Surgical aspects on patients with diabetes mellitus and chronic limb-threatening ischemia

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DOCTORAL DISSERTATION

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Title and subtitle
Surgical aspects on patients with diabetes mellitus and chronic limb-threatening ischemia

Abstract

Background: During the 21st century, diabetes mellitus (DM) and peripheral artery disease (PAD) have become global problems. It is estimated that 19-34% of individuals with DM will develop a foot ulcer during their lifetime, and many will be amputated.

Aim:
-To study dietary and lifestyle factors associated with prevention of PAD among individuals with DM.
-To evaluate outcomes after vascular and endovascular treatment in patients with DM and chronic limb-threatening ischemia (CLTI).

Methods: Paper I, based on the Malmö Diet and Cancer study focuses on patients with prevalent DM. Papers II and III are based on the Swedish Vascular Register and the Swedish National Diabetes Register. A propensity score adjusted Cox regression analysis was conducted to compare outcomes following endovascular therapy and open vascular surgery, respectively, between patients with and without DM. Paper IV compares outcome following open and endovascular surgery for patients with DM, PAD, and heel ulcers presenting at the multidisciplinary diabetes foot clinic.

Results: A higher intake of fish and shellfish tended to confer a protective effect against the development of PAD among individuals with DM (HR per additional gram per week 0.99, 95% CI 0.99-1.00, p=0.051). Incidence rates (IR) of major amputation and acute myocardial infarction (AMI) were 43% (95% CI 1.23-1-67) and 37% (95% CI 1.13-1.67) higher, respectively, among patients with DM compared to patients without DM following endovascular therapy for CLTI. IR of major amputation or death was 13% higher (95% CI 1.04-1.23; p=0.004) higher among patients with DM after endovascular therapy for CLTI.
IR of stroke and AMI were 70% (95% CI 1.11-2.59) and 39% (95% CI 1.00-1.92) higher, among patients with DM compared to patients without DM following open vascular surgery, whereas there was no difference in major amputation (HR 1.28, 95% CI 0.98-1.66; p=0.070) or the compound variable major amputation or death (HR 1.15, 95% CI 0.98-1.35; p=0.090) following open vascular surgery.
Open vascular surgery was associated with higher amputation-free survival (AFS, HR 2.1, 95% CI 1.1-3.9) compared to endovascular therapy among patients with DM, PAD, and heel ulcers.

Conclusions: A higher intake of fish and shellfish tended to confer a protective effect against the development of PAD among individuals with DM. In contrast to patients undergoing endovascular therapy, there was no difference in major amputation or death after open vascular surgery between those with and without DM. Amputation-free survival (AFS) was higher after open than endovascular surgery among patients with DM and PAD with heel ulcers. Open vascular surgery remains a first-line option for a substantial part of patients with CLTI, especially for limb salvage in patients with DM. These results suggest that open vascular surgery should be offered more often as opposed to current practice.

Key words: Diabetes mellitus, chronic limb-threatening ischemia, peripheral artery disease, vascular surgery

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Cover photo: Footprints in the snow. Diabetic neuropathy causes diminished pain perception of the cold snow and foot ulcer. Chronic limb-threatening ischemia complicates ulcer healing. By Klara Albertsson.

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To babi and deda

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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. Lilja E, Bergwall S, Sonestedt E, Gottsäter A, Acosta S. The association between dietary intake, lifestyle and incident symptomatic peripheral arterial disease among individuals with diabetes mellitus: insights from the Malmö Diet and Cancer study. Therapeutic Advances in Endocrinology and Metabolism. 2019 Feb;53(2):118-125. PMID: 30466379

II. Lilja E, Gottsäter A, Miftaraj M, Ekelund J, Eliasson B, Svensson AM, Zarrouk M, Nilsson P, Acosta S. The impact of diabetes mellitus on major amputation among patients with chronic limb threatening ischemia undergoing elective endovascular therapy - a nationwide propensity score adjusted analysis. Journal of Diabetes and its Complications. 2021 Feb;35(2):107675. PMID: 32828647

III. Lilja E, Gottsäter A, Miftaraj M, Ekelund J, Eliasson B, Svensson AM, Zarrouk M, Acosta S. Diabetes mellitus was not associated with lower amputation-free survival after open revascularization for chronic limb-threatening ischemia – A nationwide propensity score adjusted analysis. Vascular Medicine. 2021 Oct;26(5):507-514. PMID: 34004125

IV. 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. Vascular and Endovascular Surgery. 2019 Feb;53(2):118-125. PMID: 30466379

Abbreviations

ABI	Ankle brachial index
AFS	Amputation-free survival
AMI	Acute myocardial infarction
BASIL	Bypass versus Angioplasty in Severe Ischaemia of the leg
BEST-CLI	Best Endovascular versus Best Surgical Therapy in patients with critical limb ischaemia
CI	Confidence Interval
CKD	Chronic kidney disease
CLTI	Chronic limb-threatening ischemia
CTA	Computed Tomography Angiography
CVD	Cardiovascular disease
DFU	Diabetic foot ulceration
DM	Diabetes mellitus
DUS	Duplex ultrasound scanning
GLASS	Global Limb Anatomic Staging
GLP-1	Glucagon-like peptide
GVG	Global Vascular Guidelines
HR	Hazard Ratio
ICD	International Classification of Diseases
IDF	International Diabetes Federation
IPTW	Inverse probability of treatment weighting
LDL	Low-density lipoprotein
MACE	Major adverse cardiovascular events
MDCS	Malmö Diet and Cancer Study
MRA	Magnetic resonance angiography
NDR	National Diabetes Register
PAD	Peripheral artery disease
PTA	Percutaneous transluminal angioplasty
RCT	Randomized controlled trial
SGLT-2	Sodium-glucose cotransporter-2 inhibitor
SMD	Standardized mean difference

Swedvasc	The Swedish Vascular Register
$TcPO_2$	Transcutaneous oxygen pressure
TMA	Transmetatarsal amputation
TP	Toe pressure
WHO	World Health Organization
WIfI	Wound Ischemia foot Infection

Thesis at a glance

Paper	Aim	Method	Main results
I. The association between dietary intake, lifestyle and incident symptomatic peripheral arterial disease among individuals with diabetes mellitus: insights from the Malmö Diet and Cancer study	To study dietary and lifestyle factors associated with prevention of PAD among patients with DM.	Prospective study of a subgroup of individuals with DM from the Malmö Diet and Cancer cohort Study.	A higher intake of fish and shellfish tended to confer a protective effect against the development of PAD among individuals with DM.
II. The impact of diabetes mellitus on major amputation among patients with chronic limb-threatening ischemia undergoing elective endovascular therapy - a nationwide propensity score adjusted analysis	To compare outcome between patients with and without DM following elective endovascular therapy for CLTI.	Retrospective study of patients registered in Swedvasc having undergone elective endovascular therapy for CLTI. Patients with DM had a registration in NDR.	After elective endovascular therapy the incidence rate of major amputation and AMI was higher among those with DM. No difference was seen in mortality.
III. Diabetes mellitus was not associated with lower amputation-free survival after open revascularization for chronic limb-threatening ischemia – a nationwide propensity score adjusted analysis	To compare outcome between patients with and without DM following elective open revascularization for CLTI.	Retrospective study of patients registered in Swedvasc having undergone elective open vascular surgery for CLTI. Patients with DM had a registration in NDR.	After elective open vascular surgery the incidence rate of stroke and AMI was higher among those with DM. No difference was seen in major amputation or mortality.
IV. Amputation-Free Survival in Patients With Diabetes Mellitus and Peripheral Arterial Disease With Heel Ulcer: Open Versus Endovascular Surgery	To evaluate the difference in amputation-free survival between open and endovascular revascularization among patients with DM, PAD, and heel ulcers.	Retrospective study including patients at a multidisciplinary diabetes foot clinic with DM, PAD, and heel ulcers.	The amputation-free survival was higher after open vascular surgery compared to endovascular therapy among patients with DM, PAD, and heel ulcers.

DM, diabetes mellitus; PAD, peripheral artery disease; CLTI, chronic limb-threatening ischemia; NDR, National Diabetes Register; Swedvasc, Swedish Vascular Registry; AMI, acute myocardial infarction.

Introduction

Diabetes mellitus (DM)

Diabetes mellitus (DM) is a serious and chronic condition occurring when the pancreas cannot produce enough, or any, insulin, or when the body cannot effectively use the produced insulin, resulting in hyperglycaemia. Today there are three main types of DM; type 1, type 2, and gestational DM, with type 2 being the most common (approximately 90%).[1]

If left untreated, hyperglycaemia and insulin deficit can cause long-term macro- and microvascular complications. Macrovascular complications include cardio- and cerebrovascular disease and peripheral artery disease (PAD). Microvascular complications include neuropathy, retinopathy, and nephropathy.[2]

Globally, DM is among the top 10 causes of death, with 87% of all diabetes-related deaths happening in low- and middle-income countries.[1] According to the International Diabetes Federation (IDF) 463 million people suffered from DM in 2019, and approximately 10% of global health expenditure is spent on DM. It is estimated that the prevalence of DM will have increased by 51% in 2045, to 700 million globally. Seventy-nine percent of people with DM reside in low- and middle-income countries.[1] The prevalence of DM in Sweden is approximately 450,000.[3]

Diabetic foot ulcer

Foot complications are amongst the most costly and severe diabetic complications,[4] affecting approximately 2% of subjects with DM per year.[5] The global epidemic of DM type 2 will ensure that the incidence of diabetic foot ulcers (DFU) increase as well.[6] The global prevalence of DFU has been estimated to be approximately 6.3%, with a higher prevalence in men, patients with DM type 2, and in North America (approximately 13%).[7] DFU is the most common cause for hospitalizations among individuals with DM.[8]

In middle- and high-income countries, it is estimated that up to 50% of patients with DFU have underlying PAD.[9] A German study including 247 patients with DM and

foot ulceration pointed at a 15.9% five-year risk of major amputation.[10] The prognosis of a patient with PAD and DFU is worse than in many common cancers - approximately 50% of patients will not survive 5 years, with a majority dying from cardiovascular disease.[10]

The pathway to a DFU usually consists of two or more risk factors occurring at the same time, with diabetic neuropathy playing a central role as over half of elderly patients with DM type 2 suffer from this complication.[11] Small-fibre nerve dysfunction leads to the loss of pain and temperature perception, which normally would protect from injury. Large-fibre dysfunction leads to impaired balance increasing the risk of trips and falls.[11]

Furthermore, PAD is a risk factor for DFU as patients with both ischemic ulcers and neuropathy may have lost the ability to feel pain, despite severe ischemia.[12] Motor neuropathy causes small muscle wasting and contributes to a deformed foot anatomy, affecting pressure loading of the foot. Increased pressure is seen on the plantar surfaces of the metatarsal heads and the heels. Another consequence of changes in foot anatomy is the formation of hammer toes and claw toes due to contraction of ligaments.[13]

Autonomic neuropathy decreases sweating which leads to dry skin and formation of callus, further increasing the risk of ulcers. Charcot neuroarthropathy is a severe inflammatory syndrome often missed among patients with diabetic neuropathy. The Charcot foot is red, hot, and swollen due to a dislocation process affecting bones, ligaments, and joints of the extremity among people with severe diabetic neuropathy.[14]

Minor trauma and ill-fitting shoes precipitate skin breakdown, and PAD affects the healing process negatively.[11] Long duration of DM, age, male sex, and nephropathy are factors increasing the risk of DFU.[11]

According to the IDF, diabetic foot and lower limb complications affect 40 to 60 million people with DM globally.[1] A person with DM has an up to 25% lifetime risk of developing a foot ulcer, with a recurrence rate of 50%.[11,15] Chronic ulcers and amputations substantially reduce the quality of life and increase the risk of early death in DM.

In the United States in 2005, an estimated 359,000 individuals were living with a major amputation due to PAD, a number that was projected to more than double by 2050. This increase in prevalence is driven by an aging population and an increasing number of people living with DM.[16]

The widely used Wagner classification system for DFU[17] is described below (Table I).

Table I. Wagner classification of diabetic foot ulcers.[17]

Ulcer grading	Description
Grade 0	No ulcer
Grade 1	Superficial ulcer
Grade 2	Deep ulcer, no abscess or bone
Grade 3	Abscess and/or osteomyelitis
Grade 4	Gangrene on portion of the foot
Grade 5	Extensive gangrene, involves whole foot

Peripheral artery disease

PAD is caused by atherosclerosis of extremity arteries leading to reduced blood flow, most commonly to the lower extremities. A non-invasive diagnostic method for lower-extremity PAD is the ankle-brachial index (ABI). The ABI is the ratio of the systolic blood pressure measured at the ankle to the pressure measured at the brachial artery.[18] Risk factors for PAD include DM, hypertension, age, smoking, and hyperlipidemia.[19] Smoking has been established as a risk factor for PAD only after 10 years of smoking among women, compared to after 30 years among men.[20] DM is also a risk factor for PAD, as the risk of lower extremity PAD increases up to 4 times with the diagnosis of DM.[21] Symptoms of PAD include thigh or calf pain while walking i.e., intermittent claudication. However, many patients lack the classical symptoms and are asymptomatic.[22]

A subgroup of patients has severe PAD without any symptoms, explained by their incapacity to walk far enough (e.g., heart failure) and/or a reduced sensitivity to pain (e.g., peripheral neuropathy). This group is at a particularly high risk of limb events as they already show signs of severe PAD at diagnosis.[19]

The atherosclerosis causing PAD is often generalized, and PAD patients therefore face an overall risk for fatal and non-fatal cardiovascular events such as stroke and acute myocardial infarction. Asymptomatic PAD patients are also at high cardiovascular risk.[19, 23] An ABI $\leq$0.90 is linked to more than a doubling of the 10-year risk of coronary events, cardiovascular, and total mortality.[24]

It is widely known that patients with DM and PAD represent a special subgroup.[25] In comparison to patients without DM, PAD among those with DM usually develops at younger age and is more distal and multisegmented with more medial calcification and impaired collateral formation. PAD is also more common and progress faster among patients with DM compared to patients without DM.[25]

Chronic limb-threatening ischemia

Chronic limb-threatening ischemia (CLTI) is the end-stage of PAD, affecting approximately 10% of patients with PAD.[26] CLTI should be seen as a sign of a systemic atherosclerosis with a high mortality in acute myocardial infarction and stroke.[24] Among untreated patients with CLTI, one in five will undergo major amputation and one in five will die, all within one year of the diagnosis.[27]

While CLTI is a clinical diagnosis with rest pain, foot ulcers, or gangrene >2 weeks among patients with PAD, it is often associated with an ABI ≤0.4 or toe pressure <30 mmHg.[26] Among all ulcers seen in patients with DM, the heel ulcer is considered to be the most serious due to the high risk of amputation at ankle level.[28] Furthermore, other common ulcer localizations include areas of bony prominence, such as the dorsal portion of the toes and the plantar side of the metatarsal heads.[29]

Prevention of peripheral artery disease and diabetes mellitus

Modifiable risk factors for PAD are similar to those for other cardiovascular diseases; smoking, dyslipidaemia, overweight, poor diet quality, and physical inactivity.[19] Smoking is the single most common preventable risk factor for PAD.[30, 31]

WHO states that physical inactivity is one of the leading risk factors for noncommunicable diseases mortality.[32] Higher levels of physical activity lower the risk of many common diseases such as DM and hypertension, and decrease the risk of cardiovascular mortality which is the leading cause of death globally. WHO recommends adults to do muscle-strengthening activities twice a week along with at least 75-150 minutes of high-intensity aerobic physical activity or 150-300 minutes of moderate-intensity aerobic physical activity per week.[32]

It is well-known that a healthy diet reduces the risk of atherosclerosis.[33] Furthermore, a Mediterranean diet has been shown to reduce the risk of death from cardiovascular disease and is therefore recommended for patients with type 2 DM.[34, 35] The Mediterranean diet generally includes unsaturated fats such as olive oil, a high intake of fruits and vegetables, nuts, beans, whole-grains, and fish, with a lower intake of meat and dairy foods.[36]

As DM is a well-known risk factor for cardiovascular disease,[37] factors affecting the severity of DM should be mentioned when discussing PAD as well. Increased physical activity improves glycaemic control and should therefore be highly recommended to patients with type 2 DM.[38]

A well-structured diet is considered to be the cornerstone for diabetes treatment, and prevention of type 2 DM can be achieved with an appropriate diet and physical activity usually leading to weight-loss.[39, 40, 41] The US Diabetes Prevention program performed a randomised controlled trial (RCT) with more than 3000 people at risk of developing DM. Results showed that diet and physical activity reduced the incidence rate of type 2 DM with 58%, a more effective reduction than with metformin.[42] Specific recommendations on prevention of type 2 DM apart from weight loss of at least 5% for overweight individuals, can be seen in table II.[35]

Table II. Prevention of type 2 diabetes mellitus. Modified from Diabetes UK nutrition guidelines.[35]

High risk group	General population
Restrict energy intake	Follow a Mediterranean diet
Reduce intake of total and saturated fats	Include wholegrains, leafy greens, some fruit, cheese and yoghurt
Increase intake of fibres	
Increase physical activity	Reduce red meat, sugar-sweetened beverages and refined carbohydrates

Diagnostics of peripheral artery disease and chronic limb-threatening ischemia

The National Swedish Diabetes Register (NDR) uses a risk stratification model to assess the risk of ulcers and adverse limb events among individuals with DM, see table III[3] also displaying current Swedish treatment guidelines.[43] The foot examination should always lead to a risk stratification in accordance with table III. Twenty-five percent of Swedish patients with type 2 DM and 20 % of those with type 1 DM have signs of neuropathy or angiopathy and are therefore assigned to risk group 2.[3]

As screening for PAD, the feet of all patients with DM should be examined once a year, even if no foot ulcer is present.[43] Examination should be performed by taking relevant history, inspection of the feet for ulcers, callus, and erythema due to pressure, and by palpation of foot pulses. The patient's shoes and toenails should also be inspected.[43] Neuropathy should be tested with monofilament at three locations: digitorum I and the metatarsophalangeal joints I and V, and the patient should be asked about numbness or a tingling sensation from their feet. The loss of sensation from one of these three locations equals risk category 2 (bright orange). Vibration testing is performed on the medial malleolus, the top of digitorum I, and the medial side of metatarsophalangeal joint I. Loss of vibration sensation on one of these locations equals risk category 2 (bright orange).[43]

If the examination or history leads to the suspicion of PAD, the ABI should be examined. Generally, an ABI <0.9 is suggestive of PAD.[12] The absence of any of the foot pulses equals risk category 2 (bright orange).[43]

The patient's role to examine their feet cannot be stressed enough; the Swedish Diabetes Foundation recommends patients to check, wash, and put softening cream on their feet daily.[44]

Table III. Risk stratification and treatment guidelines of individuals with DM and foot disease. Modified from the National Diabetes Register and the National Guidelines on the Prevention of Diabetic Foot Complications.[3, 43]

Risk grading	Definition	Diabetic foot care team	Annual foot examination	Podiatric care
1	Healthy foot - DM without complications.	Patient education about self-care	Yes	No
2	Neuropathy +/- angiopathy.	Yes	Yes	Yes
3	Previous diabetic ulcer, foot deformity, extensive callus formation or previous amputation.	Yes	Yes	Yes
4	Current ulcer, CLTI, infection or Charcot foot.	Yes	Yes	Yes

To rule out PAD in a patient with DFU, palpation of foot pulses and examination of foot Doppler pulses with measurements of ABI or TBI are warranted. An ABI ≤0.9 has a sensitivity of 75% and specificity of 86% for PAD.[45] The sensitivity is worse among patients with DM and end-stage chronic kidney disease due to medial calcification.[46] However, PAD is unlikely if ABI is between 0.9 and 1.3, TBI ≥0.75, and Doppler shows triphasic pedal waveforms.[12]

Imaging of the arteries in the lower limbs

Non-invasive imaging should be performed in all patients with CLTI prior to endovascular or open surgical revascularization.[26] Duplex ultrasound scanning (DUS) measures flow volume and velocity and is a well-established tool for assessment of level of arterial occlusion or stenosis without patient exposure for nephrotoxic iodine contrast or ionizing radiation. DUS is operator-dependent and time consuming, and its performance may be suboptimal in the aortoiliac and infra-popliteal segments.[47] Computed tomography angiography (CTA) has high sensitivity (95%) and specificity (94%) for detection of stenoses at aorto-iliac and femoro-popliteal levels, and provides high quality images of extra-vascular pathology.[48] It may for instance be used to gain additional diagnostic and prognostic information in a patient with a suspected or known intra-abdominal tumour. CTA has lower diagnostic performance when there are several calcifications in the infra-popliteal segment, and exposes the patient to both iodine contrast and ionizing radiation.[49] Magnetic resonance angiography (MRA) has a sensitivity and specificity of approximately 95%[50] and produces images of high quality, especially in the infra-popliteal segment.[50, 51] Standard MRA fails to visualize calcifications in

the vessel walls[52] and might overestimate the degree of stenosis, however, but these shortcomings may be overcome with more advanced technology.[53] Other drawbacks of MRA are artefacts produced by previously implanted stents[54] in the lower extremity arteries. MRA should not be used in patients with cardiac pacemaker, implantable cardioverter defibrillator, claustrophobia, or poor compliance.[55] Angiography produces images of highest quality of the arteries in the lower limbs and is considered the reference method when evaluating other comparative imaging methods. Angiography may be used for subacute examinations if previous imaging assessments has been inconclusive, and when subsequent intervention during the same session is considered necessary for limb salvage.[56, 57] During angiography, the iodine contrast may be exchanged for carbon dioxide (CO_2), to reduce the amount of iodine contrast sparing renal function.[58, 59]

Classification of peripheral artery disease and foot ulcers

The Fontaine and Rutherford classification systems have been used to assess the risk of amputation and possible benefit from revascularization.[26] However, the extent of the wound and presence of infection also impact the outcome of the limb. Therefore, the International Working Group on the Diabetic Foot recommend that patients with PAD and DFU should be assessed with the Wound, Ischemia and foot Infection (WIfI) classification system (see table IV) to assess the risk of amputation and potential benefits of revascularization.[12, 60] The WIfI system renders a combination of numbers from 0-3, e.g. 2-2-1 (2 for wound, 2 for ischemia, 1 for foot infection) used to divide patients into four threatened limb clinical stages, predicting the risk of amputation at one year and the likely benefit of revascularization.

Table IV. Wound, Ischemia and foot Infection classification system. Modified from the Society for Vascular Surgery.[61]

	0	1	2	3
Wound	No ulcer or gangrene but rest pain	Shallow ulcer on distal leg, no exposed bone unless distal phalanx, no gangrene Minor tissue loss. Salvageable with amputation of 1-2 digits	Deeper ulcer, exposed bone/joint/tendon shallow heel ulcer Gangrene on digits Major tissue loss. Salvageable with amputation of ≥3 digits or TMA +/- skin coverage	Deep ulcer on forefoot/midfoot, full thickness heel ulcer +/- calcaneal involvement Extensive tissue loss. Salvageable with complex reconstruction/TMA at Lisfranc/Chopart level, flap coverage/complex wound management
Ischemia	ABI: ≥0.8 Ankle systolic pressure: >100 mmHg TP/TcPO2: ≥60 mmHg	ABI: 0.6-0.79 Ankle systolic pressure: 70-100 mmHg TP/TcPO2: 40-59 mmHg	ABI: 0.4-0.59 Ankle systolic pressure: 50-70 mmHg TP/TcPO2: 30-39 mmHg	ABI: ≤0.39 Ankle systolic pressure: <50 mmHg TP/TcPO2: <30 mmHg
foot Infection	No signs or symptoms of infection	Infection present, at least 2 of: -Local swelling -Erythema >0.5 - ≤2 cm -Local pain -Local warmth -Purulent discharge Infection of skin and subcutaneous tissue	Local infection (see previous) with erythema >2 cm, or involving structures deeper than skin and subcutaneous tissue No systemic inflammatory response	Local infection with signs of systemic inflammatory response, 2 or more: -Temperature >38 or <36 °C -Heart rate >90 beats/min -Respiratory rate >20 -Leukocytes >12 or <4 x 10^9

If ABI is incompressible (>1.3) measure TP or TcPO2. TMA, transmetatarsal amputation; ABI, ankle-brachial index; TP, toe pressure; TcPO2, transcutaneous oxygen pressure.

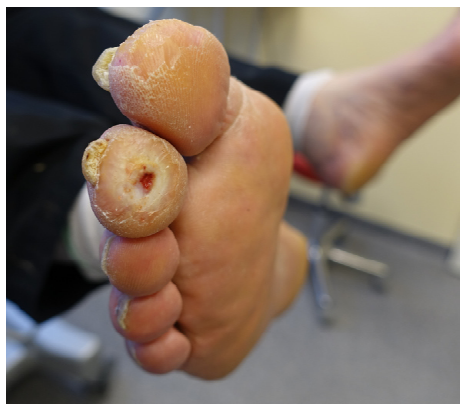


Figure I. Eighty year-old female patient with diabetes mellitus type 2 and an ulcer on digitorum 2 in the right foot. Revision of the ulcer has been performed to remove hyperkeratosis. The photo displays a superficial ulcer without signs of infection where the distal phalanx is widened due to inflammation and oedema. WifI stage 1 due to the minor ulcer (W1), normal toe pressure (I0) and no signs of infection (fI0).[26] © Erika Lilja

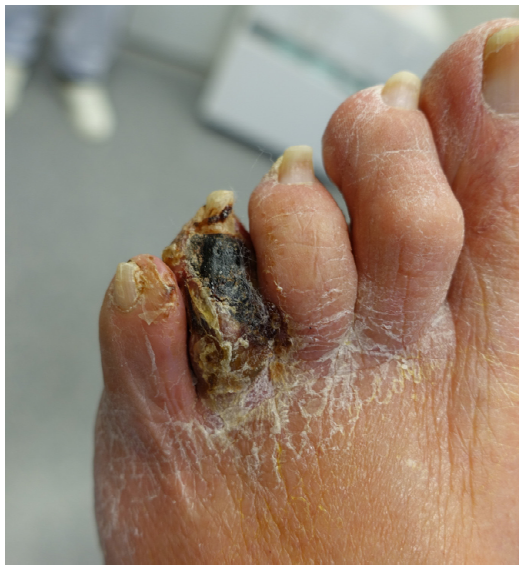


Figure II. Seventy-five year-old male patient with diabetes mellitus type 2, history of smoking, hypertension, atrial fibrillation and a dry gangrene on digitorum 4 in the left foot. Big toe pressure was 30 mmHg before endovascular procedure which was performed a few days before the photo was taken. The patient underwent stenting of the external iliac and superficial femoral artery. The patient was treated with peroral *flucloxacillin* (Heracillin®). WIfI stage 4 before revascularization: W2, I2, fI 1.[26] © Erika Lilja

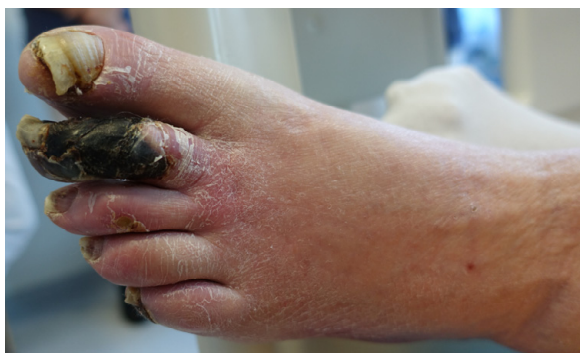


Figure III. Ninety-three-year-old male patient with diabetes mellitus type 2, history of smoking, and hypertension presenting with a dry gangrene on digitorum 2 and on distal phalanx of the digitorum 5 in the left foot. Big toe pressure was 32 mmHg and Duplex ultrasound showed an occlusion of the superficial femoral artery and the proximal part of the popliteal artery. The patient was planned to undergo endovascular therapy the following day. The photo shows a local swelling and erythema proximal to the gangrene. The patient received in-hospital care and was administered intravenous metronidazole (Flagyl®) and cefotaxime (Cefotaxim®). WIfI stage 4 before revascularization: W2, I2, fI 1-2.[26] © Erika Lilja

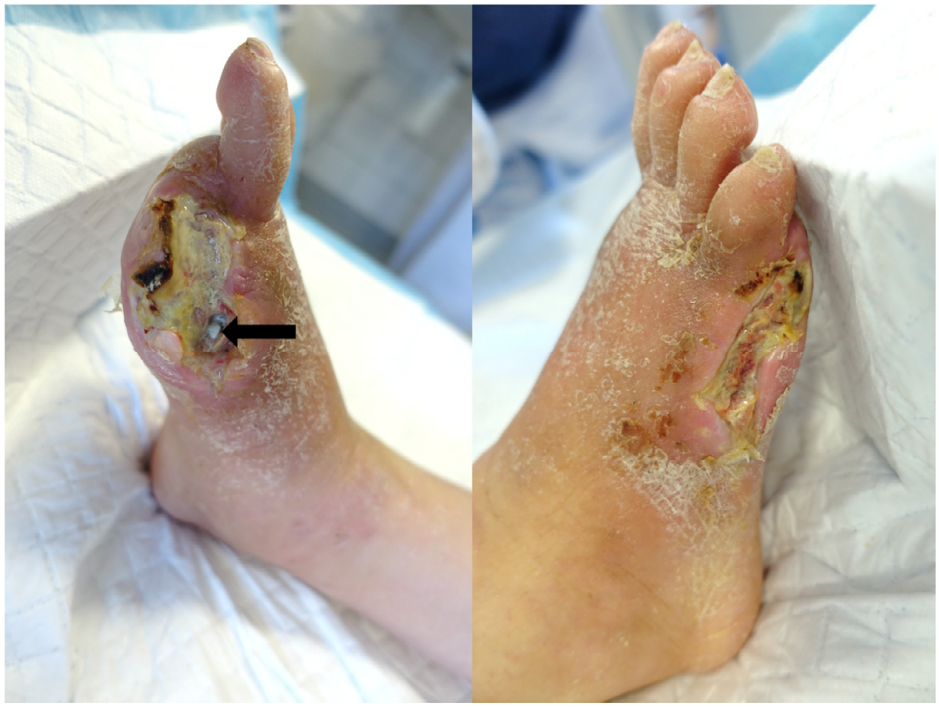


Figure IV. Seventy-nine-year-old male patient with diabetes mellitus type 2, hypertension, hyperlipidemia, previous amputation of digitorum 1, and chronic limb-threatening ischemia presenting with two ulcers in the right foot. The first ulcer is located around the first metatarsal head with visible bone (arrow) and edema of the whole foot. The second ulcer is located on the lateral side of the forefoot. Pointer toe pressure was unmeasurable. The patient had recently undergone percutaneous transluminal angioplasty (PTA) for occlusive lesion in the fibular artery and attempts to revascularize the tibialis anterior artery as well. The patient received in-hospital care and was administered intravenous antibiotics. WIfI stage 4 before revascularization: W2-3, I3, fI 2.[26] © Erika Lilja

Management of diabetic foot ulcers

Rapid vascular imaging and revascularization should be considered amongst patients with DFU and an ankle pressure <50 mmHg, ABI <0.5, or a toe pressure <30 mmHg. Vascular imaging should also be considered if a DFU does not heal within 4-6 weeks.[12]

Duplex ultrasound provides information on arterial anatomy and haemodynamics with a sensitivity of approximately 80-98% for a stenosis of >50%.[62] If revascularization is considered, another imaging technique should be performed to visualize the entire vascular tree. MRA provides excellent images, offers better imaging quality than CTA in calcified arteries[50] in the infra-popliteal segment,[51] and spares the patient from nephrotoxic iodine contrast exposure. CTA may be considered as a second option when there are contraindications to MRA, or if the patient has previously undergone stenting in the lower limb arteries.

Patients with DFU should be closely monitored at a multidisciplinary clinic specialized in DFU. It is of great importance that patients with DM and ischemic foot ulcers receive proper cardiovascular risk assessment and intensive treatment such as antihypertensives, statins, control of hyperglycaemia, and of course support to quit smoking.[12]

Medical treatment of peripheral artery disease

Due to the high risk of cardiovascular death from stroke and AMI among patients with CLTI,[26] it is crucial that they are offered the best medical treatment. Therefore, all patients with PAD should be screened for modifiable risk factors in order to minimize cardiovascular mortality.[19] Yet, Sigvant et al reported that in 2005 Swedish women with PAD received less preventive medications (statins, antihypertensives, and antiplatelet therapy) compared to Swedish men with PAD.[20] Despite the fact that antithrombotic therapy with either clopidogrel or aspirin is recommended for all patients with symptomatic PAD[19] the Swedish Vascular Registry (Swedvasc) reports that in 2020, only 74% of Swedish patients with PAD used antiplatelet medication.[63]Two randomized controlled trials,[64, 65] have shown that low-dose rivaroxaban taken twice a day plus aspirin once daily reduced major adverse cardiovascular and limb events when compared with aspirin alone; without an increased risk of fatal bleeding. Therefore, this combination should be considered in PAD patients without high risk of bleeding.[66]

Hypertension is a risk factor for PAD,[19] and antihypertensive therapy unquestionably reduces cardiovascular events and mortality.[67-70] Furthermore, current evidence suggests reducing blood pressure further than previously recommended.[67, 68] Guidelines now recommend an upper blood pressure reference limit of 129/79 mmHg among patients younger than 65 years and 139/79 mmHg for those older than 65 years, including people with DM and cardiovascular disease.[69, 70]

Statins are recommended for secondary prevention of cardiovascular events for all patients with PAD as they reduce morbidity and mortality.[19, 71] This recommendation is based on the plaque stabilizing effects of statins,[72] and should be considered for all PAD patients when tolerated, regardless of LDL levels.[71] Guidelines now recommend LDL-levels <1.4 mmol/L for patients at very high risk of cardiovascular disease, or as secondary prevention, e.g., to all patients with PAD.[71]

Yet only 83% of Swedish patients undergoing invasive treatment for PAD were prescribed statins in 2020.[63] However, there has been a clear improvement as only 26% of Swedish CLTI patients were reported to use statins in 2005.[73]

Medical treatment of diabetes mellitus

In recent years, medical treatment of people with DM has developed rapidly. The flash glucose monitoring system allows the patient to simply, just by using their smartphone, scan a sensor on their upper arm to read current glucose level. This system works by continuously measuring the glucose level in the interstitial fluid.[74] The flash glucose monitor has been shown to reduce time in hypoglycemia and improve HbA1c.[74-76] The continuous glucose monitoring system works in the same way as the flash glucose monitor, but continuously sends data to the display device. It is also possible to set alarms for a high, low, or a change in glucose levels.[77]

Glucose monitoring systems lead to improved metabolic control.[78] A Swedish study has shown that glucose monitoring systems lead to improved glucose control with a lowering of HbA1c, and improved vibration perception suggesting beneficial effects on nerve function due to improved metabolic control among patients with type 1 DM.[79]

The Diabetes Control and Complications Trial from the early 1990s demonstrated the importance of intensive insulin therapy to sustain tight glucose control and prevent diabetes complications such as nephropathy, neuropathy, retinopathy, and cardiovascular disease.[80] To achieve this tight glucose control, insulin pump therapy also known as continuous subcutaneous insulin infusion, is commonly used today. The insulin pump works by continuously providing the patient with rapid-acting insulin through a subcutaneous catheter. The insulin is delivered at a predetermined basal rate to meet the nonprandial insulin requirements, and bolus doses are provided in order to cover mealtime requirements.[77] Continuous subcutaneous insulin infusions have been shown to lower HbA1c and reduce the frequency of hypoglycemia.[81]

With the development of glucose monitoring systems, and improved insulin therapy it is possible that the incidence of diabetic foot ulcers and their recurrence rate will decrease.

