, claustrophobia	None

DSA, digital subtraction angiography; CTA, computed tomography angiography; MRA, magnetic resonance angiography; DUS, duplex ultrasonography; CI, confidence interval.

[a] For contrast-enhanced MRI.

[b]The risk of contrast-induced acute kidney injury is highest in glomerular filtration rate (GFR) <30 mL/min/1.73m^2. For patients, with GFR <45 mL/min/1.73m^{2,} the potential risk remains unknown (Davenport et al., 2015).

2.2.3.3.2 Lesion classification systems

Depending on the lesion characteristics in imaging, atherosclerosis can be classified into different categories to assess the disease severity and aid treatment planning. Historically one of the first angiographically assessed and later widely adapted classifications was created by Bollinger in 1981 (Bollinger et al., 1981). In this system (Table 4.), the lower extremity arteries are classified into smaller vascular segments and scoring is based on the presence of atherosclerotic occlusion, stenoses and plaques (Bollinger et al., 1981; Hardman et al., 2014). The number and length of these lesions are calculated, and these scores are then summed together. When occlusions are present, plaques and stenoses are not evaluated (Bollinger et al., 1981; Hardman et al., 2014). When repetitive angiograms are performed and the occlusion either grows or decreases at least 2 cm in length, then one point is accordingly summed or subtracted from the prior overall score (Bollinger et al., 1981; Hardman et al., 2014).

Table 4. Bollinger classification system (Bollinger et al., 1981). Modified from Hardman et al (Hardman et al., 2014).

LOCATION	PLAQUE <25%	STENOSIS ≤50%	STENOSIS >50%
SINGLE	1	2	4
MULTIPLE ≤ 50% SEGMENT	2	3	5
MULTIPLE >50% SEGMENT	3	4	6
OCCLUSIONS		<50% = 13	
		≥50% = 15	

Since the creation of the Bollinger classification, multiple other classification systems have been introduced. One of the most widely used is the TASC classification (Hardman et al., 2014). The TASC created guidelines (TASC I) in 2000 to classify lesion characteristics in both the aortoiliac and the femoropopliteal segment (Dormandy & Rutherford, 2000). In 2007, this classification was updated and in 2015, the crural segment was included in the classification (Jaff et al., 2015; Norgren et al., 2007). In the latest TASC II classification, specific lesion patterns are grouped together into TASC A-D lesions, with A representing the least and D the most severe lesion characteristics (Jaff et al., 2015). The TASC classification has been widely used, however, it has been criticized for not differentiating stenoses, occlusions or the degree of stenosis and it impedes the differentiation of single or

multiple lesions (Kukkonen et al., 2010; Ricco, 2010). In addition, significant interrater disagreement has been observed with TASC II femoropopliteal classification (Kukkonen et al., 2010). In Figures 2, 3, and 4, TASC classifications for aortoiliac, femoropopliteal, and crural lesions are presented.

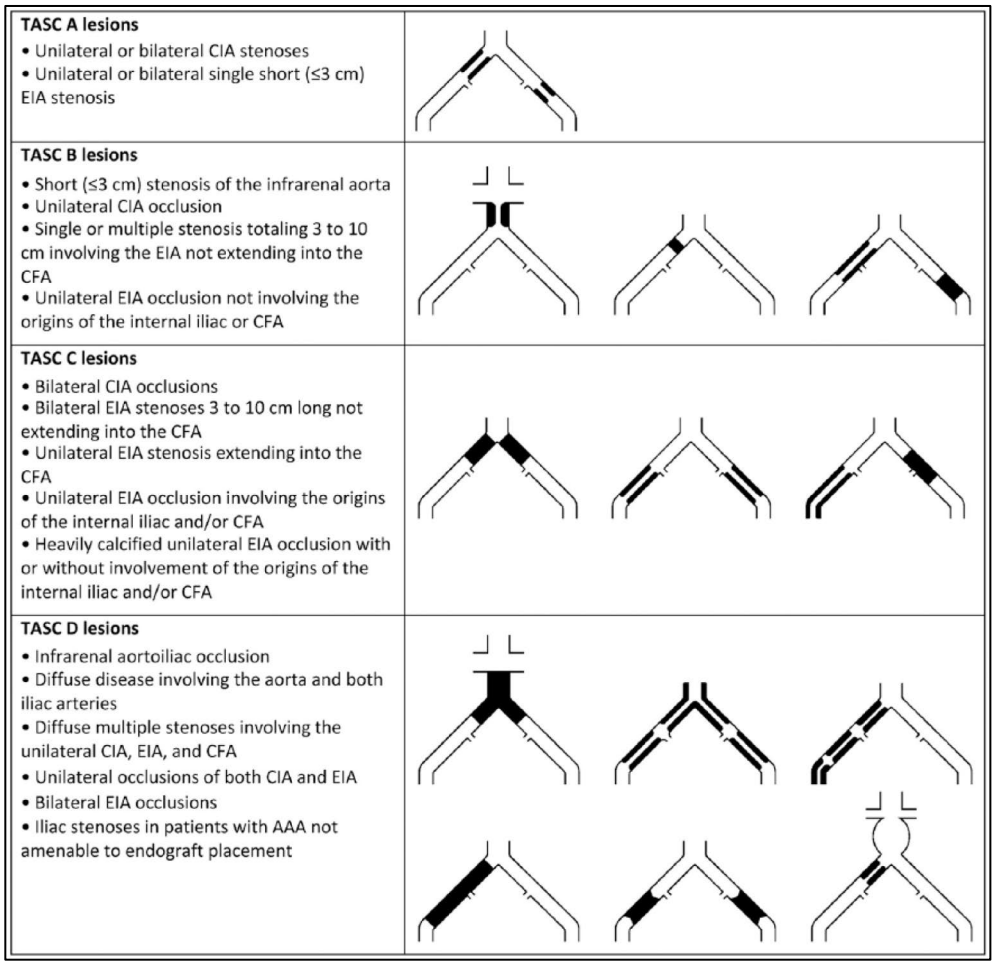


Figure 2. TASC classification of aortoiliac lesions (Jaff et al., 2015). AAA, abdominal aortic aneurysm; CFA, common femoral artery; CIA, common iliac artery; EIA, external iliac artery. Reproduced with the permission from Sage Publishing.

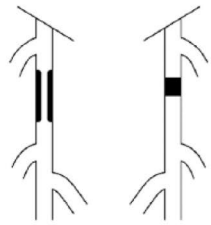
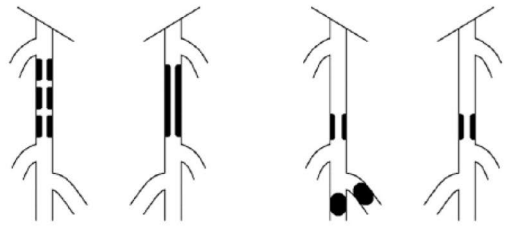
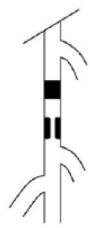
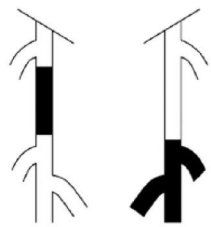
TASC A lesions • Single stenosis ≤10 cm in length • Single occlusion ≤5 cm in length	
TASC B lesions • Multiple lesions (stenoses or occlusions), each ≤5 cm • Single stenosis or occlusion ≤15 cm not involving the infrageniculate popliteal artery • Heavily calcified occlusion ≤5 cm in length • Single popliteal stenosis	
TASC C lesions • Multiple stenoses or occlusions totaling >15 cm with or without heavy calcification • Recurrent stenoses or occlusions after failing treatment	
TASC D lesions • Chronic total occlusions of CFA or SFA (>20 cm, involving the popliteal artery) • Chronic total occlusion of popliteal artery and proximal trifurcation vessels	

Figure 3. TASC classification of femoropopliteal lesions (Jaff et al., 2015). CFA, common femoral artery; SFA, superficial femoral artery. Reproduced with the permission from Sage Publishing.

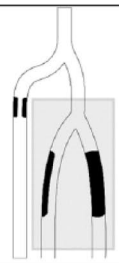
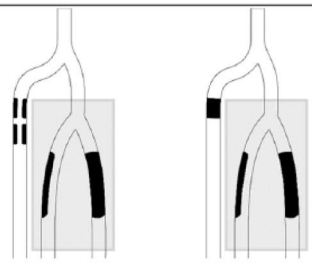
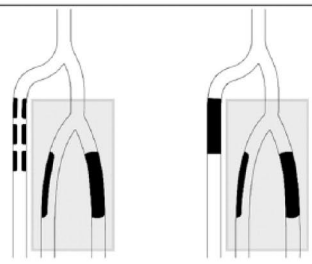
TASC A lesions Single focal stenosis, ≤5 cm in length, in the target tibial artery with occlusion or stenosis of similar or worse severity in the other tibial arteries.	
TASC B lesions Multiple stenoses, each ≤5 cm in length, or total length ≤10 cm or single occlusion ≤3 cm in length, in the target tibial artery with occlusion or stenosis of similar or worse severity in the other tibial arteries.	
TASC C lesions Multiple stenoses in the target tibial artery and/or single occlusion with total lesion length >10 cm with occlusion or stenosis of similar or worse severity in the other tibial arteries.	
TASC D lesions Multiple occlusions involving the target tibial artery with total lesion length >10 cm or dense lesion calcification or non-visualization of collaterals. The other tibial arteries occluded or dense calcification.	

Figure 4. TASC classification of crural lesions (Jaff et al., 2015). The shaded rectangle demonstrates typical background disease. Reproduced with the permission from Sage Publishing.

Recently, the Crural index (CIx), was implemented to grade the extent of crural atherosclerosis and this assessment tool was first described in a study by Jalkanen et al (Jalkanen et al., 2016b). Briefly, each of the three crural vessels are analysed individually and CIx is then assessed by the sum of these three crural vessels. (Jalkanen et al., 2016b). CIx classification system is presented in Table 5.

Table 5. CIx classification system (Jalkanen et al., 2016b).

GRADE	ANTERIOR TIBIAL ARTERY	PERONEAL ARTERY	POSTERIOR TIBIAL ARTERY
NO DISEASE OR MINOR STENOSIS	0	0	0
TOTAL OCCLUSION <5 CM	1	1	1
TOTAL OCCLUSION <10 CM	2	2	2
TOTAL OCCLUSIONS <15 CM	3	3	3
TOTAL OCCLUSION ≥15 CM	4	4	4
= CIX IS THE SUM OF ANTERIOR TIBIAL ARTERY, PERONEAL ARTERY, AND POSTERIOR TIBIAL ARTERY	Sum 0 = index 0 Sum 1-3 = index I Sum 4-6 = index II Sum 7-9= index III Sum 10-12 = index IV		

CIx, crural index.

2.2.4 Prognosis and survival

Patients with LEAD have an increased risk for both major amputations and mortality (Aboyans et al., 2018). The more severe LEAD is, the higher are the rates of amputation, mortality and also the worse the survival is (Farber & Eberhardt, 2016; Novo et al., 2004). If severe ischemia is left untreated, it progresses and almost a quarter of patients will die and another quarter will undergo major amputation within one year (Abu Dabrh et al., 2015).

2.2.4.1 Major amputations

The main goal of treatment is to preserve the limb by any reasonable means possible. Major amputation is defined as trans-tibial (below the knee amputation, BKA) or trans-femoral (above the knee amputation, AKA). Amputations below the ankle are considered as minor amputations. Major amputation impacts negatively on quality of life, survival, and overall prognosis (Pell et al., 1993; Schuyler Jones et al., 2013).

Approximately half of the amputees are able to walk with prosthesis, at least indoors, after rehabilitation (Jordan et al., 2012). The likelihood of being able to walk is higher after trans-tibial amputation compared to transfemoral amputation (Jordan et al., 2012).

The risk of amputation varies considerably. Patients with IC rarely undergo major amputation but the likelihood of amputation increases as symptoms worsen towards CLTI (Baubeta Fridh et al., 2017). More specifically, the incidence of major amputation has been reported to be 0.4% per year for IC whereas for CLTI, it rises to 2.0% per year (Baubeta Fridh et al., 2017). Among the amputees, severe ischemia Rutherford 5-6 is more prevalent than Rutherford 4 (Klaphake et al., 2017). Similarly, Fontaine III-IV is more frequently found in patients with major amputations than for their non-amputee counterparts (Anand et al., 2018).

2.2.4.2 Mortality

Despite the clinical picture, mortality in LEAD patients is high (van Haelst et al., 2018). In a study that combined data obtained from 21 countries, increasing rates of LEAD related mortality were reported for 1990-2010, especially in Asian Pacific countries (Sampson et al., 2014). In the United Kingdom during the 2006-2015 period, LEAD associated mortality rates remained high compared to CAD, for which rates declined by 43% (Sundaram et al., 2019). In a recent study by Liu et al. in 1990-2019, the worldwide burden of LEAD related mortality has not extensively increased, however, its management is insufficient and poorly handled (Liu et al., 2022).

LEAD is a significant contributor to mortality. Within the last decades, LEAD related mortality has increased in all age groups internationally (Sampson et al., 2014). Compared to healthy individuals without LEAD, the risk of mortality has been estimated to be 2.0 to 3.5 fold (Mueller et al., 2014). On average, one third of LEAD patients are estimated to die from a cardiogenic cause of death, most frequently from either heart failure or myocardial infarction (Dick et al., 2007).

Similar to that found for limb loss, the risk for mortality differs for different subtypes of LEAD. Regarding the clinical presentation, claudicants have lower mortality rates than CLTI patients (Baubeta Fridh et al., 2017). However, the risk for mortality is still high; IC patients have approximately 3 and CLTI patients 5-fold risk for mortality compared to the individuals without LEAD (van Haelst et al., 2018). The highest mortality rate is seen in those patients that underwent major amputation. Almost 25% of patients with major amputation die within the first month and 50% within the first year after primary amputation (Fortington et al., 2013). Asymptomatic LEAD associates with similar risk of mortality compared to patients with IC (Behroozian & Beckman, 2021).

2.2.4.3 Risk factors for amputation and mortality

Similar factors have been associated with higher risk of both amputations and mortality. Advanced age is a significant contributor to limb loss as a 5-year increase in age associates with 13% higher risk of major amputations in LEAD patients >65 years of age (Schuyler Jones et al., 2012). A similar risk is found for mortality (Schuyler Jones et al., 2013). The higher likelihood of adverse events can be explained by a worse risk factor profile and by frailty, both of which are common among the elderly (Takeji et al., 2018; Turrentine et al., 2006). However, senescence itself associates with higher mortality irrespective of comorbidities (Turrentine et al., 2006).

Tobacco smoking is not only a strong risk factor for developing CLTI but also, a significant negative factor for survival. An association with amputations and smoking intensity has been observed and in one study, smoking more than one pack a day was associated with 1.20 to1.39 fold the risk of major amputation (J. C. Young et al., 2019).

