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Aspects on vascular and endovascular surgery in patients with diabetes mellitus and lower limb ischemia

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2021

Document Version:
Publisher's PDF, also known as Version of record

Link to publication

Citation for published version (APA):
Butt, T. (2021). *Aspects on vascular and endovascular surgery in patients with diabetes mellitus and lower limb ischemia*. [Doctoral Thesis (compilation), Vascular Diseases - Clinical Research]. Lund University, Faculty of Medicine.

Total number of authors:
1

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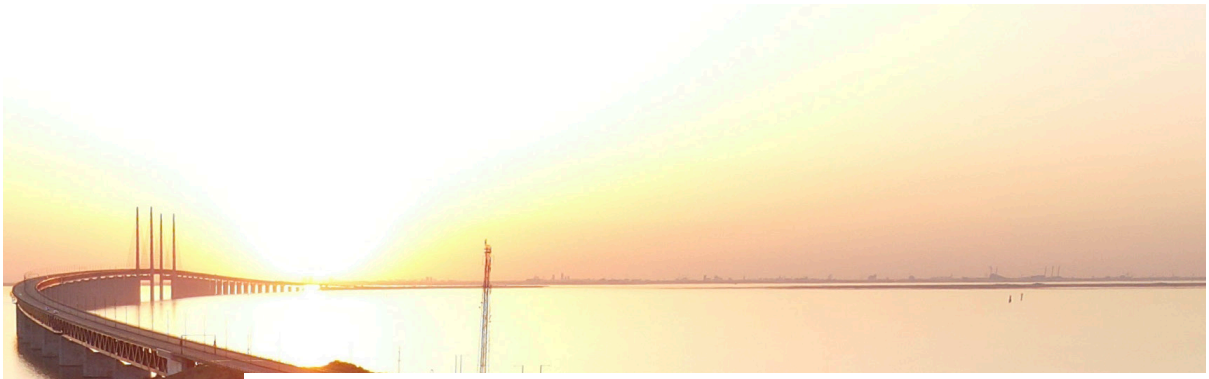

Aspects on vascular and endovascular surgery in patients with diabetes mellitus and lower limb ischemia

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Aspects on vascular and endovascular surgery in patients with diabetes mellitus and lower limb ischemia

Talha Butt



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DOCTORAL DISSERTATION

by due permission of the Faculty of Medicine, Lund University, Sweden.
To be defended at Vascular Center, Skåne University Hospital Malmö,

June 12, 2021, at 9 AM.

Faculty opponent

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Department of Radiology, University of Copenhagen, Copenhagen, Denmark

Organization LUND UNIVERSITY Faculty of Medicine Departament of Clinical Sciences, Malmö	**Document name** DOCTORAL DISSERTATION
	Date of issue June 12th 2021
Author: Talha Butt	Sponsoring organization

Title: Aspects on vascular and endovascular surgery in patients with diabetes mellitus and lower limb ischemia

Background

Diabetes mellitus (DM) is a major risk factor for peripheral arterial disease (PAD), which affects 9-24% of patients with DM during their lifetime. These patients have a 10-20-fold increased risk of amputation compared to subjects without DM. Chronic kidney disease is associated with DM, and 80% of the global end-stage renal disease are caused by DM or hypertension.

Aims

The general aim of this thesis was to evaluate the effects of DM in patients treated for acute lower limb ischemia (ALI) and revascularization options in patients with DM and chronic limb-threatening ischemia (CLTI).

The specific aims were to;

- Evaluating diagnostic performance of computed tomography angiography (CTA) of the calf arteries in ALI and to compare patients with and without DM (paper I)
- Evaluating if patients with DM undergoing CTA and local continuous thrombolysis for ALI, had an increased risk of developing contrast-associated acute kidney injury (CA-AKI) compared to patients without DM (paper II)
- Evaluating the outcome of local intra-arterial thrombolysis for ALI in patients with DM compared to those without DM (paper III)
- Evaluating the difference in amputation-free survival (AFS) after open and endovascular revascularization in patients with diabetic foot ulcer (DFU) and PAD (paper IV)
- Evaluating the difference in AFS after open and endovascular revascularization in patients with DM, PAD and heel ulcers (paper V)

Material and methods:

All studies were retrospective studies of patients with ALI and with and without DM (papers I-III) and of patients with CLTI and DM (papers IV-V) at Skåne University Hospital, Sweden. In paper I, diagnostic performance of CTA was calculated using digital subtraction angiography (DSA) as reference. Inter-rater reliability was expressed as intraclass correlation (ICC) with 95% confidence intervals (CI). Multivariable logistic regression analyses were performed in paper II, propensity score adjusted analyses in papers III and IV, and multivariable Cox regression analyses in paper V.

Results

The sensitivity of CTA for assessment of infra-popliteal Trans-Atlantic Inter-Society Consensus Document II (TASC) grade D lesions in patients with ALI was lower in patients with DM (0.14 [95% CI -0.12-0.40]) compared to those without DM (0.64 [95% 0.48-0.80]). The frequency of CA-AKI was 27.9% and 20.6% in patients with and without DM, respectively (p=0.30). When entering DM, gram-iodine dose/estimated glomerular filtration rate (eGFR) ratio, age and gender as covariates in a logistic regression model, there was a trend that gram-iodine dose/eGFR ratio (OR 1.42, 95% CI 1.00-2.02; p=0.050) was associated with an increased risk of CA-AKI. Among patients with CA-AKI, patients with DM had worse renal function at discharge compared to those without DM (p<0.001). After intra-arterial thrombolysis for ALI patients with DM showed higher rate of major amputation at one (OR 2.52; 95% CI 1.22-5.20) and three years (OR 2.52; 95% CI 1.26-5.04), and lower amputation-free survival (AFS) rate at three years (OR 0.46; 95% CI 0.25-0.85). Long-term mortality, major amputation, and AFS were all similar in patients with DM and PAD undergoing endovascular and open revascularization first. In patients with DM, PAD and isolated heel ulcer the AFS was higher after open compared to after endovascular surgery (HR 2.1, 95% CI 1.1-3.9; p=0.025).

Conclusion

The diagnostic performance of CTA of the calf arteries in patients with ALI was not acceptable for TASC D lesions in patients with DM. CTA followed by local continuous thrombolysis resulted in high frequency of CA-AKI in both patients with and without DM, without difference in risk of developing CA-AKI in patients with compared to without DM. Patients with DM who developed CA-AKI had a lower eGFR at discharge compared to at admission, and patients with DM and ALI treated with local continuous thrombolysis had a lower AFS compared to ALI patients without DM. There was no long-term difference in AFS between DFU patients treated with open or endovascular surgery first, whereas patients with DM, PAD, and isolated heel ulcer had a higher AFS when treated with open vascular surgery first.

Consideration should be given to presence of DM in patients with ALI and CLTI, both when chosing diagnostic and treatment methods.

Key words: Diabetes mellitus, Acute limb ischemia, Chronic limb-threatening ischemia

Classification system and/or index terms (if any)

Supplementary bibliographical information		**Language:** English
ISSN: 1652-8220		**ISBN 978-91-8021-072-0**
Recipient's notes	**Number of pages: 83**	Price
	Security classification	

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Cover photo: Sunset in Malmö, Sweden. “The movement meter for Lernacken-The Tower”, sculptured by Olafur Eliasson, and the Öresund bridge, symbols of stent and bypass, respectively. Revascularization options discussed in the present thesis.

Photo taken by drone dji mavic air 2 by Talha Butt and idea from Kjerstin Ädel Malmborg

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Faculty of Medicine
Department of Clinical Sciences, Malmö

ISBN 978-91-8021-072-0
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University
Lund 2021



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MADE IN SWEDEN

To my beloved family

"There is an art to flying, or rather a knack. The knack lies in learning how to throw yourself at the ground and miss. .... Clearly, it is this second part, the missing, that presents the difficulties."—Douglas Adams, Life, the Universe and Everything (The Hitchhiker's Guide to the Galaxy)

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Papers included in the thesis

This thesis is based on the following papers, referred to in the text by their Roman numerals and reprinted with permission from their respective publishers.

I. Butt T, Lehti L, Apelqvist J, Gottsäter A, Acosta S. Influence of diabetes on diagnostic performance of CTA of the calf arteries in acute limb ischemia. Acta Radiologica. 2021. http://doi.org/10.1177/02841851211006918

II. Butt T, Lehti L, Apelqvist J, Gottsäter A, Acosta S. Contrast-associated acute kidney injury in patients with and without diabetes mellitus undergoing CT angiography and local thrombolysis for acute lower limb ischemia. Submitted manuscript.

III. Butt T, Gottsäter A, Apelqvist J, Engström G, Acosta S. Outcome of intra-arterial thrombolysis in patients with diabetes and acute lower limb ischemia: a propensity score adjusted analysis. J Thromb Thrombolysis 2017; 44: 475-480.

IV. Butt T, Lilja E, Elgzyri T, Apelqvist J, Gottsäter A, Engström G, Acosta S. Amputation-free survival in patients with diabetic foot ulcer and peripheral arterial disease: Endovascular versus open surgery in a propensity score adjusted analysis. J Diabetes Complications 2020; 34: 107551.

V. Butt T, Lilja E, Örneholm H, Apelqvist J, Gottsäter A, Eneroth M, Acosta S. Amputation-free survival in patients with diabetes mellitus and peripheral arterial disease with heel ulcer: Open versus endovascular surgery. Vasc Endovascular Surg 2019; 53: 118-125.

Abbreviations

ABI	Ankle-brachial index
AFS	Amputation-free survival
ALI	Acute lower limb ischemia
AP	Ankle pressure
BASIL	Bypass versus angioplasty in severe ischemia of the leg
BEST-CLI	The best surgical therapy for patients with critical limb ischemia
CA-AKI	Contrast-associated acute kidney injury
CDT	Catheter-directed thrombolysis
CKD	Chronic kidney disease
CLTI	Chronic limb-threatening ischemia
CTA	Computed tomography angiography
CVD	Cardiovascular disease
DFU	Diabetic foot ulcer
DM	Diabetes mellitus
DPN	Diabetic peripheral neuropathy
DSA	Digital subtraction angiography
DUS	Duplex ultrasound scanning
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
GFR	Glomerular filtration rate
GVG	Global vascular guidelines
IC	Intermittent claudication
IVUS	Intravascular ultrasound
LDL	Low-density lipoprotein

LMWH	Low-molecular weight heparin
MRA	Magnetic resonance angiography
NDR	National Diabetes Register
Ox-LDL	Oxidized low-density lipoprotein
PAD	Peripheral arterial disease
RCT	Randomized controlled trial
SMC	Smooth muscle cell
SVS	Society for Vascular Surgery
SWEDEPAD	Swedish drug-elution trial in peripheral arterial disease
TASC II	Trans-Atlantic Inter-Society Consensus Document II
TP	Toe pressure
$TcPO_2$	Transcutaneous oxygen pressure
TBI	Toe-brachial index
WHO	World health organization
WIfI	Wound, Ischemia, foot Infection

Thesis at a glance

Paper	Aim	Method	Main results
I. Influence of diabetes on diagnostic performance of CTA of the calf arteries in acute limb ischemia	Evaluate diagnostic performance of CTA of the calf arteries in ALI, and to compare patients with and without DM	Retrospective study of 108 patients of whom 23 had DM. All underwent evaluable CTA and initial DSA when undergoing local intra-arterial thrombolysis. Classification according to TASC II	The sensitivity of CTA for assessment of infra-popliteal TASC D lesions in patients with ALI was not acceptable in patients with DM in contrast to those without DM
II. Contrast-associated acute kidney injury in patients with and without diabetes mellitus undergoing CT angiography and local thrombolysis for acute lower limb ischemia	Evaluate if patients with DM undergoing CTA and local continous thrombolysis for ALI ran increased risk of devoloping CA-AKI compared to patients without DM	Retrospective study of 213 patients, 43 with DM, undergoing CTA and local continous thrombolysis due to ALI	The frequency of CA-AKI was high, without difference in risk of CA-AKI in patients with compared to without DM. Among patients with CA-AKI, patients with DM had worse renal function at discharge compared to those without DM
III. Outcome of intra-arterial thrombolysis in patients with diabetes and acute lower limb ischemia: a propensity score adjusted analysis	Evaluate the outcome of local intra-arterial thrombolysis for ALI in patients with DM	Retrospective study of 399 patients of whom 83 had DM undergoing local continous thrombolysis due to ALI	Patients with DM had higher rate of major amputation at 1 and 3 years and lower amputation-free survival at 3 years in propensity score adjusted analysis
IV. Amputation-free survival in patients with diabetic foot ulcer and peripheral arterial disease: Endovascular versus open surgery in a propensity score adjusted analysis	Evaluate the difference in amputation-free survival between endovascular versus open surgery in patients with DFU and PAD	Retrospective study of 408 limbs with DFU and PAD. A total of 289 were treated with endovascular surgery and 119 with open vascular surgery	Long-term results in patients with DFU and PAD undergoing endovascular and open vascular surgery were similar. Rapid revascularization reduced the risk of amputation
V. Amputation-free survival in patients with diabetes mellitus and peripheral arterial disease with heel ulcer: Open versus endovascular surgery	Evaluate the difference in amputation-free survival between open and endovascular revascularization in patients with DM, PAD, and heel ulcers	Retrospective study of 127 patients with DM, PAD and heel ulcers. A total of 97 were treated with endovascular surgery and 30 with open vascular surgery	Amputation-free survival was higher in patients undergoing open vascular surgery

Introduction

Diabetes mellitus

Diabetes mellitus (DM) is a chronic metabolic disorder with increasing incidence during the past decades. It is characterized by abnormal carbohydrate metabolism causing hyperglycemia caused by the defect in insulin production, action, or a combination of both.[1] Long-term hyperglycemia is associated with complications which can be divided into macrovascular and microvascular complications. Macrovascular complications include cardio- and cerebrovascular disease and lower extremity arterial disease. Microvascular complications are, among others, diabetic peripheral neuropathy (DPN), diabetic nephropathy, and diabetic retinopathy.[2, 3] DM is the leading cause of cardiovascular disease, blindness, kidney failure, and lower limb amputation in almost all high-incomes countries.[1]

There are three main types of DM, of which type 2 DM is the most common, affecting about 90% of all individuals with DM.[4] The hyperglycemia in type 2 DM is caused by peripheral insulin resistance, whereas type 1 DM affecting 5-10% of individuals with DM is characterized by insulin deficiency caused by autoimmune destruction of the pancreatic beta cells.[4] The typical classical symptoms such as polydipsia and polyuria at diagnosis of type 1 DM are often lacking in an individual with type 2 DM, and many patients with type 2 DM are asymptomatic.[5] The third type of DM is gestational diabetes, causing hyperglycemia during pregnancy and usually disappears after delivery.[6]