Although metformin still remains the first line treatment option for most patients with type 2 DM, much progress has been made in the field of glucose-lowering medications. Additional glucose-lowering drugs to be combined with metformin are selected based on patient characteristics, such as cardiovascular disease, kidney disease, and heart failure. If clinical cardiovascular disease is present a sodium-glucose cotransporter-2 (SGLT-2) inhibitor or glucagon-like peptide (GLP-1) receptor antagonist is recommended as the next step.[82] Both of these drug classes have been proven to reduce cardiovascular mortality, and previous concerns on increased risk for amputation with SGLT-2 inhibitors have not been convincingly corroborated in meta-analyses.[83- 85]

If heart failure or chronic kidney disease predominates SGLT-2 inhibitors are warranted, as evidence show a reduction of heart failure and/or progress of chronic kidney disease. GLP-1 receptor antagonists or SGLT-2 inhibitors are recommended if weight loss is wanted.[82]

Along with the above-mentioned drug compounds, diet and physical activity remain cornerstones for modern diabetes treatment.[86]

Factors affecting wound healing

Both the pathway to onset and the healing of a DFU are complex processes. Apart from the extent of the ulcer, the presence of infection and peripheral neuropathy, comorbidities such as heart failure, and end-stage renal disease affect outcome.[87] Furthermore, the level of ischemia plays a great role for wound healing. The probability of wound healing among patients with DM can be assessed using factors reflecting the level of ischemia. The following factors have been shown to increase the pre-test probability of wound healing by up to 25%: ankle systolic pressure of ≥40 mmHg, a toe pressure of ≥30 mmHg, or a transcutaneous oxygen pressure ($TcPO_2$) of ≥25mmHg.[88] To predict the risk of major amputation an ankle systolic pressure <50 mmHg, ABI < 0.5, toe pressure < 30 mmHg, and $TcPO_2$ < 25 mmHg have all been shown to increase the probability of major amputation by 25%. These factors may work as guidance when deciding on which patients who should be prioritized for revascularization.[88]

Early revascularization, within 8 weeks from admittance at the multidisciplinary foot centre, has been shown to increase the probability of wound healing for an ischemic DFU. The absence of peripheral oedema has also been linked to better wound healing in a cohort of patients with DM.[89] Time from first visit to revascularization should not exceed two weeks in DFU with an ischemic component possible for revascularization. Limb salvage rates might then be equal to non-diabetic patients, as opposed to a delay of more than two weeks where limb salvage rates are worse for the diabetic population.[90] This workup schedule puts a high organizational demand on local health care systems.

Off-loading of the wound is crucial to reduce pressure and shear forces at the site of ulceration. Off-loading devices, such as therapeutic shoes or different types of casts (removable or total contact) reduce motion of the joints and protects the foot which allows tissue to bridge the wound and enable healing. According to Boulton et al, off-loading is one of the most important factors to facilitate foot ulcer healing.[11]

Apart from the above-mentioned factors affecting wound healing, the nutritional status also plays an important role in the healing process.

Omega-3 supplementation has been shown to decrease the size of diabetic foot ulcers in an RCT.[91] A review study on the effect of Omega-3 supplements for type 2 DM showed no effect on the level of HDL cholesterol, however, whereas a lowered level of triglycerides could be demonstrated. The effect on ulcers was, however, not studied.[92]

Surgical management of peripheral artery disease

According to the International Working Group on the Diabetic Foot, the decision to choose open surgery or endovascular therapy should be based on the patient's individual characteristics, such as the morphological distribution of PAD, the availability of autogenous vein, comorbidities, and local availability of expertise.[12] CLTI is usually associated with multilevel disease and therefore often require both inflow and outflow revascularization, whereas intermittent claudication more often can be treated with inflow revascularization only.[93]

The Bypass versus Angioplasty in Severe Ischaemia of the leg (BASIL) RCT which enrolled patients until 2004, showed no significant difference in AFS or survival between those undergoing bypass surgery and endovascular therapy for CLTI. However, after two years of follow-up bypass surgery was associated with a trend towards higher AFS.[94] In recent years there has been a clear shift towards more endovascular therapies at the expense of open vascular surgeries for PAD.[63] The endovascular options have been further developed after the BASIL trial, and currently both bare metal stents and drug eluting stents and balloons are available. The long awaited BASIL-2 trial in which the aim is to compare the clinical and cost-effectiveness of a "vein bypass first" strategy versus "best endovascular treatment first" for CLTI is now closed to randomisation of patients.[95] Currently, the Best Endovascular Versus Best Surgical Therapy for Patients With Critical Limb Ischemia (BEST-CLI) RCT study is enrolling patients in North America until approximately June 2022.[96]

Open vascular surgery

Open vascular surgery can be performed in mainly two different ways: endarterectomy or by-pass surgery.

Endarterectomy is usually performed on the common femoral artery and chosen when there are short segments of highly calcified lesions. The endarterectomy may extend into the superficial femoral and profunda arteries. Closure is usually performed with a synthetic or bovine patch to avoid restenosis.[97] This technique

offers great long-term patency and is considered first line treatment in this anatomical region, and superior to endovascular technique.[93]

Bypass surgery is dependent on good inflow and outflow. It is performed by suturing a vascular conduit proximal to the level of the arterial obstruction to a distal unaffected part of the artery (figure V, letter A). Bypass surgery can be performed with either synthetic or vein grafts, but better patency is seen for vein grafts.[98] To allow for arterial circulation in the vein graft the venous valves are destroyed by a valvulotome and the vein can then be used in situ or non-reversed. However, if the vein is reversed there is no need to destroy the venous valves.[93] An autogenous vein, preferably the great saphenous vein with good quality and length is associated with a better graft patency.[99]

Endovascular therapy

Endovascular therapy is enabled by catheter led revascularization where recanalization is performed either by luminal or subintimal recanalization. Short arterial occlusions or high-grade stenoses are passed intra-luminally with a guidewire and thereafter treated by balloon angioplasty i.e., percutaneous transluminal angioplasty (PTA) and/or stenting (figure V, letters B and C).

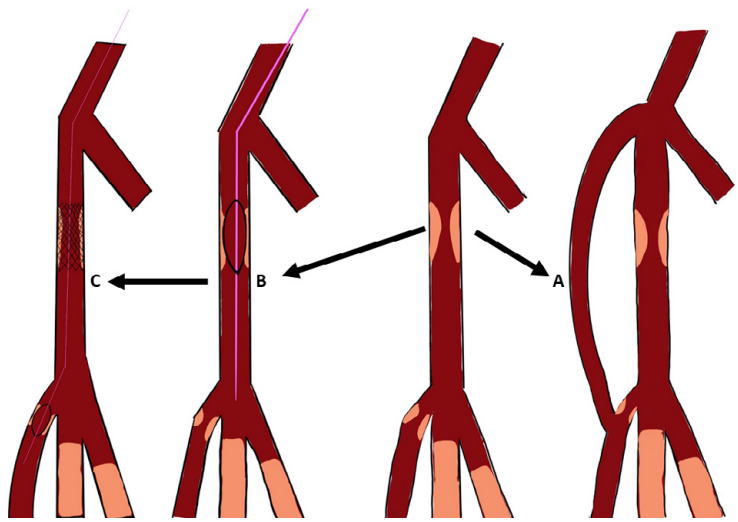


Figure V. Schematic drawing of a patient with chronic limb-threatening ischemia and a single severe atherosclerotic stenosis in the superficial femoral artery, occlusion of two crural arteries and one severe stenosis of the third crural artery. Treatment options may be either open vascular by-pass surgery (A) using a vein conduit from the common femoral artery to the target crural artery beyond the stenotic area or endovascular therapy using percutaneous transluminal angioplasty (PTA) (B) with subsequent stenting (C) in the superficial femoral artery (SFA) followed by PTA of the crural artery (C). *Artist: Talha Butt MD, PhD.*

In long arterial occlusions with hard plaques, subintimal recanalization is often required as normal transluminal angioplasty often fails. The subintimal space at the start of the occlusion is entered with a guidewire loop, which is used to cross the occlusion with the support of a catheter and re-enter the arterial lumen of the patent distal artery to form a new blood flow channel.[100] This new blood channel is in its entire length dilated via PTA and can be partly or entirely adjunctive stented if angiography shows a remaining flow-limiting lesion, such as an intimal flap or stenotic recoil after PTA (figure VI).[101]

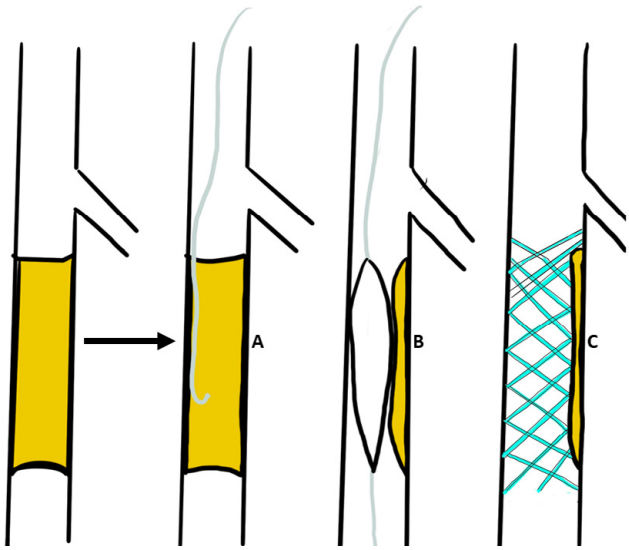


Figure VI. Schematic drawing of a patient with a long occlusion of the superficial femoral artery (SFA) undergoing subintimal angioplasty (A) with PTA (B) and subsequent stenting (C). *Artist: Talha Butt MD, PhD.*

Drug eluting stents, as used in coronary artery disease[102] are being introduced as a treatment option for PAD as well. The most common drug is paclitaxel, a drug used against different cancers such as ovarian malignancies due to its antimitotic effect.[103] In the vascular surgical field it is considered to prevent restenosis.[104] However, a meta-analysis from 2018 showed an increased two-year mortality associated with the use of paclitaxel stents and balloons for PAD where most patients had intermittent claudication.[105] Drug eluting devices are currently further investigated in the SWEdish Drug-Elution trial in Peripheral Arterial Disease (SWEDEPAD) RCT study, in which interim results showed no difference in mortality between groups with and without paclitaxel-coated devices.[106]

Aims

The general aim of this study was to study dietary and lifestyle factors associated with prevention of PAD among patients with DM, and to evaluate outcome after vascular and endovascular surgery in patients with DM and CLTI. The specific aims were to;

Paper I: examine the association between dietary intake and lifestyle on the risk of developing PAD among individuals with DM.

Paper II: investigate the risk of major amputation after urgently planned endovascular therapy in patients with CLTI comparing patients with and without DM.

Paper III: compare outcomes between patients with and without DM following urgently planned open revascularization for CLTI.

Paper IV: evaluate the difference in amputation-free survival between open and endovascular revascularization in patients with DM, PAD, and heel ulcers.

Patients and methods

Overview of the studies

Table V. Overview of Studies I-IV

	STUDY I	STUDY II	STUDY III	STUDY IV
Design	Prospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study
Study sample	Subgroup of individuals with DM at baseline in the Malmö Diet and Cancer cohort Study (n=1112).	Subgroup of patients registered in Swedvasc (n=4578) with or without registration in NDR.	Subgroup of patients registered in Swedvasc (n=1537) with or without registration in NDR.	Patients at the multidisciplinary diabetes foot clinic (n=127 limbs).
Enrolment	1991–1996	2010–2014	2010–2014	1983–2013
Methods	Individuals with prevalent PAD, or other cardiovascular disease were excluded. 7-day food diary, interviews, questionnaire with food and lifestyle questions. Comparison of dietary and lifestyle characteristics between the group developing PAD and the group not developing PAD. Median follow-up was 19.7 years.	Patients with and without DM, undergoing elective endovascular therapy for infrainguinal CLTI. Outcome was compared between the group with and the group without DM. Median follow-up was 4.0 and 3.6 years for patients with and without DM.	Patients with and without DM, undergoing elective open vascular surgery for infrainguinal CLTI. Outcome was compared between the group with and the group without DM. Median follow-up was 4.3 and 4.5 years for patients with and without DM.	Patients with DM, PAD and heel ulcers. Comparison of major amputation, death and amputation-free survival at 1 and 3 years between groups undergoing open vascular and endovascular therapy. Median follow-up was 3.3 years.
Data analysis	Descriptive statistics. Spearman's or Pearson correlation tests. Multivariate Cox regression analysis. Kaplan-Meier with life tables. Log-rank test.	Descriptive statistics. Kaplan-Meier with life tables. Cox proportional hazards model. IPTW adjusted Cox regression analysis.	Descriptive statistics. Kaplan-Meier with life tables. Cox proportional hazards model. IPTW adjusted Cox regression analysis.	Descriptive statistics. Kaplan-Meier with life tables. Log-rank test. Multivariate Cox regression analysis.

DM, diabetes mellitus; PAD, peripheral artery disease; CLTI, chronic limb-threatening ischemia. NDR, National Diabetes Register; Swedvasc, Swedish Vascular Registry; IPTW, inverse probability of treatment weighting.

Ethical approval

The study reported in paper I was approved by the ethical committee at Lund University with registration number LU 51/90, and the studies in papers II-IV were approved by the regional ethical review board in Lund with registration numbers 2016/232, 2016/544, and 2007/120.

Patients included in paper I had given their consent of being registered and agreed to long-term follow-up when included in the Malmö Diet and Cancer study. As all patients in paper II and III had given their consent of being registered in NDR and Swedvasc, no further individual consent was required to be included in these studies according to Swedish law. Paper IV was performed as a clinical follow-up study, thus not requiring patients' consent.

Data collection

Paper I was based on the Malmö Diet and Cancer Study (MDCS), paper II and III on merged data from Swedvasc and NDR.

Data collection for paper IV was based on electronic and paper charts from the archives at Skåne University Hospital.

Malmö Diet and Cancer Study

Paper I was based on the Malmö Diet and Cancer Study (MDCS), a prospective cohort study based in Malmö, Sweden. Although the MDCS was originally designed to investigate the relationship between diet and cancer, its use was extended for research on other exposures and disease endpoints. The MDCS was designed by representatives from the International Agency for Research and Cancer (IARC), till the Swedish Cancer Society, and the Faculty of Medicine at Lund University. Baseline data collection took place between 1991 and 1996.[107] Individuals who were residing in Malmö were invited by letter to participate. Two more reminders were sent to each individual. In addition to the personal letters, advertisements in local newspapers, in public places and in primary health care centres were posted. Women born 1923-1950 and men born 1923-1945 were eligible to participate in the study.

The wider age span set for women was motivated by the desire to study breast cancer among pre-menopausal women. Participants also had to comprehend the Swedish language and be able to complete the extensive questionnaire. In total, 74 138 individuals were eligible to participate according to the population register, of whom 65 599 individuals were invited by letter, and 5505 volunteered based on the posted

advertisements.[108] Paper I utilized data generated from the European Prospective Investigation into Cancer and Nutrition (EPIC)[109] cohort of the MDCS (n= 28 098).

At baseline, the participants of the MDCS filled in a dietary assessment, a self-administered lifestyle questionnaire and underwent anthropometric measurements. The dietary assessment consisted of a 7-day menu book, a food frequency questionnaire, and an interview. In the menu book participants were asked to register their cooked meals, cold beverages including alcohol, medicines, natural remedies, and dietary supplements. The food frequency questionnaire was designed to map the general food pattern, including frequency and portion size, of foods with low day-to-day variation, such as hot beverages, sandwiches, snacks, and fruits. The questionnaire included a booklet where photographs of different portion sizes were included, and the participants could choose which photograph best represented their own portion size. The interview was conducted by a dietician where the menu book and the questionnaire were verified and ensured that there were no overlaps in food intake and that the overall food pattern was correct.[110]

The lifestyle questionnaire was handed out to the participants at the first visit and was returned at the second, approximately two weeks later. The questionnaire contained questions on education, occupation, social network and support, physical activity, tobacco consumption, alcohol consumption, previous weight and diet change, and medications and illnesses.[111] Prevalent diagnoses were obtained from the National Population Register.

National Diabetes Register

In papers II and III the NDR was used to identify patients with a diagnosis of DM. The NDR was founded in 1996 and serves as an assurance and improvement tool for health care providers, as it covers 87% of Swedish adult patients with DM.[3] The NDR covers clinical characteristics, risk factors, laboratory analyses, complications related to DM, and different treatments for individuals 18 years or older.[112] The registry includes more than 500 000 individuals with DM.

A flow chart describing the data collection process, merging of data across registries and analysis in papers II and III are outlined in figure VII.

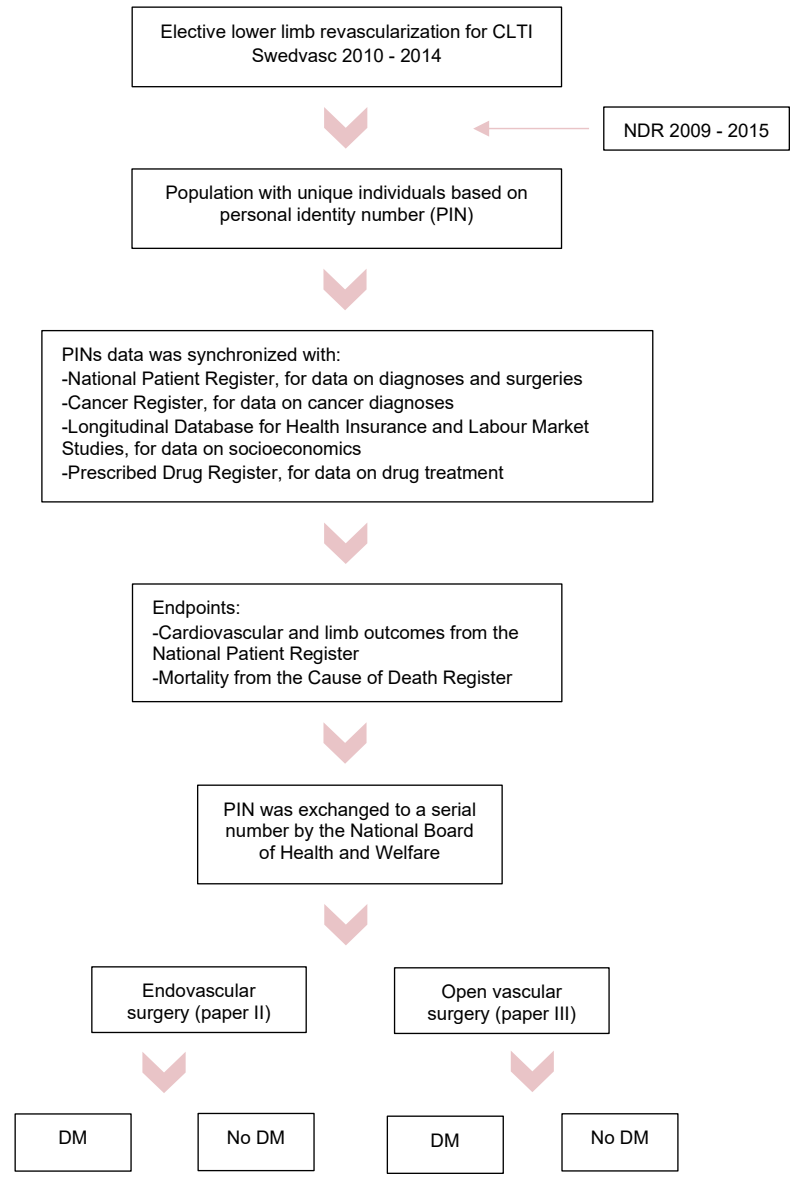


Figure VII. Flow chart of the data collection process for paper II and III.
Data from the National Patient Register and the Cancer Register were retrieved up to 10 years prior to baseline. Data from Longitudinal Database for Health Insurance and Labour Market Studies and the Prescribed Drug Register were retrieved up to 1 year prior to baseline. CLTI: chronic limb-threatening ischemia; Swedvasc: Swedish Vascular Registry; NDR: National Diabetes Register; DM: diabetes mellitus.

Swedvasc

Swedvasc was used for data collection in paper II and III. All patients undergoing vascular surgery in Sweden since 1994 are registered in Swedvasc.[113] In 2020, approximately 3,300 patients underwent surgery for CLTI. The frequency of complications such as amputation, AMI and mortality at 30-days follow-up is registered. The information on patient mortality was reported automatically to Swedvasc within 2 weeks from the Swedish population registry, based on the patient's personal identity number, rendering highly reliable mortality data.

One-year follow-up is performed with all patients, and mortality data are registered. The one-year mortality rate following vascular surgery for CLTI was 18% in 2020.[63] The national coverage rate of revascularization procedures in Swedvasc varies between 82-95% when compared with the National Patient Register.[63] Eighty eight percent of lower extremity arterial procedures are registered in Swedvasc within 30 days. Swedvasc has been validated for carotid artery disease and abdominal aortic aneurysms,[114] but no formal validation has been performed regarding procedures related to PAD. However, Djerf et al reported that among 109 patients registered as having undergone an ipsilateral lower limb amputation after revascularization for claudication during a median follow-up of 3.9 years, 17 were duplicate registrations, 51 had CLTI and not claudication, one was not revascularized, one had acute limb ischemia, one was revascularized for a popliteal aneurysm, one underwent a minor, not major amputation, and one was not amputated at all. In total, only 33% (36/109) of patients registered in Swedvasc as having undergone major amputation after revascularization for claudication were registered correctly.[115] A recent validation of major amputation for CLTI has been performed by reviewing 1,366 patients' medical records, showing <10% missing data for amputation with remaining uncertainty on amputation laterality.[116]

Definitions used in papers I-IV

Acute myocardial infarction was defined by code I21 according to the International Classification of Diseases, tenth revision (ICD-10).

Amputation was defined as amputation above the ankle e.g., major amputation if not stated otherwise.

Anaemia in paper IV was defined as haemoglobin <134 g/L in men and <117 g/L in women.

Body mass index was calculated using weight divided by height^2, expressed in kg/m2.

Chronic limb-threatening ischemia (CLTI) was defined as the presence of peripheral artery disease along with rest pain, gangrene or ulcers for > 2 weeks.

Diabetes mellitus (DM) was in paper I defined as fasting blood glucose >6.0 mmol/l, use of antidiabetic drugs or self-reported physician's diagnosis. In paper IV, DM type 2 was defined as patients younger than 31 years without insulin treatment, and DM type 1 was defined as patients younger than 31 years with insulin treatment. These definitions were used up until 1997 as the ICD coding system did not differ between type 1 and 2 DM.

Drug treatment was defined according to the Prescribed Drug Register in papers II and III. Use of lipid lowering drugs, acetylsalicylic acid, metformin and other glucose-lowering medications, and anticoagulant therapy was included.

Duration of DM was in paper IV defined as the year from diagnosis until the presentation of a foot ulcer at the foot clinic.

End-stage renal disease in paper IV represented creatinine >300 μmol/L, past renal transplantation, or dialysis.

Good concordance in paper IV was defined as participating in 50% or more of the appointments at the multidisciplinary foot clinic.

Home aid was defined as any specialized assistance (not a family member) in paper IV.

Hypertension was in papers II and III defined as collecting a minimum of one prescription of antihypertensive drugs one year prior to index operation. Three months of medicine use is equivalent to one prescription. In paper I and IV hypertension was defined as use of antihypertensive drugs or blood pressure ≥140/90 mmHg.

Ischemic heart disease in paper IV was defined as previous myocardial infarction or angina pectoris.

Major adverse cardiovascular events in paper II and III, included angina pectoris, acute myocardial infarction and related complications such as papillary muscle rupture, hemopericardium, and ventricular septal rupture. Chronic ischemic heart disease, cerebral infarction, intracerebral haemorrhage, and subdural haemorrhage was also included.

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

Nonischaemic heart disease in paper IV included atrial fibrillation or valvular disease.

Psychiatric disorders excluded dementia.

Renal disorder included kidney transplant, renal failure or dialysis in paper II and III.

Renal impairment used in paper II and III was defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 with data from NDR on individuals with DM only.

Retinopathy in paper IV was defined as preproliferative or proliferative based on retinal photographs scored by an ophthalmologist.

Severe peripheral vascular disease was used in paper IV as toe pressure <45 mmHg or ankle pressure <80 mmHg.

Smoking was in paper II and III defined as currently smoking at baseline with data from Swedvasc and when missing, the National Diabetes Register was used to complement. In paper I smoking was defined as former or current smoking. In paper IV current smoking was defined as currently smoking or having quit smoking less than a year ago.

Stent in paper II included drug eluting stent or stent graft.

Ulcer duration in paper IV was expressed in weeks and reflected the time from admission at the foot clinic to healing of the heel ulcer.

Validation of diagnosis of peripheral artery disease

In paper I, one hundred of the patients with the diagnosis of peripheral artery disease in MDCS were randomly selected for the validation procedure using patient record data. Among 100 patients, 69 had CLTI, 12 had thrombotic and one embolic acute limb ischemia, 15 had intermittent claudication, and one had asymptomatic peripheral artery disease. Two patients with venous insufficiency were misdiagnosed. The diagnosis of atherosclerotic symptomatic PAD could therefore be confirmed in 97%.[117]

Statistical analyses

Continuous variables such as age were expressed in median with inter quartile range. The Mann-Whitney U-test (non-parametric) and Student's t test (parametric) were used for comparison of continuous variables, and differences in proportions were compared with Pearson's chi square test. Ordinal data such as for income groups were compared with Kendall's tau-b test. P-values <0.05 and standardized mean differences (SMD) >0.2 were considered statistically significant.

In paper I, the correlation between fish and shellfish consumption and potential risk factors for PAD were analysed with Spearman's correlation test for ordinal data and Pearson's test for continuous data. Variables differing ($p<0.1$) between incident PAD and not, in a univariable analysis, were further entered as covariates in a multivariate Cox regression analysis and expressed in hazard ratios (HR) with 95% confidence interval (CI). The cumulative incidence of PAD was described according

to the Kaplan Meier method with life tables, and sex differences were analysed with a log-rank test.

An additional and refined statistical re-analysis was performed after the publication of paper I. The variables age, and fish and shellfish intake were tested for normal distribution with the Kolmogorov-Smirnov test. The distributions of these two variables were found to be skewed. Since the Cox regression is semi-parametric[118] age, fish and shellfish were log transformed to calculate the respective z-scores. The participants z-scores for age and fish and shellfish were entered as covariates together with "male sex", "hypertension" and "smoking" in the multi-variate Cox regression analysis. HRs of age and fish and shellfish were expressed per 1 standard deviation (SD) increment to enable comparisons of effect sizes.

In papers II and III, propensity score analysis was performed (see below). The cumulative incidence of mortality and major amputation were described using crude Kaplan Meier curves.

In paper IV group differences in amputation-free survival (AFS) were analysed with the Kaplan Meier method and life tables. Differences between open and endovascular surgery were analysed with log-rank test. Variables differing ($p < 0.1$) between endovascular and open vascular surgery groups were further entered as covariates in a multivariate Cox regression analysis for evaluation of AFS, and expressed in HR with 95% CI.

Propensity score analysis

When using multivariate adjustments by logistic regression, a limited number of baseline variables should be used, according to "the rule of ten" a minimum of 10 endpoints should be used per baseline variable.[119] The rule was applied to keep the risk of overfitting low. When adjusting for several baseline variables such as in papers II and III with approximately 30 variables, the propensity score adjusted analysis is more suitable.

The propensity score analysis is as a way to minimize confounding when estimating the treatment effect on outcome. The propensity score estimates the probability of receiving treatment based on the baseline variables which renders a score. In papers II and III the treatment group is the group with DM and the control group those without DM.

The propensity score is a way to minimize selection bias and some even say that the propensity score is a way to design and analyze an observational study so that it mimics an RCT.[120, 121] An example of this would be to try and balance covariates so that the distribution of the covariates are very similar between the treatment and control group.[120] There are four different ways in which the propensity score can be utilized: matching on the propensity score, stratification on the propensity score,

inverse probability of treatment weighting (IPTW), and covariate adjustment using the propensity score.[121]

IPTW was used in papers II and III. Each study participant was assigned weights based on their propensity score. The study participant's weight was equal to the inverse probability of it having DM or not. A high weight means being atypical for the group that the person is included in, e.g., a person without DM will get a higher weight if its baseline variables are more similar to those in the group with DM.

Individuals with the same weights but from different groups (DM or no DM) had the same distribution of baseline variables. These two individuals were then compared. Two individuals with the same propensity score (and weight), but from different treatment groups, will have the same distribution of baseline variables.

Put simply, IPTW tried to answer the question: "What would be the outcome if the group with DM and the group without DM were equal in all other baseline variables at the time of the vascular surgical procedure?"

Results

Study I

Main findings

I. A higher intake of fish and shellfish tended to confer a protective effect against the development of PAD among individuals with DM (HR per additional gram per week 0.99, 95% CI 0.99-1.00, p=0.051). See table VI. Additional refined statistical re-analysis (see statistical analysis, page 38) showed that fish consumption was associated with a reduced risk of incident PAD (HR/standard deviation [SD] increment 0.84, 95% CI 0.73-0.97, p=0.018). See table VII.

II. Smoking was associated with an increased risk of developing PAD among individuals with DM (HR 1.96, 95% CI 1.28-3.00, p=0.002).

Table VI. Multivariate Cox regression analysis of factors associated with incident symptomatic peripheral artery disease among patients with diabetes mellitus.

	Hazard ratio	95% confidence interval	p-value
Age	1.01 per year	0.98-1.03	0.64
Male sex	1.36	0.95-1.95	0.09
Hypertension	1.86	0.87-4.02	0.11
Smoking	1.96	1.28-3.00	0.002
Fish and shellfish intake	0.99 per additional gram per week	0.99-1.00	0.051

All five variables were entered in the Cox regression analysis.

Table VII. Additional refined statistical re-analysis. Factors associated with incident symptomatic peripheral artery disease among patients with diabetes mellitus.

	Hazard ratio	95% confidence interval	p-value
Age[a]	1.09	0.90-1.31	0.40
Male sex	1.31	0.91-1.89	0.15
Hypertension	1.73	0.80-3.73	0.16
Smoking	2.07	1.34-3.22	0.001
Fish and shellfish[a]	0.84	0.73-0.97	0.018

[a] HR were expressed per 1 SD increment. One SD for the variable fish and shellfish equals 265 g per week. All five variables entered in the Cox regression analysis.

Study II

Main findings

I. Patients with DM had a higher rate of major amputation following urgently planned endovascular therapy for CLTI (HR 1.43, 95% CI 1.23-1.67, p<0.0001) compared to those without DM. The risk of major amputation or death was also higher (HR 1.13, 95% CI 1.04-1.23; p=0.004) among patients with DM after endovascular therapy for CLTI. See table VIII.

II. There was no difference in mortality between the group with and without DM following urgently planned endovascular therapy for CLTI (HR 1.04, 95% CI 0.95-1.14, p=0.362). The rate of AMI was higher in the group with DM (HR 1.37, 95% CI 1.13-1.67, p=0.002). See table VIII.

Table VIII. Inverse probability of treatment weighting adjusted Cox regression analysis of different endpoints for patients with DM compared to patients without DM following urgently planned endovascular surgery for CLTI.

	hazard ratio	95% confidence interval	p-value
Mortality	1.04	0.95-1.14	0.362
Cardiovascular death	1.01	0.95-1.14	0.921
MACE	1.13	1.04-1.23	0.003
Acute myocardial infarction	1.37	1.13-1.67	0.002
Stroke	1.11	0.89-1.38	0.363
Major amputation	1.43	1.23-1.67	<0.0001
Major amputation or death	1.13	1.04-1.23	0.004

DM, diabetes mellitus; CLTI, chronic limb-threatening ischemia. MACE: major adverse cardiovascular events.

Study III

Main findings

I. No difference in major amputation (HR 1.28, 95% CI 0.98-1.66, p=0.070) or death (HR 1.10, 95% CI 0.93-1.30, p=0.251) were seen following urgently planned open vascular surgery for CLTI when comparing patients with and without DM. Neither was there any group difference regarding the compound variable major amputation or death (HR 1.15, 95% CI 0.98-1.35; p=0.090) following open vascular surgery. See table IX.

II. Patients with DM had higher rates of stroke (HR 1.70, 95% CI 1.11-2.59 p=0.014) and AMI (HR 1.39, 95% CI 1.00-1.92, p=0.047) following urgently planned open vascular surgery for CLTI. See table IX.

Table IX. Inverse probability of treatment weighting adjusted Cox regression analysis of different endpoints for patients with DM compared to patients without DM following urgently planned open vascular surgery for CLTI.

	hazard ratio	95% confidence interval	p-value
Mortality	1.10	0.93-1.30	0.251
Cardiovascular mortality	1.09	0.89-1.33	0.403
MACE	1.15	0.98-1.34	0.090
Acute myocardial infarction	1.39	1.00-1.92	0.047
Stroke	1.70	1.11-2.59	0.014
Major amputation	1.28	0.98-1.66	0.070
Major amputation or death	1.15	0.98-1.35	0.090

DM, diabetes mellitus; CLTI, chronic limb-threatening ischemia. MACE: major adverse cardiovascular events.

Overview of outcomes in study II compared to study III

For comparison of outcomes following urgently planned endovascular therapy (study II) with open vascular surgery (study III) for CLTI, please see table X.

Table X. Summary of outcomes following urgently planned endovascular therapy (study II) and open vascular surgery (study III) for CLTI.

	Endovascular therapy	Open surgery
Mortality	0	0
Cardiovascular mortality	0	0
MACE	+	0
Acute myocardial infarction	+	+
Stroke	0	+
Major amputation	+	0
Major amputation or death	+	0

Results based on propensity score adjusted Cox regression analysis in study II and III, respectively. + means increased risk for the group with DM and 0 means no difference in risk between the group with DM compared to the group without DM. MACE: major adverse cardiovascular events.

A summary of the effects of diabetes duration, HbA1c, renal impairment, and tissue loss on outcomes among patients with DM undergoing endovascular as opposed to open revascularization for CLTI are shown in table XI.

Table XI. Summary of effects of diabetes duration, HbA1c, renal impairment and tissue loss on six endpoints among patients with DM undergoing revascularization for CLTI.

	Diabetes duration		HbA1c		Renal impairment		Tissue loss	
	Endo	Open	Endo	Open	Endo	Open	Endo	Open
Total mortality	+	0	0	0	+	+	+	0
Cardiovascular mortality	0	0	0	0	+	+	+	0
MACE	+	+	0	0	+	+	+	0
Acute myocardial infarction	+	0	+	0	0	0	+	0
Stroke	0	0	0	0	0	0	0	0
Major amputation	+	0	0	0	+	0	+	+

Analysis are adjusted for age and gender in the “Endo” and “Open” group, respectively. + means that the diabetes related factor increases the risk for the different outcomes. 0 means no increased risk associated with the diabetes related factor. MACE: major adverse cardiovascular events.

Study IV

Patient characteristics

Patients undergoing open vascular surgery more often had local foot pain (p=0.038), foot oedema (p=0.006), and previous vascular surgical procedures (p=0.023). On the contrary, previous foot ulcer (p=0.001), retinopathy (p=0.035), and insulin treatment (p=0.024) were more common in the endovascular group.

