Population-based studies on lower limb ischemia

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UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on 29th of November 2024 at 13.00 in Agardhsalen, Clinical Research Centre, Jan Waldenströms gata 35, Malmö

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Title and subtitle: Population-based studies on lower limb ischemia

Abstract:

Background: Peripheral artery disease (PAD) is a common cardiovascular disease, and these patients have a high risk of myocardial infarction, stroke, amputation and death. Acute lower limb ischemia (ALI) can affect patients with or without PAD and is limb- and life-threatening.

Aims: The overall aim of this thesis was to identify factors that are associated with lower limb ischemia and adverse outcomes. The specific aims were to:

- Evaluate if the risk of developing PAD is influenced by diet quality and fiber intake in the Malmö Diet Cancer cohort.
- Calculate the current incidence of ALI and factors associated with major amputation/death at one year.
- To evaluate the quality of initial clinical examination in patients presenting with ALI, and the association between quality of clinical examination and major amputation/death at one year.
- Estimate the incidence of extravascular incidental findings (EVIFs) of immediate clinical relevance in patients with ALI diagnosed with CTA and estimate the association between these findings and revascularization rate and major amputation/mortality at one year.

Material and Methods: Paper I is a prospective study on PAD patients using data from the Malmö Diet and Cancer cohort. Paper II-III are retrospective studies on ALI patients from the Malmö population between 2015 and 2018. In paper IV, ALI patients undergoing computed tomography angiography (CTA) between 2015 and 2018 were reviewed, evaluating the incidence of EVIFs. Cox regression was used in paper I, and multivariable logistic regression analysis in paper II-IV. Sensitivity analysis was performed in paper I, and intraclass correlation coefficient was calculated for inter-rater reliability in paper IV.

Results: A total of 1122 patients developed PAD during a median follow-up of 21.7 years in the Malmö Diet and Cancer cohort. Adherence to recommended levels of fiber intake was associated with a lower risk of PAD (HR 0.84; 95% CI 0.72-0.99). The incidence of ALI in the Malmö population was 12.2/100 000 person years (95% CI 10.3-14.1). In adjusted analysis, higher risk of major amputation/mortality at one year was linked to Rutherford > IIb (OR 4.19; 95% CI 1.94-9.02), age (OR 1.03/year; 95% CI 1.00-1.06), anemia (OR 2.46; 95% CI 1.08-5.62) and female sex (OR 2.37; 95% 1.07-5.26). A satisfactory first clinical examination occurred in 55.3% of ALI patients. Measuring ABI (OR 0.25; 95% CI 0.11-0.55), performing a complete pulse status (OR 0.41; 95% CI 0.20-0.85), evaluating paralysis (OR 0.43; 95% CI 0.20-0.89), and a bedside score of $\geq$ 5 points (OR 0.48; 95% CI 0.23-0.97) were independently associated with decreased risk of major amputation/mortality at one year. Intra-class correlation coefficient between the two radiologist raters was 0.94 (95% CI 0.92-0.96). Among the EVIFs, 46 (34 patients) of them were category I findings. Category I EVIFs findings were associated with decreased rate of emergency revascularization (OR 0.26; 95% CI 0.10-0.66) and higher rate of major amputation/mortality at one year (OR 2.9; 95% CI 1.1-8.2).

Conclusions:

- A healthy diet, specifically a high intake of dietary fiber, was associated with a decreased risk of incident PAD.
- The overall ALI incidence was 12.2/100 000 person years with no differences between sexes. The rates of major amputation and/or mortality at one year was 46.6% .
- The quality of initial clinical examination in ALI patients was considerably unsatisfactory in 44.7% of the cases, and it was associated with a higher risk of major amputation and/or mortality at one year.
- EVIFs of immediate clinical relevance were found in 29% of the ALI patients undergoing CTA and they were associated with a lower rate of emergency revascularization and higher risk of major amputation and/or mortality at one year.

Key words: Peripheral artery disease, Acute lower limb ischemia

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Coverphoto photo: “Kula Beograd” (Belgrade tower) in the capital of Serbia. The narrowing of the tower symbolizes a blood vessel with restricted blood flow, which is the main subject of this thesis.

Photo taken by Zoran Mesarovic

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Kulezic A, Bergwall S, Fatemi S, Sonestedt E, Zarrouk M, Gottsäter A, Acosta S. Healthy diet and fiber intake are associated with decreased risk of incident symptomatic peripheral arterial disease- a prospective cohort study. Vasc Med. 2019; 24: 511-518.

Paper II

Kulezic A, Acosta S. Epidemiology and prognostic factors in acute lower limb ischaemia- a population-based study. Eur J Vasc Endovasc Surg. 2022; 63: 296-303.

Paper III

Kulezic A, Macek M, Acosta S. Inadequacies of physical examination in patients with acute lower limb ischemia are associated with dreadful consequences. Ann Vasc Surg. 2022; 82: 190-96.

Paper IV

Kulezic A, Acosta S, Ekberg O, Lehti L. Extravascular incidental findings in computed tomography angiography are associated with lower amputation-free survival in patients with acute lower limb ischaemia. Vascular. 2024; 32: 126 – 131.

Papers not included in the thesis

Acosta S, Kulezic A, Zarrouk M, Gottsäter A. Management of acute lower limb ischemia without surgical revascularization- a population-based study. Vasc Endovascular Surg. 2024; 58: 316-325.

Abbreviations

ABI	Ankle brachial index
ACVD	Atherosclerotic cardiovascular events
AF	Atrial fibrillation
ALI	Acute lower limb ischemia
CDT	Catheter-directed thrombolysis
CI	Confidence intervals
CLTI	Chronic limb threatening ischemia
CRP	C-reactive protein
CTA	Computed tomography angiography
DSA	Digital subtraction angiography
DUS	Duplex ultrasound
EFSA	European Food Safety Association
ESVS	European Society for Vascular Surgery
EVIFs	Extravascular incidental findings
HDL	High density lipoprotein
HR	Hazard ratio
IC	Intermittent claudication
ICC	Intraclass correlation
IQR	Interquartile range
LDL	Low density lipoprotein
MDCS	Malmö Diet and Cancer Study
MRA	Magnetic resonance angiography
PAD	Peripheral artery disease
PTA	Percutaneous transluminal angioplasty
QoL	Quality of life
SPSS	Statistical Package for the Societal Sciences
WHO	World Health Organization

Thesis at a glance

Paper	Aim	Methods	Results
I. Healthy diet and fiber intake are associated with decreased risk of incident symptomatic peripheral artery disease- A prospective cohort study	Investigate the long-term impact of diet on the development of PAD among middle-aged individuals.	Prospective cohort study with 26 010 participants from MDCS. Data on dietary intake were collected through a 7-day food diary, food questionnaire and an interview. A diet quality index was assessed based on adherence to diet recommendation.	1122 participants developed PAD. Diet score was associated with a reduced risk of PAD in multivariable analysis. Adherence to recommended levels of fiber intake was associated with a reduced risk of incident PAD.
II. Epidemiology and Prognostic Factors in Acute Lower Limb Ischaemia: A Population Based Study	Evaluate the contemporary population based incidence of ALI and factors associated with major amputation/death at one year.	Retrospective study where in-hospital, operation, radiological, and autopsy registries were scrutinized to capture 161 citizens of Malmö with ALI 2015-2018. Incidence rates were calculated, expressed as numbers of patients per 100 000 person years.	The ALI incidence was 12.2/100 000 person years and embolism was the most common cause of ALI. Age, female sex, anemia and Rutherford $\geq$IIb were associated with an increased risk of major amputation/death at one year.
III. Inadequacies of Physical Examination in Patients with Acute Lower Limb Ischemia Are Associated with Dreadful Consequences	Explore the association between adherence to guidelines on clinical diagnosis of ALI and outcome at one year.	Retrospective study with the same cohort as paper II. Bedside evaluation was scored based on evaluation of the 6 “Ps”, ranging from 0-7 points. A score $\geq$5 points was defined as satisfactory.	A satisfactory examination was performed in 55.3% of the patients. ABI measurement, complete pulse status, evaluating paralysis, and a score $\geq$5 points were associated with reduced risk of major amputation/mortality at one year.
IV. Extravascular incidental findings in computed tomography angiography are associated with lower amputation-free survival in patients with acute lower limb ischaemia	Evaluate the incidence of EVIFs of immediate clinical relevance in patients with ALI undergoing CTA and evaluate the association between EVIFs and emergency revascularization and amputation-free survival at one year.	Retrospective study. Emergency CTA in 118 ALI patients between 2015 and 2018 were scrutinized. EVIFs were classified into categories: immediate (category I), potential (category II), or no clinical relevance (category III).	Forty-six EVIFs were category I and these were associated with reduced rate of emergency revascularization and increased rate of major amputation/mortality at one year.

ABI; ankle brachial index, ALI; acute lower limb ischemia, CTA; computed tomography angiography, EVIFs; extravascular incidental findings, MDCS; Malmö Diet and Cancer Study, PAD; peripheral artery disease

Introduction

Atherosclerosis

The term atherosclerosis originates from the Greek words *athere* meaning gruel, and *skleros* meaning hardness. Over 200 years ago, Albrecht Von Haller, a Swiss physician, used the term *atheroma* to describe a plaque with a core that exuded yellow content. The term *atherosclerosis* was later, in 1908, applied to describe the association between fatty degeneration and arterial stiffening by Marchand (1).

Atherosclerosis affects the blood vessels throughout the body and is characterized by endothelial dysfunction, oxidative stress, and inflammation (2). It begins with a dysfunctional endothelium due to hypercholesterolemia and hemodynamic disturbances. Chronic stress on the vessels eventually causes increased permeability and oxidation of low density lipoproteins (LDL)(1, 3), the most atherogenic among all lipoproteins (4), which will gather in the intima of the vessel. The endothelial cells will express adhesion molecules when LDL oxidation occurs, where monocytes will adhere (1, 3). Monocytes will wander to the intima of the vessel wall, differentiate into macrophages, and eventually engulf oxidized LDL and becoming foam cells (5), which is the initial step of the fatty streak formation (Figure 1)(1).

Vascular smooth muscle cells will migrate from the media to the intima of the vessel and further proliferate (1) and stimulate collagen synthesis (5) and forming a fibrous plaque. The plaque may rupture over time (1, 3), leading to severe cardiovascular events due to thrombosis and distal embolization (6).

Turbulent stress areas are more vulnerable to atherosclerosis, as well as bifurcations, branch points and major curvatures that are favorable for lipid deposition (7). Formation of an atherosclerotic plaque in the arteries in the lower extremities may impair blood flow and reduce delivery of oxygen to the limbs (8).

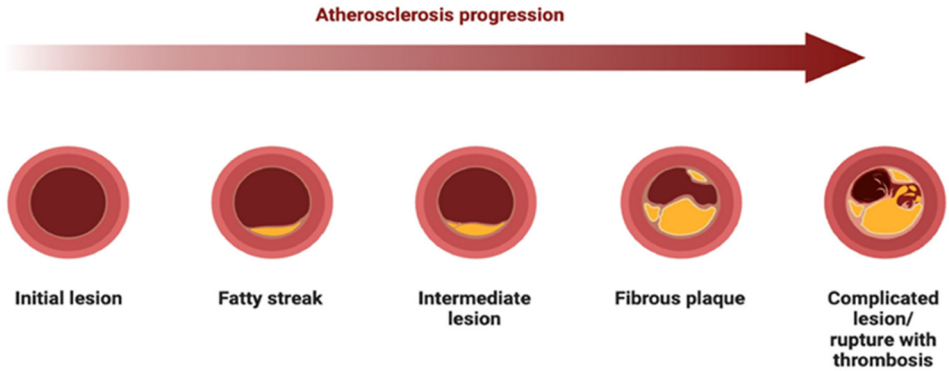

Figure 1: Imaging of the atherosclerotic process. Adapted using BioRender.

Peripheral artery disease

Peripheral artery disease (PAD) is caused by atherosclerosis in 95% of cases, resulting in obstructive lesions of the arteries in the lower limbs (9), distal to the aortic bifurcation, significantly affecting quality of life (QoL) and increasing the risk of amputation and mortality (10, 11).

Atherosclerosis is often detected in an advanced stage since the subclinical phase is often prolonged (12). It is necessary to detect atherosclerosis in an early stage by identifying treatable risk factors in order to decrease the development of the disease (13). It is estimated that 40% of symptomatic PAD might be prevented if the population adopted to healthy lifestyle factors such as avoidance of heavy alcohol consumption, high adherence to a healthy diet, moderate to high level of physical activity, and never smoking (14).

Patients with PAD have an increased risk of experiencing adverse cardiovascular events, including myocardial infarction and stroke (15, 16).

Although most patients with PAD are asymptomatic (17), a significant number suffer from severe disease, which can be explained by their disability to expose themselves to enough walking to develop any symptoms because of heart failure or diabetic neuropathy. Symptomatic disease can present as intermittent claudication (IC)(16), but some suffer from chronic limb threatening ischemia (CLTI) with worse prognosis including both limb- and life survival (18).

Intermittent claudication

PAD patients may suffer from IC, defined as an inadequate blood supply to the legs, mainly to the skeletal muscles, that cause pain while walking and is relieved by rest (19), and is the most common clinical manifestation of the disease (20).

Depending on the level of occlusion, the location of symptoms presents differently. Proximal muscle symptoms, such as buttock, hip, or thigh, is often due to disease in the aorto-iliac segment, whereas disease in the femoro-popliteal segment usually manifests as symptoms in the calf muscles (21).

It is shown that IC affects QoL (22), which is often underestimated by clinicians (20), mostly related to growing walking impairment (23). The goal with treatment of IC is to improve functional status with increasing walking distance, and thereby increase QoL, and to reduce future risk of cardiovascular events (24, 25).