According to the World Health Organization (WHO) the number of people suffering from DM worldwide is about 422 million, and 10% of the global health expenditure is spent on DM.[7] The prevalence is increasing, and it is projected that by the year 2045 there will be 700 million people with DM.[1] The number of diabetic individuals in Sweden is about 450,000.[8]

Diabetic nephropathy

Hyperglycemia causes dysfunction of the filtration mechanism of the kidney which leads to diabetic nephropathy with microalbuminuria. Microalbuminuria can progress into macroalbuminuria and finally to end-stage renal disease (ESRD).[9] There are several treatments available to prevent the development of diabetic nephropathy or halter the progression of kidney disease.[10] Swedish registry data [11, 12] show a decrease in ESRD in type 1 DM patients, due to better glycemic control and more rigorous control of hypertension. Increasing rates of ESRD has been reported in patients with type 2 DM, however, and 25% of all kidney transplants and initiation of dialysis are attributed to diabetic nephropathy.[4] DM also appears to amplify the risk of developing contrast-associated acute kidney injury (CA-AKI) in patients with underlying chronic kidney disease (CKD).[13] The mechanism explaining development of CA-AKI is a synergeic negative impact upon the kidney by DM and radiocontrast.[14] Both DM and radiocontrast causes altered renal oxygen supply, enhancing renal oxygen consumption and production of reactive oxygen species leading to tubular and vascular endothelial cell injury and finally to reduced glomerular filtration rate (GFR). GFR is commonly estimated in clinical settings by using serum creatinine levels.[14]

Diabetic foot ulcer

A diabetic foot ulcer (DFU) is defined as a "Foot ulcer in a person with currently or previously diagnosed diabetes mellitus and usually accompanied by neuropathy and/or peripheral arterial disease (PAD) in the lower extremity".[15]

Diabetic foot complications result from multicausal long term negative effects of DM, and it is important to understand their pathophysiology to be able to correctly treat these patients (Figure 1).[16] DFUs constitute a burden both for the individual patient and for the society, causing high healthcare expenditures.[17] Rice et al showed a cost of DFU in USA as high as 9-13 billion dollars.[18]

Atherosclerotic PAD is estimated to affect 9-24% of patients with DM during their lifetime,[19-21] and 8-25% of patients with DM will develop a foot ulcer.[19, 22] One in five DM patients with a DFU will be amputated, corresponding to a 10-20-fold increased risk of amputation compared to in subjects without DM.[1] The most common cause of hospitalization in patients with DM is the combination of DFU and PAD, and PAD is implicated as an important potentially treatable factor influencing the outcome of DFU.[23, 24]

Peripheral sensorimotor dysfunction of small- and large-fiber nerves causes loss of pain, temperature perception, and unsteadiness which might lead to trips and falls.[16] Patients with sensory neuropathy are also prone to repetitive minor trauma caused by ill-fitting shoes or foreign bodies inside a shoe, because of the decreased sensory function.[16] Motor neuropathy causes small-muscle wasting and foot deformities due to imbalances in the flexor and extensor function.[16] Autonomic neuropathy leads to a decrease in the sweating of the foot, which causes dry skin and promotes callus formation. With the callus in place, the pressure load on the foot increases, leading to subcutaneous hemorrhage and skin ulceration.[16] The majority of DFUs occur as a consequence of neuropathy or neuro-ischemia (Figure 2-3), and only a small percentage of DFUs are caused by PAD alone.[25] The combination of diabetic neuropathy and PAD predisposes the foot to injury and is a major risk factor for reduced wound healing and amputation.[26] The pathway from DM to amputation is best described by the "stairway to an amputation" (Figure 4).[27]

WHO and the International Diabetes Federation have concluded that 80% of all DM related amputations are preventable.[1, 7] Fitzgerald and co-workers[28] proposed that a limb salvage team need to comprise seven skills. The Global Vascular Guidelines (GVG) on the Management of Chronic Limb-Threatening Ischemia (CLTI) modified the seven essential skills and increased these to nine (Table 1).[27]

The idea of a multidisciplinary diabetic foot team is not new, Larsson et al published a paper on the topic already in 1995 reporting a 78% decrease in major amputation of DM patients after the introduction of a multidisciplinary foot care team consisting of a diabetologist, an orthopedic surgeon, a diabetes nurse, a podiatrist, and an

orthotist in close co-operation with a vascular surgeon.[29] A 34% decline in nationwide amputation rate has later been reported from the Netherlands after the implementation of a multidisciplinary team,[30] and decreases in hospitalization and amputation for the diabetic foot have also been reported from Italy.[31] Creating a functional multidisciplinary team to care for these patients seems to be successful. The management of the DFU is complex, and there is a huge need for specialists caring for these patients. Firstly, the glycemic control needs to be optimized,[32] special care and meticulous clinical examination is needed, and both local and deep cultures need to be taken from the wound in cases with suspected infection.[16, 33] Plain X-ray is valuable for the determination of osteomyelitis, and diabetic foot infection should be diagnosed and treated quickly to reduce amputation rate.[20, 33] Wound debridement, when needed, creates better conditions for tissue healing.[34] Furthermore, off-loading of the foot should be prescribed when a DFU is identified.[35] The sensory deficit in DM patients with DPN deprives the patient from the feeling of pain, and continuous pressure on the ulcer compromises healing.[33] Several options for off-loading are available and can be adapted to the needs of the individual patient. Total contact casts are regarded as the gold standard for off-loading, and several studies have shown positive effects of the method in patients with DFU.[36-38] Neurological examination, with use of monofilament for the examination of sensation and a tuning fork for the detection of vibratory sensation should also be performed.[16, 33] The monofilament is first placed on for instance the patients' hand to demonstrate the type of sensation induced, after which the monofilament is placed on three different points on both feet. The patient is asked whether he or she can feel the monofilament and locate the feeling on the foot. The tuning fork is placed on the elbow first to demonstrate the sensation, after which it is placed on a bony part of the dorsal side of the distal phalanx of the first toe. Wounds should be monitored by a health care organization interested in DFU, and leg revascularization should be considered in ulcers of arterial origin that does not heal or worsen during surveillance.[33]

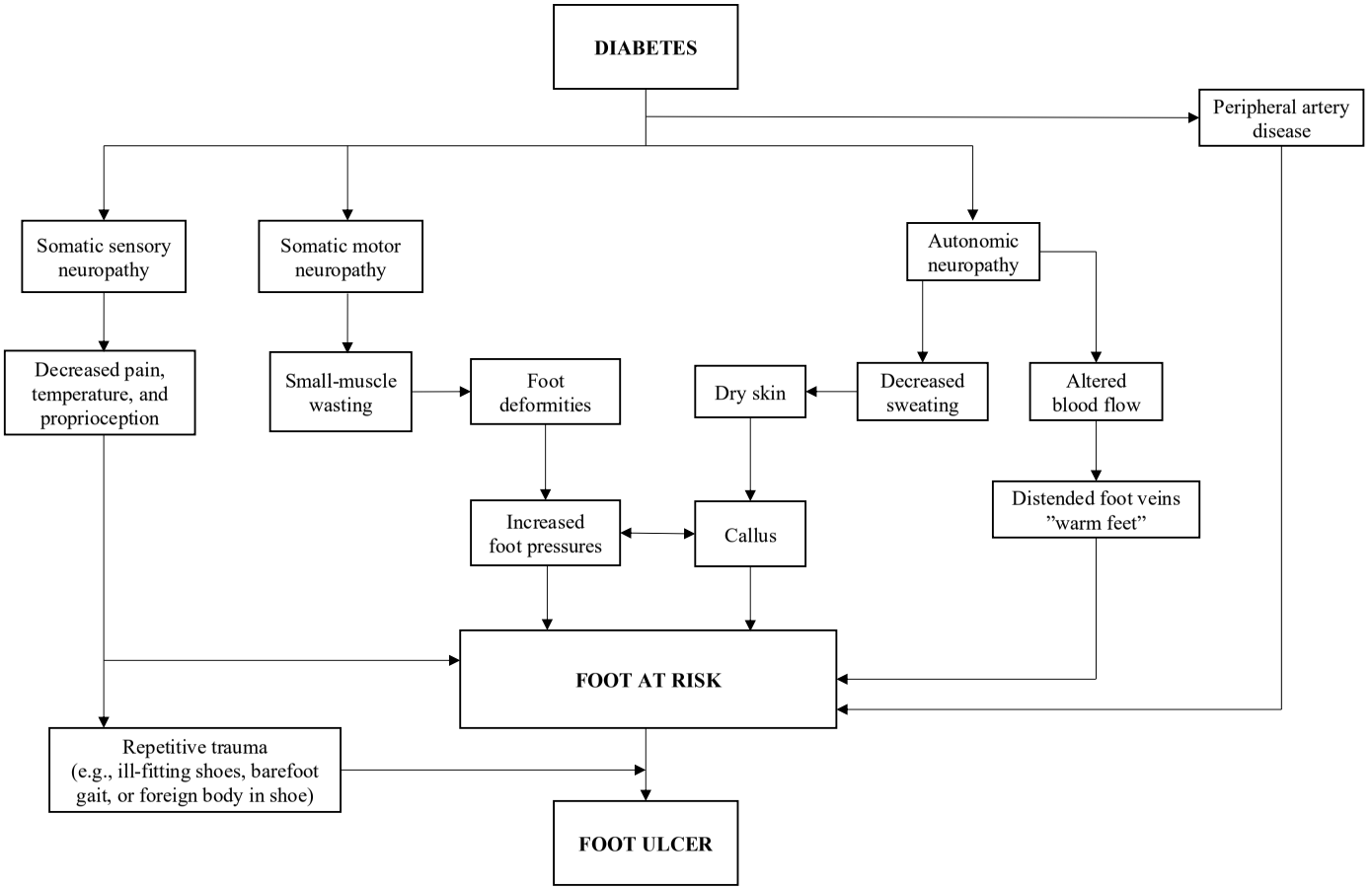


Figure 1[17] Showing the pathway to a DFU.



Figure 2 Individual with diabetes cardio/cerebrovascular disease. Previous below knee amputation. Now necrotic ulcer of unknow duration with rest pain on the dorsal area of digits in the remaining foot with signs of muscle wasting and decreased function. Systolic toe-brachial index of 0.20 and short occlusion of the superficial femoral artery and tibial anterior artery with continuity to the foot arteries (Wagner grade 2).



Figure 3 Individual with diabetes with peripheral neuropathy and foot ulcer with communication to bone caused by repeated paronychia. Bone destruction confirmed by X-ray on the distal phalange. Appearance of reddishness as sign of vasodilatation and edema. PAD with open vessels to the popliteal artery and multiple stenosis in two and occlusion in one below the knee artery (Wagner grade 3).

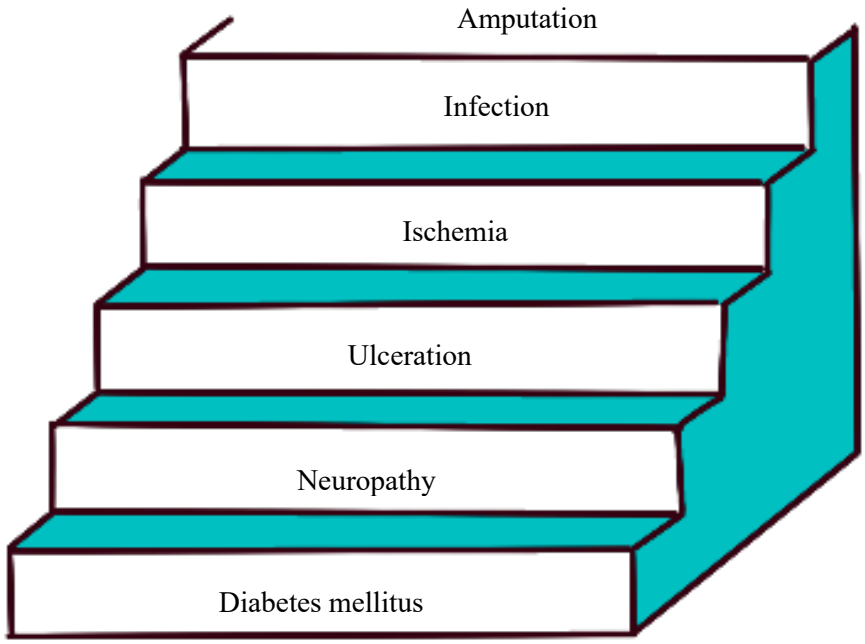


Figure 4 "Stairway to an amputation" showing the pathway from diabetes mellitus to amputation. Modified from Global vascular guidelines.[27]

Table 1 Essential skills for limb salvage team

Essential skills	Possible team members
The ability to perform hemodynamic and anatomic vascular assessment	Vascular surgeon Interventionalist (cardiologist or radiologist) Vascular physician
The ability to perform a peripheral neurologic workup	Neurologist Endocrinologist Podiatrist
The ability to perform site-appropriate culture technique	Infectious disease specialist Surgeon Wound nurse Physical therapist
The ability to perform wound assessment and staging or grading of infection and ischemia	Vascular surgeon Podiatrist Surgeon Infectious disease specialist Wound nurse Physical therapist
The ability to perform site-specific bedside and intraoperative incision and drainage or débridement	Podiatric surgeon Orthopedic surgeon Plastic surgeon Surgeon Vascular surgeon
The ability to initiate and to modify culture-specific and patient-appropriate antibiotic therapy	Infectious disease specialist Endocrinologist Primary care physician Vascular surgeon Podiatrist Surgeon
The ability to perform revascularization	Vascular surgeon Interventionalist (cardiologist or radiologist)
The ability to perform soft tissue or osseous reconstruction of deformities and defects	Podiatric surgeon Plastic surgeon Orthopedic surgeon Surgeon
The ability to perform appropriate postoperative monitoring to reduce risks of reulceration and infection	Podiatrist Wound nurse

Modified from Fitzgerald el al.[28]

Classification

There are several classification systems[39] in use for patients with CLTI and ulceration, focusing either on ischemia or ulcer characteristics. This multitude causes confusion and constitutes an obstacle in the development of treatment algorithms and assessments.[27] The most frequently used classification systems by vascular surgeons are the Fontaine[40] and Rutherford[41] classifications. The Fontaine classification is based on patient clinical presentation and does not require any diagnostic testing. The Rutherford classification for CLTI is similar to the Fontaine classification, with the addition of results of objective examinations such as treadmill test, ankle pressure (AP), toe pressure (TP), and pulse volume recording.[39] Diabetic foot specialists often use the Wagner[42] and University of Texas classifications.[43] The Wagner classification focuses solely on ulcer characteristics, with no reference to presence or absence of PAD (Table 2). The Trans-Atlantic Inter-Society Consensus Document II (TASC II) classification[25] grades the extent of the lesions to A-D in three anatomic locations: aorto-iliac, femoro-popliteal, and infra-popliteal (Figure 5). TASC II further recommends which modality, endovascular or open vascular surgery, that should be used for treatment of a particular type of lesion.[25]