Main findings

I. AFS was higher following open vascular surgery compared to endovascular therapy for patients with DM, PAD, and heel ulcers (HR 2.1, 95% CI 1.1- 3.9, p=0.025). See figure VIII and table XII.

II. An increase in the proportion of patients undergoing endovascular surgery at the expense of open vascular surgery over time was observed, when comparing the former (1983-2000) and latter (2001-2013) time periods (p< 0.001).

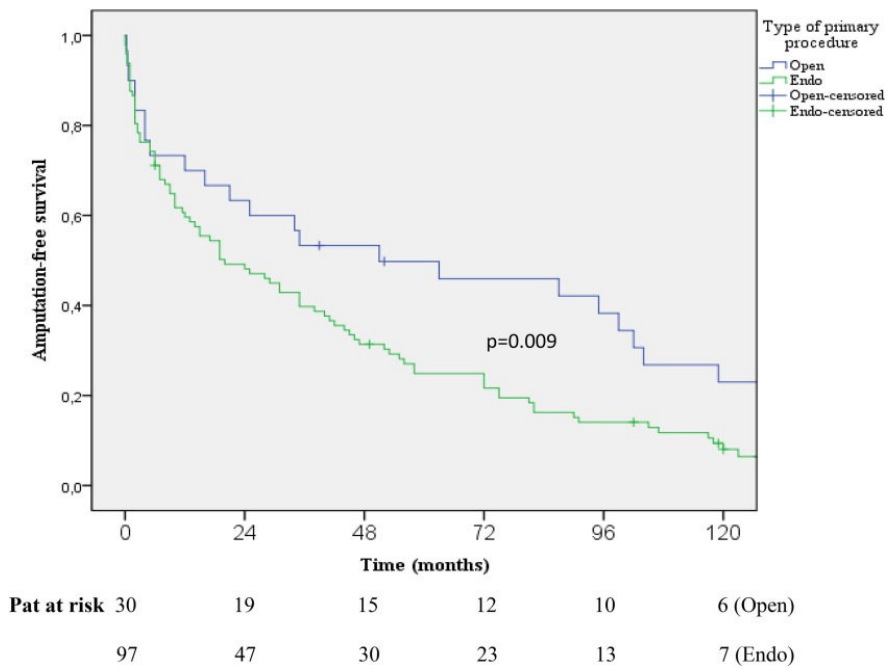


Figure VIII. Crude Kaplan-Meier analysis of amputation-free survival following open and endovascular surgery among patients with diabetes mellitus, peripheral artery disease and heel ulcers.

Table XII. Analysis of factors associated with amputation-free survival among patients with diabetes mellitus, peripheral artery disease and heel ulcers undergoing open and endovascular surgery.

	hazard ratio	95% confidence interval	p-value
Type of primary procedure (open versus endovascular surgery)	2.06	1.10 – 3.86	0.025
Retinopathy	1.24	0.78 – 1.96	0.36
Diabetes treatment (insulin versus no insulin)	1.10	0.67 – 1.80	0.70
Previous ulcer	1.15	0.72 – 1.83	0.55
Edema	0.90	0.58 – 1.42	0.66
Pain	1.04	0.65 – 1.66	0.87
Previous vascular surgery	1.95	1.02 – 3.74	0.044

All seven variables were entered into the Cox regression analysis.

Discussion

Diet and peripheral artery disease in individuals with DM

Previous studies on the impact of different dietary components upon the risk of PAD have been scarce,[122, 123] particularly among individuals with DM.[124] Previous studies have focused on traditional cardiovascular risk factors and the incidence of PAD among patients with type 2 DM.[125]

In paper I we found a trend towards a protective effect of a high intake of fish and shellfish against the risk of PAD in subjects with DM. After further statistical re-analysis, this protective effect was even stronger. Another study based on a non-diabetic population from MDCS showed that a high intake of dietary fibres and a generally healthy diet reduced the risk of developing PAD, whereas fish and shellfish alone were not associated with a reduced incidence of PAD.[126] In an extended study from the MDCS cohort[127] including individuals with DM and evaluating diet and risk of atherosclerotic cardiovascular disease, however, a higher diet score with adherence to recommended intake of fish and shellfish, fibre and saturated fatty acid were associated with decreased risk for incident atherosclerotic cardiovascular disease. A randomized controlled trial with approximately 50% of study participants having type 2 DM showed that a Mediterranean diet known to be rich in fish and shellfish, reduced the risk of developing PAD compared to a low-fat diet.[122] A healthy diet, rich in fish, might help to achieve and maintain body weight goals, reach individual glycaemic, blood pressure, and lipid targets, and prevent diabetic complications.[128] It is also possible that high consumers of dietary fibres, fish and shellfish have a different lifestyle in general compared to low consumers, contributing to the presumed protective effect.

Effects of DM in patients with chronic limb-threatening ischemia undergoing revascularization

The summary of outcomes following revascularization (table X) for patients with and without DM showed that the risk of AMI was higher among those with DM after both endovascular and open vascular surgery. However, this did not affect the mortality rates which were similar for patients with and without DM following either revascularization method.

In paper II we found that patients with DM had a higher risk of major amputation, combined major amputation and mortality, and AMI following endovascular therapy for CLTI compared to those without DM. However, cardiovascular mortality was not increased among patients with DM compared to those without DM. In recent years there has been a reduction in mortality and cardiovascular complications among Swedish patients with DM. Data from NDR, however, still show an excess mortality due to coronary heart disease among those with DM compared to the general population.[129] The study included almost 500,000 Swedish patients with DM whereas the number of patients with DM in paper II were 2,251. We can therefore not exclude that the nonsignificant association of increased cardiovascular mortality in the group with DM in paper II is a result of type II statistical error, and that a larger study sample might have rendered a statistically significant association between DM and cardiovascular mortality. Furthermore, patients in paper II had higher rates of previous AMI, stroke, and heart failure in the two comparative groups, compared to the study by Rawshani et al,[129] possibly contributing to the nonsignificant association between DM and cardiovascular mortality.

In paper III, the risks of AMI and stroke following open vascular surgery for CLTI were higher in the group with DM. It is well-known that individuals with DM have a more distal distribution of their arterial disease, and generally more significant perfusion-related end-organ damage.[12] Nevertheless, the risks of major amputation and the combined endpoint major amputation or mortality were not increased in patients with DM after open vascular surgery, which may be partly attributed to the fact that by-pass surgery with vein conduit was performed slightly more often in patients with DM (73% versus 68%). This might possibly have contributed to the comparable results on major amputation, as vein conduits previously have been shown superior to synthetic grafts.[98] In contrast to results presented in paper III, data from Swedvasc on patients undergoing open vascular surgery for CLTI between 2001-2003 showed an increased mortality among patients with DM,[130] which partly might be explained by lower rates of secondary prevention with statins and antiplatelet agents.[131]

Effects of specific characteristics in patients with DM and chronic limb-threatening ischemia undergoing revascularization

A summary of outcomes following revascularisation for CLTI among patients with DM with respect to diabetes related factors is displayed in table XI, reflecting data in paper II and III. For instance, tissue loss was associated with an increased risk of major amputation following both endovascular therapy and open vascular surgery. Tissue loss in patients with CLTI has previously been shown to be an independent factor associated with major amputation and mortality.[132] A previous study, comparing outcomes after open vascular surgery and endovascular interventions for

patients with tissue loss and CLTI, in which approximately 65% had DM, showed a better limb salvage rate following open vascular surgery.[133]

When compared to endovascular surgery, open vascular surgery (paper IV) was associated with higher AFS. However, insulin treatment, retinopathy, and previous foot ulcers were more common in the group undergoing endovascular therapy compared to those having open vascular surgery, which could reflect a more advanced diabetic disease in the group of patients receiving endovascular therapy. Furthermore, local foot pain was more prevalent in the open vascular surgical group, which could be interpreted as a sign of less advanced neuropathy. Diabetic neuropathy leads to worse pain perception and frequently masks progressive PAD[66] which might contribute to patient's delay in seeking medical attention for DFU. After multivariate Cox regression analysis neither foot pain, previous ulcer, insulin treatment, or retinopathy remained as factors affecting AFS among patients with DM, PAD, and heel ulcers. The finding that previous vascular surgery was associated with improved outcome is puzzling. A detailed analysis on the type of previous vascular surgery in the open vascular and endovascular surgery groups might perhaps have given a clue.

CLTI should be viewed as a sign of systemic atherosclerosis with high mortality in cardiovascular diseases.[26, 134] With this in mind, patients with DM that are planned to undergo vascular surgery for CLTI require specific pharmacological considerations preoperatively in order to improve their cardiovascular outcome postoperatively. Antihypertensive drugs, statins, and optimization of blood glucose levels are recommended for optimal cardiovascular risk management.[12, 26]

Renal impairment among patients with DM was associated with a higher mortality, cardiovascular mortality and MACE in both studies II and III. Chronic kidney disease along with PAD has also previously been linked to inferior survival rates.[135]

Risks associated with type of revascularization for chronic limb-threatening ischemia

Whereas endovascular therapy can be performed in local anaesthesia, open vascular surgery is associated with much greater cardio-pulmonary stress as the patient has to be anesthetized. However, this did not affect mortality rates following open vascular surgery compared to endovascular technique in paper IV. Of note, we have not presented short-term data or 30-day outcomes data due to issues related to insufficient statistical power in those analysis. Nevertheless, the endovascular-first strategy[136] should not be performed swiftly keeping in mind that the BASIL RCT showed a higher risk of early failure amongst patients revascularized with endovascular technique. Patients would then require second line by-pass surgery associated with inferior outcome compared to a primary revascularization with by-pass surgery.[137] Moreover, patient suffering and excessive health care costs related

to inadequately treated CLTI cannot be ignored. The BEST-CLI trial has completed recruitment of patients and short-term outcome data is expected to be published in 2022 (https://clinicaltrials.gov/ct2/show/NCT02060630), supplemented later by mid and long-term outcome and cost-effectiveness analysis. This large-scale randomized trial on 1843 patients from 116 US BEST-CLI vascular centre sites will provide important results for future management of CLTI patients. The investigators have claimed that a large proportion, around 70% of the study population, has DM and that a sub-study of the trial, "The Impact of Diabetes on REvascularization (TIDE)", is planned.

Amputation-free survival after revascularization in patients with DM

In paper IV, AFS was higher following open vascular surgery compared to endovascular therapy among patients with DM, PAD, and heel ulcers. Furthermore, we found that the proportion of patients undergoing endovascular therapy increased at the expense of open vascular surgery during the study period. Some might therefore argue that the experience of endovascular technique might have been limited, which might possibly have contributed to the inferior results associated with the endovascular procedures. Another explanation may be that vascular surgeons are becoming more active at retreating patients, and therefore perform more repeat endovascular procedures. Nonetheless, endovascular techniques have been the most commonly used for revascularization of PAD since 2004 in Sweden.[138]

The higher AFS following open vascular surgery in paper IV might have been even larger keeping in mind that pharmacological coverage with statins[73] and aspirin has improved over time.[63, 139] In addition, the substantial and ongoing decrease in smoking prevalence in high income countries, including Sweden since the 1970s,[140] (figure IX) has most certainly conferred general beneficial health effects including less prevalence and severity of PAD.[141] Adjusting for improvement in medical risk factor treatment along with smoking cessation and time period in a multivariate Cox regression analysis would have been most interesting, and might have unveiled an even more evident advantage of open vascular surgery.

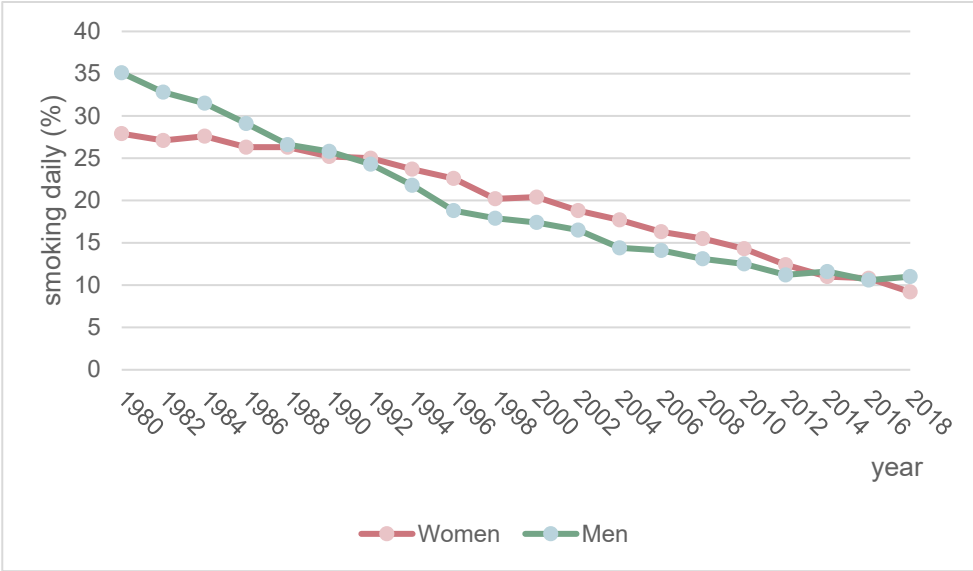


Figure IX. Prevalence of daily smoking in Sweden from 1980 to 2019 in ages 16-84 years, divided by sex. Data from Statistics Sweden.[142]

Guidance on revascularization options for chronic limb-threatening ischemia

During the last decades there has been a clear shift towards more endovascular techniques in high-income countries, at the expense of open vascular surgery.[143] Nevertheless, to ensure the best clinical outcome for individuals with CLTI it is crucial that the surgeon has access to both endovascular and open vascular techniques.[26] The Global Vascular Guidelines recommend, in order to aid clinical decision making on patients with CLTI, an approach based on the PLAN method (Patient risk assessment, Limb staging [WIfI] and ANatomic pattern [GLASS]) (table XIII).

Table XIII. Preferred primary mode of revascularization in chronic limb-threatening ischemia in an average-risk patient with autologous vein conduit accessible for bypass.

Patients with low WIfI scores (green) eg. low risk should be conservatively considered for revascularization. Areas coloured grey indicate scenarios with least consensus. Modified from the Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischemia.[26] WIfI, Wound, Ischemia, foot Infection; GLASS, Global Limb Anatomic Staging.

Current evidence suggests that benefit of revascularization among patients with CLTI is related to both the degree of ischemia and stage of limb threat (WIfI stage).[144, 145] A patient's individual and anatomic factors should guide the decision on open vascular surgery or endovascular therapy. The GVG recommends combining the WIfI score with anatomic pattern of disease (GLASS)[26] (see table XIII). GLASS is used to classify the pattern of arterial disease in CLTI with the primary goal to restore flow to the foot. The target arterial path, usually the least atherosclerotic infrapopliteal artery is selected and usually correlates best with endovascular outcome. As such, the GLASS stage is best correlated with endovascular outcome as it does not pay attention to the quality of vein conduits. A subgroup analysis from the BASIL-1 RCT showed that GLASS is not associated with outcome following by-pass surgery.[146] Patients in whom autologous vein conduits are not available should be paid specific consideration, as vein conduits are important factors for bypass success rates.[98] For this specific group endovascular techniques should be considered as first line strategy.[137]

The patients in paper IV undergoing endovascular and open vascular surgery had the WIfI spectrum scores of Wound 2-3, Ischaemia 2-3, foot Infection 0-3, which means that these patients all had WIfI stage 3-4 even if no data on foot infection was collected.[26] According to table XIII, patients with low-complexity arterial disease (GLASS-1) benefit more from endovascular therapy, and those with high-complexity arterial disease (GLASS-3) benefit more from open bypass surgery. Differences in GLASS stages between the endovascular and open vascular surgery group in paper IV were not possible to evaluate, but this factor reflecting the extent of lower extremity arterial disease is important to include in prospective studies.

Methodological considerations

Selection bias

The participant rate in the MDCS was 40% (paper I), which can be considered relatively low and as reducing the generalizability of the study.[111] A health survey was mailed to the same population, resulting in a participation rate of 75%. The health survey showed a comparable socio-demographic structure between participants and non-participants in the MDCS cohort, but both cancer incidence during study recruitment, and mortality during and following the recruitment period was higher in non-participants.[108]

The present thesis is focused on patients with DM thus reducing the number of study participants, which might not have rendered sufficient statistical power to gain statistical significance in some analyses. In paper III we found a nonsignificant association between DM and major amputation. Even though the study cohort is relatively large, we cannot exclude that this nonsignificant association was a result of type II statistical error, and that a larger study sample would have rendered a statistically significant association between DM and major amputation.

Papers II and III were based on national materials of patients undergoing endovascular alternatively open vascular surgery, respectively, for infrainguinal CLTI, reducing the risk of treatment selection bias.

Among all patients with DM and heel ulcer, patients in paper IV were composed by a subgroup diagnosed with lower extremity arterial occlusive disease. Selection for either vascular or endovascular surgery had probably to a great extent been based upon physician preferences and advances in endovascular therapy throughout the long study period.

Information bias

A substantial part of baseline collection data including dietary and lifestyle data was self-reported in the MDCS (paper I). Potential misreporting might therefore to some extent have resulted in erroneous results and incorrect interpretations. Non-adequate reporters of energy data were identified by comparing their reported energy intake with their total energy expenditure (estimated from their calculated basal metabolic rate and self-reports of leisure-time physical activity, work activity, household work, and sleep hours). Individuals with reported energy intake above or below the 95% CI for total energy expenditure were categorized as “misreporters”. Individuals acknowledging that they substantially changed their dietary habits in the past in the questionnaire were categorized as “dietary changers”.[147] Individuals with DM at baseline were considered to be dietary changers, but since the cohort in paper I

comprised those with DM only, study population was considered homogenous and scientific rigor was considered to be reasonably maintained. Moreover, in a cohort study in middle-aged individuals attempting fat reduction, over 70% of the individuals still maintained the same diet after 24 months.[148] No sensitivity analysis by removing "misreporters" in paper I was performed due to concerns about reduced sample size and statistical power.

The present thesis is based on data retrieved from registries and medical records, which might potentially lead to the risk of misclassifications, incorrect data collection, and missing data. Previous studies on Swedvasc suggest that up to 50% of data on smoking status is missing.[149] Therefore, NDR data were used as a complement in the group with DM for which Swedvasc data on smoking status were lacking in papers II and III, which enabled more reliable assessment of smoking status in patients with DM.

Swedvasc has previously been validated regarding surgery of abdominal aortic aneurysm and carotid artery disease[114] whereas no validation of patients having procedures for PAD has been performed. Even though no validation of CLTI patients registered in Swedvasc was completed, we have no reason to believe that a significant part of patients with CLTI were misclassified as CLTI instead of claudication. It is possible that some patients were misclassified as having CLTI after a failed revascularization for intermittent claudication. On the contrary, a previous study showed that patients registered in Swedvasc due to intermittent claudication who later underwent major amputation had in fact been misclassified to a large extent and actually suffered from CLTI.[115]

Paper IV was due to its retrospective design and long study period from 1983 to 2013, particularly prone to information bias with difficulties in finding information in the medical records (paper charts) used during the former half of the study period.

Confounding

Papers I – IV were all observational cohort studies and the main results were based on statistical analysis adjusting for confounders. While observational studies examine associations in real world settings, causality between exposure and outcomes cannot be determined. Adjusting for potential confounders during statistical modelling can to some extent reduce the risk of drawing incorrect conclusions. Adjustments for age and sex were performed in paper I, II, and III and are often included as a first line adjustment in basic statistical models. Age and sex were not included in the adjusted model in paper IV, however, since there were no differences between these two variables in the two comparative groups in the uni-variate analysis. In addition, the limited sample size in paper IV did not permit extensive adjustments for confounders. As a rule of thumb, one covariate can be entered per ten events in a multi-variate analysis.[150] Seven covariates were entered

in the Cox regression analysis in paper IV, which was allowed since there were 89 events of either major amputation or death at 5 year.

Adjustments for confounders by using propensity score model in paper II and III is an excellent tool to account for observed differences between two groups, the DM compared to the non-DM group, in order to isolate the effect of DM. However, propensity scores cannot adjust for unobserved differences between groups. It is possible that unobserved co-variables such as level of arterial occlusions in the lower limb might have influenced the choice of revascularization as well as the outcomes, a distortion labelled residual confounding.

In this thesis no separate analysis of patients with insulin-treated DM and non-insulin-treated DM was performed. Since previous studies have shown an association between insulin treatment and worse limb salvage rates among individuals with CLTI, it would have been highly interesting to perform separate analysis of insulin treatment.[151]

In particular in paper, I and IV, changes in pharmacological secondary prevention with platelet aggregation inhibitors, statins, and smoking cessation during the respective long study periods were identified as confounders not possible to adjust for in the analysis.

Another confounder not addressed was the change of different pre-interventional imaging modalities during the respective study periods. The frequencies of diagnostic angiography (74%) and MRA (39%) in paper IV have likely not been consistent throughout the study. Higher proportions of diagnostic angiographies and MRA, respectively, were performed in the former and latter part of the study period.

Strengths

The large prospective population-based cohort study of middle-aged individuals at baseline, a median follow-up duration of 20 years, and validation of the diagnosis of symptomatic PAD were major strengths in paper I.

In papers II and III, the use of two disease-specific nationwide data registries, Swedvasc and NDR, and propensity score statistical modelling adjusting for approximately 30 variables were major strengths.

In paper IV, the patients were consecutively recruited from a diabetic foot care section at the Department of Endocrinology. The diabetic foot rounds consist of experienced specialists in endocrinology, vascular surgery, and orthopaedic surgery, guaranteeing a high-quality multidisciplinary approach to DFU patients.

Conclusions

- A higher intake of fish and shellfish was tended to protect against the development of PAD among individuals with DM.
- The risk of major amputation was higher for patients with DM compared to those without DM after urgently planned endovascular therapy for CLTI.
- There was no difference in major amputation or mortality between patients with and without DM following urgently planned open vascular surgery for CLTI.
- Amputation-free survival was higher after open than endovascular surgery among patients with DM, PAD, and heel ulcers.

Future perspectives

According to the IDF, it is possible to reduce amputation rates by between 49% and 85% through a combination of education of both patients with DM as well as healthcare professionals and a multi-disciplinary treatment of DFU with close monitoring.[1] In order to reach this goal not only treatment of PAD and DFU are important, prevention of the development of PAD and DFU's are most crucial.

Future research with prospective studies on modifiable risk factors such as diet, smoking, obesity, and physical activity for the development of PAD, with subgroup analyses of subjects with DM would hopefully render useful insights on how to prevent PAD. Agenda 2030 has set a global goal to reduce premature mortality from non-communicable diseases with one third by 2030.[152] Cardiovascular disease is the primary cause of death globally,[153] and in order to reach the goal it is crucial to reduce its incidence in the first place. Therefore, further research on modifiable risk factors is warranted.

In paper IV the DFU's were classified with the Wagner classification system, a system that has been widely used to assess ulcer depth and presence of osteomyelitis.[17] In 2014 the Society for Vascular Surgery introduced the WIfI classification system for assessment of CLTI.[154] The WIfI system is better adapted to reflect the extent and severity of lower extremity arterial disease. In paper IV, 85% of the patients with DM were classified as having Wagner grade 1 (superficial ulcer) at baseline, which is the lowest out of five stages.[17] Even if WIfI staging was not possible to assess accurately, the study patients belonged to WIfI stages 3-4, the two highest WIfI stages.[154] When comparing the WIfI system with the Wagner classification in the assessment of 63 patients with DFU, there was no difference in the ability to assess the risk of major amputation.[155] However, no revascularization was performed in this study. Hence, future prospective studies comparing these two classification systems in especially vascular surgical patients are needed.

To date, no prospective study has randomized patients based on WIfI stage to either open or endovascular surgery. The efficacy of WIfI classification[154] together with GLASS[26] staging (table XIII) would be highly interesting to study in a prospective RCT comparing open with endovascular surgery, especially with subgroup analysis of patients with DM as these patients have a different clinical presentation and outcome.[12]

In papers II and III subgroup analysis of the clinical presentation of CLTI with tissue loss or rest pain would have been interesting as some evidence suggest that the benefit of open vascular surgery over endovascular therapy to avoid amputation applies to those presenting with tissue loss, but not to patients presenting with rest pain only.[133] Tissue loss among patients with DM was indeed associated with increased risk of major amputation after open revascularization (paper III).

The global prevalence of DM and PAD are increasing, and yet research on the development of PAD among individuals with DM is scarce. Baseline data in paper I was collected in the early 1990s, and since then major changes in risk factor profile for cardiovascular disease have occurred, such as improvement in medical risk factor control and increased rates of smoking cessation at least in high income countries.[156] On the other hand, the incidence of DM has risen in low-, middle- and high-income countries.[157] Hence, new prospective cohort studies with collection of contemporary baseline data are warranted. In fact, the Malmö Offspring study, representing children and grandchildren of index subjects from the first generation, examined in the MDCS, has recently completed recruitment of individuals.[158] This study will provide rich data and opportunities to analyze family traits of chronic disease across three generations.

Populärvetenskaplig sammanfattning

Diabetes innebär att kroppen har svårt att hålla blodsockerhalten tillräckligt låg. För att cellerna ska kunna ta upp socker från blodet krävs hormonet insulin. Men vid diabetes tillverkas inte insulin, eller så fungerar insulinet sämre. De vanligaste typerna är diabetes typ 1 och typ 2, se tabell XIV för mer information om de olika diabetestyperna.

Tabell XIV. Skillnader mellan typ 1 och 2 diabetes.

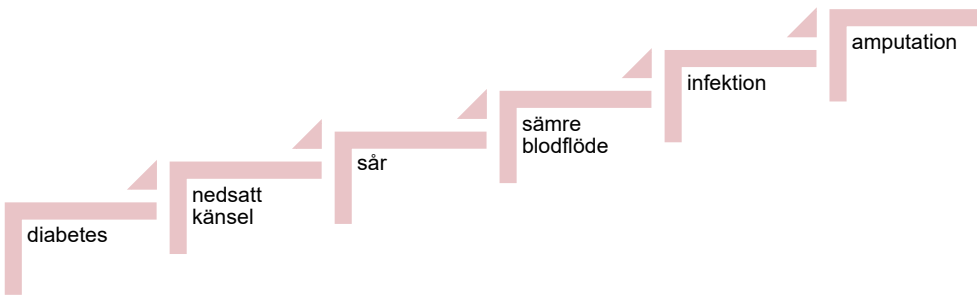
Diabetes typ 1	Diabetes typ 2
• Kroppen slutar tillverka insulin. • Debuterar oftast hos barn. • Kräver behandling med insulin. • Till viss del ärftligt. • Normal kroppsvikt. • Ovanligare än typ 2 diabetes.	• Cellernas känslighet för insulin minskar och ger då högt blodsocker. Till slut minskar insulinproduktionen. • Drabbar oftast vuxna. • Kan behandlas med tabletter, kostförändringar, motion och insulin. Fysisk aktivitet gör att cellerna kan ta upp blodsockret utan insulin. • Mer ärftlig än typ 1 diabetes. • Ofta förknippad med övervikt.

Diabetes leder till att blodkärlen blir förkalkade, detta kallas också för åderförkalkning och kan drabba alla utåtgående kärl från hjärtat. Åderförkalkningen leder till att blodkärlen blir trängre och blodflödet minskar. Om åderförkalkningen drabbar hjärtats kärl så att det till slut blir stopp i blodflödet kallas det hjärtinfarkt och om hjärnans kärl drabbas heter det stroke.

Riskfaktorer för åderförkalkning är bland annat rökning, diabetes, högt blodtryck och högt kolesterolvärde. Skyddande faktorer är viktnedgång om man är överviktig, rökstopp, motion samt att äta medelhavskost. Det är också viktigt att sätta in läkemedelsbehandling mot förhöjt blodtryck. Om blodfetterna är förhöjda är det viktigt att ta blodfettssänkande läkemedel eftersom detta skyddar mot att åderförkalkningen förvärras. Åderförkalkning är kort och gott bakgrunden till hjärt-kärlsjukdom, som är den vanligaste dödsorsaken globalt sett, och ca två tredjedelar av alla individer med diabetes typ 2 avlider i hjärt-kärlsjukdom.

Om åderförkalkningen drabbar benens blodkärl kallas det för benartärsjukdom (PAD). Den här avhandlingen fokuserar på benartärsjukdom och diabetes eftersom diabetes ju är en riskfaktor för såväl åderförkalkning som benartärsjukdom.

Diabetes leder, utöver åderförkalkning, till försämrad känsel eftersom det höga blodsockret inte bara påverkar blodkärl utan också känselnerver. Känselnedsättningen kan göra att en person med diabetes har svårt att känna en sten i skon eller inte känner av ett skoskav, som gör att risken för allvarliga fotsår är högre för en person med diabetes. Eftersom diabetes leder till försämrat blodflöde läker ett sår hos en person med diabetes sämre än hos en frisk person, och risken för sårinfektioner ökar. Sammantaget gör alla de här faktorerna att en person med diabetes löper 10–20 gånger högre risk att behöva amputera sitt ben jämfört med en person utan diabetes. Figur X illustrerar vad som leder till amputation hos någon med diabetes.



Figur X. "Stairway to amputation". Bakgrundsmekanismer till varför diabetiker drabbas av svårläkta sår och amputation. Risken för amputation ökar för varje trappsteg. Modifierad från Global Vascular Guidelines.[24]

Hälften av patienter med diabetes och fotsår har underliggande benartärsjukdom (PAD). Slutstadiet av PAD kallas kronisk kritisk ischemi (CLTI) och betyder att patientens blodflöde ut i benen är så pass försämrat att sår har svårt att läka. CLTI och det minskade blodflödet kan också göra att personen har konstant ont i foten pga. syrebrist (ungefär som mjölksyra). Ungefär 10% av alla patienter med benartärsjukdom har CLTI.

Både diabetes och benartärsjukdom ökar globalt och ökningen sker framförallt i låg- och medelinkomstländer. Inom kärlkirurgin behandlar man sjukdomar i blodkärlen med läkemedel, kateterledd kirurgi och öppen kirurgi. Det är fortfarande inte helt klarlagt i vilka fall kateterledd respektive öppen kirurgi är att föredra, och forskningen på patienter med diabetes och benartärsjukdom är bristfällig. De senaste årtiondena har kateterledd kirurgi blivit allt vanligare, samtidigt som öppen kirurgi görs mer sällan.

Vid kateterledd kirurgi används röntgenkontrast och man röntgar flera gånger under ingreppet. Ingreppet görs ofta i lokalbedövning via ett litet stick i ljumsken på patienten som är vaken under operationen. Man gör ofta en ballongvidgning av blodkärlsförträningen och ibland sätts en stent (metallnät) in för att hålla uppe blodkärlets diameter.

Vid öppen kärlkirurgi sövs patienten och man genomför ofta en bypass-operation. Förenklat kan man tänka sig en motorväg där det blivit trafikstockning pga. en krock, bilarna får då köra en omväg på en intilliggande landsväg och kör sedan ner på motorvägen igen längre fram. Samma tänk används vid en by-pass operation där patientens egna vener sys in till blodkärlet strax ovanför förträngningen och venen sys sedan åter in till blodkärlet strax efter förträngningen. På så vis har man lett om blodflödet förbi förträngningen. Figur V (sidan 27) visar en jämförelse av kateterledd teknik och bypass-operation.

I den här avhandlingen undersöktes följande;

Artikel I: Hur kost och livsstil påverkar risken att utveckla benartärsjukdom hos personer med diabetes.

Artikel II: Hur går det för en person med diabetes jämfört med någon utan diabetes när båda behandlas med kateterledd teknik för svår benartärsjukdom (CLTI)?

Artikel III: Hur går det för en person med diabetes jämfört med någon utan diabetes när båda behandlas med öppen kärlkirurgi av svår benartärsjukdom (CLTI)?

Artikel IV: Är kateterledd teknik eller öppen kärlkirurgi bättre för behandling av patienter med diabetes, benartärsjukdom och hälsår?

Sammanfattningsvis blev resultaten av avhandlingen följande;

Artikel I: Vi såg en trend till att ett högt intag av fisk och skaldjur skyddar mot utveckling av benartärsjukdom hos personer med diabetes.

Artikel II: Risken för amputation är större hos de med diabetes jämfört med de utan diabetes efter kateterledd behandling av svår benartärsjukdom (CLTI).

Artikel III: Vi såg ingen ökad risk för amputation eller död hos de med diabetes jämfört med de utan diabetes efter öppen kärlkirurgi av svår benartärsjukdom (CLTI).

Artikel IV: Den amputationsfria överlevnaden var högre efter öppen kärlkirurgi jämfört med efter kateterledd behandling av patienter med diabetes, benartärsjukdom och hälsår. Vi såg också att andelen patienter som genomgått kateterledd kirurgi ökade under studieperioden.

Sammanfattningsvis visar den här avhandlingen att öppen kärlkirurgi fortfarande kan vara ett förstahandsalternativ för många patienter med svår benartärsjukdom (CLTI), framförallt när målet är att undvika amputation hos de med diabetes. Resultaten visar på att man sannolikt borde erbjuda öppen kärlkirurgi oftare än vad som görs i nuläget.