Diabetics are five times as likely to undergo major amputation and have a three-fold risk of mortality than their non-diabetic counterparts (Jude et al., 2001). Diabetic ulcers are a common macrovascular complication of DM and are the main cause of limb loss in diabetics (Jeffcoate & Harding, 2003; Ramsey et al., 1999).

Patients with dialysis-dependent kidney failure have 181% increase in risk of either limb loss or mortality at one year after open surgery (Schanzer et al., 2008). Severe renal insufficiency (glomerular filtration rate (GFR) <30 ml/min/1.72 m^2), associates with almost 3-fold higher risk of mortality and a stepwise, inverse association has been detected between decreasing GFR and the risk of 1-year mortality (O'Hare et al., 2005).

Nearly a quarter of LEAD patients have concomitant CAD (Cacoub et al., 2009). CAD has been associated with increased risk of both amputation and mortality (Biancari et al., 2007; Schanzer et al., 2008). The co-existence of both CLTI and CAD is a high-risk condition that associates with a four-fold risk for adverse events compared to patients with less severe LEAD (D. C. Chen et al., 2017).

Hyperlipidemia associates with an increased risk of adverse events as well; LDL-cholesterol of >3.4 mmol/l increases the risk of mortality, cerebral and cardiac events with a 1-year event rate of 22% (Westin et al., 2014). Previously it had been shown that hypertension impacts negatively on the amputation-free survival and predicts mortality (Londero et al., 2019). In one study, patients with hypertension were 23% more likely to undergo either amputation or die after primary revascularization (Londero et al., 2019).

In addition to the aforementioned conventional cardiovascular risk factors, the location of the predominant disease associates with survival i.e., the more distal the LEAD site is, the higher is the risk for major amputation and mortality (Q. Chen et

al., 2013; Jalkanen et al., 2016b, 2016a). Similarly, the extent of crural atherosclerosis has been reported to associate with a poor prognosis and also patients with the most severe lesion characteristics have the highest adverse event rates (Jalkanen et al., 2016b, 2016a; Wickström, Jalkanen, et al., 2017). Abnormal peripheral limb pressures, ABI, TP, and TBI are not only useful in the diagnosis of LEAD; they also provide useful information on patient survival. For example, there is a U-shaped association between ABI and mortality (Hyun et al., 2014; Resnick et al., 2004). Decreased TBI and TP have both been shown to be predictive of higher mortality and lower survival (Carter & Tate, 2001; Chisalita et al., 2020; Vallabhaneni et al., 2016; Zobel et al., 2017). A similar association of decreased ABI, TBI, and TP and risk of limb loss has been observed (Hämäläinen et al., 1999; Vallabhaneni et al., 2016; Wickström, Laivuori, et al., 2017).

2.2.4.4 Risk estimation

As described in the previous paragraphs, a significant proportion of patients end up as amputees. Over the years, multiple risk estimation models have been published to predict adverse events. For example, the Finnish National Vascular Registry (FINNVASC) study found emergency surgery, DM, CAD, and the presence of gangrene to be predictors of poor ampution free survival (Biancari et al., 2007). However, the investigators in that study only investigated surgically operated patients for 30 days after the initial revascularization (Biancari et al., 2007). In database study of the Project of Ex-Vivo graft Engineering Transfection III (PREVENT III), dialysis-dependency, tissue loss, advanced age, low hematocrit, and CAD associated with poor amputation free survival in surgically revascularized patients within a 1-year follow up period (Schanzer et al., 2008). A study of both endovascular and surgically operated CLTI patients, i.e. the Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) study, found a risk factor profile similar to that of PREVENT III that associates with higher risk of amputation and mortality within a 2 year follow-up (Bradbury et al., 2010a). However, less typical risk factors, Bollinger score, ankle pressures, and BMI were included as risk factors in the model of the BASIL study as well (Bradbury et al., 2010a).

A recent validation study by Wijnand et al. compared FINNVASC, PREVENT III, and BASIL risk estimation models in three different CLTI cohorts (Wijnand et al., 2020). In their study, the prediction of 12-month amputation free survival was assessed using receiver operating characteristic (ROC) curves (Wijnand et al., 2020). For all the models, the area under curve (AUC) ranged from 0.60 to 0.71 for amputation free survival, which indicates poor to fair accuracy in risk estimation (Mandrekar, 2010; Wijnand et al., 2020). For 12-month mortality, AUC for all the models ranged from 0.52 to 0.81 (Wijnand et al., 2020). For mortality, BASIL model

performed best in a CLTI cohort who were not candidates for revascularization whereas in patients who had underwent endarterectomy, it performed poorly (AUC 0.63-0.81) (Wijnand et al., 2020).

Supportive to the study of Wijnand et al., the abovementioned models were found to show modest predictive abilities for poor outcome in a review study (Chung et al., 2014). First, it is evident that the evolving and heterogeneous definition of severe limb ischemia complicates the comparisons between different studies (Chung et al., 2014). Considerable variety and inconsistency exist among the predictive variables, patient cohorts, comorbidial profiles, follow-up times, and endpoints, which hinders the generalization of these models to the entire CLTI population and clinical practice (Chung et al., 2014). For example, the less traditional risk factors, including the location and extent of atherosclerosis and sex of the patient, have been associated with poor outcomes although these are not included in all the aforementioned risk models (Chang et al., 2013; Choi et al., 2019; Jalkanen et al., 2016b, 2016a; Wickström, Jalkanen, et al., 2017). Moreover, most of the present risk estimation tools do not include DM although a significant proportion of CLTI patients are diabetics with the highest odds of amputations and mortality (Spreen et al., 2016; Vrsalovic et al., 2017). Interestingly, DM was added to the PREVENT III risk factor model, which enhanced the predictivity of amputation and amputation-free-survival 12 months post-operation (Wijnand et al., 2020).

Due to the limited effectiveness of the current risk estimation models, it is still uncertain which patients develop CLTI with a poor outcome (Chung et al., 2014; Wijnand et al., 2020). An accurate risk estimation should be able to guide the timing and selection of the most appropriate treatment modality, therefore, its importance cannot be overemphasized. For example, for patients with a life-expectancy of more than two years, surgical revascularization is recommended (Bradbury et al., 2010b) and therefore, an accurate estimation of the patient survival is crucial for the most optimal treatment of CLTI. In Table 6, FINNVASC, PREVENT III, and BASIL risk estimation models are presented.

Table 6. Comparisons of FINNVASC, PREVENT III, and BASIL risk estimation models. Modified from the original studies (Biancari et al., 2007; Bradbury et al., 2010a; Schanzer et al., 2008).

STUDY	FINNVASC	PREVENT III	BASIL
PATIENTS	3925 patients (Fontaine III-IV) who underwent infrainguinal bypass	1404 patients (Rutherford 4-6) who underwent either infrainguinal bypass with autologous conduit	452 patients (Rutherford 4-6) who underwent either bypass or endovascular revascularization
YEARS	1991-1999	2001-2003	1999-2004
EXCLUSION CRITERIA	Other procedures than femoral endarterectomy, femopopliteal, and infrapopliteal bypass, patients missing data	Claudication, non-autologous conduit	None
END-POINTS	30 day amputation free survival	1-year amputation free survival	1- and 2-year amputation free, 1- and 2-year overall survival
RISK FACTORS (POINTS)	DM (1), CAD (1), gangrene (1), urgent operation (1)	Dialysis (4), tissue loss (3), age ≥75 years (2), hematocrit ≤30% (2), CAD (1)	Tissue loss, serum creatinine, age, below knee Bollinger score, smoking, BMI, number and highest AP, CAD, stroke/TIA
INTERPRETATION	Score indicates risk	Low risk ≤3, medium risk 4-9, and high risk ≥8.	Online model, (http://basiltrial.com/)

FINNVASC, Finnish National Vascular Registry; PREVENT III, Project of Ex-Vivo graft Engineering Transfection III; BASIL, Bypass versus Angioplasty in Severe Ischemia of the Leg; DM, diabetes mellitus; CAD, coronary artery disease; BMI, body mass index; TIA, transient ischemic attack; AP, ankle pressure.

2.2.5 Treatment

2.2.5.1 Conservative treatment

The goal of conservative treatment is to reduce cardiovascular morbidity and lower the risk of adverse outcomes (Conte et al., 2019). Similar to the treatment of other atherosclerotic manifestations, oral hydroxymethyl glutaryl coenzyme-A reductase inhibitors, namely statins, are recommended for all LEAD patients despite the clinical manifestation (Mach et al., 2020). The goal is to lower LDL-cholesterol by at least 50% and below 1.4mmol/ despite the presence of DM (Mach et al., 2020). If that goal is not achieved with high dose statin treatment alone, a statin plus ezetimibe, or a statin plus ezetimibe combined with a proprotein convertase subtilisin/kexin type 9 (PSCK9) inhibitor should be considered (Aung et al., 2007; Mach et al., 2020; Subherwal et al., 2015).

For all patients, it is recommended to lower blood pressure ≤140/90 mmHg (Williams et al., 2018). If this is achieved without side-effects, then the goal should be ≤130/80 mmHg (Williams et al., 2018). The use of ramipril has especially been associated with the reduced rates of cardiovascular events in patients with LEAD (Östergren et al., 2004). Moreover, it has been shown that telmisartan has a similar risk reduction capacity as ramipril in high-risk patients (Yusuf et al., 2008).

Glycemic control and a glycated hemoglobin HbA1c below 53 mmol/mol (7%) is recommended for diabetics (M. J. Davies et al., 2018). The preferred first-line medication for T2DM is metformin, combined with either a sodium glucose cotransporter 2 (SGLT2) inhibitor or glucagon-like peptide 1 (GLP-1) receptor agonist (M. J. Davies et al., 2018). However, it has been recommended that SGLT2 inhibitor usage should be carefully evaluated in patients with CLTI as it has been associated with an almost 2-fold risk of amputation in one study (Buse et al., 2019; Neal et al., 2017). Moreover, the treatment strategy should be individualized for each patient and factors such as frailty, comorbidity profile, risk of hypoglycemia and obesity should be kept in mind (M. J. Davies et al., 2018).

Primary prevention with aspirin is not advised if the patient has isolated asymptomatic LEAD (Aboyans et al., 2018; Fowkes et al., 2010). In symptomatic LEAD, either aspirin or clopidogrel is recommended to reduce the risk of adverse events (Aboyans et al., 2018). A long-term antithrombotic regimen is advised for all symptomatic patients and those who have undergone revascularization (Aboyans et al., 2018). In high risk patients after revascularization, a combination of both aspirin and small-dose rivaroxaban associates with lower mortality and amputation rates (Bonaca et al., 2020).

An exercise program is the most effective method to treat the limb symptoms and improve the functional capacity (Hamburg & Creager, 2017). A minimum of 30

to 45 minutes of exercise should be completed at least three times a week (Anderson et al., 2013). If possible, a walking program should be supervised and it should last for at least 12 weeks as it associates with a lower morbidity and mortality (Sakamoto et al., 2009). All patients should be encouraged to quit smoking since smoking cessation associates with a better survival (Anderson et al., 2013; E. J. Armstrong et al., 2014).

Conservative treatment is the first line treatment of IC whereas CLTI often requires invasive treatment. However, smoking cessation and management of hypertension, dyslipidemia, and hyperglycemia improve survival in CLTI and form the foundation of the treatment (Aboyans et al., 2018; E. J. Armstrong et al., 2015; Takahara et al., 2010; Westin et al., 2014).

2.2.5.2 Revascularizations

The goal of revascularization is to preserve the ischemic limb and it can be performed either with open surgery or endovascularly (Norgren et al., 2007). The decision to revascularize for IC depends on the severity of symptoms and the location of the atherosclerotic lesions (Aboyans et al., 2018; Thukkani & Kinlay, 2015). When IC impacts negatively on the patient's quality of life, daily activities are compromised, and the impact of conservative treatment is found to be inadequate, then elective revascularization could be considered with the proviso that the overall condition qualifies for an invasive operation (Aboyans et al., 2018; Thukkani & Kinlay, 2015). In a recent randomized controlled trial (RCT) The Invasive Revascularization or Not in Intermittent Claudication trial (IRONIC), medication therapy (aspirin/clopidogrel, statin, cilostazol) together with revascularization improved patients' quality of life more than medication alone (Nordanstig et al., 2016). Lesions that cause IC are most commonly located in aortoiliac or femoropopliteal regions whereas isolated crural disease is rare (Aboyans et al., 2018).

Revascularization is the principal treatment of CLTI and all patients should be quickly referred to a vascular center (Conte et al., 2019). CLTI is most commonly multisegmental rather than isolated disease in only one arterial segment (Gray et al., 2010; Ozkan et al., 2009), which limits the use of the endovascular method. CLTI typically involves the infrapopliteal arteries and presents severe stenoses and total occlusions (Thukkani & Kinlay, 2015). Another indication for revascularization is acute limb ischemia (Thukkani & Kinlay, 2015), which is its own disease entity and not discussed in this thesis.

2.2.5.2.1 Surgical revascularizations

Surgical revascularizations are the traditional gold-standard of the operative treatment of LEAD (DeWeese et al., 1993). They can be performed as bypass or endarterectomy (Norgren et al., 2007). Bypasses are widely used in LEAD and a conduit can be constructed with an autologous vein or with artificial material (Norgren et al., 2007). Endarterectomies are typically performed in the proximal disease, but not in the distal arteries due to the smaller vessel diameter (DeWeese et al., 1993).

Surgical bypasses have been appraised to offer superior anatomic patency and durability compared to other methods (Indes et al., 2013). Unfortunately, not all patients are eligible for open revascularization due to a lack of conduit material, anaesthesia risks, and other conditions and comorbidities, which limit the use of surgery on some patients. Surgery has been linked to longer hospital stays, readmissions, increased complications risk and higher mortality compared to the endovascular approach (Garimella et al., 2017; Indes et al., 2013; Khoury et al., 2019). It has been reported that approximately 18-36% of bypass patients have complications. Such complications are graft failures, wound or graft infections, wound seromas and also include cardiac complications and pneumonia (Indes et al., 2013; Patel et al., 2016). Bypass patients have higher 30-day mortality, however, similar or even better long-term survival at 1 year compared to patients operated by the endovascular method (Bradbury et al., 2010b; Indes et al., 2013; Patel et al., 2016).

2.2.5.2.2 Endovascular revascularizations

There are two main ways to perform an endovascular revascularization; balloon angioplasty (PTA) and stenting (Thukkani & Kinlay, 2015). Within the last years, the technology has developed even further and newer drug-coated balloons and drug-eluting stents have been introduced (E. J. Armstrong et al., 2016). During the last decade, endovascular methods have been widely adopted in Finland (Nikulainen et al., 2019). Perhaps the most significant advantage of the endovascular method is that it has made revascularizations accessible for patients that are unfit for traditional bypass (Conte, 2012). In some studies, it has been reported that the selection of these more seriously ill patients for endovascular revascularization results in comparable amputation-free survival (Bisdas et al., 2016; Iida, Takahara, Soga, Kodama, et al., 2017). Being less invasive compared to surgery, the endovascular method associates with shorter hospital stays and fewer complications (Bradbury et al., 2010b; Garimella et al., 2017). The major weaknesses of endovascular strategy are however, poorer durability and patency rates, which may lead to poorer sustained hemodynamic success (Indes et al., 2013; Patel et al., 2016).

