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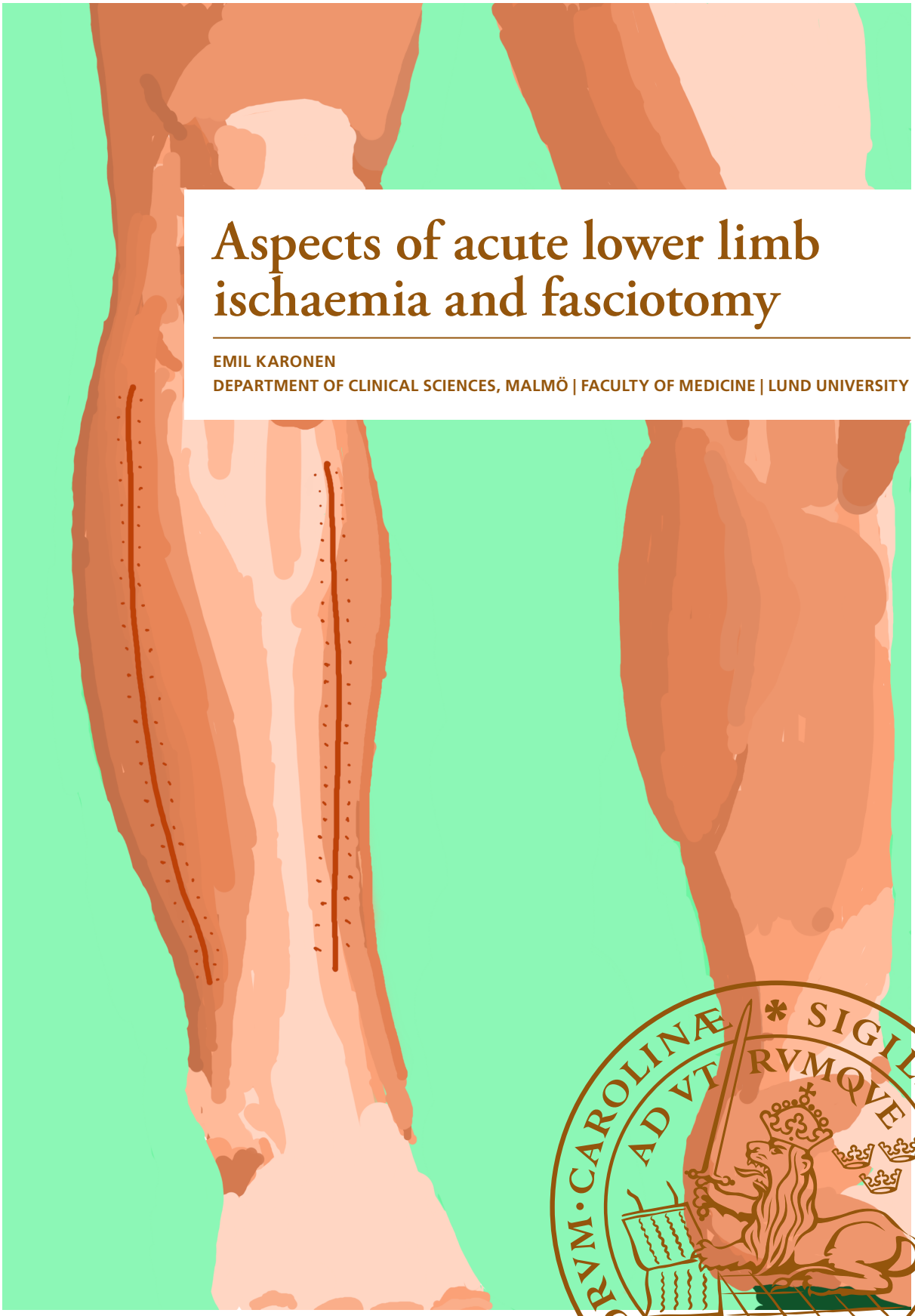

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Emil Karonen

LUND
UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Emil Karonen at Lund University to be publicly defended on May 22nd at 13.00 in Jubileumsaulan, Department of Clinical Sciences, Jan Waldenströms gata 1, Malmö Sweden.

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Abstract:

Background: Acute lower limb ischaemia (ALI) is a threat to life and limb, with diligent handling necessary for a favourable outcome. Limb-saving revascularisation may, however, come with the risk of the development of acute compartment syndrome in the calf, which must be treated through fasciotomy, either with a therapeutic, or prevented through a prophylactic, fasciotomy.

Aims

- To investigate the factors associated with fasciotomy after revascularisation for ALI.
- To compare wound and renal outcomes in patients who underwent prophylactic or therapeutic fasciotomies after revascularisation for ALI.
- To investigate the impact of sex, type 2 diabetes mellitus (T2DM), and the COVID-19 pandemic on ALI outcomes, with a special focus on fasciotomy.

Methods: Papers I–III were retrospective cohort studies of patients who underwent revascularisation for ALI at Skåne University Hospital, Malmö, Sweden. Paper IV was a retrospective cohort study of all patients in Sweden, both with and without T2DM, who underwent infrainguinal revascularisation for ALI; the study made use of data from the Swedish Vascular Registry and the National Diabetes Registry. Paper V used data from patients treated prior to and during the COVID-19 pandemic at Hospital Clínico Universidad Católica, Santiago, Chile. Confounding was addressed using propensity score-adjusted analyses in paper III, and direct acyclic graph, Cox regression analysis, and competing risk analysis (Fine-Gray subdistribution hazard model) in paper IV.

Results: Renal insufficiency (odds ratio [OR] 1.77, 95% confidence interval [CI] 1.04–3.01), motor deficit (Rutherford IIb) (OR 4.40, 95% CI 2.45–7.92), popliteal artery aneurysm thromboembolism (OR 2.26, 95% CI 1.06–4.80), and undergoing open vascular surgery (OR 3.43, 95% CI 1.97–5.98) were associated with increased odds of undergoing fasciotomy. Female sex (OR 0.43, 95% CI 0.24–0.76) and anaemia (OR 0.43, 95% CI 0.22–0.83) were associated with reduced odds of undergoing fasciotomy. In paper IV, T2DM was associated with lower odds of undergoing fasciotomy (OR 0.1, 95% CI 0.01–0.51). Undergoing surgery for ALI during the COVID-19 pandemic was not associated with a higher rate of fasciotomy (OR 0.81, 95% CI 0.17–3.80). Change in estimated glomerular filtration rates did not differ significantly between the patients who underwent prophylactic fasciotomy and those who underwent therapeutic fasciotomy (0.3ml/min/1.73 m², 95% CI 6.7–7.4) in the adjusted analysis. Neither total wound complications (p=0.16) nor median wound-healing time (p=0.44) differed between patients who underwent prophylactic or therapeutic fasciotomy. Female sex was associated with one-year mortality in the crude (hazard ratio [HR] 1.50, 95% CI 1.05–2.13) but not adjusted analysis (HR 0.99, 95% CI 0.67–1.46). Patients with T2DM had a higher major amputation rate in the crude analysis (HR 1.52, 95% CI 1.12–2.07, p=0.01), but this did not remain significant in the adjusted analysis (HR 1.45, 95% CI 0.99–2.11, p=0.05) and the competing risk analysis (HR 1.38, 95% CI 0.96–1.99). The patients who underwent surgery for ALI during the COVID-19 pandemic had a higher rate of major amputation in the crude analysis (OR 4.87, 95% CI 1.27–18.53) than the adjusted analysis (OR 3.52, 95% CI 0.88–14.05).

Conclusions: Several factors were found to be associated with increased (renal insufficiency, motor deficit, popliteal artery aneurysm thromboembolism, and open vascular surgery), and decreased (female sex, anaemia, and T2DM) odds of undergoing fasciotomy. Undergoing therapeutic or prophylactic fasciotomy did not significantly differ regarding wound or renal outcomes. In adjusted analyses, female sex, T2DM, and undergoing treatment during the COVID-19 pandemic were not significantly associated with increased rates of major amputation, mortality, or combined major amputation and mortality

Key words: acute lower limb ischaemia, reperfusion injury, acute compartment syndrome, fasciotomy

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To my mother

The question arises of whether it is possible to improve our present-day results in acute ischemia of the limbs.

- D.J. Tibbs 1962

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Papers included in the thesis

Paper I: Karonen E, Wrede A, Acosta S. Risk Factors for Fasciotomy After Revascularization for Acute Lower Limb Ischaemia. Front Surg. 2021 Mar 29;8:662744.

Paper II: Karonen E, Eek F, Butt T, Acosta S. Prophylactic and Therapeutic Fasciotomy for Acute Compartment Syndrome after Revascularization for Acute Lower Limb Ischemia–Renal and Wound Outcomes. Ann Vasc Surg. 2023 Jan;88:154-163.

Paper III: Karonen E, Eek F, Butt T, Acosta S. Sex differences in outcomes after revascularization for acute lower limb ischemia: Propensity score adjusted analysis. World J Surg. 2024 Mar;48(3):746–755.

Paper IV: Karonen E, Eek F, Drake I, Butt T, Carlsen HK, Eliasson B, Gottsäter A, Acosta S. Comparison of Outcomes After Revascularization for Acute Lower Limb Ischemia in Patients with and without Type 2 Diabetes Mellitus – A Nationwide Registry Study. Vasc Health Risk Manag. 2025 Apr 11;21:229–238.

Paper V: Karonen E, Acosta S, Quezada T, Eek F, Butt T, Bergoeing M, Mertens R, Valdes F, Vargas JS, Marine L. One Year Outcomes of Patients Surgically Treated for Acute Lower Limb Ischemia Before and During the Covid-19 Pandemic – a Retrospective Cohort Study in a Chilean Vascular Center. (Submitted).

Papers not included in the thesis

The following list includes papers by the author of this thesis that are on the subject of ALI but are not included in the PhD thesis.

Acosta S, Karonen E, Eek F, Butt T. Short-Term Complications and Outcomes in Pharmaco-Mechanical Thrombolysis First and Catheter-Directed Thrombolysis First in Patients with Acute Lower Limb Ischemia. Ann Vasc Surg. 2023;94:253–262.

Karonen E, Butt T, Eek F, Acosta S. A threat to life and limb: acute lower limb ischaemia. Br J Surg. 2024 Jul 2;111(7):znae150. doi: 10.1093/bjs/znae150. PMID: 39028764.

Abbreviations

ACS	Acute compartment syndrome
ALI	Acute lower limb ischaemia
CDT	Catheter directed thrombolysis
CLTI	Chronic limb threatening ischaemia
CI	Confidence interval
DM	Diabetes Mellitus
E-GFR	Estimated glomerular filtration rate
HR	Hazard ratio
ICD	International classification of disease
ICP	Intracompartmental pressure
IQR	Interquartile range
IHD	Ischaemic heart disease
MAP	Mean arterial pressure
NDR	National diabetes registry
OR	Odds ratio
PAA	Popliteal artery aneurysm thromboembolism
PAD	Peripheral arterial disease
SD	Standard deviation
SWEDVASC	Swedish vascular regristry
T2DM	Type 2 Diabetes Mellitus

Table I: The thesis in brief

Paper	Aim	Methods	Main results
Paper I	1. To investigate factors associated with undergoing fasciotomy (prophylactically or therapeutically) after revascularisation for acute lower limb ischaemia. 2. To investigate factors associated with mortality and major amputation.	Retrospective cohort study. 843 revascularisations and 84 fasciotomies.	Female sex and anaemia were associated with lower odds of fasciotomy. Rutherford IIb, Popliteal artery aneurysm thromboembolism, renal insufficiency, and open vascular surgery were associated with increased odds of fasciotomy.
Paper II	To compare prophylactic fasciotomy and therapeutic in terms of their association with renal injury and fasciotomy wound complications.	Retrospective cohort study. 76 fasciotomies: 40 prophylactic and 36 therapeutic.	Prophylactic and therapeutic fasciotomy had similar rates of wound complications and renal function outcomes.
Paper III	To investigate whether sex was associated with fasciotomy, mortality, major amputation, and combined major amputation/mortality after revascularisation for ALI.	Retrospective cohort study. 709 patients: 326 female and 383 male.	Sex was not associated with mortality, major amputation, combined major amputation, and mortality when adjusting for propensity score. Female sex retained an inverse association with fasciotomy in adjusted analysis.
Paper IV	1. To investigate whether type 2 diabetes mellitus was associated with mortality, major amputation, or combined major amputation and mortality after revascularisation for ALI. 2. To investigate whether there was an association with fasciotomy.	Nationwide retrospective cohort study: National Diabetes Registry and the Swedish Vascular Registry. 245 patients with type 2 diabetes mellitus, and 370 without.	Type 2 diabetes mellitus was associated with an increased risk of mortality and major amputation, but a lower risk of mortality in the crude analysis. The difference did not remain significant in the adjusted analyses. Type 2 diabetes mellitus was associated with lower odds of fasciotomy in the crude and adjusted analyses.
Paper V	To investigate differences in mortality, major amputation, and fasciotomy in a Chilean vascular centre, before and during the COVID-19 pandemic.	Comparison between patients treated prior to the COVID-19 pandemic (n=59) and during the COVID-19 pandemic (n=53).	Receiving treatment during the COVID-19 pandemic was associated with higher odds of major amputation in the crude analysis. It was not associated with mortality, combined major amputation and mortality, nor fasciotomy in the crude analysis, and in the adjusted analysis the difference in major amputation was no longer significant.

Introduction

Peripheral arterial disease

Peripheral arterial disease (PAD) is the manifestation of atherosclerotic disease in peripheral arteries, and mainly affects the lower limbs[1]. It primarily affects the elderly, and is initially often asymptomatic[2]. It has a high prevalence in the global population, with estimates of 200 million people worldwide being affected in 2010 – a figure that is estimated to rise due to an ageing global population[3]. Important risk factors for the development of PAD are smoking, diabetes mellitus (DM), hypertension, and hypercholesterolemia[4,5]. The first signs of PAD are usually the development of exercise-induced pain in the calves, commonly referred to as intermittent claudication[6]. The first line of treatment for intermittent claudication is smoking cessation, an exercise programme, medical therapy with statins and anti-platelet medication, and optimisation of antihypertensive and DM treatments[7]. Patients with PAD often develop collateral vessels that may, at least in part, compensate for the reduced flow in the atherosclerotic arteries[8]. In incapacitating intermittent claudication that has failed first-line treatment, an endovascular or open vascular revascularisation procedure may be considered; however, early revascularisation procedures are associated with further reinterventions, without improved long-term outcomes[9].

The end stage of PAD, occurring in a minority of patients with PAD, is chronic limb-threatening ischaemia (CLTI), wherein the flow in the atherosclerotic arteries and collaterals is not sufficient for long-term limb viability[10]. The patient suffers from extremity pain at rest and has a high risk of developing ischaemic ulcers, and CLTI is a major threat to limb viability[11]. For the diagnosis of CLTI, the duration of symptoms must have persisted for more than 14 days[12]. CLTI is treated through open or endovascular revascularisation and aggressive medical treatment[13]. If revascularisation is not feasible or is unsuccessful, amputation of the limb is usually necessary.

Outside of symptomology in the lower limbs, PAD is associated with increased coronary heart disease and cerebrovascular disease rates[14], and with mortality[15]. The risk of coronary heart disease and cerebrovascular disease is primarily due to the presence of atherosclerosis in the coronary, carotid, and cerebral arteries[16].

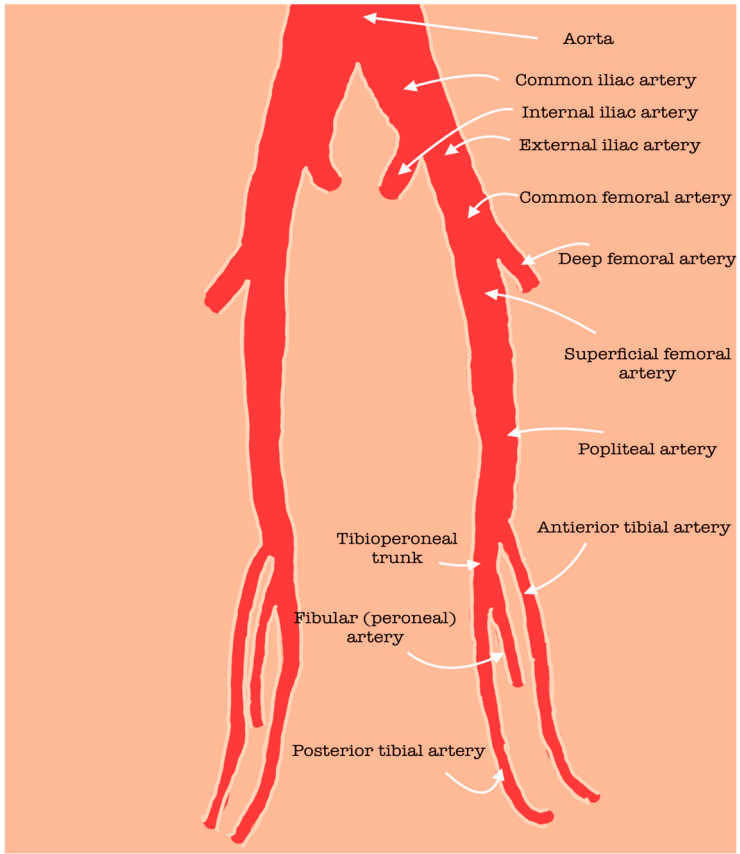

Figure I: Schematic drawing of the arteries of the lower limbs. ©Emil Karonen

Diabetes mellitus

DM is an umbrella term for hyperglycaemia caused by decreased secretion and/or decreased sensitivity to insulin, with the two most common types being type 1 and type 2 diabetes mellitus (T2DM)[17]. Type 1 DM is an autoimmune disease that is characterised by an inert immune response against the insulin-producing beta cells in the endocrine pancreas[18]. This results in loss of both beta cells and thus production of insulin, which is crucial for glucose metabolism. Type 1 DM usually develops during childhood or adolescence, but may also develop in adulthood, and requires lifelong substitution with exogenous insulin[19]. T2DM differs in its pathophysiology from type 1 DM as it is caused by decreased sensitivity to insulin; this is caused by long-term high glucose intake and insulin levels, progressing to insulin resistance and hyperglycaemia[20]. T2DM is heavily dependent on lifestyle factors such as diet

and exercise, and closely associated with metabolic syndrome, but it also has a strong genetic aspect[21]. Initially, T2DM is treated through lifestyle changes, oral medications such as metformin and sodium glucose transporter-2 inhibitors, and incretins such as oral or subcutaneous glucagon-like peptide-1 analogues[22]. T2DM may progress by pancreatic beta cell degradation with a loss in insulin production, making the patient dependent on exogenous insulin injections. DM is associated with micro- and macrovascular disease, with increased rates of PAD, chronic kidney disease, and ischaemic heart disease[23]. In patients with intermittent claudication the prevalence of DM is around 30%, rising to between 50 and 70% in patients with CLTI[23]. DM is associated with major amputation of the lower limb(s)[24], and having diabetic ulcer and concomitant PAD is associated with even higher odds of major amputation than only having a diabetic ulcer[25].