Chronic limb threatening ischemia

The definition of CLTI in patients with PAD include symptoms with rest pain, gangrene, or an ulceration in the lower limb persisting for more than two weeks (17). The pain may be worsened when elevating the limb and improved when lowering the limb (26). CLTI is the most critical form of PAD (17), and these patients have a high risk of cardiovascular events (27, 28), while men with CLTI suffer from worse consequences compare to women (29). According to the European Society of Vascular Surgery (ESVS), these patients should be urgently referred to a vascular centre urgently for further management (17).

Acute lower limb ischemia

Acute lower limb ischemia (ALI) is characterized as an abrupt decrease in arterial blood flow in the limb, which might be limb- and life threatening (30). The symptom duration is less than two weeks (30, 31) and there are several causes of non-traumatic ALI (32). The main causes include *embolism*- a blood clot formed in another region of the body, predominantly originating from the heart (33), wandering through the blood to attach in one of the arteries of the limb (31), *thrombosis* in both native and reconstructed arteries, and *arterial aneurysm* with thromboembolism (32). The primary treatment options for ALI patients are open, endovascular or hybrid revascularization, conservative treatment with anticoagulation, amputation, or palliative treatment (31, 34). Antithrombotic medication prevents formation of blood clots by either stopping platelets from working (antiplatelet tablets, such as aspirin), or by decreasing the rate of coagulation (anticoagulants, such as warfarin). Anticoagulants are more potent than

antiplatelet tablets in stopping blood clot formation (35). Amputation may be considered if a patient presents too late or when revascularization has failed or is not an option due to high comorbidity burden and/or extensive occlusive lesions (34). For patients who cannot benefit from either revascularization, amputation or conservative treatment, palliative care may be considered (36).

Risk factors for peripheral embolism

It has been estimated that over 3% of the adult population is affected by atrial fibrillation (AF), the most commonly lasting arrhythmia (37, 38). These patients have an increased risk of stroke or systemic embolism that varies depending on different factors. A clinical score, CHA_2DS_2-VAS_C, is used to determine the risk of thromboembolic arterial events, where higher points on the risk score indicate an increased risk of thromboembolism. The scoring system is based on history of heart failure, hypertension, age, diabetes, previous stroke, vascular disease, and sex (37).

Rutherford classification

To determine the severity of ischemia in the affected limb, the Rutherford classification (32) is mostly used (Table 1). It helps to guide clinical management based on if the limb is threatened or irreversibly ischemic (31).

Table 1. Modified from Rutherford's classification for acute lower limb ischemia (32).

Grade	Category	Sensory loss	Motor deficit	Prognosis	Doppler Signals (Arterial)	Doppler Signals (Venous)
I	Viable	None	None	Not immediately threatened	Audible	Audible
IIa	Marginally threatened	None-minimal (toes)	None	Salvageable if promply treated	Inaudible	Audible
IIb	Immediately threatened	More than toes	Mild-moderate	Salvageable if promptly revascularised	Inaudible	Audible
III	Irreversible	Profound, anesthetic	Profound, paralysis (rigor)	Major tissue loss Amputation Permanent nerve damage inevitable	Inaudible	Inaudible

Epidemiology

PAD is one of the leading causes of atherosclerotic morbidities in the world, together with coronary artery and cerebrovascular disease (18), and it is estimated that around 200 million individuals worldwide are affected by PAD (39). However, it is challenging to estimate the exact number of PAD individuals since few studies clearly specify PAD stage and target asymptomatic stage, and because of methodological issues such as different cut-offs in studies for a normal ankle-brachial index (ABI). There are several studies that state that asymptomatic PAD is more common than symptomatic disease (9). In high-income countries, men and women seem to be equally affected by PAD, but in low-income countries women appear to be at higher risk (21). Approximately 11% of the total PAD population suffer from CLTI (17, 40).

The true incidence of ALI is somewhat uncertain due to epidemiological studies including both ALI and chronic limb ischemia (31), but a study from Gloucestershire, UK, in 1994 showed an ALI incidence of 14.3/100 000 person years (41).

There is limited data available on the epidemiology of CLTI (17). The prevalence has been estimated to range from 0.3-2%, meaning that around 2 million individuals in the United States have CLTI (21).

Primary prevention

Risk factors for developing PAD include smoking, hypertension, physical inactivity, diabetes mellitus and hyperlipidemia (Figure 2) (42). Advanced age is a major risk factor for PAD. Younger individuals (< 40 years) rarely suffer from PAD, while approximately 10% of individuals aged > 70 years will be affected by the disease (40).

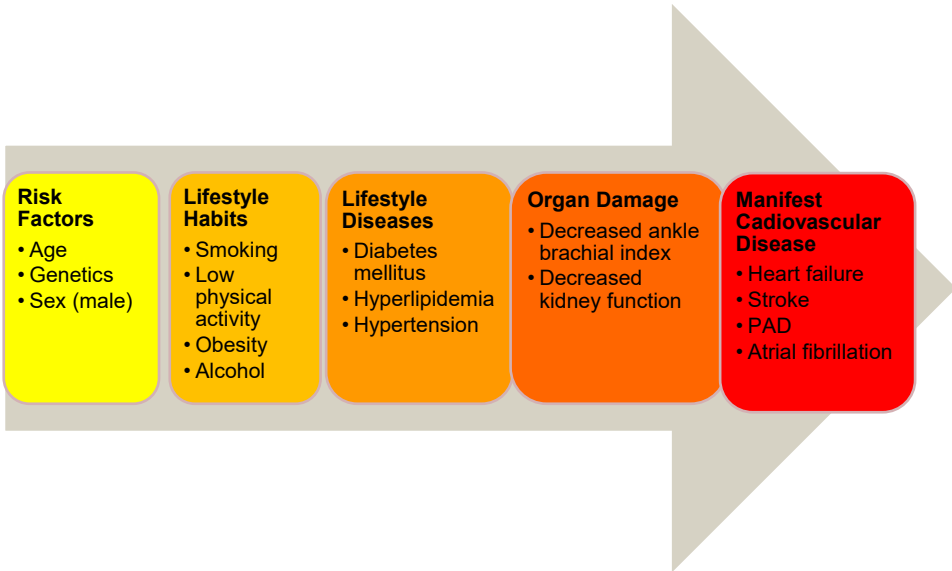

Figure 2. Showing how risk factors for atherosclerosis develop to a manifest disease.

Smoking

Smoking is widely recognized as a major risk factor for atherosclerosis (43). The levels of triglycerides are increased, and high density lipoprotein is decreased by smoking, which is known to be associated with cardiovascular disease (43). Smoking also leads to a prothrombotic state by increasing the activation of platelets and induces endothelial dysfunction because of oxidative stress (44-46). Cigarette smoking has been shown to increase blood pressure (46), which is a known risk factor for PAD (42).

Physical activity

According to the World Health Organization (WHO), "any bodily movement produced by skeletal muscles that requires energy expenditure" defines the term physical activity (47, 48). It includes any type of movement, whether it occurs during leisure, transportation to various locations, or household activities. In 2021, 67% of the population in Sweden, aged 16-84 years, were adequately physically active (> 150 minutes of physical activity elevating the heart rate per week) (49).

Continuous exercise is known to increase the numbers of mitochondria and capillaries in skeletal muscles (50). Physical activity might mitigate inflammation

and lower the risk of cardiovascular disease (51) since inflammation is involved in the pathogenesis of this condition (52).

Diet

Macronutrients provide energy to our body and are composed of carbohydrate, fat, and protein. Carbohydrates are monosaccharides or connected monosaccharides forming chains (such as starch) and are either resistant to hydrolysis (dietary fiber) or they are hydrolysed in the small intestine. Glycerol and fatty acids are the components of fat, and accumulations of amino acids constitutes protein .

According to Riksmaten, the energy in food in the Swedish diet comes from approximately 18% protein, 35% fat and 47% carbohydrates, including fiber (53).

Fiber

Dietary fiber is mainly found in whole grain cereals, fruit, vegetables, and potatoes. The European Food Safety Association (EFSA) recommends a fiber consumption of > 25 g/day in adults (54), which is in line with the Nordic Nutrition Recommendations. According to the Swedish Food Agency (Swedish: Livsmedelsverket), the Swedish population does not achieve these recommendations, with a fiber intake of 20 g/day (55).

Dietary fiber plays a protective role in cardiovascular health in terms of controlling body weight, lowering blood pressure, and reducing the risk of developing diabetes (56).

The emptying of the stomach is prolonged by soluble fiber by forming a gel, which decreases the development of atherosclerosis by lowering postprandial blood glucose levels and lipid increase. Satiation is increased by hormone secretion secondary to fiber distending the stomach, and thereby reducing food intake and weight. By losing body weight, the blood pressure is also reduced. It is also shown that dietary fiber increases the rate of bile acid excretion and lowers total cholesterol and LDL. Fiber has several protective effects since hyperglycemia, hypertension, and hyperlipidemia are all risk factors for developing atherosclerosis (56, 57).

Investigation

Vascular status

The signs of ALI involve the 6 “P”s: pain, pallor, pulselessness, perishing cold, paresthesia, and paralysis (Figure 3). These indicators are instrumental in assessing the severity of ischemia (31), though it is important to note that symptoms advance

as the ischemia progresses, and not all “P”s may manifest simultaneously (58). Sensory symptoms usually occur before motor symptoms, which appears to stem from higher sensitivity of sensory axons to ischemia (59).

Physical examination of the pulses of the lower extremities provides a great part in the management of patients with PAD and ALI (60, 61). By completing an accurate examination, it can guide the clinician to locate the arterial occlusion (17) and in a proper way select appropriate diagnostic testing, avoiding unnecessary or harmful investigations (60).

Pulses that are compulsory to palpate in a correct examination include the common femoral artery, popliteal artery, and dorsalis pedis and posterior tibial artery in the foot (9, 60). Lateral to the symphysis pubis, the femoral artery can be palpated below the inguinal ligament. With the patient’s knee slightly flexed, the popliteal artery is accessible to palpation. The posterior tibial artery is easiest palpated behind the medial malleolus (62) and the dorsalis pedis artery is most commonly palpated lateral to the extensor tendon of the big toe on the dorsum of the foot (63).

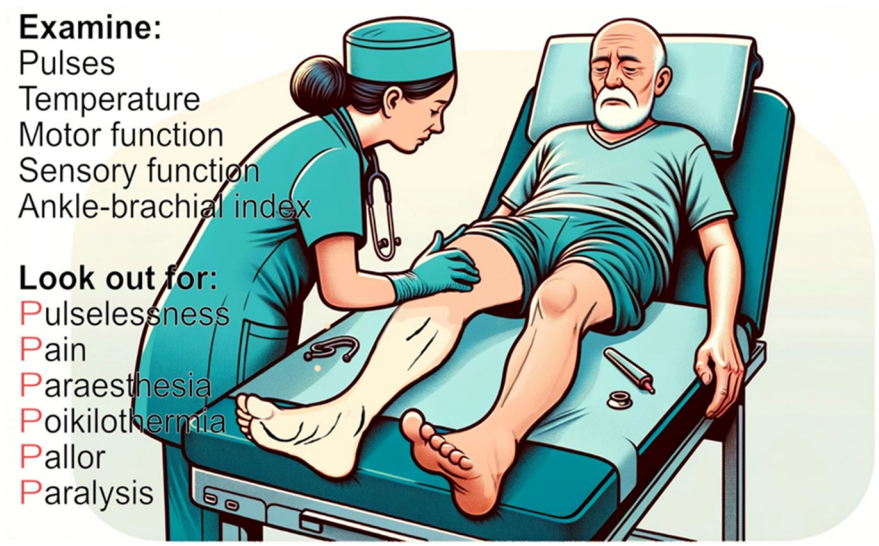

Figure 3. A picture of the 6 “P”s. ©*Talha Butt*

Ankle brachial index

Following the clinical examination, diagnostic testing typically involves measuring the ankle brachial index (ABI) (64). ABI is calculated by dividing the systolic blood pressure measured in the limb by the systolic blood pressure in the arm (65). The blood pressure of the limb should be measured at the posterior tibial artery and

dorsalis pedis artery, while the blood pressure in the arm is measured at the brachial artery and is recorded in each arm (Figure 4). Of the two pedal pulse pressures, the highest one is used to calculate the ABI, together with the highest pressure measured in the arms (66).

An ABI $\leq$ 0.90 or > 1.4 is regarded as abnormal (Figure 4)(65), while an ABI < 0.7 is considered as critical (31). An ABI < 0.9 has a high specificity of 86%, and a sensitivity of 75%, for diagnosing PAD (64). In patients with diabetes, the vascular media calcifies leading to less compressible or incompressible arteries (67) and thus a higher blood pressure and ABI. In diabetic patients it is useful to measure the toe-brachial index instead since the digital arteries rarely calcify (65).

The mortality risk correlates well with the ABI, unrelatedly to if the patient is asymptomatic or experiences leg symptoms (68), and a low ABI is inversely associated with mortality (69). In a systematic review and meta-analysis enrolling 43 observational prospective studies in individuals screened for PAD, an ABI < 0.9 compared to normal ABI (0.9-1.3) was associated with increased risk of mortality, cardiovascular mortality, cerebrovascular event, myocardial infarction, fatal myocardial infarction, and fatal stroke (70). It is, however, important to not use ABI as a continuous variable or ordinal data without adjusting for ABI > 1.4 (71).

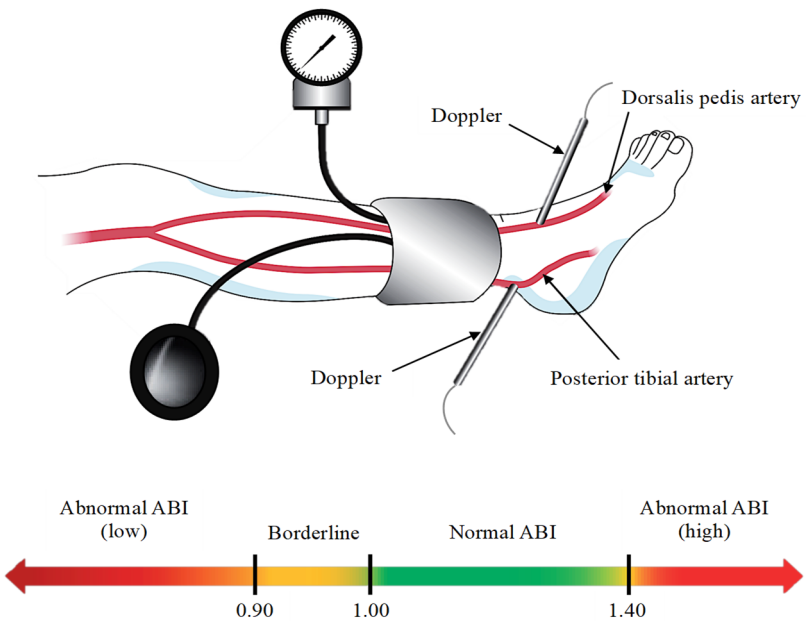

Figure 4. Showing where to measure ankle brachial index and interpretation, modified from Aboyans (16).