2.2.5.2.3 The most appropriate treatment strategy

Most of the patients with IC are revascularized endovascularly with excellent results (De Vries et al., 2002; Fakhry et al., 2015). In one study, successful revascularization improved maximum walking distance, pain-free walking distance, and quality of life compared to exercise alone (Fakhry et al., 2015). However, eligible evidence on the most appropriate treatment strategy for CLTI remains scarce, especially for infrapopliteal disease. Over the years, studies in varying settings have been published that favour either surgical or endovascular methods, and some studies report no difference (Bradbury et al., 2010b; Hicks et al., 2017; Lin et al., 2019; Patel et al., 2016). The heterogeneity of the existing studies hinders the comparison of one technique over another.

The TASC II revascularization guidelines were based on the extent of lesion characteristics and extensive aortoiliac and femoropopliteal TASC C-D lesions were recommended to be operated surgically when an acceptable conduit vein exists (Norgren et al., 2007). For TASC A-B lesions, endovascular treatment was preferred (Norgren et al., 2007). However, patients may present multiple lesions with variable complexity in more than one segment, which causes challenges in deciding the appropriate class and revascularization strategy (Kukkonen et al., 2010). For both multilevel and crural lesions, TASC II guidelines had no recommendation regarding the revascularization strategy (Conte, 2012; Norgren et al., 2007). In addition, not all patients are eligible for invasive surgery as patients with CLTI typically present high risk factor profile and the autologous conduit reservoir may be used or saved instead for a possible coronary bypass surgery. Multimorbidity, DM, and frailty associate with a poor prognosis after revascularization and should be kept in mind in the treatment planning (Morisaki et al., 2017; Schanzer et al., 2008; Shammas et al., 2017). Unfortunately, TASC II guidelines did not acknowledge the patient comorbidity profile nor their overall condition (Conte, 2012).

In 2015, the TASC II update on methods and new infrapopliteal classification was released (Jaff et al., 2015). In this publication, however, the authors stated that no recommendations for treatment strategy could be provided due to the lack of eligible evidence (Jaff et al., 2015). Moreover, the authors stated that the experience of the vascular center, lesion characteristics, patient overall condition and prognosis should be considered when selecting the revascularization strategy (Jaff et al., 2015).

In ESC 2017 guidelines, endovascular strategy was recommended for stenotic lesions and short occlusions and surgery for long occlusions in patients with CLTI (Aboyans et al., 2018). Surgical bypass with autologous conduit was recommended for infrapopliteal lesions (Aboyans et al., 2018). Endovascular revascularization could be preferred over surgery if the patient has considerable surgical risks or no available vein for conduit (Aboyans et al., 2018). The authors stated that existing eligible evidence is limited and for each patient, both methods should be considered

(Aboyans et al., 2018). In GVG, the authors also acknowledge the lack of high-quality data (Conte et al., 2019). They recommend that the decision of the most appropriate method should be based on patient risk factor profile, life-expectancy, WIfI classification, anatomic extent of the disease, and availability of venous conduit material (Conte et al., 2019).

In most cases, the choice of treatment is decided by the operating surgeon as no comprehensive consensus exists for the most appropriate treatment strategy. The guidelines do not provide a recommendation for diabetics although a significant proportion of CLTI patients are diabetics (Rymer et al., 2020; Takahara et al., 2020). For the high-risk patients, the decision between revascularization and primary major amputation is demanding. For some patients, revascularization may not be the most suitable option in the long-term. Especially for patients with poor life-expectancy, non-ambulatory condition, or extensive tissue loss primary amputation should be considered (Conte et al., 2019).

It is important to evaluate the current revascularization practice as a non-optimal strategy may lead to unnecessary repetitive procedures and unwanted outcomes. Moreover, revascularizations are expensive for public healthcare systems and non-optimal treatment strategy should therefore be avoided. Although avoiding major amputation is the primary goal in the treatment of LEAD, amputation may be the most appropriate option for some patients. Furthermore, investigation of the characteristics of these primary amputees is important to evaluate further the current revascularization practice and the current management of CLTI.

3 Aims

The main purpose of the studies reported in this dissertation was to investigate patients with CLTI.

The specific aims of this thesis were:

I. Investigate the clinical features of CLTI and the distribution and extent of atherosclerosis.

II. Evaluate the current management of CLTI, with a special emphasis on revascularizations and their impact on amputations.

III. Explore the prognosis and survival in patients with CLTI and evaluate the impact of severe distal atherosclerosis, sex, and ABI, TBI, and TP on limb-related outcomes and mortality.

4 Materials and Methods

4.1 Background information

All the three CLTI cohorts consisted of patients from the Hospital District of Southwest Finland. It comprises Turku University Hospital and three other regional hospitals, namely Salo, Loimaa, and Uusikaupunki hospitals. Revascularizations in the Hospital District of Southwest Finland are centralized and performed solely in Turku University Hospital, whereas amputations have been performed in all hospitals. In 2004, the vascular service unit serving the area of Hospital District of Southwest Finland was established and vascular surgery and amputation practice were centralized under one surgical specialty.

All the three study protocols were approved by the local Ethics Committee of the Hospital District of South-West Finland, and the protocols conform to the ethical guidelines of the 1975 Declaration of Helsinki. Due to the retrospective nature of the studies, patient written informed consent was not required.

Table 7. Summary of all study cohorts included in this thesis.

STUDY	COHORT	N	AIMS
I	A retrospective cohort of all consecutive patients with DSA and limb pressure measurements (ABI, TBI, TP) from Jan 1st 2007 to Aug 31st 2011	729 patients	To evaluate whether the predictive effect of ABI, TBI, and TP differ according to the predominant atherosclerotic lesion location.
II	A retrospective cohort study of all consecutive patients with major amputation due to atherosclerotic or diabetic origin from Jan 1st, 2007 to Dec 31st, 2017	891 patients	To investigate the characteristics and survival of amputees and changes in the regional incidence of major amputations in Southwest Finland 2007-2017.
III	A retrospective cohort of all consecutive patients with either LEAD and/or DM and a crural revascularization from Jan 1st, 2007 to Dec 31st, 2015	497 patients	Compare amputations and mortality after infrapopliteal open and endovascular revascularization in patients with and without DM.

DSA, digital subtraction angiography; ABI, ankle-brachial index; TBI, toe-brachial index; TP, toe pressure; DM, diabetes mellitus; N, number.

4.2 Patients and data processing

4.2.1 Study I - Peripheral pressures in different predominant disease locations

A total of 729 patients who underwent DSA between January 1, 2009 and August 31, 2011 and who also had standardized peripheral pressure measurements in vascular laboratory were reviewed and included in the study. For additional analysis, patients were distributed into two groups, CLTI and Non-CLTI, according to the Rutherford classification. The CLTI group consisted a total of 400 patients. The first DSA was considered as a starting point and this primary DSA was used to assess the distribution and extent of atherosclerosis.

4.2.2 Study II – Major amputations in an aging population in Southwest Finland during 2007-2017

All patients who underwent major amputation of atherosclerotic or diabetic origin in the Hospital District of Southwest Finland between January 1, 2007 and December 31, 2017, were retrospectively reviewed. In total, 891 patients with major amputations during the 11-year study period were included in the study. The amputations were either AKA or BKA. The time of the major amputation was considered as the index date for the study. If more than one major amputation (for example BKA+AKA) was performed on the ipsilateral leg of the patient, or major amputation was performed on both limbs, the first major amputation was considered as the index operation. The annual size of population of the area was collected from the Finnish public government statistics authority, Statistics Finland ("Official Statistics of Finland (OSF): Population Structure [e-Publication].," 2020).

4.2.3 Study III - Outcome after infrapopliteal revascularization in diabetic and non-diabetic patients

All consecutive CLTI patients with a diagnosis of LEAD and/or DM who underwent infrapopliteal revascularizations at Turku University Hospital Department of Vascular surgery between January 1, 2007 and December 31, 2015 were retrospectively reviewed. In total, 497 patients with 552 revascularized limbs were included in the study. The diagnosis of DM was defined as the use of insulin or other hypoglycemic inducing agents. Patients were categorized into three main groups; insulin treated diabetics (IT-DM-group), non-insulin treated diabetics (NIT-DM group), and non-diabetics (Non-DM group). The IT-DM group consisted of 180, NIT-DM 94, and Non-DM 223 patients.

4.3 Surgical protocol

4.3.1 Protocol for revascularizations

The treatment strategy of whether to revascularize or to amputate was based on the vascular status and overall condition of the patient. Both open and endovascular revascularizations are actively considered when feasible in the Hospital District of Southwest Finland. A revascularization procedure is generally offered for all patients fit for invasive operations. Endovascular revascularizations in Turku University Hospital during the study period were technically in the phase of development and the long-term outcomes after endovascular revascularization during that phase were observed to be poorer compared to surgery. Therefore, distal bypasses were preferred

for patients with CLTI when the patient was considered eligible enough for surgery. A multitude of patient-derived factors, such as poor overall health, anaesthesia risks, a lack of autologous conduit, and lesion characteristics guided the decision towards endovascular intervention. The patients with short stenosis were more likely to be treated using endovascular methods. Patients with short life-expectancy or non-ambulatory condition were not considered to benefit from revascularization and thus, amputation was preferred over revascularization.

4.3.2 Surgical protocol for amputations

A revascularization was always considered first when feasible but if not, major amputation was then indicated. In general, the goal was to aim for BKA but in cases of poor prognosis, AKA level was then the inevitable option. For all the studies, major amputations were either AKA or BKA. Trans-pedal or toe amputations were not counted as an endpoint in any of the studies.

4.4 Peripheral pressure measurements

Hemodynamic measurements were performed with Nicolet VasoGuard (Nicolet Vascular Inc. Madison, WI, USA) photoplethysmography by vascular nurses. All measurements were standardized and obtained in a systematic manner; patients lay in the supine position with the limb at the level of the heart. Pneumatics cuffs were inflated until the flow signal ceased and then slowly deflated until the pulsatile signal reappeared to obtain the pressure measurements. Overall, the lowest value of the pressured measurement was recorded for the limb.

To assess ABI, the systolic ankle pressure was divided by the systolic brachial pressure. TP of the big toe was measured and if the toe was missing, it would be taken from the nearest available toe. To reduce the effect of local vasoconstriction, the patient's feet were pre-warmed before the measurements. TBI was measured by dividing the toe's systolic pressure by the brachial systolic pressure. Peripheral pressure measurements were then categorized. For TP, classification categories were <30 mmHg, 30-49 mmHg, and ≥50 mmHg and for TBI, <0.25, 0.25 – 0.49, and ≥0.50. For ABI, the categories were <0.25, 0.25 – 0.89, 0.90 – 1.29, and ≥1.30, respectively.

4.5 Crural Index

The assessment of the CIx was first described in a study authored by Jalkanen (Jalkanen et al., 2016b). To obtain CIx, each of the three crural vessels were analyzed individually. Only total occlusion were analyzed and each vessel numerically

categorized by the state of atherosclerosis thus: No detectable or minor disease: 0; Total occlusion less than 5 cm: 1; Total occlusion less than 15 cm: 3; Total occlusion more than 15 cm: 4. Finally, the CIx was calculated from the sum of the these three crural vessels thus: when the sum total was 0 the CIx was 0; when the sum total was 1-3 the CIx was I; when the sum total was 4-6 the CIx was II; when the sum total was 7-9 the CIx was III and when the sum total was 10-12, the CIx was IV. Operated limbs were divided into subgroups by the presence of DM and CIx. In the study III, limbs with CIx I-III were grouped together due to the low number obtained.

4.6 Classification of the most diseased arterial segment

The process of the determination of the most diseased arterial segment (MDAS) by DSA images was initially introduced by (Jalkanen et al., 2016b). Aortoiliac and femoropopliteal segments were classified according to TASC II criteria as described in the Introduction-section. To assess the state of atherosclerosis in each segment, aortoiliac and femoropopliteal segments were coded as follows; no disease:0, TASC II A = 1; TASC II B = 2; TASC II C = 3 and TASC II D = 4. In crural segment, atherosclerosis was graded by CIx.

Based on these TASC II and CIx classifications, each segment was scored from 0-4 and the arterial segment that reached the highest score was defined as the MDAS. According to this, patients were assigned into either 1) MDAS AOI (aortoiliac), 2) MDAS FP (femoropopliteal), or 3) MDAS CR group (crural). For instance, CIx III (3) ruled out proximal lesions of 0-2 and therefore, the predominant disease location was CR and patients were analysed in the group MDAS CR. If the highest grade was equal in two or even three locations, the most proximal location was then chosen as the predominant location.

4.7 Study endpoints and outcome measures

The aim of study I was to analyse the associations between the predominant disease locations, peripheral pressure measurements, and cardiovascular mortality. Data were collected until August 31, 2011 or cardiovascular cause of death.

The main goal of study II was to investigate changes in the major amputation incidence in Southwest Finland between 2007-2017 and to describe patient characteristics, vascular history of amputees and survival. Data were collected until all-cause death of or until March 28, 2018. The latter was considered the endpoint of this study.

The aim of study III was to investigate survival after infrapopliteal endovascular and surgical revascularizations in patients with insulin treated DM, non-insulin

treated DM, and patients without DM. Special emphasis was placed on investigating whether survival was affected by the severity of atherosclerosis. Two major outcomes were investigated for this study; amputation free survival was defined as either major ipsilateral limb amputation or death and overall survival as all-cause mortality of patient. Data were collected until either all-cause death of the patient or the end of the study period at December 31, 2015.

4.8 Statistical methods

All statistical analyses were performed in a comprehensive manner. Normal distribution was assessed using the Shapiro-Wilk tests. Categorical variables were expressed as frequency and percentage and comparisons were performed by Fisher's Exact test. Continuous variables were either expressed as mean ± and standard deviation (SD) or standard error (SE) or median and inter-quartile range (IQR), which were calculated according to Brookmeyer and Crowley (Brookmeyer & Crowley, 1982). The comparisons were performed using the Student's T-test, Mann-Whitney U-test or the Kruskal-Wallis test. The statistical significance threshold was set at 0.05.

For the study I, Cox regression analysis was performed to assess the predictive value of factors affecting survival. The following confounding variables were added to the model; age, male sex, CAD, hypertension, DM, and smoking history. In multivariable Cox regression analyses, the highest group was selected as the reference for categorical pressures and indices except for ABI, where ABI 0.90 – 1.29 were selected as the reference range category. Survival curves were estimated for each group using the Kaplan-Meier method and compared statistically using the Log-rank statistics. All statistical analyses were performed using the IBM SPSS ® version 26 statistics program.