Acute lower limb ischaemia

Presentation, aetiology, and incidence

Acute lower limb ischaemia (ALI) is a life- and limb-threatening surgical emergency. It is characterised by a sudden onset of tissue ischaemia due to reduced or no arterial blood flow in the lower limb(s), and the symptoms of ischaemia should not have been present for more than 14 days at the time of diagnosis[26]. As the disease develops suddenly, it provides no opportunity for collateral vessels to develop. In some patients with pre-existing PAD, there may already be existing collateral networks at the onset of ALI; however these are usually not sufficient to prevent ALI, but may limit or delay tissue damage[27]. In a clinical setting it can be difficult to distinguish between acute-on-chronic ALI (ALI on the basis of established PAD) and CLTI due to the often similar underlying aetiologies of the two conditions and uncertain symptom duration. In developed countries, the estimated yearly incidence is 10–26 cases per 100,000 people[28-30].

ALI is an umbrella term for acute onset ischaemia affecting the lower limbs irrespective of aetiology, with the most common aetiologies being thrombotic or embolic occlusion of the arteries of the lower limb, and/or the aorta and iliac arteries, limiting blood flow to one or both limbs. Historically, peripheral arterial embolism has been the primary aetiology of ALI, due to a combination of rheumatic heart disease, congenital heart disease, ischaemic heart disease, heart valve disease, and atrial fibrillation[31-34], meaning that ALI affected both young and old patients. However, with the introduction of paediatric heart surgery and antibiotic treatment for streptococcal pharyngitis, which has almost eradicated rheumatic heart disease in the developed world[35], there has been a change towards ALI generally affecting an older population with often underlying comorbidities[36]. In developed nations

today, embolic disease is usually related to atrial fibrillation or proximal mural aortic thrombosis[37].

Due to an ageing population, increase in the prevalence of PAD, and persistently high levels of smoking, the most common causes of ALI today are thrombosis from atherosclerotic plaque rupture in underlying PAD, in a stent, stent-graft, or graft after previous vascular reconstruction[38, 39]. The severity of ischaemia is usually not as profound in patients with thrombotic occlusions as in embolic occlusions; however, treatment is often more challenging, as treatment of the underlying PAD, in addition to initial treatment of the thrombus, is usually necessary to retain patency of the arteries long term[40].

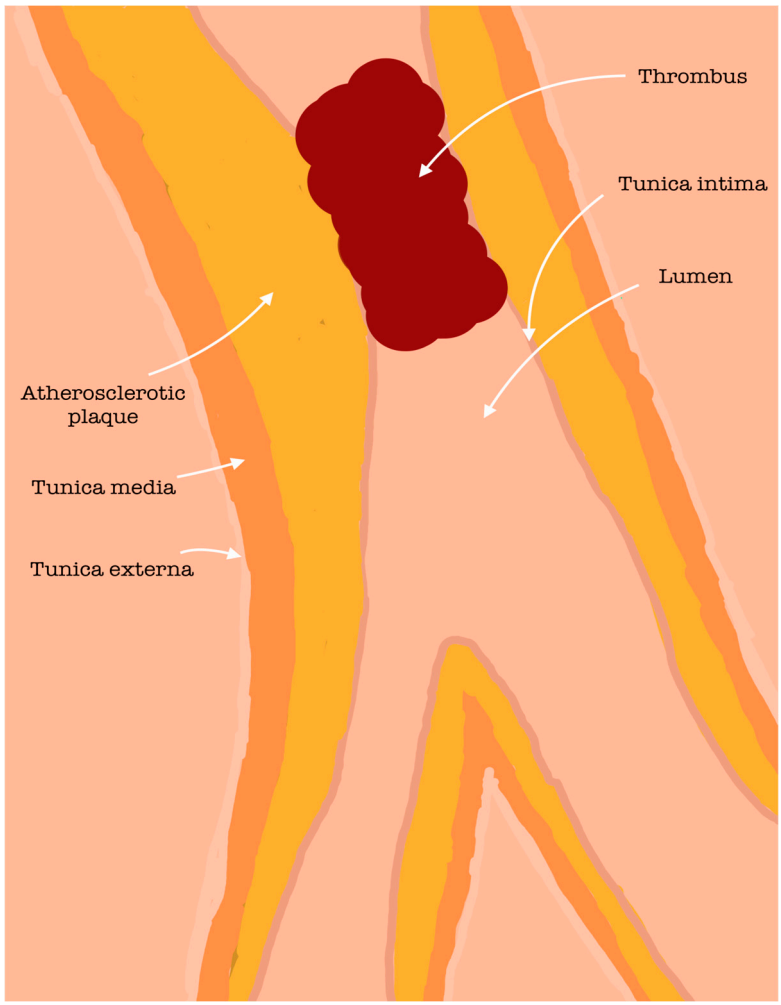

Figure II: Thrombotic occlusion of atherosclerotic artery. ©Emil Karonen

In patients with PAD, a lower ankle-brachial index, undergoing surgical intervention to the arteries, and having atrial fibrillation have been associated with a higher likelihood of developing ALI[41]. Thromboembolism due to popliteal artery aneurysm is another important aetiology, primarily affecting men[42]. ALI may also develop as a surgical complication due to trauma, arterial dissection, severe deep venous thrombosis, or circumferential burns, among other causes[42-45]. Non-thromboembolic ALI differs in treatment, and is not within the scope of this thesis.

In textbooks, the mnemonic 'the 6 P's' is often used to remember the cardinal signs of ALI. These consist of pain, pallor, pulselessness, poikilothermia (perishing cold), paraesthesia, and paralysis, but they are not generally all present at one time[46]. The initial sign is usually a cold and painful limb. The sensory nerves are the first structures to be affected by tissue ischaemia leading to paraesthesia, followed by the motor nerves (motor deficit); ultimately, the muscle and skin tissue turn necrotic[47]. Thus, the findings of clinical examinations can be used to estimate the severity of ischaemia and provide some insight as to whether the limb is viable, and how urgently the revascularisation procedure must be performed. The Rutherford classification is used to stratify the severity of ischaemia, and can be used to guide decision-making[48]; however, it is not validated, and consultation with a vascular surgeon is important to create an optimal treatment plan[26].

Table II: The Rutherford classification[48]

Rutherford level	Severity	Sensory function	Motor function	Arterial doppler signal	Venous doppler signal
I	Viable	Intact	Intact	Yes	Yes
IIA	Viable with urgent treatment	Mild sensory deficit	Intact	No	Yes
IIB	Viable with immediate treatment	More profound sensory deficit	Mild to moderate deficit	No	Yes
III	Unviable	Profound sensory deficit or anaesthetic	Severe motor deficit or paralysis	No	No

Clinical examination and imaging

Upon suspicion of ALI, a thorough clinical examination of the patient is warranted, including manual examination of the aorta and peripheral arteries, testing of the ankle-brachial index, and motor and sensory examination of the feet/limbs[49]. These basic physical examinations, which are performed bedside in the emergency department, can give the treating surgeon valuable information about the likely level of occlusion and the severity of the ischaemia. Usually, computed tomography angiography of the lower extremities is performed for diagnosis, to evaluate the

level of occlusion, and to facilitate planning of the revascularisation procedure[50]. In some cases, magnetic resonance angiography or duplex ultrasound can also be used for diagnostic purposes[51]. Imaging is important not only for evaluating the level and distribution of occlusion, but to provide information about the possible presence of concomitant PAD or aneurysms[52]. In some instances, with severe ischaemia, the vascular surgeon may prefer immediate transfer of the patient to an operating theatre, with percutaneous diagnostic angiography being performed in tandem with emergency revascularisation, as a means to prevent delays in revascularisation[53]. One study found that computer tomography angiography of patients with severe ischaemia was associated with improved outcomes compared to immediate revascularisation, suggesting that the latter is usually performed in cases where there is an expected high risk of poor outcome if treatment is delayed[50]. Where underlying atrial fibrillation is suspected as an embolic source, an electrocardiogram should be conducted to confirm the diagnosis, and an echocardiogram may be used to determine whether residual thrombus exists; however, the necessity of performing a transthoracic echocardiogram has been questioned[51, 54].

Treatment of ALI

Where there is a strong suspicion of ALI, clinical practice is to start the patient on unfractionated heparin drip with a bolus dose, and then adjust treatment according to the activated clotting time values, with the rationale of hindering further progression of the embolus/thrombus[55]. In some centres, low-molecular-weight heparin is used due to its ease of administration and no need of titration[56]. Heparinisation is also maintained throughout the revascularisation procedure to minimise perioperative thrombosis[57].

Open vascular surgery

Surgery has been conducted for ALI since at least the 1800s, initially with poor outcomes[58]. The first successful embolectomies were performed in the early 1910s and the 1920s[58]; as early as the 1930s, pioneering attempts were made to treat aortic thrombi using local anaesthesia with a retrograde femoral artery access, introducing an oiled catheter for thromboaspiration or flushing with saline[31, 59]. In the 1960s, Fogarty embolectomy was introduced; this used an open vascular access, usually at the femoral artery, or for more distal emboli at the popliteal artery, and involves a balloon-tipped catheter being introduced into the artery and inflated in order to retrieve an embolus or a thrombus[60]. This marked a paradigm shift in ALI treatment, and it is still widely used today. It has, however, a limitation in that it is most optimally used in embolic ALI without chronic atherosclerotic plaques[61] – and, due to the ageing population, this is an increasingly rare situation. A specific risk of a

thrombus or embolus in the aorta or common iliac artery is the potential for it to be dislodged and cause contralateral limb embolisation[60].

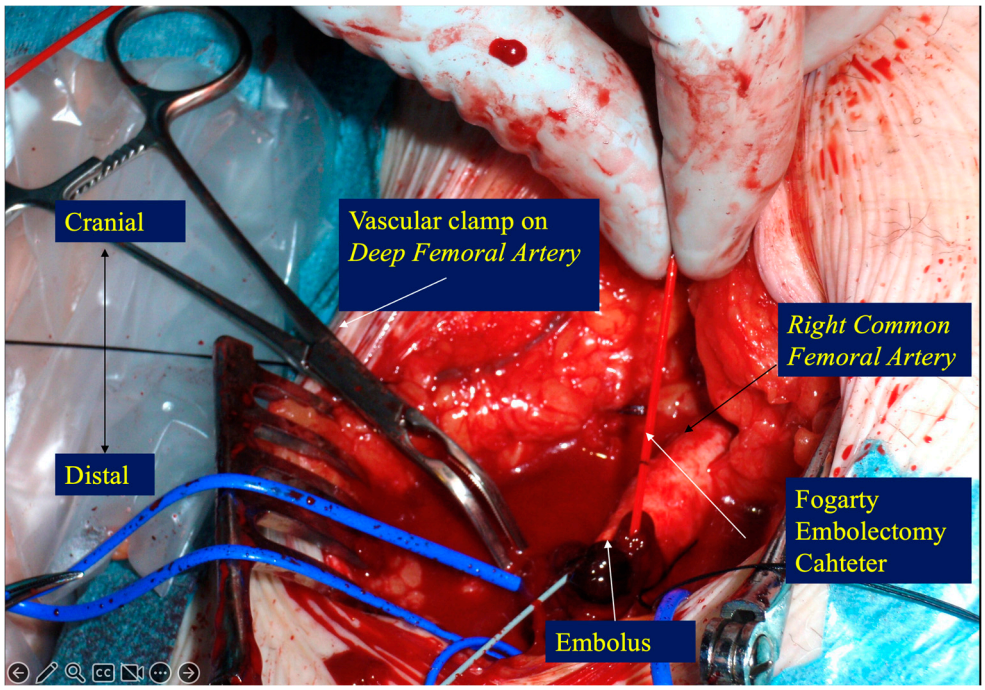

Figure III: Vascular surgeon conducting fogarty embolectomy to remove embolus causin ALI through access in the right common femoral artery. ©Stefan Acosta.

Bypass surgery, using vein or synthetic grafts, can be utilised as a primary or secondary revascularisation procedure, especially for patients with acute-on-chronic ischaemia where an endovascular-first approach either is not suitable or was previously unsuccessful[62,63]. This is usually time-consuming, poses a high risk of major bleeding, and requires a surgeon who is experienced in open vascular surgery[63]. It is also dependent on having a distal vessel with sufficient run off[64]. Endarterectomy may be used as an adjunct to treating underlying PAD in the common femoral artery to improve patency in the native vessels or in distal reconstructions[65].

Endovascular treatment

Endovascular surgery has revolutionised how vascular diseases are treated[66], and facilitates minimally invasive surgery without the need for general anaesthesia, greatly reducing the risk of wound infections and other wound complications – all important considerations given the increasing age and frailty of patients[67, 68].

Catheter-directed thrombolysis (CDT) was introduced in the 1980s, and was the first endovascular procedure to be performed to treat ALI; here, a fenestrated catheter is introduced into the occlusion, thrombolytics agents are continuously administered [69], and a diagnostic angiogram is performed (usually once a day) to evaluate the treatment until clot resolution[70]. Intracranial haemorrhages are rare (approximately 1% of patients) but often fatal, and contraindications to CDT – such as recent stroke, intracranial trauma, recent neurosurgery, or known intracranial tumour – should be followed to minimise risk[71]. In recent years, endovascular treatment has further progressed, with the introduction of thromboaspiration and pharmacomechanical thrombolysis, which reduces or even omits the use of thrombolytic agents, potentially reducing bleeding complications and resulting in a faster revascularisation than classic CDT[72, 73]. To date, no adequate randomised controlled trial has been conducted to compare these new endovascular treatments to classic CDT or open vascular surgery[74].

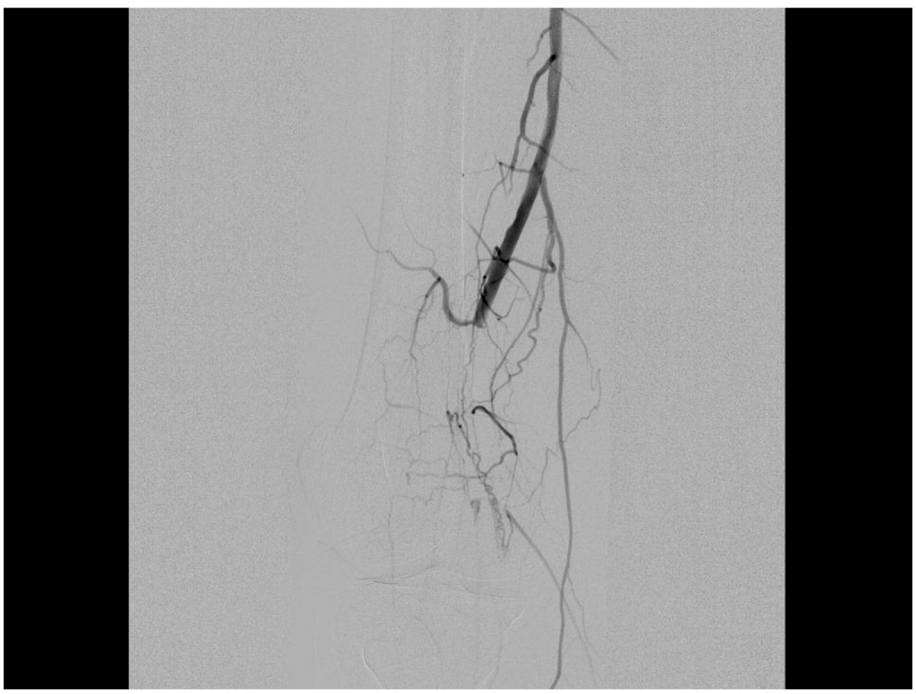

Figure IV: Percutaneous angiography of an occlusion of the popliteal artery, causing acute lower limb ischaemia. ©Stefan Acosta.

Endovascular procedures also enable any underlying PAD to be treated with percutaneous transluminal/intimal balloon angioplasty, with or without stenting being performed as an adjunctive procedure or part of a hybrid treatment for underlying PAD, as a way to improve blood flow and for the reconstruction to retain

patency[65]. Endovascular atherectomy has also been introduced as an option for vessel preparation prior to angioplasty in atherosclerotic vessels[75]. Angioplasty is often performed using drug-eluting balloons/stents in order to minimise intimal hyperplasia and improve long-term patency[76]; however, the use of drug-eluting devices has not been shown to reduce the risk of major amputation[77, 78].

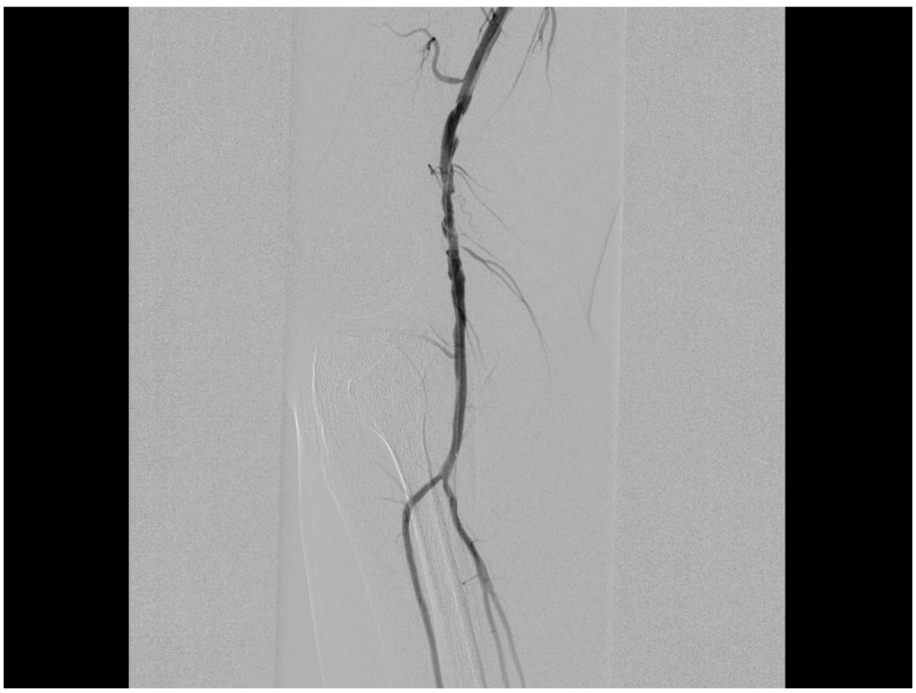

Figure V: Follow-up angiography after successful catheter-directed thrombolysis for a popliteal artery occlusion. ©Stefan Acosta.