Non-invasive imaging methods

Duplex ultrasound

Duplex ultrasound (DUS) is valuable for localizing the anatomic location and extent of the stenosis, as well as providing velocity measurements in the arteries (72, 73). It is beneficial because of its non-invasive method, and the technique is cheaper and does not require any radiation or contrast administration (74-76). However, it is operator-dependent and time consuming as well as inadequate in determining collateral blood supply (17).

Computed tomography angiography

Computed tomography angiography (CTA) is commonly used due to the advantage of being fast and providing information about structures outside the vascular system (77). Stenoses in the aorto-iliac segment > 50%, and in the femoro-popliteal segment, can be detected by CTA with a sensitivity and specificity of 96% and 98% respectively (78). CTA is beneficial in visualizing calcifications, stents, and bypasses but careful caution is necessary regarding radiation and nephrotoxicity (64, 79). It is known that radiation increases the risk of cancer (80), and this should be noted when considering CTA, particularly in children (81).

CTA plays a big role in selecting the most appropriate choice of technique, either endovascular, open, vascular or hybrid vascular surgery, and it helps to identify patients that are most suitable for revascularization (82). CTA is also beneficial in its ability to identify extravascular findings that may be of clinical importance or helpful in detecting the aetiology of ALI (31). It can also be useful from a differential diagnostic perspective, since spinal stenosis can mimic symptoms of ALI for instance and may be seen in CTA (80).

Magnetic resonance angiography

Magnetic resonance angiography (MRA) is superior at detecting arterial occlusions with a sensitivity and specificity around 95%, but may misjudge the degree of stenosis by overestimating it (83). It is not particularly effective in visualizing arterial calcifications, which is a limitation when considering revascularization options, especially when a surgical bypass is preferred (64).

MRA is beneficial since the quality of the images are comparable to DSA but without exposing the patient to ionizing radiation or iodinated contrast (17). However, it is sensitive to motion artefacts and is not available for patients with claustrophobia, pacemakers, or implantable cardioverter defibrillators (64). Its use is also limited because it is not available out of office hours (31).

Invasive imaging methods

Digital subtraction angiography

Digital subtraction angiography (DSA), once the gold standard in vascular imaging, is now increasingly being replaced by non-invasive imaging techniques. It is only used together with endovascular therapy or to evaluate run-off prior to eventual distal bypass (64).

Treatment

Intermittent claudication and chronic limb threatening ischemia

There are different treatment options for patients with IC including exercise therapy, pharmacological interventions, and revascularization (open or endovascular surgery). Revascularization is only considered in suitable patients when conservative treatment is less effective (9).

The primary goal of treatment in patients with CLTI is to reduce cardiovascular mortality with medical treatment, to save limb function (84-86) by improving limb perfusion, and to control infection and optimize wound healing together with local care (87).

PAD patients are recommended to be treated in a stepwise manner, meaning that risk factor management is considered initially together with exercise therapy, followed by revascularization only if necessary (9).

Lifestyle factors

Patients with PAD are advised to stop smoking since it is a significant risk factor for the development of PAD and progression of the disease (88, 89). Smoking is associated with an elevated risk of CLTI and need for revascularization and amputation (88).

High cholesterol, hypertension, diabetes, and obesity have impact on cardiovascular disease and can be managed partly by dietary change (90-94). Weight reduction is desired in obese people, with a body mass index (BMI) goal of 18.5 – 24.9 kg/m^2 (95).

The management goals in patients with IC are to decrease the risk of cardiovascular events and improve walking performance, and exercise therapy is considered to be the first step in treatment and may affect both walking improvement and cardiovascular risk (15, 64). A study showed that home-based structured exercise is not less effective than hospital-based supervised exercise (96).

Medical therapy

It has been shown that patients with PAD have increased platelet activity which is associated with a higher risk of thrombotic events (97, 98). All patients with symptomatic PAD are recommended to initiate treatment with antiplatelet agents to decrease the risk of cardiovascular events (99-101), while patients with asymptomatic PAD are not recommended to have antiplatelet treatment as it has not shown any significant benefits (102).

One of the aims of antiplatelet therapy is to reduce the risk of severe cardiovascular events such as stroke, myocardial infarction, and cardiovascular death (103). Another aim is to reduce the risk of developing CLTI and preventing an event of ALI from occurring (104, 105).

As a result of lipid lowering therapies, primarily statins, the burden of cardiovascular disease has decreased (106), and it has been shown to be beneficial in patients with PAD regarding major cardiovascular events (107). Both asymptomatic and symptomatic PAD patients are recommended statin therapy according to the ESVS Guidelines from 2024 (9). Addition of ezetimibe, a non-statin drug that reduces the absorption of cholesterol from the intestine, is recommended if lifestyle advice and statin treatment is not sufficient to reach suggested levels of LDL (108). Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors are primarily considered in patients failing to reach adequate LDL-levels despite treatment with statin and ezetimibe (9).

One study showed that the risk of major adverse limb events in PAD patients was reduced by lowering LDL-levels using lipid lowering therapy (109).

Revascularization

Patients with IC who are unresponsive to conservative therapy may be candidates for revascularization. It is necessary to evaluate the anatomical location and the extent of the obstruction when deciding for revascularization (9). Endovascular therapy and open vascular surgery affect symptom relief positively in claudicants, however, revascularization may be associated with mortality (64) and amputation (18), why suitable patients must be carefully chosen (64).

In patients with CLTI, revascularization should be attempted if possible (110-113). CLTI patients who are candidates for revascularization, further management is dependent on the length of the occlusions. Short occlusions are suitable for endovascular therapy while lengthier occlusions may be treated with open or hybrid vascular surgery (64).

One recent randomized trial compared the effectiveness of treatment in CLTI patients, who needed an infra-popliteal revascularization, concerning open surgery with a vein bypass first, with endovascular treatment first regarding outcomes of

major amputation and death. The study showed that treatment with endovascular revascularization strategy was associated with better amputation-free survival (114).

In another randomized trial, CLTI patients with an adequate great saphenous vein treated with open surgery had a lower incidence of major amputation or death compared to endovascular treated patients. In CLTI patients without an adequate great saphenous vein, there was no difference between open or endovascular treatment (115).

Acute limb ischemia

Treating ALI patients presents a challenge for vascular specialists due to the high rates of amputation and mortality (116-119). ALI is primarily caused by embolism or thrombosis and when the condition is critical, both forms are associated with high mortality (120). Anatomical features and the underlying reason of ischemia are crucial for determining appropriate treatment strategies (30). There is not enough evidence showing that endovascular surgery is more beneficial than open surgery, or vice versa, regarding management of acute limb ischemia (121).

Appropriate treatment options are based on the severity of the ischemia, where sensory or motor deficit requires urgent restoration of blood flow (Figure 5). The choice of technique will depend on several factors including duration and severity of the disease, underlying cause and location of the occlusion, and comorbidities (31). Patients with multilevel occlusions may be best treated with hybrid treatment, combining endovascular and open vascular surgical techniques (122-124).

ALI patients treated with only conservative treatment alone, medical antithrombotic or anticoagulation, may be useful in frail patients (31).

ALI patients should be initially treated with analgesia and heparin while awaiting further treatment. Heparin will decrease the risk of additional embolization or clot propagation while providing an anti-inflammatory effect (15, 64). Patients presenting with Rutherford I or IIa may be candidates for initial imaging, such as CTA or MRA, to investigate the extent of the occlusion before further intervention (125). In addition, performance of CTA versus not prior to revascularization in patients with Rutherford IIb was associated with decreased risk of combined major amputation/mortality at 1 year in a propensity score adjusted analysis (82).

Open vascular surgery

ALI caused by embolism is mainly treated with femoral balloon thrombo-embolectomy, introduced by Fogarty in 1962 (126), especially if the occlusion is affecting a previously normal artery (31).

For patients with acute on chronic ischemia, usually indicating thrombotic disease, thrombendarterectomy or bypass surgery is preferred (31), and the most commonly used vein for reconstruction is the great saphenous vein (127).

Endovascular surgery

Endovascular treatment is almost always performed under local anesthesia and is a less invasive method compared to open vascular surgery, but it may be more time consuming, especially if continuous intra-arterial catheter-directed thrombolysis (CDT) is performed, to reset the arterial blood flow (128).

There are different mechanical recanalization techniques including percutaneous aspiration thrombectomy and percutaneous mechanical thrombectomy (30).

The introduction of local intra-arterial CDT occurred in the 1980s and has become a favorable technique for acute occlusions. After preferably an ultrasound guided puncture into the common femoral artery, a catheter is introduced percutaneously, guided towards the occlusion using fluoroscopy and placed into the occlusion. There are small perforations in the distal segment of the thrombolysis catheter allowing thrombolytic agent to be continuously administered for 24-48 hours. Thrombolysis is an option in ALI patients with native artery occlusions such as, embolic or thrombotic occlusions, or popliteal aneurysms thromboembolism, and graft and stent thrombosis (129, 130). It is often necessary to perform adjunctive procedures such as percutaneous transluminal angioplasty (PTA) with or without stenting, to improve long-term patency to address underlying PAD immediately during the procedure. One complication of this thrombolysis involves hemorrhage, such as bleeding at the introducer site or intracerebral hemorrhage and gastrointestinal bleeding (131). Several studies have shown that the bleeding complication rate is 33% in thrombolytic procedures (131, 132). Other complications include distal embolization (133), as well as progressive ischemia and acute compartment syndrome (31).

Patients presenting with Rutherford class I do not have an immediately threatened limb and are instead considered to have a relatively high risk of major amputation and mortality at one year and beyond after treatment with thrombolysis (134). The benefit of thrombolysis for this patient category can therefore be questioned. Instead, the benefit-risk balance may speak in favour of conservative treatment with pharmacological and exercise therapy (Figure 5)(135).

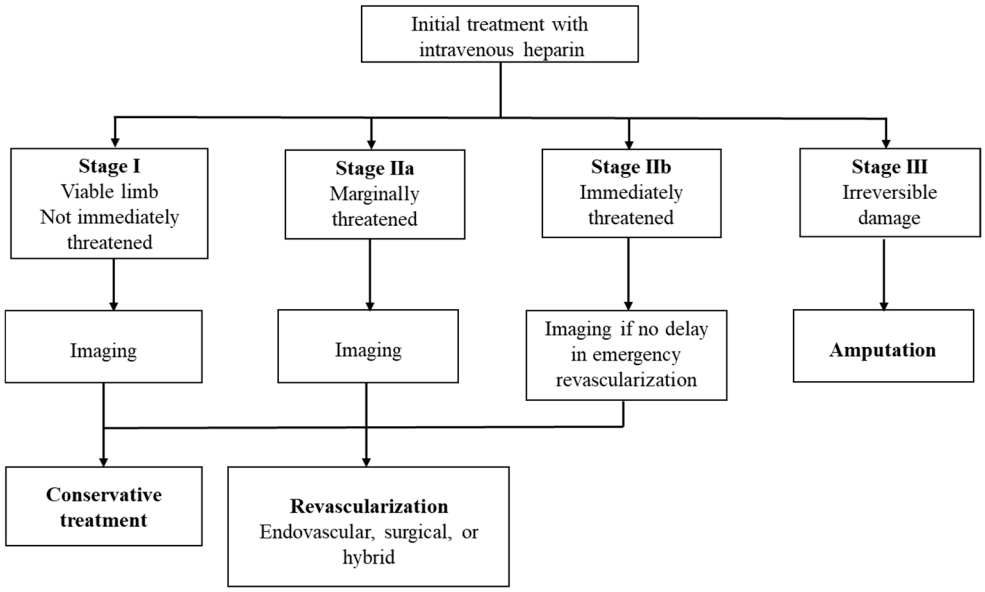

Figure 5. Algorithm for diagnosis and treatment of acute lower limb ischemia, modified from Creager (125).

Amputation

There are several risk factors that contribute to the risk of amputation in patients with CLTI, including wounds, ischemia and foot infection extent and severity (64). It is crucial to detect tissue loss and infection at an early stage to improve limb salvage (136). Patients with CLTI that have been revascularized have an increased risk of amputation during the first six months following revascularization (18), while limb loss is quite uncommon in patients with IC (137). For patients presenting with irreversible ALI (Rutherford III), amputation is recommended (31).

Aims

The overall aim of this thesis was to identify factors that are associated with lower limb ischemia and adverse outcomes.

The specific aims were to:

- Paper I: Evaluate if the risk of developing PAD is influenced by diet quality and fiber intake in the Malmö Diet Cancer cohort.
- Paper II: Calculate the current incidence of ALI and factors associated with major amputation/death at one year.
- Paper III: To evaluate the quality of initial clinical examination in patients presenting with ALI, and the association between quality of clinical examination and major amputation/death at one year.
- Paper IV: Estimate the incidence of extravascular incidental findings (EVIFs) of immediate clinical relevance in patients with ALI diagnosed with CTA and estimate the association between these findings and revascularization rate and major amputation/mortality at one year.

Methods

Ethical approval

This thesis consists of sensitive personal data related to health and all study participants received a coded ID, with the decoding key stored separately. Regarding invasion of privacy, all the results are presented on group level, ensuring that participants cannot be identified individually.

