UNIVERSITY OF TURKU

INVASIVE TREATMENT OF LOWER EXTREMITY ARTERIAL DISEASE

National Procedure Rates and Challenges in Wound Healing

Veikko Nikulainen

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA - SER. D OSA - TOM. 1528 | MEDICA - ODONTOLOGICA | TURKU 2020

UNIVERSITY
OF TURKU

INVASIVE TREATMENT OF LOWER EXTREMITY ARTERIAL DISEASE

National procedure rates and challenges in wound healing

Veikko Nikulainen

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA – SER. D OSA – TOM. 1528 | MEDICA – ODONTOLOGICA | TURKU 2020

University of Turku

Faculty of Medicine
Department of Vascular Surgery
Surgery
Turku University Hospital
Doctoral Programme in Clinical Research

Supervised by

Adjunct Professor Harri Hakovirta
Turku University and Turku University Hospital, Department of Vascular Surgery
Turku, Finland

M.D. PhD. Päivi Helmiö
Turku University and Turku University Hospital, Department of Vascular Surgery
Turku, Finland

Reviewed by

Adjunct Professor, Ilkka Uurto
Tampere University and Tampere University Hospital, Department of Vascular Surgery
Tampere, Finland

Adjunct Professor, Riikka Tulamo
Helsinki University and Helsinki University Hospital, Department of Vascular Surgery
Helsinki, Finland

Opponent

Adjunct Professor, Matti Pokela
Oulu University and Oulu University Hospital, Department of Vascular Surgery
Oulu, Finland

ISBN 978-951-29-8320-9 (PRINT)
ISBN 978-951-29-8321-6 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama Oy, Turku, Finland 2020

To my family

UNIVERSITY OF TURKU
Faculty of Medicine
Department of Vascular Surgery
Surgery
VEIKKO NIKULAINEN: Invasive treatment of lower extremity arterial disease – National procedure rates and challenges in wound healing
Doctoral Dissertation, 96 pp.
Doctoral Programme in Clinical Research
January 2021

ABSTRACT

Globally, over 200 million people suffer from lower extremity arterial disease (LEAD). The population is aging and with it the prevalence of LEAD is increasing especially in developing countries. The number of revascularization procedures for LEAD has also increased significantly in Western countries. The most severe form of LEAD is chronic limb threatening ischemia (CLTI). The prognosis for patients with CLTI is poor and patients with CLTI require a revascularization procedure to avoid lower limb extremity amputation (LEA).

Current guidelines state that patients with a life expectancy of more than two years should undergo an open revascularization procedure for CLTI. Bypass surgery is however major surgery that causes significant post-operative morbidity. Ischemic wound healing and surgical incision healing in the ischemic limb is impaired and challenging. For example, wound dehiscence and infections frequently occur. In addition to open bypass surgery, the development of endovascular techniques enables less invasive treatment of LEAD.

This thesis explores the current trends in the numbers of open- and endovascular revascularization procedures and major LEA in Finland 2007–2017 inclusive. The study also reports certain challenges and pitfalls after open revascularization procedures. The vein harvest wound (VHW) healing time after surgery was assessed as were the rates of inguinal surgical incision infections.

The rates of vascular procedures increased significantly during the study period. The increase was most prominent in endovascular procedures. The overall rate of major LEA remained constant for all study participants. However, the number of amputations decreased in the oldest population cohort. VHW dehiscence was frequently reported after revascularization. The VHW healing was remarkably slower after revascularization surgery in patients with an ischemic foot ulcer than for those without ischemic ulcers. The infection rates of inguinal surgical incisions were lower when the skin was closed using intradermal absorbable sutures compared to transdermal sutures.

The increasing prevalence of LEAD due to an aging population, is a major burden on the healthcare system. Our finding is that the number of revascularization procedures is increasing rapidly. This is associated with a decrease in the number of major LEAs. However, the morbidity and mortality after open bypass surgery has to be taken into account when making the decision on which patients can be offered a revascularization procedure, and which patients are best served with a primary LEA.

KEYWORDS: lower extremity arterial disease, chronic limb threatening ischemia, open revascularization, endovascular revascularization, major lower extremity amputation, wound dehiscence, wound infection

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Verisuonikirurgia
Kirurgia
VEIKKO NIKULAINEN: Alaraajojen tukkivan valtimotaudin kajoava hoito – Kansalliset toimenpidemäärät ja haavanparanemisen haasteet
Väitöskirja, 96 s.
Turun kliininen tohtoriohjelma
Tammikuu 2021

TIIVISTELMÄ

Alaraajojen tukkivalla valtimotaudilla (LEAD, lower extremity arterial disease) tarkoitetaan alaraajojen ateroskleroosia. Maailmanlaajuisesti yli 200 miljoonaa ihmistä kärsii LEAD:sta, määrä on nousussa väestön ikääntymisen seurauksena varsinkin kehitysmaissa. Länsimaissa alaraajojen verenkiertoa palauttavien toimenpiteiden määrä kasvaa jyrkästi. LEAD:n pitkälle edenneen muodon, eli kriittiseen iskemian ennuste on erittäin huono ja potilaat tarvitsevat verenkiertoa palauttavan toimenpiteen välttyäkseen alaraaja-amputaatiolta.

Nykyiset hoitolinjat suosittelevat ohitusleikkausta potilaille, joilla on kriittinen iskemia ja joiden eliniänennuste on yli kaksi vuotta. Alaraajojen ohitusleikkaukset ovat suuria ja raskaita toimenpiteitä, joihin liittyy usein pitkittynyt parantuminen ja usein myös komplisoitunut toipuminen. Verenkierron vajeesta kärsivässä raajassa kroonisten haavojen paraneminen on hidasta, myös kirurgiset leikkaushaavat paranevat hitaasti ja haavatulehdukset ovat yleisiä. Suonensisäiset hoitomenetelmät ovat viime vuosikymmenten aikana kehittyneet nopeasti ja tarjoavat uusia vaihtoehtoja LEAD:n hoitoon.

Tämän väitöskirjan tarkoitus oli selvittää nykyisiä trendejä LEAD:n hoidossa. Tutkimuksessa analysoitiin ohitusleikkausten, suonensisäisten hoitomenetelmien ja alaraaja-amputaatioiden määriä Suomessa 2007–2017. Tämän lisäksi tarkasteltiin yksityiskohtaisemmin leikkaushaavojen paranemista ja leikkaushaavatulehduksia ohitusleikkausten jälkeen.

LEAD:n vuoksi tehtyjen toimenpiteiden määrä Suomessa nousi merkittävästi tarkastelujakson aikana. Kaikkein selvin määrän nousu todettiin suonensisäisten hoitomenetelmien kohdalla. Samalla tarkastelujaksolla alaraaja-amputaatioiden kokonaismäärä pysyi vuosi vuodelta samana. Kun alaraaja-amputaatioiden määrää suhteutettiin ikääntyvään väestön määrään, todettiin että vanhimpien ikäryhmien alaraaja-amputaatioiden määrä väheni merkittävästi. Ohitusleikkaushaavat paranivat hitaasti. Erityisen hidasta paraneminen oli potilailla, joilla leikkauksen aikana oli niin syvä verenkierron vajaus jalassa, että se ilmeni kudospuutoksina. Nivusalueen leikkaushaavojen infektoiden ilmaantuvuutta saatiin vähennettyä sulkemalla iho sulavalla ompeleella.

LEAD yleistyy väestön ikääntymisen seurauksena aiheuttaa suurta kuormitusta terveydenhoitojärjestelmälle, lisääntyneiden hoitopäivien ja toimenpiteiden vuoksi. Tutkimuksemme löydösten perusteella verenkiertoa palauttavien toimenpiteiden määrä on vähentänyt alaraaja-amputaatioita merkittävästi vanhimmissa ikäryhmissä. Kuitenkin sairastuvuus ja kuolleisuus näihin toimenpiteisiin liittyen pitää ottaa huomioon, kun tehdään päätöksiä siitä ketkä potilaat hyötyvät verenkiertoa palauttavista toimenpiteistä ja kenelle alaraaja-amputaation on paras ensilinjan hoito.

AVAINSANAT: LEAD, kriittinen iskemia, ohitusleikkaus, amputaatio, haavakomplikaatio

Table of Contents

Abbreviations

AAA	abdominal aortic aneurysm
ABI	ankle brachial index
AKA	above the knee amputation
ALI	acute limb ischemia
AP	ankle pressure
ASA	acetylsalicylic acid
BASIL	Bypass versus Angioplasty in Severe Ischemia of the Leg trial
BEST-CLI	Best Endovascular Versus Best Surgical Therapy for Patients with Critical Limb Ischemia Trial
BMI	body mass index
BKA	below the knee amputation
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CAPRIE	a randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events
CDC	Centre for Disease Control and Prevention
CFAe	common femoral artery endarterectomy
CI	95% Confidence Interval
CLTI	chronic limb threatening ischemia
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies trial
CTA	computed tomography angiography
CVD	cerebrovascular disease
DAPT	dual anti-platelet therapy
DSA	digital subtraction angiography
DU	duplex ultrasonography
ESC	European Society of Cardiology
ESVS	European Society for Vascular Surgery
EVAR	endovascular aneurysm repair
Finnvasc	National vascular registry of vascular procedures from Finland collected in 1991-1995

GLASS	Global Limb Anatomic Staging System
GSV	great saphenous vein
IC	intermittent claudication
ISCVS	International Society of Cardiovascular Surgery
LEA	lower extremity amputation
LEAD	lower extremity arterial disease
MRA	magnetic resonance angiography
NNIS	The National Nosocomial Infection Surveillance
NPWT	negative pressure wound therapy
OR	odds ratio
PAD	peripheral arterial disease
PREVENT	Edifoligide for Prevention of Infrainguinal Vein Graft Failure trial
PTA	percutaneous transluminal angioplasty
PTFE	polytetrafluoroethylene (synthetic vascular graft material)
RCT	randomized controlled trial
REACH	Reduction of Atherothrombosis for Continued Health (registry)
SAP	systolic ankle pressure
SIRS	systemic inflammatory response syndrome
SSI	surgical site infection
SSV	small saphenous vein
StatFin	online database governed by Statistics Finland
STP	systolic toe pressure
SVS	Society for Vascular Surgery
TAP	optimal target arterial path
TASC	Trans-Atlantic Inter-Society Consensus (for management of peripheral arterial disease)
TcPO2	transcutaneous partial oxygen pressure
THL	The Finnish National Institute for Health and Welfare
TUH	Turku University Hospital
VHW	vein harvest wound
(Voyager-PAD)	Rivaroxaban in Peripheral Artery Disease after Revascularization trial
WHO	World Health Organization
WIfI	Society for Vascular Surgery Lower Extremity Threatened Limb Classification System (based on wound, ischemia and foot infection)

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 Nikulainen V, Helmiö P, Hakovirta H. Changes in rates of vascular procedure types and lower extremity amputations in Finland for 2007-2017, a population cohort study of 69,523 revascularizations. *Int J Surg*, 2019 Dec; 72: 118–125.

II Nikulainen V, Helmiö P, Hurme S, Hakovirta H. Vein Harvest Wound Healing after Bypass Surgery for Critical Limb Ischemia. *Ann Vasc Surg*, 2020 Jan; 62: 375–381.

III Nikulainen V, Helmiö P, Hurme S, Hakovirta H. Intra-Dermal Absorbable Suture in the Groin Incision Associated with Less Groin Surgical Site Infections than Trans-Dermal Sutures in Vascular Surgical Patients. *Surg Infect (Larchmt)*, 2019 Jan; 20(1):45–48.

1 Introduction

Atherosclerosis is the most common cause of lower extremity arterial disease (LEAD), coronary artery disease (CAD) and cerebrovascular disease (CVD) (Aboyans et al. 2006). Patients with LEAD commonly have a more widespread burden of atherosclerosis than patients with CAD or CVD (Bhatt et al. 2006).

LEAD patients can either be asymptomatic or have symptoms of intermittent claudication (IC) or chronic limb threatening ischemia (CLTI). IC patients can be managed conservatively, whereas patients with CLTI require a revascularization procedure to avoid amputation (Norgren et al. 2007). However, patients with extensive comorbidities and poor functional status may be best served by undergoing a primary amputation (Aboyans et al. 2018).

The treatment of LEAD should always include the management of cardiovascular risk in order to reduce the overall cardiovascular mortality and improve the results of invasive revascularization procedures (Conte et al. 2006, Hirsch et al. 2006, Eikelboom et al. 2017, Aboyans et al. 2018).

Historically, open surgery has been the treatment of choice for LEAD (Shah et al. 1995, Adam et al. 2005). The advancement of endovascular techniques over the last three decades has enabled more complex arterial lesion to be treated without major surgery (Sachs et al. 2011, Bosiers et al. 2012). The effect on limb salvage and cost-effectiveness of endovascular procedures has however been questioned (Stoner et al. 2008, Forbes et al. 2010, Childres et al. 2019).

Current recommendation based on the Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial (Adam et al. 2005) is that patients with a life expectancy of more than two years should undergo open surgery for CLTI (Aboyans et al. 2018). Infrainguinal bypass surgery is major surgery and predisposes the initially ischemic tissues to major surgical trauma. The healing process in such patients is slow and causes major post-operative morbidity (Eid et al. 2014, Santo et al. 2014, Santo et al. 2014).

In addition to delayed surgical wound healing, patients with LEAD have an increased risk of developing surgical site infections (SSI) after revascularization procedures. The rate of SSIs after peripheral vascular surgery is considerably higher than in other clean surgery (Turtiainen et al. 2010). The elevated risk is both patient and procedure related. SSIs cause major morbidity and mortality. They have a negative effect on the outcome of revascularization procedures and have major financial implications (Giles et al. 2010, Turtiainen et al. 2010, Greenblatt et al. 2011).

LEAD is the least studied and most poorly known of the atherosclerotic diseases despite having the worst outcomes (Hirsch et al. 2001, Fowkes et al. 2014). This thesis aims to explore the clinical challenges and pitfalls in the treatment of LEAD in order to guide treatment modalities and resources in the future.

2 Review of the Literature

2.1 Atherosclerotic disease

Atherosclerosis is the most common cause of CAD, LEAD and CVD (DeBakey et al. 1985, Aboyans et al. 2006). These diseases cause major morbidity and mortality especially in Western countries.

The current understanding is that atherosclerosis is a systemic inflammatory disease of the arterial wall (Ross 1999), in which a large number of inflammatory mediators contribute to the accumulation of lipids and immune cells within the arterial intima (Libby and Hansson 2015). The lipid and leucocyte accumulation causes arterial wall thickening, which can lead to occlusion of the artery either from a gradual thickening of the arterial wall, or from local thrombosis i.e. atherothrombotic disease (Ross 1993). The inflammatory process starts many years before clinical symptoms occur (Raitakari et al. 2003). The clinical symptoms may progress gradually over many years, but a thrombosis can cause sudden and acute symptoms (van der Wal et al. 1994).

There is considerable overlap in the clinical manifestations of the atherosclerotic disease. Patients with LEAD tend to have a more widespread burden of atherosclerosis compared to CAD and CVD patients. Two studies, the Reduction of Atherothrombosis for Continued Health (REACH) registry study and the Randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events study (CAPRIE) (Gent et al. 1996, Bhatt et al. 2006) found that approximately 60% of patients with LEAD have either CAD, CVD or both (Norgren et al. 2007) see Figure1. More recent data showed that 11% to 12% of patients with stable symptomatic LEAD suffered myocardial infarction, stroke or cardiovascular death, and 2% to 4% were hospitalized for acute limb ischemia over a 36 month follow-up (Bonaca et al. 2013).

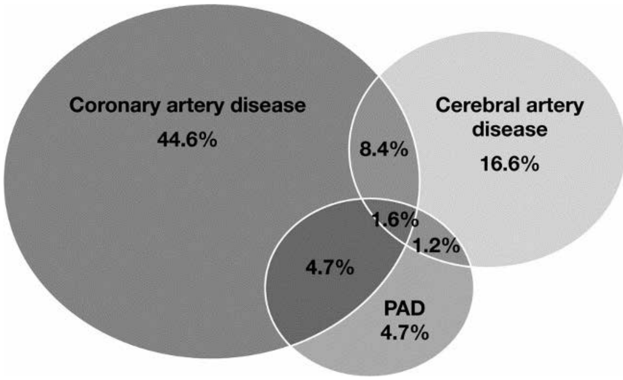

Figure. 1. Overlap of atherosclerotic diseases based on the REACH registry data, from TASC II (Norgren et al. 2007). Reproduced with the permission of Elsevier Ltd.

The percentages have been obtained from those REACH registry patients that had symptomatic atherosclerotic disease (81.8%). In the REACH registry dataset 18.2% of patients were asymptomatic but had over three major cardiovascular risk factors, thus data from this group of patients are excluded from the percentages in the figure above.

2.2 Lower extremity arterial disease

LEAD is defined as a partial or complete obstruction of one or more peripheral arteries (Hiatt et al. 2008).

It is estimated that > 240 million people worldwide have LEAD (Criqui and Aboyans 2015, Song et al. 2019). The overall incidence of LEAD has increased from approximately 164 million in 2000 to 202 million in 2010. As a result of the aging of populations, the prevalence of LEAD increased by 13% in high-income countries and by 29% in low-income countries between 2000 and 2010. A growing proportion of LEAD patients in low-income countries are women (Fowkes et al. 2013).

It has been predicted that the prevalence on LEAD will continue to increase in the future due to aging of the global population and to the increase of the major risk factors; especially diabetes and tobacco smoking (Mendez et al. 2013, Guariguata et al. 2014, Song et al. 2019).

Despite this, LEAD is less known to the public and even healthcare professionals than coronary artery disease and cerebrovascular disease (Hirsch et al. 2001, Hirsch et al. 2007).

2.2.1 Risk factors for LEAD

The risk factors and comorbidities among patients with different manifestations of atherosclerotic disease are very similar. These include the following Odds Ratios

(ORs) for the risk factors: diabetes 1.89, smoking 2.82, hypertension 1.67, dyslipidaemia 1.51, age 1.55 per 10-year increment, obesity 1.55, chronic kidney disease 1.79, chronic inflammation 1.89 (Murabito et al. 1997, Vartiainen et al. 2000, Manjunath et al. 2003, Norgren et al. 2007, Gabriel 2008, Song et al. 2019).

Among the risk factors diabetes and cigarette smoking are considered to be most strongly associated with LEAD. Cigarette smoking is the single most significant risk-factor for developing LEAD in both men and women (Murabito et al. 1997). The severity of LEAD is proportional to the number of cigarettes smoked and smoking cessation is associated with a risk reduction for developing LEAD (Powell et al. 1997, Huxley and Woodward 2011). The risk of developing LEAD is greater as it depends on the severity and duration of diabetes. The prevalence of LEAD is up to 30% higher in patients with diabetes than for the general population (Wattanakit et al. 2005, Marso and Hiatt 2006).

The incidence of LEAD increases with age (OR 1.55 per 10-year increment). Globally the age groups that contribute the largest share of patients are aged 60–69 years in high income countries and 45-55 years in low-income countries (Song et al. 2019).

Different arterial segments are affected by different risk factors for LEAD. Young age, smoking and dyslipidaemia are more often associated with proximal, above the knee arterial segments. Old age, diabetes and chronic kidney disease are more commonly associated (Figure 2.) with tibial disease (Diehm et al. 2006).

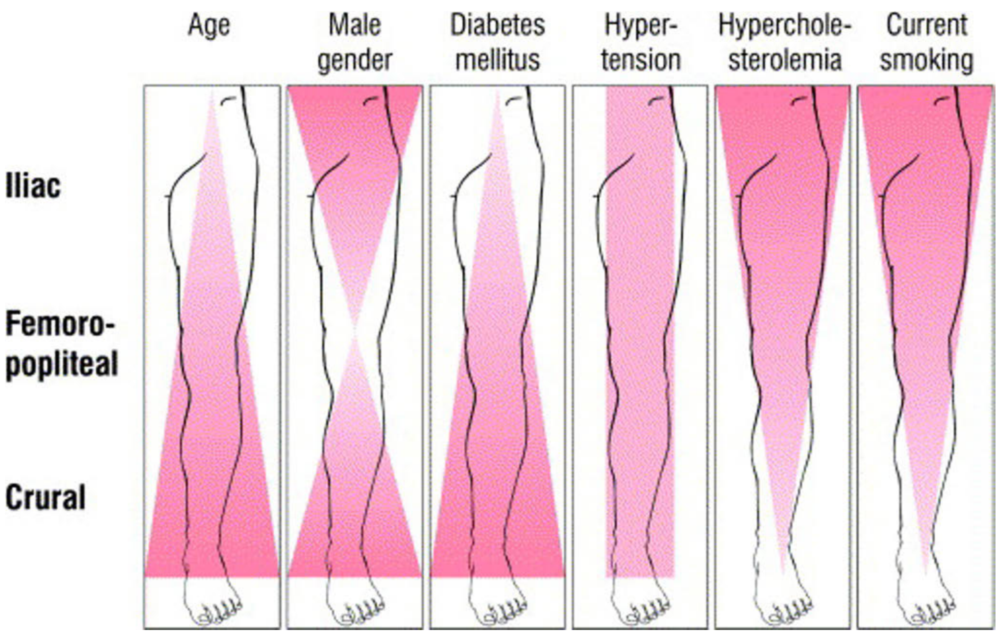

Figure. 2. Anatomical distribution on LEAD according to known risk factors (Diehm et al. 2006). Reproduced with the permission from Elsevier Ltd.