In study II, patients were grouped into four age groups of 0-64, 65-74, 75-84, and >85 years of age. The incidence rate of major amputations was standardized for each age group and reported major amputations/100 000 inhabitants. To detect the possible trends, the Mann-Kendall trend test was performed. The comparisons of survival between groups were assessed by Log-rank statistics. All statistical analyses were performed using the IBM SPSS ® version 26 statistics program except for Mann-Kendall trend tests, for which R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) and the packages 'readxl'(Wickham & Bryan, 2019), 'openxlsx'(Schauberger & Walker, 2020), and 'Kendall'(McLeod, 2011) were used.

In study III, the Mann-Kendall trend test was used to determine the possible revascularizations trends. The Kaplan-Meier and Log-rank statistics were used for the survival analyses. An age-adjusted Cox regression model was assessed for the analyses of the possible risk factors. Only the statistically significant risk factors

($p<0.20$) in Univariable analyses were forced into the Multivariable regression analysis. The R-program was used for the data processing and analyses. The following packages were used: 'rms'(Harrell Jr, 2020), 'survival'(Therneau, 2020), 'comorbidity (Gasparini, 2018)', 'Kendall'(McLeod, 2011), 'readxl (Wickham & Bryan, 2019)'. 'openxlsx'(Schauberger & Walker, 2020), and 'prodlim'(Gerds, 2019).

5 Results

5.1 CLTI cohorts

A summary of all the study cohorts I-III is presented in Table 8. An abundance of cardiovascular comorbidities was found in all cohorts and nearly half of the patients were diabetics.

Table 8. Summary of study cohorts I-III.

	STUDY I, N, (%)	STUDY II, N, (%)	STUDY III, N, (%)
N	729	891	497
DM	298 (40.9)	451 (50.6)	274 (55.1)
CAD	315 (43.2)	402 (45.1)	106 (21.3)
HYPERTENSION	506 (69.4)	580 (65.1)	357 (71.8)
RENAL IMPAIREMENT	68 (9.3)	178 (20.0)	51 (10.3)
DYSLIPIDEMIA	273 (37.4)	159 (17.8)	180 (36.2)
ATRIAL FIBRILLATION	161 (22.1)	340 (38.2)	190 (38.2)

N, number of patients; %, percentage; DM, diabetes mellitus; CAD, coronary artery disease.

5.2 Study I - Peripheral pressures in different predominant disease locations

This study cohort consisted of 729 LEAD patients, of which 400 had CLTI (54.9%), which manifested in Rutherford 4-6. The crural segment was the most diseased segment in CLTI whereas claudicants had the most diseased femoropopliteal and aortoiliac segments, demonstrated in Table 9.

Table 9. The most diseased arterial segment in CLTI and Non-CLTI patients.

	CLTI, N (%)	NON-CLTI, N, (%)	P-VALUE
N	400	332	
AORTOILIAC	41 (10.3)	88 (26.5)	<0.001
FEMOROPOPLITEAL	175 (43.8)	192 (57.8)	<0.001
CRURAL	181 (45.3)	52 (15.7)	<0.001

CLTI, chronic limb-threatening ischemia; NON-CLTI, LEAD patients without CLTI; N, number of patients; %, percentage; P-value with Fisher´s Exact test.

5.2.1 The overall disease burden according to the predominant disease location

According to the location of the most extensive atherosclerosis in DSA and TASC II and CIx classifications, all 729 patients were distributed into aortoiliac (MDAS AOI), femoropopliteal (MDAS FP) and crural (MDAS CR) groups (Table 10). The aortoiliac segment was spared in 81.7 % in MDAS FP and 88.8% in MDAS CR patients. The crural arteries were severely diseased in 47.2% cases of all patients.

Table 10. Lesion characteristics in different predominant disease locations.

		MDAS AOI, N, (%)	MDAS FP, N, (%)	MDAS CR, N, (%)	ALL (%)	P-VALUE
N		129	367	233	729	
TASC II AOI	0	0	300 (81.7)	207 (88.8)	507 (69.5)	<0.001
	A-B	64 (49.6)	53 (14.4)	20 (8.6)	137 (18.8)	<0.001
	C-D	65 (50.4)	14 (3.8)	6 (2.6)	85 (11.7)	<0.001
TASC II FP	0	63 (48.8)	0	109 (46.8)	172 (23.6)	<0.001
	A-B	30 (23.3)	87 (23.7)	73 (31.3)	190 (26.1)	0.111
	C-D	36 (27.9)	280 (76.3)	51 (21.9)	367 (50.3)	<0.001
CIX	0	40 (31.0)	74 (20.2)	0	114 (15.6)	<0.001
	I-II	59 (45.7)	164 (44.7)	48 (20.6)	271 (37.2)	<0.001
	III-IV	30 (23.3)	129 (35.1)	185 (79.4)	344 (47.2)	<0.001

MDAS AOI, most diseased arterial segment (aortoiliac); MDAS FP, most diseased arterial segment (femoropopliteal); MDAS CR, most diseased arterial segment (crural); TASC II, Trans-Atlantic Inter-Society Consensus II for the Management of Peripheral Arterial Disease; CIx, crural index; N, number; %, percentage. P-value with Fisher´s Exact test.

5.2.2 Mortality

At the time of study, 38.3% (N=153) participants had died due to a cardiovascular cause of death. Of these patients, 6.5% were of MDAS AOI (N=10), 35.3% of MDAS FP (N=54), and 58.2% of MDAS CR group (N=89) ($p<0.001$). For MDAS AOI, 1- and 3-years survival was 92.4.0%, and 80.6%, respectively. For MDAS FP, the 1- and 3-years survival were 96.5%, and 76.8%, and for MDAS CR, the 1- and 3-years survival were 78.2%, and 57.2%, respectively.

5.2.3 TP and pressure indices

In Table 11., the Cox regression analysis between TP and pressure indices, different MDAS types, and cardiovascular mortality are presented. Age, male sex, CAD, hypertension, DM, renal insufficiency, and smoking history were added to the final multivariate model as potential confounding variables. Due to the small number of cases in ABI, i.e. the categories of <0.25 (N=9), 0.25 – 0.89 (N=4), and ≥1.30 (N=1), HR, 95% CI and significant p-values were only obtained for patients with ABI 0.9-1.29 in MDAS AOI. The findings show that TBI and TP measurements were predictive of cardiovascular mortality despite the predominant disease location, however, the findings were not statistically significant in MDAS AOI.

Table 11. Multivariate Cox regression analyses for cardiovascular mortality for MDAS types.

		MDAS AOI, HR (95% CI)	**MDAS FP, HR (95% CI)**	**MDAS CR, HR (95% CI)**
TP	<30	3.00 (1.13 – 7.99)	2.31 (1.36 – 3.94)	4.26 (2.19 – 8.27)
	30-49	0.83 (0.29 – 2.41)	1.34 (0.76 – 2.38)	2.55 (1.28 – 5.08)
	≥50	Reference	Reference	Reference
TBI	<0.25	2.40 (0.71 – 8.09)	3.20 (1.34 – 7.63)	7.71 (1.86 – 32.1)
	0.25 – 0.49	1.14 (0.35 – 3.71)	1.96 (0.82 – 4.67)	4.67 (1.12 – 19.5)
	≥0.50	Reference	Reference	Reference
ABI	<0.25	NA	5.45 (1.56 – 19.0)	2.59 (1.15 – 5.85)
	0.25 – 0.89	NA	1.86 (0.57 – 6.04)	1.16 (0.61 – 2.19)
	0.90 – 1.29	Reference	Reference	Reference
	≥1.30	NA	6.71 (1.89 – 23.8)	1.08 (0.50 – 2.32)

MDAS AOI, most diseased arterial segment (aortoiliac); MDAS FP, most diseased arterial segment (femoropopliteal); MDAS CR, most diseased arterial segment (crural); TP, toe pressure; TBI, toe-brachial index; ABI, ankle-brachial index; HR, hazard ratio; CI, confidence interval; NA, not available. HRs and 95% CI produced with Multivariate cox regression analyses.

5.3 Study II – Major amputations in an aging population in Southwest Finland for 2007-2017

In this study, a total of 891 patients underwent 891 atherosclerotic or diabetes-related major amputations in the Hospital District of Southwest Finland over the 11-year study period. Diabetics comprised 50.6% of the cohort. A high proportion of patients were bed-ridden (18.7%) or had Alzheimer´s disease or dementia (20.3%). In total, 118 of the amputations (13.2%) were performed urgently due to severe infection. Minor amputations had been performed on 300 limbs (33.7%). In 80.1% of cases, the level of amputation was AKA and 19.9% BKA. Adjunct procedures were performed for 94 (10.5%) patients after index amputation and altogether, 71.3% of these re-operations were needed after BKA. The 1-, 3- and 5-year overall survival were 51.9%, 22.6%, and 10.1%, respectively. Overall, 696 patients of cohort (78.1%) died within the 11-year follow-up.

5.3.1 Major amputation incidence

Within the 11-year study period, the annual overall major amputation incidence was 17.2/100 000. The mean major amputation incidence was age-dependent (3.1/100 000 for 0-64 years, 34.3/100 000 for 65-74 years, 81.5/100 000 for 75-84 years, 216.0/100 000 for ≥85 years). The overall major incidence of amputations remained stable during the study period (p=0.64). For the 0-64 years age group, major amputation incidence decreased over the study period (p=0.002). In the other age groups, no significant trends were observed. The yearly major amputation incidences by age groups are presented in Table 12.

Table 12. The age standardized annual incidences of major amputation per 100 000 inhabitants in the Hospital District of Southwest Finland over the 2007-2017 period.

YEARS	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	P
0-64	4.98	4.71	4.19	3.14	2.6	2.37	3.19	2.13	2.94	2.15	1.88	0.002
65-74	31.5	35.5	34.4	30.6	26.7	40.7	35.2	30.3	41.0	32.0	37.2	0.53
75-84	70.2	83.9	70.2	110	79.1	98.3	71.2	102	96.2	52.4	65.1	0.70
>85	212	192	295	194	304	171	264	217	194	190	166	0.18
ALL	16.0	16.8	18.0	17.3	17.4	17.2	18.4	18.1	19.3	14.8	15.6	0.64

P-value with Mann-Kendall trend test.

5.3.2 Aging regional population

In 2017, the population of the region of Southwest Finland comprised 480 626 inhabitants. Patients ≥65 years of age comprised 22.6% of the whole regional population. During the 2007-2017 study period, the population aged as the number of inhabitants in the 0-64 years age-group decreased ($p<0.001$) whereas in other age groups, the number of inhabitants increased ($p<0.01$). In total, ≥65 years cohort increased from 81 042 to 108 569 with 22 705 inhabitants (+34.0%) whereas the number of inhabitants 0-64 years decreased from 381 598 to 372 057 with 9541 inhabitants (-2.5%). The data concerning the yearly age distribution were collected from OSF ("Official Statistics of Finland (OSF): Population Structure [e-Publication].," 2020).

5.3.3 Preceding vascular procedures

Before major amputation, 764 revascularization procedures were performed on 472 patients (53.0%). In total, 360 surgical (47.1%) and 404 endovascular procedures (52.9%) were performed. The mean time from revascularization to major amputation was 26.8 months (CI 95% 22.4-31.3) for surgery and 33.2 (CI 95% 28.7-37.7) months for endovascular.

The patient history of revascularizations prior to major amputation was age-depended as revascularizations were more common in the two younger age group (patients 0-64 years 58.1%, 65-74 years 62.7%, 75-84 years 51.1% and ≥85 years 46.1%). Patients with a history of revascularization were younger compared to patients without prior procedures (76.2 years SD 11.5 vs. 78.6 years SD 12.2, $p=0.002$). Hence the older, patients without prior revascularization had fewer cardiovascular comorbidities than the previously revascularized patients (Table 13.).

Table 13. Comparisons of the major amputees, based on history of revascularization before the amputation.

	REV, N (%)	NREV, N (%)	P-VALUE
N	472	419	
SEX (MEN)	245 (51.9)	209 (49.9)	0.591
CAD	250 (53.0)	151 (36.0)	<0.001
CHRONIC HEART FAILURE	179 (37.9)	128 (30.5)	0.024
HYPERTENSION	334 (70.8)	246 (58.7)	<0.001
ATRIAL FIBRILLATION	183 (38.8)	157 (37.5)	0.730
DM	248 (52.5)	203 (48.4)	0.228
COPD	72 (15.3)	43 (10.3)	0.028
DYSLIPIDEMIA	109 (23.1)	50 (11.9)	<0.001
CHRONIC KIDNEY DISEASE	107 (22.7)	71 (16.9)	0.036
CEREBROVASCULAR DISEASE	147 (31.1)	142 (33.9)	0.211

REV, patients with history of revascularization before the major amputation; NREV, patients without history of revascularization before major amputation; COPD, chronic obstructive pulmonary disease; %, percentage; SD, standard deviation; n, number of patients; P-value for continuous variables the Student's t-test and for categorical variables the Fisher´s Exact test.

5.3.4 Alzheimer's disease, dementia, and bed-ridden patients after amputation

The univariate and multivariate analyses Alzheimer´s disease and dementia was associated with an increased risk of death (HR 1.3, 95% CI 1.06-1.59; p<0.012) and the 1, 2 and 3-years survival was 29, 14 and 3%. Correspondingly, the bed-ridden patients had increased risk of death (HR 1.4, 95% CI 1.14-1.69, p<0.001) and corresponding 1, 2, and 3-years survival of 26%, 13%, and 3%, respectively.

5.4 Study III - Outcome after infrapopliteal revascularization in diabetic and non-diabetic patients

5.4.1 Revascularizations

Overall, 552 limbs were revascularized in this study. The primary revascularization method was endovascular for 231 (41.8%) and surgical for 321 (58.1%) limbs. The majority of endovascular procedures were performed with PTA (90.0%). Drug-coated balloons were placed in 17 (7.4%) and a stent was placed in 6 (2.3%) cases. In total, 295 (91.9%) surgical interventions were performed with a venous and 26 (8.1%) with a prosthetic conduit.

Both diabetic groups, IT-DM and NIT-DM, underwent more endovascular revascularizations than the Non-DM group (IT-DM 56.2% vs. NIT-DM 39.8% vs. Non-DM 30.9 p <0.001). However, surgery was predominantly performed on non-diabetics (IT-DM 43.8% vs. NIT-DM 60.2% vs. Non-DM 69.1%, p<0.001). IT-DM patients were younger at the time of primary revascularization than their NIT-DM and Non-DM counterparts (IT-DM median 72.4 years, IQR 15.5 vs. NIT-DM 76.0 years, IQR 15.7 vs. Non-DM 77.3 years, IQR 15.2, p<0.001).