The first paper received ethical approval from Lund University (Dnr §LU5190, date 1990-02-14), that aligns with the ethical guidelines of the Declaration of Helsinki 1975. Informed consent was gathered from all participants. In 2013, a supplementary request was complete (Dnr 2013/566, date 2013-08-12) to study cardiovascular disease, approved by the Regional Ethical Review Board in Lund.

Until 31st December 2018, the ethical review boards were conducted by six regional boards in Gothenburg, Lund, Stockholm, Umeå, Uppsala and Linköping. Since January 1st, 2019, a single authority was conducted, the Swedish Ethical Review Authority, to achieve greater equality. Remaining papers (II-IV) were approved by the Swedish Ethical Review Authority (Dnr §2020-00764, date 2020-05-10). The application was broadly phrased, including several aspects for further research. No written consent was required with respect to the retrospective design.

Setting

Paper II-III are population-based studies comprising patients registered as living in the city of Malmö, whereas paper IV comprised patients from the catchment area treated at the vascular centre. The vascular centre in Malmö is a part of Skåne University Hospital and is a tertiary referral centre for peripheral vascular disease and is the greatest vascular clinic in Skåne. The hospital is in the city of Malmö, which is the third largest city in Sweden, and both endovascular and open vascular surgery is performed here around the clock.

There was a total of 338 583 citizens of Malmö during 2018: 170 97 women and 167 595 men (Statistics Sweden; www.scb.se). There were 10 634 deaths between

2015 and 2018 in Malmö, and a total of 773 forensic autopsies and 678 clinical autopsies were performed in Malmö citizens.

Data collection

Electronic medical charts from Skåne University Hospital were reviewed to extract information about the patients. This was primarily used for paper II, III and IV but in paper I it was also used for validation of the diagnosis of PAD.

Malmö Diet and Cancer Study

In paper I, we used data from the Malmö Diet and Cancer study (MDCS) cohort. The primary aim of MDCS initiated in the 1990's was to evaluate the association between diet and development of cancer (138). The cohort has been used to investigate associations between diet and several non-cancer diseases.

The baseline examinations in the prospective MDCS were carried out between 1991 and 1996. Men included in the study were born 1923-1945 and women 1923-1950, living in Malmö. The female group had a wider age span due to the strive to study breast cancer in pre-menopausal women (138). The participants were required to have Swedish writing and reading skills.

The baseline examination included a self-reported questionnaire with dietary habits. Dietary habits were collected through a 7-day food diary including food intake at lunch and dinner, and cold beverages. The study also required data of the foods that the participant had consumed during the past year with a 168-item food frequency questionnaire (139).

After registration of foods, an interview followed to clarify missing values or any other question marks and detailed data about portion sizes and cooking practices regarding the food that was collected in the diary.

Anthropometric measurements and blood samples were also collected during baseline as well as a self-reported questionnaire regarding lifestyle factors. A total of 28 098 participants underwent baseline examination including dietary assessment.

Diet quality index

In paper I, we used a diet quality index that was created from a previous study (140) and was designed based on the Swedish nutrition recommendations and the Swedish dietary guidelines. The index is used to evaluate adherence to the recommendations

by the Swedish dietary guidelines. The six components in the index include saturated fat, polyunsaturated fat, fish and shellfish, fiber, fruit and vegetables, and sucrose, and one point was given for every achieved recommendation. Adherence to recommended levels was categorized into groups: low (0-1 points), medium (2-4 points) and high (5-6 points). The cut-offs for reaching recommendations are listed in Table 2.

Table 2. Cut-off values of dietary components included in the diet quality index.

Dietary components	Cut-offs for adherence to recommendation
Saturated fat	≤ 14 E%
Polyunsaturated fat	5-10 E%
Fish and shellfish	≥ 300 g/week
Fiber	≥ 2.4 g/MJ
Fruit and vegetables	≥ 400 g/day
Sucrose	≤ 10 E%

Validation of PAD diagnosis

One hundred patients with PAD diagnosis were randomly selected for validation. Patient record data was used for validation and 69 had critical limb ischemia, 13 had ALI, 15 had intermittent claudication, and one had asymptomatic PAD. Among the 13 patients with ALI, one had an embolic occlusion. Two patients were misdiagnosed and suffered from venous insufficiency. Therefore, symptomatic PAD was confirmed in 97% of the cases.

Data extraction of the whole Malmö population

In paper II and III, the same population was used, and only patients registered as Malmö citizens with ALI were included. Aorto-iliac or infrainguinal occlusions were considered caused by embolism, thrombosis, occluded bypass graft or endoprosthesis, and thromboembolism secondary to popliteal artery aneurysms. In-hospital, operation, radiological and autopsy registries were reviewed, covering every patient with ALI occurring in the population.

Data classification

Paper III: Clinical score for examination of lower extremities in patients with ALI

A scoring system was used to evaluate the accuracy of bedside examination in patients presenting with ALI. The scoring system was based on the 6 "P"s, and the ABI, where 1 point was given for every item that was included in the examination (Table 3). The score ranged from 0 to 7 points, and a score of 5 points or higher was regarded as a satisfactory vascular status.

Table 3. Clinical score for examination of leg circulation in patients with acute lower limb ischemia.

Bedside evaluation	Required to earn 1 point
Pain	Any description of history of pain by the patient.
Pallor	Examined and described in status by physician for 1 point.
Pulselessness	Pulses had to be palpated at the femoral, popliteal, posterior tibial and dorsal pedal arteries bilaterally, to award 1 point. If the arteries were only examined by an imaging modality such as duplex, no point was awarded.
Perishing cold	Temperature of the limb had to be assessed and described in status by physician for 1 point.
Paresthesia	Sensory deficits were examined and described in status by physician for 1 point.
Paralysis	Motor function was examined and described in status by physician. If the patient only described shortened walking distance in the anamnestic part of the medical record, no point was awarded.
ABI (ankle brachial index)	Calculation of an ABI or notion of no doppler signals in the foot arteries awarded 1 point. Detection of doppler signals without measuring ABI awarded no point.

Paper IV: Extravascular incidental findings

Patients with ALI underwent CTA, and images were re-evaluated independently by two senior radiologists. The patients were either scanned with Siemens Somatom Definition Flash (Siemens Healthineers, Erlangen, Germany) or Canon Aquilion One (Canon Medical Systems, Ötawara, Tochigi, Japan). Iohexol followed by saline flush were injected in an antecubital vein with a flow rate of 5 mL/s. Five seconds after bolus detection in the suprarenal aorta, the arterial phase images were obtained. The scanning was done in a two series management: from the level of right atrium to middle of femur and from hips to forefoot.

The incidence of EVIFs was calculated. These findings were classified into three different categories, based on the relevance of the findings: immediate (category I), potential (category II), or no clinical relevance (category III)(141). Agreement of EVIFs between two senior radiologists was estimated.

Definitions

Acute lower limb ischemia was defined as a limb-threatening condition caused by a rapid decrease in arterial blood flow in the limb with a symptom duration less than two weeks.

Alcohol consumption was categorized into six different groups based on their total consumption, where zero-consumers indicated that they had not consumed alcohol in the last year.

Anemia was counted as present if the level of hemoglobin was < 134 g/L for men and < 117 g/L for women.

Cerebrovascular disease was defined as previous cerebral infarction, hemorrhage, or transient ischemic attack.

CHA_2DS_2-VAS_C include Congestive heart failure, Hypertension, Age $\geq$ 75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category (female) (142). A score $\geq$ 1 point in males and $\geq$ 2 point in females are indications of anticoagulant medication in a patient with AF.

Charlson Comorbidity Index was calculated according to www.mdcalc.com/calc/3917/charlson-comorbidity-index-cci. A value $\geq$ 5 is considered as severe comorbidity.

Computed tomography angiography includes a two series scanning, from the level of right atrium to the femur, and from hips to forefoot.

Diabetes mellitus included dietary, oral, or insulin treatment.

Diet quality index was based on the recommendations from the Swedish Nutrition Recommendations on dietary intake to evaluate the quality of diet.

Education level was categorized into five different groups based on the highest level of education that was accomplished: less than 9 school years, elementary school, upper secondary school, university without a degree, and university degree.

Extravascular incidental findings were classified into three different groups: immediate clinical relevance, potential clinical relevance, or no clinical relevance.

HAS-BLED include Hypertension, Abnormal renal/liver function, Stroke, Bleeding history of predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly (142). A score $\geq$ 3 points indicates an elevated risk of bleeding.

Hypertension was defined as a blood pressure $\geq$ 140/90 mm Hg, previously known hypertension, or ongoing anti-hypertensive medication.

Ischemic heart disease was defined as previous myocardial infarction, angina, coronary artery bypass grafting, or percutaneous transluminal coronary angioplasty.

Non-vascular therapy was defined as major amputation or palliative treatment.

Physical activity was expressed in MET (metabolic equivalent of task) hours per week, divided into five groups based on level of intensity and how much spent on 17 different activities.

Renal insufficiency was defined as levels of creatinine above 105 µmol/L for men and above 90 µmol/L for women.

Smoking was defined as never smoked, former smoker, or current smoker.

Symptom duration was counted in hours from symptom debut to start of operation, endovascular or open vascular surgery. The time was counted as hours from symptom debut to admission at the emergency department if the patients received conservative care, palliative care, or major amputation.

Vascular therapy was defined as endovascular or open revascularization or anticoagulation therapy.

Statistical methods

The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) Statistics, version 25-27.

In paper I, Cox proportional hazards regression model was used to discover associations between diet variables and PAD incidence, presented in hazard ratios (HR) with 95% confidence intervals (CI).

To be able to investigate how different variables impact each other, a sensitivity analysis was completed in paper I after removing mis-reporters and dietary-changers to evaluate if there was still an association between the diet quality index and incident PAD.

The rates of incidence were expressed as number of patients per 100 000 person years. Poisson distribution of events was assumed to calculate 95% confidence intervals. The exact method was used for $n < 15$ and for $n \geq 15$, the normal approximation was used (143).

In paper II, a Kaplan-Meier curve was used to describe amputation free survival.

In paper IV, intraclass correlation (ICC) with 95% CI was used to evaluate the inter-rater reliability between the two raters regarding the radiology reports. A value of > 0.7 was defined as adequate (144). Unweighted kappa was calculated to ensure that the ICC was an appropriate measure.

In paper II-IV, continuous variables were expressed in median together with interquartile range (IQR) and group differences were calculated with Mann-Whitney U-test. To analyse differences in frequencies between groups, Pearson's Chi square test or Fisher's exact test was used. Multivariable logistic regression analyses were performed and expressed in odds ratio (OR) together with 95% CI.

A p-value of < 0.05 was regarded as statistically significant in all four studies.

Overview of methods

	Paper I	Paper II	Paper III	Paper IV
Study design	Prospective observational cohort	Retrospective observational	Retrospective observational	Retrospective observational
Study sample	26 010 participants from the MDCS	161 patients (Malmö citizens)	161 patients (Malmö citizens)	118 patients
Study period	1991- 31st Dec 2016	1st January 2015 – 31st December 2018	1st January 2015 – 31st December 2018	1st January 2015 – 31st December 2018
Methods	Individuals in the MDCS. Data on dietary intake through a 7-day food diary + a food questionnaire + a 1-hour interview. Adherence to a recommended intake of six dietary components was scored (sum 0-6) to assess a diet quality index.	In hospital, operation, radiological, and autopsy registries, capturing 161 patients with ALI. Age and specific incidence rates were calculated, expressed as number of patients per 100 000 person years	Initial bedside evaluation by the doctor in the emergency department. Scoring was based on evaluation of the 6 “P”s and ABI. One point was given for every 1 “P”. The performance was scored (range 0-7), and a score $\geq$5 was defined as a satisfactory vascular leg status	Emergency CTA in patients with ALI scrutinized by two radiologists. EVIFs were classified into immediate (category I), potential (category II), or no clinical relevance (category III)
Data analysis	Cox regression analysis. HR with 95% CI	Multivariable logistic regression. OR with 95% CI	Multivariable logistic regression. OR with 95% CI	Multivariable logistic regression analysis. OR with 95% CI
Ethical approval	Ethical approval by Lund University in 1990 (Dnr §LU5190) and the Regional Ethical Review Board in 2013 (Dnr 2013/566)	Ethical clearance from the Swedish Ethical Review Authority (Dnr §2020-00764)	Ethical clearance from the Swedish Ethical Review Authority (Dnr §2020-00764)	Ethical clearance from the Swedish Ethical Review Authority (Dnr §2020-00764)

ALI; acute lower limb ischemia, CI; confidence intervals, CT; computed tomography angiography, EVIFs; extravascular incidental findings, HR; Hazard ratio, MDCS; Malmö Diet and Cancer Study, OR; Odds ratio.

Results

Paper I

Main findings

- With a median follow-up for 21.7 years, it was shown that adherence to a healthy diet decreased the risk of incident PAD. A reduced risk was primarily seen among those who fulfilled the fiber intake recommendations in the mutually adjusted multivariable model (HR 0.84; 95% CI 0.72-0.99).
- Participants that complied with the recommendations on intake of fruit and vegetables also had a reduced risk of PAD (HR 0.85; 95% CI 0.74-0.96) but when adjusting for diet variables, this association was attenuated (HR 0.91; 95% CI 0.78-1.05).
- Mis-reporters and dietary-changers were removed in the sensitivity analysis, showing that the association between diet quality index and PAD incidence was unaffected. Also, the association between fiber intake and decreased risk of PAD was persistent.

Patient characteristics

Male participants (HR 1.31; 95% CI 1.16-1.47) and smokers (HR 1.56; 95% CI 1.34-1.81) were at higher risk of PAD-development.

Kaplan Meier analyses

According to the Kaplan-Meier curve, the cumulative incidence of PAD was higher in men compared to women ($p < 0.001$)(Figure 6). When stratifying fiber intake as an ordinal variable in quartiles, the risk in cumulative incidence of PAD was reduced over the quartiles ($p < 0.001$)(Figure 7).