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References

1. International Diabetes Federation. IDF Diabetes Atlas 9th edition. [Internet]. 2019 [cited 2021 Nov 3]. Available from: https://www.diabetesatlas.org/upload/resources/material/20200302_133351_IDFATLAS9e-final-web.pdf
2. Vithian K, Hurel S. Microvascular complications: pathophysiology and management. Clinical Medicine. 2010 Oct;10(5):505-9. PMID: 21117389.
3. Nationella Diabetesregistret. Årsrapport 2020 [Internet]. 2020. [cited 2021 Nov 16]. Available from: https://www.ndr.nu/pdfs/Arsrapport_NDR_2020.pdf
4. Ramsey SD, Newton K, Blough D, McCulloch DK, Sandhu N, Reiber GE, et al. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. Diabetes Care. 1999 Mar;22(3):382-7. PMID: 10097914.
5. Abbott CA, Carrington AL, Ashe H, Bath S, Every LC, Griffiths J, et al. The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. Diabetic Medicine : a journal of the British Diabetic Association. 2002;19(5):377–84. PMID: 12027925.
6. Boulton AJ. The diabetic foot—An update. Foot and Ankle Surgery. 2008 Jan 1;14(3):120–4. PMID: 19083628.
7. Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis. Annals of Medicine. 2017 Mar;49(2):106-116. PMID: 27585063.
8. Brownrigg JRW, Apelqvist J, Bakker K, Schaper NC, Hinchliffe RJ. Evidence-based management of PAD & the diabetic foot. European Journal of Vascular and Endovascular Surgery: the official journal of the European Society for Vascular Surgery. 2013 Jun ;45(6):673–81. PMID: 23540807.
9. Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggesi A, Bakker K, et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia. 2007 Jan; 50(1):18–25. PMID: 17093942
10. Morbach S, Furchert H, Gröblinghoff U, Hoffmeier H, Kersten K, Klauke GT, et al. Long-term prognosis of diabetic foot patients and their limbs: amputation and death over the course of a decade. Diabetes Care. 2012 Oct;35(10):2021–7. PMID: 22815299
11. Boulton AJM, Armstrong DG, Kirsner RS, Attinger CE, Lavery LA, Lipsky BA, et al. Diagnosis and Management of Diabetic Foot Complications. Diabetes. 2018;2018(2):1–20. PMID: 30958663

12. Apelqvist J, Bakker K, van Houtum WH, Nabuurs-Franssen MH, Schaper NC. International consensus and practical guidelines on the management and the prevention of the diabetic foot. International Working Group on the Diabetic Foot. Diabetes/metabolism Research and Reviews. 2000;16. PMID: 11054895

13. Aldana PC, Cartron AM, Khachemoune A. Reappraising Diabetic Foot Ulcers: A Focus on Mechanisms of Ulceration and Clinical Evaluation. The International Journal of Lower Extremity Wounds. 2020. PMID: 32734837

14. Rogers LC, Frykberg RG, Armstrong DG, Boulton AJM, Edmonds M, Ha Van G, et al. The Charcot foot in diabetes. Diabetes Care. 2011;34(9):2123–9. PMID: 21868781

15. Peter-Riesch B. The Diabetic Foot: The Never-Ending Challenge. Endocrine Development. 2016;31:108–34. PMID: 26824745

16. Ziegler-Graham K, MacKenzie EJ, Ephraim PL, Travison TG, Brookmeyer R. Estimating the prevalence of limb loss in the United States: 2005 to 2050. Archives of Physical Medicine and Rehabilitation. 2008;89(3):422–9. PMID: 18295618

17. Wagner FW. The diabetic foot. Orthopedics. 1987;10(1):163–72. PMID: 3809012

18. Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, et al. Measurement and interpretation of the Ankle-Brachial Index: A scientific statement from the American Heart Association. Circulation. 2012 Dec 11;126(24):2890–909. PMID: 23159553

19. Aboyans V, Ricco JB, Bartelink MLEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. European Heart Journal. 2018 Mar 1;39(9):763–816. PMID: 28886620

20. Sigvant B, Wiberg-Hedman K, Bergqvist D, Rolandsson O, Wahlberg E. Risk factor profiles and use of cardiovascular drug prevention in women and men with peripheral arterial disease. European Journal of Cardiovascular Prevention and Rehabilitation. 2009; 16(1):39–46. PMID: 19237996

21. Newman AB, Siscovick DS, Manolio TA, Polak J, Fried LP, Borhani NO, et al. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Heart Study (CHS) Collaborative Research Group. Circulation. 1993 ;88(3):837–45. PMID: 8353913

22. Dolan NC, Liu K, Criqui MH, Greenland P, Guralnik JM, Chan C, et al. Peripheral artery disease, diabetes, and reduced lower extremity functioning. Diabetes Care. 2002 Jan;25(1):113-20. PMID: 11772911

23. Sartipy F, Lundin F, Wahlberg E, Sigvant B. Cardiovascular long-term outcome and prophylactic treatment patterns in peripheral arterial disease in a population-based cohort. European Heart Journal Quality of Care & Clinical Outcomes. 2019 Oct;5(4):310–20. PMID: 31304962

24. Fowkes G, Fowkes FGR, Murray GD, Butcher I, Heald CL, Lee RJ, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. Journal of the American Medical Association. 2008 Jul 9;300(2):197–208. PMID: 18612117

25. Hinchliffe RJ, Forsythe RO, Apelqvist J, Boyko EJ, Fitridge R, Hong JP, et al. Guidelines on diagnosis, prognosis, and management of peripheral artery disease in patients with foot ulcers and diabetes (IWGDF 2019 update). Diabetes/metabolism Research and Reviews. 2020 Mar 1;36 Suppl 1(S1). PMID: 31958217

26. Conte MS, Bradbury AW, Kolh P, White J v, Dick F, Fitridge R, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. Journal of Vascular Surgery. 2019 Jun 1;69(6S):3S-125S.e40. PMID: 31159978

27. Abu Dabrh AM, Steffen MW, Undavalli C, Asi N, Wang Z, Elamin MB, et al. The natural history of untreated severe or critical limb ischemia. Journal of Vascular Surgery. 2015 Dec 1;62(6):1642-1651.e3. PMID: 26391460

28. Younes NA, Albsoul AM, Awad H. Diabetic heel ulcers: a major risk factor for lower extremity amputation. Ostomy/wound Management. 2004 Jun;50(6). PMID: 15218204

29. Armstrong DG, Lavery LA. Diabetic foot ulcers: prevention, diagnosis and classification. American Family Physician. 1998 Mar 15;57(6). PMID: 9531915

30. Cole CW, Hill GB, Farzad E, Bouchard A, Moher D, Rody K, et al. Cigarette smoking and peripheral arterial occlusive disease. Surgery. 1993 Oct;114(4):753-6. PMID: 8211690

31. Willigendael EM, Teijink JA, Bartelink ML, Kuiken BW, Boiten J, Moll FL, et al. Influence of smoking on incidence and prevalence of peripheral arterial disease. Journal of Vascular Surgery. 2004 Dec;40(6):1158-65. PMID: 15622370

32. World Health Organization. Global recommendations on physical activity for health. [Internet]. 2010. [cited 2021 Nov 18]. Available from: https://www.who.int/publications/i/item/9789241599979

33. Yu E, Rimm E, Qi L, Rexrode K, Albert CM, Sun Q, et al. Diet, Lifestyle, Biomarkers, Genetic Factors, and Risk of Cardiovascular Disease in the Nurses' Health Studies. American Journal of Public Health. 2016 Sep 1;106(9):1616–23. PMID: 27459449

34. Mitrou PN, Kipnis V, Thiébaut ACM, Reedy J, Subar AF, Wirfält E, et al. Mediterranean dietary pattern and prediction of all-cause mortality in a US population: results from the NIH-AARP Diet and Health Study. Archives of Internal Medicine. 2007 Dec 10;167(22):2461–8. PMID: 18071168

35. Dyson PA, Twenefour D, Breen C, Duncan A, Elvin E, Goff L, et al. Diabetes UK evidence-based nutrition guidelines for the prevention and management of diabetes. Diabetic Medicine. 2018 May;35(5):541-547. PMID: 29443421

36. Widmer RJ, Flammer AJ, Lerman LO, Lerman A. The Mediterranean diet, its components, and cardiovascular disease. American Journal of Medicine. 2015 Mar;128(3):229-38. PMID: 25447615

37. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard B v, et al. Diabetes and Cardiovascular Disease. Circulation. 1999 Sep 7;100(10):1134–46. PMID: PMID: 10477542

38. Ades PA, Savage PD, Marney AM, Harvey J, Evans KA. Remission of Recently Diagnosed Type 2 Diabetes Mellitus with Weight Loss and Exercise. Journal of Cardiopulmonary Rehabilitation and Prevention. 2015 Dec 1;35(3):193. PMID: 25636149

39. Eriksson KF, Lindgärde F. Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise. The 6-year Malmö feasibility study. Diabetologia. 1991 Dec;34(12):891–8. PMID: 1778354

40. Eriksson KF, Lindgärde F. No excess 12-year mortality in men with impaired glucose tolerance who participated in the Malmö Preventive Trial with diet and exercise. Diabetologia. 1998 ;41(9):1010–6. PMID: 9754818

41. Pozzilli P, Fallucca F. Diet and diabetes: a cornerstone for therapy. Diabetes/metabolism Research and Reviews. 2014 Mar 1;30(S1):1–3. PMID: 24353260

42. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. The New England Journal of Medicine. 2002 Feb 7;346(6):393-403. PMID:11832527

43. Sveriges Kommuner och Landsting. Fotundersökning vid diabetes. Nationellt vårdprogram för prevention av fotkomplikationer vid diabetes. [Internet]. 2020. [cited 2021 Nov 22]. Available from: https://webbutik.skr.se/sv/artiklar/fotundersokning-vid-diabetes.html

44. Diabetesförbundet. Fina fötter - en daglig checklista [Internet]. [cited 2021 Nov 23]. Available from: https://www.diabetes.se/diabetes/lar-om-diabetes/sa-paverkas-kroppen/fotter2/hur-mar-dina-fotter/fina-fotter---en-daglig-checklista/?_t_id=1B2M2Y8AsgTpgAmY7PhCfg%3d%3d&_t_q=fina+f%c3%b6tter&_t_tags=language%3asv%2csiteid%3aaaf9ca4c-d5a9-4627-8053-94a18f41fb7e&_t_ip=84.216.60.202&_t_hit.id=diabetes_se_Models_Pages_ArticlePage/_3a4e4355-9567-460b-a4bf-b95fbe73f182_sv&_t_hit.pos=1

45. Xu D, Zou L, Xing Y, Hou L, Wei Y, Zhang J, et al. Diagnostic value of ankle-brachial index in peripheral arterial disease: a meta-analysis. The Canadian Journal of Cardiology. 2013 Apr;29(4):492–8. PMID: 22926041

46. Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. Circulation. 2012 Dec 11 ;126(24):2890–909. PMID: 23159553

47. Larch E, Minar E, Ahmadi R, Schnurer G, Schneider B, Stumpflen A, et al. Value of color duplex sonography for evaluation of tibioperoneal arteries in patients with femoropopliteal obstruction: a prospective comparison with anterograde intraarterial digital subtraction angiography. Journal of Vascular Surgery. 1997;25(4):629–36. PMID: 9129617

48. Preuß A, Elgeti T, Hamm B, Werncke T. Extravascular incidental findings in run-off CT angiography in patients with acute limb ischaemia: incidence and clinical relevance. Clinical Radiology. 2015 Jun 1;70(6):622–9. PMID: 25819627

49. Heijenbrok-Kal MH, Kock MC, Hunink MG. Lower extremity arterial disease: multidetector CT angiography meta-analysis. Radiology. 2007 Nov;245(2):433–9. PMID: 17848679

50. Menke J, Larsen J. Meta-analysis: Accuracy of contrast-enhanced magnetic resonance angiography for assessing steno-occlusions in peripheral arterial disease. Annals of Internal Medicine. 2010 Sep 7;153(5):325–34. PMID: 20820041

51. Leiner T, Kessels AG, Schurink GW, Kitslaar PJ, de Haan MW, Tordoir JH, et al. Comparison of contrast-enhanced magnetic resonance angiography and digital subtraction angiography in patients with chronic critical ischemia and tissue loss. Investigative Radiology. 2004 Jul;39(7):435–44. PMID: 15194915

52. McDermott MM, Liu K, Carroll TJ, Tian L, Ferrucci L, Li D, et al. Superficial femoral artery plaque and functional performance in peripheral arterial disease: walking and leg circulation study (WALCS III). Journal of the American College of Cardiology: Cardiovascular imaging. 2011 Jul;4(7):730–9. PMID: 21757163

53. Serhal A, Koktzoglou I, Aouad P, Carr JC, Giri S, Morcos O, et al. Cardiovascular magnetic resonance imaging of aorto-iliac and ilio-femoral vascular calcifications using proton density-weighted in-phase stack of stars. Journal of Cardiovascular Magnetic Resonance. 2018 Aug 6;20(1):1–8. PMID: 30078377

54. Lakshminarayan R, Simpson JO, Ettles DF. Magnetic resonance angiography: current status in the planning and follow-up of endovascular treatment in lower-limb arterial disease. Cardiovascular and Interventional Radiology. 2009 May;32(3):397–405. PMID: 19130124

55. D'Alto M, Dimopoulos K, Budts W, Diller GP, Salvo G di, Dellegrottaglie S, et al. Multimodality imaging in congenital heart disease-related pulmonary arterial hypertension. Heart (British Cardiac Society). 2016 Jun 15;102(12):910–8. PMID: 27013702

56. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Journal of Vascular Surgery. 2007 Jan;45 Suppl S. PMID: 17223489

57. Singh H, Cardella JF, Cole PE, Grassi CJ, McCowan TC, Swan TL, et al. Quality improvement guidelines for diagnostic arteriography. Journal of Vascular and Interventional Radiology. 2002;13(1):1–6. PMID: 14514834

58. Aspelin P, Aubry P, Fransson S-G, Strasser R, Willenbrock R, Berg KJ. Nephrotoxic effects in high-risk patients undergoing angiography. The New England Journal of Medicine. 2003 Feb 6;348(6):491–9. PMID: 12571256

59. Sharafuddin MJ, Marjan AE. Current status of carbon dioxide angiography. Journal of Vascular Surgery. 2017 Aug 1;66(2):618–37. PMID:28735955

60. Hardman RL, Jazaeri O, Yi J, Smith M, Gupta R. Overview of classification systems in peripheral artery disease. Seminars in Interventional Radiology. 2014;31(4):378–88. PMID: 25435665

61. Mills JL, Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, et al. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: Risk stratification based on Wound, Ischemia, and foot Infection (WIfI). Journal of Vascular Surgery. 2014 Jan 1;59(1):220-234.e2. PMID: 24126108

62. Collins R, Cranny G, Burch J, Aguiar-Ibáñez R, Craig D, Wright K, et al. A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease. Health Technology Assessment. 2007;11(20). PMID: 17462170

63. Vascular Registry in Sweden (Swedvasc). Årsrapport 2021 [Internet]. 2020. [cited 2021 Nov 8]. Available from: https://www.ucr.uu.se/swedvasc/arsrapporter

64. Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomized, double-blind, placebo-controlled trial. Lancet. 2018 Jan 20;391(10117):219–29. PMID: 29132880

65. Bonaca MP, Bauersachs RM, Anand SS, Debus ES, Nehler MR, Patel MR, et al. Rivaroxaban in Peripheral Artery Disease after Revascularization. The New England Journal of Medicine. 2020 May 21;382(21):1994–2004. PMID: 32222135

66. Frank U, Nikol S, Belch J, Boc V, Brodmann M, Carpentier PH, et al. ESVM Guideline on peripheral arterial disease. Vasa. 2019 Dec 2;48:1–80. PMID: 31789115

67. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. The New England Journal of Medicine. 2015 Nov 26;373(22):2103–16. PMID: 26551272

68. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 7. Effects of more vs. less intensive blood pressure lowering and different achieved blood pressure levels - updated overview and meta-analyses of randomized trials. Journal of Hypertension. 2016 Apr 1;34(4):613–22. PMID: 26848994

69. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal. 2018 Sep 1;39(33):3021–104. PMID: 30165516

70. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: Executive summary: A report of the American college of cardiology/American Heart Association task force on clinical practice guidelines. Hypertension. 2018;71(6):1269–324. PMID: 29133354

71. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. European Heart Journal. 2020 Jan 1;41(1):111–88. PMID: 31504418

72. Libby P, Aikawa M. Mechanisms of plaque stabilization with statins. The American Journal of Cardiology. 2003 Feb 20;91(4):4–8. PMID: 12615292

73. Vascular Registry in Sweden (Swedvasc). Årsrapport 2006. 2005 [Internet]. [cited 2021 Nov 17]; Available from: https://www.ucr.uu.se/swedvasc/arsrapporter/swedvasc-2006/viewdocument/5

74. Krakauer M, Botero JF, Lavalle-González FJ, Proietti A, Barbieri DE. A review of flash glucose monitoring in type 2 diabetes. Diabetology and Metabolic Syndrome. 2021 Dec 1;13(1):1–10. PMID: 33836819

75. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline JP, Rayman G. Flash Glucose-Sensing Technology as a Replacement for Blood Glucose Monitoring for the Management of Insulin-Treated Type 2 Diabetes: A Multicenter, Open-Label Randomized Controlled Trial. Diabetes Therapy. 2017 Feb 1;8(1):55–73. PMID: 28000140

76. Eeg-Olofsson K, Svensson A-M, Franzén S, Ismail H, Levrat-Guillen. Sustainable HbA1c Decrease at 12 Months for Adults with Type 1 and Type 2 Diabetes Using the FreeStyle Libre System: A Study within the National Diabetes Register in Sweden. Diabetes. 2020 Jun 1;69:74-LB. https://doi.org/10.2337/db20-74-LB

77. Lenhard MJ, Reeves GD. Continuous Subcutaneous Insulin Infusion: A Comprehensive Review of Insulin Pump Therapy. Archives of Internal Medicine. 2001 Oct 22;161(19):2293–300. PMID: 11606144

78. Fokkert M, van Dijk P, Edens M, Barents E, Mollema J, Slingerland R, et al. Improved well-being and decreased disease burden after 1-year use of flash glucose monitoring (FLARE-NL4). BMJ Open Diabetes research & Care. 2019 Dec 9;7(1). PMID: 31875133

79. Dahlin LB, Elgzyri T, Löndahl M, Ekman L, Lindholm E. Improved metabolic control using glucose monitoring systems leads to improvement in vibration perception thresholds in type 1 diabetes patients. Acta Diabetologica. 2020 Apr 1;57(4):433–8. PMID: 31705298

80. Nathan DM, DCCT/EDIC Research Group. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study at 30 Years: Overview. Diabetes Care. 2014 Jan 1;37(1):9–16. PMID: 24356592

81. Bode BW, Sabbah HT, Gross TM, Fredrickson LP, Davidson PC. Diabetes management in the new millennium using insulin pump therapy. Diabetes/metabolism Research and Reviews. 2002 Jan 1;18(S1):S14–20. PMID: 11921425

82. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2018 Dec;41(12):2669-2701. PMID: 30291106

83. Rådholm K, Figtree G, Perkovic V, Solomon SD, Mahaffey KW, de Zeeuw D, et al. Canagliflozin and heart failure in type 2 diabetes mellitus: Results from the CANVAS program. Circulation. 2018;138(5):458–68. PMID: 29526832

84. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. The New England Journal of Medicine. 2016 Jul 28;375(4):311-22. PMID: 27295427

85. Gottsäter A, Nilsson PM. Sodium-Glucose Cotransporter 2 Inhibitors in Diabetes and Peripheral Arterial Disease - Do We Really Have to Choose Between Limb and Heart? European Journal of Vascular and Endovascular Surgery: The Official Journal of the European Society for Vascular Surgery. 2021 Oct 21 ;62(6):991–991. PMID: 34690071

86. Sigal RJ, Kenny GP, Wasserman DH, Castaneda-Sceppa C, White RD. Physical Activity/Exercise and Type 2 Diabetes: A consensus statement from the American Diabetes Association. Diabetes Care. 2006 Jun 1;29(6):1433–8. PMID: 16732040

87. Prompers L, Schaper N, Apelqvist J, Edmonds M, Jude E, Mauricio D, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. Diabetologia. 2008 May;51(5):747–55. PMID: 18297261

88. Forsythe RO, Apelqvist J, Boyko EJ, Fitridge R, Hong JP, Katsanos K, et al. Performance of prognostic markers in the prediction of wound healing or amputation among patients with foot ulcers in diabetes: A systematic review. Diabetes/metabolism Research and Reviews. 2020 Mar 1;36 Suppl 1(S1). PMID 32176442

89. Elgzyri T, Larsson J, Nyberg P, Thörne J, Eriksson KF, Apelqvist J. Early revascularization after admittance to a diabetic foot center affects the healing probability of ischemic foot ulcer in patients with diabetes. European Journal of Vascular and Endovascular surgery: The Official Journal of the European Society for Vascular Surgery. 2014 Oct ;48(4):440–6. PMID: 25106090

90. Noronen K, Saarinen E, Albäck A, Venermo M. Analysis of the Elective Treatment Process for Critical Limb Ischaemia with Tissue Loss: Diabetic Patients Require Rapid Revascularisation. European Journal of Vascular and Endovascular Surgery: the Official Journal of the European Society for Vascular Surgery. 2017 Feb 1 ;53(2):206–13. PMID 27889202

91. Soleimani Z, Hashemdokht F, Bahmani F, Taghizadeh M, Memarzadeh MR, Asemi Z. Clinical and metabolic response to flaxseed oil omega-3 fatty acids supplementation in patients with diabetic foot ulcer: A randomized, double-blind, placebo-controlled trial. Journal of Diabetes and its Complications. 2017 Sep 1;31(9):1394–400. PMID: 28716357

92. Hartweg J, Perera R, Montori V, Dinneen S, Neil HAW, Farmer A. Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus. The Cochrane Database of Systematic Reviews. 2008;(1). PMID: 18254017

93. Kinlay S. Management of Critical Limb Ischemia. Circulation: Cardiovascular Interventions. 2016 Feb 1;9(2). PMID: 26858079

94. Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FGR, Gillespie I, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: An intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy. Journal of Vascular Surgery. 2010;51(5 Suppl):5S-17S. PMID: 20435258

95. Popplewell MA, Davies H, Jarrett H, Bate G, Grant M, Patel S, et al. Bypass versus angio plasty in severe ischaemia of the leg - 2 (BASIL-2) trial: study protocol for a randomised controlled trial. Trials. 2016 Jan 6;17(1):11. PMID: 26739146

96. Menard MT, Farber A, Assmann SF, Choudhry NK, Conte MS, Creager MA, et al. Design and Rationale of the Best Endovascular Versus Best Surgical Therapy for Patients with Critical Limb Ischemia (BEST-CLI) Trial. Journal of the American Heart Association. 2016 Jul 8;5(7). PMID: 27402237

97. Slovut DP, Lipsitz EC. Surgical technique and peripheral artery disease. Circulation. 2012 Aug 28;126(9):1127-38. PMID: 22927475

98. Pereira CE, Albers M, Romiti M, Brochado-Neto FC, Pereira CAB. Meta-analysis of femoropopliteal bypass grafts for lower extremity arterial insufficiency. Journal of Vascular Surgery. 2006;44(3). PMID: 16950427

99. Schanzer A, Hevelone N, Owens CD, Belkin M, Bandyk DF, Clowes AW, et al. Technical factors affecting autogenous vein graft failure: observations from a large multicenter trial. Journal of Vascular Surgery. 2007 Dec ;46(6):1180–90. PMID: 18154993

100. Chang Z, Zheng J, Liu Z. Subintimal angioplasty for lower limb arterial chronic total occlusions. The Cochrane Database of Systematic Reviews. 2016 Nov 18;11(11). PMID: 27858952

101. Åkesson M, Riva L, Ivancev K, Uher P, Lundell A, Malina M. Subintimal angioplasty of infrainguinal arterial occlusions for critical limb ischemia: long-term patency and clinical efficacy. Journal of Endovascular Therapy: an Official Journal of the International Society of Endovascular Specialists. 2007 Aug;14(4):444–51. PMID: 17696617

102. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. The New England Journal of Medicine. 2003 Oct 2 ;349(14):1315–23. PMID: 14523139

103. Rowinsky EK, Donehower RC. Paclitaxel (Taxol). The New England Journal of Medicine. 1995; 332:1004-1014. DOI: 10.1056/NEJM199504133321507

104. Candy N, Ng E, Velu R. Paclitaxel-coated balloon reduces target lesion revascularization compared with standard balloon angioplasty. Journal of Vascular Surgery. 2017 Feb 1;65(2):558-570.e10. PMID: 28126182

105. Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Journal of the American Heart Association. 2018 Dec 1;7(24). PMID: 30561254

106. Information - SWEDEPAD [Internet]. [cited 2021 Nov 19]. Available from: https://www.ucr.uu.se/swedepad/om-swedepad/information

107. Berglund G, Elmståhl S, Janzon L, Larsson Sa. Design and feasibility. Journal of Internal Medicine. 1993;233(1):45–51. PMID: 8429286

108. Manjer J, Carlsson S, Elmståhl S, Gullberg B, Janzon L, Lindström M et al. The Malmö Diet and Cancer Study: representativity, cancer incidence and mortality in participants and non-participants. European Journal of Cancer Prevention. 2001;10(6):489-499. PMID: 11916347

109. Riboli E. Nutrition and cancer: background and rationale of the European Prospective Investigation into Cancer and Nutrition (EPIC). Annals of Oncology: Official Journal of the European Society for Medical Oncology. 1992;3(10):783–91. PMID: 1286041

110. Wirfält E, Mattisson I, Johansson U, Gullberg B, Wallström P, Berglund G. A methodological report from the Malmö Diet and Cancer study: development and evaluation of altered routines in dietary data processing. Nutrition Journal. 2002 Dec 19;1(1):1–16. PMID: 12537595

111. Manjer J, Elmståhl S, Janzon L, Berglund G. Invitation to a population-based cohort study: differences between subjects recruited using various strategies. Scandinavian Journal of Public Health. 2002;30(2):103–12. PMID: 12028859

112. Eliasson B, Gudbjörnsdottir S. Diabetes care – improvement through measurement. Diabetes Research and Clinical Practice. 2014 Dec 1;106(S2):S291–4. PMID: 25550056

113. Swedvasc. About Swedvasc. [Internet]. [cited 2021 Nov 25]. Available from: https://www.ucr.uu.se/swedvasc/about-swedvasc

114. Venermo M, Lees T. International Vascunet Validation of the Swedvasc Registry. European Journal of Vascular and Endovascular surgery: the official journal of the European Society for Vascular Surgery. 2015 Dec 1;50(6):802–8. PMID: 26338474

115. Djerf H, Hellman J, Baubeta Fridh E, Andersson M, Nordanstig J, Falkenberg M. Low Risk of Procedure Related Major Amputation Following Revascularisation for Intermittent Claudication: A Population Based Study. European Journal of Vascular and Endovascular Surgery: the Official Journal of the European Society for Vascular Surgery. 2020 May 1;59(5):817–22. PMID: 31866238

116. Baubeta Fridh E, Andersson M, Thuresson M, Sigvant B, Kragsterman B, Johansson S, et al. Editor's Choice - Impact of Comorbidity, Medication, and Gender on Amputation Rate Following Revascularisation for Chronic Limb Threatening Ischaemia. European Journal of Vascular and Endovascular Surgery: the Official Journal of the European Society for Vascular Surgery. 2018 Nov 1;56(5):681–8. PMID: 30093176

117. Fatemi S, Gottsäter A, Zarrouk M, Engström G, Melander O, Persson M, et al. Lp-PLA2 activity and mass and CRP are associated with incident symptomatic peripheral arterial disease. Scientific Reports. 2019 Apr 4;9(1):1–6. PMID: 30948779

118. Sestelo M. A short course on Survival Analysis applied to the Financial Industry [Internet]. Madrid. BBVA Data & Analytics; 2017. [cited 2021 Dec 21]. Available from: https://bookdown.org/sestelo/sa_financial/the-semiparametric-model.html

119. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. American Journal of Epidemiology. 2007 Mar;165(6):710–8. PMID: 17182981

120. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behavioral Research. 2011 May;46(3):399–424. PMID: 21818162

121. Rubin DB. On principles for modeling propensity scores in medical research. Pharmacoepidemiology and Drug Safety. 2004 Dec;13(12):855–7. PMID: 15386710

122. Ruiz-Canela M, Estruch R, Corella D, Salas-Salvadó J, Martínez-González MA. Association of Mediterranean Diet with Peripheral Artery Disease: The PREDIMED Randomized Trial. The Journal of the American Medical Association. 2014 Jan 22;311(4):415–7. PMID: 24449321

123. Chen GC, Arthur R, Mossavar-Rahmani Y, Xue X, Haring B, Shadyab AH, et al. Adherence to Recommended Eating Patterns Is Associated with Lower Risk of Peripheral Arterial Disease: Results from the Women's Health Initiative. Hypertension. 2021;78(2):447–55. PMID: 34176290

124. Ciccarone E, di Castelnuovo A, Salcuni M, Siani A, Giacco A, Donati MB, et al. A high-score Mediterranean dietary pattern is associated with a reduced risk of peripheral arterial disease in Italian patients with Type 2 diabetes. Journal of Thrombosis and Haemostasis. 2003 Aug;1(8):1744–52. PMID: 12911588

125. Althouse AD, Abbott JD, Forker AD, Bertolet M, Barinas-Mitchell E, Thurston RC, et al. Risk factors for incident peripheral arterial disease in type 2 diabetes: results from the Bypass Angioplasty Revascularization Investigation in type 2 Diabetes (BARI 2D) Trial. Diabetes Care. 2014;37(5):1346–52. PMID: 24595631

126. Kulezic A, Bergwall S, Fatemi S, Sonestedt E, Zarrouk M, Gottsäter A, et al. Healthy diet and fiber intake are associated with decreased risk of incident symptomatic peripheral artery disease – A prospective cohort study. Vascular Medicine. 2019 Dec 1;24(6):511–8. PMID: 31431146

127. Acosta S, Johansson A, Drake I. Diet and lifestyle factors and risk of atherosclerotic cardiovascular disease—a prospective cohort study. Nutrients. 2021 Nov 1 ;13(11). PMID: 34836078

128. Look AHEAD Research Group, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. The New England Journal of Medicine. 2013 Jul 11;369(2):145-54. PMID: 23796131

129. Rawshani A, Rawshani A, Franzén S, Eliasson B, Svensson A-M, Miftaraj M, et al. Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes. The New England Journal of Medicine. 2017 Apr 13;376(15):1407–18. PMID: 28402770

130. Malmstedt J, Leander K, Wahlberg E, Karlström L, Alfredsson L, Swedenborg J. Outcome after leg bypass surgery for critical limb ischemia is poor in patients with diabetes: a population-based cohort study. Diabetes Care. 2008 May;31(5):887–92. PMID: 18268064

131. Høgh A, Lindholt JS, Nielsen H, Jensen LP, Johnsen SP. Secondary medical prevention after primary vascular surgery between 1996 and 2006: a shift towards more evidence-based treatment. European Journal of Preventive Cardiology. 2013 Oct;20(5):763–70. PMID: 22637739

132. Brahmandam A, Gholitabar N, Cardella J, Nassiri N, Dardik A, Georgi M, et al. Discrepancy in Outcomes after Revascularization for Chronic Limb-Threatening Ischemia Warrants Separate Reporting of Rest Pain and Tissue Loss. Annals of Vascular Surgery. 2021 Jan;70:237-244. PMID: 32659417

133. Lee KB, Macsata RA, Lala S, Sparks AD, Amdur RL, Ricotta JJ, et al. Outcomes of open and endovascular interventions in patients with chronic limb threatening ischemia. Vascular. 2021 Oct 1;29(5):693–703. PMID: 33190618

134. van Haelst STW, Koopman C, den Ruijter HM, Moll FL, Visseren FL, Vaartjes I, et al. Cardiovascular and all-cause mortality in patients with intermittent claudication and critical limb ischaemia. British Journal of Surgery. 2018 Feb 5;105(3):252–61. PMID: 29116654

135. Liew YP, Bartholomew JR, Demirjian S, Michaels J, Schreiber MJ. Combined effect of chronic kidney disease and peripheral arterial disease on all-cause mortality in a high-risk population. Clinical Journal of the American Society of Nephrology. 2008 Jul ;3(4):1084–9. PMID: 18337552

136. Goodney PP, Beck AW, Nagle J, Welch HG, Zwolak RM. National trends in lower extremity bypass surgery, endovascular interventions, and major amputations. Journal of Vascular Surgery. 2009 Jul;50(1):54–60. PMID: 19481407

137. Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FGR, Gillespie I, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: Analysis of amputation free and overall survival by treatment received. Journal of Vascular Surgery. 2010;51(5 Suppl):18S-31S. PMID: 20435259

138. Vascular Registry in Sweden (Swedvasc). Årsrapport 2005. 2004 [Internet]. [cited 2021 Dec 25]. Available from: https://www.ucr.uu.se/swedvasc/arsrapporter/swedvasc-2005/viewdocument/14

139. Sigvant B, Kragsterman B, Falkenberg M, Hasvold P, Johansson S, Thuresson M, et al. Contemporary cardiovascular risk and secondary preventive drug treatment patterns in peripheral artery disease patients undergoing revascularization. Journal of Vascular Surgery. 2016 Oct 1;64(4):1009-1017.e3. PMID: 27209402

140. Backman H, Vanfleteren L, Lindberg A, Ekerljung L, Stridsman C, Axelsson M, et al. Decreased COPD prevalence in Sweden after decades of decrease in smoking. Respiratory Research. 2020 Dec 1;21(1):1–12. PMID: 33115506

141. Eraso LH, Fukaya E, Mohler ER, Xie D, Sha D, Berger JS. Peripheral arterial disease, prevalence and cumulative risk factor profile analysis. European Journal of Preventive Cardiology. 2014;21(6):704–11. PMID: 22739687

142. Statistics Sweden. Andel dagliga tobaksanvändare 2018-2019 [Internet]. [cited 2021 Dec 21]. Available from: https://www.scb.se/hitta-statistik/statistik-efter-amne/levnadsforhallanden/levnadsforhallanden/undersokningarna-av-levnadsforhallanden-ulf-silc/pong/tabell-och-diagram/halsa/andel-dagliga-tobaksanvandare-2018-2019/

143. Londero LS, Høgh A, Houlind K, Lindholt JS. Danish Trends in Major Amputation After Vascular Reconstruction in Patients with Peripheral Arterial Disease 2002–2014. European Journal of Vascular and Endovascular Surgery. 2019 Jan 1;57(1):111–20. PMID: 30293885

144. Zhan LX, Branco BC, Armstrong DG, Mills JL. The Society for Vascular Surgery lower extremity threatened limb classification system based on Wound, Ischemia, and foot Infection (WIfI) correlates with risk of major amputation and time to wound healing. Journal of Vascular Surgery. 2015 Apr 1;61(4):939–44. PMID: 25656592

145. Causey MW, Ahmed A, Wu B, Gasper WJ, Reyzelman A, Vartanian SM, et al. Society for Vascular Surgery limb stage and patient risk correlate with outcomes in an amputation prevention program. Journal of Vascular Surgery. 2016 Jun 1;63(6):1563e2-1573.e2. PMID: 27036309

146. Kodama A, Meecham L, Popplewell M, Bate G, Conte MS, Bradbury AW. Editor's Choice – Relationship Between Global Limb Anatomic Staging System (GLASS) and Clinical Outcomes Following Revascularisation for Chronic Limb Threatening Ischaemia in the Bypass Versus Angioplasty in Severe Ischaemia of the Leg (BASIL)-1 Trial. European Journal of Vascular and Endovascular Surgery. 2020 Nov 1;60(5):687–95. PMID: 32778491

147. Sonestedt E, Hellstrand S, Drake I, Schulz CA, Ericson U, Hlebowicz J, et al. Diet Quality and Change in Blood Lipids during 16 Years of Follow-up and Their Interaction with Genetic Risk for Dyslipidemia. Nutrients. 2016 May 9;8(5). PMID: 27171109

148. Yusufov M, Paiva AL, Redding CA, Lipschitz JM, Gokbayrak NS, Greene G, et al. Fat Reduction Efforts: A 24-Month Longitudinal Comparison of a Large Sample of Maintainers, Relapsers, and Non-Changers. Health Promotion Practice. 2016 Jan 1;17(1):116–26. PMID: 26452769

149. Baubeta Fridh E, Andersson M, Thuresson M, Sigvant B, Kragsterman B, Johansson S, et al. Amputation Rates, Mortality, and Pre-operative Comorbidities in Patients Revascularized for Intermittent Claudication or Critical Limb Ischaemia: A Population Based Study. European Journal of Vascular and Endovascular Surgery. 2017 Oct 1;54(4):480–6. PMID: 28797662

150. Harrell FE, Lee KL, Mark DB. Tutorial in Biostatistics Multivariable Prognostic Models: Issues in Developing Models, Evaluating Assumptions and Adequacy, And Measuring and Reducing Errors. Statistics in Medicine. 1996;15:361–87. PMID: 8668867

151. Darling JD, Bodewes TCF, Deery SE, Guzman RJ, Wyers MC, Hamdan AD, et al. Outcomes after first-time lower extremity revascularization for chronic limb-threatening ischemia between patients with and without diabetes. Journal of Vascular Surgery. 2018 Apr 1;67(4):1159–69. PMID: 28947228

152. Statistics Sweden. Statistical review 2021 - Implementation of the 2030 Agenda in Sweden. [cited 2022 Jan 2]; Available from: www.scb.se.