Open vascular or endovascular surgery for ALI

Randomised controlled trials were conducted in the 1990s without a clear superiority for either open or endovascular options[79-83]. Since then, endovascular procedures have undergone extensive development, but the lack of new randomised controlled trials means that the previous ones are potentially outdated. Due to the multifaceted surgical approach required in order to treat ALI, a randomised controlled trial would be very difficult to design today. In high-income countries, endovascular-first approaches are widespread; however, endovascular revascularisation is associated with increased costs compared to open vascular surgery[84]. The use of CDT in Rutherford IIb patients has been controversial due to the prolonged time until resolution of the clot, and thus presumably longer duration of ischaemia. However, CDT has also been used for with Rutherford IIB, although only recommended in selected patients[26, 85]. Open vascular

surgery is still usually preferred for Rutherford IIB, as it usually allows revascularisation to be achieved more rapidly[26]. Although new endovascular treatment methods have been developed, giving vascular surgeons many potential options for revascularisation, the evidence lags the practice; as such, which option is selected is the discretion of the treating surgeon.

Hybrid treatment

It is recommended, where possible, to treat ALI without significantly delaying the treatment, at a high-volume vascular centre in a hybrid suite[26]. This enables both open vascular surgery and endovascular techniques to be utilised, providing the surgeon with an arsenal of instruments with which to treat ALI. This is especially beneficial for patients with underlying PAD, which may necessitate the use of different modalities within the same surgical session.

Primary amputation, medical therapy, and end-of-life care

Almost half of patients with ALI do not undergo revascularisation[86]. In patients with very mild ischaemia, where the limb is not immediately threatened (Rutherford I), a conservative treatment with medical therapy can be applied[26]. In patients presenting with irreversible ischaemia (Rutherford III), major amputation is usually performed[48]. However, it is notable that a study found that two thirds of patients with Rutherford III at admission who underwent revascularisation survived with an intact limb, challenging the dogma that all Rutherford III patients have irreversible ischaemia[87]. For some patients with severe but non-irreversible ischaemia, the action of revascularisation may pose a direct and significant threat to their life, and these patients may benefit from primary amputation as a life-saving surgery[88].

For patients who are old and frail, neither emergency revascularisation nor amputation may be in their best interest. In these cases, best supportive care may be the preferred option. ALI may also develop as a sign of the process of dying, known as agonal thrombosis, and should in those circumstances not be actively treated[26].

Revascularisation outcomes

Short-term outcomes after revascularisation are still, despite decades of surgical and pharmacological advances, a 30-day mortality rate of 4.5–8.9% and a 30-day major amputation rate of 7.6–11.0%[89-92]. One-year figures are even less inspiring, with a reported mortality rate of 14.2–24.4%, and amputation rate of 14.3–19.2%[89-92]. These figures reflect patients who underwent revascularisation for ALI, but a large proportion of patients with ALI do not undergo revascularisation[28]. Some patients

with ALI, especially patients with mild ischaemia, may not need emergency surgical revascularisation, and can thus be treated medically[86]. Patients with ALI who do not undergo revascularisation are rarely included in published cohorts, resulting in the published figures being overly flattering due to patient selection. There have been two epidemiological studies where a complete population has been screened for a year for ALI, famously in Gloucestershire, the United Kingdom in the 1990s and more recently in Malmö, Sweden. The Gloucestershire study reported a 30-day major amputation rate of 7.1% and a mortality rate of 26.2%, and the Malmö study a one-year major amputation rate of 22.4% and mortality rate of 32.3%[28, 30]. These studies provide valuable information regarding the real-world incidence and outcomes of ALI for patients, but may underestimate the risk of major amputation for patients who undergo revascularisation. This is on the basis that mortality is a competing risk to major amputation, and it can be presumed that mortality figures are higher in patient populations that do not undergo revascularisation. In the USA, a study of patients with ALI who required in-hospital treatment showed a 30-day mortality rate of 19.2%, and a one-year mortality rate of 42.5%; the amputation rate was 8.1% for 30 days, and 11.0% for one year[29].

Reperfusion injury

Completely ischaemic muscle cells without collateral blood flow seem to be viable for four hours[93]. During ischaemia, aerobic production of adenosine triphosphate is inhibited, which leads to shifts of intracellular ions due to adenosine triphosphate-dependent ion pump dysfunction[94]. After reperfusion, the cellular milieu in the previously ischaemic limb may be initially worsened by the reintroduction of oxygenated blood, as the oxygen leads to the creation of pro-inflammatory reactive oxygen species[94]. Reperfusion of a limb with a significant amount of necrotic muscle cells may lead to a washout of toxic compounds such as myoglobin and potassium, with a direct risk of acute kidney injury and cardiac arrythmia[95].

Attempts have been made to reduce the severity of reperfusion injury, especially with so-called ‘controlled reperfusion’. Studies on rodents were performed in the late 1980s, leading to the finding that hindlimbs with ischaemia treated with controlled reperfusion had less oedema, decreased leg volume, and better-preserved contractile function compared to limbs where full reperfusion was performed initially[96, 97]. Controlled reperfusion for ischaemic limbs was experimentally introduced in clinical settings in the late 1990s, and several retrospective studies and case studies report promising results[97-101]. Despite these early encouraging findings, and rational molecular mechanisms, a randomised controlled trial of controlled reperfusion in patients revascularised for ALI failed to yield meaningful improvements in limb salvage and survivability[102].

Acute compartment syndrome

Pathophysiology, presentation, and implications

A severe complication of reperfusion injury in the lower limb is the development of acute compartment syndrome (ACS), most commonly in the calf[103]. The calf muscles are contained within a semi-strict structure called fascia, which forms compartments[104]. During swelling of the muscle, for example because of severe inflammation or oedema after reperfusion, the fascia only allows for some expansion[105]. When the fascia is maximally stretched, the pressure within the fascia – the intracompartmental pressure (ICP) – starts to increase. An increase in ICP affects arterio-venous circulation, and a sufficient increase leads to tissue ischaemia, as oxygenated blood cannot pass through the capillaries[106]. It is hypothesised that this is the main mechanism that leads to ACS. It is a surgical emergency, as myocyte necrosis may start within four hours of onset[107]. In contrast to ALI, ACS is primarily a disease of the microcirculation, therefore the muscle may be severely ischaemic but the patient may still have normal pulses in the foot.

The development of ACS is insidious, with pain often being an early sign[104]. A rigid muscle compartment, usually in the lower leg, and pain with passive stretching are also signs of ACS[108]. More specific signs, such as pulselessness, pallor, and paralysis are usually late presenting, and associated with poor outcomes[109]. The '6 P's' mnemonic that is used for ALI can be used; however, on clinical examination one is only likely to find pain when the ACS is still certainly within the treatable window[107]. If treatment is delayed, there is a high risk of muscle necrosis and nerve damage, and a particular risk of drop foot from peroneal nerve damage[110]. Muscle necrosis due to ACS has the same potential systematic effect as that caused by revascularisation injury after revascularisation for ALI, with the release of potassium ions and myoglobin, and risk of cardiac arrythmia and acute kidney injury[111]. Ultimately, muscle necrosis and nerve damage after ACS may lead to loss of function in the limb, chronic pain, and the need for amputation, even with patent vessels[112, 113].

Diagnosis

The diagnosis of ACS may be challenging as early signs are vague, and a delayed diagnosis often has dire consequences[109]. Treatment is generally performed on suspicion, but attempts have been made to standardise diagnosis using measurement of the intracompartmental pressure, and sometimes relating this to the mean arterial pressure (MAP) or the diastolic pressure. A normal ICP in the calf musculature is between 0 and 22.5 mmHg in healthy adults, and may rise as high as 60mmHg while exercising; pressures are somewhat lower for healthy women compared to men, and

decrease as age increases[116]. Several cutoff points for ICP, alone and related to MAP or diastolic pressure (such as diastolic pressure – ICP being less than or equal to 30), have been proposed, but at the time of writing there is no consensus on any specific values[109, 115]. Further complicating diagnosis is that patients may often have higher ICP than proposed threshold ICP, without the development of ACS[116]. Some studies have suggested continuous monitoring of compartment pressures in patients with tibial fractures (risk of ACS due to haematoma/oedema in calf compartments and not due to reperfusion injury), but this is invasive and may lead to overdiagnosis and overtreatment[115]. A similar approach in ALI could potentially also result in overdiagnosis and overtreatment. There have been suggestions of other modalities for diagnosis, including ultrasound, intracompartmental pH indicators, and near-infrared spectroscopy, but none of these are in routine clinical use[109, 117].

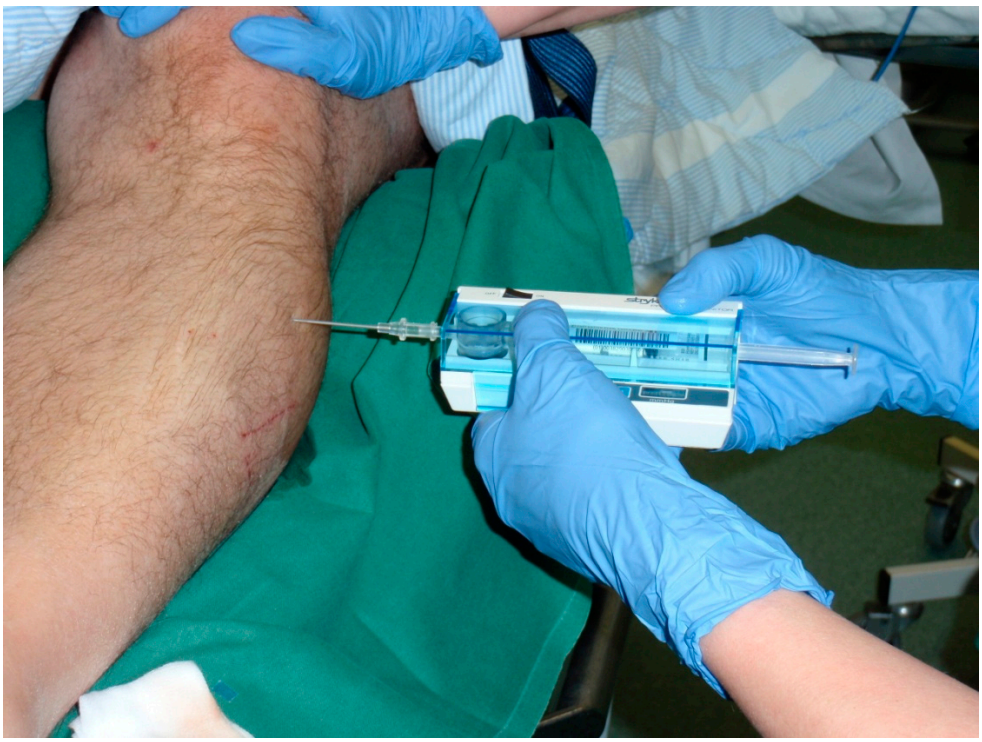

Figure VI: Measurement of the intracompartmental pressure in the anterior compartment of the lower leg. ©Stefan Acosta.

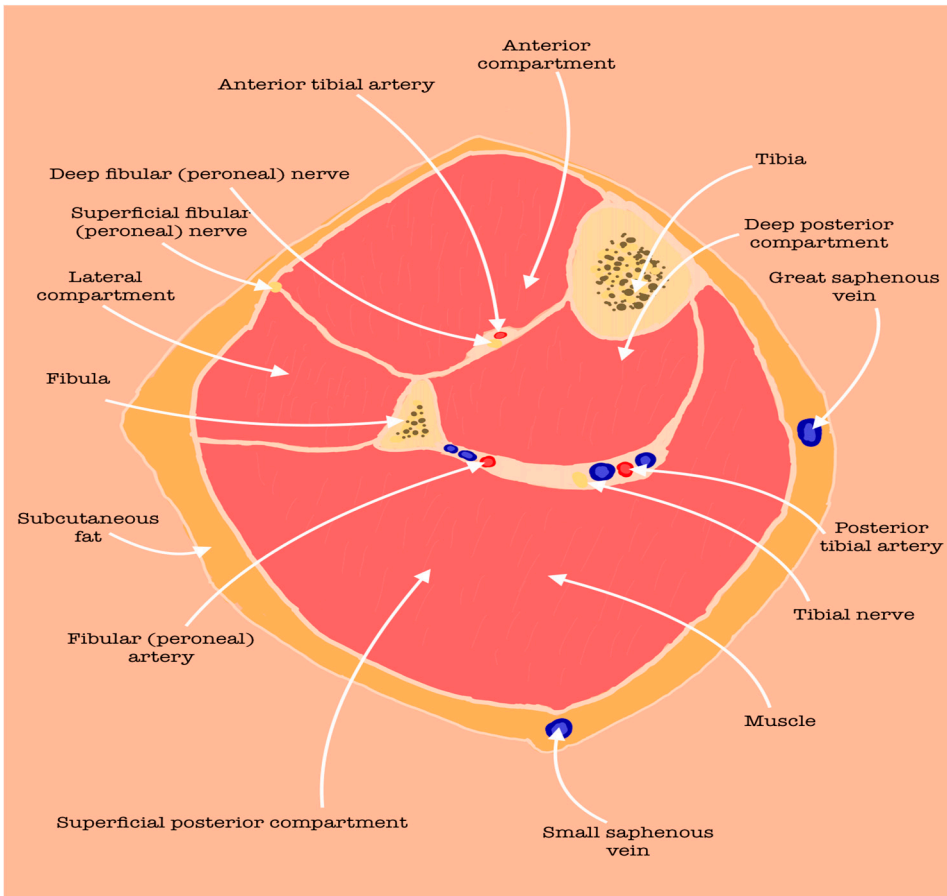

Figure VII: Transverse view of the anatomy of the lower leg, including the four compartmtens. ©Emil Karonen

Fasciotomy

The only curative treatment for ACS is fasciotomy. This can also be performed prophylactically in high-risk patients, which in the calf entails incisions that release the four muscle compartments therein[26]: the anterior, lateral, deep posterior, and superficial posterior compartments. Within the anterior compartment are the anterior tibial muscle, the extensor digitorum longus, the extensor hallucis longus, the deep peroneal nerve, and the anterior tibial artery and vein[118]. Within the lateral compartment are the short and long peroneal muscles and the superficial peroneal nerve[119]. Within the deep posterior compartment are the flexor digitorum longus, tibialis posterior, peroneal artery/vein, posterior tibial artery/vein, and tibial nerve[120]. In the superficial posterior compartment there are the soleus and gastrocnemius

muscles[120]. The standard way to perform a fasciotomy is to make two skin incisions along the calf, one medial and one lateral; the cleavage of the four fascias must extend the full length of the compartment in order to be fully effective[121]. There is also a technique that enables the release of all four compartments with a single incision, with similar success rate and complications[122, 123].

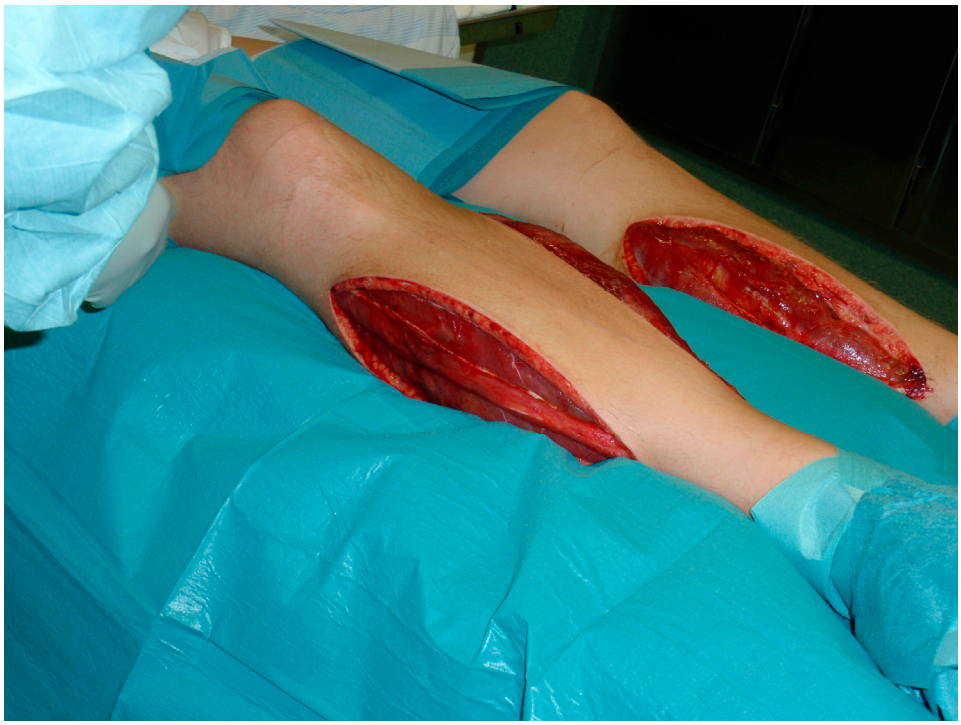

Figure VIII: Bilateral two-incision fasciotomy in a patient with bilateral acute lower limb ischaemia. ©Stefan Acosta.

In a two incision fasciotomy, the lateral incision should be made one finger width anteriorly of the fibula, while the medial incision should be made a thumb width posteriorly of the tibia[108]. The lateral incision is used to open the anterior and lateral compartments, and the medial incision is used to open the deep posterior and superficial posterior compartments[121]. With the lateral incision there is a risk of injuring the lesser saphenous vein and the peroneal nerve[124].

The often-insidious nature of ACS and devastating consequences if treatment is delayed have led some surgeons to opt for a proactive approach, with prophylactic fasciotomies in high-risk patients. With this, there is of course overtreatment, with some patients undergoing unnecessary surgery.

Complications and wound care

Complications during or after a fasciotomy may include nerve damage, bleeding, infection, wound rupture, pain, and failure to close the fascia. A swollen muscle may result in difficulties closing the fascia, but a so-called 'shoelace' technique may be used to close the fascia over the course of a few days as swelling subsides[125]. Negative-pressure wound therapy is often used to prevent infections and reduce swelling and promote healing[126]. No randomised controlled trials have been conducted to compare the outcomes of the shoelace technique to vacuum-assisted wound closure in patients who underwent lower leg fasciotomy after emergency revascularisation for ALI. Sometimes closure of the fascia is not possible, and the patient needs to undergo split skin grafts to cover the wound[127]. However, split skin grafts mean an additional need for surgery with a long recovery, risk of infection, and graft non-adhesion[128].