Table 2 The Wagner grading system for foot ulcers.[42]

Wagner grade	Characteristics
0	No ulcer
1	Superficial ulcer (up to but not through dermis)
2	Ulcer extension involving ligament, tendon, joint capsule, or fascia (no abscess or osteomyelitis)
3	Deep ulcer with abscess and/or osteomyelitis
4	Gangrene of portion of the foot
5	Extensive gangrene of the foot

Given the increasing prevalence of DM[1] many cases of CLTI are now due to this disorder. Both the changing features of CLTI over time and the increased possibilities for revascularization have led to the need of a new classification system able to assess all the multiple factors associated with limb threat.[27] The Society for Vascular Surgery (SVS) therefore recently introduced the wound, ischemia, and foot infection (WIfI) classification system.[44] WIfI is recommended by the GVG in the management of CLTI[27] (figure 6[44]). The benefits of this classification system are that it is based on the extent of the foot wound, limb perfusion, and foot infection. Furthermore, it can also be used to estimate both amputation risk at one year and the likelihood of benefit of revascularization.[44]

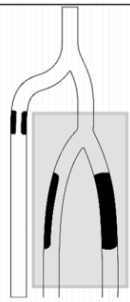
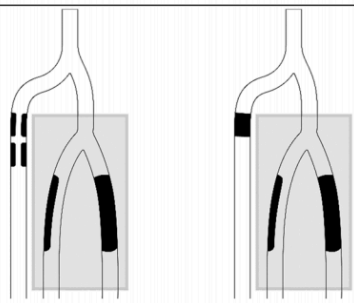
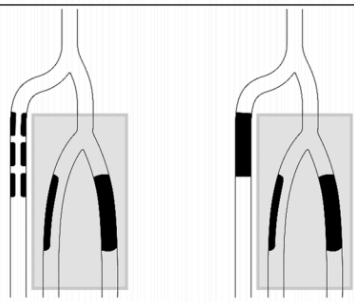
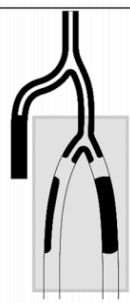
TASC A lesions Single focal stenosis, ≤5 cm in length, in the target tibial artery with occlusion or stenosis of similar or worse severity in the other tibial arteries.	
TASC B lesions Multiple stenoses, each ≤5 cm in length, or total length ≤10 cm or single occlusion ≤3 cm in length, in the target tibial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

Figure 5 Trans-Atlantic inter-society consensus document II (TASC II) for the management of peripheral arterial disease - classification of infrapopliteal lesions.[45] The figure was reused by permission from Lars Norgren.

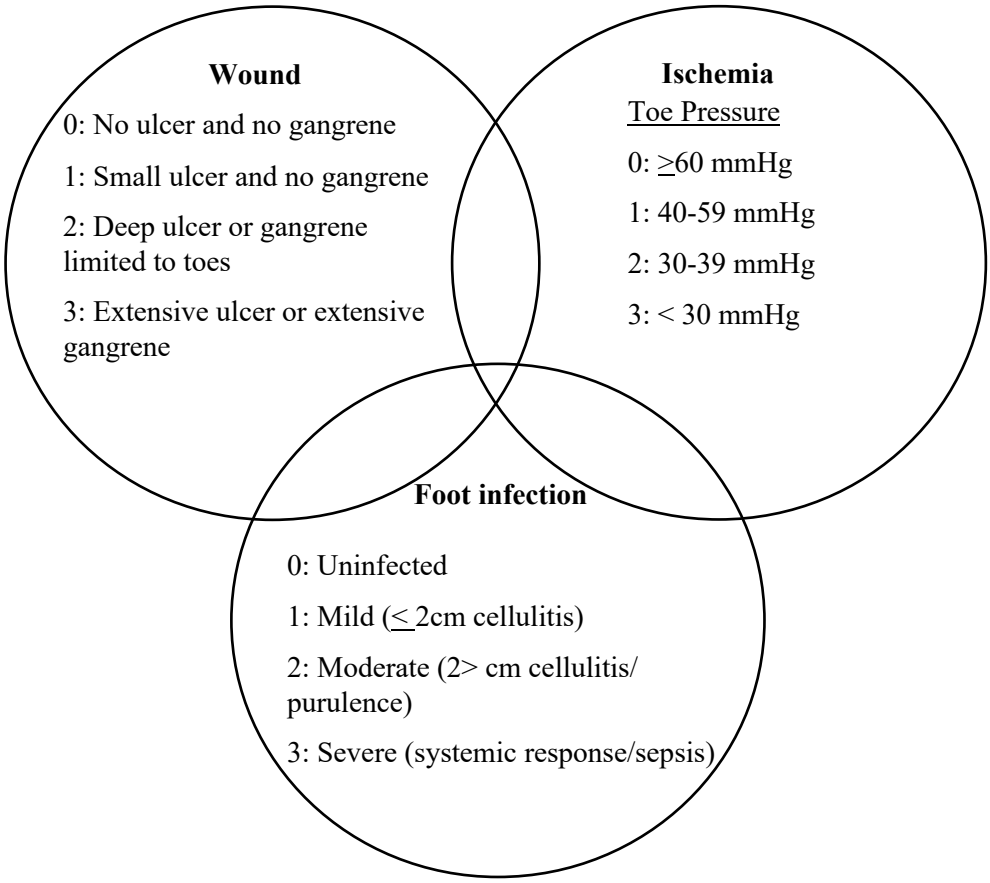


Figure 6 Society for Vascular Surgery, wound, ischemia, foot infection (WIfI) classification.[44]

Atherosclerosis

Atherosclerosis is a multifactorial disease which might affect arterial beds throughout the body.[46] Since the process of atherosclerosis begins early and progresses slowly, it is often asymptomatic during a period of years, and when the symptoms occur they are often related to the narrowing or thrombotic occlusion of an artery causing blood flow disturbances.[47] Such symptoms can be acute or chronic (Table 3). Development of aortic dissection[48] and aneurysm,[49] on the other hand, appear to be only partly mediated by atherosclerosis or its risk factors.

Table 3 Clinical manifestations mediated by atherosclerosis.

Carotid and cerebral arteries	Coronary arteries	Aorta	Renal arteries	Mesenteric arteries	Peripheral arteries
→Stroke →TIA →Vascular dementia	→ACS →Stable angina → Silent myocardial ischemia	→Aortic rupture →Aortic occlusion →Aortic dissection →Aortic aneurysm	→Renal artery occlusion →Worsening renal function →Renovascular hypertension	→Acute mesenteric ischemia →Chronic mesenteric ischemia	→Acute peripheral arterial occlusion →CLTI →IC

TIA= transient ischemic attack. ACS= acute coronary syndrome. CLTI= chronic limb-threatening ischemia. IC= intermittent claudication

The arterial wall is composed by three layers, the outermost adventitia, the middle media, and the innermost intima (Figure 7).[50] Atherosclerosis affecting medium and large sized arteries by the deposit of fatty materials in the intima can manifest as cardiovascular disease,[51] the leading cause of death worldwide causing 31% of all deaths globally in 2016.[52] PAD is defined as atherosclerosis affecting the lower extremity arteries, and can cause intermittent claudication (IC) and CLTI.[53]

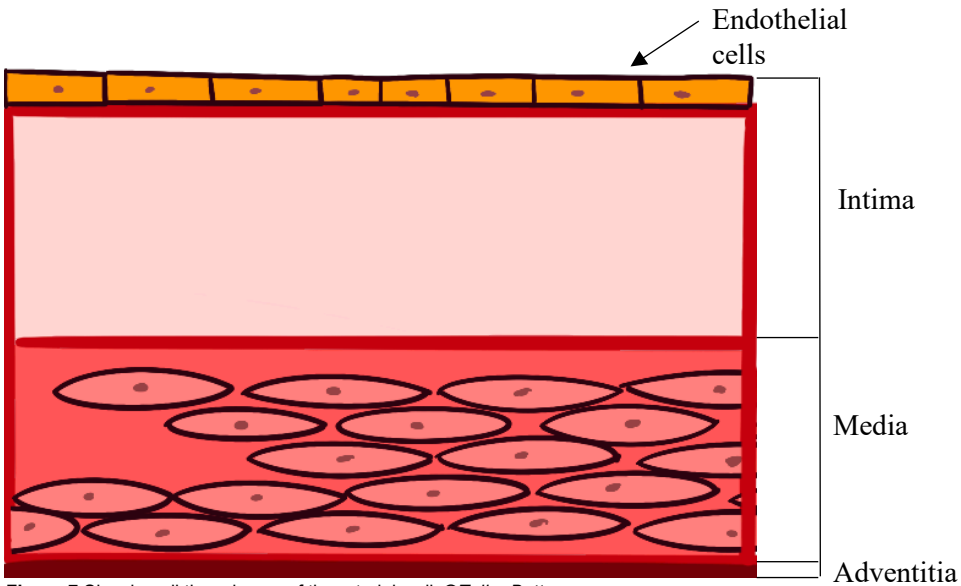


Figure 7 Showing all three layers of the arterial wall. ©*Talha Butt*

Pathophysiology

The pathophysiology of atherosclerosis is multifactorial. The atherosclerotic process starts with dysfunction of the endothelium, the cells that line the intima. This allows deposition in the tunica intima of low-density lipoprotein (LDL), which is subsequently oxidized to Oxidized- LDL (Ox-LDL) (Figure 8).[51]

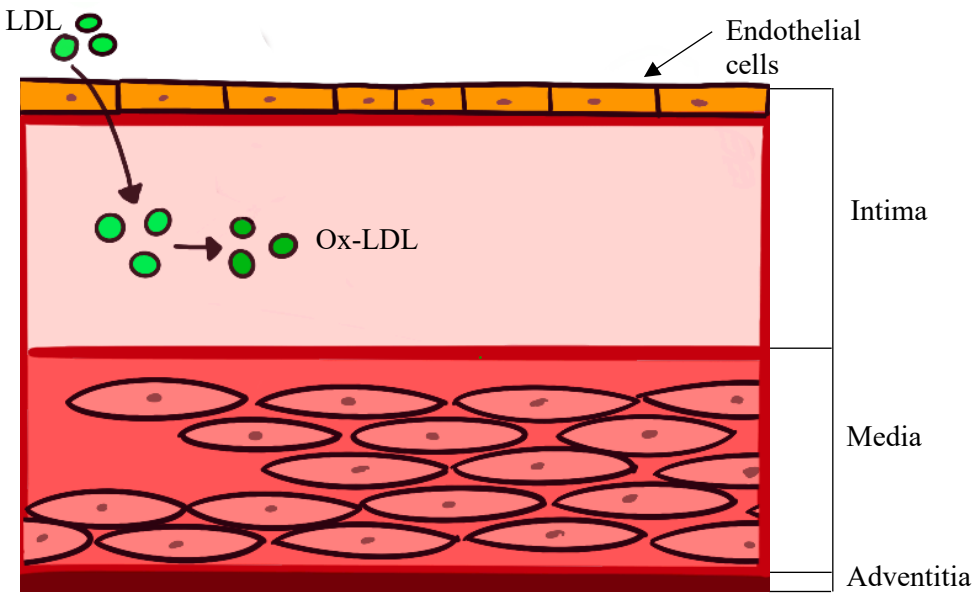


Figure 8 Showing the deposit of circulating LDL to the intima, which becomes oxidizied.
©Talha Butt

The Ox-LDL hereafter activates endothelial cells, allowing adhesion of white blood cells, monocytes. The monocytes aggregate into the intima, differentiate to macrophages, and take up the Ox-LDL to form foam cells. Foam cells promote both the migration of smooth muscle cells (SMC) from the tunica media of the vessel wall to the tunica intima, and smooth muscle cell proliferation (Figure 9).[51]

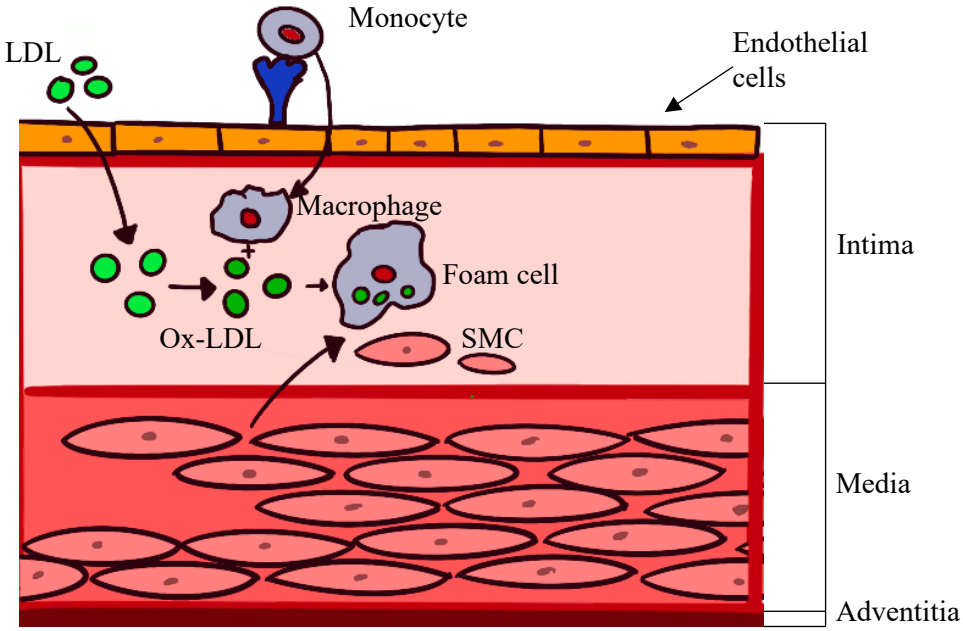


Figure 9 Showing the entry of monocytes into the intima and maturing into macrophages and forming foam cells after taking up Ox-LDL. Migration of SMC from the media to the intima is also seen. ©*Talha Butt*

Smooth muscle cell proliferation increases the synthesis of collagen, hardening the plaque. As the atherosclerotic process continues, foam cells die and release their content. The plaques continue to grow and develop a lipid-rich core which is covered by fibrous tissue and with smooth muscle cells. The growing plaque can thereafter rupture due to increased pressure, leading to the formation of a thrombus[51] (Figure 10). The thrombus will eventually either partly dislodge, causing peripheral embolization within the arterial circulation, or totally occlude the artery.[51]