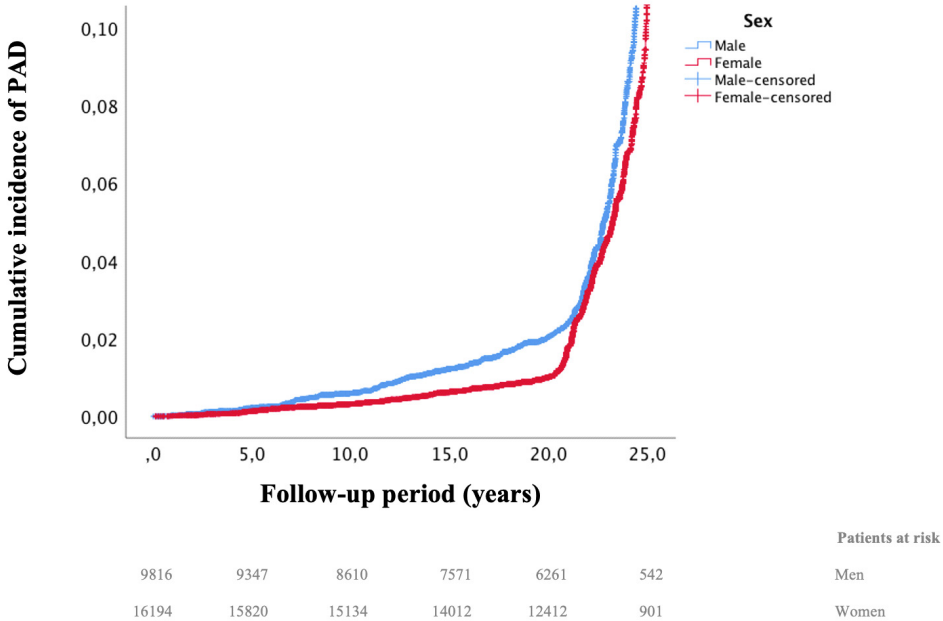

Figure 6: Cumulative incidence of peripheral artery disease (PAD) in men and women throughout the study period.

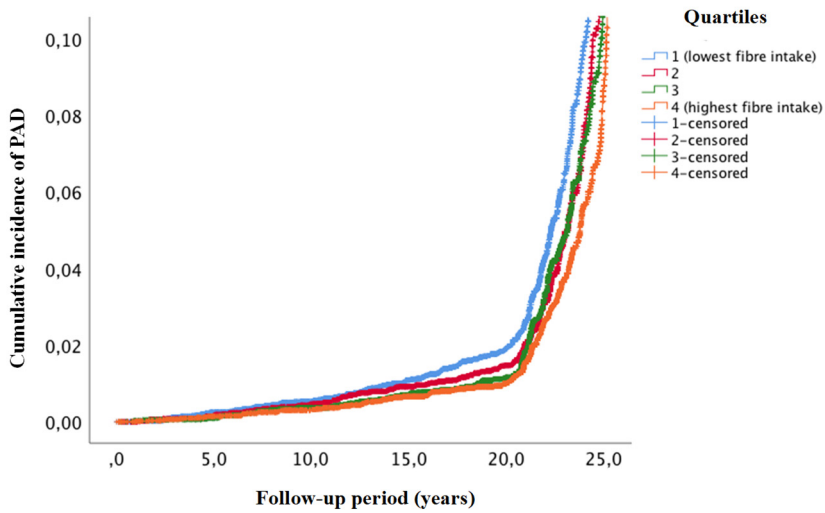

Figure 7: Cumulative incidence of peripheral artery disease (PAD) in individuals with lower and higher intake of fiber.

Paper II

Main findings

- The contemporary ALI incidence rate in Malmö was 12.2/100 000 person years (95% CI 10.3-14.1) without differences between sexes, and the most common cause of ALI was embolism with a rate of 42.2%. In 54.7% of patients with ALI, endovascular or open vascular revascularization was performed (Figure 8).
- A total of 52 patients had AF, of which 75% (n= 39) had embolism, and 38.5% (n= 20) had anticoagulation. Among the 68 patients with embolism, only 19.1% (n= 13) were on anticoagulation therapy. The median score of CHA_2DS_2-VAS_c (IQR 4-6; range 1-9) among 28 patients with AF and embolic occlusion and no anticoagulation was 5 (Figure 9), and the median score of HAS-BLED (IQR 1-3; range 1-4) was 2 (Figure 10).
- An increased risk of major amputation/death at one year was associated with female sex (OR 2.37; 95% CI 1.07-5.26), Rutherford $\geq$ IIb (OR 4.19; 95% CI 1.94-9.02), anemia (OR 2.46; 95% CI 1.08-5.62), and age (OR 1.03/year; 95% CI 1.00-1.06).

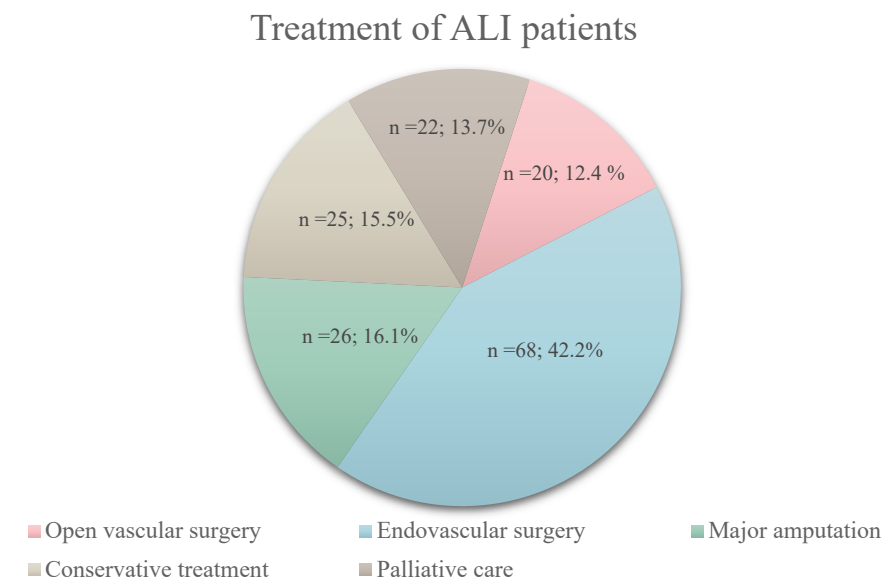

Figure 8. Management of patients with acute lower limb ischemia in Malmö between 2015-2018.

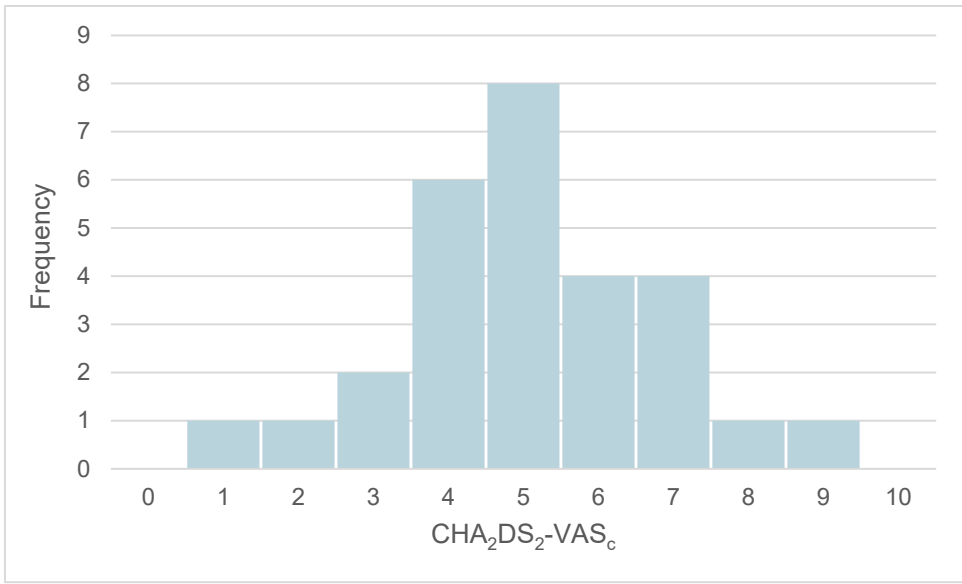

Figure 9. The distribution of CHA_2DS_2-VAS_c-score among patients with atrial fibrillation, embolic occlusion and no anticoagulation.

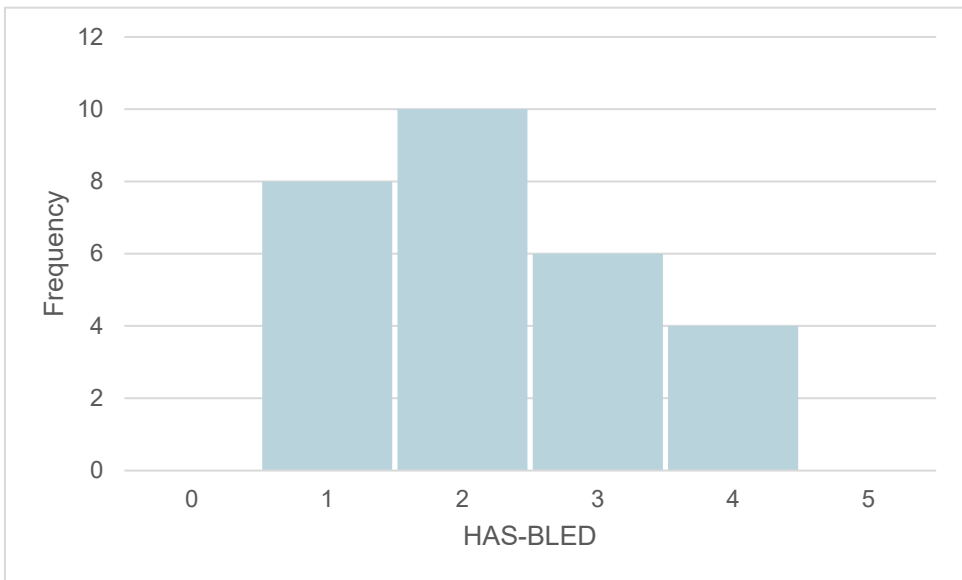

Figure 10. The distribution of HAS-BLED among patients with atrial fibrillation, embolic occlusion and no anticoagulation.

Paper III

Main findings

- A clinical bedside examination was performed satisfactorily in 55.3% of the cases and a full score of 7 points was noted in 14.9% of the examinations (Figure 11). Among 161 patients with ALI, 56 underwent CTA.
- An only ocular inspection was performed in 6.7% of examinations by physicians working at the vascular department, and 4.6% by physicians not working at the vascular department (p= 0.64). Score $\geq$ 5 points was seen in 46.6% of the examinations performed by physicians at the vascular department and 57.3% by physicians not working at the vascular department (p= 0.29).
- After adjustment for confounders, it was shown that palpation of pulses correctly (OR 0.41; 95% CI 0.20-0.85), measuring ABI (OR 0.25; 95% CI 0.11-0.55), evaluating paralysis (OR 0.43; 95% CI 0.20-0.89), and a score of 5 points or higher (OR 0.48; 95% CI 0.23-0.97), were associated with decreased risk of major amputation/mortality at one year.

Patient characteristics

Patients that underwent operative revascularization (n= 88) had a median symptom duration of 96 hours (IQR 24-282), counting from onset of symptoms to start of operation. Patients undergoing open and endovascular surgery had a symptom duration of 24 hours (IQR 7-145) and 96 hours (IQR 48-336), respectively (p=0.007).

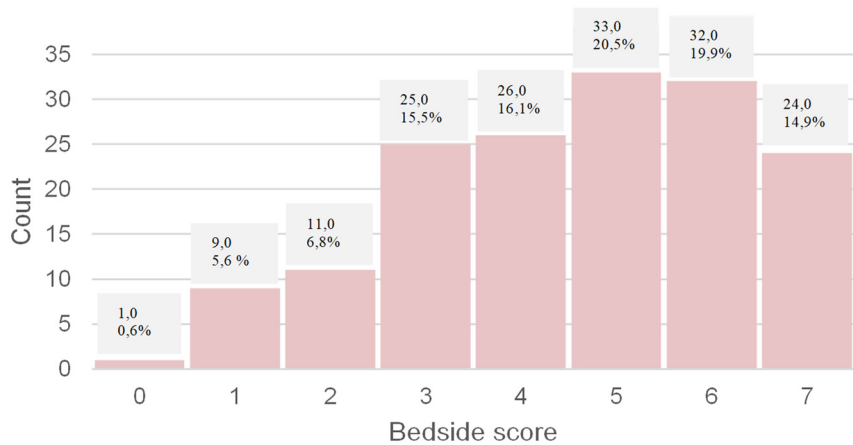

Figure 11: Distribution of initial bedside score evaluation among patients with acute lower limb ischemia.

Paper IV

Main findings

- Inter-rater reliability for EVIFs category I, expressed as ICC coefficient, was 0.94 (95% CI 0.92-0.96) between the two radiology raters. The unweighted kappa was 0.89 (95% CI 0.80-0.98).
- Twenty-nine percent of the patients with ALI that underwent CTA had EVIFs of immediate clinical relevance (category I). These findings were associated with a decreased rate of emergency revascularization (OR 0.26; 95% CI 0.10-0.66) and increased rate of major amputation/mortality at one year (OR 2.9; 95% CI 1.1-8.2)(Table 4).

Table 4. Factors associated with major amputation/mortality at 1 year in patients with acute lower limb ischemia evaluated by computed tomography angiography.

	Odds ratio	95% CI for Odds ratio	p-value*
Category 1 EVIFs (immediate clinical relevance)	2.9	1.1-8.2	0.038
Emergency revascularization	0.15	0.05-0.42	< 0.001

*Multivariable logistic regression analysis

Patient characteristics

A total of 62 patients presented with Rutherford IIb at admission to the hospital. Most patients (66.1%) underwent surgical revascularization. Patients undergoing operative revascularization (n= 78) in the study had a median symptom duration of 72 hours (IQR 19-120), counting from onset of symptoms to operation start. For individuals managed without operative revascularization, the median symptom duration from symptom debut to hospital admission was 18 hours (IQR 5-44).