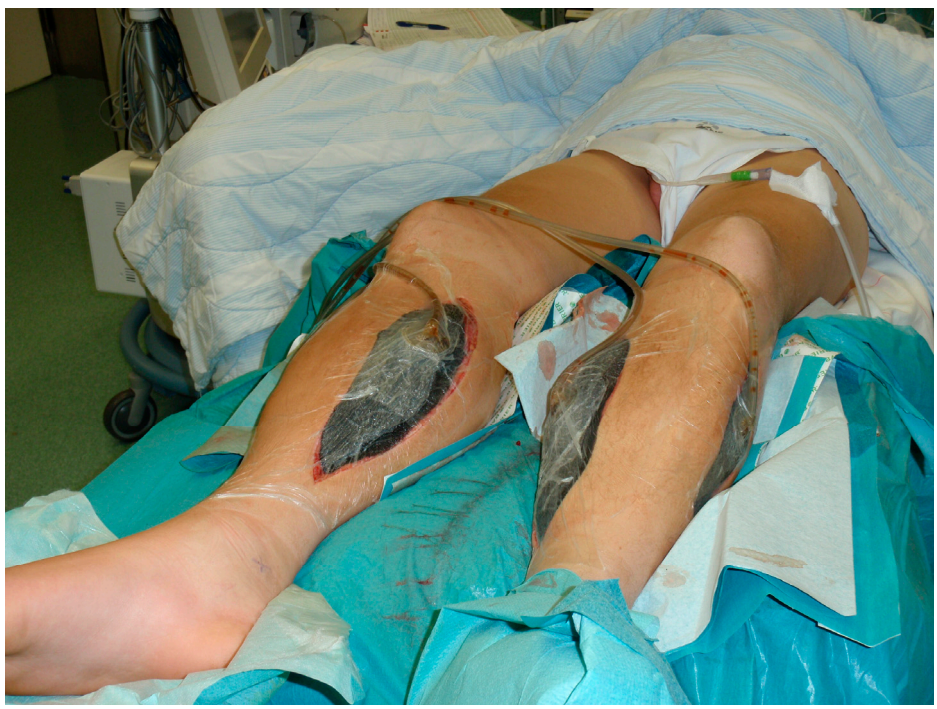

Figure IX: Vacuum-assisted wound therapy is used to treat the fasciotomy wounds in a patient with bilateral two-incision fasciotomies. ©Stefan Acosta.

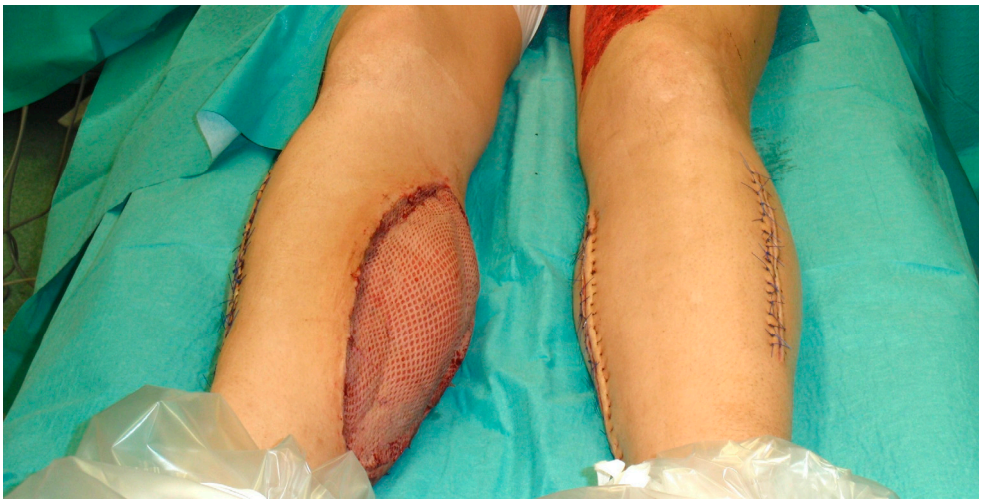

Figure X: Direct closure of three fasciotomy wounds, with the medial fasciotomy wound on the right leg covered with a split skin graft. ©Stefan Acosta.

Rationale

ALI, ACS, and fasciotomy

The main focus of this thesis is the use of fasciotomy to treat and prevent ACS after revascularisation for ALI. Fasciotomy can be a life- and limb-saving procedure, and is a necessity for patients who have developed ACS after revascularisation for ALI. A prophylactic fasciotomy can prevent ACS from developing, but may in some patients be an unnecessary surgery. As stated previously, fasciotomy opens two large wounds on the lower leg, and is often performed on patients with established PAD, DM and who are smokers – a high-risk group for wound complications. A fasciotomy may also confer pain, both short-term and long-term, on the patient, and there is a risk of damaging nerves perioperatively. It is therefore to the benefit of the patient that before every fasciotomy, the decision is carefully contemplated. For the vascular surgeon to make a fully informed decision, additional information about the potential benefits and drawbacks of performing a prophylactic fasciotomy is warranted, as this is a poorly researched field.

Understanding which factors are associated with fasciotomy is important, as a starting point for assessing whether to perform a prophylactic fasciotomy or wait. It is also important that the vascular surgeon knows whether performing an early fasciotomy has clear benefits over waiting and conducting a fasciotomy only when ACS has developed. If a clear benefit does not exist, a more cautious approach could be beneficial, as it may reduce unnecessary fasciotomies.

First, it is important to map the complications associated with a fasciotomy; these include how often wound complications can be expected, how many wound revisions in the operating room are needed, how often patients require readmission due to wound complications or prolonged hospital stays, how often split skin grafts are needed, and how long the wound-healing period is. It is also important to know whether performing a prophylactic fasciotomy can reduce the complication rate compared to performing a therapeutic fasciotomy in a calf where ACS has already developed. It is important to know whether a prophylactic fasciotomy can protect renal function in this often-fragile group, as many already have reduced renal function and additional damage may put the patient at risk of needing dialysis.

The quality of evidence generated would be higher if this was studied in a randomised controlled trial; however, because ALI is a rare disease and ACS as a

complication only affects a handful of patients, this would be a very challenging study to conduct, requiring a multi-centre study design. Additionally, there are no clear diagnostic criteria for ACS, nor any non-invasive techniques to diagnose it, making such a study design potentially dangerous. This leaves the possibility to conduct research on patients we have already treated, and to carefully extrapolate the results by comparing those patients who underwent fasciotomy and those who did not, to try to improve clinical practice.

The influence of type 2 diabetes mellitus on ALI and fasciotomy

T2DM is an important risk factor for the development of PAD, and is associated with significant risk of limb loss as well as cardiovascular disease. This may entail an increased risk of a type 2 myocardial infarction in patients with T2DM after revascularisation due to blood loss from thrombolysis or surgery. Prevalent PAD, especially with distal lengthy atherosclerotic plaques, can entail a more difficult revascularisation procedure and may reduce patency. It would also be of interest to explore whether there are higher or lower fasciotomy rates in patients with T2DM, who often have poor wound-healing capabilities. It is also of importance to know whether T2DM is associated with mortality, major amputation, or major adverse cardiovascular events, as this would help clinicians to be more aware of risks, potentially change their limb surveillance, and optimise medical treatment.

Sex differences in ALI

Sex differences in medicine have been a topic of increasing interest over the last few decades, with one key finding being that female patients often have worse outcomes after treatment for coronary and peripheral arterial disease[129, 130]. Even with this increased interest, the 2020 European Society for Vascular Surgery's ALI guidelines do not mention any aspects of sex in relation to the diagnosis, treatment, nor outcomes for ALI[26]. At the point in time at which this PhD project was being commenced, there were signals of similarly poor outcomes for female patients who underwent revascularisation for ALI, but no studies had been conducted with a primary aim to compare men and women treated for ALI. This motivated us to conduct such a study, and, importantly, to compare hard endpoints such as mortality and major amputation, and to contextualise this in relation to the characteristics of men and women with ALI. It was also of interest to explore whether women undergo therapeutic fasciotomies for ACS or prophylactic fasciotomies more or less often than men.

ALI before and during COVID-19 pandemic

During the early stages of writing of this thesis, the COVID-19 pandemic placed healthcare systems globally under severe pressure and affected patients – not only directly, through the possibility of contracting COVID-19, but indirectly, by affecting the treatment of non-communicable diseases. Outpatient clinic visits were postponed or changed to telemedicine, patients avoided seeking healthcare, and surgeries were limited. How this affected the long-term outcomes of patients with ALI, and whether there was an increase in ALI due to lower detection of atrial fibrillation and less surveillance of previous reconstructions in patients with PAD, is unknown. The opportunity to compare ALI patients at *Hospital Clínico Universidad Católica* in Chile prior to and during the COVID-19 pandemic was a great opportunity for several reasons: firstly, it meant that a different country with a different healthcare system than Sweden was explored, which is especially important as the vast majority of papers, especially the ones included in guidelines, are written in developed countries. Chile is a high-income country with an impressive healthcare system, but it is also a developing country.

Secondly, vascular surgery in high-volume vascular centres in developed countries is increasingly endovascular in nature, whereas Fogarty embolectomy can be performed by a general surgeon in a smaller hospital. National comparisons can be expected to suggest preferable outcomes on the part of endovascular procedures as these are almost exclusively performed by vascular surgeons, who have more experience of treating ALI and a better understanding of vascular surgery. Outside high-income countries, Fogarty embolectomy is still routinely performed in tertiary centres by vascular surgeons to treat ALI, and because of that, there can be a more faire comparison of actual attainable results from open vascular surgery in the hands of an experienced vascular surgeon.

Finally, the opportunity to visit and collaborate with surgeons and researchers in Chile gave me new perspectives on vascular surgery and healthcare, and the possibility to make contacts among very talented surgeons and researchers.

Aims

The general aim of this thesis was to investigate patients who underwent treatment for ALI who may also have undergone a fasciotomy for prevention or treatment of ACS. The special interests were sex differences, differences between institutions, the impact of T2DM, and the COVID-19 pandemic.

Paper I: The primary aim was to find factors associated with undergoing fasciotomy in patients that had undergone revascularisation for ALI. The secondary aim was to determine whether fasciotomy was associated with major amputation and mortality.

Paper II: The aim was to compare kidney and wound outcomes in patients who underwent prophylactic or therapeutic fasciotomy after revascularisation for ALI.

Paper III: Compare mortality, combined major amputation/mortality, and fasciotomy rate in men and women who underwent revascularisation for ALI, adjusting for potential differences in characteristics.

Paper IV: Compare patients with and without T2DM who underwent revascularisation for ALI, to ascertain whether T2DM was associated with mortality, major amputation, fasciotomy, or major adverse cardiovascular events.

Paper V: Compare major amputation, mortality, and fasciotomy rates in patients treated for ALI before and during the COVID-19 pandemic in a Chilean university hospital.

Methods

Table III: Overview of methods used.

	Paper I	Paper II	Paper III	Paper IV	Paper V
Design	Single-centre retrospective cohort	Single-centre retrospective cohort	Single-centre retrospective cohort	Nationwide retrospective cohort	Single-centre retrospective cohort
Data source	Medical records from Skåne, Sweden	Medical records from Skåne, Sweden	Medical records from Skåne, Sweden	Swedish Vascular Registry and National Diabetes Registry	Medical records from Santiago, Chile
Enrolment	2001–2018	2006–2018	2001–2018	2010–2014	2016–2023
Sample	843 revascularisations with 84 fasciotomies	76 fasciotomies: 40 prophylactic, 36 therapeutic	709 patients: 326 women, 383 men	615 patients, 245 with type 2 diabetes mellitus	112 patients, 53 who underwent treatment during the COVID-19 pandemic
Methods	Analysis of factors associated with fasciotomy. Analysis of factors associated with combined major amputation/mortality at one year.	Comparison of patients who underwent prophylactic and therapeutic fasciotomy. Estimated glomerular filtration rate at admission, lowest point, and discharge. Compilation of wound complications. Wound-healing time.	Comparison of fasciotomy-, major amputation-, and mortality rate between men and women who underwent revascularisation for acute lower limb ischaemia.	Comparison of mortality, major adverse cardiovascular events, major amputation, and fasciotomy between patients with and without type 2 diabetes mellitus. Directed acyclic graph used for development of adjustment model.	Comparison of patients treated before and during the COVID-19 pandemic regarding major amputation, mortality, and fasciotomy.
Data analysis	Univariable and multivariable logistic regression for fasciotomy and combined major amputation/mortality.	Analysis of variance for change in estimated glomerular filtration rate. Log-rank test and Kaplan–Meier curves with life tables for wound-healing time.	Propensity score-adjusted logistic regression for dichotomous variables.	Uni and multivariable ogistic and Cox-Regression. Competing risk analysis with Fine-Gray model.	Logistic regression analysis adjusted for open vascular surgery.

Setting

Papers I–III

For the first three papers, data were collected from all patients who underwent revascularisation at *Vascular Centre, Skåne University Hospital*, which is the university hospital in Malmö, Sweden's third-largest city, and Lund. It is the tertiary referral centre for vascular patients in the Southern Healthcare Region in Sweden, which has approximately 1.4 million inhabitants. It is fully equipped for open vascular surgery and endovascular treatment around the clock, every day of the year. The hospital is affiliated with Lund University.

Paper IV

Paper IV was based on data on patients who underwent revascularisation in any hospital in Sweden, which has a total population of 10 million people. Sweden is a high-income developed country with a publicly funded healthcare system covering any necessary treatment, including for ALI[131].

Paper V

Paper V was based on data from *Hospital Clínico Universidad Católica,* which is a tertiary referral private university hospital in Santiago, Chile. Due to its private status it does not have a primary catchment area, but surgery for ALI is available regardless of insurance status. Chile is a high-income developing country with significant income inequalities, and parallel public and private health-insurance systems[132]. Public health insurance covers the vast majority of the population but has been scrutinised in relation to inaccessibility and insufficient quality compared to privately funded health insurance[133]. Changes have been made to the publicly funded health-insurance system to fund treatment in privately driven clinics with the publicly funded insurance, but there is still a divide in accessibility and quality[133, 134]. The national vaccination programme for COVID-19 in Chile was introduced on February 2, 2021[135].

Ethical approval

Papers I–IV

Ethical approval was granted by the Swedish Ethical Review Authority for papers I–III (Dnr 2020/00,764), and by the Regional Ethical Review Board in Lund for paper IV (DNR: 2016-232 and 2016-544).

Paper V

Paper V received ethical approval from the local ethical committee at *Pontificia Universidad Católica de Chile* (ID 231211006).

Sample selection

For paper I, all revascularisation procedures at the Vascular Centre in Malmö between 2001 and 2018 were included, totalling 843 revascularisations and of which 84 underwent fasciotomy. The same database was used for papers II and III, although in these latter only index revascularisations were included, resulting in a cohort of 709 patients. Paper II also only included patients from 2006–2018, as specific additional data regarding wound outcomes from 2001–2005 would have been difficult to procure due to the use of paper files prior to 2006. Between 2006 and 2018, 76 patients underwent fasciotomy and thus were included in paper II; 40 underwent prophylactic fasciotomy, and 36 underwent therapeutic fasciotomy. In paper III, of the 709 patients included, 326 (45.9%) were women and 383 (53.1%) were men.

For paper IV, data were retrieved from the *Swedish Vascular Registry* (SWEDVASC) for the period 2010–2014. In all, 6936 patients were included in the infrainguinal module in SWEDVASC; however, of these, only 615 had the *International Classification of Disease* codes associated with ALI. The data for these 615 patients were cross-referenced with the *National Diabetes Registry* (NDR), and it was found that 245 patients had a T2DM diagnosis. Paper IV included all patients who underwent revascularisation for ALI in Sweden during the period, were included in SWEDVASC, and had an index revascularisation.

Paper V included all patients treated for ALI at Hospital Clínico Universidad Católica, Santiago, Chile. This study included only index procedures, including primary amputations; these were performed by vascular surgeons, and on patients with ALI and CLTI. The inclusion period was January 1, 2016 to May 5, 2023. A total of 112 patients were included, of which 53 underwent treatment during the COVID-19 pandemic. A sub-analysis was conducted of the patients treated before and after the introduction of the vaccination programme on February 2, 2021, with 17 patients who underwent treatment before the introduction of the vaccination programme but during the COVID-19 pandemic.

None of the studies used data from patients under the age of 18.

Data collection

Data for papers I–III were collected from electronic and paper charts from Region Skåne, and follow-up data were requested from other municipalities. Paper IV used data from the NDR and SWEDVASC, as well as supplementary data from the *National Patient Registry, Longitudinal Integration Database for Health Insurance and Labour Market Studies*, *Cancer Registry*, and the *Swedish Cause of Death Registry*. For paper V, data were collected from electronic and paper charts from

Hospital Clínico Universidad Católica, and dates of death were requested from *Chilean National Social Registry.*

Registries for paper IV

The *Swedish Vascular Registry* was founded in 1987 and covers close to 18,000 vascular procedures yearly, across all hospitals in which vascular surgery is conducted in Sweden[136]. In the Registry, 30-day and one-year follow-up are registered for patients who undergo vascular surgery. However, there has not been any external validation of the patients registered in the Registry for ALI. Data regarding date of surgery, ALI diagnosis, fasciotomy, and smoking status were retrieved from the Registry.

The NDR is a registry of all patients with any type of DM in Sweden, and has a coverage of roughly 83% of adults with DM[137]. Data are collected on key patient characteristics, risk factors for complications, treatment, laboratory values, and DM-related complications[138]. The data are routinely collected at least once per year at hospital outpatient and primary healthcare clinics. The NDR covers roughly 412,000 patients over the age of 18 with any type of diabetes in Sweden[137].

Data regarding major amputation, major adverse cardiovascular events, stroke, myocardial infarction, and ischaemic heart disease following revascularisation for ALI were retrieved from the National Patient Registry using International Classification of Disease codes. The Swedish Cause of Death Registry was used for data regarding death and cause of death. Socioeconomic background information, including sex, education, and country of origin were retrieved from the Longitudinal Integration Database for Health Insurance and Labour Market Studies registry.

Directed acyclic graphs

Directed acyclic graphs are a means of selecting variables for an adjustment model to reduce confounding[139]. All factors relevant to the exposure and outcome in a study are displayed visually on a graph as nodes, and vectors are then placed between the nodes in assumed unidirectional causal pathways; the nodes cannot connect back to themselves, hence the term 'acyclic'[140]. By selecting one factor to be the exposure and one to be the outcome, this model can be used to calculate which adjustments are necessary in order to address potential confounding[141]. This intuitive way of creating a visual model also adds transparency and reproducibility to the process of identifying potential confounders[142]. A directed acyclic graph, utilising the software DAGity, was used in paper IV to create an adjustment model[143].

Propensity scores

A propensity score can be used to calculate the predisposition of a person to receive a specific treatment or to belong to a certain group based on characteristics; the resulting value can then be used to address potential confounding, in order to estimate treatment effect in observational studies[144]. The major benefit of propensity scores is that they are not limited by the so-called 'rule of ten', whereby (as in e.g. a logistic or Cox regression model) only one factor can be introduced per ten outcomes[145]. This 'rule of ten' limits the number of covariables that can be used in a model, especially in smaller samples or with rare outcomes, causing a high risk of residual confounding and thus biased estimated treatment effects[146]. Because the propensity score is only a single variable, this enables the researcher to include all relevant variables. The ambitious aim of the propensity score is to try to mimic the environment of a randomised controlled trial, through adjusting for all potential confounders[147]. Using propensity scores has been shown to sufficiently remove bias from all observed confounders as to obtain unbiased estimates of treatment effect[144]. However, it is important to note that there is still the risk of residual confounding, from unmeasured systematic differences between the two groups[148].