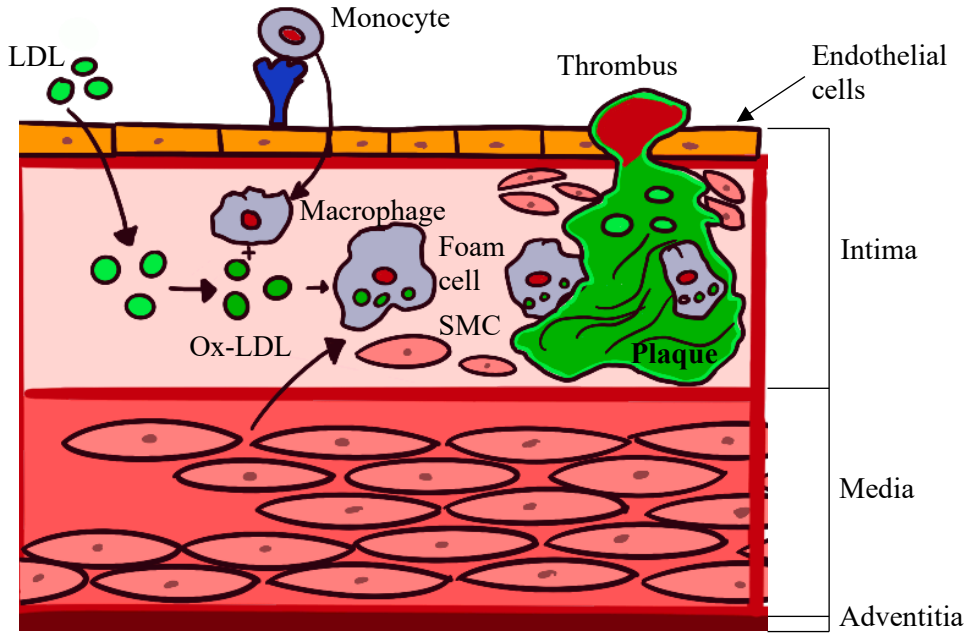


Figure 10 Showing the final plaque formation and thrombus formation. ©*Talha Butt*

Risk factors

There are several known risk factors for the development of atherosclerosis, which can be divided into unmodifiable and modifiable (Figure 11).[54] Male sex[55] and family history[56, 57] are examples of unmodifiable risk factors. An individual with a first-degree male relative with ischemic coronary heart disease before the age of 55 has a 2.5-7 times higher risk of developing the same disease.[58] Obesity is also associated with higher risk of atherosclerosis,[59] and obese individuals can reduce their risk of cardiovascular disease by regular physical activity.[60, 61] The fact that the process of atherosclerosis is still not fully elucidated is reflected by its potential occurrence in individuals without established risk factors,[62] whereas some individuals may remain disease free despite an evident risk factor load.[63]

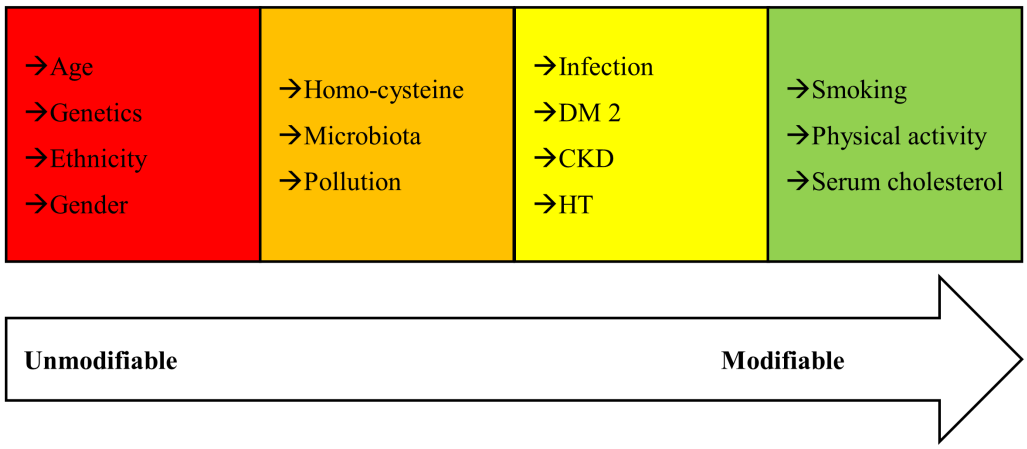


Figure 11 Showing risk factors for atherosclerosis running from unmodifiable to modifiable.[54]
DM 2= Diabetes mellitus type 2, CKD=chronic kidney disease, HT=hypertension

Treatment

Risk factor exposure early in life might affect later incidence of cardiovascular disease (CVD),[64] causing a heavy burden for global health care.[65] Apart from treatment, preventive measures such as increased physical activity, healthy diet, and cessation or abstinence of smoking have all been proven efficient and should therefore be thoroughly implemented.[66] A healthy diet and regular physical activity might help reduce the risk of obesity and negative lipid profile.[67] Furthermore preventive pharmacological treatment should be implemented to reduce the risk of cardiovascular events in DM patients using antihypertensive, lipid-lowering, and antithrombotic drugs,[68] along with good glycemic control.[69]

Peripheral arterial disease

The development of PAD is asymptomatic in 20-50% of individuals,[68, 70, 71] and the disease might in such cases be detected only as a slightly lowered ankle-brachial index (ABI).[68] Commonly occurring symptoms in later stages of PAD are IC or CLTI.[68] Furthermore, PAD patients often have concomitant atherosclerotic manifestations elsewhere in the arterial tree, and a 6-fold higher risk of dying from CVD over 10 years compared to those without PAD.[72-74] Among patients who are diagnosed with CLTI and untreated, one in five will die within one year of diagnosis.[75]

Intermittent claudication

IC manifests itself as pain in the affected leg while walking, which resolves with rest.[68] Depending on the distribution of atherosclerosis, different muscle groups are affected. Aortoiliac disease causes IC in buttocks and hip, whereas femoropopliteal lesions cause IC in thighs and calves.[76] The primary investigation and treatment of patients with IC should focus on assessing and treating their cardiovascular risk factors, since patients with IC have significant cardiovascular morbidity and mortality.[77] Regular exercise has been shown to increase the maximal walking distance in patients with IC, it does not improve ABI, however.[68]

Chronic limb-threatening ischemia

The definition of CLTI has been updated in the GVG on the management of the condition, published in 2019.[27] CLTI is now defined as atherosclerotic PAD causing rest pain or tissue loss. The symptoms should have been present for more than two weeks and combined with abnormal hemodynamic parameters.[27] The cause of CLTI is often multilevel arterial occlusive disease. An increasing number of cases are caused by crural and pedal artery occlusive disease due mainly to DM or CKD. [27] Patients with CLTI are often elderly and have major cardiovascular risk factors, high mortality, and highly increased risk for amputation. Public awareness of the condition is low, however, and the diagnosis is therefore often delayed in relation to onset of symptoms.[27]

Acute lower limb ischemia

Acute lower limb ischemia (ALI) is defined as acute onset of decreased blood supply to the limb threatening its viability, and associated with significant risk of morbidity, amputation, and mortality.[78] To qualify as acute, the symptoms cannot have been present for longer than two weeks.[79] Ischemia occurs when the decreased blood flow causes a shift towards anaerobic metabolism, resulting in increased production of lactate.[80] The highly sensitive sensory nerves are first affected by ischemia, followed by the motor nerves, and the limb might become immediately threatened within 4 to 6 hours after onset of severe ALI.[79] The severity of ALI is graded by Rutherford's ALI classification, ranging from viable (grade I) to irreversible (grade III). (Table 4).[41, 81]

Table 4 Rutherford's classification for ALI[41]

Grade	Category	Sensorry loss	Motor deficit	Prognosis	Doppler signals	
					Arterial	Venous
I	Viable	None	None	No immediate threat	Audible	Audible
IIa	Marginally threatened	None-minimal	None	Salvagable if promptly treated	Inaudible	Audible
IIb	Immediately threatened	More than just toes	Mild/moderate	Salvagable if promptly revascularised	Inaudible	Audible
III	Irreversible	Profound, aneshetic	Profound, paralysis (rigor)	Major tissue loss. Amputation. Permanent nerve damage inevitable	Inaudible	Inaudible

ALI can be caused by either embolic or thrombotic vessel occlusions.[79] The proportion of ALI caused by thrombotic occlusions of previous endovascular or bypass reconstructions has increased.[82] Furthermore, ALI might also be caused by either a thrombotic occlusion of a peripheral aneurysm, most often in the popliteal artery,[83] or distal embolization from such an aneurysm to the calf arteries. Both aortic and other arterial dissections and traumatic arterial injuries are other important causes of ALI.[78, 79] It is not always clear cut to distinguish between embolic and thrombotic causes of ALI. ALI caused by embolization is associated with more sudden onset of symptoms, whereas thrombotic events more often cause gradually aggravated symptoms due to the existence of a more developed collateral circulation in patients with previous atherosclerotic stenoses.[78] The symptoms of ALI are classically divided into the six Ps: pain, pallor, pulselessness, perishing cold, paresthesia, and paralysis (Figure 12). It is, however, uncommon that a patient presents with all six "Ps" occurring simultaneously.[79] The presence of paralysis of the lower extremity is associated with the worst prognosis.[41] This urgent and possibly fatal condition needs to be immediately assessed by a vascular specialist to

determine diagnostic and treatment options. There are several treatment options for ALI: open vascular surgery, endovascular surgery, combinations of open and endovascular surgery (hybrid surgery), conservative therapy with anticoagulation alone, amputation, or palliative treatment. The treatment option is based on the severity of ischemia, anatomic location, duration of symptoms, etiology, and the general condition of the patient.[27, 84]



Figure 12 Embolism to the lower extremities.
A 95 year old female patient with atrial fibrilation and arterial embolization to the right external iliac artery and left iliaco-femoral arterial segment causing acute limb ischemia. Rutherford classes I and III, respectively. ©*Talha Butt*

Investigation of chronic limb-threatening ischemia and acute limb ischemia

A thorough review of a patient's history, including past and current illnesses, drug history, physical examination, non-invasive hemodynamic tests, and arterial imaging are the cornerstones for diagnosis and determination of the extent and severity of the arterial disease.[68]

Non-invasive hemodynamic tests

There are several non-invasive hemodynamic tests that can be performed to assess the degree of ischemia. The first line examination is ABI, which can be easily and quickly performed by the clinician in both emergency and non-emergency settings. An ABI ≤0.9 or >1.4 is considered abnormal.[53] In patients with DM or CKD the crural vessels are often less compressible, and it is therefore recommended to measure toe-brachial index (TBI) in the non-emergency setting.[27] A TBI lower than 0.7 is considered abnormal.[85] Transcutaneous oxygen pressure ($TcPO_2$) measurement is another alternative, used in some centers.[53, 86] The perfusion of the foot can also be evaluated after an intravenous injection of indocyanine green followed by fluorescence imaging using an infrared camera.[87] The correlation between $TcPO_2$ and an increased rate of fluorescence intensity has been shown to be strong in patients with DM.[87] Fluorescence imaging can therefore contribute valuable complementary information in for instance patients with falsely elevated ankle pressure or inability to measure TBI due to previous minor amputations.[88] The drawbacks of the fluorescence technique are its inability to measure circulation in necrotic surface areas and the high costs of the necessary equipment.[88]

Imaging

Non-invasive imaging should preferably be performed prior to intervention in all patients with CLTI and most patients with ALI. It is debatable, however, if patients with ALI and motor deficit should undergo non-invasive imaging first or immediate on-table angiography at operation.[78]

Duplex ultrasound scanning (DUS) both provides a portable and rapid assessment of the anatomic level of the arterial occlusion or stenosis without exposure for iodine contrast or ionizing radiation, and measures flow volume and velocity. It is, however, operator dependent, time consuming, and has suboptimal performance in the aortoiliac and infrapopliteal arterial segments.[89, 90]

Computed Tomographic Angiography (CTA) is widely available around the clock, providing images of high quality of both vascular and extra-vascular pathology.[91, 92]

It may, however, have a lower diagnostic performance in the infrapopliteal segment and exposes the patient to both iodine contrast and ionizing radiation.[93]

Magnetic Resonance angiography (MRA), on the other hand, has the benefit of not exposing the patient to the hazards of iodine contrast or ionizing radiation.[94] It can produce high quality images, especially in the infrapopliteal segment.[95, 96] Because of the long examination time and the availability of the method during office hours only, it is, however, not suitable for use in most patients with ALI. MRA also fails to visualize calcifications in the vessel walls and might overestimate the degree of stenosis, drawbacks that are clinically important for the surgeon.[27]

Digital subtraction angiography (DSA) is still considered the gold standard in arterial imaging, yielding high resolution images of the arterial tree. It is, however, invasive, and therefore mostly used in patients undergoing subsequent intervention during the same session.[97, 98] With this method the vascular surgeon can combine repeated diagnostic imaging with treatment, and to end the procedure with an accurate completion control. The exposure to iodine contrast may have adverse effects on renal function,[99] but with the use of carbon dioxide (CO_2) angiography exposure to iodine contrast might be reduced, sparing renal function.[100]

Management of chronic limb-threatening ischemia and acute limb ischemia

Chronic limb-threatening ischemia

As patients with CLTI have high-risk not only for amputation but also for CVD and death by stroke or myocardial infarction,[75] they benefit from both medical and surgical treatment. All patients with PAD should therefore be evaluated for treatment of modifiable risk factors to lower their cardiovascular mortality.[53]

Best medical treatment

Antithrombotic therapy with either aspirin or clopidogrel is recommended for all patients with symptomatic PAD.[101] Both the Cardiovascular Outcome for People Using Anticoagulation Strategies (COMPASS)[102] and Vascular Outcomes study of ASA along with rivaroxaban in Endovascular or surgical limb Revascularization for Peripheral Artery Disease (VOYAGER PAD)[103] studies indicated that low dose rivaroxaban 2.5 mg twice daily combined with aspirin lowers the risk of cardiovascular complications without substantially increasing the risk for bleeding complications. The combination can therefore be considered in patients with CLTI.[101]

The use of statins lower LDL cholesterol and has been convincingly shown to confer both reductions in overall and cardiovascular mortality, among patients with PAD.[68, 104, 105] Furthermore, use of statins have shown an increased 1 year survival in patients undergoing infrainguinal bypass surgery for CLTI.[106] The inflammatory component of atherosclerosis[107] seems to be reduced by statin treatment in patients with PAD, explaining the reduction of major vascular events,[108] further strengthening the recommendations for use of statins in the PAD setting.[27, 68, 101]

Among patients with hypertension and coronary artery disease, those with CLTI and PAD, have a substantially increased risk for major adverse cardiovascular events compared to patients without PAD.[109] As this risk is clearly related to higher blood pressure,[110, 111] the GVG[27] strongly recommends hypertension control with target blood pressure levels of <140 mm Hg systolic and <90 mm Hg diastolic in patients with CLTI.[27]

Optimal glycemic control in patients with DM is also recommended by the GVG,[27] since type 2 DM is a well-established risk factor for PAD[112]. General lifestyle changes are recommended to optimize control of risk factors, in particular cessation of smoking[113] which has been extensively studied with regard to cardiovascular disease.[114] DM patients are recommended either a Mediterranean diet with low content of saturated fats and high content of monosaturated fats, or a general low-fat diet,[115] which are both associated with decreased risk for development and progression of atherosclerosis.[116] In individuals with DM, higher intake of fish and shellfish has been associated with reduced incidence of symptomatic PAD.[117] Exercise in the form of walking is also recommended for patients with PAD. Most studies on the health benefit of exercise have been conducted among patients with IC,[118] however, and studies on this topic are for natural reasons lacking in CLTI. Metformin is the primary oral hypoglycemic treatment for type 2 DM,[119] but newer drugs such as sodium glucose co-transporter 2 inhibitors have recently been shown to confer specific cardiovascular benefits and might therefore be considered in type 2 DM patients with PAD.[120]

Open and endovascular surgery

The Bypass versus Angioplasty in severe ischemia the Leg (BASIL)-1 study[121] completed in 2004 showed similar amputation-free survival (AFS) in CTLI patients undergoing open and endovascular surgery.[122] Since then, however, advances in endovascular equipment and techniques have emerged and the endovascular treatment options have been substantially expanded.[121, 123] The BASIL-2 study[123] which started in 2014 is now closed for randomization between its two treatment arms; either an open vein by-pass first strategy or a best endovascular revascularization first strategy. The study results are eagerly awaited. The Best Surgical Therapy for Patients With CLI (BEST-CLI)[124] trial which started in 2014 is estimated to be completed by June 2022. Also in this study, CLTI patients are randomized to either open or endovascular surgery (Figure 13).