5.4.2 Amputations

During the follow-up, a total of 194 major amputations were performed, and they were predominantly performed for IT-DM (IT-DM 46.9% vs. NIT-DM 17.5% vs. Non-DM 35.6%, p<0.001). When comparing the age of the patient at the time of major amputation, IT-DM had the youngest median age compared to others (IT-DM median 74.0 years, IQR 15.0 vs. NIT-DM 82.5 years, IQR 13.8 vs. Non-DM 81.6 years, IQR 14.5, p<0.001).

5.4.3 Survival

Amputation free survival was poorer for IT-DM after endovascular revascularization compared to surgical bypass (median bypass 64.7, IQR 6.8-NA vs. endovascular 22.0, IQR 6.1-NA, p=0.046). For overall survival, no statistically significant difference was found between the procedures for the IT-DM group (median bypass 90.4, IQR 17.6-NA vs. endovascular NA, IQR 21.6–NA, p=0.708). Similarly, within NIT-DM, a difference between revascularization methods was detected (median bypass NA, IQR 9.6-NA vs. endovascular 19.2, IQR 1.4-NA, p=0.011). No significant difference was observed between the treatment modalities for the overall survival of the NIT-DM group (median bypass NA, IQR 28.6–NA vs. endovascular

NA, IQR 30.8–NA, p=0.098). Similarly, no significant difference was detected between the revascularization modalities for the Non-DM group (median bypass 90.5, IQR 9.2-NA vs. endovascular 30.9, IQR 6.5-NA p=0.15). The overall survival was similar after both treatments in Non-DM group (median bypass NA, IQR 24.2-NA vs. endovascular 64.7, IQR 19.2-NA, p=0.654.

Below in Figure 5., 6. and 7., the Kaplan Meier Survival curves in IT-DM, NIT-DM, and Non-DM groups are illustrated.

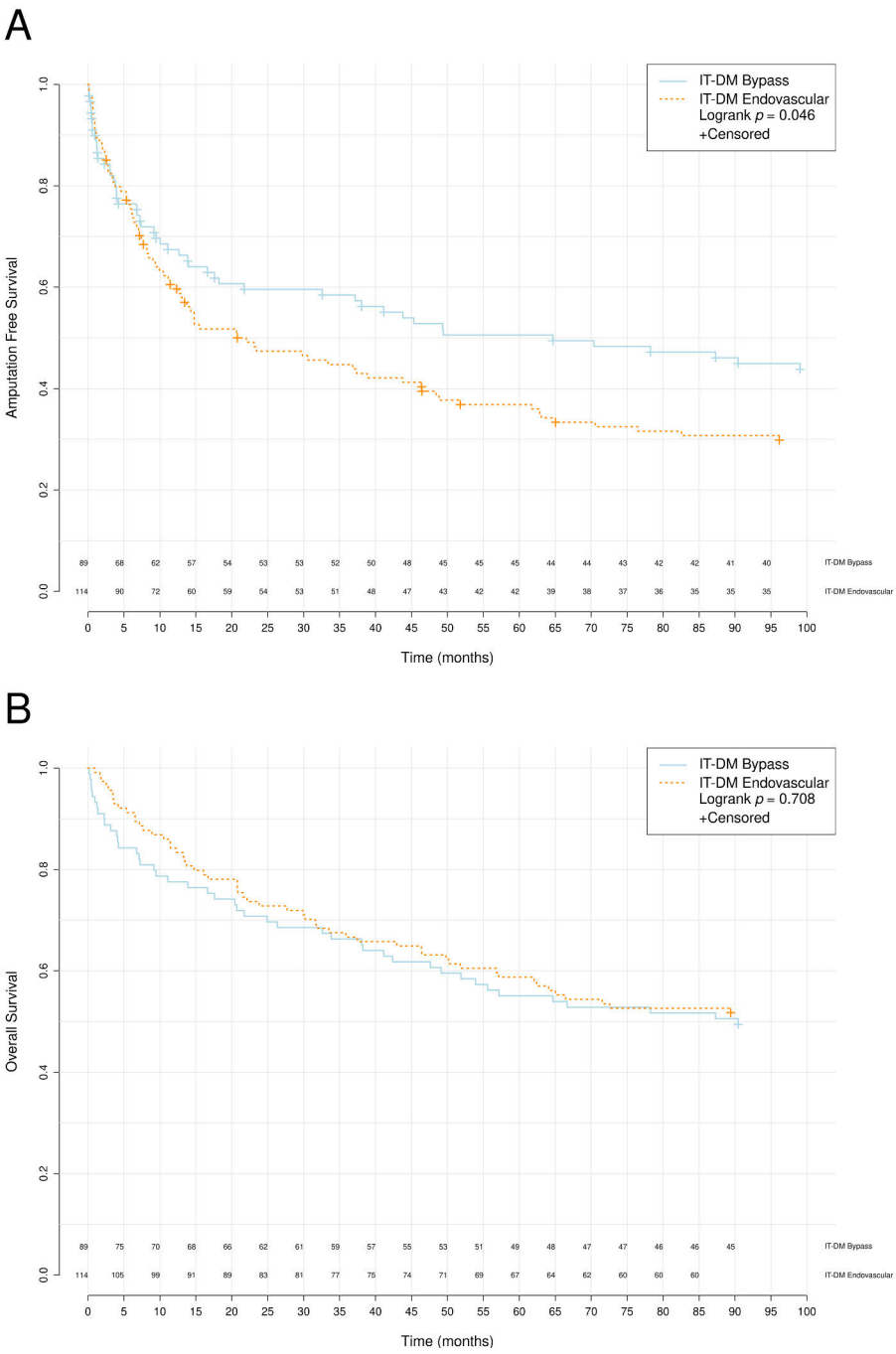


Figure 5. Survival analyses of IT-DM. A) amputation free survival between bypass vs. endovascular revascularization, B) overall survival between bypass vs. endovascular revascularization. P-value with Log-rank statistics.

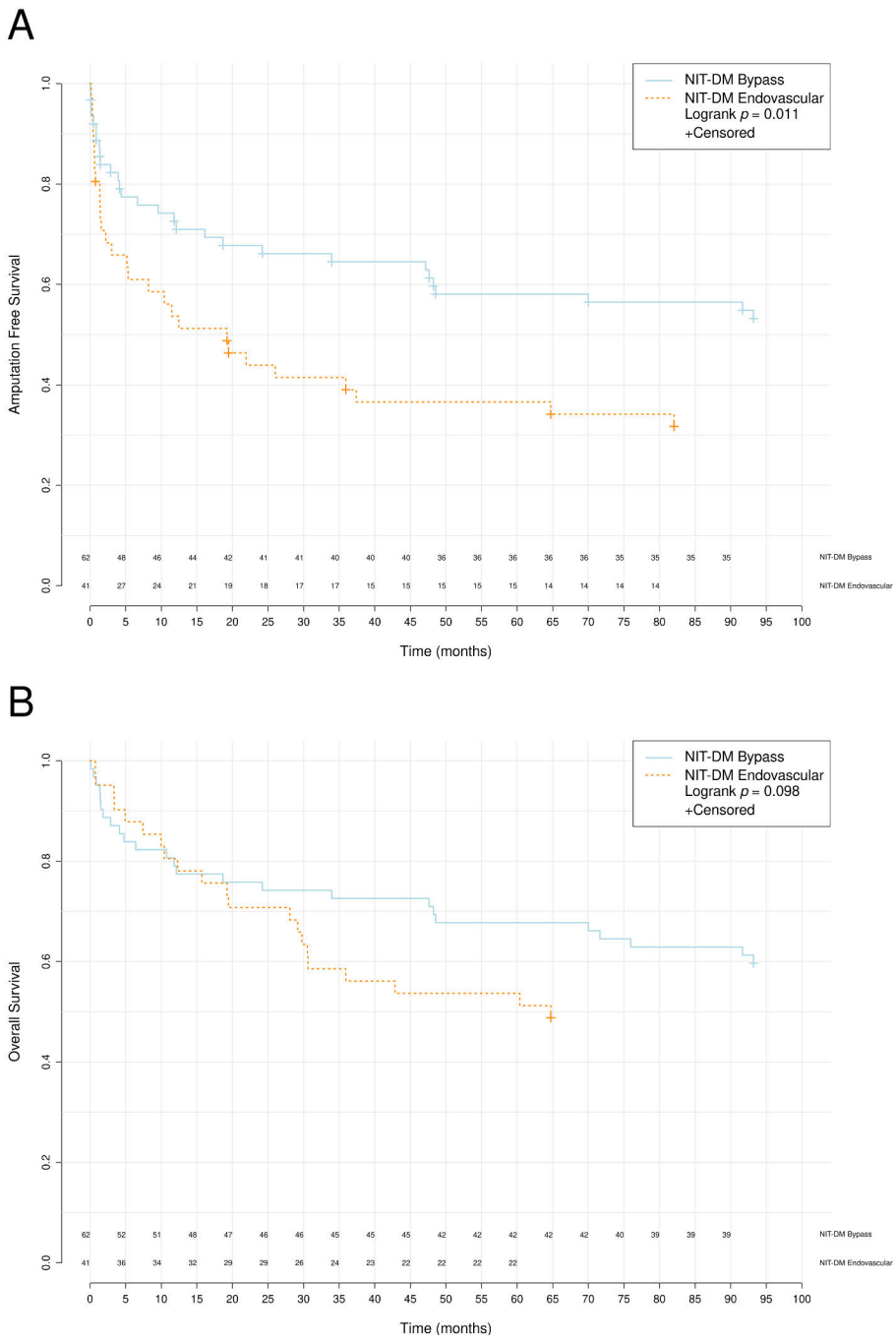


Figure 6. Survival analyses of NIT-DM. A) amputation free survival between bypass vs. endovascular revascularization, B) overall survival between bypass vs. endovascular revascularization. P-value with Log-rank statistics.

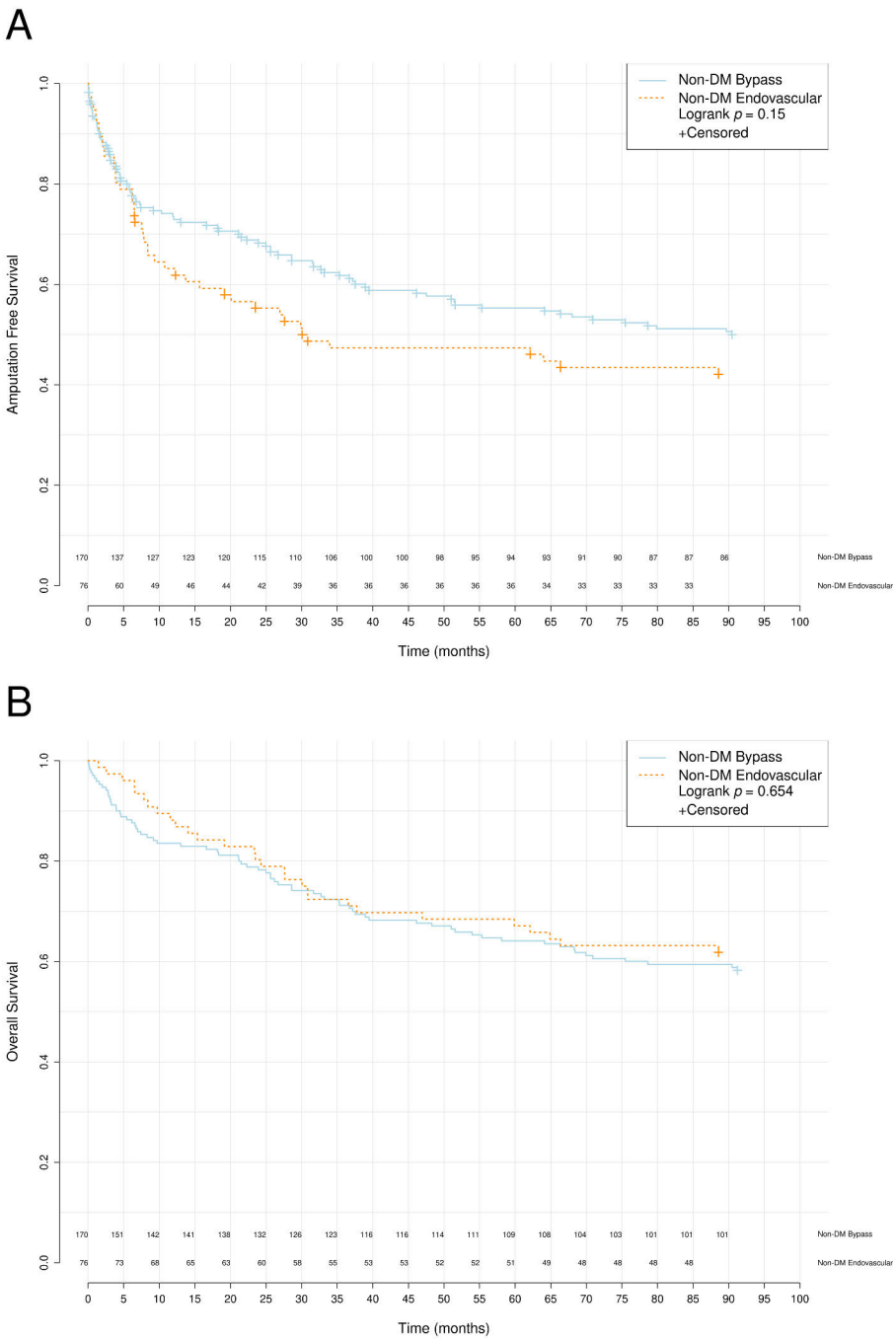


Figure 7. Survival analyses of Non-DM. A) amputation free survival between bypass vs. endovascular revascularization, B) overall survival between bypass vs. endovascular revascularization. P-value with Log-rank statistics.

5.4.4 Risk factors for amputation and mortality

The following risk factors expressed as hazard ratios (HR) were predictors of amputation; advanced age (HR 1.04 per year, 95% CI 1.02 – 1.05, p<0.001), myocardial infarction (HR 1.37, 95% CI 1.04 – 1.81, p=0.024), heart failure (HR 1.33, 95% CI 1.02 – 1.74, p=0.037), and CIx IV (HR 1.37, 95% CI 1.08 – 1.74, p=0.008). Dyslipidemia associated with better limb preservation (HR 0.63, 95% 0.48 – 0.81, p<0.001). Similarly, mortality associated with advanced age (HR 1.04 per year, 95% CI 1.03 – 1.06, p<0.001), DM (HR 1.39, 95% CI 1.01 – 1.90, p=0.043), myocardial infarction (HR 1.39, 95% CI1.02 – 1.89, p=0.039), and heart failure (HR 1.60, 95% CI 1.17 – 2.18, p=0.003). Dyslipidemia was associated with a better survival (HR 0.68, 95% CI 0.51 – 0.90, p=0.008).

5.4.5 Risk factors for extensive atherosclerosis (CIx III-IV)

According to the significance in the initial univariable logistic regression for CIx III-IV risk factors (p <0.20), age, female sex, and CAD were selected for further Multivariable analysis and presented in Table 14. The following risk factors were not selected for the final multivariable analysis; BMI, insulin usage, myocardial infarction, heart failure, hypertension, dyslipidemia, atrial fibrillation, renal insufficiency, and ACE-inhibitor.