2.2.2 Classification of LEAD

Historically two different classification systems have been used to grade the severity of LEAD according to clinical symptoms. The first is the Fontaine classification (Fontaine et al. 1954), which is purely based on symptoms and does not include any haemodynamic measurements. The second is the Society of Vascular Surgery/International Society of Cardiovascular Surgery (SVS/ ISCVS) standards for reporting lower limb ischemia, which were first published in the Journal of Vascular Surgery (Rutherford 1986) and included a classification that is currently known as the Rutherford classification (Rutherford et al. 1997). The Rutherford system involves, inter alia, ankle pressure (AP) and toe pressure (TP) measurements as objective criteria. These two classifications are presented in Table 1.

Table 1. Historical classification on LEAD according to the Fontaine and the Rutherford classification systems. Modified from (Fontaine et al. 1954, Rutherford et al. 1997). AP = Ankle pressure, TP = Toe pressure

FONTAINE		**RUTHERFORD**			
STAGE	**Clinical presentation**	**GRADE**	**CATEGORY**	**Clinical presentation**	**Objective criteria**
I	Asymptomatic	0	0	Asymptomatic	Normal exercise tolerance
IIA	Mild claudication		1	Mild claudication	AP after exercise > 50 mmHg
IIB	Moderate-severe claudication	I	2	Moderate claudication	Between 1 and 3
III	Ischemic rest pain		3	Severe claudication	Diminished exercise tolerance, AP < 50 mmHg after exercise
IV	Ulceration / gangrene	II	4	Ischemic rest pain	AP < 40 mmHg TP< 30 mmHg
		III	5	Minor tissue loss	Ulcers on digits TP < 50 mmHg
			6	Major tissue loss	Severe ulcers/ gangrene TP < 50 mmHg

The Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC and the updated TASC II) is a system that classifies the lower limb atherosclerotic lesions according to length and severity in the different anatomical segments (Dormandy and Rutherford 2000, Norgren et al.

2007). The TASC classification categorizes the occlusive lesion from A to D and aims to provide a practical guideline to assess different treatment modalities for specific lesions.

More recently, the Society for Vascular Surgery (SVS) Lower Extremity Threatened Limb Classification System (WIfI- classification), has been introduced (Mills et al. 2014) and is based on wound ischemia and foot infection. WIfI-classification was developed by merging the existing LEAD and diabetic foot ulcers classifications, which are stratified according to the risk for major amputation for three major factors: wound, ischemia and foot infection. The SVS WIfI-classification shown in Table 2 has since been validated by numerous studies that predict limb salvage and ischemic wound healing after endovascular and open revascularization (Cull et al. 2014, Zhan et al. 2015, Darling et al. 2016).

Table 2. Society for Vascular Surgery (SVS) Wound, Ischemia, and foot Infection (WIfI) grades. Modified from (Mills et al. 2014).

GRADE	WOUND	ISCHEMIA	INFECTION
0	No wound	STP > 60 mmHg SAP > 100 mmHg ABI > 0.8	No infection
1	Small, shallow ulcer No exposed bone No gangrene	STP 40–59 mmHg SAP 70–100 mmHg ABI 0.6–0.79	Local skin infection
2	Deep wound Exposed bone / joint /tendon Shallow heel ulcer Gangrene limited to digits	STP 30–39 mmHg SAP 50–70 mmHg ABI 0.4–0.59	Local infection involving structures deeper than skin (e.g. abscess, osteomyelitis)
3	Extensive deep ulcer with bone involvement Full thickness heel necrosis	STP < 30 mmHg SAP < 30 mmHg ABI < 0.39	Local infection in combination with SIRS

ABI = Ankle-brachial index
SAP = Systolic ankle pressure
STP = Systolic toe pressure
SIRS = Systemic inflammatory response syndrome

A new Global Limb Anatomic Staging System (GLASS) was incorporated in the Global Vascular Guidelines published in 2019 (Conte et al. 2019). The GLASS system relies on high quality images of the lower limb arteries. It grades the inflow (femoro-popliteal) and outflow (infrapopliteal or inframalleolar) arteries from 0 to 4 depending on the lesion severity. The aim is to provide the most optimal target arterial path (TAP) to ensure best possible technical success and graft patency. The system has not yet been validated in large trials (Conte et al. 2019).

2.2.3 Diagnosis of LEAD

Patient history and clinical examination are essential in the diagnosis of LEAD. It is important to examine whether the distal pulses are absent and to examine the limb closely for sensory and motor-function deficits. In addition, the limb should be inspected for ischemic or gangrenous tissue. The deficit in arterial circulation can be measured by an abnormally low ankle-brachial-index (ABI), systolic toe pressure (STP) measurements or transcutaneous partial oxygen pressure measurements (TcPO2) (Aboyans et al. 2018).

2.2.3.1 Peripheral pressure measurements

Insufficient blood flow to the lower limb is measured by ABI. This entails measuring the systolic pressure of the ankle and dividing this by the systolic pressure of the arm. The normal value range for ABI is 0.9-1.3. Values below 0.9 are considered insufficient blood flow and diagnostic for LEAD, whereas values over 1.3 are considered falsely high due to non-compressible arteries. The false measurements caused by the non-compressibility of the ankle arteries can be eliminated by measuring STPs, as digital arteries in the toes do not generally suffer from non-compressibility (Bhamidipaty et al. 2015). When evaluating the toe pressure measurement, the absolute systolic value in mmHg is more accurate (Table 1) than the toe-brachial-index (Holtman and Gahtan 2008).

In addition to being measures of LEAD severity, ABI and STP are independent predictors of cardiovascular mortality among LEAD patients, thus, low ABI and STP measurements predict increased cardiovascular mortality (Dormandy and Murray 1991, Mehler et al. 2003, Wickstrom et al. 2019). An abnormally high ABI (over 1.3) is similarly associated with poor overall survival (Suominen et al. 2010).

2.2.3.2 Imaging techniques

Imaging of the lower limb arteries is indicated when it has been established that the patient has LEAD and the symptoms require treatment.

There are several options including: duplex ultrasonography (DU), computed tomography angiography (CTA), magnetic resonance angiography (MRA) and digital subtraction angiography (DSA). The choice of imaging depends on availability, local practice, cost and patient related factors (Collins et al. 2007). Full leg digital subtraction angiography (DSA) is often needed to evaluate the revascularization options to treat the tibial lesions (Teraa et al. 2016).

2.2.4 Clinical presentation of LEAD

The symptoms from LEAD determine the severity of the disease. It can be asymptomatic or present as intermittent claudication (IC) or chronic limb threatening ischemia (CLTI) (Norgren et al. 2007).

2.2.4.1 Intermittent claudication

IC is the most common presentation of LEAD. The prevalence is approximately 7% in individuals over 60 years (Sigvant et al. 2007). IC is defined as limb pain distal to the arterial occlusion. The pain is provoked by exercise and it subsides when exercise ceases (Sidawy et al. 2019).

The natural course of IC is relatively benign and marked by slow progression to shorter walking distances. In only about a quarter of patients with IC do the symptoms progress to CLTI (Norgren et al. 2007). Risk factor control and walking exercises are essential in order to prevent disease progression. A study of 224 nondiabetic patients with IC that was followed for 6 years noted that only 8% of patients who stopped smoking progressed to CLTI, whereas 79% of those who continued to smoke developed signs of CLTI (Jonason and Ringqvist 1985). The overall risk for major amputation in IC patients is low, only 1–3% (Kannel et al. 1970, Dormandy et al. 1999).

2.2.4.2 Chronic Limb Threatening Ischemia

Chronic limb threatening ischemia is the most severe form of LEAD. It is characterized by rest pain or tissue loss and defined by ischemic rest pain with AP < 50 mmHg and STP < 30 mmHg or ischemic tissue loss with AP < 70 mmHg or STP < 50 mmHg (Table 1). Typically, the tissue loss presents as gangrene in the distal parts of the digits or in more advanced cases as gangrene and non-healing ulcers of the heel and foot at the metatarsal level.

CLTI is a result of widespread and advanced LEAD. It is unlikely to be related to only the aorto-iliac lesions or femoro-popliteal lesions, it is rather, a combined involvement of different arterial segments and often involves the tibial arteries (Jalkanen et al. 2016). The prognosis for patients with CLTI is poor, without revascularization up to 40% of patients undergo major lower extremity amputation (LEA) and 20% die within 6 months of the diagnosis (Norgren et al. 2007).

The mortality rates in CLTI exceed those for every other form of atherosclerotic disease, including symptomatic CAD, which highlights the systemic atherosclerotic burden of CLTI see Figure 1. (Steg et al. 2007, Fowkes et al. 2014). Furthermore, it has been demonstrated that LEAD is associated with significantly increased cardiovascular mortality and this is especially case for LEAD in the tibial vessels (Jalkanen et al. 2016, Wickstrom et al. 2017).

2.3 Treatment of LEAD

The treatment of LEAD consists of medical therapy, lifestyle modification including walking exercises and smoking cessation in addition to revascularization procedures. The revascularization procedures can be either endovascular or open surgical procedures. The aim of the treatment of CLTI is the preservation of the limb, healing of the ischemic ulcers and the elimination of the ischemic rest pain in order to facilitate independent living. For patients with claudication, the aim is the improvement of the quality of life (Norgren et al. 2007, Aboyans et al. 2018).

2.3.1 Conservative management

Medical management of cardiovascular risk factors in order to reduce adverse cardiovascular events is a cornerstone in the treatment of LEAD. This treatment regime includes medical treatment with antithrombotic agents, treatment of hypercholesterolaemia, hypertension, diabetes mellitus and coronary artery disease in combination with exercise therapy and cessation of smoking (Hirsch et al. 2006, Eikelboom et al. 2017, Aboyans et al. 2018).

In addition to reducing cardiovascular adverse events (Burns et al. 2003), the appropriate medical therapy is essential to achieve satisfactory results after endovascular and open revascularization procedures (Conte et al. 2006, White and Gray 2007, Schanzer et al. 2008).

2.3.2 Operative management

Operative management is often indicated for CLTI and for IC when the functional status is severely compromised. Revascularizations can be either open surgical, endovascular or hybrid procedures that combine open and endovascular procedures (Aboyans et al. 2018).

2.3.2.1 Femoral endarterectomy

Endarterectomy is a vascular procedure that involves the removal of the atherosclerotic plaque along with the thickened intima and inner media that compromise the arterial lumen. Endarterectomy is almost exclusively used in the femoral bifurcation for the treatment of LEAD.

Common femoral artery endarterectomy (CFAe) involves an incision in the inguinal area in order to gain proximal and distal control of the femoral bifurcation (Figure 3a). CFAe is usually done under general or spinal anaesthesia but the exposition of the femoral vessels can also be done under local anaesthesia (Kang et al. 2008, Ballotta et al. 2010). The literature supports the use of local anaesthesia when appropriate, especially in the elderly population (Uhl et al. 2020). In the traditional open endarterectomy technique, the vessels are clamped, a longitudinal arteriotomy is made and the thickened intima and atherosclerotic plaque is removed (Figure 3b).

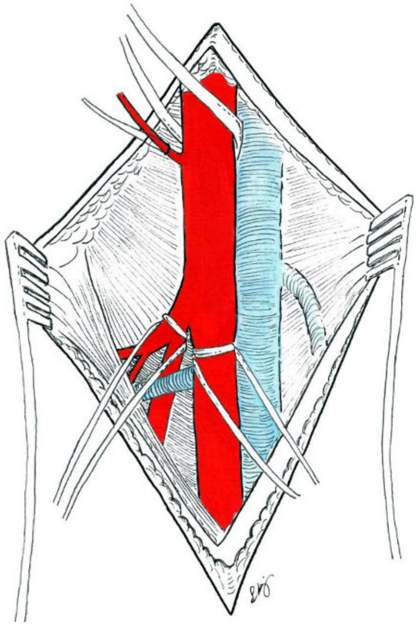

Figure 3a. Common femoral artery endarterectomy (CFAe). Vertical skin incision in the inguinal area exposing the common femoral, superficial femoral and profunda arteries (Copyright Saara Nikulainen).

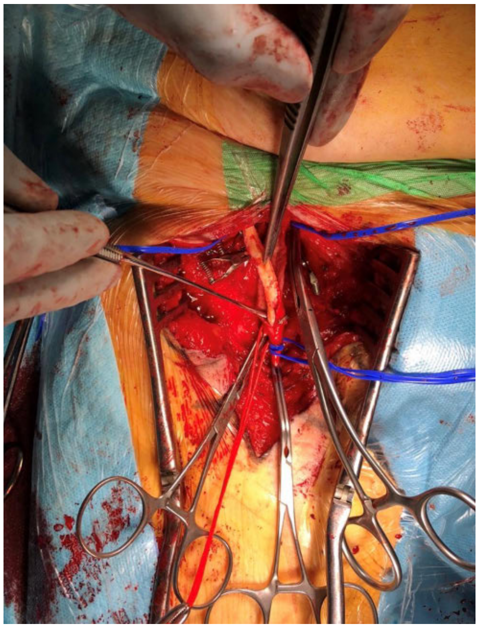

Figure 3b. The common femoral artery, superficial femoral artery and profunda arteries were exposed in the groin. A longitudinal arteriotomy was made and the atherosclerotic plaque is being removed from the artery using forceps (Copyright Veikko Nikulainen).

CFAe can be used as a sole procedure or in combination with a bypass or an endovascular intervention in a hybrid procedure in order to secure outflow or inflow. The safety and efficacy of CFAe has been demonstrated in several studies (Kang et al. 2008, Wieker et al. 2016, Uhl et al. 2020). The revascularization results after femoral endarterectomy are good, however the inguinal incision is one of the most frequently infected surgical incisions, infection rates up to 27% have been reported (Piano 1995, Turtiainen et al. 2010).

2.3.2.2 Infrainguinal bypass surgery

Historically bypass surgery has been the treatment of choice for peripheral arterial occlusive disease. The principle of infrainguinal bypass surgery is that there is unimpeded inflow at the proximal anastomosis and that the least diseased artery with the best distal out-flow is selected as a site for distal anastomosis (Conte 2009).

Bypass procedures can be performed using autologous vein grafts or prosthetic vascular grafts. The superiority of autologous vein grafts over prosthetic grafts in below-the-knee procedures has long been recognized (Veith et al. 1986). The recent European Society of Cardiology (ESC)/European Society for Vascular Surgery (ESVS) guidelines have also emphasised the superiority of the autologous Great Saphenous Vein (GSV) graft over polytetrafluoroethylene (PTFE) graft in the above-the-knee reconstructions (Aboyans et al. 2018).

2.3.2.3 Vein graft harvesting

The ipsilateral GSV graft has been considered the gold standard for below-the-knee bypass surgery (Bergan et al. 1982). The current treatment guidelines state that patients presenting with CLTI with a life expectancy of over two years benefit from a bypass procedure with an autologous vein (Adam et al. 2005, Aboyans et al. 2018). However, revascularization surgery with harvested GSV exposes an initially ischemic tissue to major surgical trauma (Figure 4).

Pre-operative vein mapping with DU is recommended pre-operatively. If the ipsilateral GSV is insufficient to be used as a graft the contralateral GSV, Small Saphenous Vein or arm veins can be harvested. An adequately sized single-segment GSV is reported to have the best patency rates, deviation from this increases the risk of graft failure (Conte et al. 2006, Schanzer et al. 2007).

Figure 4. Vein harvest wounds of a patient that had a tibial bypass procedure with a converted saphenous vein graft from the ipsilateral limb. The indication of the procedure was CLTI with tissue loss (Copyright Veikko Nikulainen).

There are different surgical techniques for harvesting the GSV. It can be harvested from a continuous incision, skip incisions or endoscopically. The open vein harvest technique, from either continuous or skip incisions, is associated with better primary graft patency and fewer re-intervention, but the number of surgical site infections and wound dehiscence is also 5-15% higher. However, all of these vein harvest techniques are associated with similar limb salvage and secondary patency (Eid et al. 2014, Santo et al. 2014, Teixeira et al. 2015).

The vein graft orientation can be converted or non-converted. In the non-converted orientation, the valves have to be destroyed in order to achieve flow. No significant differences in the long-term outcomes of these different techniques has been demonstrated (Wengerter et al. 1991, Belkin et al. 1996, Mamode and Scott 2000).

The technique of the open vein harvest method using converted ipsilateral vein is illustrated in Figure 5.

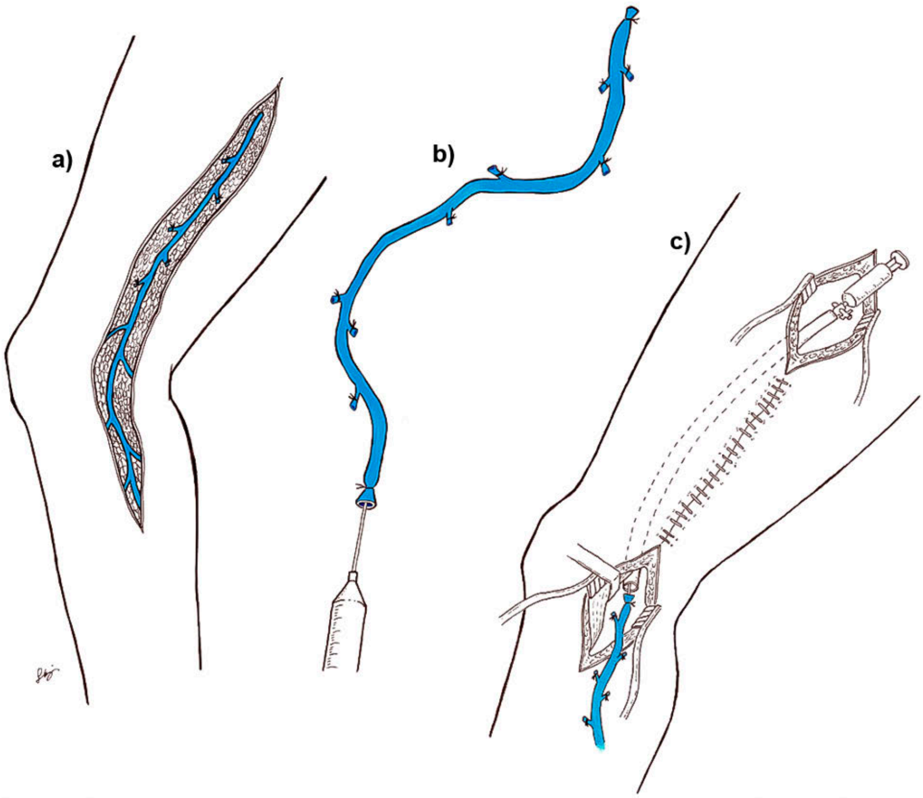

Figure 5. Ipsilateral GSV harvesting for femoro-popliteal bypass procedure with GSV. **a)** The vein graft is harvested from a continuous incision and the side branches are ligated. After this, the skin over the long incision is closed. **b)** The vein graft is pressurized with saline and checked for leaks. **c)** The converted vein is tunneled in an anatomical or sub-fascial position after which the proximal and distal anastomosis are constructed (Copyright Saara Nikulainen).

2.3.3 Endovascular revascularization procedures

Endovascular revascularization has historically been simple percutaneous transluminal angioplasty (PTA) with selective adjunctive stenting. Over the last decades endovascular techniques have evolved by introducing drug eluting stents and balloons, atherectomy, shock-wave balloons and stent-grafts. This has enabled more complex arterial lesions in CLTI to be treated with endovascular techniques. Outcomes of treatment of femoro-popliteal lesions are good, but infrapopliteal lesions remain challenging (Sachs et al. 2011, Goodney et al. 2015, Mustapha et al. 2016, Teraa et al. 2016, Bjorkman et al. 2018).

It is recognized that endovascular procedures can require several redo-procedures (Baer-Bositis et al. 2018, Mohapatra et al. 2018). The larger number of redo-procedures becomes apparent in cost-effectiveness analysis that compare endovascular to open surgery (Stoner et al. 2008, Forbes et al. 2010).

2.3.4 Application of different treatment modalities

Historically the treatment of infrainguinal LEAD has been open bypass surgery and it is associated with good limb salvage and clinical durability (Shah et al. 1995, Adam et al. 2005). However, an infrainguinal bypass surgery remains a high-risk surgical procedure with significant morbidity and mortality.

The endovascular procedures are traditionally associated with lower peri-procedural mortality and morbidity and therefore can be offered to high-risk surgical patients. This has lowered the threshold for invasive treatment especially for claudication (O'Brien-Irr et al. 2012).

2.3.4.1 Intermittent claudication

The primary treatment of IC is conservative. Revascularization may be considered in combination with conservative management when daily life activities are severely compromised (Greenhalgh et al. 2008, Fakhry et al. 2015, Gerhard-Herman et al. 2017).