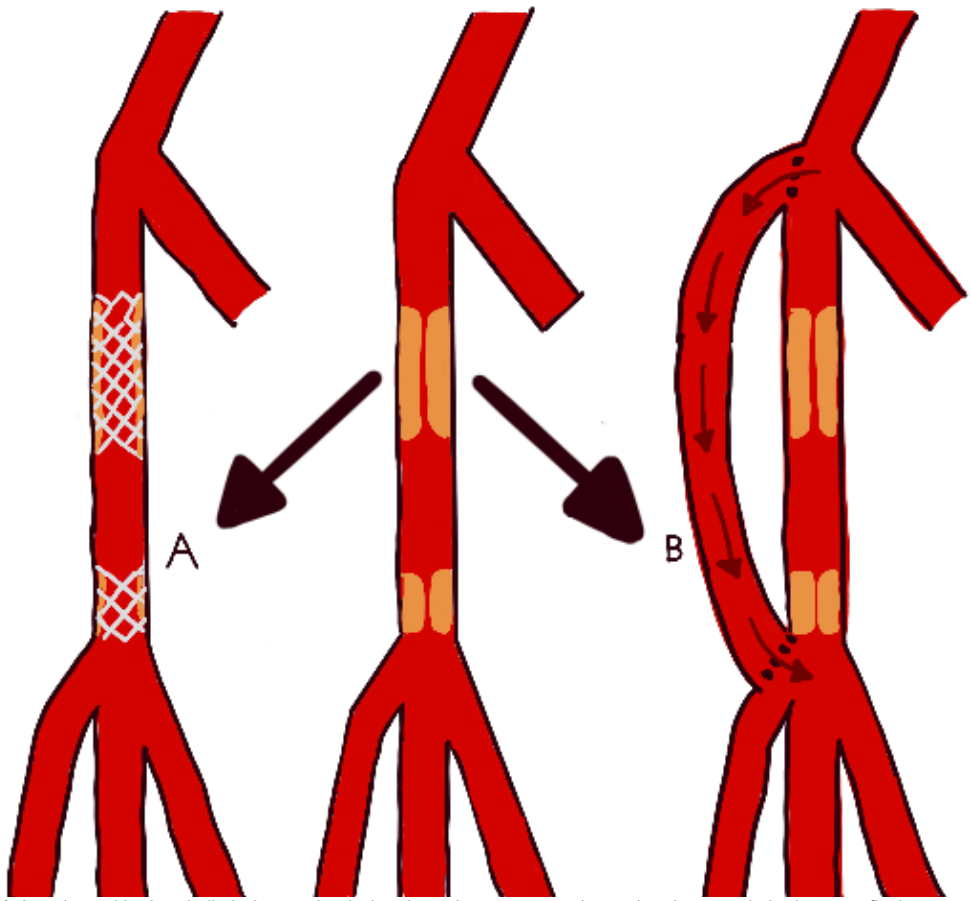


Figure 13 A patient with chronic limb-threatening ischemia and two severe atherosclerotic stenosis in the superfical femoral artery amenable with either endovascular surgery using two stents (A) or open vascular by-pass surgery using a vein conduit (B). ©*Talha Butt*

Open vascular surgery can be performed with an endarterectomy of the common femoral artery, which can be extended into the superficial femoral and deep femoral arteries. This method has a high long-term patency and is considered as first line treatment in highly calcified plaques in the area.[125] Studies[126, 127] have investigated the patency of infrainguinal bypass surgery, and shown that its patency is highly dependent on both inflow and outflow vessels and whether a good vein conduit is available (Figure 14). When a good autogenous conduit is lacking, different prosthetic grafts are available as alternatives.[125]



Figure 14 A female patient with chronic limb-threatening ischemia presented with a heel ulcer (A) and a black necrosis of the left great toe with visible bone (arrow, B). Magnetic resonance angiography of the lower extremities showed a long occlusion of the superficial, popliteal, and proximal calf arteries and run-off via the anterior tibial artery to the foot. As the patient had previously undergone varicose vein surgery in the left leg, the right great saphenous vein was marked for harvesting (C). A femoro-tibial anterior bypass with reversed saphenous vein (D) in the left leg was performed. The ultrasonic transit-time flow meter probe is placed around the vein just proximal to the distal end to side anastomosis. Wound healing was documented after three (E, F) and eight (G, H) months, respectively. ©*Stefan Acosta*

The development of endovascular surgery has enabled a wide range of treatment options by catheter lead revascularization. Luminal or subintimal recanalization can be performed with angioplasty and/or stenting. The use of drug eluting stents in coronary artery disease[128, 129] has been followed by the introduction of drug eluting balloons and stents also in the treatment of PAD.[130] One of the drugs used is the antimicrotubule agent paclitaxel.[131] Antimicrotubule agents inhibit cell growth by stopping mitosis, an effect considered valuable for prevention of restenosis.[132-134] Effects of drug-eluting options for endovascular treatment of infrainguinal occlusive disease is currently under investigation in the SWEdish Drug-Elution trial in Peripheral Arterial Disease (SWEDEPAD) trial (Clinical Trials.gov number; NCT02051088). The study has two arms, one for CLTI and the other for patients with IC. Concerns of increased risk of mortality associated with the use of paclitaxel-coated angioplasty balloons and stents[135] prompted a temporary halt of recruitment in SWEDEPAD, but as an unplanned interim analysis by the investigators documented no such associations[136] the enrollment of patients into the study has been resumed in 2020.[136] The balloon versus stenting in severe ischemia of the leg (BASIL-3) study is another randomized controlled trial (RCT) in which the effectiveness of drug eluting stents and balloons in severe limb ischemia will be investigated.[137]

Acute lower limb ischemia

The severity and urgency in the setting of ALI vary considerably depending on the clinical presentation of the patient (Table 4).[41] The most common causes of embolic ALI are atrial fibrillation or a mural thrombus in the left ventricle after myocardial infarction, whereas ALI caused by thrombotic occlusion is often due to advanced atherosclerotic disease.[138] The medical treatment should be customized to the etiology of the ischemia, and all the general cardiovascular risk factors discussed in the above section on CLTI should be assessed.[68]

Open and endovascular surgery

The choice between open or endovascular surgery is not clear cut in ALI,[139] and according to the European Society for Vascular Surgery (ESVS) "2020 Clinical Practice Guidelines on the Management of Acute Limb Ischemia",[78] ALI patients should be treated at a center offering a full range of both open and endovascular interventions.

Open femoral thromboembolectomy is among the most important management options for ALI (Figure 15), preferably performed as selective thrombectomy over a guidewire using fluoroscopy and DSA.[140] Bypass surgery is predominantly used in patients with acute on chronic disease.[141]

Local continuous thrombolysis

Local continuous intra-arterial catheter-directed thrombolysis (CDT) is a percutaneous endovascular treatment option in ALI. The procedure is minimally invasive, and catheterization is performed under local anesthesia. There has been concerns whether this treatment is a viable option in patients with ALI and motor deficit, due to the slower revascularization than during open thrombectomy.[78] The drawbacks are the increased risk of bleeding, either locally from the introducer site or distant bleeding.[142] The most serious adverse event, however, is intra-cerebral hemorrhage which occurs in 0.4% of the patients and is not seldom fatal.[143] Endovascular approach to ALI with CDT, may sometimes be combined with aspiration of the thrombus and/or pharmacomechanical thrombectomy to achieve faster revascularization.[144] Repetitive angiograms are performed during thrombolytic therapy with a mean duration of 1-2 days. After puncture and access of the common femoral artery, CDT is usually performed by catherization through the occlusion, leaving a thrombolysis catheter with side holes in the occlusion, whereby a controlled continuous infusion of the lytic agent is administered (Figure 16).[145] The two most commonly used lytic agents are the tissue plasminogen activators alteplase and urokinase, and in Sweden alteplase has virtually been the only option for a long time.

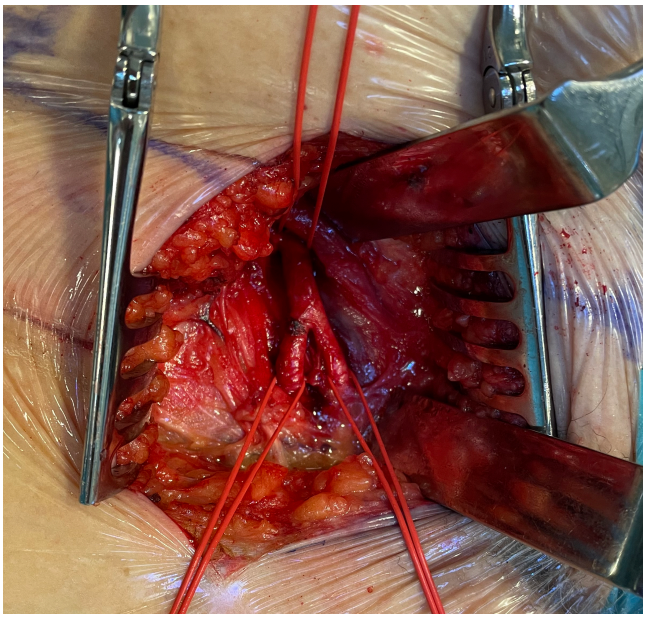


Figure 15a Patient with untreated atrial fibrillation presenting with acute limb ischemia, Rutherford IIb. The common femoral artery, superficial femoral artery, and deep profunda artery are exposed in the right groin. ©*Talha Butt*

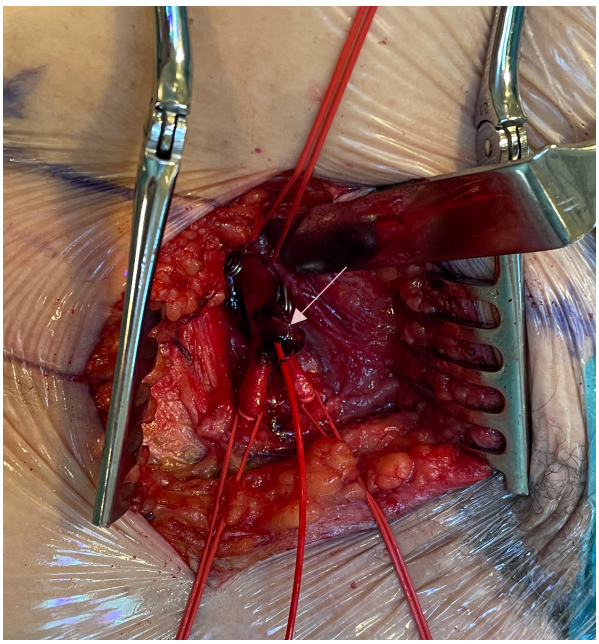


Figure 15b Embolectomy upstream, extraction of embolus (arrow) with Fogarty catheter. ©*Talha Butt*

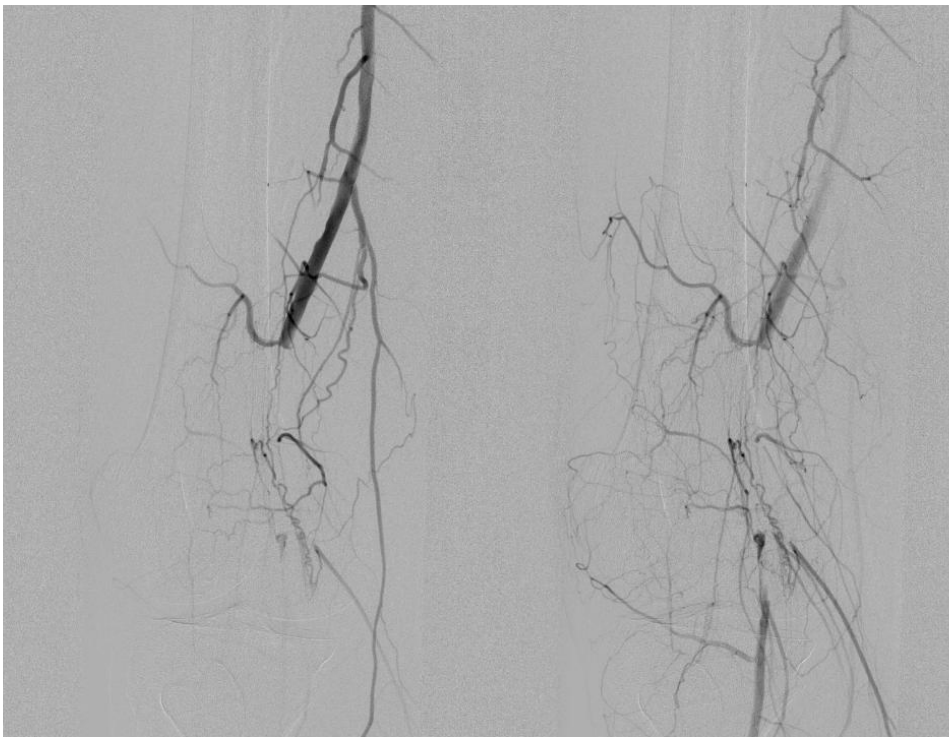


Figure 16a Acute right popliteal artery occlusion causing ALI. ©*Stefan Acosta*

Figure 16b Total length of occlusion visualized. ©*Stefan Acosta*



Figure 16c The same patient after successful complete local continous thrombolysis. There is a residual irregular appearance of the popliteal artery. Although the patient had atrial fibrillation the cause of the occlusion, embolism or thrombosis, was considered as undetermined and the patient was treated with anticoagulation. ©*Stefan Acosta*

Amputation

Amputation is a definitive treatment option in patients presenting too late with Rutherford[41] grade III ischemia in ALI or Wagner[42] grade 5 ischemia in CLTI, after failure of previous revascularization attempts, or in cases where revascularization is not an option.[146] The amputation should remove all infected, necrotic, and ischemic tissue and provide the patient with the longest functional limb possible. Amputation level above knee, patient age > 70 years, limited preoperative ambulatory ability, dementia, end-stage renal disease, advanced coronary artery disease, and chronic obstructive pulmonary disease, all constitute factors associated with less likelihood for the patient of being a suitable candidate for limb prosthesis to maintain some walking ability.[147] DM[148] and renal failure[146] are both associated with increased risk for re-amputation and worse outcomes for amputees.