There are several different approaches to using propensity scores: matching, inverse probability of treatment weighting, stratification, and covariable adjusting[147]. The propensity score is calculated through logistic regression, where selected variables are added to the model to predict how likely each patient is to undergo a treatment or exposure[149]. Logistic regression results range between zero and one for each individual, and this is their specific propensity score. This score can then be utilised to match patients in the two groups or stratify the patients, or as covariables in a multivariable analysis[147]. Another popular approach is to use inverse probability of treatment weighting, where the propensity score is used to create a 'pseudo' population; here, the inverse probability of undergoing a treatment is used as a weight for each patient, which balances the patient characteristics in the 'pseudo' population and thus reduces bias[149]. If conducted appropriately, propensity score-adjusted models in theory result in unbiased estimates of causal treatment effect, similar to a randomised controlled trial, but this is dependent on a correct model and no unmeasured confounders[144].

Statistical analysis

Commonly used statistical analyses

Dichotomous variables were expressed in percentages, and the chi-square test was used to compare between the groups in the non-adjusted analyses. For non-normally distributed data, median and inter-quartile range (IQR) or range were used, and the Mann-Whitney U test was used to compare groups. Continuous normally distributed

data were presented with mean and standard deviation. A p-value of <0.05 was considered to be statistically significant in papers I–V.

Paper I

The primary endpoints were factors associated with 1. fasciotomy, and 2. combined major amputation/mortality at one year. Factors with p<0.1 in univariable analysis for each outcome were considered for inclusion in the models for multivariable logistic regression analysis. Due to the exploratory nature of the study and in order to investigate which factors were important for the outcomes, all factors of potential clinical interest were to be included in the model but limited by the 'rule of ten' (i.e. one covariate was included in the regression model per ten major amputation/mortality or fasciotomy events). Clinical and research experience was used to deduce which factors were to be included in the final regression models. In this thesis, summary reanalysis of the endpoints fasciotomy and major amputation/mortality was performed using only index patients.

Table IV. Factors included in regression models in Paper I

Factors included in regression model for combined major amputation/mortality	Factors included in regression model for fasciotomy
Admission 2010–2018	Admission 2010–2018
Open vascular surgery	Open vascular surgery
Sex	Sex
Anaemia	Anaemia
Rutherford IIb	Rutherford IIb
Renal insufficiency	Renal insufficiency
Stent/stent-graft occlusion	Popliteal artery aneurysm thromboembolism
Native artery occlusion	Bilateral occlusions
Age >75	
Embolus	
Level of occlusion	
Cerebrovascular disease	
Atrial fibrillation	
Ischaemic heart disease	
Acetylsalicylic acid use	
Foot/leg ulcer	
Major bleeding	
Fasciotomy	

Paper II

Estimated glomerular filtration rate (e-GFR) was compared at three different points (admission, lowest, discharge) for patients who underwent prophylactic and therapeutic fasciotomy using analysis of variance, adjusting for sex and Rutherford IIb. The same model was used for comparison between mean change in e-GFR, but

with the addition of e-GFR at admission as a covariable. The variables were chosen through a change-in-estimate analysis, where potential confounders were individually tested and included in the model if they resulted in a change in outcome of more than 15%. Wound healing was compared using the log-rank test and illustrated using Kaplan–Meier survival curves with life tables.

Paper III

This study aimed to compare mortality, major amputation, and fasciotomy for men and women who underwent revascularisation for ALI. A propensity score was built on factors deemed potentially important for outcome and that differed between the two groups. Due to the chronology, they cannot be considered true confounders. However, it was of interest to estimate the direct effect of sex, which is why a propensity score-adjusted analysis was performed. The factors that were used to calculate the propensity score for each patient were: age, anaemia, atrial fibrillation, DM, e-GFR, hypertension, ischaemic heart disease, popliteal artery aneurysm occlusion, open vascular surgery, and Rutherford IIb. The propensity score was used as a covariable in Cox and logistic regression analyses for time-to-event and non-time-dependent dichotomous outcomes, respectively. For this thesis, additional uni- and multivariable logistic regression was performed for the factors in the propensity score to mortality, for each sex. A sensitivity analysis using univariable logistic regression was performed to compare mortality in men and women, where patients with popliteal artery aneurysm thromboembolism were excluded.

Paper IV

This study aimed to investigate whether T2DM is associated with a higher rate of mortality, major amputation, major adverse cardiovascular events, and fasciotomy after revascularisation for ALI. A directed acyclic graph was created to deduce potential confounding factors, with T2DM as the exposure and mortality, major amputation, and fasciotomy as outcomes. The model included sex, age, country of birth, socioeconomic status, and smoking status as potential confounders. These factors were included in multivariable Cox and logistic regression analysis for time-to-event and non-time-dependent dichotomous variables, respectively. Competing risk analysis to mortality was performed using a multivariable Fine-Gray sub-distribution hazard model for the following endpoints: major amputation, major adverse cardiovascular events, acute myocardial infarction, and stroke.

Paper V

A chi-square test was used to compare dichotomous variables. Fisher's exact test was used for comparison of dichotomous data when the data were deemed to be too low power to perform a chi-square test or logistic regression analysis. Kendall's tau-b test was used to compare ordinal data. Logistic regression was used for univariable and multivariable analysis. A change-in-estimate analysis, with a 15% change per

variable threshold, was used to choose factors that were seen as clinically important for outcome, to include in the logistic multivariable regression analysis. The only factor meeting the threshold was open vascular surgery.

Variable definitions

Acute lower limb ischaemia – In papers I–III and V: Acute onset of lower limb ischaemia due to thromboembolic occlusions, with a maximum duration of 14 days. In paper IV: ICD-10 codes: I74.0-5, I74.8-9.

Acute myocardial infarction – In paper IV: ICD-10 code: I21.

Anaemia – In papers I–III and V: Blood haemoglobin levels of <134g/L and <117g/L in men and women, respectively.

Anticoagulation treatment – In papers I and III: Use of vitamin-k antagonist, direct-acting oral anticoagulant, or treatment dose of low-molecular-weight heparin prior to ALI.

Adjunctive procedure/reintervention during same hospital stay – In papers III and V: Any additional open or endovascular procedure performed during the same hospital stay to improve flow and/or chances of retaining patency.

Atrial fibrillation – In papers I and III–V: Any prior diagnosis of atrial fibrillation.

Cancer – In paper IV: Any history of cancer, excluding non-melanoma skin cancers.

Cerebrovascular event – In paper I: Previous stroke or transient ischaemic attack.

Cerebrovascular disease – In paper IV: Any prior diagnosis of cerebrovascular disease.

Chronic obstructive pulmonary disease – In paper IV: Prior diagnosis of chronic obstructive pulmonary disease.

Claudication – In papers I–III: Ipsilateral claudication prior to onset of ALI.

Country of birth – In paper IV: Divided into being born in Sweden, in Europe outside Sweden, and in a non-European part of the world.

Dialysis following revascularisation – In paper II: New onset dialysis during in-hospital stay, after development of ALI.

Dialysis prior to admission – In paper II: Dialysis due to previous chronic kidney disease.

Diabetes mellitus (DM) – In papers I–III and V: Prior diagnosis of any type of diabetes mellitus.

Diabetes mellitus (type 2) (T2DM) – In paper IV: Diabetes mellitus with the use of oral antihyperglycemic agents, treated through dietary changes or using insulin in patients diagnosed after the age of 40.

Dyslipidaemia – In paper V: Prior diagnosis of dyslipidaemia.

Education – In paper IV: Categorised as non-complete elementary education (<9 years); complete elementary education to complete upper-secondary education (9–12 years); and higher education (>12 years).

Endovascular surgery – In all papers: Any revascularisation performed through endovascular means, including catheter-directed thrombolysis, thromboaspiration, pharmaco-mechanical thrombolysis, and percutaneous angioplasty. However, not including hybrid procedures.

Estimated glomerular filtration rate (e-GFR) – In papers II, III, and V: Calculated based on serum-creatinine levels, age, and sex, with the Lund-Malmö model used in paper 2[150] and Chronic Kidney Disease Epidemiology Collaboration[151] used in papers 3 and 5.

Fasciotomy – In papers I–III and V: Any surgical procedure involving incisions along the fascia to prevent or treat acute compartment syndrome. In papers I–II: Prophylactic fasciotomy was any fasciotomy where acute compartment syndrome was not noted; therapeutic fasciotomy was a fasciotomy where acute compartment syndrome was known to be present. In paper 4: *Klassifikation Av Vårdåtgärder* codes: NGM09 (fasciotomy of the lower leg), NFM09 (fasciotomy of the thigh and/or glutes).

Foot ulcer – In papers I and III: Foot ulcer prior to admission in the ipsilateral limb.

Healed fasciotomy – Full skin epithelisation on all applicable fasciotomy wounds.

Hypertension – In all papers: Prior diagnosis of hypertension, use of antihypertensive drugs to treat hypertension.

Income – In paper IV: Ordered into quartiles of yearly income.

Ischaemic heart disease – In papers I and V: Stated previous acute myocardial infarction, coronary revascularisation, or angina pectoris.

Kidney disease – Paper IV: Any prior diagnosis of chronic kidney disease.

Level of occlusion – In papers I–III: Level of most proximal occlusion; referred to as suprainguinal or infrainguinal. In paper V: Categorised based on aorta/iliac arteries, femoral/popliteal arteries, and distal arteries.

Liver disease – Paper IV: Any prior diagnosis of liver disease.

Major adverse cardiovascular event – Paper IV: The following diagnoses and procedures were included: cardiovascular mortality (death by I00-I99, R570, R960,

R961 (ICD-10)), coronary revascularisation 'FNA' 'FNB' 'FNC' 'FND' 'FNE' 'FNG' 'FNP12B' 'FNQ05B' 'FNQ12B' 'FNR22B' (*Klassifikation av vårdåtgärder*), ischaemic heart disease I20-I25 (ICD-10) or stroke I61, I62, I63, I64 (ICD-10).

Major amputation – In all papers: Any amputation of an ischaemic or revascularised limb above the ankle.

Major bleeding – In papers I and III: Bleeding that necessitated two units of erythrocyte transfusion, thrombolysis cancelled due to bleeding, or reoperation due to bleeding.

Marital status – In paper IV: Categorised as married, separated, single, or widowed.

Native artery occlusion – In papers I–III and V: Any occlusion due to thromboembolism, not including occlusions of stents, stent-grafts, or grafts.

Open vascular surgery – In all papers: Any type of open vascular surgery, including Fogarty embolectomy, bypass surgery, endarterectomies, and hybrid procedures.

Peripheral arterial disease – In paper IV: ICD-10 codes: I70.2 and I73.9 (all subgroups accepted except I73.9A) In paper V: prior surgery for, or presence of, claudication, rest pain, or ischaemic ulcers prior to the development of ALI.

Renal insufficiency – In paper I: Serum-creatinine level of above 105 μg/L in men and 90 μg/L in women. Paper II: e-GFR below 60 ml/min/1.73 m^2.

Reduced motor function – In paper II: New onset of peroneus paresis, reduced motor function, need for physiotherapy, or new walking aid at discharge.

Rutherford criteria – In papers I–III and V: Used to assess ischaemic severity[48].

Smoker – In papers IV–V: Current smoker at admission. In paper II: Current smoker or cessation within one year. Previous smoker: cessation >1 year.

Symptom duration – In papers I–III and V: Hours since start of the symptoms at the time of admission.

Stent/stent-graft/graft occlusion – In papers I–III and V: Any occlusion occurring in any vascular endoprosthesis or autograft.

Psychiatric disorder – In paper IV: Any prior diagnosis of psychiatric disorder.

Wound complication (other): In paper II: Skin necrosis, significant wound bleeding, or wound rupture.

Wound infection – In paper II: The definition used by the *Center for Disease Control and Prevention Classification*[152]

Definition of thrombosis and embolism

In papers I–III and V, a diagnosis of thrombosis or embolism was based on the surgical note and imaging report; if neither defined the type of occlusion,

classification was based on the clinical features suggesting embolic or thrombotic aetiology. Images after emergency CT angiography, magnetic resonance angiography, and angiography were mainly read and reported by vascular surgeons in papers I–III. Embolic occlusion often appears as an oval-shaped clot surrounded by contrast in a noncalcified arterial segment, whereas a thrombotic occlusion usually appears as a clot superimposed on a heavily calcified occlusive lesion. The presence of synchronous embolism, atrial fibrillation, previous embolism, and/or no or inadequate anticoagulation therapy at the onset of ALI suggested embolism.

Results

Paper I

Main findings

I. The multivariable logistic regression analysis showed that renal insufficiency, motor deficit (Rutherford IIb), popliteal artery aneurysm thromboembolism, and undergoing open vascular surgery were associated with increased odds of undergoing fasciotomy. Female sex and anaemia were associated with reduced odds of undergoing fasciotomy.

II. Cerebrovascular disease, female sex, fasciotomy, foot ulcers, infrainguinal occlusion, major bleeding, and Rutherford IIb were associated with increased odds of one-year major amputation/mortality.

Table V. Factors associated with fasciotomy after revascularisation for ALI.

Variable	Odds ratio (95% CI)	p-value
Rutherford IIb	4.40 (2.45–7.92)	<0.001
Primary open vascular surgery	3.43 (1.97–5.98)	<0.001
Popliteal artery aneurysm thromboembolism	2.26 (1.06–4.80)	0.035
Renal insufficiency	1.77 (1.04–3.01)	0.034
Anaemia	0.43 (0.22–0.83)	0.012
Female sex	0.43 (0.24–0.76)	0.004

ALI: Acute lower limb ischaemia, CI: Confidence interval

Table VI. Factors associated with combined major amputation/mortality in the first year after revascularisation for ALI.

Variable	Odds ratio (95% CI)	p-value
Cerebrovascular disease	1.86 (1.23–2.82)	0.003
Fasciotomy	1.94 (1.11–3.40)	0.021
Female sex	1.44 (1.00–2.08)	0.049
Foot ulcers	2.47 (1.46–4.18)	0.001
Infrainguinal occlusion	1.62 (1.07–2.46)	0.024
Major bleeding	1.94 (1.30-2.90)	0.001
Rutherford IIb	2.43 (1.66–3.56)	<0.001

ALI: Acute lower limb ischaemia, CI: Confidence interval

Table VII. Logistic regression model for fasciotomy, only index revascularisations.

Factors	Univariable analysis p-value	Multivariable analysis OR (95% CI)	p-value
Anaemia	0.09	0.38 (0.19-0.77)	0.007
Popliteal artery aneurysm thromboembolism	<0.001	2.43 (1.11-5.32)	0.027
Rutherford IIb	<0.001	5.01 (2.60-9.66)	<0.001
Renal insufficiency	0.01	2.01 (1.13-3.56)	0.018
Female sex	0.01	0.39 (0.21-0.72)	0.003
Open vascular surgery	<0.001	4.53 (2.47-8.29)	<0.001
Bilateral occlusion	<0.001	1.24 (0.52-2.94)	0.629
Admission 2010–2018 vs. 2001–2009	<0.001	Not included	

CI: Confidence interval, OR: Odds ratio

Due to the inclusion of not only index revascularisations in Paper I, additional analyses with only index revascularisations were created for this thesis. The comparison of admission in 2010–2018 versus in 2001–2009 was excluded from the multi-variable analysis so as to not exceed the 'rule of ten'. However, a supplementary analysis was performed wherein admission in 2010–2018 versus 2001–2009 was included in the model, where it was found to be significantly associated with fasciotomy (odds ratio [OR] 3.00, 95% confidence interval [CI] 1.54–5.85, p=0.001). The other factors in Table VII remained similar in terms of OR with the inclusion of admission 2010–2018 versus 2001–2009. This was performed to ensure that the omission of this variable did not significantly affect the results, and thus that the new results were comparable to those reported in the original article. Some suggest that the 'rule of ten' is overly strict, but we chose to follow it in order to have consistency in the application of multivariable regression models[153].

This re-analysis, which only included patients who underwent index revascularisation procedures, found the same factors associated with fasciotomy as in Paper I. This demonstrates that the results did not differ substantially as a result of the inclusion of non-index revascularisation procedures in patients who underwent subsequent revascularisation procedures in the same or contralateral leg for ALI. The endpoint, fasciotomy, was a peri-operative variable, and might have been performed at the second or third emergent revascularisation in redo patients. Sometimes, fasciotomy must be performed in redo emergency revascularisation in the contralateral leg.

Table VIII. Logistic regression model for combined major amputation/mortality at one year, only index revascularisations.

Factors	Univariable analysis p-value	Multivariable analysis OR (95% CI)	p-value
Open vascular surgery	<0.001	1.09 (0.69–1.72)	0.71
Admission 2010–2018 vs. 2001–2009	0.50	0.81 (0.55–1.20)	0.29
Female sex	0.30	1.10 (0.73–1.62)	0.67
Anaemia	0.003	1.51 (0.98–2.31)	0.06
Rutherford IIb	<0.001	2.70 (1.79–4.08)	<0.001
Renal insufficiency	0.005	1.16 (0.77–1.73)	0.48
Fasciotomy	0.003	1.42 (0.76–2.62)	0.27
Age >75	<0.001	1.38 (0.91–2.09)	0.13
Atrial fibrillation	0.002	1.23 (0.76–2.00)	0.40
Infrainguinal occlusion	0.004	1.45 (0.91–2.31)	0.12
Acetylsalicylic acid use	0.077	0.80 (0.54–1.18)	0.26
Ischaemic heart disease	0.222	1.15 (0.76–1.75)	0.50
Cerebrovascular disease	<0.001	2.05 (1.32–3.19)	0.001
Foot/leg ulcer	0.007	2.71 (1.55–4.76)	<0.001
Native artery occlusion	0.004	0.99 (0.54–1.82)	0.98
Stent/stent-graft occlusion	0.006	0.76 (0.37–1.52)	0.43
Embolus	0.003	1.12 (0.69–1.81)	0.66
Major bleeding	<0.001	1.87 (1.21–2.88)	0.005

CI: Confidence interval, OR: Odds Ratio

In this re-analysis of only index revascularisations, female sex, fasciotomy, and infrainguinal occlusion were no longer significantly associated with major amputation/mortality at one year. This re-analysis demonstrates that inserting the same patient twice in the database was incorrect, because one of the endpoints (death at one year) is a mid-term variable and can only occur once. Redo emergent revascularisation procedures should have been carefully excluded in Paper I, as the redo procedure was not independent of the first procedure for each patient.