153. World Health Organization. The top 10 causes of death [Internet]. [cited 2021 Dec 19]. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

154. Mills JL, Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, et al. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: Risk stratification based on Wound, Ischemia, and foot Infection (WIfI). Journal of Vascular Surgery. 2014 Jan 1;59(1):220-234.e2. PMID: 24126108

155. Vera-Cruz PN, Palmes PP, Tonogan LJM, Troncillo AH. Comparison of WIFi, University of Texas and Wagner Classification Systems as Major Amputation Predictors for Admitted Diabetic Foot Patients: A Prospective Cohort Study. Malaysian Orthopaedic Journal. 2020;14(3):114–23. PMID: 33403071

156. Alhadad A, Wictorsson C, Alhadad H, Lindblad B, Gottsäter A. Medical risk factor treatment in peripheral arterial disease. Need for further improvement. International Angiology. 2013 Jun;32(3):332-8. PMID: 23711686

157. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Kaabi J al. Epidemiology of Type 2 Diabetes - Global Burden of Disease and Forecasted Trends. Journal of Epidemiology and Global Health. 2020 Mar;10(1):107–11. PMID: 32175717

158. Brunkwall L, Jönsson D, Ericson U, Hellstrand S, Kennbäck C, Östling G, et al. The Malmö Offspring Study (MOS): design, methods and first results. European Journal of Epidemiology. 2021 Jan 1;36(1):103–16. PMID: 33222051

Paper I

Cardiovascular Disease and Diabetes: Risk Factors, Prevention and Management

Special Collection

Therapeutic Advances in Endocrinology and Metabolism

Original Research

The association between dietary intake, lifestyle and incident symptomatic peripheral arterial disease among individuals with diabetes mellitus: insights from the Malmö Diet and Cancer study

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***Abstract*:** With the rising prevalence of both diabetes mellitus (DM) and peripheral arterial disease (PAD), the aim of this project was to examine the association between dietary intake and lifestyle on the risk of developing PAD among individuals with DM. The Malmö Diet and Cancer study was a prospective cohort study with baseline examinations carried out between 1991 and 1996 in Malmö, Sweden ($n = 30{,}446$). Individuals with prevalent PAD and cardiovascular disease (prior stroke or myocardial infarction) were excluded from the study, resulting in a total study population of 1112 patients with prevalent DM. The diagnosis of incident PAD was validated and confirmed in 98% of patients. Of the 1112 individuals, 136 (12.2%) were diagnosed with PAD during a median follow up of 19.7 years (interquartile range 12.9–22.4). Kaplan–Meier analysis showed that men with DM more often developed incident PAD compared with women (cumulative incidences 15.5% and 8.9%, respectively, $p = 0.012$). In Cox multivariable regression analysis, smoking (hazard ratio of 1.96, 95% confidence interval of 1.28–3.00) was associated with increased risk of PAD, and there was a trend that a higher intake of fish and shellfish (hazard ratio per additional gram per week of 0.99, 95% confidence interval of 0.99–1.00; $p = 0.051$) was associated with a decreased risk of PAD. In conclusion, the present study demonstrated a trend towards a protective effect of higher intake of fish and shellfish upon incident symptomatic PAD among individuals with DM.

Keywords: diabetes mellitus, diet, fish and shellfish, incident peripheral arterial disease

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Introduction

In 2018, more than 435,000 individuals had been diagnosed with diabetes mellitus (DM) in Sweden, out of whom 89% had type 2 DM.[1] In 2015, 30.3 million Americans were estimated to have DM, with 23.8% being unaware of their diagnosis.[2] Peripheral arterial disease (PAD) defined as atherosclerotic occlusions of lower- or upper-extremity arteries is reported to affect approximately 8.5 million Americans aged ⩾40 years.[3,4] Between 2000 and 2010 the prevalence of PAD increased with 23% worldwide due to a growing and aging global population, an increased number of patients with diabetes, and smoking. By 2010, nearly two thirds of patients with prevalent PAD resided in low- and middle-income countries.[5] The proportion of generalized atherosclerosis is higher among patients with PAD compared with patients with cardiovascular or cerebrovascular disease.[5] Furthermore, symptomatic PAD is associated with a high rate of silent myocardial infarction, 29%.[5] According to previous epidemiological studies, patients with PAD experience higher cardiovascular mortality than patients with coronary heart or cerebrovascular disease.[6] However, patients with PAD in a

primary-care setting received less intensive treatment for hypertension and hyperlipidemia, and were prescribed antiplatelet medication less frequently compared with patients with cardiovascular disease.[7] Therefore, primary prevention of PAD calls for increased attention due to the growing global burden of the disease.

Among individuals with DM, symptomatic PAD is about twice as common compared with individuals without DM.[8] Previous studies have shown that insulin resistance is associated with a higher risk of developing PAD among individuals >65 years.[9] It is well known that a healthy diet reduces the risk of atherosclerosis.[10] A Mediterranean diet has been shown to reduce the risk of death from all causes including death due to cardiovascular disease.[11] However, not many previous studies have focused on dietary components and its effects on the development of PAD in a high-risk group, such as individuals with DM. The Malmö Diet and Cancer study (MDCS) was a large prospective cohort with a long duration of follow up, thus offering a unique opportunity to study the association between dietary components and the risk of developing PAD among individuals with DM.

Therefore, the main aim of this longitudinal cohort study was to investigate how different dietary components and lifestyle affect the development of PAD among individuals with DM.

Method

Study sample and data collection

The MDCS with baseline examinations carried out between 1991 and 1996 was a prospective cohort study. The study included 30,446 middle-aged individuals residing in Malmö, Sweden.[12] A total of 28,098 individuals participated in diet assessment, anthropometric measurements, and answered a comprehensive questionnaire. Among these, 1230 participants had prevalent DM. Among those, individuals with prevalent PAD or other forms of cardiovascular disease (prior stroke or myocardial infarction) were excluded in the present study, resulting in a total study population of 1112 (Figure 1).

Informed consent was obtained from the study participants and the Regional Ethical Review Board in Lund, Sweden, gave ethical approval to the study (Dnr LU 51/90). All research was performed in accordance with relevant ethical guidelines.

Definitions

Using the civic registration number of each individual, the age and sex of each could be determined. DM was defined as fasting blood glucose >6.0 mmol/l, use of antidiabetic drugs or self-reported physician's diagnosis. Body mass index (BMI) was calculated using weight divided by height^2, expressed in kg/m^2. Hypertension was defined as use of antihypertensive drugs or blood pressure ⩾140/90 mmHg. Smoking was defined as former or current smoking.

Diet variables

Dietary habits were collected at baseline through a combination of a 7-day food diary, a 168-item food frequency questionnaire and a 1-hour interview, where detailed information on cooking practises, portion sizes and recipes of the food recorded in the diary was gathered during the interview.[13] Average daily food intake (g/day) was calculated by combining the information from the food diary and the questionnaire. The summary variable whole grains (servings/day) includes all high-fiber bread and cereals and the summary variable refined grains (servings/day) contains all low-fiber bread and cereals. Total energy intake (kcal/day, including alcohol and fiber), and fiber intake (g/day) was estimated by combining the intake from foods and supplements with the food composition database. Fish and shellfish intake was expressed in g/week, and 250 g/week corresponded to two servings per week.[14]

Lifestyle

Lifestyle variables were evaluated through a self-administered questionnaire. Based on the highest educational level attained, the study participants were divided into three categories, that is, <9 years, elementary (9–10 years) ± upper secondary school (11–13 years), and university level. Leisure-time physical activity level was defined as metabolic equivalent of task (MET) hours per week based on the intensity level and the time spent on 17 different activities and was divided into three groups. Alcohol consumption was divided into three groups based on the participant's reported intake in the 7-day food diary.

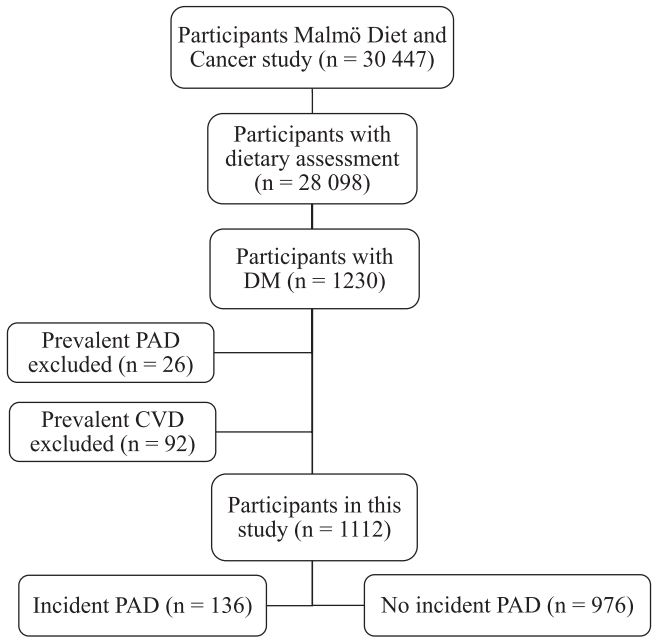

Figure 1. Descriptive flow diagram of study participants, dietary data and exclusions.
DM, diabetes mellitus; CVD, cardiovascular disease (prior stroke or myocardial infarction); PAD, peripheral arterial disease.

Endpoint ascertainment

The personal number of individuals from the MDCS was used to identify the first registered diagnosis of PAD in the Swedish national registers. The included registers were the Inpatient and Outpatient Register and the Cause of Death Register. In both registers, diagnoses are coded using a revised Swedish version of the International Classification of Disease, version 8, 9, and 10.

Validation of PAD diagnosis during follow up

A total of 100 patients with the diagnosis of PAD were randomly selected. Using patient record data, the validation showed that PAD could be confirmed in 98% of the cases, symptomatic in 97%, and only misdiagnosed in 2%.[15]

Statistics

The baseline characteristics for age, sex, BMI, diet and lifestyle variables were expressed as median and interquartile range for continuous variables and as total count and percentage for the categorical variables. Differences in proportions were analyzed with Pearson Chi-square test or Kendall tau-*b* test. The Mann–Whitney *U* test and Student's *t* test were used to test differences in continuous variables. Correlations between fish and shellfish consumption and potential risk factors for PAD were assessed by Spearman's or Pearson correlation coefficients and *p* values. Variables differing ($p < 0.1$) between incident PAD and not, in a univariable analysis, were further entered as covariates in a Cox multivariate regression analysis adjusting for age, sex, hypertension and smoking. Differences were expressed in hazard ratios (HR) with 95% confidence interval (CI). The cumulative incidence of PAD was described according to the Kaplan–Meier method with life tables, and the difference between sex was analyzed with a log-rank test. A *p* value <0.05 was considered significant. Statistical analyses were performed using IBM SPSS Statistics 25 (SPSS, Chicago, IL, USA).

Results

Baseline characteristics of diabetic patients with and without incident symptomatic PAD

In the study population of 1112 patients with DM, 136 (12.2%) were diagnosed with PAD, during a median follow up of 19.7 years (interquartile range of 12.9–22.4). Baseline characteristics of diet variables and lifestyle factors for individuals with and without incident PAD are shown in Table 1. The cumulative incidences of PAD in men and women were 15.5% and 8.9%, respectively ($p = 0.012$ in Kaplan–Meier analysis, Figure 2). Patients with DM developing PAD during follow up were more often smokers ($p < 0.001$) and there was a trend for hypertension ($p = 0.086$) at baseline. Individuals with DM developing PAD had a lower intake of fish and shellfish ($p = 0.036$).

Correlation between fish and shellfish and potential risk factors for PAD

There was a significant correlation between fish and shellfish consumption and age ($r = 0.11$, $p < 0.001$), alcohol consumption ($r = 0.18$, $p < 0.001$), leisure-time physical activity ($r = 0.094$, $p = 0.002$) and educational level ($r = 0.086$, $p = 0.004$; Table 2).

Factors associated with incident symptomatic PAD among patients with DM. In the Cox regression multivariable analysis, smoking (HR of 1.96, 95% CI of 1.28–3.00) was associated with an increased risk of PAD (Table 3), and there was a trend that a higher intake of fish and shellfish (HR of 0.99, 95% CI of 0.99–1.00; $p = 0.051$) was associated with a decreased risk of PAD.

Discussion

In the present study of individuals with DM from the MDCS, a trend towards a protective effect of high intake of fish and shellfish upon risk of PAD could be demonstrated.

Previous studies on how different dietary components affect the risk of PAD among individuals with DM have been scarce, and most reports have focused on the association between traditional cardiovascular risk factors and incident PAD.[16] Moreover, incident PAD has seldom been a prespecified endpoint in the study protocols and associations of dietary components with incident PAD have almost always been based on *post hoc* analyses and not on individuals with DM exclusively, thereby downgrading the evidence.[17]

In particular, no prospective longitudinal studies evaluating the role of isolated dietary compounds and incident PAD among individuals with DM have previously been published. A Mediterranean diet pattern, characterized by high consumption of plant-based foods, olive oil as the main source of fat, moderate consumption of fish, dairy products and poultry, low consumption of red and processed meat, and low-to-moderate consumption of wine with meals,[18] has been recommended by the American Diabetes Association and the American Heart Association for improving glycemic control and reducing cardiovascular risk in type 2 DM.[19] The relationship between a Mediterranean diet and the risk of PAD has been studied in a cross-sectional Italian study, showing that the highest Mediterranean diet score was associated with a significant 56% risk reduction of symptomatic PAD among individuals with type 2 DM.[20] With fish being a well-known dietary component in the Mediterranean diet, such results are in line with the present study findings. The Mediterranean diet has also been shown to lower markers of inflammation and blood lipids, which in turn reduces the burden and development of cardiovascular disease.[21] A healthy diet, rich in fish, might help to achieve and maintain body weight goals, reach individual glycemic, blood pressure, and lipid targets, and to some extent prevent diabetic complications.[22] It is possible that high consumers of fish and shellfish have a different lifestyle to low consumers, which might help explain the putative protective effects towards PAD development. Consuming less fish at the expense of more saturated fats and meat products appears to be associated with the progression of PAD.[23] Apart from studies on the Mediterranean diet, there is high-level evidence showing that diet patterns such as dietary approaches to stop hypertension and a low-fat diet is beneficial for primary and secondary prevention of cardiovascular disease.[24]

The present study has several limitations and strengths that deserve clarification. A limitation is the low number of participants with DM which may not have rendered sufficient power to attain statistical significance in some of the analyses. Another limitation is that the study was limited to symptomatic PAD cases only. It would have been of value to determine the ankle-brachial index,

Table 1. Baseline characteristics of study participants with DM with and without incident symptomatic PAD in the Malmö Diet and Cancer cohort. Data are *n* (%), mean (SD) or median (IQR).

	Incident PAD, DM (*n* = 136)	**No PAD, DM (*n* = 976)**	***p* value**
Male sex (%)	87 (64)	475 (49)	0.001
Age (years)	61.37 (6.26)	60.72 (6.90)	0.294
Total energy intake (kcal/day)	2090 (589.06)	2191 (677.10)	0.136
BMI (kg/m^2)	27.74 (4.36)	28.15 (4.76)	0.419
Hypertension	129 (94.9)	878 (90.3)	0.086
Alcohol consumption			0.950
<265 g/week	52 (38.2)	343 (35.1)	
265–722	43 (31.6)	368 (37.7)	
>722	41 (30.1)	265 (27.2)	
Smoking status			<0.001
Never	28 (20.7)	373 (38.3)	
Former or current	107 (79.3)	602 (61.7)	
Leisure-time physical activity			0.149
<447.5 MET-h/week	77 (57.9)	497 (51.4)	
447.5–742.5	37 (27.8)	299 (30.9)	
>742.5	19 (14.3)	171 (17.7)	
Educational level			0.140
<9 years	77 (56.6)	482 (49.6)	
Elementary (9–10 years) ± upper secondary school (9–13 years)	39 (28.7)	320 (33.0)	
University	20 (14.7)	169 (17.4)	
Saturated fat (E%)	14.31 (3.71)	14.74 (3.74)	0.328
Polyunsaturated fat (E%)	6.23 (1.47)	6.09 (1.58)	0.414
Fish and shellfish (g/week)	248.93 (244.83)	300.64 (267.60)	0.036
Fiber (g/MJ)	2.36 (0.78)	2.35 (0.74)	0.923
Fruits and berries (g/1000 kcal)	78.68 (63.88)	81.55 (59.73)	0.479
Vegetables (g/1000 kcal)	85.29 (64.44)	83.97 (59.63)	0.659
Sucrose (E%)	5.26 (2.67)	5.92 (3.35)	0.107
Whole grains (servings/1000 kcal)	0.23 (0.36)	0.28 (0.32)	0.814
Refined grains (servings/1000 kcal)	1.12 (0.61)	1.10 (0.55)	0.848

BMI, body mass index; DM, diabetes mellitus; IQR, interquartile range; MET, metabolic equivalent of task; PAD, peripheral arterial disease; SD, standard deviation.

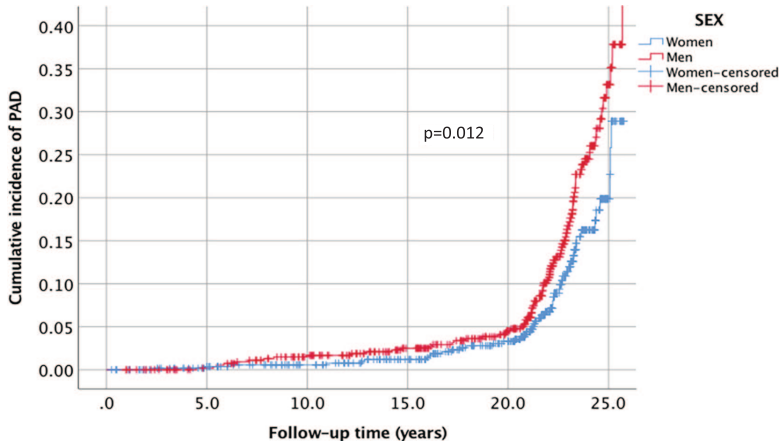

Figure 2. Cumulative incidence of symptomatic peripheral arterial disease (PAD) in relation to sex among participants with diabetes mellitus in the Malmö Diet and Cancer cohort.

Table 2. Correlation between fish or shellfish consumption and potential risk factors for peripheral arterial disease among individuals with diabetes mellitus at baseline.

	Fish or shellfish consumption	
	r	*p*
Potential risk factors		
Age	0.11	<0.001
Male sex	0.059	0.050
Body mass index	0.050	0.097
Hypertension	0.046	0.12
Smoking	−0.001	0.96
Alcohol consumption	0.18	<0.001
Leisure-time physical activity	0.094	0.002
Educational level	0.086	0.004

Table 3. Factors associated with incident symptomatic peripheral arterial disease among patients with diabetes mellitus in the Malmö Diet and Cancer cohort.

	HR (95% CI)	*p* value
Age	1.01 (0.98–1.03) per year	0.64
Male sex	1.36 (0.95–1.95)	0.090
Hypertension	1.86 (0.87–4.02)	0.11
Smoking	1.96 (1.28–3.0)	0.002
Fish and shellfish intake	0.99 (0.99–1.00) per additional gram per week	0.051

All five variables were analyzed using the Cox regression analysis.
CI, confidence interval; HR, hazard ratio.

both at baseline and at follow up to identify participants with asymptomatic PAD. This could both have helped exclude patients with prevalent asymptomatic PAD at baseline, and rendered a larger sample size of incident asymptomatic PAD cases, possibly strengthening the associated trend between a high intake of fish and shellfish and a reduced risk of PAD development. The study cohort focused on dietary habits in a middle-aged Swedish population. However, self-reported dietary habits are prone to be misreported to some extent and might have changed during follow up, and individuals with DM are known to be dietary changers.[25] On the other hand, the study population was homogenous since it only included individuals with DM at baseline. Other confounders not accounted for are changes in smoking habits, antihypertensive medications and anti-atherosclerotic agents during follow-up time. The shown correlation between fish and shellfish consumption and educational level is interesting, but associations of properly defined socioeconomic status[26] and dietary components and development of PAD in this cohort were not evaluated and were not within the scope of this study. The main strengths of this study are its longitudinal study design and the extensive (19.7 years) duration of follow up.

In conclusion, the present study found a trend towards a protective effect of higher intake of fish and shellfish against incident symptomatic PAD among individuals with DM.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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References

1. Nationella Diabetesregistret. Årsrapport 2018, www.ndr.nu/pdfs/Arsrapport_NDR_2018.pdf (2018, accessed 18 May 2019).
2. Centers for Disease Control and Prevention. National diabetes statistics report 2017, www.cdc.gov/diabetes/data/statistics-report/index.html (2017, accessed 3 June 2019).
3. Hiatt WR, Goldstone J, Smith SC, *et al.* Atherosclerotic peripheral vascular disease symposium II: nomenclature for vascular diseases. *Circulation* 2008; 118: 2826–2829.
4. Writing Group Members, Mozaffarian D, Benjamin EJ, *et al.* Heart disease and stroke statistics-2016 update: a report from the American Heart Association. *Circulation* 2016; 133: e38–e360.
5. Weir-McCall JR, Duce SL, Gandy SJ, *et al.* Whole body cardiovascular magnetic resonance imaging to stratify symptomatic and asymptomatic atherosclerotic burden in patients with isolated cardiovascular disease. *BMC Med Imaging* 2016; 16: 18.
6. Steg PG, Bhatt DL, Wilson PW, *et al.* One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA* 2007; 297: 1197–1206.
7. Hirsch AT, Criqui MH, Treat-Jacobson D, *et al.* Peripheral arterial disease detection, awareness,

and treatment in primary care. *JAMA* 2001; 286: 1317–1324.

8. Norgren L, Hiatt WR, Dormandy JA, *et al.* Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg* 2007; 45: S5–S67.
9. Britton KA, Mukamal KJ, Ix JH, *et al.* Insulin resistance and incident peripheral artery disease in the Cardiovascular Health Study. *Vasc Med* 2012; 17: 85–93.
10. Yu E, Rimm E, Qi L, *et al.* Diet, lifestyle, biomarkers, genetic factors, and risk of cardiovascular disease in the nurses' health studies. *Am J Public Health* 2016; 106: 1616–1623.
11. Mitrou PN, Kipnis V, Thiébaut ACM, *et al.* Mediterranean dietary pattern and prediction of all-cause mortality in a US population: results from the NIH-AARP Diet and Health Study. *JAMA Intern Med* 2007; 167: 2461–2468.
12. Manjer J, Elmståhl S, Janzon L, *et al.* Invitation to a population-based cohort study: differences between subjects recruited using various strategies. *Scand J Public Health* 2002; 30: 103–112.
13. Drake I, Gullberg B, Ericson U, *et al.* Development of a diet quality index assessing adherence to the Swedish nutrition recommendations and dietary guidelines in the Malmö Diet and Cancer cohort. *Public Health Nutr* 2011; 14: 835–845.
14. Brugård Konde Å, Bjerselius R, Haglund L, *et al. Swedish dietary guidelines—risk and benefit management report.* Report No. 5/2015, 6 June 2015. Uppsala, Sweden: Livsmedelsverket (National Food Agency).
15. Fatemi S, Gottsäter A, Zarrouk M, *et al.* Lp-PLA_2 activity and mass and CRP are associated with incident symptomatic peripheral arterial disease. *Sci Rep* 2019; 9: 5609.
16. Althouse AD, Abbott JD, Forker AD, *et al.* Risk factors for incident peripheral arterial disease in type 2 diabetes: results from the Bypass Angioplasty Revascularization Investigation in type 2 Diabetes (BARI 2D) Trial. *Diabetes Care* 2014; 37: 1346–1352.
17. Ruiz-Canela M, Estruch R, Corella D, *et al.* Association of Mediterranean diet with peripheral artery disease: the PREDIMED randomized trial. *JAMA* 2014; 311: 415–417.
18. Esposito K, Maiorino MI, Bellastella G, *et al.* Mediterranean diet for type 2 diabetes: cardiometabolic benefits. *Endocrine* 2017; 56: 27–32.
19. Fox CS, Golden SH, Anderson C, *et al.* Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American heart association and the American diabetes association. *Diabetes Care* 2015; 38: 1777–1803.
20. Ciccarone E, Di Castelnuovo A, Salcuni M, *et al.* A high-score Mediterranean dietary pattern is associated with a reduced risk of peripheral arterial disease in Italian patients with type 2 diabetes. *J Thromb Haemost* 2003; 1: 1744–1752.
21. Widmer RJ, Flammer AJ, Lerman LO, *et al.* The Mediterranean diet, its components, and cardiovascular disease. *Am J Med* 2015; 128: 229–238.
22. Look AHEAD Research Group, Wing RR, Bolin P, *et al.* Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013; 369: 145–154.
23. Redmond ML, Dong F, Goetz J, *et al.* Food insecurity and peripheral arterial disease in older adult populations. *J Nutr Health Aging* 2016; 20: 989–995.
24. Nosova EV, Conte MS and Grenon SM. Advancing beyond the "heart-healthy diet" for peripheral arterial disease. *J Vasc Surg* 2015; 61: 265–274.
25. Paisley J, Beanlands H, Goldman J, *et al.* Dietary change: what are the responses and roles of significant others? *J Nutr Educ Behav* 2008; 40: 80–88.
26. Sonestedt E, Wirfält E, Gullberg B, *et al.* Past food habit change is related to obesity, lifestyle and socioeconomic factors in the Malmö Diet and Cancer cohort. *Public Health Nutr* 2005; 8: 876–885.

Paper II

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The impact of diabetes mellitus on major amputation among patients with chronic limb threatening ischemia undergoing elective endovascular therapy- a nationwide propensity score adjusted analysis

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ABSTRACT

Aim: To investigate the risk of major amputation after elective endovascular therapy in patients with chronic limb threatening ischemia (CLTI) comparing patients with and without diabetes mellitus (DM).
Methods: In this nationwide cohort study, all patients registered in the Swedish Vascular Register after elective endovascular therapy for CLTI caused by infra-inguinal arterial disease from 2010 to 2014 were included. Among 4578 individuals, 2251 had DM and were registered in the National Diabetes Register between 2009 and 2014. A propensity score adjusted Cox regression analysis was conducted to compare outcomes between groups. Median follow-up was 4.0 and 3.6 years for patients with DM and without DM, respectively.
Results: The incidence rates of major amputation and acute myocardial infarction (AMI) were 43% (95% CI 1.23–1.67) and 37% (95% CI 1.13–1.67) higher, respectively, among patients with DM compared to patients without DM. There was no difference in mortality (HR 1.04, 95% CI 0.95–1.14).
Conclusions: Patients with DM had a higher risk of major amputation and AMI compared to those without DM after elective endovascular therapy for CLTI. Prevention of DM with CLTI is of utmost importance to reduce the risk of adverse limb and cardiovascular outcomes.

1. Introduction

Chronic limb-threatening ischemia (CLTI) is the end stage of peripheral artery disease (PAD) and is associated with an increased risk of amputation, higher mortality, and impaired quality of life. The Global Vascular Guidelines on CLTI state that CLTI is a clinical syndrome characterized by PAD together with gangrene, rest pain or ulceration >2 weeks.[1]

Between 2000 and 2010 the prevalence of PAD increased with almost 29% in low-and middle-income countries (LMIC) and 13% in high income countries due to a growing and aging global population, a rise in the prevalence of diabetes mellitus (DM), and smoking. In 2010, >200 million people lived with PAD, with nearly two thirds residing in LMIC. With a rise in PAD prevalence, CLTI is also considered a growing global health care problem. However, epidemiologic data are highly limited.[2]

Individuals with DM and PAD have a more distal distribution of the arterial disease and tend to have more significant comorbidities. Therefore, it might be more appealing to perform endovascular than open surgical therapy for CLTI among patients with DM.[3] The proportion of patients with DM and CLTI undergoing elective endovascular therapy is increasing compared to open vascular surgery.[4–6]

The influence of DM on major amputation for CLTI has not been consistent. Several studies have failed to demonstrate a difference in limb salvage rate among patients with DM versus those without DM.[7,8] Therefore, a propensity score adjusted analysis based on a nationwide real-world sample from all vascular centers in Sweden with high external validity was warranted. The aim of this study was to explore the risk of major amputation after

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elective endovascular therapy in patients with CLTI and infra-inguinal arterial disease, comparing patients with DM versus without DM in a nationwide propensity score adjusted analysis.

2. Methods

This cohort study analyzed prospectively collected data on all patients with CLTI undergoing elective endovascular interventions for infra-inguinal arterial disease in Sweden from 2010 to 2014, with a total of 4763 patients. Patients with (n = 88) and without (n = 118) DM undergoing elective hybrid (endovascular plus open vascular) surgery were excluded. CLTI was defined as having PAD along with rest pain, gangrene, or ulcers for >2 weeks.[1] Patients without tissue loss were considered to have rest pain.

2.1. Databases and procedures

The study participants were identified by linking the Swedish Vascular Register (Swedvasc)[9] and the Swedish National Diabetes Register (NDR).[10] Information on individual level was linked by using unique personal identity number from nationwide population-based registries. Duplicated patients were excluded.

All patients undergoing vascular surgery in Sweden are registered in Swedvasc, a national patient register. Preoperative data such as risk factors, type of treatment (open or endovascular, acute or elective), complications, and reinterventions are registered in Swedvasc. Patients are followed up at 30 days and 12 months after the surgical procedure. Only the index endovascular revascularization procedure within the study period was analyzed. Repeat endovascular procedure in the ipsilateral or contralateral limb was not analyzed. The database could not differ if the procedure was a repeat endovascular procedure or index endovascular procedure.

The NDR is estimated to cover 94% of Swedish citizens with DM over the age of 18.[11] The registry includes data on clinical characteristics, diabetes treatment, risk factors, and diabetic complications. Every individual give consent to being included in the register.

The Swedish National Patient Register (NPR) was used to obtain information on outcomes and co-morbidities, since Swedvasc only provides one-year follow-up after revascularization.

Amputation was defined as amputation above the ankle e.g. major amputation. Since NPR is a code-based register, information on amputation laterality was not always possible to determine. A recent validation of major amputation for CLTI has been performed by reviewing 1366 patients' medical records, showing <10% missing data for amputation with remaining uncertainty of the laterality of the amputation.[12] Cause of death was retrieved from the Cause of Death Register. Both registries are administered by the National Board of Health and Welfare (https://www.socialstyrelsen.se/en/). The NPR was founded in 1964 and has >99% coverage with a positive predictive value of >99% for vascular interventions for lower limb ischemia.[13]

In this observational study, patients registered in Swedvasc after elective endovascular therapy for CLTI from 2010 to 2014 were identified, and those with an associated registration in NDR from 2009 to 2014 were compared with those without such registration (Fig. 1).

2.2. Baseline data

Data files were linked to the cancer registry[14] with information about comorbidities and drug treatment at baseline and the Prescribed Drug Register (PDR) with data of prescriptions since 2005.[15]

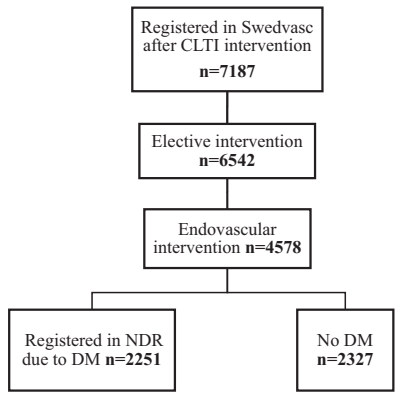

Fig. 1. Flow chart of patients in the Swedish Vascular Register (Swedvasc) undergoing elective endovascular intervention for CLTI during 2010–2015 with and without registration in the NDR with a diagnosis of DM. NDR, National Diabetes Register; DM, diabetes mellitus, CLTI, chronic limb threatening ischemia.

The National Patient Register uses the International Classification of Diseases, Tenth revision (ICD-10) for classification of diagnoses. Drug treatment and comorbidities including atrial fibrillation, congestive heart failure, coronary heart disease (CHD), stroke, and hypertension were registered at baseline. Acute myocardial infarction (AMI) was defined as I21 (ICD-10). Psychiatric disorders (excluding dementia), liver diseases, chronic obstructive pulmonary disease (COPD), renal disorder (renal failure, dialysis or kidney transplant), cancer disease, previous amputation were also included.

Smoking was defined as currently smoking at baseline and the information was collected from Swedvasc, when data was missing in Swedvasc, NDR was used to complement. Drug treatment was defined according to the Prescribed Drug Register. Use of lipid lowering drugs, acetylsalicylic acid (ASA), and anticoagulant therapy was included. Hypertension was defined as collecting a minimum of one prescription of antihypertensive drugs one year prior to index operation. Three months of medicine use is equivalent to one prescription. Use of ASA and lipid lowering medication was defined similarly. Estimated glomerular filtration rate (eGFR) data was retrieved from NDR and eGFR <60 ml/min/1.73 m^2 was defined as renal impairment. The definition of stent included drug-eluting stent or stent graft.

The longitudinal integration database for health insurance and job market studies (LISA) was used to retrieve socioeconomic characteristics. Educational level was defined as compulsory school, upper secondary school and college or university and marital status as married, separated, single or widowed. Country of origin was defined as either Sweden, Europe, or the rest of the world.

There were no missing data for age, gender and medications used. Income and civil status were missing for one patient (0.02%). Educational level was missing for 77 patients (1.7%), tissue loss and the use of stent were missing for 470 and 471 patients (10.3%), respectively. Smoking status was missing for 982 patients (21.5%). There were no missing data for event type variables (prior and future).

2.3. Ethical approval

The study was approved by the research ethical committee of Lund, Sweden (2016/232 and 2016/544). All patients have consented to being reported in NDR and Swedvasc, while no individual consent is required to be included in this study according to Swedish law.

2.4. Follow-up

Study participants were followed from the first revascularization, defining the index date, until December 31, 2016 for endpoints using Swedvasc and until December 31, 2017 for mortality through linkage between NDR and the Cause of Death Register with causes and time of death, administered by the National Board of Health and Welfare (https://www.socialstyrelsen.se/en/).

2.5. Statistical analysis

Outcomes were compared after elective endovascular intervention for CLTI between patients with and without DM by propensity score-adjusted analysis. A propensity score technique to adjust for multiple risk factors[16,17] was used since multivariate adjustments by logistic regression is limited by the number of endpoints, and a limited number of covariates should be modelled.[18] The propensity scores were estimated using a generalized boosted multinomial regression model with an interaction depth of 3, a maximum of 10,000 trees, and a shrinkage of 0.01. The optimal number of trees was selected using a stopping rule applied to the degree of balance.

The distribution of propensity scores differs between infrainguinal CLTI patients with and without DM, making some form of adjustment for confounding necessary. In order to avoid losing patients in a matching procedure we used inverse probability of treatment (here defined as having DM) weighting (IPTW). It should be noted that pre index diabetes treatment is excluded from the estimation of the weights and therefore not adjusted for. The developed propensity score model was validated (Appendix, Fig. 1).

2.6. Sensitivity analysis of the inverse probability of treatment weighting adjusted analysis

The IPTW adjusted analysis was performed using all patients. Sensitivity analyses have been performed by placing a threshold on the weight (eg. Max weight = 10) and by trimming the data set based on the value of the propensity score (eg. Keeping datapoints above the 2.5% and 1% percentile determined for the DM + CLTI group and below the 97.5% and 99% percentile determined for the CLTI group).

Results when truncating max weight at 10 are very similar to the main results indicating that there is no large influence by larger weights on the analysis. Results when trimming data based on percentiles of the propensity scores are largely consistent with the main analysis, for the primary endpoint, the composite of major amputation or death, estimated hazard ratios are 1.13 ($p = 0.0043$), 1.16 ($p = 0.0010$) and 1.20 ($p = 0.0001$) for the main analysis, trimming 1%-percentiles and trimming 2.5%-percentiles, respectively. For all-cause mortality, the corresponding figures are 1.04 ($p = 0.36$), 1.08 ($p = 0.077$) and 1.14 ($p = 0.0092$) respectively.