Aorto-iliac occlusive disease commonly presents as varying degrees of IC. However, due to a large number of collaterals, aorto-iliac occlusive disease seldom presents as CLTI. The current guidelines state that an 'endovascular first' strategy is recommended for patients with short occlusive lesions or when the patient has multiple comorbidities that are unfit for open surgery (Jongkind et al. 2010, Ye et al. 2011, Fakhry et al. 2015, Aboyans et al. 2018). Primary stenting has become the first line of endovascular therapy rather than PTA with selective stent placement, because of the high frequency of distal embolization after PTA alone. If there is combined occlusive disease in the femoral bifurcation a hybrid procedure with a femoral endarterectomy is recommended (Aboyans et al. 2018).

Endovascular therapy has become the first line of therapy for isolated femoro-popliteal lesions in patients with IC (Schillinger et al. 2007). Drug eluting balloons and stents have become new treatment options in the femoro-popliteal segment, especially in restenosis of a previously treated segment (Tosaka et al. 2012, Geraghty et al. 2013). Bypass surgery with autologous GSV is the first-line therapy in long lesions of the femoro-popliteal segment, followed by PTFE grafting but only when there is no usable GSV in either leg. IC the treatment is focused on supra-popliteal lesions, thus tibial bypass and endovascular procedures are not indicated (Aboyans et al. 2018).

Recent prospective RCTs have however demonstrated a lack of long-term benefit and cost-effectiveness from an invasive treatment strategy for IC. The positive effect on pain free walking distance and quality of life improvement was lost 5 years after the revascularization procedure (Djerf et al. 2020).

2.3.4.2 Chronic Limb Threatening Ischemia

The initial choice of treatment for patients with CLTI in not easily made. It depends on several procedure- and patient-related factors such as: age, comorbidities, presence of a usable vein graft, extent and location of the arterial occlusive disease, and severity of the ischemia.

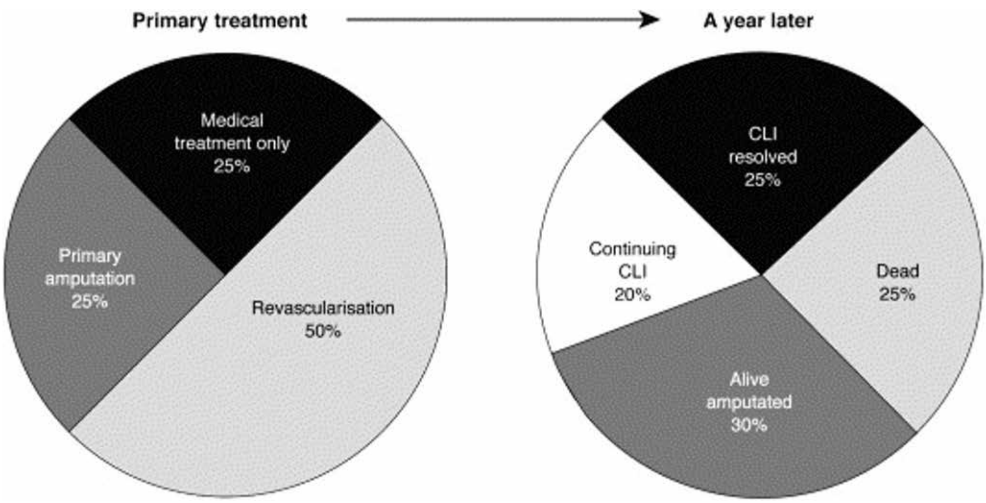

Figure 6. Fate of patients presenting with CLTI (Norgren et al. 2007). Reproduced with the permission of Elsevier Ltd.

The BASIL trial concluded that patients who present with CLTI with a life expectancy of more than two years should be offered a bypass procedure as a first line of therapy rather than an endovascular intervention (Adam et al. 2005). In the Edifoligide for Prevention of Infrainguinal Vein Graft Failure trial (PREVENT III), the researchers developed a system that stratifies CLTI patients into low-, medium- and high-risk categories based on end-stage renal failure, tissue loss, advanced age (75 years), presence of CAD and low haematocrit i.e. < 30% (Conte et al. 2006). According to this classification, high-risk patients have extremely poor amputation free survival after open bypass surgery and therefore surgery is contraindicated (Schanzer et al. 2008, Schanzer et al. 2009).

The existing randomized trials have not provided uniform consensus on whether a surgical or an endovascular revascularization strategy should be undertaken as a first line of treatment for CLTI (van der Zaag et al. 2004, Adam et al. 2005, Kedora et al. 2007, McQuade et al. 2009, Bradbury et al. 2010). Moreover, the treatment protocols and guidelines are largely based on RCTs that are over 10 years old.

Patients with CLTI often have multi-segment disease: usually femoro-popliteal disease combined with aorto-iliac disease or tibial disease. Up to 40% of CLTI patients that have femoro-popliteal disease also need inflow treatment in the aorto-iliac segment (Zeller et al. 2014). Tibial occlusive disease in CLTI is often associated with end-stage renal disease and diabetes making patients with CLTI often medium to high risk patients according to the PREVENT III trial (Conte et al. 2006).

Current literature indicate it is not easy to defend an endovascular-first or bypass-first approach treatment of tibial disease in CLTI. The 2017 ESC/ESVS guidelines state that a bypass surgery with GSV is indicated for limb salvage and that endovascular therapy should also be considered (Aboyans et al. 2018, Conte et al. 2019).

The Best Endovascular Versus Best Surgical Therapy for Patients with Critical Limb Ischemia (BEST-CLI) study is a RCT designed to compare treatment efficacy, quality of life and cost accrued to patients undergoing an endovascular or surgical revascularization (Menard et al. 2016). BEST-CLI aims to answer the question whether an endovascular-first or surgical-first approach should be taken.

2.3.5 Postoperative antithrombotic therapy

The TASC II guidelines state that patient should be started on antiplatelet therapy preoperatively and this should be continued indefinitely as a secondary prevention of thrombosis (Norgren et al. 2007). The more recent Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial suggested that all patients should be treated indefinitely with a combination of rivaroxaban and acetylsalicylic acid (ASA) (Eikelboom et al. 2017).

The Rivaroxaban in Peripheral Artery Disease after Revascularization -trial (Voyager PAD) was published in May 2020. It investigated adverse cardiovascular and limb events after revascularization procedures for LEAD in patients with ASA alone versus ASA in combination with rivaroxaban. Patients that had a combination of rivaroxaban and ASA had significantly (hazard ratio 0.85, 95% CI 0.76-0.96, P=0.009) lower number of cardiovascular and limb adverse events than those patients who received ASA alone (Bonaca et al. 2020).

The risk for non-fatal myocardial infarction, ischemic stroke or cardiovascular death after revascularization procedures for LEAD is as high as 34% for CLTI patients 36 months post-operatively (Sigvant et al. 2016). The risk of acute limb ischemia (ALI) is also increased after infrainguinal revascularization procedures, compared to patients with stable LEAD. These risks are further elevated with redo-revascularization procedures (Sigvant et al. 2016). This highlights the importance of secondary prevention, including appropriate antithrombotic therapy (Gent et al. 1996, Bhatt et al. 2006, Eikelboom et al. 2017, Bonaca et al. 2020).

2.4 Wound healing

2.4.1 Skin anatomy and physiology

Human skin is the largest organ in the body. It has several important functions such as thermoregulation, sensory-, metabolic- and immune functions it also acts as a dynamic barrier for the underlying organs. The skin is composed of two layers: epidermis and dermis, which are separated by a basement membrane. Beneath these two skin layers is the subcutaneous tissue. The anatomy of the normal skin is illustrated in Figure 7. (Bryant et al. 2016).

The outer-most layer of the epidermis is composed of dead keratinocytes and is avascular. The epidermis is composed of keratinocytes, which mature in the deep layers of the epidermis and migrate outwards. The dermis underlies the epidermis and it is made from dense collagenous tissue. The dermis provides the blood, nerve and lymphatic supply to the skin. It has a complex vascular network of arterioles and venules, which are responsible for the thermoregulation of the skin by vasoconstriction of vasodilatation. The bulk of the subcutaneous tissue is subcutaneous fat. It has fibrous septae through which the vessels, lymphatics and nerves pass to and from the skin (Bryant et al. 2016).

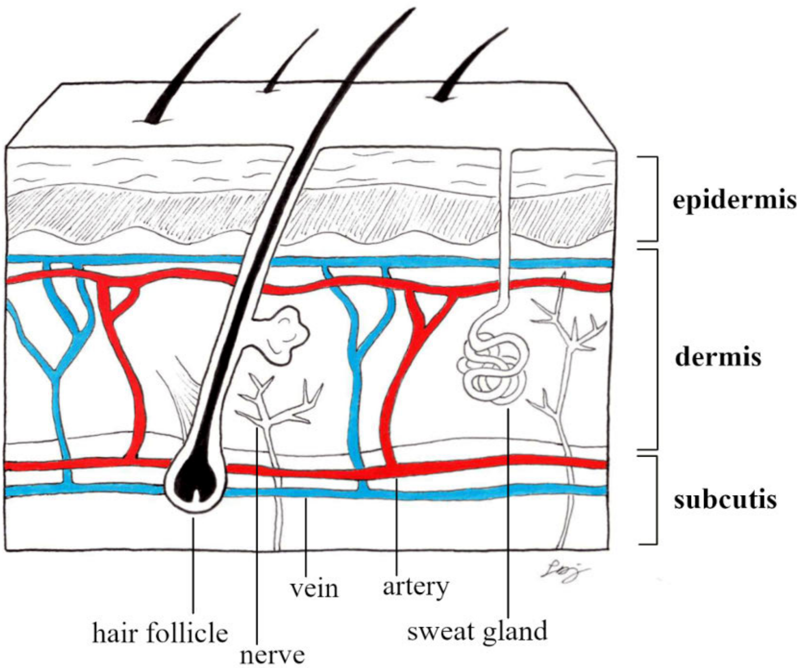

Figure 7. The anatomy of the normal skin. (Copyright Saara Nikulainen).

2.4.2 Wound healing physiology

Skin wound healing is a complex process that requires optimal circumstances to occur. The normal physiology of wound healing can be divided into three phases: 1. haemostasis and inflammation, 2. proliferation and 3. maturation and remodelling (Schilling 1976).

The normal function of haemostasis and inflammation in an acute wound is to prepare the wound bed for healing and removal of all necrotic tissue, the process is normally not active for more than 72 hours. The proliferation phase consists of repairing the wound site by restoring different parts of the skin that have been damaged i.e. the epidermis, dermis and other structures (such as glands). During the remodelling and maturation phase the extra-cellular matrix, epidermal thickness and cellular content will normalize (Bryant et al. 2016).

2.4.3 Pathologic wound healing

Non-healing, chronic wounds are a significant problem, that are a major burden to, and incur additional costs for the healthcare system. The increasing prevalence of diabetes and LEAD combined with the aging population is expected to increase the number of patients with non-healing chronic wounds in the future (Gottrup 2008, Markakis et al. 2016).

The whole process of wound healing requires sufficient blood and nutrient supply. In order for a wound to heal properly, the transition from the inflammatory phase to the proliferation phase must occur rapidly (Strecker-McGraw et al. 2007).

In chronic wounds this process is disturbed, and the inflammation phase is prolonged. The inflammatory process is upregulated, and neutrophils are present throughout the healing process. The persistent recruitment of neutrophils can be due to ischemic-reperfusion injury, bacterial growth or tissue trauma (Menke et al. 2007). Tobacco smoke is also known to be harmful for wound healing, as it contains inter alia carbon monoxide, which causes hypoxia, and nicotine which causes vasoconstriction in the skin arterioles. Nicotine also has other biological effects that inhibit wound healing (Sorensen 2012).

2.4.3.1 Wound healing in CLTI

The aim of revascularization in CLTI is to provide sufficient perfusion for the ischemic ulcers to heal or for rest pain to subside. Often this involves a bypass procedure that predisposes the initially ischemic tissue to major surgical trauma. These surgical incisions may take as long a time to heal post-operatively as the initial ischemic ulcers (Chung et al. 2006).

In CLTI the macrovascular arterial disease has several consequences for the microcirculation of the skin and skeletal muscles. The primary compensatory mechanism for ischemia is vasodilatation of the arterioles, which leads to a reduction in the peripheral vascular resistance (Coats and Hillier 2000). The chronic vasodilator stimuli lead to arteriolar dysfunction due to chronic exposure to vasorelaxant factors. This leads to the paradoxical finding of oedema in the ischemic limb, despite persistent hypo pressure and hypoperfusion. The oedema in CLTI further impairs the metabolic function by compressing the capillaries, which in turn impairs the diffusion of nutrients (McEwan and Ledingham 1971). In addition to the oedema CLTI is associated with haemostasis and micro thrombosis in the capillaries, this leads to endothelial dysfunction and increased vascular permeability (Maier and Bulger 1996).

Significant oedema occurs after the revascularization procedures when higher perfusion pressures are re-introduced in the limb. The oedema often complicates the healing process of the ischemic wounds in addition to the surgical incisions. Even after successful revascularization surgery the surgical incision can take considerable time to heal and wound dehiscence is reported in up to 20% of cases (Chung et al. 2006, Eid et al. 2014, Santo et al. 2014, Santo et al. 2014, Teixeira et al. 2015). The status of the microcirculation in the ischemic foot is proposed to be a key factor in the healing of wounds after successful revascularization especially for diabetic patients (Akbari and LoGerfo 1999, Rother et al. 2017).

2.5 Surgical site infection after peripheral vascular surgery

2.5.1 Incidence of SSI in vascular surgery

The majority of vascular surgery procedures are considered clean surgery (Bandyk 2008). According to the National Nosocomial Infection Surveillance (NNIS) the rate of SSI after clean surgery is approximately 2.1% (Culver et al. 1991).

Reported rates of SSIs after vascular surgery differ according to procedure types, carotid surgery is reported to have the lowest rate of SSI between 0.2-0.5%, whereas lower limb revascularization the highest between 3.5-32.0% (Knight and Tait 2009, Turtiainen et al. 2010, Turtiainen et al. 2012). The incidence of SSI is especially high in the inguinal area for the commonly used groin incision that is required for femoral artery exposure. The reported infection rates in the inguinal wound are from 5% up to 27%. This is considerably higher than in other clean surgery (Derksen et al. 2009, Turtiainen et al. 2010).

2.5.2 Classification of SSI in vascular surgery

The Centre for Disease Control and Prevention (CDC) infection grading differentiates between superficial and deep infections without putting emphasis on the vascular graft involvement (Horan et al. 2008). Vascular SSIs are traditionally graded using the Szilagyi or Samson grading system (Szilagyi et al. 1972, Samson et al. 1988). According to the Szilagyi grading system, grade I is a superficial infection of the skin, grade II an infection involving the subcutaneous tissues and grade III an infection involving the vascular graft. The extent of the graft infection can be graded using the Bunt grading system (Bunt 1983).

Most reported infections associated with peripheral vascular procedures are superficial and the percentage incidence of deep infections in considerably lower, between 0% and 3.1% (LaMuraglia et al. 1989, Kimmel et al. 1994, Piano 1995, Giacometti et al. 2002). Gram positive bacteria (*Enterococci, Staphylococcus aureus* and coagulase negative *Staphylococcus*) are responsible for 58% of vascular SSIs and graft infections, whereas Gram negative bacteria account for 34% and anaerobes for 8% (Chakfe et al. 2020). These bacteria colonize normal skin, but when they invade the tissues, they can cause infections (Homer-Vanniasinkam 2007).

2.5.3 Risk factors for SSI after vascular surgery

The high infection rates are both patient and procedure related. The patient-related risks for SSI are the multiple co-morbidities associated with LEAD patients, which are reported as follows: CLTI (OR 4.1), obesity (OR 2.1), COPD and renal failure (Greenblatt et al. 2011, Ott et al. 2013).

The procedure-related risks include long operating time, site of the surgical incision, blood loss, hypothermia, retractor related trauma to the wound edges and breaks in sterility (Greenblatt et al. 2011, Tan et al. 2013). Redo-surgery or previous angiography procedure with a puncture to the inguinal area in addition to wound drainage are also procedure-risk factors for developing SSI (Derksen et al. 2009, Turtiainen et al. 2010, Ott et al. 2013).

2.5.4 Prevention of SSI in vascular surgery

Numerous studies have been carried out to investigate the best infection prevention schemes. Stewart el al. conducted a meta-analysis to determine the effectiveness of perioperative strategies in infection prevention. They reviewed 34 RCTs, of these, 22 were trials on the prophylactic systemic antibiotics, 3 rifampicin-bonded grafts, 3 preoperative skin antisepsis, 2 suction wound drainage, 2 of minimally invasive in situ bypass techniques and the remaining 2 individual trials on intraoperative glove change and wound closure technique. Using ORs with 95% Confidence Intervals (CI) they concluded that systemic prophylactic antibiotics reduced the risk for wound infection (OR 0.25, 95% CI 0.17-0.38) and early graft infection (OR 0.31 95% CI 0.11-0.85, P=0.02) but no significant reduction for other infection prevention methods was discovered (Stewart et al. 2007).

Meticulous surgical technique and haemostasis of the operated area with preferably a two-team approach in order to reduce the operating time is a feasible option for the prevention of SSI (Chang et al. 2003, Greenblatt et al. 2011). The groin incision for femoral artery exposure can be done either horizontally crossing through the lymphatic tissues or vertically sparing the lymphatics.

Incisional negative pressure wound therapy (NPWT) is a newer approach in the prevention of surgical site complications. It is hypothesised that negative pressure aids the wound healing by reducing haematoma and seroma formation by fluid removal across the wound edges (Kilpadi and Cunningham 2011). In a recent RCT, a significantly lower number of SSIs and other wound complications in the inguinal wound were detected 90 days post-operatively when NPWT was used (Hasselmann et al. 2020).

2.5.5 Impact of SSI on outcome

SSIs cause major morbidity and mortality after revascularization procedures. Fortunately, most are superficial (Szilagyi I) and heal with an appropriate antibiotic therapy (Turtiainen et al. 2010). The deeper infections and especially infections that involve the vascular graft increase the risk of graft failure (Giles et al. 2010) amputation (Nguyen et al. 2007) and 30-day mortality (Greenblatt et al. 2011).

It is reported that SSIs lengthen the hospital stay between 2-14 days (Giles et al. 2010) and a Finnish study estimated that the cost of a single SSI after vascular surgery is 3320€, this amount does not include the cost of the antibiotic treatment (Turtiainen et al. 2010).

2.6 Major lower extremity amputations

Major LEA refer to above-the-knee (AKA) i.e. transfemoral amputations and below-the-knee (BKA) i.e. transtibial amputations and, in rare cases, hip joint disarticulation procedures. In contrast minor amputation refer to amputations of the foot and toes.

Major LEA continue to be a part of treatment in vascular surgical patients despite the advancements in revascularization procedures. The Finnvasc registry data from Finland of the early to mid-nineties (1991–1995) reported the rate of major LEA to be 22/100,000 for the whole population (Luther et al. 2000). Another Finnish study from the city of Turku that covered the period between 1998-2002 reported the incidence of major LEA 24.1/100,000 (Remes et al. 2008).

The prevalence of major LEAs in the U.S. between 2007 and 2009 was 89/100,000 for Medicare patients > 65 years old (Goodney et al. 2013). In a more recent Danish study of data obtained from 2002 to 2014, this number varied between 70/100,000 and 130/100,000 patients > 50 years old (Londero et al. 2019).

It has been reported that up to 90% of all LEAs are related to diabetes and that patients with diabetes have a 10-fold increase in the risk of amputation compared to those without (De Frang et al. 1991). Advanced diabetes predisposes patients to infections, neuropathy and especially tibial LEAD (Diehm et al. 2006). Despite the increased prevalence of diabetes, an overall decrease in the number of major LEAs has been reported (Goodney et al. 2009). In Finland, the annual number of major LEAs in diabetic patients decreased from 477 to 424 between 1997 and 2007 (Winell et al. 2013). The decreased number of major LEAs could be explained by the more effective treatment of patient comorbidities and podiatric care and also an increased number of revascularizations (Golomb et al. 2006, Hirsch et al. 2006, Goodney et al. 2013, Aboyans et al. 2018).

Significant differences in the numbers of major LEAs and vascular procedures have been reported across different regions and it has been suggested that increasing the number of vascular specialists in underserved areas may reduce these regional differences (Ho et al. 2005, Goodney et al. 2013). Numerous studies have found an inverse correlation between the numbers of bypass procedures, especially tibial bypass procedures and major LEAs (Luther et al. 2000, Eskelinen et al. 2004, Goodney et al. 2013).

The increased numbers of endovascular procedures have not had a significant effect on the number of major LEAs (Goodney et al. 2013). Aggressive revascularization attempts (especially endovascular revascularizations) have led to limb salvage attempts in higher risk patients. This has resulted in data that show a lower number of primary amputations, although the number of secondary amputations has correspondingly increased (Khan et al. 2009).

2.6.1 Preservation of functional status

The aim of revascularization in CLTI is to prevent amputation and preserve the patient's functional status in order to facilitate independent living (Taylor et al. 2006). The most important decision in treating CLTI is whether to attempt limb salvage or proceed with a primary amputation.

An amputation shouldn't always be considered a failure of therapy, but an important treatment option. This has been demonstrated in a study of patients under 60 years of age for whom functional outcomes of BKAs were similar to those patients undergoing successful revascularization (Taylor et al. 2005).

Despite good results with revascularization, there are groups of patients that are best served by a primary amputation. The current guidelines state that advanced diabetes, end-stage renal disease, tissue loss and poor functional status have been considered predictors of treatment with amputation, rather than revascularization (Aboyans et al. 2018).