Aims

The general aim of this thesis was to evaluate the effects of DM in patients treated for ALI and revascularization options in patients with DM and CLTI. The specific aims were to;

- Compare diagnostic performance of CTA of the calf arteries in ALI in patients with and without DM (paper I)

- Compare the risk of developing CA-AKI after CTA and local continuous thrombolysis for ALI in patients with and without DM (paper II)

- Compare the outcomes of local intra-arterial thrombolysis for ALI in patients with and without DM (paper III)

- Compare amputation-free survival after open and endovascular revascularization in patients with DFU and PAD (paper IV)

- Compare amputation-free survival after open and endovascular revascularization in patients with DM, PAD and heel ulcers (paper V)

Patients and methods

Ethical approval

All studies included in the thesis conform to the ethical guidelines of the 1975 Declaration of Helsinki. Papers I and II were approved by the Swedish Ethical Review Authority, and papers III-V by the regional ethical review board in Lund.

Setting

Skåne University Hospital was created in 2010 by merging Lund University Hospital with the University Hospital in Malmö. It is the third largest university hospital in Sweden with facilities located both in Malmö and Lund. The hospital has a regional catchment population of 1.7 million, and daily 128 surgeries and 1025 diagnostic examinations are performed. Additionally, an average of five scientific papers are daily published with one or more authors from Skåne University Hospital.[149]

All patients included in this thesis underwent lower limb revascularization at either Lund University Hospital, the University Hospital in Malmö or Skåne University Hospital. In 2000 the Vascular Departments in Lund and Malmö were merged and located in Malmö, where all revascularizations since then have been performed.

The multi-disciplinary foot round

The Diabetic foot section of the Department of Endocrinology at Skåne University Hospital had a primary catchment population of approximately 700,000 in 2013 and is the only provider of specialized diabetic foot care in the region.

The Vascular Center and the Diabetic foot section of the Department of Endocrinology in both Malmö and Lund have evaluated patients with DFU and PAD in a multi-disciplinary weekly round since around 1983.[29] The rounds apply a multidisciplinary approach to the patients with specialists in endocrinology, vascular surgery, and orthopedic surgery. The multidisciplinary approach moreover

provides regular podiatric care and ulcer dressing, both inpatient and outpatient visits, and individually adjusted footwear.

During the period studied in this thesis both imaging modalities and endovascular methods have undergone rapid development, and a shift has occurred towards use of endovascular surgery as first treatment option, instead of open surgical revascularization.

Overview of the studies

Table 5 Study design, number of patients and time frame of papers I-V.

Paper	Design	n patients	Time frame
I	Retrospective cohort study	108	2001-2018
II	Retrospective cohort study	213	2001-2018
III	Retrospective cohort study	399	2001-2013
IV	Retrospective cohort study	408	1984-2006
V	Retrospective cohort study	127	1983-2013

Data collection

Data collection for all five papers was based upon the electronic medical charts of Skåne University Hospital, and for papers IV and V supplementary data were obtained from paper charts in the archives of Lund University Hospital and the University Hospital in Malmö.

Definitions used in papers I-V

Acute limb ischemia was defined as sudden decrease in arterial perfusion of the limb with a duration of less than two weeks, threatening the survival of the limb.

Anemia was considered present when hemoglobin levels were below 134g/L in men and 117g/L in women.

Cerebrovascular accident (CVA), cerebrovascular disease was defined as previous stroke (haemorrhagic or ischemic) or transient ischemic attack.

Contrast-associated acute kidney injury (CA-AKI) was considered present if the patient had a 25% increase in serum creatinine within 72 hours after latest iodine contrast administration.

Current smoking was defined as ongoing smoking or if the patient had quit less than a year ago.

End-stage renal disease (ESRD) was defined as uremia (creatinine >300 μmol/L), past renal transplantation or dialysis.

Degree of acute limb ischemia was defined according to Rutherford classification[41] at admission.

Degree of lysis was defined as complete, partial, lysis but no run-off, or no lysis.

Extent of ulcer was defined according to the Wagner classification system.[42]

Diabetes mellitus (DM) was defined when patient had ongoing antidiabetic therapy with either diet, oral hypoglycemic agents, insulin, or a combination of these.

Diabetes mellitus type. When classifying DM as either type 1 or 2, patients diagnosed with DM before the age of 31 years and treated with insulin were considered as having DM type 1. This definition was used up until 1997 as the International Classification of Diseases coding system did not allow separation between DM type 1 and 2.[150, 151]

Diabetic retinopathy was defined as preproliferative or proliferative based on retinal photographs scored by an ophthalmologist.

Duration of DM was determined as years from diagnosis until the presentation of the foot ulcer at the foot center.

Glomerular filtration rate was calculated with a simplified variant of the Modification of Diet in Renal Disease Study Group (MDRD).[152]

Good concordance with treatment was defined as a patient being able to participate in at least 50% of the appointments at the multidisciplinary foot center.

Hypertension was defined as either a blood pressure above 140/90 mm Hg[111] or ongoing treatment with antihypertensive drugs.

Ischemic heart disease (IHD) was defined as a history of myocardial infarction, angina pectoris, coronary artery bypass, or percutaneous coronary angioplasty.

Major amputation was defined as amputation above ankle-level.

Nephropathy was defined as urine albumin >300mg/L.

Preadmission eGFR was defined as eGFR collected at least 90 days apart from admission eGFR.

Primary patency was defined as patent primary intervention without the need for additional intervention.

Renal insufficiency was defined when serum creatinine levels were > 105 μmol/L in men or >90 μmol/L in women.

Rest pain was defined as severe persistent pain localized to the foot.

Run-off after lysis was determined by using angiographic images evaluated at both the beginning and end of the thrombolytic procedure.

Secondary patency was defined as complete occlusion of primary intervention and need of additional intervention.

Severe peripheral vascular disease (SPVD) was defined as toe pressure <45 mm Hg or ankle pressure <80 mm Hg.

Wound healing time was defined as time from admission at the foot clinic to healed ulcer and expressed in weeks.

Statistical analyses

Data management and statistical analyses were performed using SPSS version 26.0. In papers I and IV a post-hoc power analysis was performed by using Fisher's exact test in G*Power 3.2.9.2 and 3.1.9.7, respectively.

Continuous variables were expressed as median and inter quartile range (IQR). Comparisons between continuous variables were performed by using the Mann-Whitney U test, and differences in proportions were analyzed with Pearson's chi square test. Kendall's tau-b test was used when comparing ordinal data. Risk factors associated with the endpoint chosen were tested in multivariable logistic regression analyses and expressed in terms of Odds Ratio (OR) with 95% confidence intervals (CI). Cox multivariate regression analyses were expressed as hazard ratios (HR) with 95% CI. P-values of <0.05 were considered statistically significant.

In paper I, the diagnostic performance (Figure 17) was analyzed, and inter-rater reliability was expressed as intraclass correlation (ICC) with 95% CI.

In paper II, continuous variables were tested for normal distribution with Kolmogorov-Smirnov test. When skewness occurred, the variable was logarithmized and entered as covariate in the logistic regression model.

In papers III and IV propensity score adjusted analyses were performed.

In papers IV and V, group differences in AFS were analyzed according to the Kaplan Meier method with life tables. Differences between endovascular and open vascular surgery were analyzed with the log-rank test. The Spearman test was used to test correlations, and expressed with a correlation coefficient (r) in paper V.

Propensity score adjusted analysis

When using multivariate adjustment by logistic regression a limited number of covariates should be used. But when adjustment for multiple risk factors is needed, a propensity score adjusted analysis produces a better adjustment. Such analysis is performed by first identifying possible risk factors for adverse outcome, and hereafter calculating a propensity score which is used in an analysis of the outcomes.[153, 154]

Diagnostic performance

Diagnostic performance of CTA of the lower legs in patients with and without DM was calculated by using the initial diagnostic angiographies as reference. Sensitivity, specificity, positive and negative predictive values, and accuracy were calculated with 95% CI.

Results

Study I

Main finding(s)

I. The sensitivity of CTA for assessment of intra-popliteal TASC D lesions in patients with ALI was lower in patients with DM than in those without DM, 0.14 (95% CI -0.12-0.40) and 0.64 (95% 0.48-0.80), respectively (Figure 17).

II. Inter-rater reliability expressed as ICC between CTA and DSA was 0.33 (95% CI -0.22-0.56) for patients with DM and 0.71 (95% CI 0.38-0.68) for patients without DM.

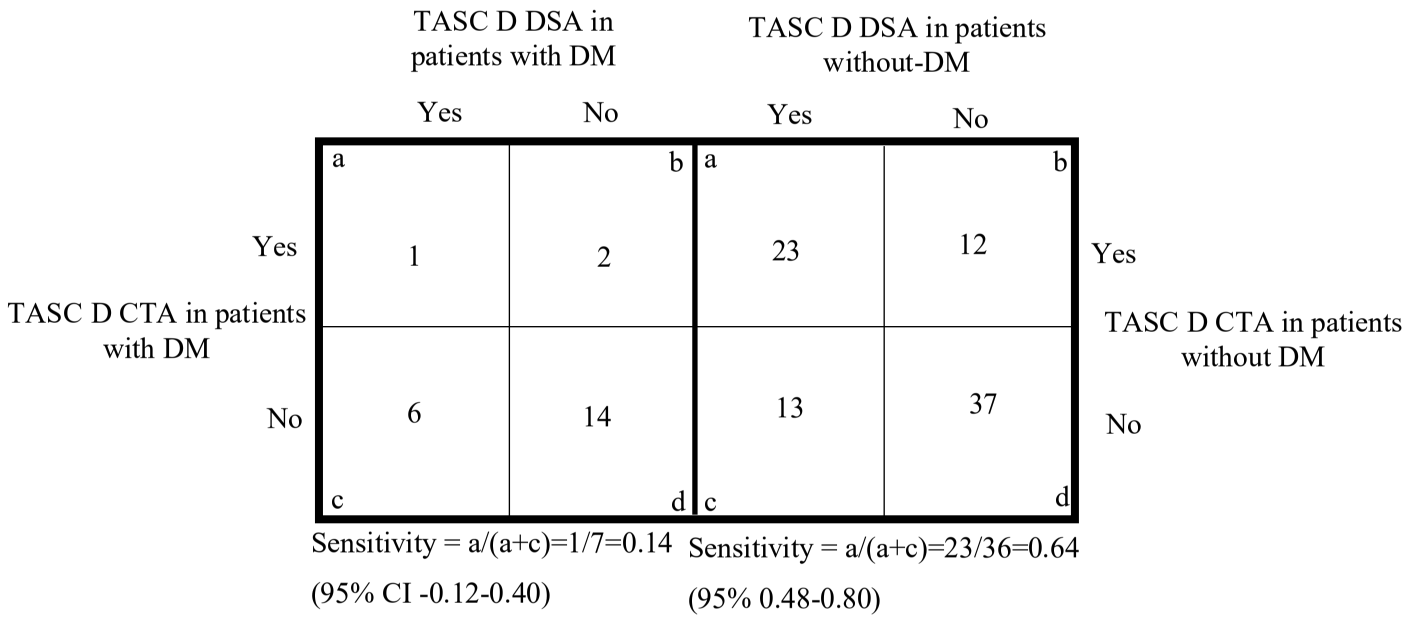


Figure 17 Sensitivity of CTA for assessment of intra-popliteal TASC D lesions in patients with ALI was lower in patients with DM compared to those without DM

Study II

Main finding(s)

I. Among patients with CA-AKI, patients with DM had a worse renal function at discharge compared to at admission ($p<0.001$).

II. The frequencies of CA-AKI were high among patients undergoing CTA and local continuous thrombolysis for ALI; 27.9% and 20.6% in patients with and without DM, respectively ($p=0.30$).

Iodine contrast and renal function outcomes

The total amount of administered iodine contrast ($p=0.037$) and the contrast given during the thrombolytic procedure ($p=0.02$) were both higher in patients without DM compared to in patients with DM.

The median gram-iodine dose/eGFR ratio was higher in patients with CA-AKI compared to in those who did not develop CA-AKI (1.49 versus 1.05, $p<0.001$). Among patients with CA-AKI, the total median amount of iodine contrast administered to patients with DM was 52.6 g compared to 58.5g in patients without DM ($p=0.092$). When entering DM, gram-iodine dose/eGFR ratio, age and gender as covariates in a multivariable logistic regression model, there was a trend that gram-iodine dose/eGFR ratio (OR 1.42, 95% CI 1.00-2.02; $p=0.050$) was associated with an increased risk of CA-AKI.

Study III

Main finding(s)

I. Patients with DM have both higher rates of major amputation at 1 (OR 2.52; 95% CI 1.22-5.20) and 3 years (OR 2.52; 95% CI 1.26-5.04), and lower AFS rate at 3 years (OR 0.46; 95% CI 0.25-0.85) than patients without DM in propensity score adjusted analysis after intra-arterial thrombolysis for ALI (Table 6).

II. Patients with ALI and DM differ in ALI etiology compared to ALI patients without DM. Underlying thrombosis was found in 27 out of 83 (32.5%) patients with DM and 67 out of 316 (21.2%) patients without DM (p=0.032). Popliteal artery aneurysm, on the other hand, was not present in any patient with DM compared to 25 (7.9%) patients without DM (p=0.008).

Table 6 Propensity score adjusted analysis of outcomes in patients with and without diabetes mellitus undergoing index thrombolysis for acute lower limb ischemia.

	OR (95% CI)
Amputation	
30 day	1.61 (0.60-4.31)
1 year	**2.52 (1.22-5.20)**
3 year	**2.52 (1.26-5.04)**
Death	
30 day	2.60 (0.33-20.58)
1 year	1.12 (0.44-2.86)
3 year	1.46 (0.74-2.87)
Amputation free survival	
30 day	0.95 (0.37-2.45)
1 year	0.53 (0.28-1.02)
3 year	**0.46 (0.25-0.85)**

Patient characteristics

Patients with DM were younger (p=0.001), and had more often renal insufficiency (p=0.004) and foot ulcers (p<0.001) than patients without DM. The degree of ischemia according to Rutherford classification[41] was lower in patients with DM compared to patients without DM (p=0.023).