Table 14. Multivariable and age-adjusted logistic regression analysis of crural atherosclerosis CIx III-IV risk factors.

	OR (95% CI)	**P-VALUE**
AGE PER YEAR	1.03 (1.01-1.05)	0.002
FEMALE SEX	1.62 (1.06-2.47)	0.026
CAD	0.83 (0.54-1.28)	0.339
STATIN	0.77 (0.52-1.13)	0.182

CIx, crural index; OR, odds ratio; CI, confidence interval. P-value with multivariable logistic regression analysis.

5.4.6 Impact of sex and severity of atherosclerosis on major amputation and death

Median follow-up for women was 20 months (IQR 9 – 51) and for men 23 months (IQR 9 – 47.5) and correspondingly 20 months (IQR 9 – 46) CIx I-III and 23 months (IQR 8 – 49) for CIx IV. The median age at revascularization for women was 81.3 years (IQR 74.7 – 86.8) and 70.7 years (IQR 64.7 – 78.0) for men (p<0.001). The

median age at the time of death was 86.0 years (IQR 80.9 – 89.5) for women and 76.7 years (IQR 67.9 – 82.8) for men (p<0.001).

Multivariable regression analysis was conducted to investigate the association of sex of the patient and the extent of crural atherosclerosis on major amputation and mortality. The following confounding variables were added to the model; age, CIx III-IV, hypertension, DM, chronic kidney failure, myocardial infarction, and CAD. In both unadjusted (RR 1.14, 95% CI 1.14 – 1.78, p=0.003) and adjusted risk estimation (RR 1.63, 95% CI 1.15 – 2.63, p=0.009), the female sex was a risk factor for major amputation. However, no likewise increased risk of mortality was observed in unadjusted (RR 1.08, 95% CI 0.89 – 1.31, p=0.432) and adjusted risk estimation in females (RR 1.00, 95% CI 0.65 – 1.53, p=0.999). The risk estimation is illustrated in Figure 8.

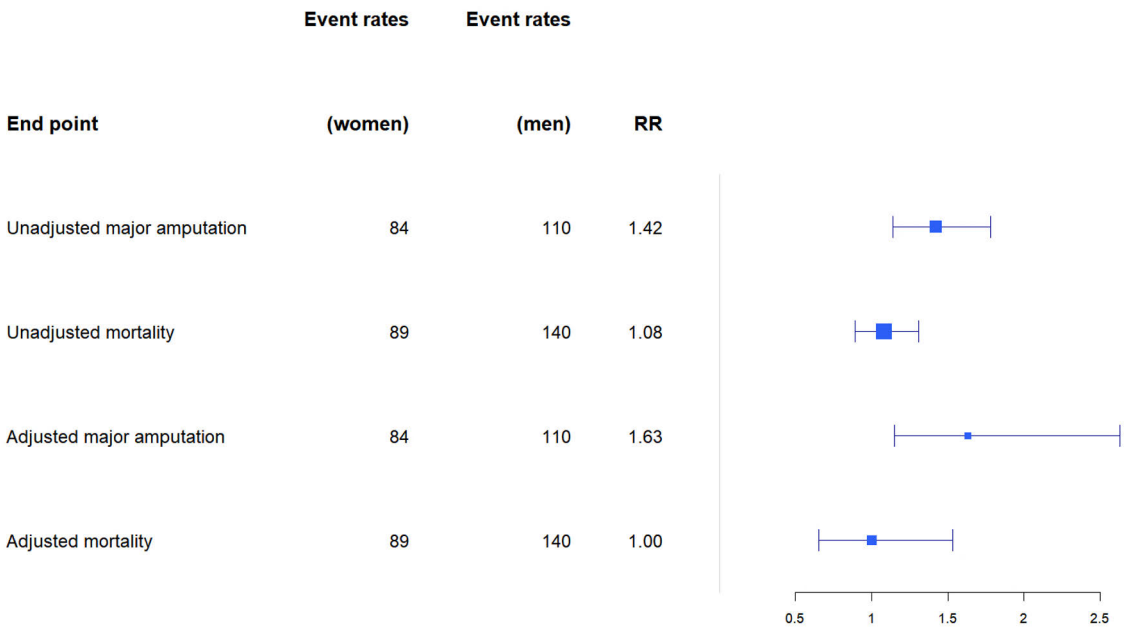


Figure 8. Risk ratios for adverse outcomes in CLTI patients for women vs. men. CLTI, chronic limb-threatening ischemia; RR, risk ratio.

The risk estimation according for CIx grades is illustrated in Figure 9 and the same confounding variables were added to the model. The risk of limb loss was higher for CIx IV in unadjusted (RR 1.31, 95% CI 1.05 – 1.65, p=0.02) and adjusted risk estimation (RR 1.38, 95% CI 0.97 – 2.10, p=0.07), however, the findings were not statistically significant in adjusted analysis. A higher risk of mortality was observed

in both unadjusted (RR 1.32, 95% CI 1.09 – 1.59, p=0.005) and adjusted risk estimation (RR 1.53, 95% CI 1.08 – 2.40, p=0.020).

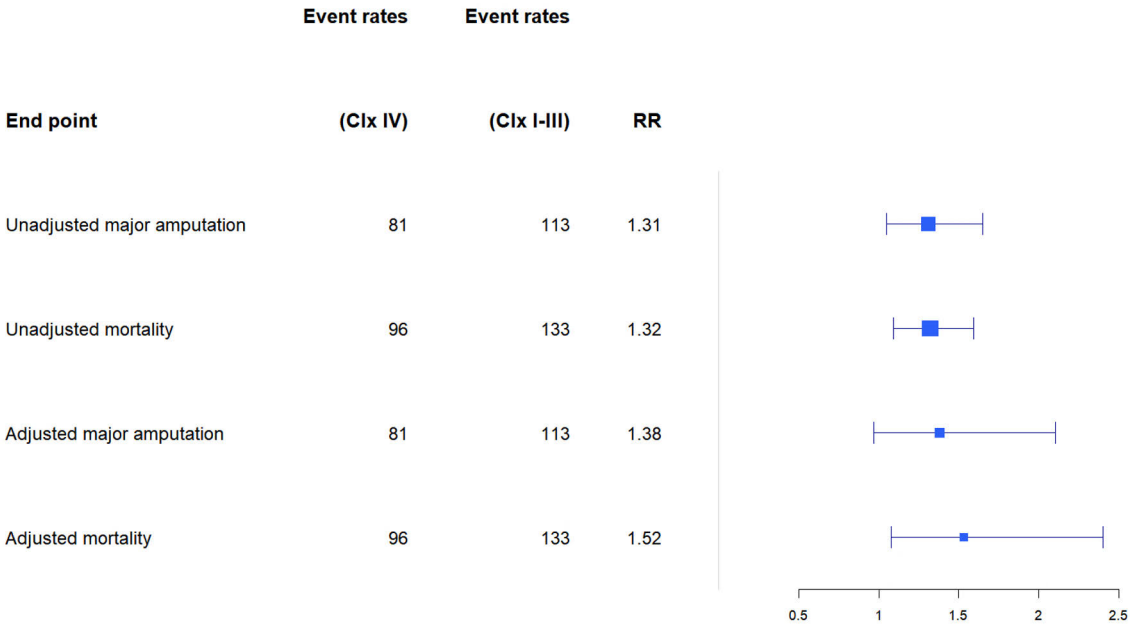


Figure 9. Risk ratios for adverse outcomes in CLTI patients for CIx IV vs. CIx I-III. CLTI, chronic limb-threatening ischemia; CIx, crural index; RR, risk ratio.

6 Discussion

6.1 Findings of the studies I-III

This thesis investigates patients with the most extensive form of LEAD, i.e. CLTI, that associates with multimorbidities, detrimental outcome, and poor survival. The main objectives of this thesis were to investigate the clinical features, treatment, and risk estimation in CLTI patients. The main findings of the studies I-III are summarized in Table 15.

Table 15. The summarized findings of the studies I-III.

STUDY	THE MAIN FINDINGS
I	The multisegmental nature and severe crural involvement are features of CLTI. TBI and TP are predictive of mortality regardless of the predominant lesion location and they should be obtained from all patients and recorded together with ABI.
II	Despite the high availability of vascular surgery services in an aging population, the incidence of major limb amputations remains constant. At the time of the presentation of CLTI, almost half of the amputees had no earlier history of revascularization before amputation. Major amputation remains as the only realistic treatment option for a considerable number of CLTI patients.
III	In both insulin and non-insulin medicated diabetics, surgery associates with better limb preservation compared to the endovascular method. Female sex associates with higher risk of amputations. Extensive crural atherosclerosis is a risk factor for amputations and mortality.

CLTI, chronic limb-threatening ischemia; TBI, toe-brachial index; TP, toe pressure; ABI, ankle-brachial index.

6.2 Diagnosis of CLTI

6.2.1 Clinical features of CLTI

The classifications of Fontaine, Rutherford, Second European consensus, and TASC classifications, were primarily focused on ischemia due to atherosclerosis (Conte et al., 2019). According to the most widely used classifications, CLTI patients represent Fontaine III-IV and Rutherford IV-VI classes (Fontaine et al., 1954; Rutherford et al., 1997). These early classifications were developed when smoking was observed to be the main contributive risk factor for LEAD (Conte et al., 2019). Globally from 1980 to 2012, the prevalence of smoking has been decreasing (Ng et al., 2014). A similar trend was observed in Finland during 1978-2016 (Ruokolainen et al., 2019). However, active smoking is still common in both worldwide and nationally in Finland (Ng et al., 2014; Ruokolainen et al., 2019).

In the International Vascular Symposium, it was stated that diabetics should be excluded or at least separated from the definition. (Bell et al., 1982; Mills et al., 2014). In this statement, diabetes related neuropathy, ischemia, and infection were acknowledged to complicate the clinical decision making. Due to the rapid increase of the diabetic population, the incidences of diabetic ulcers and diabetic foot syndrome remain high and increase the risk for limb loss (D. G. Armstrong et al., 2011; L. Chen et al., 2012; Paisey et al., 2019; Vibha et al., 2018). The new WIfI classification acknowledges that ischemia, wound, and infection are all risk factors for major amputation (Mills et al., 2014). According to this new definition, ischemia is not the only factor that threatens the vitality of the limb (Conte et al., 2019). Therefore, the diagnosis of CLTI does not solely rely on specific threshold values, however, abnormal pressure measurements demonstrate peripheral ischemia and support the diagnosis of CLTI.

The clinical presentation of CLTI is heterogeneous and the disease progression is unpredictable. One explanation to this is the high proportion of diabetics, in which the vitality of the limb can be threatened by ulcers and infection too (Mills et al., 2014). The divergent nature of CLTI is demonstrated by survival rates that range considerably (studies I-III). The onset of CLTI is rapid in approximately one third of patients and CLTI may be the first manifestation of LEAD (Mätzke & Lepäntalo, 2001). In a recent meta-analysis, the risk of disease progression from mild LEAD to CLTI was reported to be higher than expected as 21% of IC patients progress eventually to CLTI over 5-years (Sigvant et al., 2016).

CLTI patients present with a high-risk factor profile and poor overall health (studies I-III). Nearly half of the CLTI patients have DM (studies I-III)(Spreen et al., 2016; Stavroulakis et al., 2018; Westin et al., 2014). The majority of CLTI patients are elderly and age is also a significant contributor to atherosclerosis in the lower

limb arteries (Sigvant et al., 2016; Takahara et al., 2020). Patients with end-stage renal failure, DM, and non-ambulatory condition have a higher risk to progress to CLTI without previous symptoms (Takahara et al., 2015). It is obvious therefore, that this unforeseeable and possibly aggressive disease progression may cause diagnostic difficulties, delays in treatment, and hinders the selection of the most appropriate treatment strategy.

6.2.2 The distribution and extent of atherosclerosis

Vascular imaging is crucial for both diagnosis and treatment planning in CLTI. The most common imaging modalities, DSA, CTA, MRA, and DUS, have been introduced in the Literature review. DSA was the gold-standard when assessing the lesion anatomy for invasive treatment in Turku University Hospital Department of Vascular Surgery during the 2007-2017 period. However, since that period, CTA and MRA have been increasingly used in Turku University Hospital and they are becoming the first-line imaging for patients with LEAD. Even so, DSA is still widely used together with MRA due to its accuracy in evaluating the crural and pedal arteries and also for the ability to simultaneously revascularize during the imaging process. CLTI is typically multisegmental with severe crural involvement, therefore, methods that offer precise and accurate illustration of the distal vasculature are crucial (study I)(Gray et al., 2010; Ortmann et al., 2012; Ozkan et al., 2009).

Extensive crural atherosclerosis associates with the worst survival and is also a risk factor for poor outcome, therefore, the timely detection of extensive crural atherosclerosis is important (Q. Chen et al., 2013; Jalkanen et al., 2016b, 2016a; Wickström, Jalkanen, et al., 2017). Advanced age associates with extensive atherosclerosis and severe lesion characteristics are typically seen among the elderly (study III). Aging has been reported to increase the risk for predominantly crural LEAD (N. Diehm et al., 2006). Similarly, a CLTI cohort study reported that patients with three vessel disease were older compared to one vessel disease although the findings were not statistically significant (Shishehbor et al., 2016).

A comparable observation is seen between the sexes as women seem to associate with extensive crural atherosclerosis (study III). In one study, women presented with more severe lesion characteristics and the infrapopliteal vessels were more involved compared to those of men (Choi et al., 2019). The older age of women at the time of revascularization may partly explain this as advanced age is also a risk factor for severe crural atherosclerosis. Moreover, women often present atypical symptoms of LEAD, which may cause delays or even misdiagnosis (Jelani et al., 2018). It also may explain the more extensive atherosclerosis women have and their older age at the time of revascularization (Gallagher et al., 2011).

Interestingly, traditional cardiovascular risk factors and a high comorbidial profile do not seem to associate with the extent of distal atherosclerosis (study III). A similar observation was found in a study that compared infrapopliteal TASC A-B with C-D patients (Singh, Brinza, et al., 2017). In another study, similar demographics were reported concerning the prevalence of hyperlipidemia, DM, CAD, and renal insufficiency in patients with infrapopliteal 3-vessel and 1-vessel LEAD (Shishehbor et al., 2016).

6.3 Prognosis and survival

6.3.1 Amputation

CLTI associates with the highest risk of limb loss compared to less severe forms of LEAD (Baubeta Fridh et al., 2017). If left untreated, almost a quarter of the patients will undergo amputation within 12 months (Abu Dabrh et al., 2015). However, not all CLTI patients possess similar risks for amputation as some factors have a stronger impact on limb preservation than others. Risk factors that strongly associate with higher amputation rates are smoking, DM, advanced age, and concomitant CAD (Schanzer et al., 2008; Spreen et al., 2016; J. C. Young et al., 2019). The highest amputation rates are seen in diabetics (study III) and CLTI patients with DM have been reported to have a 5-fold risk of major amputation than non-diabetics (Jude et al., 2001). It has been estimated that within a five-year follow-up, one in every three diabetic CLTI patients will undergo major amputation (Spreen et al., 2016). Another group with a high incidence of amputations are those with extensive crural atherosclerosis (study III) (Jalkanen et al., 2016a). Isolated crural disease has been associated with poorer amputation free survival after revascularization compared multilevel atherosclerosis (Fernandez et al., 2011; Gray et al., 2010).