The indications for major amputations can be divided into acute ischemia, chronic ischemia and severe foot infection. The goal of an amputation is to remove all ischemic and infected tissue and leave the patient with the longest functional limb possible. When evaluating the level of the LEA, the vascular surgeon must consider the elimination of all necrotic and ischemic tissue and achieve uncomplicated wound healing while trying to leave an appropriate remnant stump to accommodate a possible prosthesis (Aboyans et al. 2018).

The ambulation rate after AKA is significantly lower than for BKA. Prosthetic use after major LEA is reported 50-100% after BKA but only 10-30% after AKA (Toursarkissian et al. 2002, Nehler et al. 2003). These studies included all major LEA patients, not only LEAD patients. A too optimistic BKA is revised to an AKA in 15-25% of patients and the revision procedures are associated with a mortality rate greater than 5% (De Frang et al. 1991, Abou-Zamzam et al. 2003, Nehler et al. 2003).

Apart from the remediation of ischemia and infection, the objective of a BKA is that patients can ambulate with prosthetics. Taylor et al. documented that patients over the age 70 had a threefold chance of not using a prosthetic and a 3.1-fold chance of death, 2.3-fold chance of being non-ambulatory and a 4-fold chance of losing independent functional status compared to patients younger than 50 years. According to this same study, patients over 70 years old with multiple comorbidities, and poor functional status should be offered an AKA as a definitive treatment (Taylor et al. 2005).

3 Aims

The main purpose of the present study was to assess clinical perspectives involved in the treatment of patients presenting with LEAD.

The specific aims were:

1. To assess the national trends in different types of revascularization procedures and analyse their effect on the prevalence of major amputations in the aging population in Finland (I)
2. To determine the risk factors for delayed vein harvest wound healing after infrainguinal bypass surgery for CLTI (II)
3. To evaluate whether the number of SSIs can be reduced in the inguinal incisions with an intradermal wound closure method in comparison to the more commonly used metal stapleskin closure. (III)

4 Materials and Methods

The data in the original publications described in this thesis were obtained from three different patient cohorts which are summarized in Table 3. One nationwide patient cohort obtained from The Finnish National Institute for Health and Welfare (THL). In addition, two different retrospective patient cohorts comprised patients operated in Turku University Hospital (TUH) Vascular Surgery Department. Approvals for these studies were obtained from the Ethics committee of the Hospital District of South-west Finland.

Table 3. Summary of patient cohorts and study methodology described in original publications included in this dissertation.

ORIGINAL PUBLICATION	COHORT	COHORT SIZE	STUDY METHODOLOGY
I	National THL registry cohort from all revascularizations and amputations in Finland between Jan 1st 2007 and December 31st 2017	69,523 revascularizations 11,851 major amputations	Evaluation of numbers and types of vascular procedures and their effect on major lower extremity amputations
II	A retrospective cohort of all patients that underwent an infrainguinal bypass operation in the TUH Vascular Surgery Department between Jan 1st 2015 and Dec 31st 2017	195 patients	Evaluation of the vein harvest wound healing time after revascularization surgery. Evaluation of risk factors that affect vein harvest wound healing.
III	Retrospective cohort of all vascular surgery patients operated in the TUH Vascular Surgery Department that had an isolated inguinal surgical incision between Jan 1st 2015 and Dec 31st 2016.	256 patients on whom 330 inguinal incisions were performed	Retrospective analysis of SSIs in the inguinal incision after vascular surgery

4.1 Patients

4.1.1 Nationwide Vascular Procedure Cohort I

The Finnish National Institute for Health and Welfare (THL) is a state funded organization that operates under the auspices of the Social Affairs and Health political ministry. THL holds a database on all treatment periods and procedures conducted by official healthcare providers in Finland, both public and private. All data are coded according to the ICD-10 system.

A data search for all revascularizations and amputations between January 1st 2007 and December 31st 2017 listed in the THL registry was conducted, the search was executed according to operation codes (operation codes were: PDH, PEE, PEF, PEN, PEH, PFA, PFN, PFH, PD3AT, PD3BT, PD3YT, PE1AT, PE1BT, PE1YT, PF1AT, PF1BT and PF1YT, NFQ20, NGQ20). A total of 69,523 revascularizations and 11,851 major LEAs were included in the cohort.

Statistics Finland is a public Finnish organization established as repository to provide statistics. Statistics Finland provides an online database (StatFin). The SatFin database was utilized in this cohort to determine the age and gender distribution in the Finnish population between January 1st, 2007 and December 31st, 2017.

4.1.2 Turku University Hospital Bypass Cohort II

All consecutive patients between January 1st, 2015 and December 31st, 2017 that underwent an infrainguinal bypass procedure with autologous vein for CLTI in the Vascular Surgery Department of TUH were retrospectively included in this cohort. A total of 195 patients were included.

4.1.3 Turku University Hospital Groin Incision Cohort III

Consecutive patients that underwent a vascular surgery operation including an isolated groin incision during a two-year time period between January 1st, 2015 and December 31st, 2016 in the Vascular Surgery Department of TUH were retrospectively included in this cohort. A total of 256 patients comprised the cohort and a total of 330 isolated groin incisions were performed for these patients. The patients of this cohort had undergone the following operations: femoral endarterectomies, embolectomies and femoral access procedures for endovascular aneurysm repair (EVAR) in addition to femoro-femoral bypass procedures and femoropopliteal bypass procedures with prosthetic graft. The exclusion criteria were that the groin incision was a part of a larger wound as in bypass procedures using the autologous converted GSV.

4.2 Data Collection

4.2.1 Nationwide Vascular Procedure Cohort I

The THL database was searched for revascularization procedures and amputation that took place over an 11-year period between January 1st, 2007 and December 31st, 2017. The open and endovascular revascularization procedures were categorized according to the vascular segment into iliac (PDH, PD3AT, PD3BT, PD3YT), femoropopliteal (PEE, PEF, PEN, PEH, PE1AT, PE1BT, PE1YT) and tibial procedures (PFA, PFN, PFH, PF1AT, PF1BT, PF1YT). The amputations included in the data were major amputations and they were divided into AKA (NFQ20) and BKA (NGQ20). Patients were divided into four cohorts according to age at the time of the index procedure (< 65y, 65–74y, 75-84y and > 85y).

The StatFin database was utilized for background data in study III with regard to the gender and end age distribution of the Finnish population between 2007 and 2017. The database was searched in order to assess the growth and age distribution of the Finnish population.

4.2.2 Turku University Hospital Bypass Cohorts II and III

The data of the TUH cohorts were collected retrospectively by using the operation monitoring system Opera™ , General Electric (GE) Medical and the patient record system Uranus™ CGI. In study III a part of the information was collected prospectively for quality control purposes. Additional data from January 1st and March 31st, 2017 was collected and entered in the file retroactively.

Both patient related and operation related risk factors for (SSI were recorded as listed below: patient age, gender, body mass index (BMI), presence of LEAD, CLTI, diagnosis of hypertension, diabetes mellitus or rheumatoid disease and smoking). Indication and urgency of the operation, vein harvest site, inflow and outflow vessels according to the surgeon’s evaluation after the surgery and skin closure methods were recorded. LEAD was verified as ABI measurements below 0.9, CLTI was verified as STP measurements below 30 mmHg or 50 mmHg when the patient had an ischemic ulcer. In study II, the WIfI classification and Rutherford classification of the CLTI was evaluated retrospectively based on patient records.

The number of SSIs were recorded. SSI was defined as an infection occurring 30 days post-operatively, the CDC criteria for nosocomial infections was used (Yangco 1989). The severity of SSI was determined from the patient charts and classified according to the Szilagyi classification of vascular surgical site infections. The follow-up data for study II was collected until February 28, 2018.

4.3 Surgical protocol at Turku University Hospital (Study II and III)

All vascular surgery operations were performed in the Vascular Surgery Department of TUH for all the patients in studies II and III.

4.3.1 Pre-operative assessment

Routine planning before bypass included the following scanning modalities: CTA, MRA or DSA. In select cases only the choice of inflow and outflow vessels was based solely on DU. The appropriate revascularization in addition to inflow and outflow vessels were determined by the findings in these images. ABI and STP measurements were also routinely taken. Ultrasonography was routinely used for vein mapping preoperatively. The ipsilateral GSV was the first choice of vein graft, followed by contralateral GSV and finally composite vein / arm vein / small saphenous vein (SSV). A diameter of 3 mm was usually considered sufficient for the vein to be used as a bypass graft.

4.3.2 Peri-operative technique

The peri-operative skin preparation used in the TUH entailed hair removal from the operation area (if necessary) 2 hours prior to the operation. The surgeon marks the place of the incision. The area is disinfected using denatured 70% alcohol (either Dermades™ or Betadine™). The area is disinfected three times, starting from the middle and moving towards the edges of the operation area. If there is an infected area of skin on the operation area, it is first washed using Desinfektol H™ and normal saline.

Antibiotic prophylaxis was routinely given 30-60 minutes pre-operatively with an additional dose after three hours. Intravenous cefuroxime 1.5g or 3.0g was used as the primary prophylactic antibiotic. Alternatively, intravenous clindamycin 900 mg was used for patients with renal failure. World Health Organization (WHO) surgical safety checklist (Haynes et al. 2009) was routinely used in the operating theatre.

The bypass operative techniques in study II were chosen by the operating vascular surgeon. Bypass with converted autologous vein were favoured over nonconverted devalvulated vein. Veins were harvested from continuous incisions.

Subcutaneous tissues were routinely closed using running multifilament sutures (Vicryl™, Ethicon Inc.) and the skin was closed using metal staples

All groin wounds in study III were made vertically with the skin incision slightly lateral to the artery. The majority of EVAR patients in the study period were operated by open femoral artery cutdown. The skin incisions were closed according to the operating surgeons' preferences either with intradermal absorbable sutures, transdermal sutures or metal staples. The closure techniques for the subcutaneous tissues were not recorded.

4.3.3 Post-operative follow-up

On the basis of our graft surveillance program in the TUH routine outpatient follow-up visits after bypass surgery with autologous graft were conducted at 1, 3, 9 and 12 months after the bypass operation or latest graft intervention. The grafts were followed up with ultrasonography, which was performed by a sonographer. The femoral endarterectomies and bypass operations with prosthetic graft material are routinely followed up at the outpatient clinic 4–6 weeks post-operatively. The patients are encouraged to be in contact with the vascular unit, if infection in the operation wound occurred.

4.4 Outcome measures

Study I. The overall number of revascularization procedures and amputations performed in Finland was analysed in order to define the annual vascular workload. The growing number of vascular procedures were compared with annual numbers of major amputations in order to assess whether there has been a reduction in the rate of amputation procedures.

Study II. Vein harvest wound healing after infrainguinal bypass surgery for CLTI was evaluated. The vein harvest wound healing (VHW) time, defined as the complete epithelialization of the incisional wound. The effect of the patient's comorbidities and preoperative manifestation of the CLTI WIfI-classification (Mills et al. 2014) and Rutherford classification (Rutherford et al. 1997) on complete incisional wound healing time were used in the analysis of patients. Patients that died or had an amputation prior to incisional wound healing were considered never to have achieved wound healing.

Study III. The relationships of SSI and wound closure method and with patient co-morbidities were assessed. The SSIs were retrospectively identified from the patient record system data and were classified according to the Szilagyi classification system (Szilagyi et al. 1972). An infection was considered an SSI when it occurred within 30 days of the index operation.

4.5 Statistical methods

In study I, the patients were divided into four cohorts of: < 65y, 65–74y, 75–84y and > 85y. The rates of vascular procedures and amputations in each age group where calculated using the number of revascularizations as the numerator and the number of inhabitants in Finland in that same age group as the denominator. The rates where expressed as the number of vascular procedures or amputations per 100,000 inhabitants of the defined age group. The association between patient counts and time was studied using regression analysis. The normality assumption was checked using standardized residuals

For study II, the survival analyses were assessed by constructing Kaplan-Meier curves. In order to assess the predictive value of factors affecting survival, univariate Cox regression analysis was performed for continuous variables.

For study III, a multivariable logistic regression model where the subject was taken into account (GEE-model) was used to analyse the data. The following variables were included in the final model: skin closure technique, diabetes mellitus, critical limb ischemia, gender, age and BMI.

The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 25 (IBM SPSS Statistics for Windows, IBM Corporation, Armonk, NY).

Categorical variables were expressed using frequency and percentage. Associations between categorical variables were analysed using the Chi-Square test or the Fisher's Exact test when appropriate (II, III). The normality of distributions was established with the Shapiro-Wilk test. Continuous variables were expressed as median or mean ± standard deviation. Continuous variables were compared using independent sample T-tests as variables were distributed normally in each group.

Statistically significant differences were assumed for p-values < 0.05. For multivariable analyses in study III, risk factors with $P < 0.2$ in univariate analysis were forced into a Cox proportional hazard model. Multivariable analysis was carried out to assess the risk for delayed wound healing.

5 Results

5.1 National numbers in revascularization procedures and amputations (I)

The population growth in Finland data were obtained from the Statfin database. In 2007 the population of Finland was 5,300,484, this had increased to 5,513,130 in 2017.

During the study period from 2007 to 2017, a total of 69,523 revascularizations were performed in Finland. The annual number of procedures increased from 3496 in 2007 to 9506 in 2017. The annual numbers of vascular procedures were expressed as rates per 100,000 inhabitants, these rates were 66/100,000 in 20017 and 172/100,000 in 2017 (P<0.01). There was a significant annual increase in this rate of 10 procedures per year (95% CI 8.6–12.3, P<0.01). These rates were further analyzed for different age cohorts and the most significant increase was in the oldest population cohort (patients over 85 years old), in which approximately a 2.5-fold increase was detected. (Figure 8)

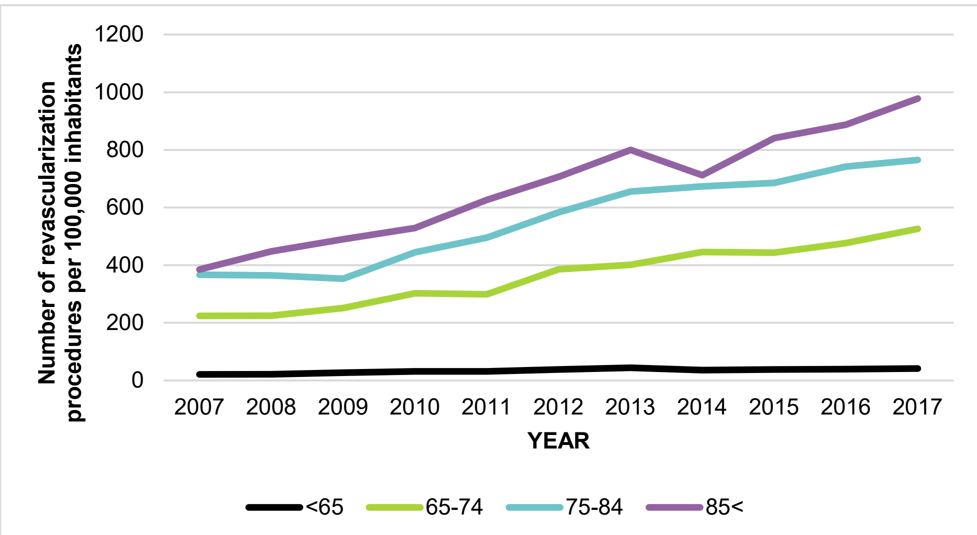

Figure 8. The numbers of revascularization procedures per 100,000 inhabitants in different age groups between 2007 and 2017. Modified from (Nikulainen et al. 2019)

5.1.1 Revascularization procedures

The total number of open revascularizations was 2705 in 2007, and this increased to 3992 operations in 2017. An annual increase of 141 operations (95% CI 110–174, P<0.01) between 2007 and 2017 was recorded, this increase was most evident in younger patients (<65 years), followed by the 65–74-year-old patients (Figure 9a).

Among revascularization procedures, the most considerable increase was seen when the endovascular procedures in 2007 were compared with those in 2017, the total number of endovascular procedures in 2007 was 791 and in 2017 this had increased to 5514 procedures. A mean annual increase of 491 (95% CI 433–550, P<0.01) procedures between 2007 and 2017 was recorded (Figure 9a). The proportion of endovascular revascularization procedures increased from 22.6% in 2007 to 60.5% in 2017. The endovascular procedures were further analysed in order to investigate the use of primary stenting versus PTA in different arterial segments. Primary stenting procedures increased from 0 in 2007 to 1810 in 2017.

5.1.2 Revascularizations according to arterial segments

The procedure numbers in different arterial segments varied considerably during the study period. There was a considerable decrease in the rate of open aorto-iliac bypass procedures giving an annual decrease of 11 per year, (95% CI -14 to -7, P<0.01) and also a decrease in the rate of extra-anatomic bypass procedures giving an annual decrease of 8 per year, (95% CI -10 to -5, P<0.01). The rate of endovascular procedures in the same aorto-iliac arterial segment showed a substantial annual increase of 154 procedures (95% CI 129–178, P<0.01). In 2007, the number of primary stenting procedures was close to zero, but by the end of the 11-year study period stenting had become the first line of endovascular treatment. In 2017, 62.7% of iliac artery lesions were treated with primary stenting (Figure 9b.).

When the femoro-popliteal arterial segment was analysed, the annual rate of endarterectomies grew by an annual increase of 168 per year, (95% CI 139–195, P<0.01), whereas the annual rate of femoro-popliteal bypass procedures remained almost unchanged at a negligible annual decrease of 3 per year (95% CI -10 to 5, P=0.39). The overall number of femoro-popliteal open revascularization increased. Again, the annual rate of endovascular revascularization procedures in the femoro-popliteal segment increased significantly by 229 procedures (95% CI 195–260, P<0.01). Primary stenting in the femoro-popliteal segment had also increased. For example, during 2017 as many as 777 (29.9%) femoropopliteal lesions were treated with primary stenting (Figure 9c).

The annual rate of tibial bypass procedures remained relatively unchanged during the study period, although a slight decrease was detected giving an annual decrease of 4 per year, (95% CI -8 to 0. P=0.03). The annual rate of endovascular procedures in the tibial segment increased at 113 procedures (95% CI 94–131, P<0.01), but the increase was not as marked as in the other arterial segments. PTA without stenting is still the first line of treatment in the tibial segment (Figure 9d).

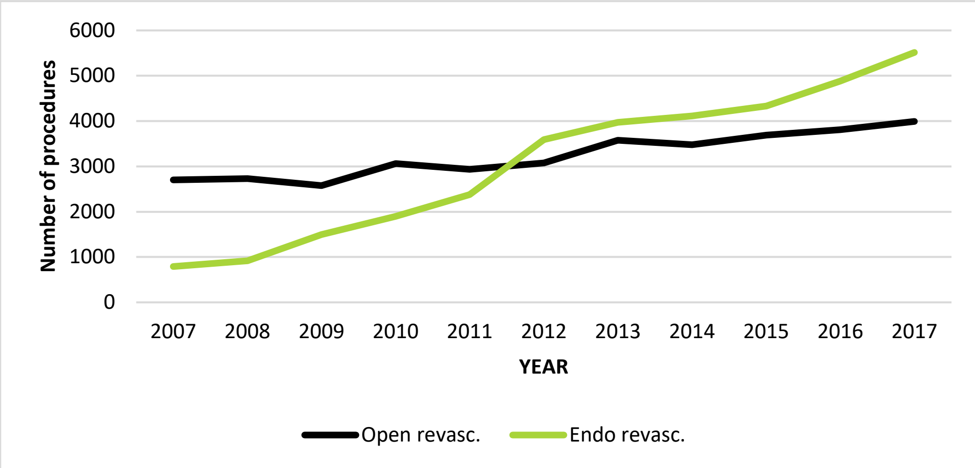

Figure 9a. The annual numbers of open- and endovascular revascularization from 2007 to 2017. Modified from (Nikulainen et al. 2019).

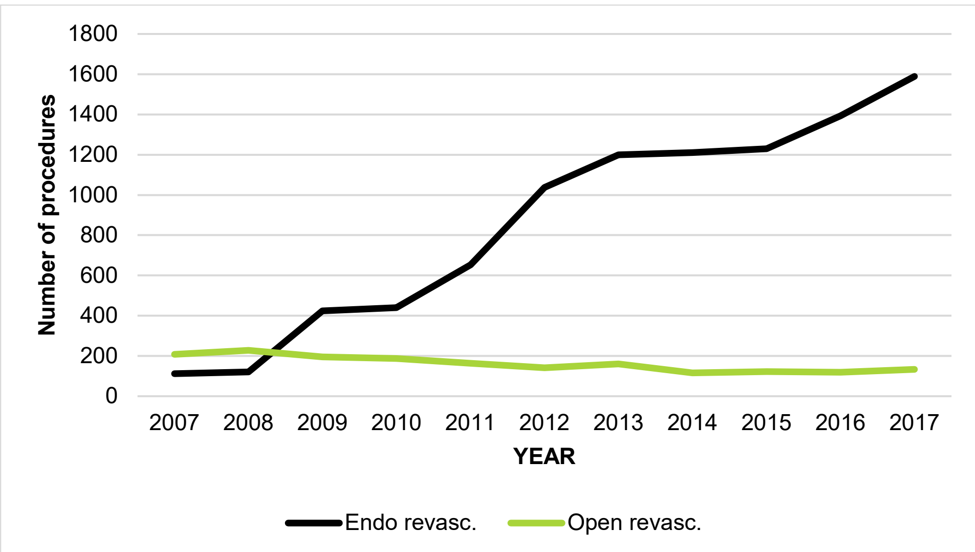

Figure 9b. The annual numbers of aorto-iliac open and endovascular revascularization procedures from 2007 to 2017. Modified from (Nikulainen et al. 2019).