Descriptive statistics were presented as mean, standard deviation for continuous variables and as counts and percentages for categorical variables. The degree of similarity between CLTI patients with and without DM was described using the standardized mean difference (SMD) and *p*-values. Incidence rates (IR) for mortality, cardiovascular (CV) death, major adverse cardiovascular events (MACE), AMI, and stroke are estimated as the number of

Table 1
Baseline characteristics of patients with CLTI with DM and without DM undergoing planned endovascular intervention.

	DM and CLTI (n = 2251)	CLTI (n = 2327)	p	SMD
Age, years, mean (SD)	75.08 (10.00)	80.75 (9.30)	<0.001	0.588
Women, n (%)	902 (40.1)	1412 (60.7)	<0.001	0.421
Smoking, n (%)	283 (14.5)	343 (20.9)	<0.001	0.169
Medication, n (%)				
Lipid lowering	1635 (72.6)	1224 (52.6)	<0.001	0.423
Metformin	749 (33.3)	0 (0.0)	<0.001	0.999
Antihypertensive	2134 (94.8)	2048 (88.0)	<0.001	0.244
Acetylsalicylic acid	1594 (70.8)	1642 (70.6)	0.878	0.005
Clopidogrel	314 (13.9)	240 (10.3)	<0.001	0.112
Anticoagulant therapy	860 (38.2)	776 (33.3)	0.001	0.101
ACE inhibitor	1152 (51.2)	844 (36.3)	<0.001	0.304
ARB	739 (32.8)	482 (20.7)	<0.001	0.276
Alpha blocker	68 (3.0)	16 (0.7)	<0.001	0.174
Beta blocker	1466 (65.1)	1262 (54.2)	<0.001	0.223
Calcium channel blocker	872 (38.7)	742 (31.9)	<0.001	0.144
Diuretic	1456 (64.7)	1403 (60.3)	0.002	0.091
Digoxin	169 (7.5)	170 (7.3)	0.838	0.008
Nitrate	553 (24.6)	458 (19.7)	<0.001	0.118
Diabetes treatment	1987 (88.3)	0 (0.0)	<0.001	3.334
Income quartile (%)			0.043	0.084
1	547 (24.3)	611 (26.3)		
2	558 (24.8)	601 (25.8)		
3	557 (24.7)	587 (25.2)		
4	589 (26.2)	527 (22.7)		
Income *100SEK/year, mean (SD)	1774.17 (2807.34)	1686.35 (2294.70)	0.246	0.034
Education, n (%)			0.002	0.105
Compulsory school	1135 (51.2)	1278 (56.0)		
Upper secondary	845 (38.1)	759 (33.2)		
College or university	237 (10.7)	247 (10.8)		
Civil status, n (%)			<0.001	0.361
Married	1015 (45.1)	756 (32.5)		
Separated	404 (17.9)	367 (15.8)		
Single	251 (11.2)	219 (9.4)		
Widowed	581 (25.8)	984 (42.3)		
Origin, n (%)			<0.001	0.162
Europe except Sweden	113 (5.0)	127 (5.5)		
Rest of the world	182 (8.1)	98 (4.2)		
Sweden	1956 (86.9)	2102 (90.3)		
Previous diseases, n (%)				
Acute myocardial infarction	590 (26.2)	397 (17.1)	<0.001	0.224
Coronary heart disease	1049 (46.6)	799 (34.3)	<0.001	0.252
Stroke	378 (16.8)	349 (15.0)	0.105	0.049
Atrial fibrillation	580 (25.8)	656 (28.2)	0.070	0.055
Heart failure	703 (31.2)	623 (26.8)	0.001	0.098
Renal disorder	456 (20.3)	277 (11.9)	<0.001	0.229
Renal impairment	689 (49.1)	NA	NA	NA
Cancer disease	237 (10.5)	320 (13.8)	0.001	0.099
Liver disease	20 (0.9)	21 (0.9)	1.000	0.001
Psychiatric disorder	112 (5.0)	101 (4.3)	0.342	0.030
COPD	202 (9.0)	293 (12.6)	<0.001	0.117
Previous amputation, minor and major	205 (9.1)	160 (6.4)	<0.001	0.103
Tissue loss	1731 (86.0)	1570 (74.9)	<0.001	0.284
Stent	560 (27.8)	732 (34.9)	<0.001	0.154

DM, diabetes mellitus; CLTI, chronic limb threatening ischemia. ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; SMD, standardized mean difference. Anticoagulant therapy includes vitamin K-antagonists, Heparin, low molecular Heparin, NOACs, Fondaparinux. Diabetes treatment includes Metformin. NA = Not applicable.
Categorical variables are presented as number (%) and continuous variables are presented as mean (standard deviation, SD).

events per 1000 person-years with exact 95% Poisson confidence intervals. Cumulative incidence of mortality, major amputation, combined major amputation and mortality, CV death, MACE, AMI, and stroke were described using Kaplan-Meier curves transformed to estimate the distribution function rather than the survival function. The statistical analyses compared CLTI patients with DM to CLTI patients without DM using both an unadjusted and an inverse probability of treatment weighting (IPTW) adjusted Cox regression model. IPTW adjusted Cox regression analysis was expressed as hazard ratios (HR) with 95% confidence intervals (CI). See Appendix 1 for a list of the adjusted variables. A p-value <0.05 was considered statistically significant.

3. Results

3.1. Study population and demographic characteristics

During the study period, 2010 and 2014 a total of 4578 individuals, of whom 2251 had DM, were registered in Swedvasc after planned endovascular intervention. DM types were distributed as follows: Type 1 DM (15.5%; n = 348), Type 2 DM (82.8%; n = 1864) and other/unspecified DM (1.7%; n = 39). Median follow-up was 4.0 (maximum 8.0) years for patients with DM undergoing elective endovascular therapy and 3.9 (maximum 8.0) years for patients without DM. Unadjusted baseline clinical and demographic characteristics for the two groups are shown in Table 1.

3.2. Outcome analysis

The incidence rate of major amputation was 43% higher (95% CI 1.23–1.67; p < 0.0001), and the incidence rate of major amputation or death was 13% higher (95% CI 1.04–1.23; p = 0.0043) among patients with DM in comparison to patients without DM. The IPTW adjusted Cox regression (Table 2) analysis showed a 37% higher AMI (95% CI 1.13–1.67; p = 0.0015) and 13% higher MACE (95% CI 1.04–1.23; p = 0.0028) incidence rate among patients with DM compared to those without DM. There was no difference in mortality, cardiovascular death, or stroke between the groups. Fig. 2 displays crude Kaplan-Meier curves for cumulative incidences of major amputation and total mortality.

3.3. Effect of diabetes duration, HbA1c, renal impairment and tissue loss on outcomes among patients with CLTI and DM

Median diabetes duration was 19 years (IQR 11–29; n = 1456) and median HbA1c was 60.0 mmol/mol (interquartile range [IQR] 51.0–71.0; n = 1515). Diabetes duration was associated with a higher risk of major amputation (Table 3) (HR 1.02, 95% CI 1.01–1.02; p < 0.0001), total mortality (HR 1.00, 95% CI 1.00–1.01; p < 0.0085), MACE (HR 1.01, 95% CI 1.00–1.01; p < 0.011), and AMI (HR 1.01, 95% CI 1.00–1.02; p < 0.047). HbA1c was associated with AMI (HR 1.01, 95% CI 1.00–1.02; p = 0.0029). Renal impairment had an increased risk of total mortality (HR 1.63, 95% CI 1.39–1.92; p < 0.0001), CV

Table 2
IPTW adjusted Cox regression analysis of hazard ratio for different endpoints for patients with (n = 2251) DM compared to patients without (n = 2327) after planned endovascular intervention for CLTI.

	IPTW adjusted analysis		
Endpoint	Hazard ratio	p-value	95% CI
Mortality	1.04	0.3623	0.95–1.14
Cardiovascular death	1.01	0.9214	0.95–1.14
MACE	1.13	0.0028	1.04–1.23
AMI	1.37	0.0015	1.13–1.67
Stroke	1.11	0.3630	0.89–1.38
Major amputation	1.43	<0.0001	1.23–1.67
Major amputation or death	1.13	0.0043	1.04–1.23

DM, diabetes mellitus; CLTI, chronic limb threatening ischemia. IPTW, inverse probability treatment weighting. MACE, major adverse cardiovascular event; AMI, acute myocardial infarction.

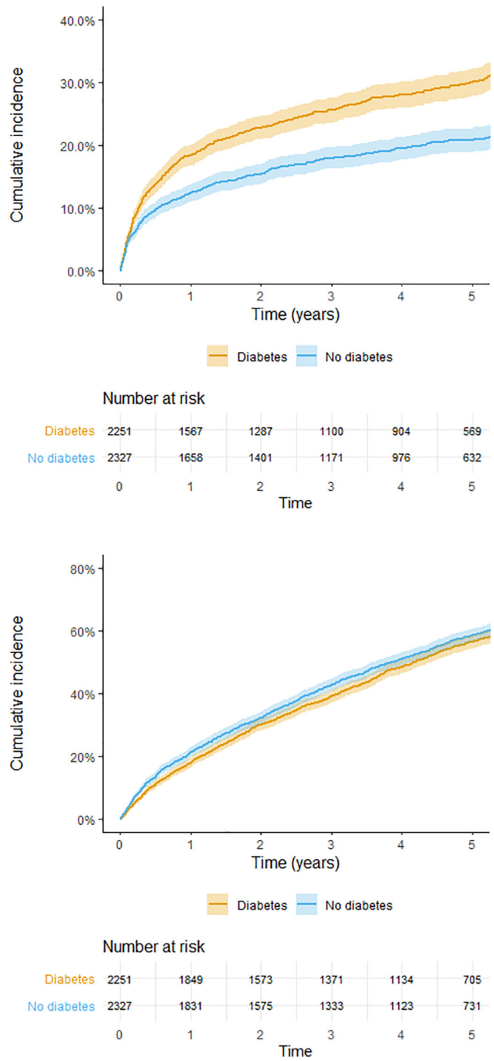

Fig. 2. Crude Kaplan-Meier curves showing cumulative major amputation and total mortality after elective endovascular interventions for CLTI among patients with DM and without DM. Shaded areas represent 95% CI. CLTI, chronic limb threatening ischemia; DM, diabetes mellitus.

Table 3
Effect of diabetes duration, HbA1c, renal impairment and tissue loss on total mortality, cardiovascular mortality, MACE, AMI, stroke and major amputation adjusted for sex and age among patients with diabetes mellitus undergoing planned endovascular intervention for CLTI.

Outcome	Covariate	Hazard ratio	p-value	95% CI
Total mortality	Diabetes duration	1.00	0.00846	1.00–1.01
Total mortality	HbA1c	1.00	0.0680	1.00–1.01
Total mortality	Renal impairment	1.63	<0.0001	1.39–1.92
Total mortality	Tissue loss	1.71	0.001	1.31–2.23
CV mortality	Diabetes duration	1.00	0.4090	1.00–1.01
CV mortality	HbA1c	1.00	0.0891	1.00–1.01
CV mortality	Renal impairment	1.65	<0.0001	1.36–1.99
CV mortality	Tissue loss	1.86	0.0002	1.34–2.56
MACE	Diabetes duration	1.01	0.0112	1.00–1.01
MACE	HbA1c	1.00	0.0876	1.00–1.01
MACE	Renal impairment	1.36	0.0001	1.17–1.58
MACE	Tissue loss	1.31	0.0195	1.04–1.64
AMI	Diabetes duration	1.01	0.0468	1.00–1.02
AMI	HbA1c	1.01	0.0029	1.00–1.02
AMI	Renal impairment	1.28	0.1005	0.95–1.72
AMI	Tissue loss	2.30	0.0022	1.35–3.91
Stroke	Diabetes duration	0.99	0.2514	0.98–1.01
Stroke	HbA1c	1.00	0.5036	0.99–1.01
Stroke	Renal impairment	1.16	0.4799	0.77–1.72
Stroke	Tissue loss	1.56	0.1684	0.83–2.93
Major amputation	Diabetes duration	1.02	0.0000	1.01–1.02
Major amputation	HbA1c	1.00	0.2490	1.00–1.01
Major amputation	Renal impairment	1.39	0.0097	1.08–1.78
Major amputation	Tissue loss	2.45	0.0002	1.53–3.92

CLTI, chronic limb threatening ischemia; MACE, major adverse cardiovascular event; AMI, acute myocardial infarction.
The effect of diabetes duration and HbA1c was evaluated by fitting a Cox proportional hazards model. The model includes gender, age, diabetes duration, HbA1c, renal impairment and tissue loss at baseline. Only patients with non-missing values on gender, age, diabetes duration, HbA1c, renal impairment and tissue loss are included.

mortality (HR 1.65, 95% CI 1.36–1.99; $p < 0.0001$), MACE (HR 1.36, 95% CI 1.17–1.58, $p = 0.0001$), and major amputation (HR 1.39, 95% CI 1.08–1.78, $p = 0.0097$). Tissue loss had an increased risk of major amputation (HR 2.45, 95% CI 1.53–3.92; $p = 0.0002$), total mortality (HR 1.71, 95% CI 1.31–2.23, $p = 0.001$), CV mortality (HR 1.86, 95% CI 1.34–2.56, $p = 0.0002$), MACE (HR 1.31, 95% CI 1.04–1.64, $p = 0.0195$) and AMI (HR 2.30, 95% CI 1.31–3.91; $p = 0.0022$).

4. Discussion

4.1. Study results in comparison to other research

This nationwide observational study found that CLTI patients with DM had a significantly higher risk of major amputation after elective endovascular therapy in a real-life setting. Furthermore, we observed a higher risk for AMI among patients with DM. However, this does not seem to increase the risk of cardiovascular death among those with DM in this cohort. In the present study, according to the compound variable major amputation or death there seem to be an increased risk of major amputation or death among patients with DM. This risk seems largely to be made up by the increased risk of major amputation.

In line with the present study results, a previous single center review study of CLTI found a four times higher risk of major amputation among patients with DM compared to patients without DM after revascularization with PTA.[19] Previous nationwide studies have also shown a higher risk of major amputation among individuals with DM. An Italian study, although not studying outcome after revascularization in particular, showed a six times higher rate of major amputation among patients with DM and a general decline in the rate of major amputation between 2001 and 2010.[20] Another nationwide study, conducted in England, demonstrated a decrease in incidence of amputation in the non-diabetic population while the rate of amputation related to DM remained unchanged.[21] A systematic review showed that the global incidence of major amputation among individuals with DM differed substantially (5.6 to 600 per 100.000 per year), whereas the corresponding figure among patients without DM was 3.6 to 68.4 per 100.000 per year.[22]

There was no difference in total mortality between the DM and non-DM group in the present study. In contrast, Swedvasc data between 2001 and 2003 has previously shown an excess mortality in patients with DM compared to non-DM after open leg bypass surgery for CLTI.[23] The inferior results after open surgery may be attributed to poorer coverage of statins and acetylic salicylic acid and higher smoking rate at admission in the more remote time period in combination with the much greater physiological cardio-pulmonary stress associated with open vascular surgery.

As expected, diabetes duration among individuals with DM and CLTI was related to a higher risk of major amputation, total mortality, MACE, and AMI in the present study. HbA1c was associated with AMI, but not major amputation. In contrast, inferior glycemic control in terms of elevated fasting glucose at the time of intervention, among 149 patients with DM was found to be associated with higher frequency of loss of patency after infrapopliteal balloon angioplasty and increased rate of subsequent major adverse limb events (MALE) after adjusting for confounders.[24] However, this cohort was mixed with an unclear proportion of patients with chronic and acute limb ischemia. Acute limb ischemia goes with a comparably decreased amputation-free survival and should therefore either be separately described or never be included together with patients with CLTI.[25] In addition, it is highly likely that elevation of fasting glucose is much more pronounced in the acute compared to elective setting. Indeed, HbA1c, reflecting glycemic control months preceding the intervention, was not found to be associated with adverse outcomes in the study by Singh et al.[24] HbA1c was in a multivariate model using six covariates found to be associated with major amputation in 197 patients with CLTI and DM.[26] Apart from entering sex and age as covariates, the authors added limb severity and infection and receiving hemodialysis in their model. While infection was not possible to enter in the present registry study, both tissue loss and renal impairment were found to be predictors of major amputation in the present study. It should be emphasized, however, that leg revascularization is just one key element in the complex management of DM and CLTI. A multidisciplinary therapeutic approach including state-of-the-art wound care, biomechanical offloading of foot ulcers, edema and blood glucose control, and effective treatment of all underlying risk factors and comorbidities is necessary to be able to improve limb salvage and mortality rates.[27]

4.2. Strengths and limitations of the study

The strengths of the present study are the use of data from two nationwide disease-specific registries, NDR and Swedvasc, along with information from other nationwide databases due to linkage of the unique personal identity number for every Swedish citizen.[28] The propensity score - adjusted analysis applied for the comparison between infrainguinal CLTI patients with DM and without DM ensures proper adjustment for confounding. The reason to only include elective endovascular therapy in the study means that we reduce major treatment selection bias by excluding those undergoing open vascular surgery.

As always when data is retrieved from registries, there is a potential risk of data collection errors, misclassifications, and lack of data on lifestyle factors resulting in possible residual confounding. In this study the indication for elective endovascular therapy was CLTI. Swedvasc has previously been validated for carotid artery disease and abdominal aortic aneurysm procedures,[29] but no validation of patients undergoing

procedures for lower extremity arterial disease has been completed. No validation of CLTI patients has been performed in Swedvasc, but we have no reason to believe that a significant proportion of patients with CLTI were misclassified as intermittent claudication instead of CLTI. Contrarily, Djerf et al. report that almost half of the patients registered as intermittent claudication in Swedvasc and later on underwent major amputation in fact had CLTI.[30] It cannot be excluded in the present study that some patients were reclassified as having CLTI after an unsuccessful revascularisation for intermittent claudication. Baubeta Fridh et al. also found that more than 82% of all confirmed amputations among patients with CLTI and intermittent claudication were ipsilateral.[31] Since the same registries, Swedvasc and NPR, were used in that study[31] we have reason to believe that the same issue with laterality applies to the present study.

Previous studies suggest that up to 50% of data on smoking status is missing in Swedvasc.[31] Complementary data on smoking status was used from NDR meaning that smoking status among patients with DM is better covered than for patients without DM. A previous study on the Swedvasc register found that tissue loss was associated with a higher risk of amputation compared to rest pain among patients revascularized for CLTI.[32] While it was not possible to adjust for the severity of the wound, location of wound and the presence of wound infection in the present registry study, adjustment for potential differences in tissue loss and rest pain between those with versus without DM was done. In addition, further adjustment was performed for stenting, a procedure that almost exclusively is performed at the femoro-popliteal level among those with infra-inguinal arterial disease.[33]

Peripheral neuropathy is often present among patients with DM,[34] potentially leading to less expressed pain or even absence of pain. Furthermore, this may contribute to the underestimation of the severity of CLTI among patients with DM leading to a prolonged waiting time before vascular imaging and revascularization.

The worse limb and cardiovascular outcomes in patients with DM compared to non-DM undergoing endovascular surgery for CLTI, may be reduced by improvement in prevention and treatment measures for the DM group. Firstly, it should be emphasized that patients with DM needing a revascularization procedure for preventing an amputation represents a group with end stage foot disease and advanced cardiovascular burden. Therefore, implementation of nationwide prevention programs towards development of type 2 diabetes mellitus in the first place is the most important step to reduce the incidence of DM. Despite weight reduction and general health programs, there will still be a number of individuals with type 2 DM who are normal weight.[35] In addition, a smaller percentage will have type 1 DM. Therefore, regular screening for PAD including history, palpation of foot pulses, at a minimum, in persons with DM, even in the absence of foot ulceration, may be relevant to reduce the adverse limb and cardiovascular outcomes.[36] Symptoms and signs of PAD such as claudication, absent pulses and a low ankle-brachial index, has been identified as predictors for future foot ulceration.[37]

5. Conclusion

In this nationwide population-based study, patients with CLTI and DM had a higher risk of major amputation and AMI after elective endovascular therapy for infra-inguinal arterial disease compared to those without DM. Prevention of DM with CLTI is of utmost importance to reduce the risk of adverse limb and cardiovascular outcomes.

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Credit authorship contribution statement

Erika Lilja: Writing - original draft, Writing - review & editing. Project administration.
Anders Gottsäter: Conceptualization, Project administration, Methodology, Writing – review & editing.
Mervete Miftaraj: Formal analysis, Methodology, Writing - review & editing.
Jan Ekelund: Formal analysis, Methodology, Writing - review & editing.
Björn Eliasson: Formal analysis, Methodology, Writing – review & editing.
Ann-Marie Svensson: Project administration, Formal analysis, Methodology, Writing - review & editing.
Moncef Zarrouk: Writing – review & editing.
Peter Nilsson: Conceptualization, Writing – review & editing.
Stefan Acosta: Conceptualization, Supervision, Project administration, Methodology, Writing - review & editing.

Declaration of competing interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

Appendix 1

Table 1
List of baseline variables adjusted for in the inverse probability of treatment weighting (IPTW) adjusted Cox regression.

- Age
- Sex
- Smoking
- Lipid lowering treatment
- Anti-hypertensive treatment
- ASA
- Other oral anticoagulants
- ACE
- ARB
- Alpha blocker
- Beta blocker
- Calcium channel blocker
- Diuretic
- Digoxin
- Nitrate
- Disposable income
- Education
- Marital status
- Country of origin
- AMI
- CHD
- Stroke
- AF
- HF
- Renal disease
- Kidney failure
- Cancer
- Liver disease
- Psychiatric disorders
- COPD
- Previous major amputation
- Tissue loss
- Stent
- Clopidogrel

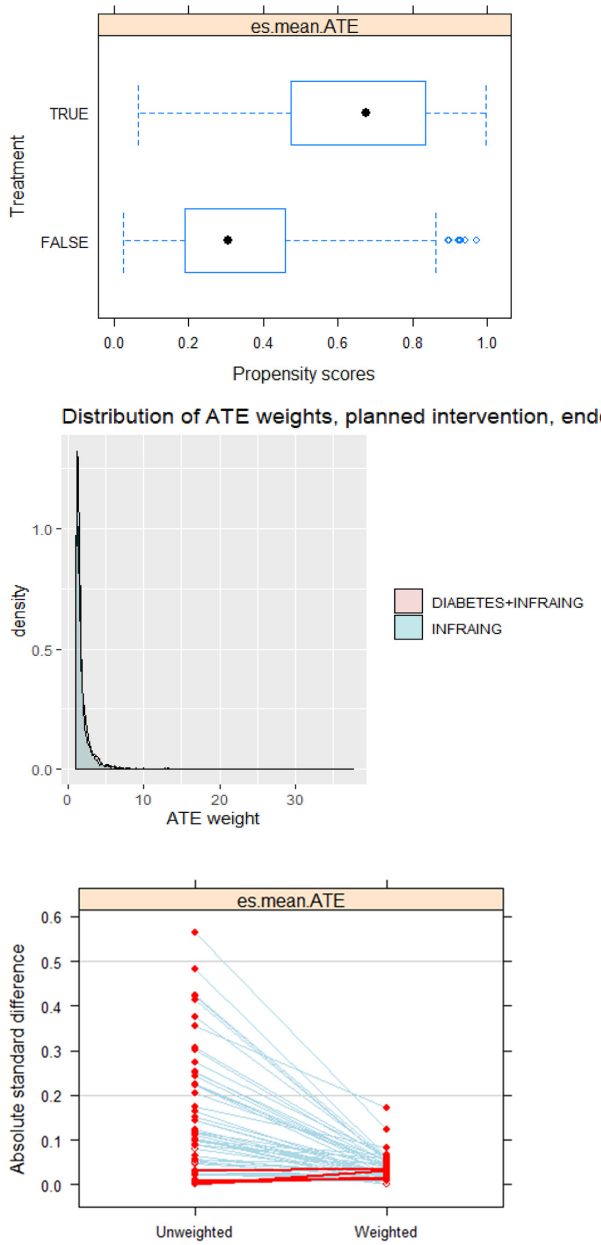

Fig. 1. Examination ,of the propensity scores and weights. The distribution of propensity scores differed between infra-inguinal CLTI patients with and without DM, making some form of adjustment for confounding necessary. In order to avoid losing patients in a matching procedure we used inverse probability of treatment (here defined as having diabetes mellitus) weighting. The weighted descriptive statistics (the top two figures) as well as the plotted standardized mean difference (the lowest figure) indicate that the used weights greatly improved the balance. It should be noted that pre index diabetes treatment is excluded from the estimation of the weights and therefore not adjusted for. es = effect size; ATE = average treatment effect.

References

1. Conte MS, Bradbury AW, Kolh P, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. Eur J Vasc Endovasc Surg 2019;58:S1-S109. e133.2019/06/12. https://doi.org/10.1016/j.ejvs.2019.05.006.
2. Fowkes FG, Rudan D, Rudan I, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet 2013;382:40https://doi.org/10.1016/S0140-6736(13)61249-0.
3. Jude EB, Oyibo SO, Chalmers N, et al. Peripheral arterial disease in diabetic and nondiabetic patients. Diabetes Care 2001;24:1433-7https://doi.org/10.2337/diacare.24.8.1433.
4. Liang P, Soden PA, Zettervall SL, et al. Treatment outcomes in diabetic patients with chronic limb-threatening ischemia. J Vasc Surg 2018 Aug;68:487-94https://doi.org/10.1016/j.jvs.2017.11.081.
5. Butt T, Lilja E, Örneholm H, et al. Amputation-free survival in patients with diabetes mellitus and peripheral arterial disease with heel ulcer: open versus endovascular surgery. Vasc Endovascular Surg 2019;53:118-25https://doi.org/10.1177/1538574418813746.
6. Butt T, Lilja E, Elgzyri T, et al. 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 Feb;6:107551https://doi.org/10.1016/j.jdiacomp.2020.107551.
7. DeRubertis BG, Pierce M, Ryer EJ, et al. Reduced primary patency rate in diabetic patients after percutaneous intervention results from more frequent presentation with limb-threatening ischemia. J Vasc Surg 2008;47:101-8https://doi.org/10.1016/j.jvs.2007.09.018.
8. Dick F, Diehm N, Galimanis A, et al. Surgical or endovascular revascularization in patients with critical limb ischemia: influence of diabetes mellitus on clinical outcome. J Vasc Surg 2007;45:751-61https://doi.org/10.1016/j.jvs.2006.12.022.
9. Troëng T, Malmstedt J, Björck M. External validation of the Swedvasc registry: a first-time individual cross-matching with the unique personal identity number. Eur J Vasc Endovasc Surg 2008;36:705-12https://doi.org/10.1016/j.ejvs.2008.08.017.
10. Eliasson B, Gudbjörnsdottir S. Diabetes care - improvement through measurement. Diabetes Res Clin Pract 2014;106:S291-4https://doi.org/10.1016/S0168-8227(14)70732-6.
11. Nationella Diabetesregistret. Årsrapport 2018. Accessed 22 January 2020.
12. Baubeta Fridh E, Andersson M, Thuresson M, et al. Editor's choice - impact of comorbidity, medication, and gender on amputation rate following revascularisation for chronic limb threatening ischaemia. Eur J Vasc Endovasc Surg 2018;56:681-8.2018/08/11. https://doi.org/10.1016/j.ejvs.2018.06.003.
13. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:450.2011/06/11. https://doi.org/10.1186/1471-2458-11-450.
14. Socialstyrelsen. The Swedish Cancer Register. , https://www.socialstyrelsen.se/en/statistics-and-data/registers/register-information/swedish-cancer-register/. Accessed January 22, 2020.
15. Wettermark B, Hammar N, Fored CM, et al. The new Swedish Prescribed Drug Register-opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf 2007;16:726-35.2006/08/10. https://doi.org/10.1002/pds.1294.
16. Cepeda MS, Boston R, Farrar JT, et al. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. Am J Epidemiol 2003;158:280-7.
17. Martens EP, de Boer A, Pestman WR, et al. Comparing treatment effects after adjustment with multivariable Cox proportional hazards regression and propensity score methods. Pharmacoepidemiol Drug Saf 2008;17:1-8.
18. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and cox regression. Am J Epidemiol 2007;165:710-8.
19. Darling JD, O'Donnell TFX, Deery SE, et al. Outcomes after first-time lower extremity revascularization for chronic limb-threatening ischemia in insulin-dependent diabetic patients. J Vasc Surg 2018;68:1455-1464.e1451.2018/10/27. https://doi.org/10.1016/j.jvs.2018.01.055.
20. Lombardo FL, Maggini M, De Bellis A, et al. Lower extremity amputations in persons with and without diabetes in Italy: 2001–2010. PLOS ONE 2014;9, e86405https://doi.org/10.1371/journal.pone.0086405.
21. Vamos EP, Bottle A, Edmonds ME, et al. Changes in the incidence of lower extremity amputations in individuals with and without diabetes in England between 2004 and 2008. Diabetes Care 2010;33:2592-7https://doi.org/10.2337/dc10-0989.
22. Moxey PW, Gogalniceanu P, Hinchliffe RJ, et al. Lower extremity amputations-a review of global variability in incidence. Diabet Med 2011;28:1144-53.2011/03/11. https://doi.org/10.1111/j.1464-5491.2011.03279.x.
23. Malmstedt J, Leander K, Wahlberg E, et al. Outcome after leg bypass surgery for critical limb ischemia is poor in patients with diabetes. Diabetes Care 2008;31:887-92.
24. Singh S, Armstrong E, Sherif W, et al. Association of elevated fasting glucose with lower patency and increased major adverse limb events among patients with diabetes undergoing infrapopliteal balloon angioplasty. Vasc Med 2014;19:307-14.
25. Londero L, Högh A, Houlind K, et al. Danish trends in major amputation after vascular reconstruction in patients with peripheral arterial disease 2002–14. Eur J Vasc Endovasc Surg 2019;57:111-20.
26. Takahara M, Kaneto H, Lida O, et al. The influence of glycemic control on the prognosis of Japanese patients undergoing percutaneous transluminal angioplasty for critical limb ischemia. Diabetes Care 2010;33:2538-42.
27. Malyar N, Freisinger E, Meyborg M, et al. Amputations and mortality in in-hospital treated patients with peripheral artery disease and diabetic foot syndrome. J Diabetes Complications 2016;30:1117-22https://doi.org/10.1016/j.jdiacomp.2016.03.033.
28. Ludvigsson JF, Emilsson L, Lindahl B, et al. Review of 103 Swedish healthcare quality registries. J Intern Med 2015;277:94-136https://doi.org/10.1111/joim.12303.
29. Venermo M, Lees T. International Vascunet validation of the Swedish registry. Eur J Vasc Endovasc Surg 2015;50:802-8https://doi.org/10.1016/j.ejvs.2015.07.021.
30. Djerf H, Hellman J, Baubeta Fridh E, et al. Low risk of procedure related major amputation following revascularisation for intermittent claudication: a population based study. Eur J Vasc Endovasc Surg 2019https://doi.org/10.1016/j.ejvs.2019.11.023. 2019/12/24.
31. Baubeta Fridh E, Andersson M, Thuresson M, et al. Amputation rates, mortality, and pre-operative comorbidities in patients revascularised for intermittent claudication or critical limb Ischaemia: a population based study. Eur J Vasc Endovasc Surg 2017;54:480-6https://doi.org/10.1016/j.ejvs.2017.07.005.
32. Baubeta Fridh E, Andersson M, Thuresson M, et al. Impact of preoperative symptoms and revascularized arterial segment in patients with chronic limb-threatening ischemia. Vasc Endovascular Surg 2019;53:365-72https://doi.org/10.1177/1538574419834765.
33. Lida O, Nakamura M, Yamauchi Y, et al. Endovascular treatment for infrainguinal vessels in patients with critical limb ischemia. OLIVE registry, a prospective, multicenter study in Japan with 12-month follow-up. Circ Cardiovasc Interv 2013;6:68-76.
34. Megallaa MH, Ismail AA, Zeitoun MH, et al. Association of diabetic foot ulcers with chronic vascular diabetic complications in patients with type 2 diabetes. Diabetes Metab Syndr Clin Res Rev 2019;13:1287-92https://doi.org/10.1016/j.dsx.2019.01.048.
35. Taylor R, Holman R. Normal weight individuals who develop type 2 diabetes: the personal fat threshold. Clin Sci 2015;128:405-10https://doi.org/10.1042/CS20140553.
36. Hinchliffe R, Forsythe R, Apelqvist J, et al. Guidelines on diagnosis, prognosis, and management of peripheral artery disease in patients with foot ulcers and diabetes (IWGDF 2019 update). Diabetes Metab Res Rev 2020;36, e3276https://doi.org/10.1002/dmrr.3276.
37. Soares MM, Boyko EJ, Ribeiro J, et al. Predictive factors for diabetic foot ulceration: a systematic review. Diabetes Metab Res Rev 2012;28:574-600https://doi.org/10.1002/dmrr.2319.

Paper III

Original Article

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Diabetes mellitus was not associated with lower amputation-free survival after open revascularization for chronic limb-threatening ischemia – A nationwide propensity score adjusted analysis

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Abstract

The risk of major amputation is higher after urgently planned endovascular therapy for chronic limb-threatening ischemia (CLTI) in patients with diabetes mellitus (DM). The aim of this nationwide cohort study was to compare outcomes between patients with and without DM following urgently planned open revascularization for CLTI from 2010 to 2014. Out of 1537 individuals registered in the Swedish Vascular Registry, 569 were registered in the National Diabetes Register. A propensity score adjusted Cox regression analysis was conducted to compare outcome between the groups with and without DM. Median follow-up was 4.3 years and 4.5 years for patients with and without DM, respectively. Patients with DM more often had foot ulcers ($p = 0.034$) and had undergone more previous amputations ($p = 0.001$) at baseline. No differences in mortality, cardiovascular death, major adverse cardiovascular events (MACE), or major amputation were observed between groups. The incidence rate of stroke was 70% higher (95% CI: 1.11–2.59; $p = 0.0137$) and the incidence rate of acute myocardial infarction (AMI) 39% higher (95% CI: 1.00–1.92; $p = 0.0472$) among patients with DM in comparison to those without. Open vascular surgery remains a first-line option for a substantial number of patients with CLTI, especially for limb salvage in patients with DM. The higher incidence rates of stroke and AMI among patients with DM following open vascular surgery for infrainguinal CLTI require specific consideration preoperatively with the aim of optimizing medical treatment to improve cardiovascular outcome postoperatively.

Keywords

amputation, bypass, chronic limb-threatening ischemia (CLTI), diabetes mellitus

Introduction

Chronic limb-threatening ischemia (CLTI) is the end-stage of peripheral artery disease (PAD) and should be viewed as a sign of systemic atherosclerosis with a high mortality in stroke and myocardial infarction.[1] The 1-year mortality rate in CLTI patients is predicted to be 22–26%.[2,3] Smoking and diabetes mellitus (DM) are the strongest risk factors for PAD,[4] with an expected increase of the DM incidence in the United States by 200% from 2005 to 2050.[5]

Individuals with both DM and PAD have a more distal distribution of the arterial disease, and tend to have more significant comorbidities.[6] In view of these factors, minimal invasive endovascular therapy for CLTI among patients with DM might induce less myocardial stress[7] compared to open surgery, and therefore be more beneficial to achieve higher amputation-free survival.