6.3.2 Mortality

Mortality in CLTI patients is high. In a Swedvasc study, a cumulative mortality rate of 41.4% was reported in CLTI patients after a 3-year follow-up (Baubeta Fridh et al., 2017). The poorest survival is seen in patients without a previous revascularization. The prognosis of these patients is serious as approximately 20% die within the first year after diagnosis (Abu Dabrh et al., 2015; Klaphake et al., 2017). Analogous to that found for limb loss, the risk for mortality has been reported to vary considerably according to the patient risk factor profile. Smokers, diabetics, elderly, patients with CAD, and with renal insufficiency have been reported to have poor survival (E. J. Armstrong et al., 2014; O'Hare et al., 2005; Ohmine et al., 2015; Vrsalovic et al., 2017). Similar to the increased risk of amputation, patients with

extensive crural atherosclerosis (study III) seem to have higher likelihood of mortality than patients with less severe lesions (Tern et al., 2018; Wickström, Jalkanen, et al., 2017).

6.3.3 Pressure measurements

Peripheral pressure measurements objectively estimate arterial perfusion and can be used as prognostic tools in risk estimation. They are feasible and straightforward to carry out, and they can be applied to everyday practice. With adequate training, peripheral pressures measurements can be done by any medical staff and are not therefore limited to the staff of vascular laboratories.

It is widely known that both low and elevated ABI associate with increased risk of limb loss (Hämäläinen et al., 1999; Mills et al., 2014; Singh, Armstrong, et al., 2017). Similar results have been reported for TBI <0.70 as it has been reported to associate with a 19-fold increase in the likelihood of having foot ulcers and amputation (Sonter & Chuter, 2017). Correspondingly the COPART study found that a TP <30 mmHg associated with a 3.5 fold risk of limb loss (Salaun et al., 2019). The studies I-III presented in this thesis did not evaluate the impact of pressure measurements on limb preservation as the results obtained from the same cohort have already been published (Wickström, Laivuori, et al., 2017). In the Wickström et al. study, ABI <0.25, TBI <0.25, and TP <30 mmHg associated with poor amputation free survival, although the findings with ABI were not statistically significant (Wickström, Laivuori, et al., 2017).

Previous studies support the use of peripheral pressure measurements as predictors of mortality. ABI is a predictor of mortality and in diabetics, ABI associates with cardiovascular mortality in a U-shaped fashion (Hyun et al., 2014). Elevated ABI has been associated with even worse survival compared to low ABI with 10-year survival of only 15.3% (Laivuori et al., 2021). Decreased TBI associates with mortality irrespective of diabetes status (Hyun et al., 2014). It was found in a non-selective LEAD cohort that TBI <0.25 has been associated with 2.5-3.7-fold risk of both overall and cardiovascular mortality (Wickström, Laivuori, et al., 2017). Corresponding to that found for TBI, TP <30 mmHg associated with HR of 2.0 with a 10-year survival rate of only 19.6% (Laivuori et al., 2021). Inline with the previous literature, ABI <0.25 associated with 2.6-5.5, ABI ≥1.30 with 1.1-6.7, TBI <0.25 with 3.2-7.7, and TP <30 with 2.3-4.3-fold risk of cardiovascular mortality (study I).

Although the association between decreased ABI and adverse events is indisputable, incompressible arteries limit the use of ABI as the ankle arteries become severely stiffened due to medial sclerosis (Aboyans et al., 2018). Incompressible arteries are predictive of adverse outcomes (Hyun et al., 2014;

Laivuori et al., 2021; Singh, Armstrong, et al., 2017), but not all patients with incompressible arteries exceed the threshold of 1.3-1.4 and some may have normal or near normal ABI, thus the reliability of ABI has limits. In one study, 13% of CLTI patients had normal ABI of 0.9-1.4 and 97% of patients had abnormal TBI of <0.7 (Bunte et al., 2015). Similarly, 66% of CLTI patients in a more recent study had TBI <0.7 despite normal ABI 0.9-1.4 (Sukul et al., 2017). Although ABI is considered to be normal when it lies within the normal range, some of these patients have elevated risk of mortality. In patients with normal ABI 0.9-1.3, TP<50 mmHg has been associated with twice the HR for mortality (Laivuori et al., 2021). In one study by Høyer et al., LEAD patients with normal ABI had similar risk factor profile compared to patients with decreased ABI (Høyer et al., 2019). ABI levels between 1.3-1.4-1.5 have been reported to have good specificity in LEAD diagnosis in patients with suspected disease (86%, 94%, 96%, respectively) although the sensitivities remain modest (44%, 38%, 36%, respectively) (Suominen et al., 2008). When acknowledging these limitations of ABI, systematic assessment of all three vascular parameters taken altogether would yield to a more precise diagnosis and risk estimation.

6.3.4 Pressure measurements and the most diseased arterial segment

As demonstrated in this thesis, the predominant location of atherosclerosis varies between patients. This is influenced by the patient risk factor profile as smoking, hypercholesterolemia increase the risk for proximal atherosclerosis whereas advanced age and DM increase the risk for distal atherosclerosis. However, despite the predominant site of atherosclerosis, a considerable proportion of patients also presented extensive atherosclerosis in the crural arteries (study I). In general, TBI and TP seem to inversely associate with the risk of mortality. However, TBI and TP were predictive of mortality in all predominant disease locations and the risk of mortality seemed to increase for distal disease. An association with cardiovascular mortality was seen with ABI in this study, although the findings are less clear in patients with predominantly crural lesions (study I).

There are several features to consider when interpreting ABI. As mentioned previously, medial sclerosis can be seen in a substantial proportion of CLTI patients, and it has been reported to diminish the reliability of ABI measurements. Similarly, severe distal atherosclerosis has been suggested to hamper the ABI measurement. In a study of a diabetic cohort, ABI was reported to correlate poorly with angiographic findings and extensive distal atherosclerosis was proposed by those authors to at least partially lower the reliability of ABI (Aerden et al., 2011).

If ankle arteries are severely affected by medial sclerosis, TBI and TP may be more reliable measurements as calcification less commonly affects the pedal arteries (M. J. Young et al., 1993). The association of TP and TBI to mortality has been evaluated in patients that typically have extensive crural disease. In a T2DM cohort, a stepwise association with low TBI and risk of mortality was observed (Chisalita et al., 2020). TBI <0.7 associated with higher risk of all-cause mortality compared to ABI <0.9 in patients with chronic dialysis-depended renal insufficiency (Prasad et al., 2019). TP has been investigated to a lesser extent compared to TBI. However, an inverse association between low TP and mortality in patients with CLTI has been reported (Vallabhaneni et al., 2016). Moreover, in the same study, when TP was stratified the risk of mortality was found to be more likely than it was for ABI (Vallabhaneni et al., 2016). The reliability of ABI in patients with DM, renal insufficiency, and advanced age has been questioned in a strong body of literature (Herraiz-Adillo et al., 2020; Prasad et al., 2019; Wukich et al., 2015). Moreover, previous studies suggest that if ABI is the only applied vascular parameter, the prevalence of arterial insufficiency and the risk of adverse outcomes may be underestimated (Høyer et al., 2019; Laivuori et al., 2021).

Despite the advantages of TBI and TP, they are not routinely used for assessments in primary care. However, with adequate training, they are both straightforward and convenient measurements to obtain. As the benefits of TBI and TP have been demonstrated in both crural and non-selected cohorts (Hyun et al., 2014; Laivuori et al., 2021; Wickström, Laivuori, et al., 2017), they should be used together with ABI for assessing all patients regardless of the most diseased arterial segment the patient may have. Previously, the inclusion of ABI measurement into Framingham Risk score enhanced the risk estimation of adverse cardiovascular outcomes (Fowkes et al., 2008). TBI and TP could and tentatively should be considered to be included in the future risk estimation models to enhance the current risk assessment in CLTI.

6.3.5 Risk estimation in CLTI

As described in the Literature review, suboptimal predictive abilities of either amputation or death have been observed in a validation study of FINNVASC, PREVENT III, and BASIL models (Wijnand et al., 2020) and thus, a precise and coherent predictive model is urgently needed for patients with CLTI.

The strongest risk factors that associate with poor outcomes; smoking, DM, advanced age, CAD, chronic renal insufficiency, dyslipidemia, and hypertension, are introduced in the Literature review of this thesis. The typical manifestations of CAD, myocardial infarction and heart failure (Gheorghiade et al., 2006), have been associated with increased risks of both amputation and mortality (study III).

Moreover, the clustering of risk factors has been linearly associated with poor survival in patients with CLTI (Ohmine et al., 2015; Schanzer et al., 2008), and therefore, the higher the risk factor burden, the higher are the probabilities of observing adverse events.

However, other factors apart from the traditional risk factors may be predictive of adverse outcomes in CLTI. In line with the risk factor analysis (study III), higher limb loss rates have been reported in women (Chang et al., 2013; Choi et al., 2019). In a CLTI cohort, female sex has been reported as an independent risk factor for a major amputation (Lejay et al., 2015). Several explanations for these sex-related disparities exist. First, women may seek treatment for LEAD less frequently and later than men as the disease tends to be more severe compared to men at the time of the revascularization (Jackson et al., 2014). Second, women have been reported to present higher rates of early graft thrombosis and embolization after revascularization, which may also play a role in limb loss (J. Wang et al., 2016). Third, sex-related factors such as smaller vessel diameter and post-menopausal shortage of estrogen that amplifies thrombosis and reduced neovascularization may also contribute to the higher rate of major amputations (Boese et al., 2017; Jelani et al., 2018). Altogether, the inclusion of sex of the patient in the future models is an interesting research topic. When acknowledging the shortage of studies concerning CLTI in women (Aboyans et al., 2018; Jelani et al., 2018), more extensive research could and should be conducted to assess the disease nature of CLTI in women.

Information on the lesion characteristics as, graded by the Bollinger score, has been included in the BASIL model (Bradbury et al., 2010a) but not in either the FINNVASC or PREVENT III models (Wijnand et al., 2020). When comparing these models, the BASIL model seems to provide the most accurate risk estimation of either major amputation or mortality compared to FINNVASC or PREVENT III (Wijnand et al., 2020). Extensive crural lesions have been associated with increased risk of both limb loss and mortality compared to atherosclerosis in other vascular beds (study III) (Q. Chen et al., 2013; Jalkanen et al., 2016b, 2016a; Wickström, Jalkanen, et al., 2017). A study that used the TASC II classification found that infrapopliteal C-D lesions associate with higher amputation rates compared to A-B lesions (Singh, Brinza, et al., 2017). According to these studies and the findings presented in this thesis, the information of lesion characteristics especially in the distal arteries, could be included in future risk estimation models to enhance the predictive abilities of these models.

The findings of this thesis together with the current literature suggest that not all significant risk factors may be covered in the present-day risk estimation models. The evaluation of the extent of distal atherosclerosis could be considered to be included in future models as it associates with worse amputation-free survival and poor overall survival. An aggregation of cardiovascular comorbidities and extensive

crural atherosclerosis is seen in most of the CLTI patients (studies I-III) and therefore, these high-risk patients require careful risk estimation and evaluation prior to a possible operative treatment. Further investigation of female sex as a risk factor could be conducted. TBI and TP measurements could be included in the future models as they are likely to overcome the limits of ABI and are predictive of cardiovascular mortality even for the most diseased arterial segment.

6.4 Treatment

6.4.1 Medication

Medication is a crucial part of the management of CLTI. A statin regimen, in particular, has been associated with a decreased risk of mortality and amputation free survival (studies I & II)(Westin et al., 2014). In the EUCLID trial, a statin regimen was found to predict better limb preservation in CLTI and resulted in a 38% decrease in the risk of amputation (Long et al., 2020). Similarly, high-dose statins associate with lower likelihood for limb loss and death (Arya et al., 2018). Alarmingly, statins are greatly underused in the treatment of LEAD and it has been estimated that only one in every four patients do not use statins despite the current recommendations (Arya et al., 2018). Poor lipid-control was already observed in 2007 in a study with a Finnish LEAD cohort (Poussa et al., 2007). Unfortunately, no recent studies exist that report statin usage in LEAD patients in Finland. In recent CLTI cohorts, 43-72% of the patients have been on statin regimen (Rymer et al., 2020; Takeji et al., 2018). In this thesis, statins were widely underused, and the usage ranged from 32% to 63% depending on the cohort (study I-III). Non-adherence to statin medication may be an explanation for this observation. Muscle pain, medical costs, and perceived poor efficacy are common reasons for discontinuation of statins (Wei et al., 2013).

In Finland, significant improvements in the management of diabetes were observed from 1994 to 2011 (Forssas et al., 2016). In this study, decreasing rates of myocardial infarction, stroke, and amputations were observed in patients with T2DM (Forssas et al., 2016). In patients with T1DM, the rates of myocardial infarction and stroke declined as well, however, the rate of amputations remained stable (Forssas et al., 2016). Nevertheless, a considerable proportion of diabetics still underwent amputation (Forssas et al., 2016). Just recently, a study by Wikström et al. investigated North Karelian T2DM patients from 2013 to 2019 (Wikström et al., 2022). According to their study, metformin was the most common diabetes medication, which is inline with the current recommendations (Wikström et al., 2022). Interestingly in their study, the second most used medications were both long- and short acting insulins and gliptins whereas SGLT2 inhibitors and GLP-1 receptor agonists were less common (Wikström et al., 2022). However, over the study period,

the use of SGLT2 inhibitors increased from 1.6% to 11% and the use of GLP-1 receptor agonists was stable 2-3% (Wikström et al., 2022). The adoption of SGLT2 inhibitors seems to occur according to the current recommendations, however, stronger efforts are needed to enhance the management of diabetes in Finland.

A recent study has shown that active smoking in patients with LEAD is common despite the diagnosis (Rymer et al., 2020). In this study, 27% of CLTI patients were current smokers at the time of discharge after revascularization (Rymer et al., 2020). In Finland, no up-to-date numbers of CLTI patients that continue active smoking exist. Decreasing rates of smoking have been reported in Finland from 1978 to 2016, however, approximately 15-17% of patients 25-64 years of age still smoked daily in 2016 (Ruokolainen et al., 2019). Interestingly, an increasing trend was observed in less educated women aged 45-64 years (Ruokolainen et al., 2019).