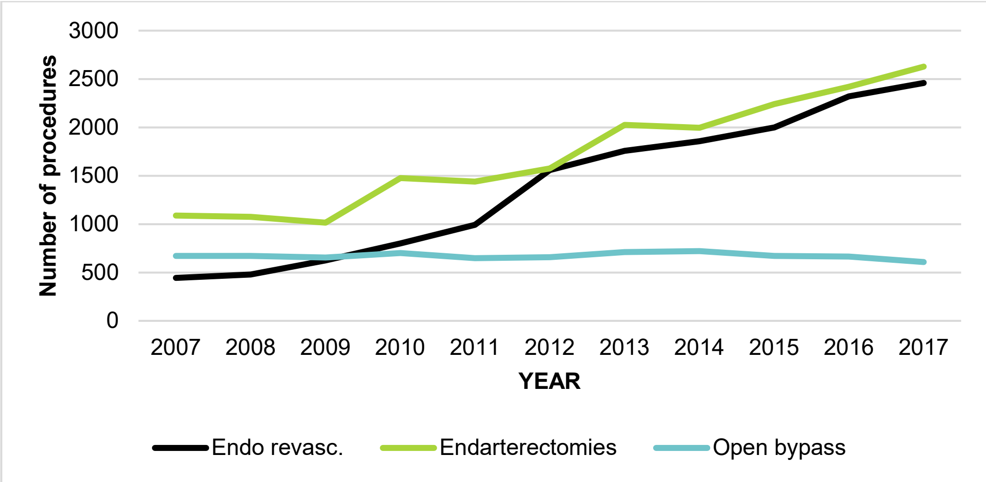

Figure 9c. The annual numbers of open and endovascular femoro-popliteal revascularization procedures from 2007 to 2017. Modified from (Nikulainen et al. 2019).

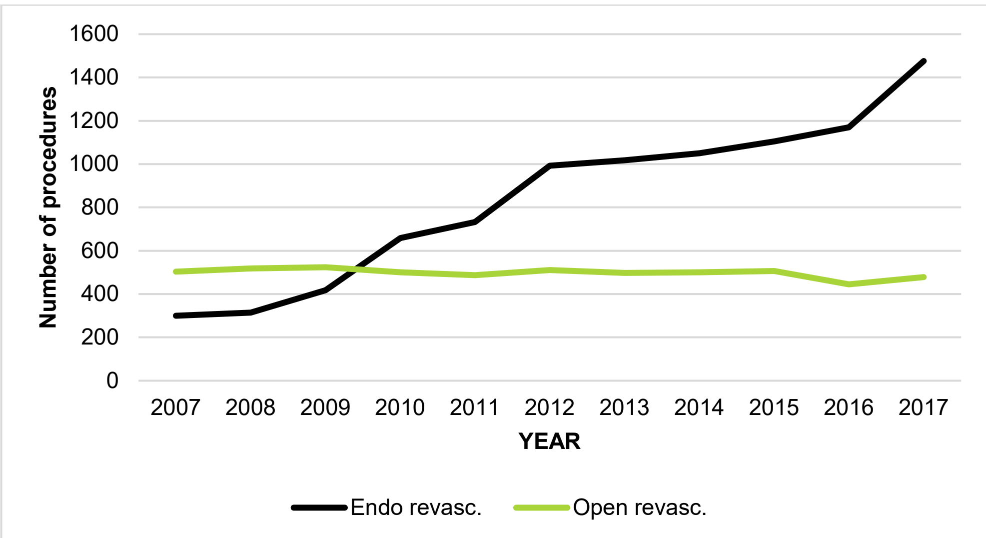

Figure 9d. Numbers of open and endovascular tibial revascularization procedures from 2007 to 2017. Modified from (Nikulainen et al. 2019).

The increase in the number of procedures is most dramatic for the endovascular group.

5.1.3 Major LEAs

During the 11-year study period 11,851 major LEAs were performed in Finland. The mean annual rate of major LEA in the whole Finnish population varied slightly by 18–20/100,000 during 2007–2017. The mean rate of amputations was 42 in 65–74 year-old patients, 103 in 75–84 year-old patients and 233 in >85 year-old patients. When these three population cohorts (65-74, 75-84 and 85< cohorts) were pooled together, the rate on amputations decreased from 93 to 72 during the 2007–2017 period (P<0.03). The reduction in the rate was most evident in the oldest age group (> 85 years): 262 in 2007, which decreased to 185 in 2017.

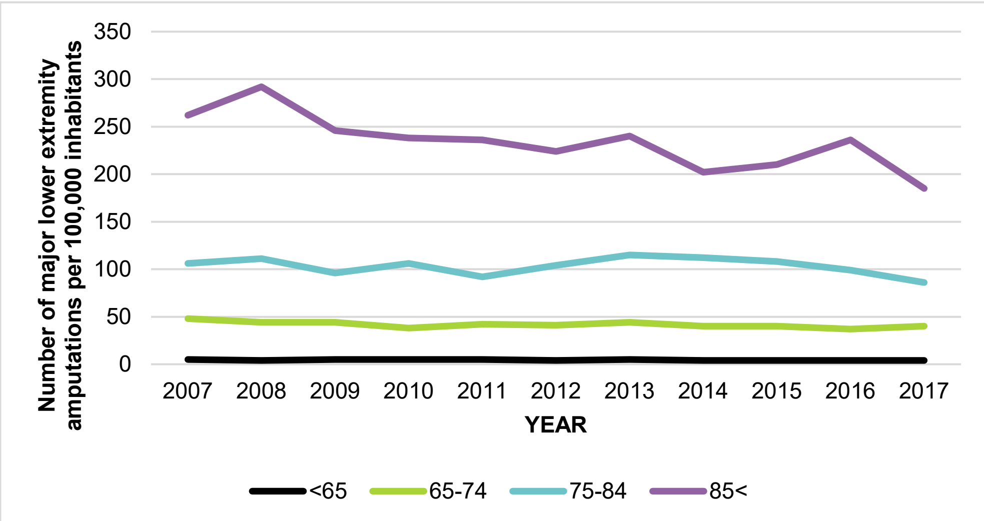

Figure 10. The annual numbers of major lower extremity amputations per 100,000 inhabitants in different age groups between 2007 and 2017. Modified form (Nikulainen et al. 2019).

5.2 Bypass incision healing (II)

In total 195 patients were operated on for CLTI during the study period. Of those patients 133 (68.2%) had ischemic ulcers (Rutherford Grade 5 and 6) prior to operation. CLTI presented as ischemic rest pain and STP < 30 mmHg (Rutherford Grade 4) for the remaining 65 patients (33.3%). The most commonly used graft was the ipsilateral GSV (160 patients, 82.0%), followed by the contralateral GSV (18 patients, 9.2%), the in-situ GSV (5 patients, 2.6%) and the composite vein graft (12 patients, 6.2%). Fasciotomies were performed during the primary procedure for 35 patients (17.9%).

The mean follow-up time was 535.0 days (Range 3.0–1143.0 days). The mean ABI pre-operatively was 0.4 (Standard Deviation (SD) 0.27) and post operatively

0.89 (SD 0.31). The mean STP pre-operatively was 24.2 mmHg (SD 20.5) and post-operatively 64.1 mmHg (SD 26.6). The mean ABI improvement was 0.49 (P=0.04) and STP improvement 39.9 mmHg (P=0.01) after revascularization. During follow-up 21 (10.7%) underwent a major amputation.

The median time it took for the vein harvest wound (VHW) to completely heal was 65.0 days (95% CI, 41.2-88.8). The VHW had healed by the first post-operative follow-up visit at 1 month after the operation for 40 patients (20.5%). VHW healing was complete for 132 (67.7%) patients, 183 (93.8%) patients, and 189 (96.9%) patients by the 3-month, 9-month, and 12-month follow-up visits, respectively. The VHW failed to heal in 6 patients (3.1%) during the one-year follow-up time

Table 4. Median vein harvest wound healing times after infrainguinal revascularization surgery for CLTI. Modified from (Nikulainen et al. 2020).

		N	MEDIAN HEALING TIME IN DAYS	95% CI	P-VALUE
RUTHERFORD CATEGORY	Rutherford 5 and 6	130	82	60.1–103.9	0.03*
	Rutherford 4	65	48	40.3–55.7	
CAD	Yes	70	68	37.1–96.9	0.06*
	No	125	65	34.1–95.9	
DIABETES	Yes	87	65	36.6–90.4	0.80*
	No	108	69	39.4–98.5	
HYPERTENSION	Yes	152	69	45.8–92.2	0.37*
	No	43	49	20.1–104.9	
RHEUMATOID DISEASE	Yes	25	49	39.7–58.3	0.87*
	No	170	68	44.1–91.9	
RENAL DYSFUNCTION	Yes	176	129	36.6–221.4	0.87*
	No	19	56	35.2–76.8	
URGENT PROCEDURE	Yes	62	82	26.9–137.1	0.20*
	No	133	65	38.9–91.1	
BYPASS TARGET*	Popliteal	62	62	22.9–93.0	0.02**
	Tibial	132	132	48.0–98.0	
ALL PATIENTS					

CAD = coronary artery disease
95% CI = 95% confidence interval
*P-Value calculated using Log-Rank test
** P-Value value calculated using the Student's T-test
*** Popliteal vs. Tibial artery bypass procedure

The VHW healing was significantly slower in patients with Rutherford 5 and 6 lesions (82.0 days, 95% CI, 60.1–103.9) compared to those with Rutherford 4 ischemic rest pain 40.8 days, (95% CI, 40.3–55.7, P=0.04) (Table 4). Significant improvement in both ABI and STP were recorded after revascularization surgery, this however did not correlate with the time of VHW healing

5.3 Groin incision healing (III)

A total of 330 groin incisions were performed on 256 patients, and the groin incisions were bilateral for 74 of these patients. The most common indication for the operations were arterial aneurysms treated by EVAR procedures (152 wounds, 46.1%); followed by peripheral arterial disease femoral endarterectomies and bypass operations (144 wounds, 43.6%). The rest of the operations were for arterial embolus (34 wounds, 10.3%). In most of the cases where the indication was arterial aneurysm, the incisions were bilateral. Moreover, 76 incisions were performed in an urgent operation setting.

The majority of the incisions were closed using intradermal absorbable sutures (262 wounds, 79.6%). Transdermal sutures were used in 68 incisions (20.4%). Incisions in hybrid and EVAR procedures were more often closed using intra-dermal sutures (90.5%) and urgent operation incisions were usually closed using transdermal sutures (60.5%).

The peri-operative death rate was 3.9% (9 patients). All cases of peri-operative death were due to cardiovascular causes.

A total of 41 (12.4%) SSIs were detected in the study period. Of these infections, 16 (39.0%) were in urgent operations. There were 24 (9.2%) infections in the group in which the incision was closed using intradermal sutures and 17 (25.0%) infections in the transdermal incision closure group. Multivariable analysis revealed that incisions with transdermal closure were 3.5 times as likely to develop an SSI compared to intradermal closure OR 3.2 (CI 95% 1.6–7.6, P= 0.02) (Table 3.) There were 10 deep infections (Szilagyi II and III) in total. The following pathogens were detected in wound cultures taken from infected incisions: *Staphylococcuss aureus* (4 cases), *Escherichia coli* (2 cases), *Pseudomonas aeruginosa* (1 case*), Streptococcuss agalactie* (1 case). The rest were mixed infection with *Staphylococcus aureus, Escherichia coli and Enterococcus faecalis.*

Table 5. Results from a multivariable analysis evaluating different risk factors for the development of SSI (Nikulainen et al. 2019).

		OR	95% CI	P-VALUE
WOUND CLOSURE	Transdermal vs. Intradermal	3.48	1.6–7.60	0.002
AGE		0.95	0.91–1.00	0.034
BMI		1.01	0.94–1.09	0.740
SEX	Female vs. Male	1.08	0.50–2.33	0.840
DIABETES	Yes vs. No	0.56	0.23–1.39	0.214
CLTI	Yes vs. No	0.84	0.25–2.78	0.780

*A multivariate (GEE) model was used to analyze these data.
OR = Odds ratio
CI = 95% confidence interval.
CLTI= Chronic Limb Threatening Ischemia

6 Discussion

The original publications presented in this dissertation demonstrate a growing vascular workload placing an increasing burden on the national healthcare system. The Finnish population is aging consequently, a growing number of vascular procedures are being performed annually in order to prevent major LEAs. Revascularization operations are major surgery and recovery from it often complicated.

6.1 Nationwide trends in revascularization procedures and amputations

The present study demonstrated an increase in the rate of vascular procedures in the study period. The rate of vascular procedures increased from 66/100,000 inhabitants in 2007 to 172/100,000 inhabitants in 2017. This is mainly due to an increase in the number endovascular procedures and, to a lesser extent, an increase in the number of open surgical revascularizations. The increased number of procedures is most likely due to the aging population and that the prevalence of diabetes is increasing. The number of vascular specialists has also increased in Finland. Endovascular techniques have evolved significantly during the study period and more complex arterial lesions can be treated with endovascular procedures. Similar results have been observed in other countries as well (Goodney et al. 2009, Goodney et al. 2015). In the same study period, the rate of major LEA in the whole population remained relatively constant 18-20/100,000 inhabitants. However, a decrease in the rate of major LEAs in the older age groups (> 65 years) from 93/100,000 in 2007 to 72/100,000 in 2017 was detected. The effect on the oldest age group is, however, diluted by the size of the whole population.

The national vascular registry of vascular procedures in Finland data for the period 1991-1995 (Finnvasc) were collected. In this registry dataset the rate of major LEAs was 22/100,000 and the rate of vascular procedures was 20/100,000 (Luther et al. 2000). In our present study, the number of vascular procedures had increased significantly from this. The number major of LEAs in the whole population has remained relatively constant. Unfortunately, the Finnvasc investigators did not report age-standardized rates of amputations or vascular procedures.

When comparing the Finnvasc registry data to those of the present study, it should be kept in mind that the population in Finland has grown older and the percentage of > 65-year-old people has increased. This same aging trend is seen globally thus, the population is aging and the prevalence of LEAD is increasing due to the known increased prevalence found in older age groups. In high-income countries the life expectancy is close to 80 years, whereas in lower income countries increasing numbers of people reach the age of 55 when the risk for developing LEAD starts to increase (Fowkes et al. 2013). It was estimated in 2008 that over 200 million people worldwide have LEAD and up to 45 million of these patients will die from CAD or CVD within a 10-year period (Fowkes et al. 2008). In 2015, this number had risen to 236 million, of which 73% were in low income countries (Song et al. 2019).

Revascularization techniques have evolved significantly over the last three decades. Previously patients that were deemed too unfit for revascularization surgery were treated conservatively with appropriate medical therapy and pain medication or offered a primary amputation. Endovascular revascularization techniques in particular have evolved, and they can now be used to treat more complex arterial lesions in higher surgical-risk patients (Sachs et al. 2011, Goodney et al. 2015). On the other hand, patients with IC might more frequently be offered a minimally invasive endovascular procedure instead of conservative management and walking exercises (Keeling et al. 2006), which could explain the increase in these numbers in endovascular procedures. The Finnvasc registry data indicate that 32% of all revascularizations were endovascular and 68% open surgical (Salenius et al. 1993). The present study showed a very different distribution; 60.5% of all revascularizations in 2017 were endovascular and 39.5% open surgical. Using this comparison, the proportion of endovascular procedures of all vascular procedures has therefore doubled in over three decades.

The population is aging and the incidence of diabetes is increasing in high income countries, at the same time LEAD is affecting younger people and especially more women in low income countries (Song et al. 2019). New and less invasive endovascular treatment modalities are being developed constantly. When taking into consideration the changing population demographic and the development of new treatment modalities, it is not difficult to see why the numbers of revascularizations, both open and endovascular, are increasing. These increases cause a major burden on healthcare systems globally.

A clear inverse correlation between the increase of the number of infrapopliteal bypass procedures and major amputations has been reported, and so far, no inverse correlation has been reported for endovascular procedures (Luther et al. 2000, Goodney et al. 2013, Mustapha et al. 2016). The number of these procedures is still increasing at a very high rate. In our study, a significant increase in the number of infrapopliteal revascularization procedures was detected, but at the same time, a slight decrease in the number of open infrapopliteal revascularization procedures was also found.

Existing randomized trials have not been able to provide a consensus on whether an open- or endovascular-first strategy should be undertaken in CLTI (Aboyans et al. 2018, Conte et al. 2019). Unfortunately, no correlation between either endovascular or open infrapopliteal revascularizations and the number of major LEAs could be investigated because our data did not contain information about the patients on an individual level. Current guidelines are largely based on studies that are over 10 years old (Adam et al. 2005). Endovascular procedures are associated with a lower peri-operative mortality and morbidity, but often require redo-procedures. Thus, the cost-effectiveness of endovascular procedures has been questioned (Stoner et al. 2008). The on-going BEST-CLI trial aims to provide answers to these questions.

6.2 Vein harvest wound healing after bypass surgery for chronic limb threatening ischemia

The present study demonstrated that although the blood flow to the ischemic limb will have been restored successfully with open bypass surgery, the VHW and other surgical wounds in the limb take a considerable time to heal depending on the severity of the ischemic lesion. For instance, the median healing time for Rutherford 4 score lesions was 48 days, whereas for Rutherford 5 and 6 lesions it was 82 days in our study. The surgical wound healing time thus, was found to correlate to the severity of ischemia in the operated limb. The surgical wounds healed faster in patients with Rutherford grade 4 ischemia than those with Rutherford grade 5 and 6 ischemia.

The reported wound dehiscence rates after infrainguinal bypass surgery range from 5% to 20% (Eid et al. 2014, Teixeira et al. 2015). In the vascular surgery field, numerous studies have been conducted that evaluated open vs. endoscopic vein harvesting techniques. It is generally recognized that open vein harvesting is associated with better graft patency but also with more wound dehiscence than endoscopic vein harvesting (Eid et al. 2014, Jauhari et al. 2014, Santo et al. 2014).

In an earlier study, the prevalence of VHW dehiscence after coronary artery bypass grafting (CABG) was 12% (Athanasiou et al. 2003). Those authors also reported that with minimally invasive techniques this can be reduced to as low as 5%. The REACH data demonstrated that the atherosclerotic burden is substantially greater in the LEAD patients compared to CAD and CVD patients (Bhatt et al. 2006) (Figure 1). Our interpretation is that the lower rate of wound dehiscence compared to lower limb revascularization surgery, could be explained by the absence of LEAD at the site of VHW.

Up to 10% of patients with CLTI also have persistent ischemic ulcers despite a successful revascularization procedure (Berceli et al. 1999, Dorros et al. 2001). In the present study, patients with Rutherford 5 and 6 ischemia lesions at the time of operation were associated with longer VHW healing than patients with Rutherford 4 ischemia. This is most likely due to the microcirculation of the limb being more severely compromised in patients with Rutherford 5 and 6 ischemia (Coats and Hillier 2000, Rother et al. 2017). We hypothesize that the patients who have delayed healing and non-healing ischemic ulcers will also have slow wound healing of surgical wounds.

Defects in the microcirculation of the capillaries of the ischemic foot has been proposed to be a key factor in ischemic wound healing after revascularization procedures (Rother et al. 2017). Chronic ischemia causes over activation of vasodilatation of the capillaries, this causes edema in the ischemic limb. The edema further impairs the metabolic function and distorts the diffusion of nutrients. This situation is exacerbated by a sudden increase in the perfusion pressure achieved by the revascularization procedure (McEwan and Ledingham 1971, Coats and Hillier 2000).

In addition to CLTI, diabetes is known to have adverse effects on the microcirculation. It causes dysfunction of the arterioles and capillaries of the skin, retina, kidneys and peripheral nerves (Malik et al. 1989, Rayman et al. 1995, Akbari and LoGerfo 1999). In the present material, diabetes was not associated with slower surgical wound healing.

Although recent guidelines emphasise the better long-term patency and better cost-effectiveness of infrainguinal bypass surgery over endovascular techniques, the time of surgical wound healing should be kept in mind before making the final decision on the preferred revascularization strategy (Aboyans et al. 2018, Conte et al. 2019).

6.3 Surgical site infections in vascular surgical groin incisions

The present study demonstrated that the number of inguinal wound infections after femoral artery exposure procedures in vascular surgery was lower when the skin was closed using intradermal sutures compared to transdermal sutures. The overall observed rate of inguinal wound infections was 12.4% in the present study. In the intradermal closure group, the rate of infections was 9.4% and in the transdermal closure group 25%. Multivariable analysis revealed an OR of 3.48 (95% CI 1.6–7.6, P=0.002) for the skin closure method and an OR 0.95 (95% CI 0.91–1.00, P=0.034) for age, which were independent risk factors for SSI, whereas diabetes, sex, obesity and CLTI were not. The prevalence of groin wound infections reported in the literature varies substantially from 5% to up to 27% (Childress et al. 2007, Derksen et al. 2009, Turtiainen et al. 2011).The infection rates reported in our study are in line with those earlier studies.