Paper II

Main findings

I. From admission to discharge, e-GFR (mL/min/1.73 m^2) improved significantly in both patients who underwent prophylactic (8.2, 95% CI 2.4–14.1) and therapeutic (4.4, 95% CI 1.1–7.7) fasciotomy after revascularisation for ALI. The increase in e-GFR did not differ significantly between the two groups (0.3, 95% CI -6.7–7.4) when adjusting for potential confounders.

II. Only 80.6% of patients who underwent therapeutic fasciotomy, and 57.5% of patients who underwent prophylactic fasciotomy, had their fasciotomy wound ever fully heal prior to death or amputation (p=0.031). The combined wound complication rate was overall high, with no significant difference between the two groups (prophylactic 78.8%, therapeutic 91.2%, p=0.16). Wound infections were more prevalent in the therapeutic fasciotomy group (prophylactic 60.6%, therapeutic 82.4%, p=0.048). The median wound-healing time was 73.0 (IQR 55.0–96.0) days, with no significant difference between the prophylactic (median time 67.5 days (IQR 53.3–94.5)) and therapeutic (median time 73.0 days (IQR 52.0–94.5)) groups (p=0.44).

Paper III

Table IX. Distribution of factors included in the propensity score for women and men in Paper III.

Factor	Women % (n=326)	Men % (n=383)
Anaemia	21.2 (68/321)	35.0 (132/377)
Age, mean (SD)	75.2±11.5	69.4±11.1
Hypertension	81.0 (264)	73.6 (282)
Ischaemic heart disease	27.0 (88)	33.7 (129)
Rutherford IIb	42.3 (138)	36.6 (140/382)
Open vascular surgery	33.4 (109)	27.2 (104)
Popliteal artery aneurysm thromboembolism	1.2 (4)	15.4 (59)
Diabetes mellitus	22.4 (73)	22.2 (85)
Atrial fibrillation	36.2 (118)	22.3 (85/382)
e-GFR mean (SD)	62.0±24.1	72.4±23.3

e-GFR: estimated glomerular filtration rate (per ml/min/1.73 m^2), SD: standard deviation

Main findings

I. During the first year of follow-up, female patients had a mortality rate of 21.2%, major amputation rate of 12.1%, and combined major amputation/mortality rate of 29.3% after revascularisation for ALI. The corresponding figures for male patients

were a mortality rate of 14.7%, major amputation rate of 14.4% and combined major amputation/mortality rate of 25.8%. In the crude analysis, the risk of mortality was significantly higher among female patients than male patients (hazard ratio [HR] 1.50, 95% CI 1.05–2.13, p=0.02), but did not remain significantly higher in the propensity score-adjusted analysis (HR 0.99, 95% CI 0.67–1.46, p=0.96). Combined major amputation/mortality during the first year did not differ significantly in the crude and adjusted analyses.

II. After revascularisation, 7.1% of female patients and 12.8% of male patients underwent fasciotomy. Female patients had lower odds of fasciotomy in the crude (OR 0.52, 95% CI 0.31–0.87, p=0.01) and adjusted (OR 0.52, 95% CI 0.29–0.91, p=0.02) analyses.

Additional analyses for paper III

In the univariable analysis, men and women shared some factors associated with mortality (age, Rutherford IIb, open vascular surgery, atrial fibrillation). However, some factors differed between the sexes, such as popliteal artery aneurysm thromboembolism, ischaemic heart disease, and e-GFR. All factors with p≤0.1 were introduced in multivariable logistic regression for both sexes.

Table X. Association of factors included in the propensity score-adjusted analysis with one-year mortality for women and men, separately.

Factor	Women n=326 OR (95% CI)	p-value	Men n=383 OR (95% CI)	p-value
Anaemia	1.01 (0.57–2.08)	0.80	2.46 (1.38–4.36)	0.02
Age	1.07 (1.04–1.10)	<0.001	1.08 (1.04–1.12)	<0.001
Hypertension	1.02 (0.52–2.01)	0.96	1.23 (0.63–2.39)	0.55
IHD	1.63 (0.92–2.89)	0.09	1.22 (0.68–2.20)	0.50
Rutherford IIb	4.29 (2.42–7.61)	<0.001	3.27 (1.82–5.87)	<0.001
Open vascular surgery	2.58 (1.50–4.49)	<0.001	3.91 (2.18–7.03)	<0.001
PAA	0.93 (0.10–8.43)	0.93	0.28 (0.08–0.92)	0.036
DM	0.67 (0.34–1.34)	0.26	1.86 (1.00–3.47)	0.051
Atrial fibrillation	2.03 (1.18–3.47)	0.01	2.77 (1.51–5.08)	<0.001
e-GFR	0.99 (0.98–1.00)	0.058	0.98 (0.96–0.99)	<0.001

CI: confidence interval, e-GFR: estimated glomerular filtration rate (per ml/min/1.73 m2), IHD: ischaemic heart disease, OR: odds ratio, PAA: popliteal artery aneurysm thromboembolism

In the multivariable logistic regression analysis, age and Rutherford IIb were independent factors associated with an elevated odds of mortality for both men and women. Interestingly, for men, open vascular surgery had, with rounding, an almost identical effect to Rutherford IIB, with an elevated odds of mortality for men who underwent open vascular surgery that was not seen for women. Popliteal artery aneurysm thromboembolism was also shown to be associated with lower odds of mortality in men. In a sensitivity analysis of all patients – men and women,

excluding patients with popliteal artery aneurysm thromboembolism – female patients had an odds ratio of 1.38 (95% CI 0.92–2.05, p=0.12) in the crude analysis for one-year mortality.

Table XI. Multivariable logistic regression for factors associated with one-year mortality for women and men.

Factor	Women n=326 OR (95% CI)	p-value	Men n=383 OR (95% CI)	p-value
Anaemia	-	-	1.74 (0.90–3.36)	0.10
Age	1.06 (1.02–1.10)	0.003	1.06 (1.02–1.10)	0.005
IHD	1.48 (0.80–2.75)	0.22	-	
Rutherford IIb	3.08 (1.65–5.75)	<0.001	2.60 (1.28–5.26)	0.008
Open vascular surgery	1.22 (0.65–2.33)	0.54	2.60 (1.28–5.26)	0.008
PAA	-	-	0.26 (0.08–0.94)	0.04
DM	-	-	1.58 (0.77–3.24)	0.21
Atrial fibrillation	1.48 (0.80–2.75)	0.74	1.52 (0.72–3.18)	0.27
e-GFR	1.00 (0.99–1.02)	0.61	1.00 (0.92–1.01)	0.59

CI: confidence interval, e-GFR: estimated glomerular filtration rate (per ml/min/1.73 m2), IHD: ischaemic heart disease, OR: odds ratio, PAA: popliteal artery aneurysm thromboembolism

Paper IV

Main findings

I: In the crude analyses, T2DM was associated with a lower risk of mortality (HR 0.64, 95% CI 0.46–0.88, p=0.01) but higher risk of major amputation (HR 1.52, 95% CI 1.12–2.07, p=0.01) and acute myocardial infarction (HR 2.24, 95% CI 1.05–4.78, p=0.04) during the first year of follow-up after revascularisation for ALI, compared to non-T2DM patients. However, none of the differences remained significant after adjusting for potential confounders with mortality (HR 0.92, 95% CI 0.61–13.9, p=0.69), major amputation (HR 1.45, 95% CI 0.99–2.11, p=0.05), and acute myocardial infarction (HR 2.15, 95% CI 0.86–5.38, p=0.10). The endpoints major amputation, major adverse cardiovascular event, acute myocardial infarction, and stroke were further tested for competing risk, but the results did not differ significantly.

II: Fasciotomy was performed on 1.2% of patients with T2DM and 3.8% of patients without T2DM. The odds of undergoing fasciotomy were lower in the T2DM group in the crude (OR 0.24, 95% CI 0.06–0.73, p=0.02) and adjusted (OR 0.1, 95% CI 0.01–0.51, p=0.01) models than in the non-T2DM group.

Paper V

Main findings

I: The patients who underwent treatment for ALI during the COVID-19 pandemic had higher odds of major amputation during the first year of follow-up (OR 4.87, 95% CI 1.27–18.53, p=0.02) compared to those treated prior to the Pandemic; however, this did not remain significant after adjusting for open vascular surgery (OR 3.52, 95% CI 0.88–14.05, p=0.08). Fasciotomy rates did not differ significantly (OR 0.81, 95% CI 0.17–3.80, p=0.79).

II: One-year mortality was significantly higher prior to the initiation of the vaccination campaign (29.4%) compared to after the initiation (2.8%, p=0.01).

Discussion

Aspects of acute lower limb ischaemia: acute compartment syndrome and fasciotomy

Female sex was associated with lower rates of fasciotomy in papers I and III, T2DM was associated with lower rates of fasciotomy in paper IV, and anaemia was associated with lower rates of fasciotomy in paper I. Renal insufficiency, severe ischaemia (Rutherford IIB ALI), and open vascular surgery were associated with an increased rate of fasciotomy in paper I. In this section we will discuss how blood flows through a tissue (in this case the calf muscle), the hypothetical effects of each variable on tissue perfusion, and how this may affect the development of ACS. No causative links have been demonstrated between the factors discussed and ACS in the papers of this thesis, nor in any other study to date. Undergoing fasciotomy after revascularisation is not a necessarily equivalent of having developed ACS, which reduces the predictive accuracy of the factors. This will thus mainly be a discussion of the pathophysiology of ACS and how certain factors could affect tissue perfusion.

Tissue perfusion in the context of acute compartment syndrome

Poiseuille's equation describes the flow of a Newtonian liquid through a cylindrical tube, and is expressed as follows[154]:

$$\text{Volume flow rate} = \frac{\pi\ (\text{pressure difference})\ \text{x}\ (\text{radius})^4}{8\ (\text{viscosity})\ \text{x}\ (\text{length})}$$

Blood is a non-Newtonian liquid as it does not have constant viscosity[155]. However, when assessing the flow through a network of vessels, it appears to have a similar flow to what is estimated through predictive models[156]. Here, I discuss the flow of blood through a vessel in a tissue using Poiseuille's equation; while this is a simplification, it gives us a mathematical foundation for discussion[157].

The arterioles regulate blood flow through tissues, and are responsible for up to 80% of systemic resistance[158]. The arterioles adapt the flow rate of blood, dilating with low MAP and constricting with high MAP, thus keeping blood flow and pressure in the arterioles approximately constant[159]. In animal models, when intracompartmental pressure increases, the radius of the arterioles remains constant,

and the arterioles do not collapse until pressure that significantly exceeds that needed to impede tissue perfusion is achieved[160]. The pressure increases by 8 mmHg in the arterioles if veniolar pressure increases by 10 mmHg[161]. Capillaries also have a critical closing pressure of 6 mmHg, which means that arteriolar pressure must be 6 mmHg higher than the pressure in the venioles to allow perfusion[162]. Thus, with increasing veniolar pressure due to high intracompratmental pressure, the MAP needs to be sufficiently high to be able to maintain tissue perfusion.

The most applicable MAP to use in this instance is the distal MAP, as this is what is responsible for perfusion in the calf, and may be significantly reduced in patients with PAD[26]. The distal MAP can easily be estimated using an automated digital sphygmomanometer placed on the left ankle[163]. Under normal circumstances, arteriolar pressure is roughly half the distal MAP, but the exact constant varies[161].

Poiseuille's equation can be adapted to the variables we have for blood flowing through a tissue, such as the muscle tissue in the calf, as follows:

$$\text{Volume flow}_{\text{rate}} = \frac{\pi\ (\sim 0.5 \times \text{MAP-(intracompartmental pressure} + 6\text{mmhg))}\ \text{x}\ (\text{radius})^4}{8\ (\text{blood viscosity})\ \text{x}\ (\text{length})}$$

The value 0.5 refers to the constant difference between the distal MAP and the arteriolar pressure, and may vary in vivo. 'Radius' is that of an individual vessel in the tissue; thus, the volume flow rate is the flow rate through that specific vessel. The total volume flow rate through the tissue is an aggregate of all volume flow rates of the vessels in the tissue. As this is a hypothetical discussion, the distinction between total volume flow rate in the tissue and specific volume flow rate of an individual vessel does not matter. Length refers to the total length of the vessel, and should remain unchanged. There are some variables that may be altered and affect flow rate in a muscle tissue after revascularisation for ALI: distal MAP, intracompartmental pressure, the radius of the microvasculature, and the viscosity of blood.

The haematocrit affects blood viscosity and decreases in anaemia, which could be an indication that the patient is euvolemic or hypervolemic, as haematocrit decreases with an increase in serum plasma volume[163]. Blood viscosity increases if a patient is hypovolemic due to low serum plasma[165]. Thus, patients with actual anaemia, who are hypovolemic, could have a false normal haematocrit. This would result in patients with anaemia having lower resistance for tissue perfusion, and patients with normal or increased haematocrit having higher resistance.

As previously stated, intracompartmental pressure in the calf increases due the calf muscle expansion in the fascia restrained compartment[104]. The increased intracompartmental pressure affects not only the flow rate directly but the radius of the microvasculature, with venioles and capillaries being compressible and collapsing at relatively low pressures, and arterioles at very high pressures[160]. With an increase in intracompartmental pressure and a reduction in radius, flow rates

decrease according to Poiseuille's equation. At a certain intracompartmental pressure, the arteriolo-venolar pressure difference is not sufficient to maintain perfusion, even with patent arterioles[166]. This leads to flow rates approaching zero, resulting in tissue ischaemia.

Of note, when blood flow ceases due to high intracompartmental pressure, a higher perfusion pressure is necessary to restart the blood flow than what was necessary to maintain circulation[160]. This is consistent with Laplace's Law[154]:

$$\text{Wall tension} = \text{internal pressure} \times \text{radius}$$

Which can be rewritten as follows:

$$\frac{\text{Vessel wall tension}}{\text{vessel radius}} = \text{internal pressure}$$

Vessel wall tension needs a higher initial pressure to expand following deflation due to the vessel's small radius. This is similar to the extra effort needed initially when inflating a balloon[154]. With severe ischaemia, as in Rutherford IIB ALI, a similar mechanism could be in action, as the microvasculature collapses due to lack of perfusion from the supplying arteries, resulting in a higher distal MAP being needed to reperfuse the previously ischaemic tissue. If reperfusion is not fully successful, the distal MAP may be insufficient to overcome the inertia of the collapsed microvasculature, and thus the muscle will remain ischaemic.

Severity of ischaemia and ACS

Severity of ischaemia also correlates with muscle tissue damage and increased inflammation and endothelial dysfunction, resulting in a dysfunctional barrier and excessive leakage from the capillaries into the extravascular space after revascularisation[167]. In rabbits with controlled aortic occlusion, capillaries decreased in diameter with an increase in resistance during occlusion; however, after restoration of blood flow, the microvasculature expanded to a greater radius than prior to occlusion, resulting in reduced resistance[168]. Seemingly, if the initial inertia is overcome and the muscle tissue is reperfused, there is vasodilation and excessive perfusion of the tissue with capillary leakage, resulting in increased volume in the extravascular space. Thus, patients with Rutherford IIB ALI could be expected to suffer more significantly from muscle swelling due to inflammation and endothelial dysfunction after revascularisation, resulting in a more significant increase in intracompartmental pressure than in patients with less severe ischaemia.

Sarcopenia as a putative protective factor against ACS

If a patient suffers from sarcopenia, their muscle will have decreased from its normal size, but the fascia will still be unchanged in size, and may allow swelling of the

muscle, without an increase in intracompartmental pressure. Thus, patients with sarcopenia could theoretically be less susceptible to ACS. Anaemia, T2DM, and female sex are all factors associated with sarcopenia, which manifests with reduced calf muscle size[169, 170]. Patients with T2DM are three times more likely to have sarcopenia than patients without T2DM[171]. For female patients, menopause decreases muscle retention, with postmenopausal women being at a high risk of sarcopenia[172]. Patients with more advanced PAD also have reduced muscle fibre size in the calf compared to patients with less severe PAD[173]. Calf muscle size decreases with age, and women in general have smaller calf muscles than men[174]. In the cohort, the mean age of female patients was 75 years, and so almost all female patients in the cohort can be expected to have been postmenopausal.

Factors affecting mean and distal arterial pressure

In paper I, renal insufficiency was found to be associated with undergoing fasciotomy. Renal insufficiency was also found to be associated with fasciotomy in a study of 292 patients who underwent CDT for ALI[175]. Interestingly, in paper II we saw that kidney function improved in patients who underwent prophylactic or therapeutic fasciotomy, which may suggest that their renal insufficiency was due to hypovolemia, and not chronic kidney disease. In a small prospective study, inadequate backflow from distal arteries during open vascular surgery and a high positive fluid balance (treatment of hypovolemia and low blood pressure) were found to be associated with ACS after revascularisation[176]. Hypovolemia could affect two aspects: the first of these is serum plasma levels could be reduced, resulting in increased haematocrit, increased serum creatinine, and low blood pressure[165]. Increased haematocrit results in higher blood viscosity, as mentioned previously, potentially increasing resistance for tissue perfusion. Secondly, low central MAP due to hypovolemia also decreases distal MAP, potentially resulting in a lower threshold intracompartmental pressure, which is necessary in the development of ACS after revascularisation.

A systemic inflammation response syndrome caused by ischaemia-reperfusion injury may induce shock, resulting in a lower distal MAP[177, 178]. Seemingly, the extent of the ischaemia is associated with the inflammatory response[179, 180]. Extrapolating from this, patients with Rutherford IIb ALI could potentially be at a higher risk of systemic inflammation, with reduced distal MAP, and thus be at higher risk of ACS after revascularisation.

Atherosclerosis, stiff arteries, and collaterals

T2DM was associated with lower rates of fasciotomy in paper IV, but DM was not associated with a decreased risk of fasciotomy in the univariable analysis in paper I. Patients with T2DM may have existing PAD more frequently than patients without T2DM, as well as collateral blood flow and less severe ischaemia[38, 181]. This is supported by patients with DM and ALI more often having foot ulcers and

thrombotic occlusions than patients without DM[182]. DM is also associated with an increased ankle pressure[183, 184]. This could theoretically result in a higher distal MAP, potentially improving resilience against ACS. As acute-on-chronic ALI can be hard to distinguish from rapidly progressing CLTI, misdiagnosis can occur because symptom duration may be unclear, and polyneuropathy from T2DM may be assumed to be sensory deficit due to ALI[185, 186]. In paper IV the fasciotomy rate was 1.2% in patients with T2DM and 3.8% in patients without T2DM, suggesting that an overlap with CLTI may exist. The database used only consists of patients with infrainguinal occlusion, which could also alter the fasciotomy rate seen in the population. As the data in SWEDVASC is not validated for ALI, the accuracy is unknown, and there may have been misclassification of ICD-10 codes, resulting in lower precision in the data. The lower rate of fasciotomy could also be due to severe cases of ALI, where significant established PAD may mean that it is futile to revascularise and these patients may undergo primary amputation. This notion is not supported by a recent population-based study, however, wherein combined major amputation and mortality was not significantly higher in patients with DM[28].