Discussion

The association between fiber and PAD

In the prospective cohort study (paper I), it was shown that participants who adhered to recommended intake of fiber had a decreased risk of PAD. The role of dietary fiber intake in PAD has not been extensively studied before. The ARIC (Atherosclerosis Risk in Communities) study, a prospective cohort study, in the US did not find an association between whole grain consumption and decreased risk of PAD (145). This might be due to the fact that other foods can contribute significantly to fiber intake, not only whole grains, which the study did not consider. Another possible explanation for the lack of association might be that the US population as a whole has a generally low intake of fiber and whole grain.

An association was found between fiber intake and decreased risk of atherosclerotic cardiovascular disease (ACVD), including coronary artery disease, atherothrombotic ischemic stroke, carotid artery disease, and peripheral artery disease, in the MDCS (146). This study also found that higher intake of fish and shellfish was associated with a reduced risk of ACVD. Since fiber has protective effects indirectly, by lowering the risk of hyperglycemia, hyperlipidemia, and hypertension (56), it is fair to assume that it can reduce the risk of PAD. Another possible explanation to these associations between fiber and fish and shellfish with ACVD, might be that individuals who consume high amounts of fish and shellfish and fiber adhere to more healthy lifestyles compared to those with a low consumption.

Another study investigated diet quality and cardiovascular disease in the same cohort as paper I (147). It was shown that recommended levels of fiber intake protected from incident cardiovascular disease, and given that myocardial infarction, stroke and PAD share the same pathogenesis (40), evidence suggests that healthy diet and nutritional components are crucial in protracting the atherosclerotic process.

Lifestyle habits and PAD

In paper I, moderate alcohol consumption was associated with a reduced risk of PAD which is in line with results from the PREDIMED (Prevention with Mediterranean Diet) study (90) and the ARIC study (145). Several studies have also reported that light-to-moderate alcohol consumption is associated with a reduced risk of cardiovascular disease (148, 149). The positive effects of alcohol are not completely understood but

they may be related to higher levels of HDL-cholesterol (150), improved insulin sensitivity (151) and reduced platelet aggregation and blood clotting (152).

Smoking was associated with an increased risk of PAD in paper I compared to individuals that had never smoked, which was consistent with the fact that smoking is a known major risk factor for cardiovascular disease (153). A prospective cohort study investigated the association between smoking and three major atherosclerotic diseases, including PAD, stroke, and coronary heart disease (154). Smoking showed a much stronger association with PAD than with stroke and coronary heart disease. Among these atherosclerotic diseases, smoking cessation led to the most significant risk reduction for PAD (154). There are number of mechanisms that might explain the risks associated with smoking, such as insulin resistance, increase in inflammatory biomarkers and platelet activation, and dyslipidemia (153). It is unknown why smoking affects the arteries in the lower extremities more than the coronary and cerebral arteries. The different anatomical structure and hemodynamics of the peripheral arteries in the legs compared with coronary and cerebral arteries could be a possible explanation (155, 156).

Healthy diet and PAD

There are multiple diet models that have gained public interest, however, the Mediterranean diet is one of the most noted (157). It includes a diet rich in fruits and vegetables, whole-grain breads, nuts and seeds, and fresh and unprocessed foods. Low to moderate amounts of red wine is consumed and higher amounts of fish is eaten, and olive oil is the primary fat source, while the consumption of cheese and red meat is limited (158).

Several studies support the results in paper I that found an association between healthy diet and lower risk of PAD development. A randomized trial investigated the effect of two Mediterranean diets and one control group, on primary cardiovascular disease prevention (159). The Mediterranean diets were based on either extra-virgin olive oil or based on nuts, and the control group with a diet with reduced fat. The participants included had no cardiovascular disease at study entry but were high-risk patients with either diabetes mellitus type II or had three of several risk factors: smoking, hypertension, elevated LDL, low high density lipoproteins (HDL), or obesity. The study showed that a Mediterranean diet with extra-virgin oil or nuts decreased the risk of major cardiovascular events.

Another study evaluated the impact of a Mediterranean dietary pattern and its specific components on cardiovascular risk factors in patients with diabetes mellitus type 2 (160). They found that there are various beneficial effects on cardiovascular risk factors from different nutrient components within the Mediterranean diet. The probability of reaching recommended levels of LDL cholesterol was improved by higher consumption of fruits and vegetables, while higher fish intake helped achieve

appropriate triglyceride levels. The study concludes that it is probably a combined effect of different components included in the Mediterranean diet that led to the beneficial health effects, rather than a single food group. This synergy effect has been discussed earlier, that may result in favorable changes in key cardiometabolic pathways, such as blood lipids, insulin sensitivity, and inflammation (161).

The link between physical activity and PAD

In paper I, there were no significant results regarding the association between physical activity and incident PAD. However, this does not mean that there is no clinical relationship between them. One possible explanation for this lack of association might be due to the fact that the groups were quite small for every MET-hours groups, reducing the statistical power and thereby, reducing the chance to find significant differences between groups. Another explanation might be that some physical activities have more impact on PAD than others, but this study assessed training with time and intensity, not by the actual activity. A previous study with the same cohort specifically investigated how different activities were associated with cardiovascular mortality (162). Running was particularly associated with a reduced risk of cardiovascular mortality when divided into quintiles and the risk reduction was particularly seen in individuals in the first quintile, who ran 1-2 times a week for less than 51 minutes per week. This supports that moderate training is beneficial and that engaging in more extreme activities, such as marathons, is not necessary. According to previous research, there has been a link between extreme physical activities and AF and sudden arrhythmogenic death (163, 164).

Studies indicate that aerobic exercise reduces blood pressure, a critical risk predictor of cardiovascular events in PAD patients. Implementing this exercise as a treatment in PAD patients might decrease the risk for further disease development (165).

There are different factors that seem to influence the protective effect of physical activity against cardiovascular disease and PAD. Arterial stiffness might be an indication of an early stage of cardiovascular disease and research regarding measurements of arterial stiffness indicates a relationship with cardiovascular events (166). It has been shown that regular physical activity can reduce age-related stiffness of the arteries (167), and since PAD patients have increased arterial stiffness (165), this could be an explanation to the protective effect of physical activity in these patients. Research indicates that shorter walking distance in PAD patients is associated with increased arterial stiffness (165). A randomized clinical trial showed that aquatic walking exercise decreases arterial stiffness in PAD patients and improve muscular strength (168).

An inverse link between physical activity and blood pressure, body mass index and glucose intolerance (51) has been shown, which could also confirm the protective effect of physical activity on PAD patients.

C-reactive protein (CRP), a liver-produced acute-phase reactant, is increased during inflammation (169) and it has been shown that increased CRP levels is associated with coronary heart disease and stroke (170). Physical activity might prevent cardiovascular disease by reducing CRP levels, due to reduced inflammation (169).

It should be noted that people being physically active may have other behaviours that are beneficial in protection of cardiovascular disease, such as refraining from smoking and having a healthier diet pattern.

Unhealthy diet and atherosclerotic cardiovascular disease

Though much attention is given to healthy diets and foods, it is equally important to highlight what is unhealthy to raise awareness and ensure that the public is informed.

Foods and drinks that contain high amounts of sugar contribute to unhealthy weight gain, that may result in overweight or obesity (171). Sugar-rich products provide less satiety than fiber-rich products (172), which may result in overeating and weight gain. It is also shown that sugar is associated with increased blood pressure and higher levels of triglycerides and LDL-cholesterol (171). Thus, sugar may increase the risk of cardiovascular disease and PAD. A meta-analysis supports these findings, where an association was shown between low intake of added sugar and lower diastolic blood pressure, total cholesterol and triglycerides (173).

A salt intake of around 9-12 gram per day is regarded as too much. Sodium is consumed mainly through salt which contributes to high blood pressure, increasing the risk of stroke and heart disease (174). Around 1,7 million deaths could be prevented by reducing the intake of salt of less than 5 grams per day (175). Most of the salt intake derives from processed foods such as bacon and ham, cheese, and salty snacks, and many people are unaware of their salt consumption (174, 175).

The rise in prevalence of cardiovascular disease, diabetes and obesity, has been linked to global dietary patterns that are more “Westernized”, including increased consumption of processed meats, saturated fat, salt, and sugars, and less intake of fruits and vegetables (176). The most important dietary risk factors include low intake of whole grains and fruits, and unnecessary high intake of sodium (177). A high consumption of saturated fat is also contributing to cardiovascular mortality (178). Due to decreased physical activity and poor diets with increased salt intake and low potassium consumption, the incidence of hypertension is increasing worldwide (179).

In paper I, healthy as opposed to unhealthy food components was associated with reduced incidence of PAD in the basic statistical model where adjustments were done for age, sex, total energy intake, diet assessment method, and season. This association was attenuated in the multivariable model.

The advantages of population-based studies

Paper I-III are population-based studies including the Malmö population. Only population-based studies such as paper II can estimate the true incidence or mortality of a specific disease within the defined catchment population. Individuals are often followed over time in prospective population-based studies, such as paper I, which helps to identify risk factors and the development of different diseases. It is also possible to evaluate the cumulative incidence of a disease during a longer follow-up period.

Typically, these types of studies contain a broad range of individuals from the population, enhancing the generalizability of the results. Population-based studies consider the natural variation within the group, making the results applicable to various groups. The inclusion of a larger number of individuals, such as in paper I, increases the statistical power. This makes it easier to detect differences and enhances external validity.

Awareness of the current incidence of ALI

The population-based incidence of ALI was 12.2/100 000 person years in paper II, which is relatively unchanged compared to the epidemiological study in Gloucestershire in 1994. It might on one hand be easier to detect ALI due to the increased availability of CTA, increasing the incidence of ALI, whereas the improved medical treatment of atherosclerotic disease and AF on the other hand, reduces the risk of ALI (33, 180).

The non-operated group with ALI

Many studies focus on the revascularized group of ALI patients, treated with open or endovascular surgery. The reason for this is that non-surgically treated patients are not entered into surgical registries such as SWEDVASC (Swedish Vascular Registry)(181), or that surgeons mainly are interested in reporting results after surgery. However, in paper II, a total of 45% of patients in the population did not undergo operative revascularization. They were treated either with conservative vascular therapy, primary amputation, or palliative care. Interestingly, patients with Rutherford IIb and treatment with anticoagulant therapy alone were found to have a surprisingly good outcome (182).

In the study from Gloucestershire in 1994, only 24% received non-operative treatment (41) and one explanation for the increased rate of a non-operative approach in paper II might be due to the thorough multisource data collection. It was also noted that 92.9% of the patients living in nursing homes were treated in a non-operative manner. It is reasonable to assume that patients living in nursing homes are fragile and suffer from multiple comorbidities and may not be suitable

for revascularization. The study conducted in 1994 did not specify whether the patients were living in nursing homes, and it is possible that the patients included in that study had less comorbid conditions compared to the patients in paper II, making them more suitable for surgical intervention.

Sex differences in ALI patients

A total of 42.2% of ALI cases were due to embolism in paper II, resulting in the most common cause of ALI. Elderly females without anticoagulation therapy constituted the majority of the patients with embolism. In a previous study, elderly women (> 75 years) with AF, were less likely to be on anticoagulant medication compared to men, which is similar to the findings in paper II (183).

The results of paper II showed that female sex was associated with higher risk of major amputation and/or mortality at one year. There are limited data on sex bias in ALI patients, but it has been researched in patients hospitalised for myocardial infarction (184). Women were less likely to receive a correct diagnose at the initial medical contact and also had an increased mortality rate at one year. It has also been shown that women treated by a male physician have a less likelihood to survive a myocardial infarction (185).

During decades, clinical trial cohorts have consisted of male patients mostly (186), and with time, sex-stratified clinical studies have received more attention. Previous studies show that women have been underdiagnosed and undertreated regarding major vascular surgery such as repair of abdominal aortic aneurysm and PAD (187). It is known that women have smaller blood vessels (188) more prone to harm during vascular surgery, and reduced responsiveness to antiplatelet therapy (189), which could make them more prone to ALI because of less effective secondary prevention. It is reasonable to believe that women are undertreated regarding secondary prevention after an ALI event, since several studies state that women are less likely to be treated with high-dose intensity statins after myocardial infarction compared to men (190, 191). It is of great importance to further investigate why treatment differs between sexes.

Anticoagulant therapy in ALI patients with AF and embolism

Among the 28 patients with AF and embolism without anticoagulant therapy prior to admission in paper II, there was a clear indication for anticoagulant treatment based on the CHA_2DS_2-VAS_C-scores. In 10 patients, the HAS-BLED scoring suggested cautiousness due to the increased risk of bleeding, but there was no absolute contraindication to anticoagulant therapy in anyone of these patients.

The relationship between AF and stroke has been largely investigated, whereas extra-cerebral arterial embolism due to AF is much less studied. A previous study

including patients with fatal intestinal infarction due to embolism to the superior mesenteric artery, found that embolization to visceral and leg arteries was more common than embolization to the brain (192). This should be taken into consideration when discussing anticoagulant therapy in patients with AF but also when discussing the rationale for screening for AF.

Prevention of lower limb ischemia

The incidence and impact of diseases can be reduced by focusing on different preventive factors, including both primary and secondary prevention strategies. Primary prevention focuses on addressing risk factors and promoting a healthy lifestyle, avoiding the onset of disease. Secondary prevention aims to decrease the progression of an already established disease.

Primary prevention

There are several modifiable health behaviours that impact on arterial health including smoking, physical activity, diet, and weight (193, 194). A prospective cohort study indicated that no smoking led to the largest risk reduction among the modifiable risk factors for atherosclerotic cardiovascular disease, followed by physical activity, no obesity, and a healthy diet (146).

There is growing recognition of the impact of lifestyle factors on the prevention of atherosclerotic cardiovascular disease in addition to traditional risk factors (195). Paper I addresses the importance of primary prevention with a healthy diet regarding development of PAD, suggesting that primary prevention programs towards PAD should include fiber recommendations. This might reduce the incidence of PAD with time.