The prevalence of SSI in vascular surgery is related to the patient's condition and to the procedure used. The procedures are long, which predispose patients to hypothermia, blood loss and breaks in sterility (Greenblatt et al. 2011). In addition to this, the patients very often have multiple co-morbidities that predispose them to SSI (Ott et al. 2013). The anatomical location of the inguinal wound also predisposes it to infections. The patient related risk-factors cannot be influenced, but with better surgical technique some of the procedure related risk factors can be reduced. It has already been demonstrated that shorter exposure times and meticulous haemostasis of the operated area can have a beneficial effect on the prevalence of SSI (Greenblatt et al. 2011).

The skin closure method has been studied extensively in cardiac surgery (Risnes et al. 2001, Risnes et al. 2002) and open gastro-intestinal surgery (Tsujinaka et al. 2013). In these well-designed studies no favourable results were found with intracutaneous wound closure compared with the often used metal staples.

The skin closure method used on the inguinal wound after vascular surgery has only been reported in one prospective study setting (Murphy et al. 1995). In the Murphy et al study, 114 patients undergoing femoro-popliteal bypass surgery were randomized to four different wound closure methods and no difference in the rates of wound infections were found between them. Obviously, their study had insufficient statistical power to be capable of providing statistically robust results.

Incisional NPWT has had promising results in reducing groin wound infections. In a recent RCT, 139 patients were randomized to equal sized groups to receive either NPWT or standard wound dressings post-operatively (Hasselmann et al. 2020). They found that the incidence of SSIs reduced in the NPWT group (11.9%) compared to (29.5%) for the standard dressing group. The sample size in that study was based on an assumption that the infection rate would be reduced from 30% to 10%, at 80% power. This resulted in relatively small sample sizes.

6.4 Strengths and limitations of our studies

6.4.1 Study I

The first original publication of this dissertation is a registry based "big data" nationwide study. Despite the national coverage of the register it has several limitations. The register does not contain information about the patients on an individual level. As a consequence, no outcome analysis of individual procedures can be evaluated. Moreover, due to the nature of the data, no analysis of time between revascularization and major amputation can be made. It is not possible to know whether the patients that had undergone a major LEA were the same patients that had previously been revascularized and how many of the patients that underwent an amputation were deemed too unfit or not ambulatory to undergo a revascularization procedure. The reliability of the entire registry is dependent on the quality of the data that are entered into the registry. Nevertheless, this is a study based on a national registry that covers all official healthcare providers in Finland and is representative of the official health sector in a developed western country.

6.4.2 Study II

The original publication was a retrospective single centre study with a moderately sized cohort. Due to the retrospective nature of the study, not all factors that affected wound healing could accurately be included in the analysis because these were not mentioned in the patient records. The follow-up visits were at 1, 3, 9 and 12 months post-operatively, as a consequence the exact date when the wound had healed could not be determined. However, patients that had problems with wound healing were followed up more intensely. Despite these limitations, the study addressed an issue that has not been reported before, and which is therefore essential when making decisions about the best revascularization strategy for each patient.

6.4.3 Study III

The original publication had several limitations. It is a retrospective single centre study that had a relatively small cohort. The closure of the wounds was not randomized but closed according to the operator's preferences. Transdermal sutures were used in urgent operations, whereas wounds made in elective operations were closed using intradermal sutures. The patients included in the analysis were mostly LEAD patients but also a substantial number (46.1%) were abdominal aortic aneurysm (AAA) patients. It is recognised that patients with PAD have a more substantial burden of co-morbidities and are more at risk for developing SSI than AAA patients (Turtiainen et al. 2010). However, patient selection in each group was evenly divided considering common risk factors for SSI.

7 Conclusions

The findings of the present studies lead to the following conclusions:

1. The rate of both open and endovascular revascularization procedures has increased during the 11-year study period of 2007 to 2017. The rate of open revascularization increased especially in the two younger patient cohorts (<74 years), whereas endovascular procedures increased in all age groups. The overall rate of major LEA remained constant, however the rate of major LEA decreased in the > 65-year-old population significantly.
2. Rutherford 5 and 6 ischemic lesions at the time of revascularization surgery are risk factors for delayed vein harvest wound healing after the revascularization procedure.
3. The number SSIs in the inguinal incision after femoral artery exposure can be reduced with an intradermal skin closure technique.

Acknowledgements

This study was carried out in the Turku University Hospital Vascular Surgery Department, University of Turku, Finland during the years 2017- 2020. I wish to express my sincere gratitude to:

My supervisor Professor Harri Hakovirta MD, PhD, (Head of Department of Vascular Surgery) for creating a favorable atmosphere for clinical research in the Vascular Surgery Department. His enthusiastic guidance and broad knowledge made it possible for me to finish this project. At times when this project seemed to be going nowhere, it was comforting to know that help could be found only two doors down the hallway from my office.

My second supervisor Päivi Helmiö, MD, PhD. I would not have been able to complete this project without her day to day guidance. There were times that she probably put more time in correcting my articles, than I in writing them. People always wondered how I got through this whole project so quickly, it was mainly because I never had to wait for any corrections for more than 24 hours.

My colleagues (both past and present) in the Department of Vascular Surgery as well as the entire nursing staff in the vascular surgery ward and operating theatre. Special thanks go to my senior colleagues Kimmo Korhonen, Jan-Erik Wickström, Olli Hautero, Juho Jalkanen and my resident colleague Juha Virtanen. You guys have endured me during my residency and continue to teach and support me now that I'm a fresh consultant. A special thanks goes to Essi for good laughs!

A warm thanks goes also to all my teachers and great friends during my surgical residency. If been privileged to have worked in many different surgical departments. From the little Rauma Regional Hospital to the massive Tygerberg Hospital Trauma Centre in Cape Town. I have learned loads and gained experiences and friends that I will never forget. The list of people is long, but I must mention a few – I'm especially grateful for Timo Lindström and Eeva Gustafsson for guiding me through my first steps in surgery. Jorma Hannukainen for patiently teaching me all the basics in vascular surgery. Elina and Jaan for all your hands-on help with this project.

I've been extremely lucky to have had good friends by my side all my life. Almost none of you have had anything to do with this project or even vascular surgery for that matter. That's exactly why I want to thank you, for reminding me that there is more to life than surgery and science! A special thanks to Tuukka, Panu, Hannes, Lauri, Tuomas, Viljami, Jaakko, Otso, Sauli, Antti and Soffe for all the good times together!

I would not be the person I am today without my parents Ulla and Markku and siblings Ilkka and Saara. I want to thank my mom and dad for believing in me and always being proud of me no matter what I decide to do. The weekly Pizza Friday (a tradition that began in the 1990's) with my parents, siblings and their spouses in Merimasku has been the best therapy one can ask for after a though week.

Last but definitely not least I want to thank Ida for all the love, support and hugs I could ever hope for. Thank you for listening to my complaining and sharing the good times together, hopefully we have lots of adventures waiting for us together!

This work was financially supported by TYKS Foundation, Aino Eerola Foundation and the Finnish Culture Foundation and Government's Special Financial Transfer tied to academic research in Health Sciences (Finland).

Turku, November 2020
Veikko Nikulainen

References

Abou-Zamzam, A. M., Jr., T. H. Teruya, J. D. Killeen and J. L. Ballard (2003). "Major lower extremity amputation in an academic vascular center." *Ann Vasc Surg* **17**(1): 86–90.

Aboyans, V., M. H. Criqui, J. O. Denenberg, J. D. Knoke, P. M. Ridker and A. Fronek (2006). "Risk factors for progression of peripheral arterial disease in large and small vessels." *Circulation* **113**(22): 2623–2629.

Aboyans, V., J. B. Ricco, M. E. L. Bartelink, M. Bjorck, M. Brodmann, T. Cohnert, J. P. Collet, M. Czerny, M. De Carlo, S. Debus, C. Espinola-Klein, T. Kahan, S. Kownator, L. Mazzolai, A. R. Naylor, M. Roffi, J. Rother, M. Sprynger, M. Tendera, G. Tepe, M. Venermo, C. Vlachopoulos, I. Desormais and E. S. C. S. D. Group (2018). "2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS)." *Eur Heart J* **39**(9): 763–816.

Adam, D. J., J. D. Beard, T. Cleveland, J. Bell, A. W. Bradbury, J. F. Forbes, F. G. Fowkes, I. Gillepsie, C. V. Ruckley, G. Raab, H. Storkey and B. t. participants (2005). "Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial." *Lancet* **366**(9501): 1925–1934.

Akbari, C. M. and F. W. LoGerfo (1999). "Diabetes and peripheral vascular disease." *J Vasc Surg* **30**(2): 373–384.

Athanasiou, T., O. Aziz, P. Skapinakis, B. Perunovic, J. Hart, M. C. Crossman, V. Gorgoulis, B. Glenville and R. Casula (2003). "Leg wound infection after coronary artery bypass grafting: a meta-analysis comparing minimally invasive versus conventional vein harvesting." *Ann Thorac Surg* **76**(6): 2141–2146.

Baer-Bositis, H. E., T. D. Hicks, G. M. Haidar, M. J. Sideman, L. L. Pounds and M. G. Davies (2018). "Outcomes of reintervention for recurrent symptomatic disease after tibial endovascular intervention." *J Vasc Surg* **68**(3): 811–821 e811.

Ballotta, E., M. Gruppo, F. Mazzalai and G. Da Giau (2010). "Common femoral artery endarterectomy for occlusive disease: an 8-year single-center prospective study." *Surgery* **147**(2): 268–274.

Bandyk, D. F. (2008). "Vascular surgical site infection: risk factors and preventive measures." *Semin Vasc Surg* **21**(3): 119–123.

Belkin, M., J. Knox, M. C. Donaldson, J. A. Mannick and A. D. Whittemore (1996). "Infrainguinal arterial reconstruction with nonreversed greater saphenous vein." *J Vasc Surg* **24**(6): 957–962.

Berceli, S. A., A. K. Chan, F. B. Pomposelli, Jr., G. W. Gibbons, D. R. Campbell, C. M. Akbari, D. T. Brophy and F. W. LoGerfo (1999). "Efficacy of dorsal pedal artery bypass in limb salvage for ischemic heel ulcers." *J Vasc Surg* **30**(3): 499–508.

Bergan, J. J., F. J. Veith, V. M. Bernhard, J. S. Yao, W. R. Flinn, S. K. Gupta, L. A. Scher, R. H. Samson and J. B. Towne (1982). "Randomization of autogenous vein and polytetrafluorethylene grafts in femoral-distal reconstruction." *Surgery* **92**(6): 921–930.

Bhamidipaty, V., A. Dean, S. L. Yap, J. Firth, M. Barron, B. Allard and S. T. Chan (2015). "Second Toe Systolic Pressure Measurements are Valid Substitutes for First Toe Systolic Pressure Measurements in Diabetic Patients: A Prospective Study." *Eur J Vasc Endovasc Surg* **49**(1): 77–82.

Bhatt, D. L., P. G. Steg, E. M. Ohman, A. T. Hirsch, Y. Ikeda, J. L. Mas, S. Goto, C. S. Liau, A. J. Richard, J. Rother, P. W. Wilson and R. R. Investigators (2006). "International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis." *JAMA* **295**(2): 180–189.

Bjorkman, P., T. Auvinen, H. Hakovirta, P. Romsi, J. Turtiainen, H. Manninen and M. Venermo (2018). "Drug-Eluting Stent Shows Similar Patency Results as Prosthetic Bypass in Patients with Femoropopliteal Occlusion in a Randomized Trial." *Ann Vasc Surg* **53**: 165–170.

Bonaca, M. P., R. M. Bauersachs, S. S. Anand, E. S. Debus, M. R. Nehler, M. R. Patel, F. Fanelli, W. H. Capell, L. Diao, N. Jaeger, C. N. Hess, A. F. Pap, J. M. Kittelson, I. Gudz, L. Matyas, D. K. Krievins, R. Diaz, M. Brodmann, E. Muehlhofer, L. P. Haskell, S. D. Berkowitz and W. R. Hiatt (2020). "Rivaroxaban in Peripheral Artery Disease after Revascularization." *N Engl J Med* **382**(21): 1994–2004.

Bonaca, M. P., B. M. Scirica, M. A. Creager, J. Olin, H. Bounameaux, M. Dellborg, J. M. Lamp, S. A. Murphy, E. Braunwald and D. A. Morrow (2013). "Vorapaxar in patients with peripheral artery disease: results from TRA2{degrees}P-TIMI 50." *Circulation* **127**(14): 1522–1529, 1529e1521–1526.

Bosiers, M., D. Scheinert, P. Peeters, G. Torsello, T. Zeller, K. Deloose, A. Schmidt, J. Tessarek, E. Vinck and L. B. Schwartz (2012). "Randomized comparison of everolimus-eluting versus bare-metal stents in patients with critical limb ischemia and infrapopliteal arterial occlusive disease." *J Vasc Surg* **55**(2): 390–398.

Bradbury, A. W., D. J. Adam, J. Bell, J. F. Forbes, F. G. Fowkes, I. Gillespie, C. V. Ruckley, G. M. Raab and B. T. Participants (2010). "Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: A survival prediction model to facilitate clinical decision making." *J Vasc Surg* **51**(5 Suppl): 52S–68S.

Bryant, R. A., D. P. Nix, D. B. Doughty and B. Sparks (2016). "Wound-Healing Physiology and Factors That Affect the Repair Process." *Acute & Chronic Wounds – Current Management Concepts, Elsevier Inc.* **5th Edition**: 63–76.

Bryant, R. A., D. P. Nix and A. B. Wysocki (2016). "Anatomy and Physiology of Skin and Soft Tissue." *Acute & Chronic Wounds – Current Management Concepts, Elsevier Inc.* **5th Edition**: 40–51.

Bunt, T. J. (1983). "Synthetic vascular graft infections. I. Graft infections." *Surgery* **93**(6): 733–746.

Burns, P., S. Gough and A. W. Bradbury (2003). "Management of peripheral arterial disease in primary care." *BMJ* **326**(7389): 584–588.

Chakfe, N., H. Diener, A. Lejay, O. Assadian, X. Berard, J. Caillon, I. Fourneau, A. Glaudemans, I. Koncar, J. Lindholt, G. Melissano, B. R. Saleem, E. Senneville, R. Slart, Z. Szeberin, M. Venermo, F. Vermassen, T. R. Wyss, C. Esvs Guidelines, G. J. de Borst, F. Bastos Goncalves, S. K. Kakkos, P. Kolh, R. Tulamo, M. Vega de Ceniga, R. Document, R. S. von Allmen, J. C. van den Berg, E. S. Debus, M. J. W. Koelemay, J. P. Linares-Palomino, G. L. Moneta, J. B. Ricco and A. Wanhainen (2020). "Editor's Choice – European Society for Vascular Surgery (ESVS) 2020 Clinical Practice Guidelines on the Management of Vascular Graft and Endograft Infections." *Eur J Vasc Endovasc Surg* **59**(3): 339–384.

Chang, J. K., K. D. Calligaro, S. Ryan, D. Runyan, M. J. Dougherty and J. J. Stern (2003). "Risk factors associated with infection of lower extremity revascularization: analysis of 365 procedures performed at a teaching hospital." *Ann Vasc Surg* **17**(1): 91–96.

Childres, Lamaina, Liu, Mak, Booth, Gibson and Shekelle (2019). "Cost-effectiveness of Leg Bypass Versus Endovascular Therapy for Critical Limb Ischemia: A Systematic Review." *VA Evidence-based Synthesis Program Reports*.

Childress, B. B., S. A. Berceli, P. R. Nelson, W. A. Lee and C. K. Ozaki (2007). "Impact of an absorbent silver-eluting dressing system on lower extremity revascularization wound complications." *Ann Vasc Surg* **21**(5): 598–602.

Chung, J., B. B. Bartelson, W. R. Hiatt, B. D. Peyton, R. B. McLafferty, C. W. Hopley, K. D. Salter and M. R. Nehler (2006). "Wound healing and functional outcomes after infrainguinal bypass with reversed saphenous vein for critical limb ischemia." *J Vasc Surg* **43**(6): 1183–1190.

Coats, P. and C. Hillier (2000). "Differential responses in human subcutaneous and skeletal muscle vascular beds to critical limb ischaemia." *Eur J Vasc Endovasc Surg* **19**(4): 387–395.

Collins, R., J. Burch, G. Cranny, R. Aguiar-Ibanez, D. Craig, K. Wright, E. Berry, M. Gough, J. Kleijnen and M. Westwood (2007). "Duplex ultrasonography, magnetic resonance angiography, and computed tomography angiography for diagnosis and assessment of symptomatic, lower limb peripheral arterial disease: systematic review." *BMJ* **334**(7606): 1257.

Conte, M. S. (2009). "Technical factors in lower-extremity vein bypass surgery: how can we improve outcomes?" *Semin Vasc Surg* **22**(4): 227–233.

Conte, M. S., D. F. Bandyk, A. W. Clowes, G. L. Moneta, L. Seely, T. J. Lorenz, H. Namini, A. D. Hamdan, S. P. Roddy, M. Belkin, S. A. Berceli, R. J. DeMasi, R. H. Samson, S. S. Berman and P. I. Investigators (2006). "Results of PREVENT III: a multicenter, randomized trial of edifoligide for the prevention of vein graft failure in lower extremity bypass surgery." *J Vasc Surg* **43**(4): 742–751; discussion 751.

Conte, M. S., A. W. Bradbury, P. Kolh, J. V. White, F. Dick, R. Fitridge, J. L. Mills, J. B. Ricco, K. R. Suresh, M. H. Murad and G. V. G. W. Group (2019). "Global vascular guidelines on the management of chronic limb-threatening ischemia." *J Vasc Surg* **69**(6S): 3S–125S e140.

Criqui, M. H. and V. Aboyans (2015). "Epidemiology of peripheral artery disease." *Circ Res* **116**(9): 1509–1526.

Cull, D. L., G. Manos, M. C. Hartley, S. M. Taylor, E. M. Langan, J. F. Eidt and B. L. Johnson (2014). "An early validation of the Society for Vascular Surgery lower extremity threatened limb classification system." *J Vasc Surg* **60**(6): 1535–1541.

Culver, D. H., T. C. Horan, R. P. Gaynes, W. J. Martone, W. R. Jarvis, T. G. Emori, S. N. Banerjee, J. R. Edwards, J. S. Tolson, T. S. Henderson and et al. (1991). "Surgical wound infection rates by wound class, operative procedure, and patient risk index. National Nosocomial Infections Surveillance System." *Am J Med* **91**(3B): 152S–157S.

Darling, J. D., J. C. McCallum, P. A. Soden, Y. Meng, M. C. Wyers, A. D. Hamdan, H. J. Verhagen and M. L. Schermerhorn (2016). "Predictive ability of the Society for Vascular Surgery Wound, Ischemia, and foot Infection (WIfI) classification system following infrapopliteal endovascular interventions for critical limb ischemia." *J Vasc Surg* **64**(3): 616–622.

De Frang, R. D., L. M. Taylor, Jr. and J. M. Porter (1991). "Basic data related to amputations." *Ann Vasc Surg* **5**(2): 202–207.

DeBakey, M. E., G. M. Lawrie and D. H. Glaeser (1985). "Patterns of atherosclerosis and their surgical significance." *Ann Surg* **201**(2): 115–131.

Derksen, W. J., B. A. Verhoeven, R. H. van de Mortel, F. L. Moll and J. P. de Vries (2009). "Risk factors for surgical-site infection following common femoral artery endarterectomy." *Vasc Endovascular Surg* **43**(1): 69–75.

Diehm, N., A. Shang, A. Silvestro, D. D. Do, F. Dick, J. Schmidli, F. Mahler and I. Baumgartner (2006). "Association of cardiovascular risk factors with pattern of lower limb atherosclerosis in 2659 patients undergoing angioplasty." *Eur J Vasc Endovasc Surg* **31**(1): 59–63.

Djerf, H., J. Millinger, M. Falkenberg, L. Jivegard, M. Svensson and J. Nordanstig (2020). "Absence of Long-Term Benefit of Revascularization in Patients With Intermittent Claudication: Five-Year Results From the IRONIC Randomized Controlled Trial." *Circ Cardiovasc Interv* **13**(1): e008450.

Dormandy, J., L. Heeck and S. Vig (1999). "The natural history of claudication: risk to life and limb." *Semin Vasc Surg* **12**(2): 123–137.

Dormandy, J. A. and G. D. Murray (1991). "The fate of the claudicant--a prospective study of 1969 claudicants." *Eur J Vasc Surg* **5**(2): 131–133.

Dormandy, J. A. and R. B. Rutherford (2000). "Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC)." *J Vasc Surg* **31**(1 Pt 2): S1–S296.

Dorros, G., M. R. Jaff, A. M. Dorros, L. M. Mathiak and T. He (2001). "Tibioperoneal (outflow lesion) angioplasty can be used as primary treatment in 235 patients with critical limb ischemia: five-year follow-up." *Circulation* **104**(17): 2057–2062.