Indeed, endovascular therapy was associated with a lower risk of mortality in patients with type 2 diabetes compared to those without DM among patients with infrainguinal CLTI.[8] However, endovascular therapy was also associated with a higher risk of major amputation in patients

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treated with insulin only compared to those without DM.[8] In a recent nationwide propensity adjusted analysis, patients with DM undergoing endovascular therapy had lower amputation-free survival and a clearly higher risk of major amputation compared to those without DM.[9] Since the proportion of patients with DM and CLTI undergoing elective endovascular therapy is increasing compared to open vascular surgery,[10–12] it is of great importance to investigate whether or not the results after urgently planned open vascular surgery are also associated with similar inferior results in DM patients.

The main aim of this study was to evaluate the risk of major amputation and mortality after urgently planned open vascular surgery in patients with CLTI and infrainguinal arterial disease, comparing patients with DM and without DM in a nationwide propensity score adjusted analysis.

Methods

The present cohort study was based on prospectively collected data of all Swedish patients with CLTI undergoing urgently planned open vascular surgery for infrainguinal arterial disease between 2010 and 2014, in total 1537 patients. CLTI was defined as the presence of PAD along with rest pain, gangrene, or ulcers for $>$ 2 weeks.[1] Individuals without tissue loss (ulcer or gangrene) were regarded to have rest pain.

Databases and procedures

By using the personal identity number, unique to every Swedish citizen, information on individual patient data was obtained from nationwide population-based databases. Subjects were identified by cross-matching the Swedish Vascular Register (Swedvasc)[13] and the Swedish National Diabetes Register (NDR).[14] Duplicated patients were excluded.

Data were also retrieved from several national registries including the National Patient Register (NPR) and the Longitudinal Integration Database for Health Insurance and Labour Market Studies which was used for information of socioeconomic characteristics.[15,16] Country of birth and level of education was retrieved and stratified in to three groups – compulsory school, upper secondary school, and college or university – and marital status as married, separated, single, or widowed.

Information of time and cause of death were retrieved from the Swedish Cause of Death Register.[17] Information about comorbidities and drug treatment at baseline was retrieved from the Prescribed Drug Register (PDR)[18] and the cancer registry.[19] The NPR provides information on discharge diagnoses and length of hospital stay since 1987 with $>$ 99% coverage, with a positive predictive value of $>$ 99% for vascular interventions for lower limb ischemia.[15]

All patients undergoing vascular surgery in Sweden are registered in Swedvasc. Pre- and perioperative data regarding type of treatment (acute or elective, endovascular or open), risk factors, complications, and reinterventions are recorded. Patient follow-up is at 30 days and 12 months following the surgical procedure. Only the first open vascular procedure within the study period was analyzed, regardless of whether it was a repeat or first procedure. Repeated open vascular surgery in the ipsilateral or contralateral limb during the study period was not assessed.

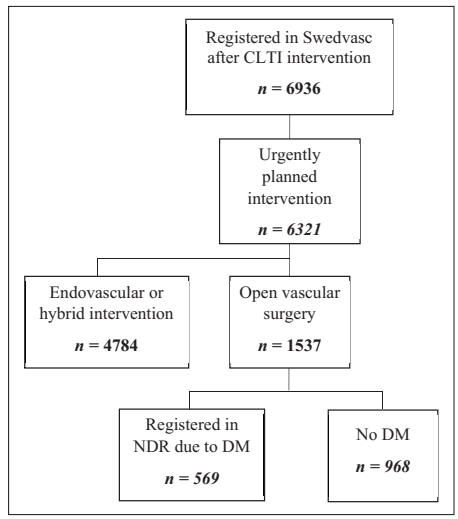

Figure 1. Flow chart of patients in the Swedish Vascular Register (Swedvasc) undergoing urgently planned open vascular surgery for CLTI during 2010 to 2014. Further division was done according to whether the patient was registered in NDR due to DM or not.
CLTI, chronic limb-threatening ischemia; DM, diabetes mellitus; NDR, National Diabetes Register.

The NDR was, in 2019, estimated to cover 88% of Swedish citizens over the age of 18 with DM.[20] It contains data on clinical characteristics, diabetes treatment, risk factors, and diabetic complications. Each individual gave consent to inclusion in the register. As Swedvasc provides only 1-year follow-up after vascular surgery, the Swedish NPR was used to gain further information on outcomes, comorbidities, and discharge diagnoses.

In this observational case–control study, patients registered in the Swedvasc infrainguinal module from 2010 to 2014 due to urgently planned open vascular surgery were identified. Patients with a corresponding registration in NDR between 2009 and 2015, thus having DM, were compared to those without such registration (not having DM) (Figure 1).

Baseline data

The NPR uses the *International Classification of Diseases, Tenth Revision* (ICD-10) for classification of diagnoses. Comorbidities at baseline included: atrial fibrillation or flutter, heart failure, coronary heart disease, hypertension, and stroke. Furthermore, renal disorder (kidney transplant, renal failure, or dialysis), cancer, liver disease, psychiatric disorders (excluding dementia), and chronic obstructive pulmonary disease were included. CLTI-related variables such as previous amputation, tissue loss, thromboendarterectomy, and previous bypass surgery were also included. The bypass variable was divided into two groups: vein bypass or synthetic bypass. Acute myocardial infarction (AMI) was defined as I21 (ICD-10). Renal impairment was

defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 with data from NDR on individuals with DM only.

Smoking was defined as current smoking at baseline and the information was retrieved from Swedvasc. When smoking data were missing in Swedvasc, NDR data were used to complement. Drug treatment was defined according to the PDR. Use of lipid-lowering drugs, acetylsalicylic acid (ASA), metformin and other glucose-lowering medications, and anticoagulant therapy was included. Hypertension was defined as collecting a minimum of one prescription of antihypertensive drugs 1 year prior to the index operation. Three months of medicine use is equivalent to one prescription. Use of ASA and lipid-lowering medication was defined similarly.

Amputation was defined as amputation above the ankle (e.g., major amputation). Since the NPR is a code-based register, information on amputation laterality was not always possible to determine. A recent validation of major amputation for CLTI has been performed by reviewing 1366 patients' medical records, showing < 10% missing data for amputation with remaining uncertainty of the laterality of the amputation.[21] MACE was defined as angina pectoris, acute myocardial infarction, ischemic heart disease, stroke and intracranial hemorrhage.

Follow-up

Follow-up started the date the patients were revascularized, defining the index date, and continued up to December 31, 2016 for endpoints using Swedvasc and until December 31, 2017 for mortality. This was enabled through linkage between NDR and the Cause of Death Register with causes and time of death.

Statistical analysis

Outcomes were compared after urgently planned open vascular surgery for CLTI between patients with and without DM by propensity score adjusted analysis. A propensity score technique to adjust for multiple risk factors[22,23] was used since multivariate adjustments by logistic regression is limited by the number of endpoints, and a limited number of covariates should be modelled.[24] The propensity scores were estimated using a generalized boosted multinomial regression model with an interaction depth of 3, a maximum of 75,000 trees, and a shrinkage of 0.01. The optimal number of trees was selected using a stopping rule applied to the degree of balance.

The distribution of propensity scores varies between infrainguinal CLTI patients with and without DM, requiring some form of adjustment for confounding. To avoid losing patients in a matching procedure inverse probability of treatment (here defined as having DM), weighting (IPTW) was chosen. It should be noted that baseline diabetes treatment was excluded from the estimation of the weights and therefore not adjusted for.

Descriptive statistics were presented using mean, SD, counts, and percentages according to variable type. The degree of similarity between infrainguinal CLTI patients with and without DM was described using the standardized mean difference (SMD) and *p*-values. Cumulative mortality and major amputation were described using Kaplan–Meier curves transformed to estimate the distribution function rather than the survival function.

The effects of diabetes duration, HbA1c, renal impairment, and tissue loss in the group with DM were evaluated by fitting a Cox proportional hazards model. The model included gender, age, diabetes duration, HbA1c, renal impairment, and tissue loss at baseline. Only patients with nonmissing values on gender, age, diabetes duration, HbA1c, renal impairment, and tissue loss were included in the analysis.

Sensitivity analysis of the inverse probability of treatment weighting adjusted analysis

The IPTW adjusted analysis was performed using all patients. Sensitivity analyses were performed by placing a threshold on the weight (e.g., maximum weight = 10) and by trimming the data set based on the value of the propensity score (e.g., keeping datapoints above the 2.5% and 1% percentile determined for the DM + CLTI group and below the 97.5% and 99% percentile determined for the CLTI group).

Results when truncating maximum weight at 10 were very similar to the main results, indicating that there is no large influence by larger weights on the analysis. Results when trimming data based on percentiles of the propensity scores were largely consistent with the main analysis.

The statistical analyses compared CLTI patients with DM to CLTI patients without DM using both an unadjusted and an IPTW adjusted Cox regression model. IPTW adjusted Cox regression analysis was expressed as hazard ratios (HR) with 95% CI. See the online supplementary material (Appendix 1) for a list of the adjusted variables. Analyses were performed using R 3.4.3 (http://cran.us.r-project.org/). A $p < 0.05$ was considered statistically significant.

Ethical approval

The study was approved by the regional research ethical committee in Lund, Sweden (2016/232 and 2016/544). As all patients had consented to being reported in NDR and Swedvasc, no individual consent was required to be included in this study according to Swedish law.

Results

Study population and demographic characteristics

Between 2010 and 2014, a total of 1537 individuals underwent urgently planned open vascular surgery for CLTI, of whom 569 had DM and were registered in Swedvasc (Figure 1). Median follow-up was 4.3 years (IQR 2.2–5.7) and 4.5 years (IQR 2.5–5.9) for patients with and without DM, respectively. Table 1 presents unadjusted baseline data along with clinical and demographic characteristics for the two groups. The majority of patients with DM (88.6%) were classified as type 2, 9.8% as type 1, and 1.6% as having other or unspecified types of DM. Among individuals with DM, 20.9% were not treated with any glucose-lowering agents.

Table 1. Baseline characteristics of patients with CLTI, with and without DM, undergoing urgently planned open vascular surgery.

	DM and CLTI	CLTI	*p*-value	SMD
	n = 569	*n* = 968		
Age, years, mean (SD)	73 (9.29)	76 (9.10)	< 0.001	0.307
Women, *n* (%)	217 (38.1)	512 (52.9)	< 0.001	0.300
Smoking, *n* (%)	113 (22.1)	238 (30.1)	0.002	0.182
Duration of DM, years (IQR)	14 (15.75)	–		
HbA1c, mmol/mol (IQR)	57 (18)	–		
Medication, *n* (%)				
Lipid-lowering	468 (82.2)	713 (73.7)	< 0.001	0.208
Metformin	228 (40.1)	–		
Glucose-lowering agents	450 (79.1)	–		
Acetylsalicylic acid	435 (76.4)	760 (78.5)	0.381	0.049
Clopidogrel	115 (20.2)	120 (12.4)	< 0.001	0.213
Anticoagulant therapy	242 (42.5)	334 (34.5)	0.002	0.166
Antihypertensive	546 (96.0)	814 (84.1)	< 0.001	0.404
ACE inhibitor	305 (53.6)	348 (36.0)	< 0.001	0.361
ARB	199 (35.0)	207 (21.4)	< 0.001	0.306
Alpha blocker	23 (4.0)	15 (1.5)	0.004	0.152
Beta blocker	365 (64.1)	496 (51.2)	< 0.001	0.264
Calcium channel blocker	258 (45.3)	345 (35.6)	< 0.001	0.199
Diuretic	330 (58.0)	468 (48.3)	< 0.001	0.194
Digoxin	38 (6.7)	38 (3.9)	0.023	0.123
Nitrate	134 (23.6)	176 (18.2)	0.014	0.132
Income, quartile (%)			0.037	0.156
1	107 (18.8)	243 (25.1)		
2	141 (24.8)	216 (22.3)		
3	155 (27.2)	256 (26.4)		
4	166 (29.2)	253 (26.1)		
Income * 100 SEK/year, mean (SD)	1,835.59 (2,939.04)	1,663.27 (1,213.73)	0.108	0.077
Education, *n* (%)			0.003	0.184
Compulsory school	310 (55.2)	460 (48.2)		
Upper secondary	203 (36.1)	363 (38.0)		
College or university	49 (8.7)	132 (13.8)		
Civil status, *n* (%)			0.007	0.186
Married	250 (43.9)	374 (38.6)		
Separated	135 (23.7)	203 (21.0)		
Single	56 (9.8)	96 (9.9)		
Widowed	128 (22.5)	295 (30.5)		
Origin, *n* (%)			0.193	0.094
Sweden	478 (84.0)	843 (87.1)		
Europe except Sweden	46 (8.1)	69 (7.1)		
Rest of the world	45 (7.9)	56 (5.8)		
Previous diseases, *n* (%)				
AMI	132 (23.2)	175 (18.1)	0.018	0.127
Coronary heart disease	282 (49.6)	337 (34.8)	< 0.001	0.302
Stroke	86 (15.1)	131 (13.5)	0.433	0.045
Atrial fibrillation	131 (23.0)	197 (20.4)	0.242	0.065
Heart failure	143 (25.1)	173 (17.9)	0.001	0.177
Renal disorder	74 (13.0)	67 (6.9)	< 0.001	0.204
Cancer disease	49 (8.6)	141 (14.6)	0.001	0.187
Liver disease	6 (1.1)	10 (1.0)	1.000	0.002
Psychiatric disorder	19 (3.3)	35 (3.6)	0.888	0.015
COPD	72 (12.7)	159 (16.4)	0.054	0.107
Renal impairment	123 (36.8)	–	–	
Amputation, minor and major	42 (7.4)	33 (3.4)	0.001	0.177
Tissue loss and surgical procedures, *n* (%)				
Tissue loss	316 (68.1)	518 (62.0)	0.034	0.128
Thromboendarterectomy	179 (31.5)	336 (34.7)	0.19	
Bypass, *n* (%)				
Synthetic or synthetic plus vein bypass	75 (13.2)	165 (17.0)	0.044	
Vein bypass	200 (35.1)	351 (36.3)	0.66	

Categorical variables are presented as number (%) and continuous variables are presented as mean (SD).
Anticoagulant therapy includes vitamin K-antagonists, heparin, low-molecular heparin, DOACs, fondaparinux. Renal impairment was defined as an eGFR <60 mL/min/1.73 m^2 with data from the Swedish National Diabetes Register. Renal disorder comprises kidney transplant, renal failure or dialysis. Glucose-lowering agents include insulin, oral hypoglycemic agents, and GLP-1 analogues.
ACE, angiotensin converting enzyme; AMI, acute myocardial infarction; ARB, angiotensin II receptor blocker;
CLTI, chronic limb-threatening ischemia; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; DOACs, direct oral anticoagulants; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; SMD, standardized mean difference.

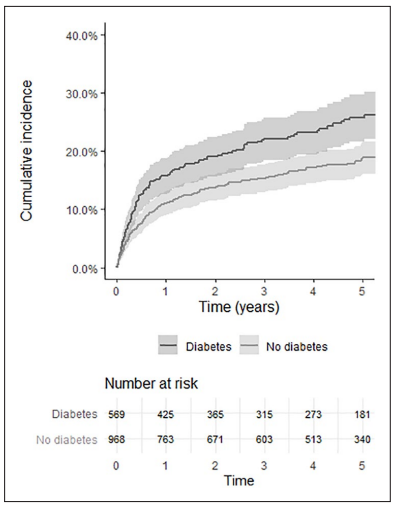

Figure 2. Crude Kaplan–Meier curves showing cumulative incidence of major amputation and total mortality after urgently planned open vascular surgery for CLTI among patients with and without DM.
Shaded areas represent standard errors.
CLTI, chronic limb-threatening ischemia; DM, diabetes mellitus.

Outcome analysis

The crude Kaplan–Meier curves for cumulative incidences of major amputation and mortality are displayed in Figure 2. The incidence rate of stroke was 70% higher (95% CI: 1.11–2.59; $p = 0.0137$) and the incidence rate of AMI 39% higher (95% CI: 1.00–1.92; $p = 0.0472$) among patients with DM compared to those without DM. There was no difference in mortality, cardiovascular death, major adverse cardiovascular events (MACE) or major amputation between patients with and without DM (Table 2).

Table 2. IPTW adjusted Cox regression analysis of hazard ratio for different endpoints for patients with DM compared to patients without DM after urgently planned open vascular surgery for CLTI.

Endpoint	Hazard ratio	*p*-value	95% CI
Mortality	1.10	0.2504	0.93–1.30
Cardiovascular mortality	1.09	0.4026	0.89–1.33
MACE	1.15	0.0904	0.98–1.34
AMI	1.39	0.0472	1.00–1.92
Stroke	1.70	0.0137	1.11–2.59
Major amputation	1.28	0.0701	0.98–1.66
Major amputation or death	1.15	0.0903	0.98–1.35

AMI, acute myocardial infarction; CLTI, chronic limb-threatening ischemia; DM, diabetes mellitus; IPTW, inverse probability treatment weighting; MACE, major adverse cardiovascular event.

Effect of diabetes duration, HbA1c, renal impairment, and tissue loss on outcome among patients with diabetes mellitus

Median diabetes duration was 14 years (IQR 7.25–23; $n = 354$), median HbA1c 57 mmol/mol (IQR 49–67; $n = 366$), and median eGFR was 70 mL/min/1.73 m^2 (IQR 54–91; $n = 334$). Tissue loss was associated with a higher risk of major amputation (HR 2.52, 95% CI: 1.26–5.05; $p = 0.009$) (Table 3). Renal impairment was associated with a higher risk of total mortality (HR 2.13, 95% CI: 1.47–3.08; $p < 0.001$), CV mortality (HR 1.93, 95% CI: 1.26–2.98; $p = 0.003$), and MACE (HR 1.74, 95% CI: 1.25–2.43; $p = 0.001$). Diabetes duration was associated with a higher risk of MACE (HR 1.01, 95% CI: 1.00–1.03; $p = 0.03$).

Discussion

The present study found a higher incidence rate of stroke and AMI among patients with DM after urgently planned open vascular surgery for infrainguinal CLTI compared to those without DM, whereas there was no difference in mortality, cardiovascular death, MACE or major amputation between patients with DM and without DM.

In the present nationwide study, no difference in major amputation rate following open vascular surgery was found in the group with DM compared to those without DM, despite a higher rate of previous minor and major amputation and tissue loss at baseline in patients with DM. Of note, most patients underwent infrainguinal bypass procedure with vein conduit[25] without differences between the two groups, which may have contributed to similar results in major amputation. This result differs from our previous study on patients endovascularly revascularized for CLTI, in which patients with DM and CLTI had a higher risk of major amputation.[9] After bypass surgery for CLTI on the other hand, two previous studies reported no difference in major amputation rate among patients with DM compared to those without DM, despite more advanced occlusive atherosclerotic lesions in DM resulting in a need of a lower level of the distal bypass anastomoses.[26,27] To be able to achieve equal results in patients with and without DM after bypass, however, it appears necessary to use the saphena magna vein as a bypass conduit, either as reversed bypass[27] or with an in situ technique,[26] and that the bypass is performed by a limited number of experienced vascular surgeons.[27] In a cohort in which approximately 40% had DM, the randomized controlled trial (RCT) BASIL-1 indicated a higher amputation-free survival at 2 years after bypass surgery compared to endovascular therapy for CLTI.[28] Furthermore, Darling et al. found lower reintervention and restenosis rates following open vascular surgery compared to endovascular therapy among individuals with insulin-dependent DM.[8] Even though the vascular surgical field in recent years has gone through a major change towards an increased use of endovascular procedures,[11] open vascular surgery is still the first-line option in a substantial number of patients with CLTI, especially for limb salvage in patients with DM.

In the present study, no difference in mortality was demonstrated, in contrast to data from Swedvasc 2001–2003 where an increased mortality was seen among patients with diabetes after bypass surgery for CLTI.[29] The results from 2001 to 2003 might partly be explained by a less aggressive use of statins and antiplatelet agents in the past.[30] The present study showed a higher cumulative incidence rate of stroke and AMI in the group with DM, whereas Swedish patients with CLTI and DM undergoing endovascular

Table 3. Effect of diabetes duration, HbA1c, tissue loss, and renal impairment on different endpoints among patients with DM undergoing urgently planned open vascular surgery for CLTI.

Outcome	Covariate	Hazard ratio	*p*-value	95% CI
Total mortality	Diabetes duration	1.00	0.695	0.98–1.01
	HbA1c	1.01	0.229	0.99–1.02
	Tissue loss	1.35	0.128	0.92–1.99
	Renal impairment	2.13	< 0.001	1.47–3.08
	Diabetes duration	1.00	0.818	0.98–1.02
CV mortality	HbA1c	1.00	0.812	0.99–1.02
	Tissue loss	1.46	0.118	0.91–2.36
	Renal impairment	1.93	0.003	1.26–2.98
MACE	Diabetes duration	1.01	0.030	1.00–1.03
	HbA1c	1.00	0.749	0.99–1.01
	Tissue loss	0.97	0.864	0.69–1.37
	Renal impairment	1.74	0.001	1.25–2.43
AMI	Diabetes duration	1.01	0.395	0.99–1.04
	HbA1c	0.98	0.103	0.95–1.00
	Tissue loss	1.05	0.899	0.52–2.10
	Renal impairment	1.66	0.164	0.81–3.37
Stroke	Diabetes duration	0.98	0.175	0.94–1.01
	HbA1c	0.99	0.597	0.97–1.02
	Tissue loss	1.08	0.829	0.52–2.25
	Renal impairment	1.42	0.339	0.69–2.93
Major amputation	Diabetes duration	1.01	0.512	0.99–1.03
	HbA1c	1.02	0.058	1.00–1.04
	Tissue loss	2.52	0.009	1.26–5.05
	Renal impairment	1.21	0.512	0.68–2.15

The effect of diabetes duration, HbA1c, tissue loss, and renal impairment was evaluated by fitting a Cox proportional hazards model. The model includes gender, age, diabetes duration, HbA1c, tissue loss, and renal impairment at baseline. Only patients with nonmissing values on gender, age, diabetes duration, HbA1c, tissue loss, and renal impairment were included.
Renal impairment was defined as an eGFR < 60 mL/min/1.73 m^2.
AMI, acute myocardial infarction; CLTI, chronic limb-threatening ischemia; CV mortality, cardiovascular mortality; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; MACE, major adverse cardiovascular event.

therapy had a higher cumulative incidence rate of AMI only.[9] It is well-known that DM patients have a twofold increased risk of atherothrombotic ischemic stroke compared to those without DM,[31] and it can be speculated that patients needing an open vascular procedure have a more advanced generalized atherosclerotic disease rendering them more susceptible for ischemic stroke. In line with the present study results, Wallaert et al. found a higher risk of major adverse composite events (myocardial infarction, dysrhythmia, congestive heart failure, wound infection, major amputation, and renal insufficiency) among patients with DM following lower extremity bypass surgery.[32] Beaulieu et al. studied the risk of postoperative myocardial infarction after major vascular surgery and found a high risk of AMI following peripheral bypass surgery, with approximately 49% having DM among those suffering from AMI postoperatively.[7] Two randomized controlled trials[33,34] have shown that low-dose rivaroxaban taken twice a day plus aspirin once a day reduced major adverse cardiovascular and limb events when compared with ASA alone; therefore, it is of great importance to consider that patients are treated with the best medical therapy not only after the procedure but perhaps at an earlier stage.

Renal impairment is a well-known risk factor for cardiovascular morbidity and mortality among patients with DM.[35] In accordance with previous studies, we found that renal impairment was related to a higher risk of MACE, cardiovascular mortality, and total mortality.

Study strengths and limitations

The major strengths of the present study are the relatively long follow-up time of over 4 years, and the use of two disease-specific nationwide data registries, Swedvasc and NDR, along with data from other nationwide registries. The propensity score adjusted analysis, adjusting for approximately 30 variables, helped in minimizing the risk of confounding. The fact that only patients undergoing urgently planned open vascular surgery for infrainguinal arterial disease with CLTI were included in this study helped to lessen the risk of treatment selection bias. Furthermore, it was possible to specify the severity of CLTI, rest pain only or tissue loss, and the type of surgery performed – vein or synthetic bypass or thromboendarterectomy.

Owing to the retrospective study design, there is a potential risk of misclassification, data collection errors, and missing data leading to residual confounding. Even though the study cohort is large, it cannot be excluded that the nonsignificant association between DM and major amputation might be attributed to a type II statistical error. However, the associations between DM and the composite endpoint major amputation/mortality and all-cause mortality were

weaker, which therefore favours the main interpretation of this study. Furthermore, no adjustment according to type of antidiabetic medication was done. Previous studies have shown a relation between insulin dependency and a higher risk of major amputation among patients with CLTI.[8] Therefore, separate analyses of insulin-treated and non-insulin-treated patients would have been interesting. It should also be noted that smoking status is more fully covered in the group with DM than in the group without DM; when data on smoking status was missing in Swedvasc, complementary data were extracted from NDR. Prior studies have indicated that almost 50% of data on smoking status is missing in Swedvasc.[36] The probably underreported level of current smoking in Swedvasc resulted nevertheless in a higher smoking rate for patients without DM compared to those with DM in the present study, which may have contributed to the comparably less unfavourable results for the DM group. Linkage of data from the prescribed drug register showed that DM and non-DM patients at baseline in the present study had rather good coverage of lipid-lowering agents and acetylsalicylic acid, but lipid-lowering therapy has improved further, as shown in the latest annual report from NDR and Swedvasc.[20,37] The results of the present study are valid for Sweden and cannot easily be generalized to other countries.

Owing to the retrospective nature of the study, information on amputation laterality could not be retrieved. Baubeta Fridh et al. have previously reviewed the medical records of 1366 patients having major amputation due to CLTI, showing $< 10\%$ missing data for amputation with remaining uncertainty of the laterality of the amputation.[21] Swedvasc has not yet been validated for procedures related to PAD, but Djerf et al. found that almost half of patients registered in Swedvasc due to major amputation following intermittent claudication in fact had CLTI.[38] Therefore, the risk of misclassification of CLTI as intermittent claudication was probably low in the present study. It cannot be ruled out, however, that some patients were reclassified as having CLTI if the surgery for intermittent claudication failed.

Conclusion

Open vascular surgery is still a first-line option in a substantial number of patients with CLTI, especially for limb salvage in patients with DM. The higher incidence rates of stroke and AMI among patients with DM following open vascular surgery for infrainguinal CLTI compared to in those without DM require specific consideration preoperatively with the aim of optimizing medical treatment in order to improve cardiovascular outcome postoperatively.

Declaration of conflicting interests

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Supplementary material

The supplementary material is available online with the article.

References

1. Conte MS, Bradbury AW, Kolh P, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. *Eur J Vasc Endovasc Surg* 2019; 58: S1–S109.
2. Abu Dabrh AM, Steffen MW, Undavalli C, et al. The natural history of untreated severe or critical limb ischemia. *J Vasc Surg* 2015; 62: 1642–1651.e3.
3. Wolfe JH, Wyatt MG. Critical and subcritical ischaemia. *Eur J Vasc Endovasc Surg* 1997; 13: 578–582.
4. American Diabetes Association. Peripheral arterial disease in people with diabetes. *Diabetes Care* 2003; 26: 3333–3341.
5. Narayan KM, Boyle JP, Geiss LS, et al. Impact of recent increase in incidence on future diabetes burden: U.S., 2005–2050. *Diabetes Care* 2006; 29: 2114–2116.
6. Jude EB, Oyibo SO, Chalmers N, et al. Peripheral arterial disease in diabetic and nondiabetic patients: A comparison of severity and outcome. *Diabetes Care* 2001; 24: 1433–1437.
7. Beaulieu RJ, Sutzko DC, Albright J, et al. Association of high mortality with postoperative myocardial infarction after major vascular surgery despite use of evidence-based therapies. *JAMA Surg* 2020; 155: 131–137.
8. Darling JD, Bodewes TCF, Deery SE, et al. Outcomes after first-time lower extremity revascularization for chronic limb-threatening ischemia between patients with and without diabetes. *J Vasc Surg* 2018; 67: 1159–1169.
9. Lilja E, Gottsäter A, Miftaraj M, et al. The impact of diabetes mellitus on major amputation among patients with chronic limb threatening ischemia undergoing elective endovascular therapy – A nationwide propensity score adjusted analysis. *J Diabetes Complications* 2021; 35: 107675.
10. Liang P, Soden PA, Zettervall SL, et al. Treatment outcomes in diabetic patients with chronic limb-threatening ischemia. *J Vasc Surg* 2018; 68: 487–494.
11. Butt T, Lilja E, Örneholm H, et al. 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.
12. Butt T, Lilja E, Elgzyri T, et al. 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; 6: 107551.
13. Troëng T, Malmstedt J, Björck M. External validation of the Swedvasc registry: A first-time individual cross-matching with the unique personal identity number. *Eur J Vasc Endovasc Surg* 2008; 36: 705–712.
14. Eliasson B, Gudbjörnsdottir S. Diabetes care – improvement through measurement. *Diabetes Res Clin Pract* 2014; 106: S291–S294.

15. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish National Inpatient Register. *BMC Public Health* 2011; 11: 450.
16. Olén O, Bihagen E, Rasmussen F, et al. Socioeconomic position and education in patients with coeliac disease. *Dig Liver Dis* 2012; 44: 471–476.
17. Brooke HL, Talbäck M, Hörnblad J, et al. The Swedish cause of death register. *Eur J Epidemiol* 2017; 32: 765–773.
18. Wettermark B, Hammar N, Fored CM, et al. The new Swedish Prescribed Drug Register – Opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf* 2007; 16: 726–735.
19. Socialstyrelsen. The Swedish Cancer Register, https://www.socialstyrelsen.se/en/statistics-and-data/registers/register-information/swedish-cancer-register/ (2019, accessed 21 December 2020).
20. Nationella Diabetesregistret. Årsrapport, https://www.ndr.nu/#/arsrapport (2019, accessed 21 December 2020).
21. Baubeta Fridh E, Andersson M, Thuresson M, et al. Editor's choice – Impact of comorbidity, medication, and gender on amputation rate following revascularisation for chronic limb threatening ischaemia. *Eur J Vasc Endovasc Surg* 2018; 56: 681–688.
22. Cepeda MS, Boston R, Farrar JT, et al. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. *Am J Epidemiol* 2003; 158: 280–287.
23. Martens EP, de Boer A, Pestman WR, et al. Comparing treatment effects after adjustment with multivariable Cox proportional hazards regression and propensity score methods. *Pharmacoepidemiol Drug Saf* 2008; 17: 1–8.
24. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and cox regression. *Am J Epidemiol* 2007; 165: 710–718.
25. Arvela E, Venermo M, Söderström M, et al. Outcome of infrainguinal single-segment great saphenous great saphenous vein bypass for critical limb ischemia is superior to alternative autologous vein bypass, especially in patients with high operative risk. *Ann Vasc Surg* 2012; 26: 396–403.
26. Fransson T, Thörne J. In situ saphenous vein bypass grafting – still first line treatment? A prospective study comparing surgical results between diabetic and non-diabetic populations. *Vasa* 2010; 39: 59–65.
27. Ballotta E, Toniato A, Piatto G, et al. Lower extremity arterial reconstruction for critical limb ischemia in diabetes. *J Vasc Surg* 2014; 59: 708–719.
28. Adam DJ, Beard JD, Cleveland T, et al. BASIL trial participants. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): Multicentre, randomised controlled trial. *Lancet* 2005; 366: 1925–1934.
29. Malmstedt J, Leander K, Wahlberg E, et al. Outcome after leg bypass surgery for critical limb ischemia is poor in patients with diabetes. *Diabetes Care* 2008; 31: 887–892.
30. Høgh A, Lindholt JS, Nielsen H, et al. Secondary medical prevention after primary vascular surgery between 1996 and 2006: A shift towards more evidence-based treatment. *Eur J Prev Cardiol* 2013; 20: 763–770.
31. Chen R, Ovbiagele B, Feng W. Diabetes and stroke: Epidemiology, pathophysiology, pharmaceuticals and outcomes. *Am J Med Sci* 2016; 351: 380–386.
32. Wallaert JB, Nolan BW, Adams J, et al. The impact of diabetes on postoperative outcomes following lower-extremity bypass surgery. *J Vasc Surg* 2012; 56: 1317–1323.
33. Anand SS, Bosch J, Eikelboom JW, et al; COMPASS Investigators. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: An international, randomised, double-blind, placebo-controlled trial. *Lancet* 2018; 391: 219–229.
34. Bonaca MP, Bauersachs RM, Anand SS, et al. Rivaroxaban in peripheral artery disease after revascularization. *N Engl J Med* 2020; 382: 1994–2004.
35. Afkarian M, Sachs MC, Kestenbaum B, et al. Kidney disease and increased mortality risk in type 2 diabetes. *J Am Soc Nephrol* 2013; 24: 302–308.
36. Baubeta Fridh E, Andersson M, Thuresson M, et al. Amputation rates, mortality, and pre-operative comorbidities in patients revascularised for intermittent claudication or critical limb ischaemia: A population based study. *Eur J Vasc Endovasc Surg* 2017; 54: 480–486.
37. Vascular Registry in Sweden. Årsrapport, https://www.ucr.uu.se/swedvasc/arsrapporter (2020, accessed 4 March 2021).
38. Djerf H, Hellman J, Baubeta Fridh E, et al. Low risk of procedure related major amputation following revascularisation for intermittent claudication: A population based study. *Eur J Vasc Endovasc Surg* 2020; 59: 817–822.

Appendix 1. List of baseline variables adjusted for in the inverse probability of treatment weighting (IPTW) adjusted Cox regression.

- Age
- Sex
- Smoking
- Lipid lowering treatment
- Antihypertensive treatment
- ASA
- Clopidogrel
- Other anticoagulant therapy
- ACE
- ARB
- Alpha blocker
- Beta blocker
- Calcium channel blocker
- Diuretic
- Digoxin
- Nitrate
- Disposable income
- Education
- Civil status
- Country of origin
- AMI
- CHD
- Stroke
- AF
- HF
- Renal impairment
- Renal disease
- Cancer disease
- Liver disease
- Psychiatric disorder
- COPD
- Previous amputation
- Tissue loss
- TEA
- Vein bypass
- Synthetic or synthetic plus vein bypass

Paper IV

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Amputation-Free Survival in Patients With Diabetes Mellitus and Peripheral Arterial Disease With Heel Ulcer: Open Versus Endovascular Surgery

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Abstract

Background: Heel ulcers in patients with diabetes mellitus (DM) and peripheral arterial disease (PAD) are hard to heal. The aim of the present study was to evaluate the difference in amputation-free survival (AFS) between open and endovascular revascularization in patients with DM, PAD, and heel ulcers. **Methods:** Retrospective comparative study of results of open versus endovascular surgery in patients with DM, PAD, and heel ulcer presented at the multidisciplinary diabetes foot clinic between 1983 and 2013. **Results:** Patients with heel ulcers were treated with endovascular intervention (n = 97) and open vascular surgery (n = 30). Kaplan-Meier analysis showed that the AFS was higher in patients undergoing open vascular surgery compared to the endovascular group ($P = .009$). Multivariate analysis showed that open vascular surgery versus endovascular therapy (hazard ratio 2.1, 95% confidence interval 1.1-3.9; $P = .025$) was an independent factor associated with higher AFS. The proportion of patients undergoing endovascular therapy in the former (1983-2000) time period was 47% compared to 89% in the latter (2001-2013) time period ($P < .001$). **Conclusion:** The AFS was higher after open than endovascular surgery among patients with DM and PAD with heel ulcer. These results suggest that open vascular surgery should be offered more often as opposed to current practice.