Approximately 74-80% of CLTI patients have used antithrombotic medication in recent CLTI cohorts (Rymer et al., 2020; Takeji et al., 2018). To the author's knowledge, no recent data exist on antithrombotic regimen in Finnish CLTI patients. Amongst the present cohorts, 46-70% of patients were under antithrombotic regimen (studies I-II). The lowest proportion was observed in the cohort that consisted of amputees. An explanation for this may be the potential risk of gastrointestinal bleeding that may limit the use of aspirin especially among the elderly. In their study, Mahady et al. found 1.6-fold risk in patients ≥ 75 years of age and 2.9-fold risk ≥80 years of age for gastrointestinal bleeding (Mahady et al., 2021). Clopidogrel associates with lower risk of bleeding than aspirin (Hallas et al., 2006). However, according to this study, a combination of both aspirin and clopidogrel associated with 7.4-fold risk of gastrointestinal bleeding (Hallas et al., 2006).

For the use of angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor (ATR) blockers, recent studies have reported rates of 39-56% in CLTI patients (Rymer et al., 2020; Takeji et al., 2018). This is similar to the observed rate of 38% in study III. Intensive antihypertensive treatment may increase the risk hypotension, syncope, electrolyte abnormality, and renal insufficiency and these adverse events may limit the use of ACE inhibitors/ATR blockers (Wright Jr et al., 2015).

It is a widely known problem that the risk factor modification is poorly handled in CLTI (Lumsden et al., 2009). Adherence to treatment is a problem in some patients. In a study by Chen et al., only 30% of CLTI patients were adherent to all four guideline recommendations of aspirin, statin, ACE inhibitor/ATR receptor blocker, and smoking abstinence (D. C. Chen et al., 2015). However, significant improvements have been observed during the last decades. From 1997 to 2016, the use of statins increased from 2 to 60%, the use of antithrombotic medication from 3.5 to 61%, and the use of ACE inhibitors from 1.2 to 21.3% in patients with LEAD

(Kamil et al., 2021). More LEAD patients are using cardioprotective medication than before, however, they are still widely underused (Kamil et al., 2021).

6.4.2 Indications for revascularization

Limb preservation is the primary goal in the treatment of CLTI. With revascularization, the risk of major amputation can be significantly reduced. In patients with previous revascularization, a better 1-year amputation free survival has been reported compared to those without revascularization (Iida, Takahara, Soga, Azuma, et al., 2017). Revascularization is generally considered for patients with; operable lesion characteristics, good preoperative condition, and if improvements in the mobility and quality of life are expected to be archived with an invasive operation. Despite an active revascularization strategy, not all patients can be revascularized as it has been estimated that approximately 20-30% of CLTI patients are treated with primary amputation (Novo et al., 2004). If major amputation is indicated, then the goal is to amputate as distal as possible, preferably BKA, assuming it has been evaluated to heal per primam.

6.4.3 Invasive treatment of CLTI

According to the TASC II guidelines, an endovascular strategy is the procedure-of-choice for aortoiliac and femoropopliteal TASC A-B lesions whereas long and extensive TASC C-D lesions are recommended to be revascularized with autologous bypass (Norgren et al., 2007). As described in the Literature review, TASC II guidelines have been largely criticized (Conte, 2012; Kukkonen et al., 2010). In 2015, classification for infrapopliteal lesions was introduced but no recommendations for treatment strategy were provided (Jaff et al., 2015). ESC 2017 guidelines recommended endovascular strategy for mild-to-moderate and surgery for extensive lesions if patient was considered eligible for surgery (Aboyans et al., 2018). For infrapopliteal lesions, surgical bypass with autologous conduit was recommended (Aboyans et al., 2018). In GVG, risk factor profile, life-expectancy, limb staging, extent of atherosclerosis, and availability of venous conduit material should be taken into account when revascularization is considered (Conte et al., 2019). Both ESC 2017 and GVG state that the lack of eligible evidence hinders the selection of the most appropriate treatment strategy.

Significant advancements have been seen in revascularized patients compared to those treated conservatively. Even in the elderly, clinical improvements without the need of major amputations and repetitive revascularizations have been demonstrated after successful revascularization (Brosi et al., 2007). Similarly, a strong body of literature supports the practice of active revascularization for diabetics as it

significantly lowers the risk of both amputation and mortality (Faglia et al., 2009; Hicks et al., 2016). In one study, the mortality rate was only 28% in revascularized patients compared to 81% for non-revascularized patients at a 4-year follow-up (Faglia et al., 2010).

The adoption of both surgical and endovascular revascularization methods has been both wide and active (Londero et al., 2019; Nikulainen et al., 2019). However, does one treatment modality offer better limb preservation over another? The comparison between endovascular and surgical revascularization is challenging since the treatment strategy is mostly decided by being based on the disease severity, overall patient condition, and the expertise of the vascular department. As a result, patients treated by a certain method may not be eligible for the other. Moreover, the patient selection may direct the high-risk patients toward an endovascular approach, which may result in higher rates of amputation, mortality, and poorer survival after endovascular revascularization. On the other hand, some studies have been performing surgical bypass with prosthetic grafts that lead to less successful outcomes compared to using an autologous venous conduit (Aboyans et al., 2018; Conte, 2010). As prospective randomized trials take years to accomplish and the technology is rapidly evolving especially for endovascular revascularizations, some comparisons may be performed with the "out-of-date" treatment approaches that favour surgery (Chung et al., 2014). Similarly, as distal bypass is one of the most technically challenging vascular procedures, the impact of skills of the operating surgeon and vascular center may also significantly contribute to the outcome (Conte, 2012). Moreover, varying lengths follow-ups, inconsistent study endpoints, and divergent patient criteria further complicate making comparisons between existing studies.

Some previous studies, however, refer to surgery as the principal method of the treatment of CLTI. In the aforementioned BASIL trial, although the 30-day follow-up was similar between surgery and endovascular strategies regarding amputation-free and overall survival, the post hoc analysis favoured surgery after two year follow-up period (Bradbury et al., 2010b). In a prospective study, surgical revascularization associated with better amputation free survival (82% vs. 56%) than endovascular revascularization (Steunenberg et al., 2018). Although these studies have provided valuable information, they do not particularly focus on diabetics and therefore, there is a shortage of studies that compare the survival of diabetic CLTI patients after surgical and endovascular revascularization.

Diabetics typically present extensive lesions in the crural arteries and compared to an endovascular approach, surgery in this region has been associated with better amputation free survival (Patel et al., 2016). Patients with tissue loss are typically diabetics and in these patients, femoropopliteal and crural surgical bypass associates with a lower 30-day major amputation rate compared to endovascular strategy (Lee

et al., 2021). Major tissue loss extending above the transmetatarsal level (Rutherford 6) associates with poor amputation free survival in endovascularly revascularized patients (Stavroulakis et al., 2018). In a recent study of diabetic CLTI patients that used propensity score matching, surgical bypass associated with a lower risk of major amputations (Elbadawi et al., 2021). Surgical bypass associates with lower incidence of amputations, reintervention, and stenosis compared to endovascular revascularization especially in insulin-medicated CLTI diabetics (Darling et al., 2018). Indeed, these studies together with the present findings of this thesis may indicate that bypass may ultimately be the most durable option in the long term for both insulin and non-insulin diabetics (study III). Despite the high-risk patient profile, survival is relatively long after surgical revascularization (study III). Therefore, diabetics with CLTI should be treated or at least be considered to be treated with surgical bypass. Although further research is needed for unanimous consensus, there is some literature that supports the management of CLTI with primary open surgery bypass, especially in patients with DM.

However, not all patients are deemed fit for surgical revascularization nor do they have an available conduit vein. In one study, patients with two or more risk factors had <50% survival at 2-years (Ohmine et al., 2015). In high-risk patients with poor long-term survival, endovascular therapy may be the only invasive treatment option. Compared to the conservative approach, endovascularly revascularized patients have been reported to have faster improvements in physical health (Steunenberg et al., 2018). Nevertheless, it has been proposed that the risk of reintervention is higher after primary endovascular revascularization compared to surgery-first approach, indicating that endovascular-first strategy should not be aggressively applied to all CLTI patient if surgery is also a feasible option (Bodewes et al., 2018). Also, treating long lesions, small arteries, and total occlusions with PTA has been associated with higher rates of arterial dissection and thus, the endovascular-first strategy may not be a completely safe approach to use for all patients (Fujihara et al., 2017).

Active revascularization is essential to prevent amputation. However, for some patients, amputation may be the only realistic treatment option to reduce ischemic pain or eliminate severe wound infection. In this (study II) and an earlier study by Abou-Zamzam et al., it has been estimated that nearly half of patients are not deemed fit for revascularization at the presentation of CLTI (Abou-Zamzam Jr et al., 2007). Previous studies have reported that severe frailty associates with increased risk of major amputation after revascularization (Morisaki et al., 2017; Takeji et al., 2018). Recently in Finland, a constant transfemoral and a decreasing transtibial amputation incidence was observed, which was explained by the high proportion of aged and immobile patients whom are often considered not to benefit from prothesis rehabilitation (Ponkilainen et al., 2021). Bearing this in mind, increasing regional

revascularizations do not seem to lower further the major amputation incidence (study II) due to high proportions of patients being unsuitable for revascularizations (Abou-Zamzam et al., 2003; Klaphake et al., 2017). Primary amputation should be considered for frail patients with reduced functional ability in preference to pointless repetitive revascularizations, multiple minor amputations, and revisions. On the other hand, minor amputations and palliative wound care may improve limb preservation and help to maintain mobility (Barshes et al., 2014), but their necessity and potential benefit needs to be carefully assessed.

Instead of comparing surgical and endovascular revascularization modalities per se, the investigation could focus on determining the patients best suited best for surgical and endovascular revascularization. It is evident that not all patients could or should be revascularized with surgery and vice versa. As the previously discussed studies together with the findings of this thesis suggest (study III) that, diabetics with CLTI especially, should be treated with an autologous vein bypass (Darling et al., 2018; Elbadawi et al., 2021; Patel et al., 2016). If a venous conduit is lacking or high preoperative risks exist, endovascular revascularization should be attempted as it associates with physical health compared to those patients not undergoing any revascularization for CLTI (Steunenberg et al., 2018). However, amputation still remains as the only realistic treatment for a significant proportion of CLTI patients.

6.5 Limitations and strengths

As in other studies, this thesis has some weaknesses and strengths. All patients were referred to vascular surgeon with intention to treat. As certain criteria exist for those finally admitted to a vascular specialist, patients with relatively mild symptoms were treated elsewhere, most commonly in a primary care setting. Such patients, however, would then have less severe forms of LEAD and not CLTI. The same policy also affects those considered too ill to be referred to a vascular surgeon. Therefore, if invasive treatment is excluded, then these patients are not evaluated by a vascular surgeon and hence, may not be included in the study cohorts. This selection limitation is nonetheless inevitable for all retrospective studies that have patient cohorts that include only those referred to a vascular or other type of surgeon.

When comparing the outcomes after surgical and endovascular revascularizations, it must be kept in mind that the patients were pre-selected before the study according to the patient characteristics and vascular status. Multiple patient-related factors, such as poor general condition, anaesthesia risks, lack of venous conduit, unreconstructable disease anatomy, and short lesions guide the decision towards endovascular revascularization. In other words, patients treated endovascularly might not be appropriately treated with open surgery and vice versa.

This is a common limitation of retrospective studies and could only be avoided with an RCT study setting.

A strength but also a limitation is the retrospective nature of this thesis. The findings rely on the accuracy of procedural and comorbidity data. Other strengths of this thesis include the long study periods and relatively large study cohorts. ABI, TP, and TBI were recorded in a vascular laboratory setting by trained nurses in a consistent manner. All patients were exclusively treated in publicly funded hospitals and none were excluded regarding insurance status or income. Similarly, no patients were lost to other healthcare districts or to private hospitals as revascularizations were and are solely performed in Turku University Hospital. Since no exclusion criteria were set, patients were unselected and therefore within a real-life setting and highly representative. The large and diverse cohorts in studies I-III were also representative of the general population.

6.6 Future perspectives

LEAD is a chronic progressive atherosclerotic disease that takes decades to develop, and patients often first encounter vascular surgeon late in the progression of the disease when the atherosclerosis is at an advanced state. Detecting the patients with the worst survival and prognosis is challenging as the current models show only modest predictive abilities and the need for better risk estimation tools is evident. Possibly enhancing the current risk models with the information on sex, distal lesion characteristics, TBI and TP could and tentatively should offer more precise risk estimation and is an intriguing research topic for the future.

Together with the previous literature, this thesis demonstrated that active revascularization is essential to reduce the risk of amputation. However, the most appropriate revascularization strategy to use remains unresolved. Although surgery associates with better survival, the specific criteria and overall consensus for patients who should be treated surgically and endovascularly are still lacking. A more tailored revascularization strategy could be applied to CLTI patients to see if it would yield even lower major amputation rates. The Best Endovascular vs. Best Surgical Therapy in Patients with Critical limb Ischemia (BEST-CLI) is an exciting ongoing RCT trial (Mills, 2019), that will hopefully provide an insight into some of these remaining questions.

A significant proportion of CLTI patients undergo primary amputation as they are considered too frail to benefit from revascularizations. When acknowledging the ongoing aging and growth of the elderly population, an increasing need of vascular services could be expected to occur in the 2020s. Advancing technologies and techniques, modified revascularization strategies, novel medication, and increasing physician education are possible tools to combat the increase. Whether the major

amputation incidence of the 2020s and the proportion of primary amputees will increase or decrease and what the possible impact of these efforts would be is an interesting question that will hopefully be answered later.

7 Summary/Conclusions

I. CLTI is multisegmental disease with severe crural involvement and typical cardiovascular risk factor profile. Age and female sex increase the risk for severe crural atherosclerosis.

II. The adequate provision of vascular services is crucial to combat the increasing incidence of amputations. Surgical reconstruction should be chosen as it seems to associate with better outcomes compared to endovascular approach especially in diabetics. However, not all patients are suitable for surgery and for these patients, endovascular revascularization or even primary amputation may be the most appropriate treatment options. At the presentation of CLTI, significant number of patients are already too frail for active revascularization.

III. The prognosis of CLTI is poor and patients only encounter the vascular surgeon at an advanced stage of atherosclerosis. High adverse event rates are seen in diabetics and those with extensive crural atherosclerosis. The need for precise risk models is evident and the inclusion in such models of the information of distal lesion characteristics, sex, TBI and TP could offer more accurate risk estimation. TBI and TP should be actively assessed for all patients despite the clinical picture as they are highly predictive of mortality and may overcome the limits of ABI.

Acknowledgements

This thesis starts with the Latin phrase “age quod agis”, which could be interpreted as “keep going, because you are inspired to do so”. This sentence of motivation deeply epitomizes my scientific journey. The driving forces of this thesis have been enthusiasm and inspiration; I feel highly influenced by the talented researchers and colleagues by which I am surrounded. One day, I wish to be like them, to get to where they are, and to follow in their footsteps. I wish that this section of my thesis highlights the amount of influence these people have impacted upon me.

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Veerakaisa Koivunen

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