Eid, R. E., L. Wang, M. Kuzman, G. Abu-Hamad, M. Singh, L. K. Marone, S. A. Leers and R. A. Chaer (2014). "Endoscopic versus open saphenous vein graft harvest for lower extremity bypass in critical limb ischemia." *J Vasc Surg* **59**(1): 136–144.

Eikelboom, J. W., S. J. Connolly, J. Bosch, G. R. Dagenais, R. G. Hart, O. Shestakovska, R. Diaz, M. Alings, E. M. Lonn, S. S. Anand, P. Widimsky, M. Hori, A. Avezum, L. S. Piegas, K. R. H. Branch, J. Probstfield, D. L. Bhatt, J. Zhu, Y. Liang, A. P. Maggioni, P. Lopez-Jaramillo, M. O'Donnell, A. K. Kakkar, K. A. A. Fox, A. N. Parkhomenko, G. Ertl, S. Stork, M. Keltai, L. Ryden, N. Pogosova, A. L. Dans, F. Lanas, P. J. Commerford, C. Torp-Pedersen, T. J. Guzik, P. B. Verhamme, D. Vinereanu, J. H. Kim, A. M. Tonkin, B. S. Lewis, C. Felix, K. Yusoff, P. G. Steg, K. P. Metsarinne, N. Cook Bruns, F. Misselwitz, E. Chen, D. Leong and S. Yusuf (2017). "Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease." *N Engl J Med* **377**(14): 1319–1330.

Eskelinen, E., M. Lepantalo, E. M. Hietala, H. Sell, L. Kauppila, I. Maenpaa, J. Pitkanen, P. Salminen-Peltola, S. Leutola, A. Eskelinen, A. Kivioja, E. Tukiainen, A. Lukinmaa, P. Brasken and M. Railo (2004). "Lower limb amputations in Southern Finland in 2000 and trends up to 2001." *Eur J Vasc Endovasc Surg* **27**(2): 193–200.

Fakhry, F., S. Spronk, L. van der Laan, J. J. Wever, J. A. Teijink, W. H. Hoffmann, T. M. Smits, J. P. van Brussel, G. N. Stultiens, A. Derom, P. T. den Hoed, G. H. Ho, L. C. van Dijk, N. Verhofstad, M. Orsini, A. van Petersen, K. Woltman, I. Hulst, M. R. van Sambeek, D. Rizopoulos, E. V. Rouwet and M. G. Hunink (2015). "Endovascular Revascularization and Supervised Exercise for Peripheral Artery Disease and Intermittent Claudication: A Randomized Clinical Trial." *JAMA* **314**(18): 1936–1944.

Fontaine, R., M. Kim and R. Kieny (1954). "[Surgical treatment of peripheral circulation disorders]." *Helv Chir Acta* **21**(5–6): 499–533.

Forbes, J. F., D. J. Adam, J. Bell, F. G. Fowkes, I. Gillespie, G. M. Raab, C. V. Ruckley, A. W. Bradbury and B. t. Participants (2010). "Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: Health-related quality of life outcomes, resource utilization, and cost-effectiveness analysis." *J Vasc Surg* **51**(5 Suppl): 43S–51S.

Fowkes, F. G., G. D. Murray, I. Butcher, A. R. Folsom, A. T. Hirsch, D. J. Couper, G. Debacker, M. Kornitzer, A. B. Newman, K. C. Sutton-Tyrrell, M. Cushman, A. J. Lee, J. F. Price, R. B. D'Agostino, Sr., J. M. Murabito, P. Norman, K. H. Masaki, L. M. Bouter, R. J. Heine, C. D. Stehouwer, M. M. McDermott, H. E. Stoffers, J. A. Knottnerus, M. Ogren, B. Hedblad, W. Koenig, C. Meisinger, J. A. Cauley, O. Franco, M. G. Hunink, A. Hofman, J. C. Witteman, M. H. Criqui, R. D. Langer, W. R. Hiatt, R. F. Hamman and C. Ankle Brachial Index (2014). "Development and validation of an ankle brachial index risk model for the prediction of cardiovascular events." *Eur J Prev Cardiol* **21**(3): 310–320.

Fowkes, F. G., G. D. Murray, I. Butcher, C. L. Heald, R. J. Lee, L. E. Chambless, A. R. Folsom, A. T. Hirsch, M. Dramaix, G. deBacker, J. C. Wautrecht, M. Kornitzer, A. B. Newman, M. Cushman, K. Sutton-Tyrrell, F. G. Fowkes, A. J. Lee, J. F. Price, R. B. d'Agostino, J. M. Murabito, P. E. Norman, K. Jamrozik, J. D. Curb, K. H. Masaki, B. L. Rodriguez, J. M. Dekker, L. M. Bouter, R. J. Heine, G. Nijpels, C. D. Stehouwer, L. Ferrucci, M. M. McDermott, H. E. Stoffers, J. D. Hooi, J. A. Knottnerus, M. Ogren, B. Hedblad, J. C. Witteman, M. M. Breteler, M. G. Hunink, A. Hofman, M. H. Criqui, R. D. Langer, A. Fronek, W. R. Hiatt, R. Hamman, H. E. Resnick, J.

Guralnik and M. M. McDermott (2008). "Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis." *JAMA* **300**(2): 197–208.

Fowkes, F. G., D. Rudan, I. Rudan, V. Aboyans, J. O. Denenberg, M. M. McDermott, P. E. Norman, U. K. Sampson, L. J. Williams, G. A. Mensah and M. H. Criqui (2013). "Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis." Lancet **382**(9901): 1329–1340.

Gabriel, S. E. (2008). "Cardiovascular morbidity and mortality in rheumatoid arthritis." *Am J Med* **121**(10 Suppl 1): S9–14.

Gent, M., D. Beumont, J. Blanchard and M.-G. Bousser (1996). "A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee." *Lancet* **348**(9038): 1329–1339.

Geraghty, P. J., M. W. Mewissen, M. R. Jaff, G. M. Ansel and V. Investigators (2013). "Three-year results of the VIBRANT trial of VIABAHN endoprosthesis versus bare nitinol stent implantation for complex superficial femoral artery occlusive disease." *J Vasc Surg* **58**(2): 386–395 e384.

Gerhard-Herman, M. D., H. L. Gornik, C. Barrett, N. R. Barshes, M. A. Corriere, D. E. Drachman, L. A. Fleisher, F. G. Fowkes, N. M. Hamburg, S. Kinlay, R. Lookstein, S. Misra, L. Mureebe, J. W. Olin, R. A. Patel, J. G. Regensteiner, A. Schanzer, M. H. Shishehbor, K. J. Stewart, D. Treat-Jacobson and M. E. Walsh (2017). "2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines." *Circulation* **135**(12): e726–e779.

Giacometti, A., O. Cirioni, R. Ghiselli, F. Orlando, F. Mocchegiani, A. Riva, M. S. Del Prete, V. Saba and G. Scalise (2002). "Efficacy of quinupristin-dalfopristin in preventing vascular graft infection due to Staphylococcus epidermidis with intermediate resistance to glycopeptides." *Antimicrob Agents Chemother* **46**(9): 2885–2888.

Giles, K. A., A. D. Hamdan, F. B. Pomposelli, M. C. Wyers, J. J. Siracuse and M. L. Schermerhorn (2010). "Body mass index: surgical site infections and mortality after lower extremity bypass from the National Surgical Quality Improvement Program 2005–2007." *Ann Vasc Surg* **24**(1): 48–56.

Giles, K. A., M. C. Wyers, F. B. Pomposelli, A. D. Hamdan, Y. A. Ching and M. L. Schermerhorn (2010). "The impact of body mass index on perioperative outcomes of open and endovascular abdominal aortic aneurysm repair from the National Surgical Quality Improvement Program, 2005–2007." *J Vasc Surg* **52**(6): 1471–1477.

Golomb, B. A., T. T. Dang and M. H. Criqui (2006). "Peripheral arterial disease: morbidity and mortality implications." *Circulation* **114**(7): 688–699.

Goodney, P. P., A. W. Beck, J. Nagle, H. G. Welch and R. M. Zwolak (2009). "National trends in lower extremity bypass surgery, endovascular interventions, and major amputations." *J Vasc Surg* **50**(1): 54–60.

Goodney, P. P., K. Holman, P. K. Henke, L. L. Travis, J. B. Dimick, T. A. Stukel, E. S. Fisher and J. D. Birkmeyer (2013). "Regional intensity of vascular care and lower extremity amputation rates." *J Vasc Surg* **57**(6): 1471–1479, 1480 e1471–1473; discussion 1479–1480.

Goodney, P. P., M. Tarulli, A. E. Faerber, A. Schanzer and R. M. Zwolak (2015). "Fifteen-year trends in lower limb amputation, revascularization, and preventive measures among medicare patients." *JAMA Surg* **150**(1): 84–86.

Gottrup, F. (2008). "Trends in surgical wound healing." *Scand J Surg* **97**(3): 220–225; discussion 225–226.

Greenblatt, D. Y., V. Rajamanickam and M. W. Mell (2011). "Predictors of surgical site infection after open lower extremity revascularization." *J Vasc Surg* **54**(2): 433–439.

Greenhalgh, R. M., J. J. Belch, L. C. Brown, P. A. Gaines, L. Gao, J. A. Reise, S. G. Thompson and P. Mimic Trial (2008). "The adjuvant benefit of angioplasty in patients with mild to moderate intermittent claudication (MIMIC) managed by supervised exercise, smoking cessation advice and best medical therapy: results from two randomised trials for stenotic femoropopliteal and aortoiliac arterial disease." *Eur J Vasc Endovasc Surg* **36**(6): 680–688.

Guariguata, L., D. R. Whiting, I. Hambleton, J. Beagley, U. Linnenkamp and J. E. Shaw (2014). "Global estimates of diabetes prevalence for 2013 and projections for 2035." *Diabetes Res Clin Pract* **103**(2): 137–149.

Hasselmann, J., J. Bjork, R. Svensson-Bjork and S. Acosta (2020). "Inguinal Vascular Surgical Wound Protection by Incisional Negative Pressure Wound Therapy: A Randomized Controlled Trial-INVIPS Trial." *Ann Surg* **271**(1): 48–53.

Haynes, A. B., T. G. Weiser, W. R. Berry, S. R. Lipsitz, A. H. Breizat, E. P. Dellinger, T. Herbosa, S. Joseph, P. L. Kibatala, M. C. Lapitan, A. F. Merry, K. Moorthy, R. K. Reznick, B. Taylor, A. A. Gawande and G. Safe Surgery Saves Lives Study (2009). "A surgical safety checklist to reduce morbidity and mortality in a global population." *N Engl J Med* **360**(5): 491–499.

Hiatt, W. R., J. Goldstone, S. C. Smith, Jr., M. McDermott, G. Moneta, R. Oka, A. B. Newman, W. H. Pearce and G. American Heart Association Writing (2008). "Atherosclerotic Peripheral Vascular Disease Symposium II: nomenclature for vascular diseases." *Circulation* **118**(25): 2826–2829.

Hirsch, A. T., M. H. Criqui, D. Treat-Jacobson, J. G. Regensteiner, M. A. Creager, J. W. Olin, S. H. Krook, D. B. Hunninghake, A. J. Comerota, M. E. Walsh, M. M. McDermott and W. R. Hiatt (2001). "Peripheral arterial disease detection, awareness, and treatment in primary care." *JAMA* **286**(11): 1317–1324.

Hirsch, A. T., Z. J. Haskal, N. R. Hertzer, C. W. Bakal, M. A. Creager, J. L. Halperin, L. F. Hiratzka, W. R. Murphy, J. W. Olin, J. B. Puschett, K. A. Rosenfield, D. Sacks, J. C. Stanley, L. M. Taylor, Jr., C. J. White, J. White, R. A. White, E. M. Antman, S. C. Smith, Jr., C. D. Adams, J. L. Anderson, D. P. Faxon, V. Fuster, R. J. Gibbons, S. A. Hunt, A. K. Jacobs, R. Nishimura, J. P. Ornato, R. L. Page, B. Riegel, S. American Association for Vascular Surgery/Society for Vascular, A. Society for Cardiovascular, Interventions, M. Society for Vascular, Biology, R. Society of Interventional and A. A. T. F. o. P. Guidelines (2006). "ACC/AHA Guidelines for the Management of Patients with Peripheral Arterial Disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Associations for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (writing committee to develop guidelines for the management of patients with peripheral arterial disease)--summary of recommendations." *J Vasc Interv Radiol* **17**(9): 1383–1397; quiz 1398.

Hirsch, A. T., T. P. Murphy, M. B. Lovell, G. Twillman, D. Treat-Jacobson, E. M. Harwood, E. R. Mohler, 3rd, M. A. Creager, R. W. Hobson, 2nd, R. M. Robertson, W. J. Howard, P. Schroeder, M. H. Criqui and C. Peripheral Arterial Disease (2007). "Gaps in public knowledge of peripheral arterial disease: the first national PAD public awareness survey." *Circulation* **116**(18): 2086–2094.

Ho, V., D. Wirthlin, H. Yun and J. Allison (2005). "Physician supply, treatment, and amputation rates for peripheral arterial disease." *J Vasc Surg* **42**(1): 81–87.

Holtman, D. and V. Gahtan (2008). "Peripheral Arterial Perfusion: Is it Adequate for Wound Healing?" *Wounds* **20**(8): 230–235.

Homer-Vanniasinkam, S. (2007). "Surgical site and vascular infections: treatment and prophylaxis." *Int J Infect Dis* **11 Suppl 1**: S17–22.

Horan, T. C., M. Andrus and M. A. Dudeck (2008). "CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting." *Am J Infect Control* **36**(5): 309–332.

Huxley, R. R. and M. Woodward (2011). "Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies." *Lancet* **378**(9799): 1297–1305.

Jalkanen, J. M., J. E. Wickstrom, M. Venermo and H. H. Hakovirta (2016). "The extent of atherosclerotic lesions in crural arteries predicts survival of patients with lower limb peripheral artery disease: A new classification of crural atherosclerosis." *Atherosclerosis* **251**: 328–333.

Jauhari, Y. A., C. O. Hughes, S. A. Black, K. G. Jones, R. J. Hinchliffe, M. M. Thompson, P. J. Holt and A. Karthikesalingam (2014). "Endoscopic vein harvesting in lower extremity arterial bypass: a systematic review." *Eur J Vasc Endovasc Surg* **47**(6): 621–639.

Jonason, T. and I. Ringqvist (1985). "Factors of prognostic importance for subsequent rest pain in patients with intermittent claudication." *Acta Med Scand* **218**(1): 27–33.

Jongkind, V., G. J. Akkersdijk, K. K. Yeung and W. Wisselink (2010). "A systematic review of endovascular treatment of extensive aortoiliac occlusive disease." *J Vasc Surg* **52**(5): 1376–1383.

Kang, J. L., V. I. Patel, M. F. Conrad, G. M. Lamuraglia, T. K. Chung and R. P. Cambria (2008). "Common femoral artery occlusive disease: contemporary results following surgical endarterectomy." *J Vasc Surg* **48**(4): 872–877.

Kannel, W. B., J. J. Skinner, Jr., M. J. Schwartz and D. Shurtleff (1970). "Intermittent claudication. Incidence in the Framingham Study." *Circulation* **41**(5): 875–883.

Kedora, J., S. Hohmann, W. Garrett, C. Munschaur, B. Theune and D. Gable (2007). "Randomized comparison of percutaneous Viabahn stent grafts vs prosthetic femoral-popliteal bypass in the treatment of superficial femoral arterial occlusive disease." *J Vasc Surg* **45**(1): 10–16; discussion 16.

Keeling, W. B., P. A. Stone, P. A. Armstrong, H. Kearney, L. Klepczyk, E. Blazick, M. R. Back, B. L. Johnson, D. F. Bandyk and M. L. Shames (2006). "Increasing endovascular intervention for claudication: impact on vascular surgery resident training." *J Endovasc Ther* **13**(4): 507–513.

Khan, M. U., P. Lall, L. M. Harris, M. L. Dryjski and H. H. Dosluoglu (2009). "Predictors of limb loss despite a patent endovascular-treated arterial segment." *J Vasc Surg* **49**(6): 1440–1445; discussion 1445–1446.

Kilpadi, D. V. and M. R. Cunningham (2011). "Evaluation of closed incision management with negative pressure wound therapy (CIM): hematoma/seroma and involvement of the lymphatic system." *Wound Repair Regen* **19**(5): 588–596.

Kimmel, R. M., R. X. Murphy, Jr. and R. P. Chowdary (1994). "Optimal management of inguinal vascular graft infections." *Ann Plast Surg* **32**(6): 623–629.

Knight, B. C. and W. F. Tait (2009). "Dacron patch infection following carotid endarterectomy: a systematic review of the literature." *Eur J Vasc Endovasc Surg* **37**(2): 140–148.

LaMuraglia, G. M., A. J. Fischman, H. W. Strauss, F. Keech, R. Wilkinson, R. J. Callahan, B. A. Khaw and R. H. Rubin (1989). "Utility of the indium 111-labeled human immunoglobulin G scan for the detection of focal vascular graft infection." *J Vasc Surg* **10**(1): 20–27; discussion 27–28.

Libby, P. and G. K. Hansson (2015). "Inflammation and immunity in diseases of the arterial tree: players and layers." *Circ Res* **116**(2): 307–311.

Londero, L. S., A. Hogh, K. Houlind and J. S. Lindholt (2019). "Danish Trends in Major Amputation After Vascular Reconstruction in Patients With Peripheral Arterial Disease 2002–2014." *Eur J Vasc Endovasc Surg* **57**(1): 111–120.

Luther, M., I. Kantonen, M. Lepantalo, J. Salenius and F. S. Group (2000). "Arterial intervention and reduction in amputation for chronic critical leg ischaemia." *Br J Surg* **87**(4): 454–458.

Maier, R. V. and E. M. Bulger (1996). "Endothelial changes after shock and injury." *New Horiz* **4**(2): 211–223.

Malik, R. A., P. G. Newrick, A. K. Sharma, A. Jennings, A. K. Ah-See, T. M. Mayhew, J. Jakubowski, A. J. Boulton and J. D. Ward (1989). "Microangiopathy in human diabetic neuropathy: relationship between capillary abnormalities and the severity of neuropathy." *Diabetologia* **32**(2): 92–102.

Mamode, N. and R. N. Scott (2000). "Graft type for femoro-popliteal bypass surgery." *Cochrane Database Syst Rev*(2): CD001487.

Manjunath, G., H. Tighiouart, H. Ibrahim, B. MacLeod, D. N. Salem, J. L. Griffith, J. Coresh, A. S. Levey and M. J. Sarnak (2003). "Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community." *J Am Coll Cardiol* **41**(1): 47–55.

Markakis, K., F. L. Bowling and A. J. Boulton (2016). "The diabetic foot in 2015: an overview." *Diabetes Metab Res Rev* **32** **Suppl 1**: 169–178.

Marso, S. P. and W. R. Hiatt (2006). "Peripheral arterial disease in patients with diabetes." *J Am Coll Cardiol* **47**(5): 921–929.

McEwan, A. J. and I. M. Ledingham (1971). "Blood flow characteristics and tissue nutrition in apparently ischaemic feet." *Br Med J* **3**(5768): 220–224.

McQuade, K., D. Gable, S. Hohman, G. Pearl and B. Theune (2009). "Randomized comparison of ePTFE/nitinol self-expanding stent graft vs prosthetic femoral-popliteal bypass in the treatment of superficial femoral artery occlusive disease." *J Vasc Surg* **49**(1): 109–115, 116 e101–109; discussion 116.

Mehler, P. S., J. R. Coll, R. Estacio, A. Esler, R. W. Schrier and W. R. Hiatt (2003). "Intensive blood pressure control reduces the risk of cardiovascular events in patients with peripheral arterial disease and type 2 diabetes." *Circulation* **107**(5): 753–756.

Menard, M. T., A. Farber, S. F. Assmann, N. K. Choudhry, M. S. Conte, M. A. Creager, M. D. Dake, M. R. Jaff, J. A. Kaufman, R. J. Powell, D. M. Reid, F. S. Siami, G. Sopko, C. J. White and K. Rosenfield (2016). "Design and Rationale of the Best Endovascular Versus Best Surgical Therapy for Patients With Critical Limb Ischemia (BEST-CLI) Trial." *J Am Heart Assoc* **5**(7).

Mendez, D., O. Alshanqeety and K. E. Warner (2013). "The potential impact of smoking control policies on future global smoking trends." *Tob Control* **22**(1): 46–51.

Menke, N. B., K. R. Ward, T. M. Witten, D. G. Bonchev and R. F. Diegelmann (2007). "Impaired wound healing." *Clin Dermatol* **25**(1): 19–25.

Mills, J. L., Sr., M. S. Conte, D. G. Armstrong, F. B. Pomposelli, A. Schanzer, A. N. Sidawy, G. Andros and C. Society for Vascular Surgery Lower Extremity Guidelines (2014). "The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIfI)." *J Vasc Surg* **59**(1): 220–234 e221–222.

Mohapatra, A., J. C. Henry, E. D. Avgerinos, A. Boitet, R. A. Chaer, M. S. Makaroun, S. A. Leers and E. S. Hager (2018). "Bypass versus endovascular intervention for healing ischemic foot wounds secondary to tibial arterial disease." *J Vasc Surg* **68**(1): 168–175.