Keywords

diabetes mellitus, heel ulcer, peripheral arterial disease, endovascular surgery, open vascular surgery, amputation-free survival

Introduction

In 2016, a total of 410 000 Swedish individuals had been diagnosed with DM, of who 90% had type 2 diabetes mellitus (DM).[1] In 2015, 30.3 million Americans (9.4% of the US population) were estimated to have DM, of who 23.8% were unaware of their diagnosis. Diabetic foot ulceration (DFU) is the single most common cause for hospitalization in diabetic patients,[2] and in 2014, 108 000 Americans with DM were admitted to hospital for lower extremity amputation.[3] Diabetic heel ulcer is a well-known, hard-to-heal ulcer and is considered a major risk factor for lower extremity amputation.[4] Peripheral arterial disease (PAD) among patients with DM is affecting more distal calf arteries and causes longer arterial occlusions than PAD among nondiabetic patients.[2,5] Presence of foot ischemia, peripheral neuropathy with external trauma, and foot deformities will further increase the risk of amputation,[6] and it is therefore highly likely that a patient with a diabetic heel ulcer with ischemia will have a great benefit from revascularization, especially if together with adequate infection control.

A recent report showed that among patients with heel ulcer treated at the multidisciplinary foot clinic at Skåne University Hospital during the period 1983 to 2000, the proportion of wounds that healed after major debridement was higher, and the proportion of deceased unhealed ulcer was lower compared to during the latter time period from 2001 to 2013.[7] The potential importance of the type of vascular surgery, open or endovascular, for these figures was however not studied. These findings might be interpreted as suggesting that the prognosis

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of invasive vascular treatment has deteriorated over the past years, perhaps because of a change toward a minimal invasive endovascular first strategy instead of open first surgery. In the absence of randomized controlled trials between open and endovascular therapy in patients with DM and critical limb ischemia (CLI),[8] comparative scientific studies of treatment modality for leg salvage are important to guide clinicians in the era of endovascular therapy. These patients need a durable operation resulting in a healed ulcer, decreased need for repeat hospitalizations, and reduced health-care costs.

The study hypothesis was that better results are achieved with open vascular surgery than with endovascular therapy. The main aim of the present study was to evaluate difference in amputation-free survival (AFS) in open versus endovascular revascularization in patients with DM, PAD, and heel ulcers.

Methods

This retrospective study was approved by the regional ethical review board in Lund (Dnr 2007/120). From January 1, 1983, to December 31, 2013, a total of 4273 patients with DM presented with a foot ulcer at the multidisciplinary Diabetes Foot Clinic at Skåne University Hospital, a tertiary referral center. According to a predefined protocol, data were retrieved from the local databases and patient records at the Departments of Endocrinology, Orthopedics and Vascular Surgery. Results of open and endovascular surgery were compared regarding major amputation, death, and AFS at 1 and 3 years in patients with DM and PAD with a heel ulcer. Patients were followed from the date of inclusion to death or to end of follow-up (March 20, 2018). Median follow-up time was 40 (interquartile range [IQR] 14-90) months. If a patient had bilateral heel ulcers, both ulcers were included in the study. Patients with multiple ulcers were not included. During this time period, 127 limbs with a heel ulcer had been treated with vascular surgery, 97 with endovascular therapy, and 30 with open vascular surgery and were thus included in the study (Figure 1).

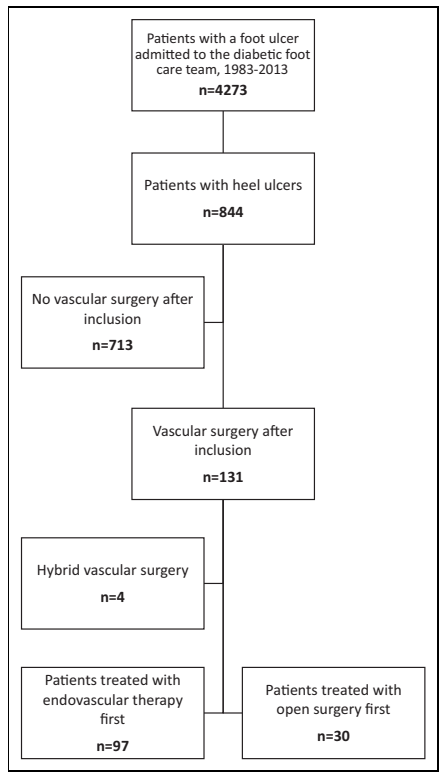

Figure 1. Flowchart of included and excluded patients.

Setting

The Diabetes Foot Clinic is located at a University Hospital with a primary care catchment area of approximately 700 000 people in 2013. From the year 2000, the center is located in 2 geographic locations and is the only provider of specialized diabetic foot care in the region. The clinic features a multidisciplinary approach based on regular podiatric care and ulcer dressing, both inpatient and outpatient visits, individually adjusted footwear, and rounds with specialists in endocrinology, vascular surgery, and orthopedic surgery. Diagnostic angiography was a common procedure in the 1980s and 1990s, prior to intervention, whereas duplex and magnetic resonance (MR) imaging replaced diagnostic angiographies in the latter time period of the study. Vascular Centre, Malmö, has since the year 2000 been an endovascular first-strategy center in patients with DM, PAD, and foot ulcer, despite adequate vein conduits and otherwise good candidates for open bypass surgery. Both interventional radiologists and vascular surgeons performed the endovascular interventions. Patients were treated by the team and followed up until final outcome.

Off-Loading

Upon arrival at the foot clinic with an ulcer located on the heel, the patients were immediately prescribed total pressure relief, both prescribed for walking, sitting, and bedridden patients. Type of off-loading was adapted to the patients' individual need and medical condition and was modified as required during the course of treatment.

Definitions

Severe peripheral vascular disease (SPVD) was defined as toe pressure <45 mm Hg or ankle pressure <80 mm Hg.[7] Major amputation was defined as amputation above the ankle. If the patient had any specialized assistance (not a family member) in his or her home, it was defined as having home care. Wound healing time was the time from admission at the foot clinic to

Table 1. General Characteristics in Patients With Diabetes Mellitus Undergoing Revascularization for Critical Limb Ischemia With a Heel Ulcer.[a]

Factors	All Limbs, N = 127	Endovascular Intervention First, n = 97	Open Vascular Surgery First, n = 30	*P* Value
Median age (IQR)	71 (60-79)	72 (60-80)	68 (62-79)	.62
Women (%)	53 (41.7)	38 (39.2)	15 (50.0)	.29
Living independently (%)	111/126 (88.1)	85 (87.6)	26/29 (89.7)	.77
Home aid (%)	42/126 (33.3)	31 (32.0)	11/29 (37.9)	.55
Good concordance (%)	111/126 (88.1)	84 (86.6)	27/29 (93.1)	.34
Current smoker (%)	31/126 (24.6)	23/96 (24.0)	8 (26.7)	.76
Hypertension (%)	97 (76.4)	76 (78.4)	21 (70.0)	.35
Congestive heart failure (%)	51/97 (52.7)	38/72 (52.8)	11 (36.7)	.40
Ischemic heart disease (%)	68 (53.5)	51 (52.6)	17 (56.7)	.70
Non-ischemic heart disease (%)	44 (34.6)	34 (35.1)	10 (33.3)	.86
Stroke (%)	31 (24.4)	25 (25.8)	6 (20.0)	.52
Anemia (%)	51/97 (52.7)	38/72 (52.8)	13/25 (48.1)	.95

Abbreviation: IQR, interquartile range.
[a]N = Limbs.

healed heel ulcer, expressed in weeks. Duration of DM was determined as the year from diagnosis until the presentation of a foot ulcer at the foot clinic. Up until 1997, the *International Classification of Diseases* coding system did not allow separation between DM type 1 and 2. Patients in this study diagnosed with DM before the age of 31 years and treated with insulin were considered as having DM type 1, whereas patients younger than 31 years of age without insulin treatment were considered to have DM type 2.[9] Treatment of DM was based on whether or not the patient had insulin treatment. Patients who were current smokers or had quit smoking less than a year ago were defined as current smokers. Having a blood pressure over 140/90 mm Hg or treatment with antihypertensive drugs was defined as hypertension. Anemia was defined as hemoglobin <134 g/L in men and hemoglobin <117 g/L in women. Being able to participate in 50% or more of the appointments at the multidisciplinary foot clinic was considered good concordance with treatment. Glomerular filtration rate was calculated with a simplified variant of the modification of diet in renal disease study group.[10] Ischemic heart disease was defined as previous myocardial infarction or angina pectoris and nonischemic heart disease as other heart disease such as atrial fibrillation or valvular disease. Having a urine albumin >300 mg/L was defined as nephropathy, and end-stage renal disease (ESRD) was defined as either having uremia (creatinine >300 μmol/L), past renal transplantation, or dialysis. Retinopathy was defined as preproliferative or proliferative based on retinal photographs scored by an ophthalmologist. Foot ulcers were graded according to the Wagner classification system (Supplementary Appendix; Table 1).

Statistics

Continuous variables were expressed as median and IQR. Differences in proportions were analyzed with Pearson χ^2 or Kendall tau-b test, and differences in continuous variables with Mann-Whitney *U* test. Correlation was tested with Spearman test and expressed with a correlation coefficient (*r*). Amputation-free survival was analyzed according to the Kaplan Meier method with life tables, and differences between endovascular and open vascular surgery were analyzed with the log-rank test. Variables differing ($P < 0.1$) between endovascular and open vascular surgery groups were further entered as covariates in a Cox multivariate regression analysis for evaluation of AFS, where differences were expressed in hazard ratios (HR) with 95% confidence intervals (CI). $P < .05$ was considered significant. Statistical analyses were performed using IBM SPSS Statistics 24.0 (SPSS, Chicago, Illinois).

Results

Baseline and Outcome in Patients With DM Having Heel Ulcer Undergoing Vascular Reconstruction Compared to those Not Operated

Patients undergoing reconstruction were more often current smokers ($P = .015$), more often had ischemic heart disease ($P = .002$), and SPVD ($P < .001$) compared to the group not undergoing vascular surgery. Major amputation rate at 2 years was higher ($P < .001$), and AFS at 2 years lower ($P = .004$) in patients undergoing vascular reconstruction compared to those not operated (Supplementary Appendix; Table 2).

Characteristics of Patients Undergoing Vascular Reconstruction

Four patients undergoing hybrid (both open and endovascular) vascular surgery were excluded from further study. A total of 121 patients with DM undergoing revascularization with a heel ulcer were included in the study. Their median age was 71 years (IQR 60-79), and 41.7% (n = 127) were women. Ninety-seven limbs were treated with endovascular first strategy and 30 limbs with open vascular first strategy, and no differences in general characteristics existed between these 2 groups (Table 1).

Table 2. Diabetes-Related Characteristics in Patients With Diabetes Mellitus Undergoing Revascularization for Critical Limb Ischemia With a Heel Ulcer.

Factors	All limbs, N = 127	Endovascular Intervention First, n = 97	Open Vascular Surgery First, n = 30	*P* Value
Median GFR (IQR), mL/min/1.73m^2	62.5 (44.2-92-8), n = 96	63.5 (41.5-92.8), n = 72	60 (45.2-94.0), n = 24	.92
End-stage renal disease (%)	18/126 (14.3)	15/96 (15.6)	3 (10.0)	.44
Nephropathy (%)	52 (40.9)	39 (40.2)	13 (43.3)	.76
Retinopathy (%)	56/103 (54.4)	46/76 (60.5)	10/27 (37.0)	.035
Median HbA_{1C} at hospital admission, % (IQR)	7.4 (6.4-8.6), n = 101	7.3 (6.4-8.6)	7.5 (6.2-9.2), n = 28	.63
Median duration of diabetes, years(IQR)	20 (12-26.2), n = 110	20 (13.0-28.0)	15.0 (10.0-25.0), n = 27	.075
Diabetes mellitus type 2 (%)	89/108 (82.4)	65/81 (80.2)	24/27 (88.8)	.31
Diabetes treatment with insulin (%)	85 (66.9)	70 (72.2)	15 (50.0)	.024
Previous amputation (%)	20 (15.7)	18 (18.6)	2 (6.7)	.12

Abbreviations: IQR, interquartile range; GFR, glomerular filtration rate.

Table 3. Ulcer-Related Characteristics in Patients With Diabetes Mellitus Undergoing Revascularization for Critical Limb Ischemia With a Heel Ulcer.

Factors	All limbs, N = 127	Endovascular Intervention First, n = 97	Open Vascular Surgery First, n = 30	*P* Value
Previous ulcer (%)	56 (44.1)	51 (52.6)	5 (16.7)	.001
Ulcer duration at inclusion, weeks	4 (2-12), n = 103	4 (2-13.5), n = 76	4 (2-9), n = 27	.72
Foot oedema (%)	54/125 (43.2)	35/96 (36.5)	19/29 (65.5)	.006
Local foot pain (%)	51/126 (40.5)	34/96 (35.4)	17 (56.7)	.038
Median Wagner grade at inclusion (IQR)				.36
1 (Superficial ulcer)	108 (85.0)	84 (86.6)	24 (80.0)	
2 (Deep ulcer)	8 (6.3)	7 (7.2)	1 (3.3)	
3 (Abscess and/or osteomyelitis)	7 (5.5)	4 (4.1)	3 (10.0)	
4 (Gangrene of portion of the foot)	0 (0.0)	0 (0.0)	0 (0.0)	
5 (Gangrene of greater part of the foot)	4 (3.1)	2 (2.1)	2 (6.7)	

Abbreviation: IQR, interquartile range.

Characteristics Related to Diabetes Mellitus

Patients undergoing endovascular therapy more often had diabetic retinopathy ($P = .035$) and insulin treatment ($P = .024$) compared to those treated with open surgery (Table 2).

Ulcer-related Characteristics

Previous ulcer was more common among patients treated with endovascular methods ($P = .001$) compared to those treated with open surgery, whereas patients treated with open vascular surgery more often had foot edema ($P = .006$) and local foot pain ($P = .038$) compared to the endovascularly treated group (Table 3).

Vascular-Related Characteristics

Previous vascular surgical procedures were more common in patients undergoing open vascular surgery ($P = .023$) compared to the endovascularly treated group. Duplex ($P = .014$) and MR angiography ($P < .001$) had more often been undertaken prior to the intervention in patients undergoing endovascular surgery compared to those treated with open vascular surgery (Table 4).

Revascularization

The following 30 procedures were performed in the open vascular surgery group: Femorodistal in situ vein bypass (n = 9), femoropopliteal below-knee in situ vein bypass (n = 7), femoropedal in situ vein bypass (n = 3), femoropedal reversed vein bypass (n = 1), femorodistal hybrid vein + synthetic bypass (n = 1), femoropopliteal below-knee biologic bypass (n = 1), aortobi-iliacal synthetic bypass (n = 2), aortobifemoral synthetic bypass (n = 2), and thrombendarterectomy common femoral artery with synthetic patch reconstruction (n = 4). Infrainguinal femoropopliteal below-knee or more distal bypass was performed in 73% of the procedures. Among patients undergoing open vascular surgery, 20 (67%) and 10 (33%) underwent reconstruction with vein and synthetic material, respectively. The following 97 endovascular procedures were performed categorized into anatomic level, multilevel interventions, multiple crural artery interventions, subintimal recanalizations, percutaneous transluminal angioplasty (PTA), or stenting: stent iliaca (n = 8), stent superficial femoral artery (SFA; n = 8), stent popliteal artery (n = 1), stent SFA + popliteal artery (n = 1), PTA SFA (n = 10), PTA popliteal artery (n = 5), PTA one crural artery (n = 8), PTA two crural

Table 4. Vascular-Related Characteristics in Patients With Diabetes Mellitus Undergoing Revascularization for Critical Limb Ischemia With a Heel Ulcer.

Factors	All limbs, N = 127	Endovascular Intervention First, n = 97	Open Vascular Surgery First, n = 30	*P* Value
Previous vascular surgery (%)	21 (16.5)	12 (12.4)	9 (30.0)	.023
Median toe pressure at admission, mm Hg (IQR)	35 (25-48.8), n = 96	35 (23-49), n = 74	34 (25-48), n = 22	.93
Ankle pressure at admission, mm Hg (IQR)	65 (50-98), n = 86	65 (53-101), n = 62	65 (38-86), n = 24	.18
Severe peripheral vascular disease (%)	82/104 (78.8)	61/78 (78.2)	21/26 (80.8)	.78
Duplex (%)	74/125 (59.2)	62/95 (65.3)	12 (40.0)	.014
CT angiography (%)	8 (6.3)	6 (6.2)	2 (6.7)	.92
MR angiography (%)	49 (38.6)	47 (48.5)	2 (6.7)	<.001
Angiography (%)	94 (74.0)	68 (70.1)	26 (86.7)	.071

Abbreviations: CT, computed tomography; IQR, interquartile range; MR, magnetic resonance.

Table 5. Outcome in Patients With Diabetes Mellitus Undergoing Revascularization for Critical Limb Ischemia with a Heel Ulcer.

Factors	All limbs, N = 127	Endovascular Intervention First, n = 97	Open Vascular Surgery First, n = 30	*P* Value
Reintervention, any (%)	34/127 (26.8)	20/97 (20.6)	14/30 (46.7)	.005
Secondary endovascular intervention (%)	21/127 (16.5)	12/97 (12.4)	9/30 (0.3)	
Secondary open vascular surgery (%)	13/127 (10.2)	8/97 (8.2)	5/30 (16.7)	
Healed heel ulcer (%)	80/126 (63.5)	58 (59.8)	22/29 (75.9)	.12
Died unhealed (%)	22/126 (17.5)	20 (20.6)	2/29 (6.9)	.088
Major amputation 30 days (%)	11/127 (8.7)	9 (9.3)	2/30 (6.7)	.66
Major amputation 1 year (%)	27 (21.3)	22 (22.7)	5/30 (16.7)	.48
Major amputation 3 years (%)	30 (23.6)	25 (25.8)	5/30 (16.7)	.30
Mortality 30 days (%)	5 (3.9)	4 (4.1)	1 (3.3)	1.0
Mortality 1 year (%)	30 (23.6)	24 (24.7)	6 (20.0)	.59
Mortality 3 years (%)	59 (46.5)	46 (47.4)	13 (43.3)	.70
Major amputation or death, 30 days (%)	16 (12.6)	12 (12.4)	3 (10.0)	.72
Major amputation or death, 1 year (%)	49 (38.6)	39 (40.2)	9 (30.0)	.31
Major amputation or death, 3 years (%)	74 (58.6)	59 (60.8)	14 (46.7)	.17
Major amputation or death, 5 years (%)	89/125 (71.2)	73/96 (76.0)	16/29 (55.2)	.030

arteries (n = 8), PTA three crural arteries (n = 3), PTA SFA + crural artery (n = 8), PTA SFA + popliteal + crural artery (n = 4), Subintimal recanalization of SFA (n = 7), subintimal recanalization from SFA to popliteal artery (n = 6), subintimal recanalization of popliteal artery (n = 1), subintimal recanalization of crural artery (n = 12), subintimal recanalization from SFA to crural artery (n = 1), mixed endovascular interventions in 2 anatomic levels (n = 5), and mixed endovascular interventions in 3 anatomic levels (n = 1). Multilevel interventions were performed in 26 (27%), crural interventions in 56 (58%), and subintimal recanalizations in 27 (28%). Reintervention rate was higher among patients undergoing open vascular surgery first ($P = .005$) compared to the endovascular group (Table 5). Patients undergoing open vascular surgery could be followed for a median of 52 months and the endovascularly treated group for a median of 38 months ($P = .27$). Unhealed heel ulcer was correlated to major amputation at 3 years ($r = .51$; $P < .001$).

Short-Term Outcomes According to Time Period of Inclusion

There was an increase in the proportion of patients undergoing endovascular therapy in relation to open vascular surgery in the latter (2001-2013) compared to the former (1983-2000) time period ($P<0.001$). Short-term outcomes in both time periods are shown in Supplementary Appendix Table 3.

Amputation-Free Survival

Amputation-free survival was higher in patients undergoing open vascular surgery compared to the endovascularly treated group ($P = .009$; Figure 2). Open vascular surgery in contrast to endovascular therapy (HR 2.1, 95% CI 1.1-3.9; $P = .025$) and previous vascular surgery (HR 2.0, 95% CI 1.0-3.7; $P = .044$) were independent factors associated with a higher AFS (Table 6).

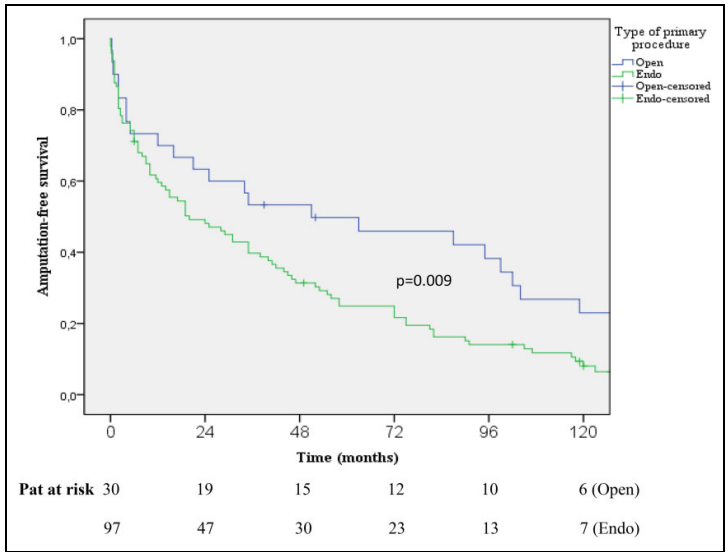

Figure 2. Kaplan-Meier curve showing amputation-free survival (months) after *open* and *endovascular surgery* in patients with diabetes mellitus with a heel ulcer.

Table 6. Multivariate Cox Regression Analysis.[a]

	P Value	Hazard Ratio	95% CI for Hazard Ratio	
			Lower	Upper
Type of procedure primary (open surgery versus endovascular)	.025	2.06	1.10	3.86
Retinopathy	.36	1.24	0.78	1.96
Diabetes treatment (insulin versus no insulin)	.70	1.10	0.67	1.80
Previous ulcer	.55	1.15	0.72	1.83
Edema	0.66	0.90	0.58	1.42
Pain	.87	1.04	0.65	1.66
Previous vascular surgery	.044	1.95	1.02	3.74

Abbreviation: CI, confidence interval.
[a]Factors associated with amputation-free survival in patients with diabetes mellitus undergoing revascularization for critical limb ischemia with a heel ulcer.

Discussion

The present study data suggest that open vascular surgery in patients with DM, PAD, and heel ulcers is a more durable option than endovascular therapy in order to improve AFS. This is a retrospective comparison, however, highlighting the need for randomized controlled studies on these patients. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL)-2 study currently open for recruitment[8] is based on the BASIL-1 study in which open vascular surgery was shown, in the long term, to be superior to endovascular therapy in terms of AFS.[11] However, since the termination of BASIL-1 in 2004, the endovascular management, expertise, equipment and tools, and medical therapy has progressed substantially, which calls upon a contemporary randomized trial comparing open vascular surgery and endovascular therapy. The Best Surgical Therapy for Patients With CLI (BEST-CLI) trial is the first randomized control trial in North America to evaluate the outcome of the 2 treatment strategies. The study started enrolling patients in 2014 with the aim to include 2100 patients.[12] It is unlikely, however, that the subgroup of patients with DM and heel ulcer undergoing revascularization will be large enough to render data of high enough quality to allow definite conclusions in this group of patients. Therefore, the present study, which spans over three decades, might contribute important information in an area with lack of knowledge.

Patients with DM and heel ulcers are considered to be a group with poor prognosis regarding the risk of major amputation, as the location of the ulcer confers a great risk of lower leg amputation. A previous study on the same cohort demonstrated that patients not treated with vascular surgery, probably because of spontaneous ulcer healing or not suffering from PAD, have a better prognosis.[7] A recent report among patients with DFU demonstrated that vascular surgery often is adopted in the most advanced stages of the disease.[13] The selected patients undergoing vascular surgery had a more generalized atherosclerosis in terms of presence of ischemic heart disease and SPVD compared to the patients with DM and heel ulcer not undergoing vascular surgery. In the present cohort study, prevalence of SPVD was 78%, compared to the 40% rate in

patients with heel ulcers not undergoing vascular surgery (Supplementary Appendix, Table 2). This makes management and efforts to heal these heel ulcers among patients in the present study particularly challenging. The rate of current smokers at baseline was higher in the vascular surgery versus nonvascular surgery group, a relation that might have been unchanged postoperative, contributing to disturbed wound healing, lower patency,[14] and AFS[15] at 2 years in the vascular surgery group. If vascular surgery fails, it is highly likely that unhealed heel ulcers will lead to a major amputation unless the patient dies with an unhealed heel ulcer.

Apart from its retrospective and nonrandomized design, there are other important limitations of the present study. Patients selected for vascular surgery had more advanced cardiovascular morbidity and lower AFS than the rest of patients with DM having heel ulcer, and it was within this selected group that the comparison between open vascular surgery and endovascular therapy was performed. Furthermore, the small study groups make some of the group comparisons prone to type 2 statistical error bias. Information bias is another limitation due to the retrospective nature of the included patients, with difficulties in finding information in the medical records. Another important confounder in the study is the change in diagnostic capacity and therapeutic activity during the comparably long study period. For instance, better high-resolution equipment may allow a more accurate diagnosis of retinopathy, and insulin treatment might have led to better control of hyperglycemia than oral agents,[16] contributing to differences in diagnosis and medical therapy, respectively, between the early and the latter time periods. Another important biases not accounted for in the study are the improved pharmacological secondary prevention with platelet aggregation inhibitors and statins and higher rates of tobacco cessation in the latter time period.[17] Hence, there is a possibility that the difference in AFS between the 2 study groups would have been even larger, in favor of open vascular surgery, if these 3 factors had been possible to adjust for.

In the group of patients undergoing open vascular surgery, it was not possible to perform subgroup analysis of those undergoing reconstructive surgery with vein or synthetic material. It is well known that patients receiving prosthetic lower limb bypass grafts fare much worse than those treated with a vein bypass.[18] Hence, the proportion of patients receiving prosthetic bypass grafts in a comparative study between open vascular surgery and endovascular therapy has great importance in interpretation of the results. Furthermore, it would have been interesting to analyze angiosome direct revascularization of the heel, an angiosome being the tissue that a specific artery and vein supplies, as this concept may help improve targeted revascularization and possibly enhance the treatment of DFU.[19] However, it was not possible to analyze angiosome direct revascularization due to the retrospective nature of the study not providing sufficient data.

It was possible to show that open vascular surgery as opposed to endovascular therapy was an independent factor associated with higher AFS. This finding is particularly important, since there is a strong trend in the Western world to adopt to endovascular therapy. It appears that some patients, like the patients with DM and PAD with a heel ulcer, may be better treated with open vascular surgery. The study findings also suggest that endovascular first vascular centers should scrutinize their results after revascularization of diabetic patients with heel ulcers. A report on the same population as the present study, analyzing the results of vein bypass, showed no difference in AFS between patients with and without DM.[20] This result may further justify that open vascular surgery should be adopted more often as a first-line vascular therapy among all patients with CLI. The reason for better results after open vascular surgery during this study period may depend upon more durable reconstructions, and the fact that almost all infraingunal bypasses were of vein. The patency of long multilevel recanalizations and crural recanalizations performed in the endovascular group appears to be clearly inferior to vein bypasses.[21]

In conclusion, AFS was higher after open vascular surgery among patients with DM and PAD with heel ulcer, whereas the proportion of endovascular treatment increased during the latter time period. These results might be interpreted as suggesting that open vascular surgery should be offered more often than in today's current practice.

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References

1. Nationella Diabetesregistret. Årsrapport 2016 [Internet]. Västra Götaland: Nationella Diabetesregistret (NDR); 2017. [Accessed May 4, 2018]. https://www.ndr.nu/pdfs/Arsrapport_NDR_2016.pdf.
2. Brownrigg JR, Apelqvist J, Bakker K, Schaper NC, Hinchliffe RJ. Evidence-based management of PAD & the diabetic foot. *Eur J Vasc Endovasc Surg*. 2013;45(6):673-681.
3. Centers for Disease Control and Prevention. National diabetes statistics report [Internet]. National Institute of diabetes and digestive and kidney diseases; 2017. [updated 2017; Accessed March 2, 2018]. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf.
4. Younes NA, Albsoul AM, Awad H. Diabetic heel ulcers: a major risk factor for lower extremity amputation. *Ostomy Wound Manage*. 2004;50(6):50-60.

5. Lowry D, Saeed M, Narendran P, Tiwari A. A review of distribution of atherosclerosis in the lower limb arteries of patients with diabetes mellitus and peripheral vascular disease. *Vasc Endovasc Surg*. 2018;52(7):535-542.
6. Mills JL Sr, Conte MS, Armstrong DG, et al. The society for vascular surgery lower extremity threatened limb classification system: risk stratification based on wound, ischemia, and foot infection (WIfI). *J Vasc Surg*. 2014;59(1):220-234.e1-e2.
7. Orneholm H, Apelqvist J, Larsson J, Eneroth M. Heel ulcers do heal in patients with diabetes. *Int Wound J*. 2017;14(4):629-635.
8. Popplewell MA, Davies H, Jarrett H, et al. Bypass Versus Angio Plasty in Severe Ischaemia of the leg - 2 (BASIL-2) trial: study protocol for a randomised controlled trial. *Trials*. 2016;17:11.
9. Jonasson JM, Ye W, Sparen P, Apelqvist J, Nyrén O, Brismar K. Risks of nontraumatic lower-extremity amputations in patients with type 1 diabetes: a population-based cohort study in Sweden. *Diabetes Care*. 2008;31(8):1536-1540.
10. Grubb A, Nyman U, Bjork J, et al. Simple cystatin C-based prediction equations for glomerular filtration rate compared with the modification of diet in renal disease prediction equation for adults and the Schwartz and the Counahan-Barratt prediction equations for children. *Clin Chem*. 2005;51(8):1420-1431.
11. Adam DJ, Beard JD, Cleveland T, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL): multicentre, randomised controlled trial. *Lancet (London, England)*. 2005; 366(9501):1925-1934.
12. Menard MT, Farber A, Assmann SF, et al. Design and rationale of the best endovascular versus Best Surgical Therapy for Patients With Critical Limb Ischemia (BEST-CLI) trial. *J Am Heart Assoc*. 2016;5(7):e003219.
13. Hicks CW, Canner JK, Mathioudakis N, et al. The society for vascular surgery Wound, Ischemia, and foot Infection (WIfI) classification independently predicts wound healing in diabetic foot ulcers. *J Vasc Surg*. 2018;68(4):1096-1103. doi:10.1016/j.jvs.2017.12.079
14. Selvarajah S, Black JH III, Malas MB, Lum YW, Propper BW, Abularrage CJ. Preoperative smoking is associated with early graft failure after infrainguinal bypass surgery. *J Vasc Surg*. 2014;59(5):1308-1314.
15. De Boer SP, Serruys PW, Valsar G, et al. Life-years gained by smoking cessation after percutaneous coronary intervention. *Am J Cardiol*. 2013;112(9):1311-1314.
16. Vos RC, van Avendonk MJ, Jansen H, et al. Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control. *Cochrane Database Syst Rev*. 2016;9:Cd006992.
17. Alhadad A, Wictorsson W, Alhadad H, Lindblad B, Gottsäter A. Medical risk factor treatment in peripheral arterial disease - need for further improvement. *Int Angiol*. 2013;32(3):332-338.
18. Conte MS. Bypass versus angioplasty in severe ischaemia of the leg (BASIL) and the (hoped for) dawn of evidence-based treatment for advanced limb ischemia. *J Vasc Surg*. 2010;51(suppl 5): 69s-75s.
19. Alexandrescu V, Soderstrom M, Venermo M. Angiosome theory: fact or fiction? *Scand J Surg SJS*. 2012;101(2):125-131.
20. Fransson T, Thorne J. In situ saphenous vein bypass grafting - still first line treatment? A prospective study comparing surgical results between diabetic and non-diabetic populations. *VASA Zeitschrift fur Gefasskrankheiten*. 2010;39(1):59-65.
21. Åkesson M, Riva L, Ivancev K, Uher P, Lundell A, Malina M. Subintimal angioplasty of infrainguinal arterial occlusions for critical limb ischemia: long-term patency and clinical efficacy. *J Endovasc Ther*. 2007;14(4):444-451.

Appendix

Table 1. The Wagner Classification system for diabetic foot ulcers.

Wagner grade	**Description**
0	No ulcer
1	Superficial ulcer
2	Ulcer extension involving ligament, tendon, joint capsule or fascia
3	Deep ulcer with abscess and/or osteomyelitis
4	Gangrene of portion of foot
5	Extensive gangrene of the foot

Table 2. Baseline and outcome in patients with diabetes mellitus with heel ulcer undergoing vascular surgery compared to no vascular surgery.

Factors	**Vascular surgery (n=125)**	**No vascular surgery (n=643)**	**P value**
Median age (IQR)	71 (61-79)	73 (62-82)	0.28
Women (%)	55 (44.0)	281 (43.7)	0.95
Current smoker (%)	30/124 (24.2)	96/628 (15.3)	0.015
Type 2 diabetes mellitus (%)	86/105 (81.9)	420/530 (79.2)	0.54
Ischemic heart disease (%)	64 (51.2)	232/640 (36.3)	0.002
Non-ischemic heart disease (%)	41 (32.8)	182/638 (28.5)	0.34
Congestive heart failure (%)	53 (42.4)	225/640 (35.2)	0.12
Stroke (%)	29 (23.2)	194/639 (30.4)	0.11
Median Wagner grade at inclusion (IQR) 1 (superficial ulcer)	108 (86.4)	545 (84.8)	0.73
2 (deep ulcer)	9 (7.2)	73 (11.4)	
3 (abscess and/or osteomyelitis)	5 (4.0)	13 (2.0)	
4 (gangrene of portion of the foot)	0 (0.0)	8 (1.2)	
5 (gangrene of greater part of the foot)	3 (2.4)	4 (0.6)	
Severe peripheral vascular disease (%)	79/101 (78.2)	158/393 (40.2)	<0.001
End-stage renal disease (%)	17/124 (13.7)	78 (12.1)	0.62
Major amputation at 2 years (%)	28 (22.4)	51 (7.9)	<0.001
Mortality at 2 years (%)	42 (33.6)	165 (25.7)	0.067
Major amputation or mortality at 2 years (%)	59 (47.2)	217 (33.7)	0.004

Table 3. Outcome according to period at inclusion among patients with diabetes mellitus undergoing revascularization for critical limb ischemia with a heel ulcer.

Factors	**All limbs (n=127)**	**1983 – 2000 (n=38)**	**2001 – 2013 (n=89)**	**P value**
Endovascular intervention first (%)	97 (76.4)	18 (47.4)	79 (88.8)	<0.001
Open vascular surgery first (%)	30 (23.6)	20 (52.6)	10/89 (11.2)	
Healed heel ulcer (%)	80/126 (63.5)	24/37 (64.9)	56 (62.9)	0.84
Major amputation, 1 year (%)	27 (21.3)	7 (18.4)	20 (22.5)	0.45
Deceased unhealed (%)	22/126 (17.5)	5/37 (13.5)	17 (19.1)	0.61