Effect of thrombolysis

The amount of tissue plasminogen activator administered in patients with DM was higher compared to in patients without DM (p=0.03).

Study IV

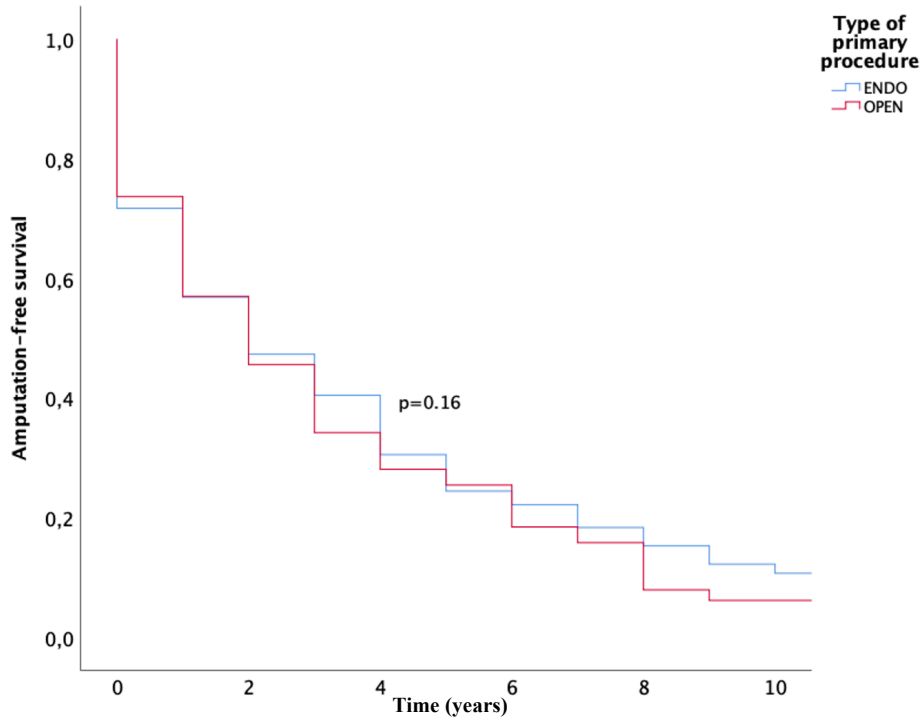
Main finding(s)

I. The long-term results regarding major amputation, mortality, and AFS (Figure 18) were similar in patients with DM and CLTI undergoing either open or endovascular revascularization first in propensity score adjusted analysis.

II. Rapid revascularization was associated with lower risk of amputation (p=0.003).

III. There was a shift from open towards endovascular surgery when comparing the first half of the study to the second half (p<0.001).

Figure 18 Kaplan-Meier analysis of amputation-free survival after open and endovascular surgery in patients with DFU and PAD



Standard error of cumulative proportion of patients AFS at end of interval is shown within parentheses. Of note, all patients have been followed up for more than 10 years, why there has been no censoring for follow up time.

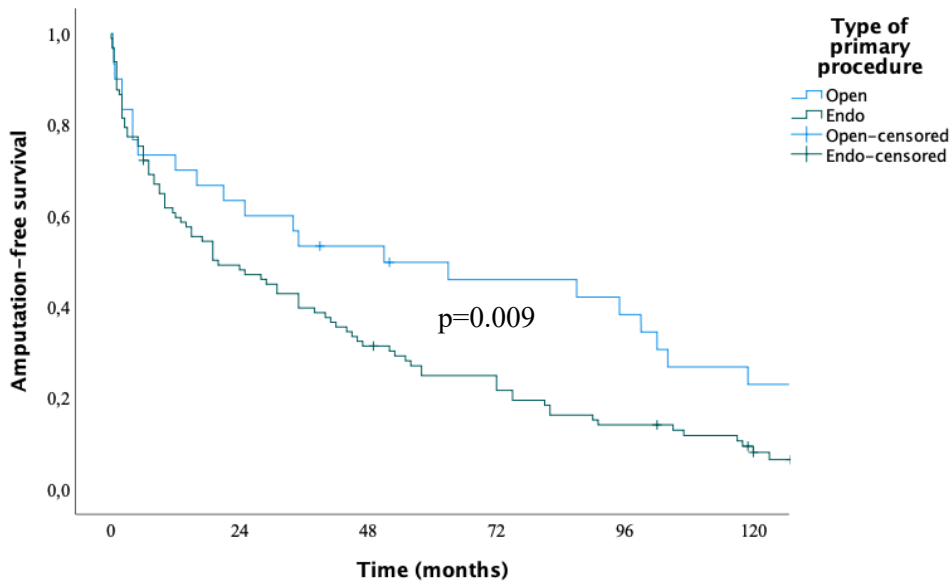
Study V

Main finding(s)

I. AFS was higher after open vascular surgery than after endovascular surgery in patients with PAD, DM, and heel ulcer (HR 2.1, 95% CI 1.1-3.9; p=0.025) (Figure 19, Table 7).

II. There was a shift from open towards endovascular surgery when comparing the first half of the study to the second half (p< 0.001).

Figure 19 Kaplan-Meier analysis of amputation-free survival after open and endovascular surgery in patients with DM, PAD and heel ulcer.



Pat at risk:						
	30	19	15	12	10	6
	97	47	30	23	13	7

Table 7 Factors associated with amputation-free survival. Multivariate Cox Regression Analysis.

	p value	Hazard Ratio	95% CI for Hazard Ratio	
			Lower	Upper
Type of primary procedure (open compared to endovascular surgery)	0.025	2.06	1.10	3.86

Patient characteristics

Patients undergoing endovascular surgery more often had diabetic retinopathy (p=0.035), insulin treatment (p=0.024), and previous foot ulcer (p=0.001). Previous vascular surgical procedures, on the other hand, were more common among patients undergoing open vascular surgery (p=0.023).

Discussion

Effects of diabetes mellitus in acute lower limb ischemia

Clinical diagnosis

The primary clinical diagnosis of ALI is largely based on the clinical examination, using "the six Ps", Rutherford's classification of ALI (Table 4),[80] and the ABI. All these parameters also help the clinician to determine the acuteness of the condition. In patients with PAD with functioning collateral circulation, the symptoms of ALI are more gradual.

In paper III we found that patients with DM had both lower degree of ischemia according to Rutherford's classification for ALI at presentation, higher rate of major amputation, and lower AFS rate during follow-up compared to those without DM. The reasons for this somewhat non-logical relationship might be difficulties in accurately assessing Rutherford class in DM patients, and that treatment might have been more challenging in the DM group. Patients with DM often have a falsely high ABI and express less pain because of peripheral neuropathy, which might falsely lessen the clinical perception of their ALI severity level. In addition, the proportion of neuropathy, albeit not investigated, could be expected to be high among patients with DM in paper III making the determination of Rutherford IIa (the sensory deficit) very difficult. It is therefore likely that a patient with DM and Rutherford class IIa might be downgraded to Rutherford I, as he or she cannot adequately distinguish the worsening of the sensory deficit in the acute setting from the chronic condition. Furthermore, the presence of a hyperemic reddish foot due to autonomic neuropathy may be misconceived as a well circulated foot. Hence, the Rutherford classification appears to be less applicable to patients with DM, and a new classification system that better reflect severity of ALI in DM is therefore warranted. The amount of tissue plasminogen activator administered in patients with DM was also higher compared to in patients without DM in paper III, which may indicate that the therapy was more ineffective in DM patients resulting in a worse outcome. Both the often poor arterial run-off[155] and the high complexity of care in patients with DM might also have contributed to their more ominous prognosis.

Computed tomography angiography

Evaluation of the diagnostic accuracy of CTA in the setting of ALI has not been performed, hence available results for comparison of CTA and DSA are therefore extrapolated from patients with chronic peripheral disease.[78] Mishra et al[156] demonstrated the inferior quality of CTA in the infra-popliteal segments where significant wall calcifications interfered with stenosis assessment, and Al-Rudaini el al [157] reported lower accuracy of CTA in the infrapopliteal compared to in the femoropopliteal segment. In paper I we found that the sensitivity of CTA for assessment of infra-popliteal TASC D lesions in patients with ALI was unacceptable in patients with DM, in contrast to in those without DM.

A possible explanation for this inferior performance of CTA in patients with DM is that the beam hardening and partial volume effect caused by calcification causes artefacts making the determination of stenosis difficult.[158, 159] Furthermore, the fact that patients with DM have more extensive tibial arterial calcification[155] might complicate assessment of stenosis (false negative test, low sensitivity). In addition, the low positive predictive value, 33%, among patients with DM and TASC D in paper I compared to 66% in those without DM, indicates that arterial wall calcification among patients with DM probably induced misclassification of significant stenosis, and thereby false positive test results.

Contrast-associated acute kidney injury after thrombolysis

There are several strategies which can and should be undertaken to reduce the amount of iodine contrast. The full potential of a modern angiography operating room should be employed for this purpose, a road map, overlay, table position recall, and fusion imaging technology should all be used. In study II we found that 22% of patients with ALI undergoing diagnostic CTA and subsequent treatment with catheter lead thrombolysis developed CA-AKI. There were no significant differences in the rates of CA-AKI between patients with DM and those without DM, but patients with DM had worse renal function at discharge compared to at admission. The gram-iodine dose/eGFR ratio was higher among the patients developing CA-AKI compared to those whose renal function remained stable, and there was a trend that gram-iodine dose/eGFR ratio was associated with CA-AKI after adjusting for confounders, indicating the need to lower the gram-iodine dose/eGFR ratio in order to improve renal outcomes. The surgeon performing the thrombolytic procedure should therefore be aware of the presence of DM, and the iodine contrast volume threshold should be based on eGFR. The use of CO_2 as contrast medium is also promising, with its lower nephrotoxicity and potential to enable high quality vascular images.[100]

The use of anatomic landmarks and stents during fluoroscopy may also be helpful to reduce use of contrast media. Use of intravascular ultrasound (IVUS) may be an

attractive option to avoid use of iodine contrast agents and help spare renal function, particularly in patients with renal insufficiency.[160, 161] RCTs comparing IVUS with angiography-guided peripheral vascular interventions should not only compare technical success, reintervention rates, periprocedural adverse events, vascular complications, myocardial infarctions, amputations, and mortality, but also the occurrence of CA-AKI and deteriorations of renal function.

Outcome after thrombolysis

The propensity score adjusted analyses confirmed that patients with DM and ALI had a worse long-term prognosis in terms of decreased limb salvage and lower AFS. Even though patients with DM in study III had lower Rutherford classification at presentation, they had a lower AFS, and higher rate of major amputation compared to non-DM patients. The possible misclassification of the degree of ALI at presentation resulting in a falsely low grade according to the Rutherford classification might have delayed limb revascularizations. In addition, the clinical appearance of a reddish foot in a patient with DM and ALI might have resulted in falsely downgrading the degree of ALI. Furthermore, paper III showed that patients with DM more often had renal insufficiency and foot ulcers, which might have contributed to the higher rates of major amputation.

Revascularization options in diabetes mellitus and chronic limb-threatening ischemia

Open versus endovascular surgery

In order to ensure best long-term outcome in patients with CLTI, it is necessary for the clinician to have access to both open and endovascular surgical methods.[27] Several considerations have to be made in the decision-making process regarding as to which procedure should be performed as first option.[27]

Even though by-pass surgery is well established and has good results regarding limb salvage,[162, 163] endovascular surgery has developed into an effective and powerful tool. Patients should therefore not only be offered endovascular surgery when deemed “in to poor condition” for open vascular surgery. A definitive benefit of endovascular surgery, in these often fragile patients, is the ability to perform the procedure in local anesthesia. Endovascular interventions are not a free shot[27] without complications, however, and patients have a worse outcome of by-pass surgery when performed after a failed endovascular procedure compared to after primary by-pass surgery.[121]

Special attention must be paid to the subgroup of DM patients with CLTI due to the common occurrence of microangiopathy, neuropathy, arthropathy, and increased vulnerability to foot infection[27]. These factors will impact both clinical presentation and the need of revascularization. In paper IV we found that the long-term results of the endovascular surgery first and the open vascular surgery first strategies were similar in patients with DFU and PAD.

Shorter time to intervention could be expected to have been associated with reduced rate of major amputation in paper IV. In this context, it should be noted that median time to intervention in all 408 limbs was eight weeks in this historical series. In a more modern series from 2010-2011, it was possible to show that when the delay from referral to revascularization was lower than two weeks, leg salvage rates were equal in patients with and without DM.[164]

Heel ulcer

In paper V, patients with DM and isolated heel ulcer had higher AFS after open vascular surgery than after endovascular surgery. The presence of a heel ulcer in a DM patient is a serious complication associated with poor outcome, and no clear consensus exists concerning the management of this condition.[1] It is important, however, to offer a durable vascular reconstruction to both enable healing of the ulcer and maintain the heel free from recurrence of ulceration.

In paper V, it was possible to show a benefit for open vascular surgery over endovascular surgery. This difference between open and endovascular surgery would probably have been even larger if it would have been possible to adjust for time period, use of platelet aggregation inhibitors, statin therapy, and smoking habits by entering these variables as covariates in the Cox regression analysis. Since open vascular surgery was more often performed during the first part of the study with expected poorer medical risk factor treatment[165] and more smokers, the advantage of the method compared to endovascular surgery might have been even more evident.

Limitations

Selection bias

Papers III on ALI and papers IV and V on CLTI in patients with DM are all subject to selection bias. In paper III, patients underwent thrombolysis as a revascularization procedure, whereas no patient underwent primary open vascular surgery, primary amputation, conservative therapy with low-molecular weight heparin (LMWH), or palliative therapy. The true proportion of patients undergoing thrombolysis among all patients with ALI is difficult to estimate. Such a contemporary study needs to be strictly conducted within a well-defined population such as Malmö, only taking patients registered as living in Malmö into account. As there is only one hospital in Malmö such a study appears feasible and is, in fact, in progress.

In paper IV, consecutive patients with DM and foot ulcers were admitted to a multidisciplinary diabetic foot center between 1984 and 2006. Among 1151 patients with DFU, 478 underwent revascularization, of whom 376 patients were evaluable for comparison of the effects of open and endovascular surgery.

Paper V is based on patients with foot ulcer admitted to the diabetic foot center between 1983 and 2013. Among 4273 patients with DFU, 844 had heel ulcers, of whom 121 patients (127 limbs) were evaluable concerning effects of open and endovascular surgery. The number of patients with DFU within the same catchment area during this period who were not evaluated at the diabetic foot center is unknown. The patients in paper V had more advanced cardiovascular morbidity and lower AFS than the rest of patients with DM and heel ulcer,[166] and therefore the comparative analyses between open and endovascular surgery was performed in a selected group. The change in diagnostic and therapeutic capacity during the long study period has led to a shift towards increasing proportion of endovascular surgery.