Secondary prevention

In terms of secondary prevention, a study conducted in Malmö, Sweden, investigated the effects of prevention in patients treated with endovascular or open surgery due to PAD (196). It showed that prescription of medical therapy was high including statins and anticoagulants. At admission to the hospital, 41% of the patients were smoking, while 24% smoked after one month follow up. Although the number of patients who smoked was reduced by nearly half, there is room for improvement. There is also a lack of adherence to lifestyle changes among patients with cardiovascular disease. This challenge may be explained by limited understanding of the disease and that patients often are asymptomatic dealing with a chronic disease (197). Therefore, it is crucial that physicians take responsibility for educating patients, increasing their chances of better health by prescribing physical activity or including them in smoking cessation programs.

Physicians are responsible for taking the patient's specific risk factors into account when considering anticoagulant treatment in patients with AF. As mentioned in the results, paper II, only 38.5% of patients with AF were on anticoagulant medication and in the 68 patients with embolism, only 19.1% were on anticoagulation. In paper II, the median HAS-BLED score was 2 among the 28 patients with AF, and no patient had an absolute contraindication to anticoagulant therapy. Guidelines from the European Society of Cardiology (ESC) 2024 state that bleeding risk scores are not recommended to decide whether anticoagulant therapy is appropriate, or if it should be withdrawn, to avoid under-treatment of anticoagulant therapy (198). This recommendation highlights the importance of physicians' responsibility for acknowledging risk factors and the need of individual treatment. It is crucial that patients receive appropriate treatment to prevent recurrent embolic events and addressing this gap in care is of great need to improve patient outcome.

There are several additional risk factors increasing the risk of stroke that are not included in CHA_2DS_2-VAS_C, such as the time spent in AF and poorly controlled hypertension (199). A study showed that adults with paroxysmal AF with greater amount of time spent in AF had higher risk of ischemic stroke, possibly explained by longer periods of blood stasis (200). Another study found that patients with high blood pressure during the study trial at any point had a higher risk of stroke (201), emphasizing the need for consistent blood pressure control. A significant number of patients with hypertension before study entry had high blood pressure at the start of the study, suggesting that blood pressure management needs more attention and that physicians regularly evaluate their patients. The ESC guidelines now recommend the scoring system CHA_2DS_2-VA, excluding female sex since it is considered to modify stroke risk in an age-dependent manner, rather than being an independent risk factor (198). A score of one point should indicate consideration of oral anticoagulation, whereas two points or more indicates initiating anticoagulant treatment.

Patients with symptomatic PAD should be treated with acetylsalicylic acid and statins, whereas asymptomatic PAD should be treated with statins according to guidelines (9). While it may be easier to adhere to secondary preventive medication in patients with persistent symptomatic PAD such as claudication or CLTI, or in a patient with AF having experienced an embolic event, there is little to remind the asymptomatic patient to take a preventive pill against atherosclerosis. Adherence to medication, commonly reported as being 50% in chronic diseases, is of great concern in healthcare (202). The reason for non-adherence to medicine may be attributed to costs, side effects, disbeliefs towards medicine, forgetfulness, do not see the need of medicine or do not experience an improvement in symptom reduction within a short time period, and is very challenging to deal with.

It is important to identify factors that may affect the outcome of a disease. Paper II found that anemia was a factor associated with worse outcome in patients with ALI. Similarly, anemia was associated with lower survival rates in a report of

nonagenarian patients with ALI (203). Concurrent anemia in patients with ALI has also been associated with increased rate of major amputation, and blood transfusion was associated with increased risk of death (204). Another study in PAD patients support these findings with anemia being an independent predictor of amputation and mortality (205).

There is need for further investigation whether patients with ALI and PAD would be favoured by blood transfusion in terms of limb survival. The association between blood transfusion and increased risk of mortality could be explained by patients' being more fragile but also due to the complexity of the surgery or blood loss during the procedure. There are several studies stating the impact of preoperative anemia in patients with chronic limb ischemia on mortality (206, 207), however, there is scarce data regarding management of ALI patients with anemia. One study showed that the negative effect of anemia on survival in ALI patients persisted up to six months (204), indicating that there is room to optimize patients after hospital discharge.

In Sweden, PAD patients are rarely monitored within specialized healthcare if they are asymptomatic or suffer from mild claudication but are perhaps rather followed in the primary care. Only patients with disabled function because of claudication or CLTI are referred to the vascular clinic. Therefore, physicians and nurses in the primary care must be aware of the crucialness of the disease and put effort in educating patients focusing on both primary and secondary prevention.

By acknowledging the importance of a satisfactory vascular clinical examination in ALI patients, the outcomes for these patients might improve since paper III show that patients exposed to unsatisfactory examination also have an increased risk of major amputation or death. EVIFs of category I were associated with both reduced rate of emergency revascularization and higher rate of major amputation or death at one year, implicating the importance of investigating all available CT images, both vascular and extravascular structures, in these patients.

Education in vascular examination

Paper III confirmed that there was poor adherence to the ESVS clinical practice guidelines in evaluating ALI. Only half of the first clinical examinations were satisfactory in this population-based study and the results indicated that the consequences of not performing a thorough clinical examination increased the likelihood of major amputation or death. This highlights the importance of improving initial clinical examinations in patients with ALI symptoms. Previous studies have shown that physicians failed to recognize ALI (208) and internal medicine residents had faulty technique and did not follow a stepwise exam (209).

In paper III, the physicians that examined the patients had at least a medical degree, working at the emergency department, vascular department, and other departments.

No vascular surgeon specialist was involved at first physical examination. Since 18.6% (30/161) of the examinations from doctors working at the vascular department were included in the study, the results may be biased. By including assessments performed by doctors who are exposed to patients with vascular disease on a daily basis, these examinations might be conducted in a more thorough way. In 55.3% of the patients, a satisfactory clinical examination was performed. However, this percentage did not decrease in a sensitivity analysis, excluding assessments by physicians working at the vascular department.

Another interesting reflection is that only ocular inspection was performed in 5% of the bedside evaluations, which might contradict the ethical principles that doctors adhere to (210-212). A patient should never get exposed to discriminatory treatment or be given advice without a detailed clinical assessment. The reason for the variation in clinical examination in ALI patients remains unclear but there are different factors that could affect the quality of the examination. Doctors working at the vascular department are focused on ALI as a differential diagnosis, which emergency doctors might not be. The workload on the ED could also be an explanation, with limited number of doctors working, making it harder to focus on one patient at the time and completing a detailed examination. At the vascular department, nurses are educated in performing ABI, saving time for the doctor to focus on other parts of the examination, which is not the case at the ED. It should be kept in mind that emergency physicians are expected to adhere to numerous guidelines to avoid missing any diagnosis and need to be skilled in diagnosing a wide array of conditions. However, every doctor with a medical degree should be able to perform a satisfactory bedside clinical examination of the vascular status of the lower extremities. If ALI is not recognized in time, consequences will be dreadful (30).

Extravascular incidental findings and ALI

In paper IV, 29% of ALI patients undergoing CTA had EVIFs of immediate clinical relevance. The results of the study indicated that EVIFs of immediate clinical relevance had a considerable impact on management in terms of lowering the revascularization rate and lowering amputation-free survival at one year.

Different EVIFs of immediate clinical relevance were found such as for instance, ascites, which may be caused by either cardiac failure, intra-abdominal inflammation or a malignant process (213). It is crucial for the vascular surgeon to be aware of the presence of cancer in a patient in need of emergency revascularization. If surgery is considered, this finding will guide the surgeon towards open surgery, due to the increased risk of hemorrhagic complications from malignant tissue that may arise from thrombolysis (214).

It would be interesting to investigate why specific EVIFs lower the amputation-free survival rate. One possible explanation could be that findings of immediate clinical relevance might indicate that the patient is more fragile and therefore, suffer from worse outcome. A previous meta-analysis discussed the importance of significant incidental findings found on CT in patients undergoing transcatheter aortic valve implantation, who are mostly elderly and frail patients (215). Significant incidental findings including malignancies, cardiac thrombus, and renal masses were common in this population and associated with increased mortality in the long term (215).

Another interesting aspect is that EVIFs of category I need immediate further investigation or treatment, which could prolong the time to treatment of ALI. An EVIF suggesting pneumonia in a patient with Rutherford IIb ALI, would need immediate antibiotics as soon as possible, and preferably before or simultaneous as any surgical treatment to improve chances of survival of limb and life. In paper IV, three out of eight (37%) patients with pneumonia did not receive antibiotics, one due to palliative care and two radiology exams were overlooked.

In this paper, it is stated that double reading would be favorable to lower the risk of missing immediate clinically relevant findings. This is an interpretation of the many EVIFs found, however, not specifically studied.

Caution in interpreting data in observational studies

There are different ethical aspects that must be considered when conducting research. One important aspect to reflect upon is the potential for the public to misinterpret the findings in the studies. Drawing conclusion about higher fiber intake and its association with a reduced risk for PAD could be misinterpreted, resulting in the public to mistakenly believing that a high fiber intake guarantees absolute protection to PAD, which may result in a false sense of safety. Only focusing on one specific component could also lead the public to miss other important factors that play an important role in atherosclerotic disease, such as smoking and physical inactivity. Paper I did not find a significant association with physical activity and PAD, but this does not mean that physical activity does not influence the risk of PAD. Therefore, the way researchers communicate their results with the public is important.

Ethical considerations

As mentioned, the MDCS was initially designed to investigate relationships between dietary intake and cancer. Later on, the study was extended to include associations with cardiovascular diseases. Separate ethical approvals of amendments to the main application in 1990 were required and approved in 2007,

2009, and 2013. An ethical issue concerns the question whether an ethical application should be written for every individual study, or if several studies can be conducted based on a broader phrased application. The advantage of writing a separate ethical application for every study ensures that rules and regulations are followed. However, the ethical review process is time consuming and may prolong the research process, which could be considered a disadvantage since relevant findings are not published in a timely manner. Paper II-IV are all conducted based on one ethical application that is broadly phrased.

Limitations

Even though this thesis contains novel data regarding PAD and ALI, there are several limitations of the included papers.

Paper I

In paper I, the MDCS depends on the participants correctness in self-reporting their dietary intake. It has previously been shown that individuals that are being observed may alter their behaviour (216) In addition, we cannot exclude that the participants reported everything correctly. Another limitation regarding this type of data collection includes the risk of recall bias, which is a significant risk when conducting retrospective research (217). This risk was reduced since the dietary habits in the MDCS were based on prospective data.

Interestingly, alcohol consumption was divided into quintiles based on daily intake and zero consumers was defined as no drinking the last year. High alcohol consumption earlier in life was therefore not acknowledged. Paradoxically, zero consumers with total abstinence to alcohol probably due to problematic overconsumption might in fact have been those with the highest alcohol consumption earlier in life (218). Individuals with a moderate alcohol consumption had a lower incidence of PAD in paper I. Belonging to the highest category of alcohol drinkers means that you consume slightly more than one glass of wine (12 cl) per day if you are a woman or slightly more than two glasses of wine per day if you are a man. Since the participation rate of the study was 40% and participants reported better health than non-participants (138), one might suspect that the amount of alcohol consumption among study participants was generally low, whereas a greater percentage of heavy alcohol drinkers were probably to be found among the non-participants. The association between alcohol consumption and incidence of PAD should be viewed in this context.

The data collection was never repeated regarding dietary intake or lifestyle factors such as smoking, physical activity, and alcohol, during the follow-up period in paper

I. Participants defined as non-smokers at baseline could possibly start smoking during the follow-up period. The study did not take pack-years into account, which would have been a more accurate and valuable variable.

The primary aim of the MDCS was to investigate the association between diet and cancer, rather than cardiovascular events (138). The MDCS recognized only participants with symptomatic PAD, since ABI was not measured at baseline. In paper I, participants with prevalent PAD were excluded at baseline, whereas those with asymptomatic PAD were not recognized and therefore included in the longitudinal cohort study. By including asymptomatic patients with PAD at baseline, the overall cumulative incidence of symptomatic PAD later on during the long follow is likely to be increased. It would have been interesting to measure ABI at baseline to identify asymptomatic PAD but also after follow-up to identify a larger number of PAD patients. Identifying asymptomatic PAD patients after follow-up would have increased the number of patients, increasing statistical power and perhaps strengthening the association between diet and PAD.

Paper II-III

The main limitation of paper II and III was the retrospective design with information bias and the relatively small number of ALI patients, resulting in a higher risk of type II statistical errors. It cannot be excluded that ALI patients from Malmö were treated in a hospital outside the city. However, it is most likely that these patients would either be transferred back to the hospital in Malmö or followed up there, identified by *International Classification of Diseases*, 10th Revision (ICD-10) codes upon hospital registration.

The Malmö hospital is centrally located with good access to vascular surgeons and specialists and is primarily endovascularly oriented with many patients undergoing revascularization. The results are not easily generalizable to other settings since this centre may differ from centers in low to middle income countries.

In paper III, the importance of improving the curriculum in medical programs in Sweden is discussed, based on the results that the vascular status was non-satisfactory in 44.7% of the cases. However, it is acknowledged that the discussions' brought up in the study may have some limitation regarding the fact that some doctors working at the ED in Malmö have studied in other universities than Lund university and abroad, making it difficult to draw firm conclusions about teaching and learning on vascular examination at Lund University. It is important to distinguish curriculum within the medical program from real life working conditions within the health care system to address areas in need of improvement within the medical program. There are ongoing efforts to systematically evaluate how teaching and examination of vascular status should be performed, including focus group interviews with thematic analysis of data in medical students who have

passed teaching, and theoretical and practical examination of arterial status of the lower limb at all seven Swedish universities educating doctors.