Murabito, J. M., R. B. D'Agostino, H. Silbershatz and W. F. Wilson (1997). "Intermittent claudication. A risk profile from The Framingham Heart Study." *Circulation* **96**(1): 44–49.

Murphy, P. G., E. Tadros, S. Cross, D. Hehir, P. E. Burke, P. Kent, S. J. Sheehan, M. P. Colgan, D. J. Moore and G. D. Shanik (1995). "Skin closure and the incidence of groin wound infection: a prospective study." *Ann Vasc Surg* **9**(5): 480–482.

Mustapha, J. A., S. M. Finton, L. J. Diaz-Sandoval, F. A. Saab and L. E. Miller (2016). "Percutaneous Transluminal Angioplasty in Patients With Infrapopliteal Arterial Disease: Systematic Review and Meta-Analysis." *Circ Cardiovasc Interv* **9**(5): e003468.

Nehler, M. R., J. R. Coll, W. R. Hiatt, J. G. Regensteiner, G. T. Schnickel, W. A. Klenke, P. K. Strecker, M. W. Anderson, D. N. Jones, T. A. Whitehill, S. Moskowitz and W. C. Krupski (2003). "Functional outcome in a contemporary series of major lower extremity amputations." *J Vasc Surg* **38**(1): 7–14.

Nguyen, L. L., S. Brahmanandam, D. F. Bandyk, M. Belkin, A. W. Clowes, G. L. Moneta and M. S. Conte (2007). "Female gender and oral anticoagulants are associated with wound complications in lower extremity vein bypass: an analysis of 1404 operations for critical limb ischemia." *J Vasc Surg* **46**(6): 1191–1197.

Nikulainen, V., P. Helmio and H. Hakovirta (2019). "Changes in rates of vascular procedure types and lower extremity amputations in Finland for 2007–2017 inclusive, a population cohort study of 69,523 revascularizations." *Int J Surg* **72**: 118–125.

Nikulainen, V., P. Helmio, S. Hurme and H. Hakovirta (2019). "Intra-Dermal Absorbable Suture in the Groin Incision Associated with Less Groin Surgical Site Infections than Trans-Dermal Sutures in Vascular Surgical Patients." *Surg Infect (Larchmt)* **20**(1): 45–48.

Nikulainen, V., P. Helmio, S. Hurme and H. Hakovirta (2020). "Vein Harvest Wound Healing after Bypass Surgery for Critical Limb Ischemia." *Ann Vasc Surg* **62**: 375–381.

Norgren, L., W. R. Hiatt, J. A. Dormandy, M. R. Nehler, K. A. Harris, F. G. Fowkes and T. I. W. Group (2007). "Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II)." *J Vasc Surg* **45 Suppl S**: S5–67.

Norgren, L., W. R. Hiatt, J. A. Dormandy, M. R. Nehler, K. A. Harris, F. G. Fowkes, T. I. W. Group, K. Bell, J. Caporusso, I. Durand-Zaleski, K. Komori, J. Lammer, C. Liapis, S. Novo, M. Razavi, J. Robbs, N. Schaper, H. Shigematsu, M. Sapoval, C. White, J. White, D. Clement, M. Creager, M. Jaff, E. Mohler, 3rd, R. B. Rutherford, P. Sheehan, H. Sillesen and K. Rosenfield (2007). "Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II)." *Eur J Vasc Endovasc Surg* **33 Suppl 1**: S1–75.

O'Brien-Irr, M. S., L. M. Harris, H. H. Dosluoglu and M. L. Dryjski (2012). "Procedural trends in the treatment of peripheral arterial disease by insurer status in New York State." *J Am Coll Surg* **215**(3): 311–321 e311.

Ott, E., F. C. Bange, D. Sohr, O. Teebken and F. Mattner (2013). "Risk factors associated with surgical site infections following vascular surgery at a German university hospital." *Epidemiol Infect* **141**(6): 1207–1213.

Piano, G. (1995). "Infections in lower extremity vascular grafts." *Surg Clin North Am* **75**(4): 799–809.

Powell, J. T., R. J. Edwards, P. C. Worrell, P. J. Franks, R. M. Greenhalgh and N. R. Poulter (1997). "Risk factors associated with the development of peripheral arterial disease in smokers: a case-control study." *Atherosclerosis* **129**(1): 41–48.

Raitakari, O. T., M. Juonala, M. Kahonen, L. Taittonen, T. Laitinen, N. Maki-Torkko, M. J. Jarvisalo, M. Uhari, E. Jokinen, T. Ronnemaa, H. K. Akerblom and J. S. Viikari (2003). "Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study." *JAMA* **290**(17): 2277–2283.

Rayman, G., R. A. Malik, A. K. Sharma and J. L. Day (1995). "Microvascular response to tissue injury and capillary ultrastructure in the foot skin of type I diabetic patients." *Clin Sci (Lond)* **89**(5): 467–474.

Remes, L., R. Isoaho, T. Vahlberg, H. Hiekkanen, K. Korhonen, M. Viitanen and P. Rautava (2008). "Major lower extremity amputation in elderly patients with peripheral arterial disease: incidence and survival rates." *Aging Clin Exp Res* **20**(5): 385–393.

Risnes, I., M. Abdelnoor, S. T. Baksaas, R. Lundblad and J. L. Svennevig (2001). "Sternal wound infections in patients undergoing open heart surgery: randomized study comparing intracutaneous and transcutaneous suture techniques." *Ann Thorac Surg* **72**(5): 1587–1591.

Risnes, I., M. Abdelnoor, R. Lundblad, S. T. Baksaas and J. L. Svennevig (2002). "Sternal wound closure in patients undergoing open-heart surgery: a prospective randomized study comparing intracutaneous and zipper techniques." *Eur J Cardiothorac Surg* **22**(2): 271–277.

Ross, R. (1993). "The pathogenesis of atherosclerosis: a perspective for the 1990s." *Nature* **362**(6423): 801–809.

Ross, R. (1999). "Atherosclerosis--an inflammatory disease." *N Engl J Med* **340**(2): 115–126.

Rother, U., W. Lang, R. E. Horch, I. Ludolph, A. Meyer and S. Regus (2017). "Microcirculation Evaluated by Intraoperative Fluorescence Angiography after Tibial Bypass Surgery." *Ann Vasc Surg* **40**: 190–197.

Rutherford, R. B., J. D. Baker, C. Ernst, K. W. Johnston, J. M. Porter, S. Ahn and D. N. Jones (1997). "Recommended standards for reports dealing with lower extremity ischemia: revised version." *J Vasc Surg* **26**(3): 517–538.

Rutherford, R. B., Flanigan, Gupta, Johnston, Karmody, Whittemore, Baker, Ernst, (1986). "Suggested standards for reports dealing with lower extremity ischemia. Prepared by the Ad Hoc Committee on Reporting Standards, Society for Vascular Surgery/North American Chapter, International Society for Cardiovascular Surgery." *J Vasc Surg* **4**(1): 80–94.

Sachs, T., F. Pomposelli, A. Hamdan, M. Wyers and M. Schermerhorn (2011). "Trends in the national outcomes and costs for claudication and limb threatening ischemia: angioplasty vs bypass graft." *J Vasc Surg* **54**(4): 1021–1031 e1021.

Salenius, J. P., M. Lepantalo, K. Ylonen and M. Luther (1993). "Treatment of peripheral vascular diseases--basic data from the nationwide vascular registry FINNVASC." *Ann Chir Gynaecol* **82**(4): 235–240.

Samson, R. H., F. J. Veith, G. S. Janko, S. K. Gupta and L. A. Scher (1988). "A modified classification and approach to the management of infections involving peripheral arterial prosthetic grafts." *J Vasc Surg* **8**(2): 147–153.

Santo, V. J., P. Dargon, A. F. Azarbal, T. K. Liem, E. L. Mitchell, G. J. Landry and G. L. Moneta (2014). "Lower extremity autologous vein bypass for critical limb ischemia is not adversely affected by prior endovascular procedure." *J Vasc Surg* **60**(1): 129–135.

Santo, V. J., P. T. Dargon, A. F. Azarbal, T. K. Liem, E. L. Mitchell, G. L. Moneta and G. J. Landry (2014). "Open versus endoscopic great saphenous vein harvest for lower extremity revascularization of critical limb ischemia." *J Vasc Surg* **59**(2): 427–434.

Schanzer, A., P. P. Goodney, Y. Li, M. Eslami, J. Cronenwett, L. Messina, M. S. Conte and E. Vascular Study Group of Northern New (2009). "Validation of the PIII CLI risk score for the prediction of amputation-free survival in patients undergoing infrainguinal autogenous vein bypass for critical limb ischemia." *J Vasc Surg* **50**(4): 769–775; discussion 775.

Schanzer, A., N. Hevelone, C. D. Owens, J. A. Beckman, M. Belkin and M. S. Conte (2008). "Statins are independently associated with reduced mortality in patients undergoing infrainguinal bypass graft surgery for critical limb ischemia." *J Vasc Surg* **47**(4): 774–781.

Schanzer, A., N. Hevelone, C. D. Owens, M. Belkin, D. F. Bandyk, A. W. Clowes, G. L. Moneta and M. S. Conte (2007). "Technical factors affecting autogenous vein graft failure: observations from a large multicenter trial." *J Vasc Surg* **46**(6): 1180–1190; discussion 1190.

Schanzer, A., J. Mega, J. Meadows, R. H. Samson, D. F. Bandyk and M. S. Conte (2008). "Risk stratification in critical limb ischemia: derivation and validation of a model to predict amputation-free survival using multicenter surgical outcomes data." *J Vasc Surg* **48**(6): 1464–1471.

Schilling, J. A. (1976). "Wound healing." *Surg Clin North Am* **56**(4): 859–874.

Schillinger, M., S. Sabeti, P. Dick, J. Amighi, W. Mlekusch, O. Schlager, C. Loewe, M. Cejna, J. Lammer and E. Minar (2007). "Sustained benefit at 2 years of primary femoropopliteal stenting compared with balloon angioplasty with optional stenting." *Circulation* **115**(21): 2745–2749.

Shah, D. M., R. C. Darling, 3rd, B. B. Chang, K. M. Fitzgerald, P. S. Paty and R. P. Leather (1995). "Long-term results of in situ saphenous vein bypass. Analysis of 2058 cases." *Ann Surg* **222**(4): 438–446; discussion 446–438.

Sidawy, A. N., B. A. Perler and M. S.Conte (2019). "Chapter 104 Lower Extremity Arterial Occlusive Disease: Epidemiology and Natural History." *Rutherford's Vascular Surgery and Endovascular Therapy* **Volume 2**(9th Edition): 1368–1376.

Sigvant, B., B. Kragsterman, M. Falkenberg, P. Hasvold, S. Johansson, M. Thuresson and J. Nordanstig (2016). "Contemporary cardiovascular risk and secondary preventive drug treatment patterns in peripheral artery disease patients undergoing revascularization." *J Vasc Surg* **64**(4): 1009–1017 e1003.

Sigvant, B., K. Wiberg-Hedman, D. Bergqvist, O. Rolandsson, B. Andersson, E. Persson and E. Wahlberg (2007). "A population-based study of peripheral arterial disease prevalence with special focus on critical limb ischemia and sex differences." *J Vasc Surg* **45**(6): 1185–1191.

Song, P., D. Rudan, Y. Zhu, F. J. I. Fowkes, K. Rahimi, F. G. R. Fowkes and I. Rudan (2019). "Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis." *Lancet Glob Health* **7**(8): e1020–e1030.

Sorensen, L. T. (2012). "Wound healing and infection in surgery: the pathophysiological impact of smoking, smoking cessation, and nicotine replacement therapy: a systematic review." *Ann Surg* **255**(6): 1069–1079.

Stewart, A. H., P. S. Eyers and J. J. Earnshaw (2007). "Prevention of infection in peripheral arterial reconstruction: a systematic review and meta-analysis." *J Vasc Surg* **46**(1): 148–155.

Stoner, M. C., D. J. Defreitas, M. M. Manwaring, J. J. Carter, F. M. Parker and C. S. Powell (2008). "Cost per day of patency: understanding the impact of patency and reintervention in a sustainable model of healthcare." *J Vasc Surg* **48**(6): 1489–1496.

Strecker-McGraw, M. K., T. R. Jones and D. G. Baer (2007). "Soft tissue wounds and principles of healing." *Emerg Med Clin North Am* **25**(1): 1–22.

Suominen, V., I. Uurto, J. Saarinen, M. Venermo and J. Salenius (2010). "PAD as a risk factor for mortality among patients with elevated ABI--a clinical study." *Eur J Vasc Endovasc Surg* **39**(3): 316–322.

Szilagyi, D. E., R. F. Smith, J. P. Elliott and M. P. Vrandecic (1972). "Infection in arterial reconstruction with synthetic grafts." *Ann Surg* **176**(3): 321–333.

Tan, T. W., A. Farber, N. M. Hamburg, R. T. Eberhardt, D. Rybin, G. Doros, J. Eldrup-Jorgensen, P. P. Goodney, J. L. Cronenwett, J. A. Kalish and E. Vascular Study Group of New (2013). "Blood transfusion for lower extremity bypass is associated with increased wound infection and graft thrombosis." *J Am Coll Surg* **216**(5): 1005–1014 e1002; quiz 1031–1003.

Taylor, S. M., C. A. Kalbaugh, D. W. Blackhurst, A. L. Cass, E. A. Trent, E. M. Langan, 3rd and J. R. Youkey (2006). "Determinants of functional outcome after revascularization for critical limb ischemia: an analysis of 1000 consecutive vascular interventions." *J Vasc Surg* **44**(4): 747–755; discussion 755–746.

Taylor, S. M., C. A. Kalbaugh, D. W. Blackhurst, S. E. Hamontree, D. L. Cull, H. S. Messich, R. T. Robertson, E. M. Langan, 3rd, J. W. York, C. G. Carsten, 3rd, B. A. Snyder, M. R. Jackson and J. R. Youkey (2005). "Preoperative clinical factors predict postoperative functional outcomes after major lower limb amputation: an analysis of 553 consecutive patients." *J Vasc Surg* **42**(2): 227–235.

Teixeira, P. G., K. Woo, F. A. Weaver and V. L. Rowe (2015). "Vein harvesting technique for infrainguinal arterial bypass with great saphenous vein and its association with surgical site infection and graft patency." *J Vasc Surg* **61**(5): 1264–1271 e1262.

Teraa, M., M. S. Conte, F. L. Moll and M. C. Verhaar (2016). "Critical Limb Ischemia: Current Trends and Future Directions." *J Am Heart Assoc* **5**(2).

Tosaka, A., Y. Soga, O. Iida, T. Ishihara, K. Hirano, K. Suzuki, H. Yokoi, S. Nanto and M. Nobuyoshi (2012). "Classification and clinical impact of restenosis after femoropopliteal stenting." *J Am Coll Cardiol* **59**(1): 16–23.

Toursarkissian, B., P. K. Shireman, A. Harrison, M. D'Ayala, J. Schoolfield and M. T. Sykes (2002). "Major lower-extremity amputation: contemporary experience in a single Veterans Affairs institution." *Am Surg* **68**(7): 606–610.

Tsujinaka, T., K. Yamamoto, J. Fujita, S. Endo, J. Kawada, S. Nakahira, T. Shimokawa, S. Kobayashi, M. Yamasaki, Y. Akamaru, A. Miyamoto, T. Mizushima, J. Shimizu, K. Umeshita, T. Ito, Y. Doki, M. Mori and M. Clinical Study Group of Osaka University on Section of Risk (2013). "Subcuticular sutures versus staples for skin closure after open gastrointestinal surgery: a phase 3, multicentre, open-label, randomised controlled trial." *Lancet* **382**(9898): 1105–1112.

Turtiainen, J., E. Saimanen, T. Partio, J. Karkkainen, V. Kiviniemi, K. Makinen and T. Hakala (2010). "Surgical wound infections after vascular surgery: prospective multicenter observational study." *Scand J Surg* **99**(3): 167–172.

Turtiainen, J., E. I. Saimanen, K. T. Makinen, A. I. Nykanen, M. A. Venermo, I. T. Uurto and T. Hakala (2012). "Effect of triclosan-coated sutures on the incidence of surgical wound infection after lower limb revascularization surgery: a randomized controlled trial." *World J Surg* **36**(10): 2528–2534.

Turtiainen, J., E. I. Saimanen, T. J. Partio, K. T. Makinen, M. T. Reinikainen, J. J. Virkkunen, K. S. Vuorio and T. Hakala (2011). "Supplemental postoperative oxygen in the prevention of surgical wound infection after lower limb vascular surgery: a randomized controlled trial." *World J Surg* **35**(6): 1387–1395.

Uhl, C., H. Gotzke, F. Zeman, S. Woronowicz, T. Betz, I. Topel and M. Steinbauer (2020). "Long-term outcome of common femoral artery endarterectomy in octogenarians and non-octogenarians." *Scand J Surg*: 1457496920907733.

van der Wal, A. C., A. E. Becker, C. M. van der Loos and P. K. Das (1994). "Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology." *Circulation* **89**(1): 36–44.

van der Zaag, E. S., D. A. Legemate, M. H. Prins, J. A. Reekers and M. J. Jacobs (2004). "Angioplasty or bypass for superficial femoral artery disease? A randomised controlled trial." *Eur J Vasc Endovasc Surg* **28**(2): 132–137.

Vartiainen, E., P. Jousilahti, G. Alfthan, J. Sundvall, P. Pietinen and P. Puska (2000). "Cardiovascular risk factor changes in Finland, 1972–1997." *Int J Epidemiol* **29**(1): 49–56.

Veith, F. J., S. K. Gupta, E. Ascer, S. White-Flores, R. H. Samson, L. A. Scher, J. B. Towne, V. M. Bernhard, P. Bonier, W. R. Flinn and et al. (1986). "Six-year prospective multicenter randomized comparison of autologous saphenous vein and expanded polytetrafluoroethylene grafts in infrainguinal arterial reconstructions." *J Vasc Surg* **3**(1): 104–114.

Wattanakit, K., A. R. Folsom, E. Selvin, B. D. Weatherley, J. S. Pankow, F. L. Brancati and A. T. Hirsch (2005). "Risk factors for peripheral arterial disease incidence in persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) Study." *Atherosclerosis* **180**(2): 389–397.

Wengerter, K. R., F. J. Veith, S. K. Gupta, J. Goldsmith, E. Farrell, P. L. Harris, D. Moore and G. Shanik (1991). "Prospective randomized multicenter comparison of in situ and reversed vein infrapopliteal bypasses." *J Vasc Surg* **13**(2): 189–197; discussion 197–189.

White, C. J. and W. A. Gray (2007). "Endovascular therapies for peripheral arterial disease: an evidence-based review." *Circulation* **116**(19): 2203–2215.

Wickstrom, J. E., J. M. Jalkanen, M. Venermo and H. H. Hakovirta (2017). "Crural Index and extensive atherosclerosis of crural vessels are associated with long-term cardiovascular mortality in patients with symptomatic peripheral artery disease." *Atherosclerosis* **264**: 44–50.

Wickstrom, J. E., J. Virtanen, E. Aro, J. Jalkanen, M. Venermo and H. Hakovirta (2019). "Bilateral low systolic toe pressure and toe-brachial index are associated with long-term mortality in patients with peripheral artery disease." *J Vasc Surg* **70**(6): 1994–2004.

Wieker, C. M., E. Schonefeld, N. Osada, C. Luhrs, R. Beneking, G. Torsello and D. Bockler (2016). "Results of common femoral artery thromboendarterectomy evaluation of a traditional surgical management in the endovascular era." *J Vasc Surg* **64**(4): 995–1001.

Winell, K., M. Venermo, T. Ikonen and R. Sund (2013). "Indicators for comparing the incidence of diabetic amputations: a nationwide population-based register study." *Eur J Vasc Endovasc Surg* **46**(5): 569–574.

Yangco, B. C. (1989). "CDC definitions for nosocomial infections." *Am J Infect Control* **17**(1): 42–43.

Ye, W., C. W. Liu, J. B. Ricco, K. Mani, R. Zeng and J. Jiang (2011). "Early and late outcomes of percutaneous treatment of TransAtlantic Inter-Society Consensus class C and D aorto-iliac lesions." *J Vasc Surg* **53**(6): 1728–1737.

Zeller, T., I. Baumgartner, D. Scheinert, M. Brodmann, M. Bosiers, A. Micari, P. Peeters, F. Vermassen, M. Landini, D. B. Snead, K. C. Kent, K. J. Rocha-Singh and I. P. D. T. Investigators (2014). "Drug-eluting balloon versus standard balloon angioplasty for infrapopliteal arterial revascularization in critical limb ischemia: 12-month results from the IN.PACT DEEP randomized trial." *J Am Coll Cardiol* **64**(15): 1568–1576.

Zhan, L. X., B. C. Branco, D. G. Armstrong and J. L. Mills, Sr. (2015). "The Society for Vascular Surgery lower extremity threatened limb classification system based on Wound, Ischemia, and foot Infection (WIfI) correlates with risk of major amputation and time to wound healing." *J Vasc Surg* **61**(4): 939–944.

UNIVERSITY
OF TURKU

Painosalama Oy, Turku, Finland 2020

ISBN 978-951-29-8320-9 (PRINT)
ISBN 978-951-29-8321-6 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)