Female sex and increased frailty

Patients with T2DM, female sex, or renal insufficiency may also be seen as frail, which could cause a surgeon to choose an endovascular revascularisation approach to treat ALI; this can be performed under local anaesthesia and does not involve major surgical wounds. However, because such an approach often includes the use of CDT, this precludes any prophylactic fasciotomy. An interesting aspect is that female patients more often had Rutherford IIB ALI than male patients in paper III, but underwent fewer fasciotomies. Even more interesting is that, of the 24 female patients who underwent fasciotomy, 15 (62.5%) underwent prophylactic fasciotomy and 9 (37.5%) therapeutic fasciotomy. In contrast, of the 52 men who underwent fasciotomy, 25 (48%) underwent prophylactic fasciotomy and 27 (52%) therapeutic fasciotomy. Seemingly, although surgeons performed fewer prophylactic fasciotomies on female patients, they also performed an even lower proportion of therapeutic fasciotomies, despite these patients having more often severe ischaemia.

Surgeon-dependent factors

Open vascular surgery is usually the treatment of choice in patients with severe ALI[26]. In a propensity-matched large cohort study, it was found that 1.9% of patients who underwent endovascular revascularisation for ALI underwent fasciotomy, compared to 8.9% in the open vascular surgery group[186]. The increased rate of fasciotomy seen in patients who underwent open vascular surgery might have been due to surgeons more often choosing this modality for patients who they feared had poor prognoses or strongly suspected needed a fasciotomy, and/or because the ability to perform an intraoperative fasciotomy lowers the threshold for the surgeon to perform the procedure. The rate of fasciotomy varies between centres, with a fasciotomy rate of 5–30% seen in the literature, without disastrous consequences in

the centres performing fewer prophylactic fasciotomies[113, 187]. An interesting aspect is that the delayed diagnosis and treatment of ACS may result in malpractice lawsuit in certain countries, with a median settlement of $750,000 in cases in the USA[188]. A large variance in prophylactic fasciotomies, seemingly without any greater loss of life or limbs in centres that perform fewer fasciotomies, suggests that local tradition, the surgeon's bias, and potential medicolegal aspects may affect the propensity of surgeons to perform prophylactic fasciotomies.

The COVID-19 pandemic and fasciotomy

During the COVID-19 pandemic, patient care and access to surgery for emergency conditions such as ALI were affected[189-191]. It was expected that there had been an increase in ischaemia-reperfusion injury, and thus higher rates of fasciotomy, due to the Pandemic causing delays in treatment. In paper V, however, this was not found to be the case, as fasciotomy rates remained similar to pre-Pandemic figures. For a centre with a strong tradition of open vascular surgery in the treatment of ALI (83.4% of patients treated through open vascular surgery), the rates of fasciotomy were still overall low (6.3%). It would still be suspected that patients with severe ischaemia would seek healthcare early even during a pandemic due to the severe symptoms associated with it, whereas patients with lower-grade ischaemia may delay seeking healthcare more compared to the pre-Pandemic period. As severe ischaemia is associated with fasciotomy, this may leave the fasciotomy rate unchanged. In a small patient series, six (42.9%) of 14 patients who underwent revascularisation for ALI with concomitant COVID-19 underwent fasciotomy[192]. Another study of 91 patients with ALI and concomitant COVID-19 found that nine (9.9%) patients underwent fasciotomy[193]. Combined, this gives a fasciotomy rate of 14.3%, which does suggest that the fasciotomy rate was not necessarily higher in patients with both COVID-19 and ALI.

Summary of discussion on ACS after revascularisation for ALI

As is clear based on this discussion, the topic of ACS after revascularisation for ALI is not well understood, and simulations and animal studies are warranted in order to better understand how different elements affect muscle tissue perfusion in situations similar to revascularisation after ALI. Such efforts would lead to a better understanding of the pathophysiology of ACS, so as to be better able to predict which patients will be at increased risk of developing the condition, with potential minimally invasive steps to be taken to minimise those risks. Regulating blood pressure by avoiding hypotension and fluid depletion to maintain a normal distal MAP may sustain the conditions for tissue perfusion. However, increased fluid resuscitation may be associated with a risk of increased tissue oedema, and high fluid resuscitation has also been found to be associated with the development of ACS after revascularisation[176,194]. The treating vascular surgeon could be encouraged to measure distal MAP using an automated external sphygmomanometer and intracompartmental pressure, prior to conducting a

fasciotomy, and use this information along with their clinical experience and other clinical findings to decide whether a fasciotomy is advisable. Using pressure measurements on select patients whom the vascular surgeon feels are at high risk would probably improve the positive predictive value for high intracompartmental pressure and putative ACS, compared to conducting routine measurements on all patients with ALI[195]. This would potentially mitigate some of the issues seen with measurement of intracompartmental pressure and overdiagnosis of ACS.

Factors associated with mortality and major amputation after treatment for ALI

Sex differences in ALI

Paper I suggested that female sex was associated with a higher rate of combined major amputation and mortality after revascularisation for ALI. Paper III investigated sex-specific outcomes further, with additional adjustments for potential differences in characteristics between male and female patients. A major difference in study design, which may have caused significant bias in paper I, is that all revascularisations, rather than only index revascularisations, were included. This bias is supported by the reanalysis that used only index revascularisations presented in this thesis, which suggested that female sex was no longer significantly associated with combined major amputation and mortality.

Female patients had a higher mortality rate than male patients in paper III, but this was no longer statistically significant after adjusting for differences in characteristics between male and female patients. In the additional analyses presented in this thesis, Rutherford IIb and age were the most important factors associated with one-year mortality, irrespective of sex. The higher mean age and higher rates of Rutherford IIb of female patients may have contributed to the differences seen in the unadjusted analysis, where female sex was associated with mortality.

For men, open vascular surgery was also associated with higher odds of mortality, and popliteal artery aneurysm thromboembolism with lower odds of mortality; this was not seen in women. Popliteal artery aneurysm is a disease with a strong male predominance, and in the cohort of paper III there were only four female patients with ALI due to popliteal artery aneurysm thromboembolism, compared to 59 male patients[196, 197]. Popliteal artery aneurysm thromboembolism is associated with significant risk of limb loss, but survival odds are favourable[198-200]. The difference in incidence of popliteal artery aneurysm thromboembolism could be a minor factor that could contribute to the difference in mortality seen between male and female patients in the crude analysis of mortality in paper III. This is further supported by the sensitivity analysis performed, which reduced the difference in one-year

mortality between the sexes when patients with popliteal artery aneurysm thromboembolism were excluded. The result should be interpreted cautiously, as age may have confounded the difference in results between the analyses.

A study of 18,000 patients who underwent revascularisation for ALI found a higher mortality rate for female patients, with similar rates of major amputation[201]. The female patients in that study were on average 1.8 years older than the men, but the severity of ischaemia was not included.

A study of 154 limbs belonging to 147 patients who underwent endovascular therapy for ALI found that female sex was not significantly associated with increased limb loss[205]. However, another study of 170 patients found that female sex, together with multi-level occlusion and Rutherford IIb, were associated with an increased rate of major amputation and mortality in patients who underwent revascularisation for ALI[204]. The female patients in that study were on average five years older, more often had Rutherford IIb, and had a higher proportion of multi-level occlusions than the men. Similarly, a study of 129 limbs in 119 patients who underwent CDT for ALI found an increased 30-day mortality rate and a higher rate of limb loss among female than male patients[204]. Another study of patients who underwent endovascular revascularisation found non-significant higher rates of one- and two-year mortality for female patients[205]. In that cohort, the female patients were on average eight years older than the male and had non-significantly higher rates of Rutherford IIb ALI.

Two traits shared by several of the studies is that female patients presented more often with severe ischaemia (Rutherford IIb) and at significantly higher ages. As both are independent factors associated with mortality, it is possible that differences in these two factors could explain the observed difference in mortality and major amputation. It is, however, unknown why female patients usually present at a higher age and with more severe ischaemia. A factor driving the development of ALI at an older age for women could be a reluctance among clinicians to prescribe anticoagulants to perceived frail elderly female patients with atrial fibrillation, even with clear indication[206]: as embolic risk is higher for women with untreated atrial fibrillation, this puts them at an increased risk of ALI[207]. In paper III, we saw a higher prevalence of atrial fibrillation and incidence of embolic ALI in female patients. The sex differences in embolic risk can be mitigated by appropriate use of anticoagulants[208]. As embolic ALI usually presents with more severe ischaemia[40], this could contribute to the higher Rutherford IIb ALI proportion in female patients.

Several studies have also associated female sex with higher mortality, and others have suggested a higher rate of major amputation. An interesting aspect of these studies, however, is that they did not include patients who underwent primary amputation, medical therapy alone, or palliative care. There is therefore a high risk of selection bias, with one sex more likely to undergo revascularisation for ALI. A population-based study of all patients with ALI during a four-year period, showed

that, regardless of treatment modality, female sex was associated with a higher combined major amputation/mortality rate, but was not an independent factor associated with undergoing revascularisation[28]. That study did not give specific rates of combined major amputation/mortality, nor exact mortality nor major amputation rate per sex. ALI-specific mortality was not significantly different between the two sexes, at 1.82 (95% CI 0.83–3.46) deaths per 1000 men and 3.34 (95% CI 1.84–4.84) deaths per 1000 women, suggesting that deaths due to ALI were the same regardless of sex. However, the confidence intervals given were quite wide and a type II statistical error may exist, and so a sex difference in ALI-specific mortality cannot be excluded with certainty[209]. Interestingly, 18.3% of men and 46.8% of women had atrial fibrillation, with only 38.5% of patients with atrial fibrillation being on anticoagulant therapy, and there was a strong association between atrial fibrillation and embolic ALI[28]. This supports the notion that female patients with ALI often have undertreated atrial fibrillation, and that the rate of ALI could possibly be reduced by proper use of anticoagulants.

Pervading all studies that have investigated sex differences in ALI to date is a lack of competing risk analysis, with the potential risk of underestimating major amputation in the sex that has a higher mortality rate[210]. In the mentioned articles this would correspond to a possible underestimation of major amputation in female patients with ALI. Importantly, limb salvage may be of the utmost importance for the vascular surgeon, but in certain cases come at the expense of the patient's life[88].

Type 2 diabetes mellitus – mortality and major amputation

In the crude analysis presented in paper IV, T2DM was found to be associated with a lower risk of mortality but a higher risk of major amputation and acute myocardial infarction. These differences were no longer significant in the adjusted analysis. A primary reason why T2DM was inversely associated with mortality could be that the T2DM patients were younger than the non-T2DM patients (mean ages of 73.7 compared to 79.2). As major amputation was higher and mortality lower in the T2DM group, a competing risk analysis was performed that did not demonstrate a significant difference between the T2DM and non-T2DM groups as regards major amputation and acute myocardial infarction. In other studies, DM has not been found to be significantly associated with limb loss after revascularisation[202]. A study of 399 patients with and without DM found that patients with DM were younger and suffered a higher rate of limb loss and had lower amputation-free survival[182]. As DM is a risk factor for major amputation due to diabetic foot and PAD, it could be hypothesised that revascularisation for ALI is more often seen as futile, resulting in a higher primary major amputation rate. This notion was, however, not supported in the previously mentioned population-based study, where DM was not associated with increased combined major amputation and mortality[28].

Mortality and major amputation during the COVID-19 pandemic

In paper V, higher rates of major amputation and reintervention were observed during than prior to the COVID-19 pandemic, in crude analyses. The higher rate of reinterventions was suggested to be partially due to an increased use of mechanical thrombectomy. A large multi-centre study of patients, which had a similar design to paper V but a total population of 7344 patients, found a higher 30-day mortality rate during the COVID-19 pandemic, and an increased reintervention rate due to increased use of mechanical thrombectomy[211]. That study did not find an increased major amputation rate during the COVID-19 pandemic; however, no competing risk analysis was performed and, as mortality is a competing risk, it is unknown whether the similar rates were due to an actual consistent rate of major amputation, or if patients at high risk of major amputation died at a higher rate during the Pandemic, and thus never underwent a major amputation. An increased need for reintervention after endovascular revascularisation was also found in a study comparing modern endovascular techniques to open vascular surgery for ALI[212]. A study of patients treated during the COVID-19 pandemic found that patients infected with COVID-19, with concurrent ALI had higher mortality and major adverse limb event rates than non-infected patients treated for ALI[213]. The COVID-19 pandemic seems to have affected outcomes and coincided with more extensive use of advanced endovascular techniques, and a higher rate of reintervention. The more extensive use of advanced endovascular techniques may have been due to increased familiarity with the devices among surgeons in the latter time period of the study, as well as the shorter treatment duration – often a single session – and shorter stays in intensive care units[214]. It should be noted that there is no proof from comparative studies that mechanical thrombectomy is better than CDT for treating ALI[74].

Methodological considerations

Causal effect, observational studies, and confounding

In medical research, the causal effect of a treatment or exposure on a certain outcome is of key interest[215]. Understanding of such effects can be achieved using randomised controlled trials; however, these are labour-, time- and resource-intense, necessitating careful consideration of whether the research question warrants this type of study[216]. Well-conducted randomised controlled trials provide a high level of scientific evidence, while observational studies provide a lower grade of evidence[217]. In some instances, randomisation is unethical, unfeasible, or even impossible due to the subject studied[218, 219]. Although not as robust as randomised controlled trials, observational studies can be used to study the effect size of treatment or exposure[220]. However, the risk of bias is high in an observational study, e.g. due to the possibility of confounding, where systematic differences between the compared groups also influence the outcome or treatment effect[221]. Methods to

adjust for confounding exist, such as matching or multivariable regression analysis, to attenuate the effects of confounders[222]. It is often difficult to intuitively derive which factors could be potential confounders, and possible interactions between variables may complicate the matter further[223]. In a review of studies published in four major epidemiological journals, it was reported that 37% of articles did not state how the selection of variables was performed[224]. A well-conducted observational study does not necessarily over-estimate treatment effect, as has been previously thought[225]. To increase transparency and aid in the standardisation of observational studies, the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) guidelines were developed in the early 2000s[220]. This framework assists researchers in improving the validity of observational studies, and in this thesis we designed and reported the results of papers II–V according to the STROBE guidelines.

Due to the primary subject studied in this thesis, fasciotomy after revascularisation for ALI, the possibility to perform any randomised studies were limited, as it is an adjunct surgery for a rare complication of a rare disease. The time and resources would be exceedingly high to conduct a randomised trial. A clear research question, warranting a randomised trial, with potential substantial benefit to the patients was not found. A randomised controlled trial comparing prophylactic fasciotomy to surveillance would be difficult to conduct, as only about 5% of patients with ALI undergo prophylactic fasciotomy, and the inclusion criteria would be difficult to define. Additionally, prophylactic fasciotomy is perceived by vascular surgeons to be a potentially life- and limb-saving intervention, and so the small benefit of the additional evidence that could be obtained through a randomised controlled trial may not outweigh the ethical implications. This is especially important considering the urgent nature and potentially disastrous consequences of ACS, the initial insidious symptoms, and the lack of non-invasive diagnostic bedside tools to verify a diagnosis. Instead, observational studies were designed to try to answer key research questions for the articles included in this thesis, however, limited by the nature of observational studies. As a means to limit the bias introduced by the nature of the study design, adjustment models were created using several different statistical approaches in the studies. In the following sections we will discuss the application and limitations of such models in each of the studies.

A method used was propensity scores. With propensity scores, the researcher is given theoretically limitless possibilities to include variables in the adjustment model, and so one potential action is to include all factors in the dataset. The best propensity score is not necessarily achieved by the model with the best prediction of group allocation; instead, the best model is the one that best addresses systematic differences[226]. Simulation studies have shown that factors that are strongly associated with the exposure but weakly associated with the outcome reduce the precision of models[227]. Instead, a propensity score should consist of factors that differ between the two groups and that are associated with a change in treatment

effect, to be able to adjust for systematic differences[228]. For example, including shoe size would be a strong predictor of patient sex, but would not be associated with the outcome major amputation; thus, this factor should be excluded from the propensity score due to risk of decreasing precision. Popliteal artery aneurysm thromboembolism, on the other hand, is also a predictor of sex, and is associated with the outcome, and is therefore a better candidate to include in a propensity score. It is important that the propensity score includes only potential confounders when estimating total effect, and not mediator or colliders, and it is preferable to use directed acyclic graphs to choose variables[229].

Paper I

The primary aim of paper I was to investigate factors associated with undergoing fasciotomy, and so all patients during the long time period, 2001–2018, were included and analysed. This included 134 repeat revascularisations. Any given patient is at risk of undergoing fasciotomy with each episode of ALI. Additional analyses with mortality and major amputation were also performed. The inclusion of recurrent episodes of ALI seems to have introduced bias to the analysis of major amputation and mortality, whereas there was no significant in the analysis of factors associated with fasciotomy. This could be explained by the possibility that some patients suffered ALI twice in a single year and underwent revascularisation twice, with the potential of death and/or major amputation being counted twice. The paper is thus overweighted regarding patients having recurrent episodes in the same year. This introduces bias due to the breach of a fundamental assumption for logistic regression: independent variables[230, 231]. As the fasciotomy data only covered the in-hospital period, it did not affect the fasciotomy data from any previous nor later episode of ALI. A more appropriate method for paper I would have been to only include index patients in the initial analysis, which would have meant some loss of sample size and statistical power. However, high power is to no benefit if the fundamental methodology is incorrectly used. An alternative route would have been to only include major amputation and mortality data from the in-hospital period, as this would have left the data points independent from previous or subsequent hospitalisation for ALI. As the primary purpose was to investigate the odds of fasciotomy, rather than survival or major amputation, the inclusion of non-index patients was not recognised as a source of methodological error at the time. To reduce the risk of similar errors in the future, a meticulous study protocol should be established and discussed prior to initiation of the study, even for retrospective studies, and the assumptions of the statistical test that will be used should be rehearsed.

Paper I investigated factors associated with fasciotomy; however, these are not necessarily the same as the factors associated with the development of ACS. If a specific factor is generally perceived by a surgeon to be important for the development of ACS, he or she may be more inclined to perform a prophylactic

fasciotomy, resulting in the factor being significantly associated with fasciotomy. Whether the factor is important for the development of ACS will still remain unclear. Excluding the patients who underwent prophylactic fasciotomy and only including ones who underwent therapeutic fasciotomy would introduce survivor treatment bias, as the factors that may be important for the development of ACS may be correctly found by the surgeon and thus the patient undergoes a prophylactic fasciotomy[232]. The remaining therapeutic fasciotomies would be an interesting subgroup of patients with unexpected ACS, but their characteristics would not necessarily reflect the true risk factors for ACS.