Paper IV

The fourth paper is limited by its small sample size, increasing the risk of type II statistical errors. Data is collected from one university hospital in Sweden which may limit the generalizability of the results. It cannot be assumed that every hospital in the world have access to perform CTA, making it harder to generalize the results of the study to low- and middle-income countries. Another limitation concerns the CTA imaging in the arterial phase that can result in missing relevant findings in the parenchyma. It is fair to consider implementation of standardized CTA radiology reports of the arterial tree in patients with ALI, which also addresses immediate clinically relevant EVIFs.

Competing risk

It is worth considering the effect of combining major outcomes such as major amputation and mortality into one composite variable. Follow-up time in paper II-IV was one year, and the composite endpoint was amputation-free survival at one year. By using this endpoint we avoid the issue of competing risks between major amputation and death, since amputation cannot be performed after death. In a recent report, comparing outcomes after revascularization for ALI between sexes, females had higher 30-day mortality rate after propensity score matching analysis, but higher limb salvage rate, which highly likely is attributed to the mistake to not account for competing risk of mortality (219). The goals of treatment for ALI is to save the limb and life, and the first event to occur will be registered. Amputation-free survival has for a long time been considered to be a robust endpoint when evaluating ALI and CLTI.

Strengths

There are numerous strengths of the thesis that should be emphasized. The prospective design with long-term longitudinal follow-up over 20 years is a major strength in paper I. The use of a sensitivity analysis to remove the misreporters and dietary-changers in paper I is considered a strength. The association between the diet quality index and incident PAD was nearly unchanged, and the association between recommended levels of fiber intake and decrease of PAD risk persisted. Paper I included a large sample size with 26 010 participants and there was a

relatively high cumulative incidence of PAD. PAD diagnosis was confirmed in 98% of the cases, resulting in high validity.

Paper II and III are population-based studies, covering every single ALI patient in the Malmö population. Patients receiving both operative and nonoperative treatment was included, which rarely are done in studies in surgical disciplines.

There was an impressive inter-rater availability of EVIFs of category I between the two radiologists that independently reviewed the CTA images in paper IV. The value of unweighted kappa did not differ significantly from the ICC score, which is seen as a strength. The evaluation of the consequences of EVIFs of immediate clinical relevance is also a strength of the fourth study.

Adjustment for confounding was performed in all papers in this thesis. For instance, in paper II and IV, we adjust for limb disease severity (Rutherford class) in patients with ALI when assessing factors associated with major amputation/mortality at one year. This is often only possible to do, when all patient records have been scrutinized meticulously, whereas no adjustment of Rutherford class is possible after retrieving data from large administrative databases (219).

Conclusions

- A healthy diet, specifically a high intake of dietary fiber, was associated with a decreased risk of incident PAD.
- The overall ALI incidence was 12.2/100 000 person years with no differences between sexes. The rates of major amputation and/or mortality at one year was 46.6% .
- The quality of initial clinical examination in ALI patients was considerably unsatisfactory in 44.7% of the cases, and it was associated with a higher risk of major amputation and/or mortality at one year.
- EVIFs of immediate clinical relevance were found in 29% of the ALI patients undergoing CTA and they were associated with a lower rate of emergency revascularization and higher risk of major amputation and/or mortality at one year.

Future perspectives

Role of diet and fiber on PAD development

As shown in paper I, a healthy diet and fiber play an important role in the prevention of PAD, however, not much is known when it comes to different aspects of this relationship such as how much fiber and how often intake is necessary. More research is needed to evaluate whether healthy diet can undo the consequences of unhealthy diet in PAD patients. It would be interesting to compare individuals without risk factors and unhealthy diet with individuals with several risk factors but with healthy diet, to understand the interplay between diet and risk factors.

Trends in incidence of ALI

The current age- and sex standardized incidence data of ALI in the population of Malmö outlined in paper II, would serve as baseline for future studies investigating changes in incidence of ALI in view of current guidelines emphasizing preventive antithrombotic or anticoagulant medication (31). Older patients with AF need stroke prevention since the risk of stroke rises with age (220), but up to 30% of patients at high stroke risk remain undertreated with anticoagulation (221, 222). In elderly and frail patients, the benefits of anticoagulation remain significant and should not be overlooked (223). However, there are different scales of frailty that indicate a contraindication to anticoagulant therapy, such as individuals completely dependent on personal care or approaching end of life (223), that need to be considered.

Sex differences in ALI

An interesting aspect of the findings in this thesis include the increased risk of major amputation and/or death at one year in females with ALI. A propensity score adjusted analysis conducted in Sweden (224) studied a group of ALI patients after revascularization and showed that females were older and had higher rates of AF, embolic disease and decreased kidney function. No sex differences were seen in mortality or combined mortality and major amputation rate, however, the crude 1

year-mortality rate was higher among women. The differences in mortality might be due to contributing risk factors rather than sex. Additionally, this study included only those undergoing surgical and endovascular revascularization, in comparison with paper II, which included non-revascularized patients as well. Another Swedish study showed that female sex was associated with not obtaining anticoagulant medication in a pharmacy among patients with AF, despite having experienced an ischemic stroke (225). This difference between sexes is worrisome, suggesting that elderly female patients with AF, does not receive equal care as men. Further investigation needs to be done to calculate sex differences to offer personalized treatment for patients presenting with ALI.

Given that patient sex cannot be randomized, prospective observational studies with propensity score adjustments would be valuable to achieve strong evidence of sex differences in outcomes.

Another study on PAD patients stated that societal factors are rarely considered as potential factors in sex differences in outcomes (226), and it would be interesting to investigate whether societal factors can explain the differences between sexes in ALI patients.

Improving clinical examination in ALI patients

This thesis states the importance of performing an initial clinical examination of high quality. The findings in paper III have been used to develop the teaching curriculum at the medical program at Lund university. In the third semester, students are taught to palpate all relevant peripheral pulses in the lower extremities, followed by introduction of the Doppler method to measure ABI in the fifth semester, which was previously introduced in the sixth semester. The students teach peripheral vascular status, repeat use of the Doppler probe and ABI measurement, and prepare for examination (Objective Structured Clinical Examination, OSCE) on ABI in the sixth semester. Then in term eight, students participate in scheduled receptions assessing and examining vascular surgical patients as has been performed consistently throughout many years. Since January of 2023 there has been an additional educational effort in vascular surgery for approximately 80 pre-registration house officers per year. This theoretical and practical education is given at two separate occasions per term under a four hour session. Theoretical education includes a seminar around what vascular surgery is about, inter-disciplinary collaboration in clinical practice, and a case in ALI and acute mesenteric ischemia, while practical education includes a repetition of ABI measurement and ultrasound examination of peripheral vessels. It would be relevant to evaluate how the development of vascular status in the medical program affects the clinical

examination at the emergency department several years from now to investigate if the results differ.

Role of EVIFs in patients with ALI

This thesis did not investigate the consequences of vascular surgeons reviewing CTA images. If ethically permitted, it would be interesting to perform a propensity score matching analysis between radiologists and vascular surgeons performing CTA reviews, to investigate the differences in findings and outcomes regarding revascularization, amputation, and mortality.

Populärvetenskaplig sammanfattning

Perifer artärsjukdom (PAD) orsakas av åderförkalkning som innebär en ansamling av fett och förkalkning i kroppens pulsådror. Detta är förenat med stopp i cirkulationen och en ökad risk för benamputation, hjärtinfarkt och död. Det finns flera bakomliggande faktorer som ökar risken för åderförkalkning, bland annat högt blodtryck, fetma, rökning och sockersjuka. Insjuknandet i PAD ökar med åldern och drabbar män och kvinnor i ungefär samma utsträckning.

PAD kan delas in i tre olika stadier baserat på hur symtomen ter sig. Man kan ha PAD utan att ha symtom (asymtomatisk PAD) och därmed fortfarande ha en ökad risk för hjärtkärlsjukdom och död. Om man har symtom kan man antingen lida av fönstertittasjuka, som innebär att man får ont i benet vid ansträngning på grund av behovet av ökat blodflöde till musklerna genom de förträngda kärlen. Smärtan avtar efter en kort stunds vila då behovet av blodförsörjningen till musklerna minskar. Detta leder till en minskad gångsträcka. Om åtgärder inte vidtas kan sjukdomen utvecklas till det mest kritiska stadiet av PAD, kallat kritisk benischemi. På grund av minskat blodflöde leder detta till vilovärk, och i slutstadiet till sår på foten. Risken för benamputation är hög i den här patientgruppen och risken för att dö ligger på 25% på ett år.

Akut cirkulationsstopp i benet (ALI) är ett tillstånd som kan drabba både patienter med PAD och de utan PAD. Tillståndet är kopplat till en hög risk för både amputation och död varför det är viktigt att det upptäcks tidigt. Det orsakas av ett plötsligt nedsatt blodflöde i benet och beror oftast på ett stopp i pulsådern, antingen på grund av en propp som bildats i hjärtat och som slungats iväg med cirkulationen och hamnat i pulsådern i benet, eller att en förkalkad pulsåder i benet plötsligt täpper igen. Symtomen är framför allt smärta, kallt och blekt ben, och så småningom nedsatt känsel och kraft i benet. Det leder till avsaknad av pulsar i benet. De flesta av dessa patienter genomgår en röntgen (datortomografi av bencirkulationen) för att kartlägga vart förträngningen sitter som kan hjälpa till att dels bekräfta diagnosen, dels att planera inför eventuell operation.

Den här avhandlingen innefattar fyra populationsbaserade delarbeten som fokuserar på PAD och ALI. Syftet med respektive delarbete är:

- Studie I: Undersöka om dieten kan påverka insjuknandet av PAD i en medelåldersgrupp.

- Studie II: Kartlägga antalet nya fall av ALI under 2015-2018 i Malmö och identifiera faktorer som kan påverka utfallet efter ett år.
- Studie III: Undersöka hur väl patienter med ALI undersöks på akuten i Malmö och hur nivån på undersökningen påverkar risken för amputation eller död
- Studie IV: Undersöka antalet fynd med datortomografi utanför pulsådrorna och hur dessa kan påverka risken för kärlkirurgisk åtgärd, amputation och död.

Det är känt att vår kost påverkar vår hälsa och att en hälsosam diet är kopplat till en minskad risk för hjärtsjukdom. Det är däremot mindre studerat hur kosten påverkar utvecklingen av PAD. Den första studien i den här avhandlingen bygger på en stor befolkningsstudie (Malmö Kost Cancer) som samlade in data på 90-talet i Malmö. Studien inkluderade 26 010 deltagare där man samlade in information om deltagarnas kostvanor, längd, vikt och midjemått. Man registrerade även deras utbildning, fysiska aktivitet, alkohol- och rökningsvanor. Patienter med redan känd PAD men också de med sockersjuka eller hjärtkärlsjukdom vid studiestart uteslöts från studien.

Deltagarnas kostvanor baserades på en sju dagars-dagbok som speglade deras nuvarande kostintag, en intervju samt ett matformulär för att täcka deltagarnas kostvanor från det senaste året. En hälsosam kost baserades på ett poängsystem, 0-6 poäng, där höga poäng indikerade en mer hälsosam kost. Poängen baserades på rekommenderat intag enligt Livsmedelsverket av mättat fett, fleromättat fett, fisk och skaldjur, frukt och grönsaker, fibrer och socker. Genom att summera poängen skapades ett diet-index som delades in i tre grupper: lågt, medel och högt index. Ett högt index indikerade den mest hälsosamma dieten.

Deltagarna har följts fram till december 2016, det vill säga en uppföljningstid på drygt 20 år. Totalt 1122 deltagare insjuknade i PAD under studieperioden. Med hjälp av statistiska metoder visar studie I framför allt att en fiberrik kost är kopplat till en minskad risk att insjukna i PAD men belyser också att det är viktigt med ett generellt hälsosamt kostmönster.

Det finns få studier som har kunnat kartlägga den sanna insjuknandefrekvensen av ALI i en population. Det finns också begränsad data gällande hur bra läkare är på att utföra ett kärlstatus och hur det i sin tur kan påverka förloppet.

För studie II och III granskade vi journaler från patienter som var folkbokförda i Malmö och som hade drabbats av ALI från 2015 till 2018. Vi hade tillgång till data från sjukhuset, operationer, obduktioner och röntgen och hade slutligen 161 patienter med bekräftad ALI.

Studie II visade att det fanns 12.2 fall av ALI per 100 000 personer per år, och att vara kvinna, äldre, ha blodbrist och ha påverkan på kraften i benet vid första undersökning var kopplat till en högre risk för amputation eller död. Studie III visade att undersökningen av cirkulationen i benen var bristfällig på

akutmottagningen i Malmö, vilket också var kopplat till en högre risk för amputation eller död efter ett års uppföljning.

Möjligheten till datortomografi har ökat drastiskt de senaste decennierna och de flesta sjukhusen har tillgång till datortomografi dygnet runt. Parallellt har kvalitén och upplösningen av röntgenbilderna blivit mycket bättre. Det fungerar som ett bra verktyg när det gäller att välja lämpliga patienter för kärlkirurgisk behandling. På datortomografin får man inte bara information om cirkulationssystemet utan även om strukturer utanför pulsådrorna, så som hjärta, lungor, lever, njurar och tarmar. Det finns begränsade studier när det gäller fynd utanför cirkulationssystemet hos patienter med ALI och hur dessa kan påverka risken för amputation och död.

I studie IV granskade vi röntgenbilder från patienter med ALI som genomgått datortomografi mellan 2015 och 2018. Vi hade totalt 118 patienter och hittade totalt 331 fynd utanför pulsådrorna. De här fynden delades in i tre olika kategorier, baserat på hur stor betydelse de hade. Totalt fann vi att 46 fynd var av direkt stor betydelse i form av att det krävde en omedelbar åtgärd eller behandling, som till exempel cancer eller infektion. Det visade sig att fynd av direkt stor betydelse var kopplat till en lägre chans att genomgå kärlkirurgisk behandling för ALI och en ökad risk för amputation eller död.

Sammanfattningsvis är det viktigt att förstå allvaret med PAD och ALI då det har livsfarliga konsekvenser och förstå vilka faktorer som kan förhindra uppkomsten samt förbättra diagnostiken för att öka överlevnaden.

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