The study results after thrombolysis in ALI and revascularization in CLTI among patients with DM should be viewed in the perspectives outlined above.

Information bias

The documented rates of tobacco use in papers II – V were poorly documented, and only current smoking was documented in the CLTI patients in papers IV and paper V. The proportion of former or current smokers among patients in the present study population receiving thrombolysis for ALI between 2001 and 2005 was reported to be high, 75%. [145] As documentation on smoking habits have a low priority in the emergency setting, it was inconsequently noted at admission. This was the reason for not pursuing the search for this data in the present papers on ALI. We fully acknowledge, however, that it would have been very valuable to be able to adjust for accurate data on smoking exposure in our outcome studies after ALI.

Data on ongoing medication at admission such as aspirin, clopidogrel, and warfarin were included in paper III (ALI), whereas no data on statins were collected. Treatment with clopidogrel was also considered in the propensity score adjusted model. The long and remote study periods in papers IV and V explain the absence of data concerning these medications at admission.

Confounding

As paper I deals with the comparison of diagnostic accuracy of CTA and DSA in patients with and without DM, there was no need to adjust for confounders. Papers II – V contain adjusted analyses of outcomes to limit the influence of possible confounding. Multivariable logistic regression analysis was performed in paper II, and Cox multivariable regression analysis in paper V to address major confounders. As a rule of thumb, one putative predictive variable per ten outcome events is allowed to fit into the multi-variable regression model[167], which was respected in both these papers. Propensity score adjusted analysis[153, 154, 168] was performed in paper III and IV to adjust for all potential risk factors that were collected and found in the database. There is a large treatment selection bias in paper IV, however; the choice of primary endovascular or open revascularization cannot be completely adjusted for in observational studies due to residual confounding.[84] In papers III - V, the continuing improvement in medical therapy with gradually better coverage of platelet antiaggregants and statins and lower rates of tobacco consumption[165] during the long study period have not been taken into account in the outcome analysis. These factors therefore constitute relevant confounders, impossible to adjust for due to the retrospective study design. Rates of continuing smoking despite having undergone a vascular intervention for a limb- and life-threatening condition have, unfortunately, in some reports shown to be high.[165, 169] Continued smoking has also been associated with both early graft failure and risk for amputation after infra-inguinal bypass surgery.[170]

Conclusions

- In the setting of ALI, the diagnostic performance of CTA of the calf arteries was not acceptable for TASC D lesions in patients with DM
- The frequency of CA-AKI was high in patients after preoperative investigation with a CTA and treatment with local continuous thrombolysis, without difference in risk of developing CA-AKI in patients with DM compared to without DM. Among patients who developed CA-AKI, DM patients had a lower eGFR at discharge compared to at admission
- After treatment of patients with ALI with local continuous thrombolysis, patients with DM have a lower AFS compared to patients without DM
- There was no long-term difference regarding AFS between patients being treated with open or endovascular surgery first for DFU
- AFS was higher in patients with DM, PAD, and heel ulcer after treatment with open vascular surgery than after treatment with endovascular surgery

Future perspectives

The use of adjunctive thrombectomy during thrombolysis

The use of CDT has been shown to be an effective treatment option for ALI even in patients with motor function deficit, and with the option of adjunctive thrombectomy, it might be possible to further improve outcomes. Outcome in terms of major amputation in patients with DM compared to in those without DM was inferior after thrombolysis. Advances have been made in adjunctive endovascular techniques during thrombolysis with percutaneous mechanical thrombectomy devices that have been designed to clear thrombo-embolic clots using rheolytic or microfragmentation catheters.[171] Fast-track thrombolysis protocol featuring pharmacomechanical rheolytic thrombectomy of the occluded arterial segment, infusion of thrombolytic agent along the occluded segment, balloon maceration of the thrombus, and stenting have shown promising results. The termination of the procedure within a single-session is 81% of the patients without occurrence of rethrombosis or major hemorrhage within 30 days.[172] There are, however, insufficient data available to support the use of these rheolytical thrombectomy systems and/or thrombus aspiration instead of standard thrombolysis.[173] Demonstration of benefits in terms of efficacy, outcomes, and cost-effectiveness of these novel techniques compared to standard local continuous thrombolysis in the setting of a randomized trial is therefore warranted, and it would also be interesting to see whether the results of these adjuvant techniques are different in patients with DM.

Need for improvement in multi-disciplinary diabetic foot management

Diabetic foot care has in observational studies been shown to improve care in terms of reduction of the number of major amputations on both regional[29] and national level.[30, 31] One contributing factor, besides the improvement in medical risk factor control, is the implementation of diabetes foot care teams. The nationwide study performed in the Netherlands[31] showed an increase in the establishment of

multidisciplinary foot care teams within the hospitals from 16% in 1991 to 40% in 2000. Another nationwide survey on all 75 Swedish hospitals with emergency departments in 2013,[174] found that 84% had a diabetic foot team with multidisciplinary outpatient evaluations, in which specialists in infectious disease, orthopedic surgeons, and vascular surgeons were present in 52%, 62% and 22% , respectively.[174] In this study it was also demonstrated that very few of the hospitals actually had written guidelines for management of DFU, in contrast to what they claimed. In addition, local registrations of the annual number of amputations and healed foot ulcers were only 48% and 21%, respectively, reflecting a poor-quality control of patients with diabetic foot problems. It would therefore be worthwhile to investigate in a nationwide study whether DM patients in regions with access to a diabetic foot care team including a vascular surgeon on site run a reduced risk of major amputation compared with their counterparts in regions without these facilities. Such a study would be possible to conduct by linkage of nationwide registers such as the National Diabetes Register (NDR).[175] In addition, linkage of registries such as Swedvasc, a nationwide register of patients undergoing vascular surgery in Sweden,[176] and NDR, may be useful to evaluate the association between revascularization rate in regional areas and risk of major amputation.[177]

Validation of the wound, ischemia and foot infection classification system

Evaluation of foot status by the Wagner classification[42] system for DFU used in papers IV and V has been performed for decades at the Diabetic foot center in Malmö. The Society for Vascular Surgery lower Extremity Guidelines Committee has in 2014 introduced the concept of risk stratification based on wound, ischemia, and foot infection (WIfI), to meet the dramatic rise in incidence of DM and rapidly expanding techniques of revascularization.[44] The WIfI takes limb perfusion, wound extent, and severity of infection into account. Recently, there have been comparative prospective studies evaluating the abilities to predict major amputation using the different classifications. In one report on 63 patients with DFU, the predictive capabilities of the Wagner and WIfI systems were equal concerning major amputation.[178] No revascularizations were performed in this study, however, and follow-up was short. In another report on 45 patients[179], inter-observer agreement was substantial in WIfI scoring, but this scoring took longer (median time one minute) to complete than the Wagner scoring (median time 15 seconds). The median scores for the Wagner classification were higher among amputees compared to among non-amputees, whereas there was no difference in WIfI scoring between these two groups.[179]Among 19 patients undergoing amputation within 30 days, 18 had a minor amputation. Again, no revascularizations were performed in any of these patients. Hence, there is a need for a large prospective study evaluating the

predictive ability of both the Wagner and WIfI classification systems for major amputation during long-term follow-up in patients with DFU treated with and without limb revascularization.

Revascularization strategy in patients with DFU

The GVG[27] has proposed the concept of Global Anatomic Staging System (GLASS) involving definitions of a preferred target artery path and estimating limb-based patency in combination with the WIfI grade. The optimal revascularization strategy for infrainguinal arterial disease is influenced by the availability of autogenous vein for open bypass surgery. GLASS stage 3 and WIfI grade 3 were recently found to be independent predictors of reduced major adverse limb event-free survival after revascularization.[180] The GLASS stage (anatomic complexity) and limb severity (WIfI stage) has been plotted in a *x*-*y* diagram to suggest initial revascularization strategy; no, endovascular, indeterminate, or open bypass revascularization (Figure 20).[27]

The efficacy of adherence to this strategy protocol, and its predictive capability for major amputation would be worthwhile to study in patients with and without DM in a prospective setting in a hospital with a full range of vascular and endovascular revascularization options. The results of paper IV and V with retrospectively collected historical data in this thesis must be interpreted very cautiously for many reasons as outlined, and there is a great need to evaluate the revascularization strategy in a randomized contemporary setting.

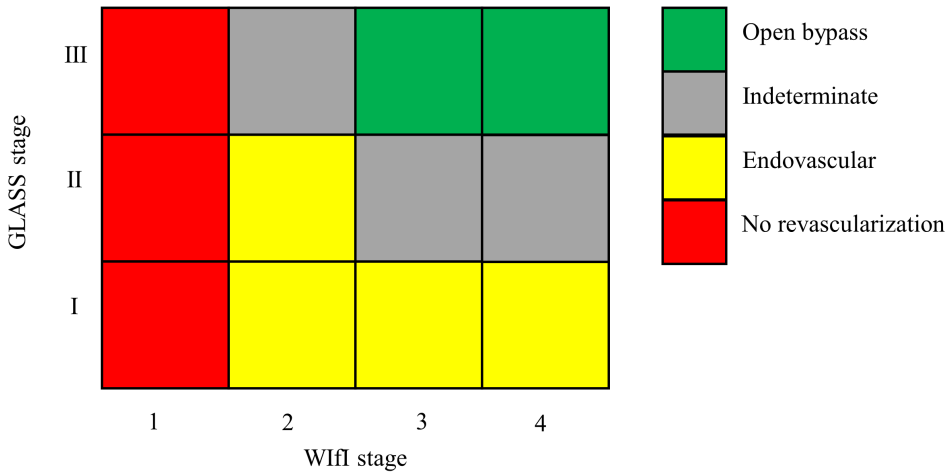


Figure 20 Primary revascularization strategi in patient with infrainguinal disease and sutiable autologous vein suggested by the GVG guidelines. [27]

Populärvetenskaplig sammanfattning

Diabetes är en folksjukdom som leder till för mycket socker i blodet. Det höga blodsockret kan göra att blodkärlen blir förkalkade och skador på njurarna kan uppstå. Förkalkningen kan drabba benens blodkärl och särskilt de små blodkärlen i underben och fötter. Detta leder till att en person med diabetes har nästan 10–20 gånger så hög risk som en person utan diabetes att behöva genomgå amputation av sitt ben.

Inom kärlkirurgin behandlar kan man sjukdomar inom blodkärlen med läkemedel, kateterburen kirurgi eller öppen kirurgi. Vilken metod man ska välja och för vilken patient är inte alltid självklart.

I denna avhandling undersöktes följande;

1. Är utredning med skiktröntgen av blodkärl nedom knäna lika tillförlitlig hos patienter med diabetes som hos patienter utan diabetes?
2. Är frekvensen för njurskada orsakad av skiktröntgen och efterföljande akut kateterburen blodproppslösande behandling i benet större hos patienter med diabetes än hos patienter utan diabetes?
3. Blir resultatet efter kateterburen blodproppslösande behandling lika bra hos patienter med diabetes som hos patienter utan diabetes?
4. Vilken behandling ger bäst resultat hos patienter med diabetes och långvarigt nedsatt blodflöde till foten med fotsår, kateterburen kirurgi eller vanlig öppen kirurgi?
5. Skiljer sig behandlingsresultaten åt efter kateterburen kirurgi och vanlig öppen kirurgi på grund av sår på hälen hos personer med diabetes och nedsatt blodflöde?

Vi gick igenom journaler hos patienter som behandlats vid Skånes universitetssjukhus med följande resultat;

1. Skiktröntgen av blodkärlen hos patienter med diabetes ger inte lika bra bedömning av cirkulationen i benen som hos patienter utan diabetes.
2. Det är ingen skillnad i frekvens för njurskada mellan patienter med och utan diabetes som genomgått skiktröntgen med efterföljande akut kateterburen blodproppslösande behandling i benet.
3. Efter blodproppslösande behandling för akut nedsatt blodcirkulation till benet löper patienter med diabetes högre risk att dö eller behöva amputeras jämfört med patienter utan diabetes.
4. Vi fann ingen skillnad avseende dödlighet och amputationsrisk hos patienter med diabetes som genomgick antingen kateterburen eller öppen kirurgi på grund av långvarigt nedsatt blodflöde till foten med fotsår.
5. Har man diabetes och hälsår och genomgår en öppen kärlkirurgisk behandling har man lägre risk för amputation och död jämfört med om man genomgår kateterburen kirurgi.

Sammanfattningsvis är det viktigt att ta hänsyn till förekomsten av diabetes under hela vårdförloppet från det att en person söker vård på grund av nedsatt blodcirkulation i benen, både gällande vilka undersökningar man väljer och hur man väljer att behandla åkomman.

Acknowledgements

This thesis would not have been possible without the invaluable collaboration, support, and contribution of countless individuals. In particular, I would like to thank:

Stefan Acosta, my principal supervisor for introducing me to the world of science in the field of vascular surgery. My appreciation for your countless hours of support, guidance and friendship is difficult to put in word. Your generosity in sharing your experience and knowledge is admirable. No obstacle has felt impossible to overcome during the work with this thesis because of your tirelessness. Thank you!

Anders Gottsäter, my co-supervisor, for being the most knowledgeable person I have met. I am grateful for your eye for detail, your strive for the best and the energy you have put into this thesis.

Jan Apelqvist, my co-supervisor, you are a true titan in the field of the diabetic foot. Thank you for taking time to explain, help and push not only this thesis but also scientific progress in this field.

My co-authors, **Gunnar Engström** for your statistical guidance, **Hedvig Örneholm** and **Magnus Eneroth** for your support and sharing of your knowledge. **Targ Elgzyri** for your help and the continued work on the multidisciplinary foot rounds. **Erika Lilja** and **Leena Lehti** thank you for your support and help. Thank you for the co-authorship!

Kärlcentrum, SUS, an extraordinary place of work where the support and freedom to grow as a clinician and scientist seems to be endless. Thanks to all my **colleagues** who makes this workplace a joy to be a part of! Special thanks to **Björn Sonesson,** my clinical supervisor, my admiration of you is no secret.

The **nurses** and **assistant nurses** at the outpatient clinic, the ward and at “angio”- the work you do is amazing.

All my friends, the **“padel crew”** for keeping me sane during the writing process of this thesis. The **“polish”** group for making medical school a rememberable and joyous journey and for your continued friendship and support.

My family- my **parents** for not only teaching me but showing me the value of hard work. My sisters, **Aisha,** and **Salma**, for being my support and cheerleaders throughout my life. My brother-in-law **Per**, my nephew **Jonas** and niece **Elsa** for being the best addition to the family one could wish for.

My late big brother **Ijaz**, for your endless love and being the glue of the family, you are missed!

- Thank you all

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Printed by Media-Tryck, Lund 2021 NORDIC SWAN ECOLABEL 3041 0903

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Department of Clinical Sciences, Malmö

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2021:66
ISBN 978-91-8021-072-0
ISSN 1652-8220