The method of univariable testing variables to select the multivariable model in Paper I could potentially have neglected important variables with $p>0.05$[233]. To reduce this risk, all factors with $p<0.1$ were considered for inclusion in the multivariable model.

Paper II

Diagnoses of prophylactic and therapeutic fasciotomy were derived retrospectively from medical records, with patient symptoms, findings at examination, and surgeons' descriptions in their operative evaluation as the basis for diagnoses. All fasciotomies performed not performed at the time of the initial revascularisation procedure were counted as therapeutic. The lack of certainty in the data regarding diagnosis of ACS makes the study more imprecise, and may mean that the potential consequences of ACS are underestimated. To better estimate the risks of delayed fasciotomies, prospectively collected data measuring intracompartmental pressure prior to fasciotomy are needed.

The paper is also limited by the low statistical power, which only allowed for minimal adjustment for potential confounding. A larger cohort with propensity score-adjusted analysis would have been beneficial in reducing the risk of type II statistical error.

Paper III

In this paper, we utilised propensity score-adjusted analysis, where the chosen factors were seen as important differences in characteristics between men and women. An alternative would have been to utilise a directed acyclic graph to create the adjustment model. This would likely have resulted in a smaller model, as some factors may have been sufficiently adjusted for solely by adjusting for a precursor factor; for example, acetylsalicylic acid would not have been necessary to adjust for if we already had adjusted for ischaemic heart disease. This could have increased precision, with minimal difference in bias adjustment[228]. Additionally, factors without differences between the sexes or with minimal effect on outcome could have been excluded. For example, the factors hypertension (minimal effect on mortality) and DM (similar distribution in the two sexes) could have been excluded from the propensity score without increasing bias.

Another popular approach is to use propensity scores for matching. This was an approach that was contemplated; however, due to the relatively small study population, a significant loss of statistical power would have resulted unless oversampling had been utilised[234]. Another approach could have been to use inverse probability weighting, which is a popular option for adjusting with propensity scores. However, the group of authors was unfamiliar with this method, and thus a simpler propensity score-adjusted analysis was conducted.

Characteristics that differ between the sexes cannot, by definition, be true confounders, as a confounder introduces an exposure that increases the likelihood of the observation[235]. In simpler terms, an exposure like smoking cannot result in a person becoming a man or a woman. By adjusting for differences in characteristics, we have instead attempted to estimate the direct effect of sex. For example, if a man and a woman had the same characteristics would there still be a difference in outcome[236]?

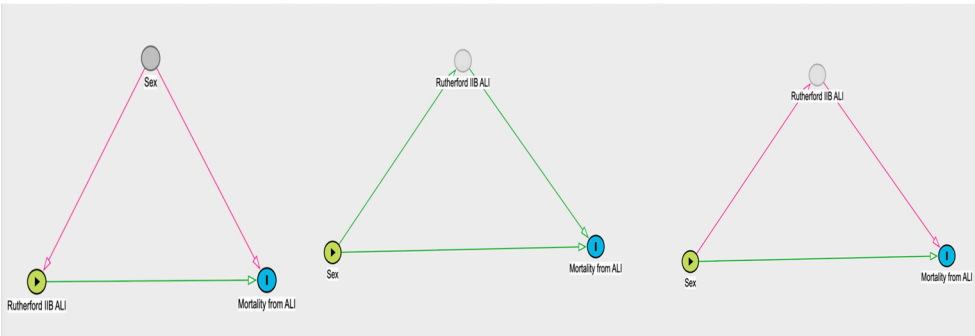

Figure XI: The interaction between three variables: sex, Rutherford IIB ALI, and mortality from ALI. In the leftmost image Rutherford IIb ALI is the exposure, with the green arrow showing the causal pathway to ALI mortality (outcome); sex is a confounder, with the confounding pathway shown in pink. In the middle image sex is the exposure, and Rutherford IIB ALI is a mediator, with both direct and mediating pathways shown in green, which combines to the total effect. In the rightmost image the direct effect pathway is visualised in green and the mediating pathways in pink; hence, adjusting for Rutherford IIb ALI is necessary to isolate the direct effect. Created using DAGity[143].

As the data were retrospectively collected, we lacked some important factors such as ethnicity and socioeconomic status that would have been important to adjust for. A prospectively collected cohort would have enabled us to overcome some of the limitations of the study.

To investigate which factors were driving the difference in total effect on mortality, a mediation analysis could, in theory, have been conducted[237]. Due to the modest cohort size, the number of factors included in the propensity score, and the combination of dichotomous and continuous variables, no mediation analysis was performed. In this thesis, a multivariable logistic regression analysis for mortality, with separate analyses for each sex, gave some insight into the important factors

associated with mortality per sex, but it is not equivalent to a proper mediation analysis.

Paper IV

The lack of external validation of the SWEDVASC registry data on patients with ALI was a major concern in paper IV. There is a possibility that patients with ALI were mixed with patients with rapidly progressing CLTI. A large proportion of data on ischaemia severity was missing, which limited the precision of the study results. Rutherford class is a key confounding variable, and needs to be adjusted for when comparing two groups of patients with ALI. Even with the excellent coverage of the National Diabetes Registry, there may still have been patients with undiagnosed T2DM in the non-T2DM cohort. This would have led to an underestimation of the true difference between the groups, and a greater risk of type II statistical error.

The use of propensity score analysis with inverse probability of treatment weighting was considered for paper IV, but was not used due to standard multivariable regression analysis being sufficient to adjust for potential confounding, based on the model derived from a directed acyclic graph.

The cohort was also of a modest size. Patients with T2DM had a higher, but not significantly so, risk of major amputation (HR 1.45, 95% CI 0.99–2.11, p=0.05) and acute myocardial infarction (HR 2.15, 95% CI 0.86–5.38, p=0.10). The wide 95% confidence interval indicates that there is a risk of type II statistical error. This would be intuitive, as having T2DM is a significant risk factor for the development of coronary artery disease and major amputation, with and without PAD, of the lower limb[7, 238, 239]. This may warrant replication studies, and a meta-analysis of pooled results.

Paper V

In the one-year amputation data there were some missing cases, which reduced the statistical power of an already small study population. We were limited by the small sample size of the study, and only able to adjust for a single covariate in the multivariable analysis. We chose to use a change-in-estimate analysis to find the factor with the highest impact. This method was found to be useful as only a single variable met the threshold of 15% change in estimate. A different approach could have been to utilise a directed acyclic graph.

A sub-analysis was also performed of patients who underwent treatment for ALI, before and after the introduction of the local COVID-19 vaccination programme. The data did not, however, specify whether the patients had actually received a vaccination. The rate of COVID-19 infections was not constant, and instead occurred in so-called ‘waves’, with periods of increased transmission[240]. At these times, the healthcare system may have been under excess strain, and this could have affected the patients with ALI, such as through prolonged waiting times in

emergency departments, delayed surgeries, and reduced possibilities for outpatient follow-up. Without performing sub-analyses of peak transmission periods, the impact of COVID-19 under such circumstances may not be fully appreciated.

Strengths

The use of a nationwide cohort in Paper IV, with prospectively collected data, gave a good overview of the specific outcomes. The data from the nationwide cohort also included excellent data on the socioeconomic status of the patients, enabling these variables to be adjusted for, which is rare in ALI research.

The use of data from both a centre with an endovascular profile (papers I–III) and a centre with a stronger open vascular surgery heritage (paper V) gave a good understanding of achievable results with all types of revascularisation option. The good access to outcome data in all studies gave few missing cases, especially regarding mortality and fasciotomy.

The use of a directed acyclic graph in paper IV introduced greater transparency in the variable selection for the multivariable adjustment models. It also increased reproducibility. Further, the inclusion of a competing risk analysis was appropriate to demonstrate whether an obvious competing risk interfered with the results, although competing risk cannot be ruled out. A strength of Paper V is that all patients who underwent any type of surgical intervention for ALI, including amputation, were represented.

Conclusions

- Female sex, T2DM, and anaemia were found to have an inverse association with fasciotomy after revascularisation for ALI. Renal insufficiency, popliteal artery aneurysm thromboembolism, Rutherford IIb ischaemia. and open vascular surgery were found to be associated with an increased risk of fasciotomy.
- Fasciotomy was not associated with increased combined major amputation/mortality in multivariable analysis with only index patients.
- Patients who underwent prophylactic and therapeutic fasciotomies had similar wound-healing times and similar rates of wound complications.
- Similar improvements in kidney function were seen in patients who underwent both prophylactic and therapeutic fasciotomies.
- Female sex was associated with a higher risk of mortality; this is potentially explained by generally higher age at onset of ALI and higher rates of Rutherford IIb ALI. There was no observed significant difference in combined major amputation/mortality between the sexes.
- T2DM was associated with a lower rate of fasciotomy. There was no significant difference in mortality, major adverse cardiovascular events, nor major amputation in the adjusted analyses.
- Patients who were treated for ALI during COVID-19 in a single vascular centre in Santiago, Chile had higher odds of major amputation but not fasciotomy compared to ALI patients treated before the Pandemic, which could be explained by systematic differences between the Pandemic and pre-Pandemic groups. There was no observed significant difference in mortality nor fasciotomy.

Future research

A large proportion of fasciotomies for ALI are performed prophylactically, as there are no diagnostic or prognostic tools used routinely in clinical practice for ACS after revascularisation for ALI. Prognostic models would be beneficial to determine whether a patient is likely to need a fasciotomy. However, such a model would require an exceptionally high specificity without sacrificing sensitivity, in order to be able to reduce the number of unnecessary fasciotomies without risking the development of ACS. The development of such models may be limited by the lack of consensus on the definition of ACS diagnosis, and treatment cannot be delayed until the diagnosis is obvious, resulting in potentially disastrous outcomes. Relying on measurements of intracompartmental pressure lacks specificity in terms of diagnosis and could risk overtreatment.

A more feasible approach would be the development of a means of directly imaging the perfusion of the calf musculature, as surveillance of the perfusion could noninvasively detect changes in perfusion, which can predate the development of ACS. As ACS causes necrosis through ischaemia, this would allow reductions in muscle perfusion to be detected, meaning that fasciotomy would be warranted. With time, patterns in the changes of perfusion could potentially be used to indicate that the patient could be entering ACS, and non-surgical treatment could be initiated. This would reduce the need for unnecessary prophylactic fasciotomies. Research regarding imaging of microvascular flow using ultrasound is ongoing, and would be an interesting technology to investigate in the context of reduced muscle perfusion[241]. In addition, intracompartmental pressure measurement is an invasive technique that is unsuitable for and risky to use in the large proportion of patients with ALI who undergo CDT[90]. There is an increased risk of needle-mediated intracompartmental bleeding during thrombolysis, further increasing the risk of ACS. Hence, the development of a non-invasive technique to measure microvascular flow in patients with suspicion of ACS is warranted.

Sex differences in ALI have received more attention over the past few years, but this topic was not included in the 2020 European Guidelines[26]. A first step would be to include aspects of sex in relation to the treatment of ALI in the next edition. Further research is needed in order to understand how to optimally treat men and women for ALI, and this would preferably be conducted through well-designed multicentre prospective studies. As several studies have investigated sex-related

outcomes of ALI in the past few years, a systematic review of current evidence would be of interest. Furthermore, an emphasis on generalisability is important, with the need for more studies from low- and middle-income countries in ALI guidelines.

Populärvetenskaplig sammanfattning

Akut benischemi är en sjukdom som orsakas av akut påkommen syrebrist i benet, på grund av ett eller flera hinder i pulsådrorna (artärerna) som förser benet med syrerikt blod. Likt en stroke uppstår akut benischemi när en propp hindrar det syrerika blodet att nå vävnaden, i detta fall benet. Anledningen till att sjukdomen uppstår är vanligtvis genom två mekanismer: en blodpropp kan uppstå i hjärtats förmak eller en mer central pulsådra, där proppen sedan följer med det syrerika blodet och fastnar nedströms i artärträdet, vilket resulterar i stopp. Den andra mekanismen är att en pulsådra med åderförkalkning får en spricka i det åderförkalkade placket som orsakar en blodpropp som hindrar blodet från att passera vidare. Oavsett mekanism så är akut benischemi en allvarlig sjukdom där det finns risk för vävnadsdöd och amputation, samt risk för patientens liv.

Riskfaktorer för åderförkalkning är framför allt rökning, högt blodtryck och diabetes, vilka över många år leder till uppbyggnad av åderförkalkade plack. Den huvudsakliga anledningen för att proppar uppstår i hjärtat är oregelbunden hjärtrytm (förmaksflimmer) och tidigare hjärtinfarkter. Dessa sjukdomar påverkar hjärtats rörelseförmåga och kan resultera i stillasittande blod, vilket i sin tur är proppbildande. Dessa proppar kan sedan lämna hjärtat och färdas ut längs pulsådrorna.

Akut benischemi kännetecknas av att man utvecklar akuta symtom såsom smärta, avsaknad av pulsar i pulsådrorna, kyla, blekhet, domningar, känselbortfall och bortfall av rörelseförmåga. När bortfall av rörelseförmåga uppstår är sjukdomen grav och man behöver återställa blodflödet snabbt. I ett sent skede kan hela benet bli lamt och helt sakna känsel, och då är det ofta för sent att återställa blodflödet.

Det finns två huvudsakliga metoder för att återställa blodflödet. Man kan använda öppen kärlkirurgi, där man öppnar blodkärlet och använder en kateter med ballong för att dra ut blodpropparna eller genom att omdirigera blodflödet förbi blodproppen genom en förbikoppling, så kallad bypass, användandes av en ven eller ett syntetiskt kärl. Med öppen teknik kan man även skala ut åderförkalkningen för att förbättra blodflödet efter operationen.

Man kan även använda minimalinvasiv kirurgi där man punkterar ett blodkärl i ljumsken och för in en kateter som man sedan kan navigera, genom röntgengenomlysning, till platsen för proppen. Via dessa katetrar kan man ge

propplösande läkemedel direkt i proppen, använda tekniker för att suga ut den, alternativt ballongvidga och stenta blodkärlet.

Efter att man har återställt blodflödet till benet finns det en risk att patientens skadade muskelceller i vaden börjar svälla. Då muskler är omslutna av en tjock bindväv som enbart kan expandera till en viss grad så finns det en risk att musklerna ej kan svälla så mycket som de behöver. Detta kan resultera i att trycket i muskeln stiger, och vid en viss punkt överstiger trycket i muskeln det från blodcirkulationen, och då upphör blodflödet till muskeln. Detta kallas kompartmentsyndrom. Om inget görs resulterar detta i muskelsönderfall med risk för amputation, potentiellt livshotande njursvikt och hjärtrytmrubbningar. Kompartmentsyndrom kan behandlas, eller förebyggas, genom ettkirurgiskt ingrepp, klyvning av bindvävshinnan eller fasciotomi, där man klyver bindvävshinnan som omsluter musklerna. Detta är ett större ingrepp som innebär att patienten får stora sår längs den inre och yttre sidan på hela underbenet, vilket kan resultera i sårinfektioner, svårläkta sår och behov av hudtransplantationer.

I studie nummer ett så analyserade vi de patienter som genomgått fasciotomi efter att man utfört en operation för att återställa blodcirkulationen. Framför allt var vi intresserad av att se ifall vissa patientfaktorer var vanligare hos patienter som genomgick fasciotomi. Till exempel kan detta röra sig om ålder, kön, tidigare sjukdomar, hur allvarlig syrebristen var vid ankomst till sjukhus samt operationsmetod. Det vi fann var att patienter med försämrad njurfunktion, mer grava symptom i benet (i form av försvagad rörelseförmåga vid ankomsten till sjukhuset), blodpropp orsakat av bråck på pulsådern i knävecket, samt patienter som genomgick öppen kärlkirurgi hade högre sannolikhet att även genomgå fasciotomi. Kvinnor och patienter med blodbrist hade lägre sannolikhet av att genomgå fasciotomi.

I studie nummer två analyserade vi de patienter som genomgått fasciotomi, och delade in dessa i en tidig grupp (profylaktisk fasciotomi) som behandlats innan symtom av högt muskeltryck uppstått, samt patienter som genomgått fasciotomi efter symtom av att högt muskeltryck uppstått (terapeutisk fasciotomi). Vi jämförde hur deras njurfunktion utvecklades under vårdtillfället, då muskelnedbrytning av syrebrist i muskeln kan leda till påverkan på njurfunktionen. Vi undersökte också ifall det var olika lång sårläkningstid och olika sårkomplikationsfrekvens i de två grupperna. Det vi fann var att det inte var någon skillnad i förändring av njurfunktionen eller i sårläkningstid, mellan de båda grupperna. Båda grupperna hade hög risk för sårkomplikaitoner, med något högre frekvens av infektioner i den gruppen som genomgick terapeutisk fasciotomi.

I den tredje studien gjorde vi en direkt jämförelse mellan män och kvinnor med akut benischemi, där vi jämförde skillnader i ålder och sjukdomsbörda. Dessa skillnader kan även ha en påverkan på risk för död, amputation och fasciotomi. Vid ojusterad analys hade kvinnor en högre odds för död, men denna skillnad försvann när vi

gjorde statistisk justering. Skillnaden i död, som försvann efter justering, stödjer tanken att skillnader i ålder och sjukdomsbörda förefaller kunna bidra till ökad dödlighet för kvinnor som genomgått operation för akut benischemi. Däremot var oddsen för fasciotomi högre hos män, både efter ojusterad och justerad analys.

I den fjärde studien jämförde vi patienter med och utan typ 2 diabetes som genomgått operation för akut benischemi i Sverige. Vi jämförde dessa patientgrupper med varandra i en enkel statistisk analys och en justerad analys, där vi justerade för rökning och socioekonomiska skillnader. I den ojusterade analysen var typ 2 diabetes associerat med lägre frekvens av död och fasciotomi, men ökad frekvens för amputation och hjärtinfarkt. I den justerade analysen försvann dock dessa skillnader förutom skillnaden i fasciotomi-frekvensen som var lägre vid typ 2 diabetes.

I den femte studien jämförde vi patienter opererade för akut benischemi innan och under COVID-19 pandemin, på ett kärlkirurgiskt center i Chile. Vi fann där att patienter under pandemin hade statistiskt högre frekvens av amputationer, men när vi justerade för operationsmetod så var denna skillnad ej längre signifikant. Detta stödjer att vissa skillnader eventuellt kan vara bidragande faktorer till den ökad amputationsfrekvensen som vi såg under pandemin i detta center i Chile. Detta kan vara skillnader i tidigare sjukdomsbörda, försenat vårdsökande, annan tillgång till möjligheter att genomföra operationer.

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