UPPSALA UNIVERSITET

Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 1511

Acute limb ischaemia

Treatment, outcome and time trends

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ACTA
UNIVERSITATIS
UPSALIENSIS
UPPSALA
2018

ISSN 1651-6206
ISBN 978-91-513-0492-2
urn:nbn:se:uu:diva-363357

Dissertation presented at Uppsala University to be publicly examined in Auditorium minus, Museum Gustavianum, Akademigatan 3, Uppsala, Saturday, 15 December 2018 at 13:00 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in English. Faculty examiner: Professor Clark Zeebregts.

Abstract

Grip, O. 2018. Acute limb ischaemia. Treatment, outcome and time trends. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 1511. 98 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-0492-2.

Acute limb ischaemia (ALI) is a frequent emergency associated with high rates of amputation and death. Traditionally, patients with ALI were treated with open surgical removal of the occlusion or bypass surgery. During the past few decades, new endovascular techniques developed.

No larger studies have investigated the optimal contemporary treatment for patients with ALI. Today, there are no international consensus for recommendations for the treatment of ALI, leaving it open to every surgeon or department to decide the best treatment option.

This thesis aimed to study patients with ALI as a means to extend the understanding of this group of patients, as well as to investigate treatment options. Data sources included hospital charts or information was gathered from the Swedish nationwide Vascular Registry (Swedvasc), the Swedish Population Registry for deaths and the Swedish Patient Registry for amputations.

Paper I compared the results from thrombolysis with and without continuous heparin infusion in 749 thrombolytic procedures, concluding that both treatment strategies were equally successful in achieving revascularisation, with acceptable complication rates for both strategies. Continuous heparin infusion during intra-arterial thrombolysis offered no advantage. Although the regime with continuous heparin infusion was associated with a higher frequency of bleeding complications ($p<0.001$), this difference disappeared after adjustment for confounders.

Paper II studied long-term outcome after thrombolysis and showed that thrombolytic therapy achieves good medium- and long-term clinical outcome, which reduces the need for open surgical treatment in most patients. More than half of the patients in paper II did not require any surgical reintervention or amputation in their remaining lifetime or during a mean of 6.2 years of follow-up. Long-term outcome differed between the aetiological groups. This information is valuable when deciding on the optimal treatment strategy for patients with ALI.

Paper III compared outcomes after open and endovascular revascularisation for the treatment of ALI in 16,229 patients treated in 1994-2014. The large propensity score-matched nationwide cohort study revealed that endovascular treatment of ALI was associated with significantly better short-term survival and amputation-free survival compared with open revascularisation.

Paper IV investigated acute aortic occlusion (AAO) and subsequent ALI. This study showed that mortality after AAO is high but has improved in the past 20 years. The proportion of AAO secondary to occluded graft/stent/stentgrafts increases over time as a result of the endovascular shift in treating aortic diseases and the proportion of AAO secondary to native artery thrombosis decreases.

Taken together, the main findings of this thesis demonstrate a gradual improvement in survival and that endovascular techniques are becoming more frequently used as a first- line treatment of patients with ALI.

Keywords: Acute limb ischaemi, Treatment, Open revascularisation, Endovascular revascularisation, Outcome

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ISSN 1651-6206
ISBN 978-91-513-0492-2
urn:nbn:se:uu:diva-363357 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-363357)

List of Papers

I Grip O, Kuoppala M, Acosta S, Wanhainen A, Akeson J, Bjorck M. Outcome and complications after intra-arterial thrombolysis for lower limb ischaemia with or without continuous heparin infusion. *Br J Surg* 2014; 101:1105-1112

II Grip O, Wanhainen A, Acosta S, Bjorck M. Long-term Outcome after Thrombolysis for Acute Lower Limb Ischaemia. *Eur J Vasc Endovasc Surg*. 2017;53: 853-61

III Grip O, Wanhainen A, Michaëlsson K, Lindhagen L, Bjorck M. Open versus endovascular revascularization for the treatment of acute lower limb ischaemia: a nationwide cohort study. *Br J Surg* 2018; 105: 1598-1606

IV Grip O, Wanhainen A, Bjorck M. Time-trends and management of acute aortic occlusion: a 21-year experience. (Manuscript)

Contents

Abbreviations

AAA	Abdominal Aortic Aneurysm
AAO	Acute Aortic Occlusion
ABI	Ankle Brachial Index
ALI	Acute Limb Ischaemia
APTT	Activated Partial Thromboplastin Time
ASA	Acetylsalicylic Acid
CI	Confidence Interval
CLI	Critical Limb Ischaemia
DAG	Directed Acyclic Graph
DOAC	Direct Oral Anticoagulants
EVAR	Endovascular Aneurysm Repair
IHD	Ischaemic Heart Disease
LMWH	Low Molecular Weight Heparin
NNT	Numbers Needed to Treat
OR	Odds Ratio
PAA	Popliteal Artery Aneurysm
PAD	Peripheral Arterial Disease
PIN	Personal Identification Number
PMT	Pharmaco-mechanical Thrombolysis
PTA	Percutaneous Transluminal Angioplasty
RCT	Randomised Control Trial
ROS	Reactive Oxygen Species
SAP	Subintimal Angioplasty
SD	Standard Deviation

Swedvasc	The Swedish Vascular Registry
t-PA	Tissue Plasminogen Activator
VS	Versus

Introduction

Acute lower limb ischaemia (ALI) is a frequent emergency, representing one of the toughest challenges encountered by vascular specialists. Amputation and death rates remain high despite intervention. In contrast, major advances have been made in the treatment of many other vascular diseases.(Earnshaw 2013)

During the past two decades, the treatment of ALI has developed considerably with the introduction of new endovascular techniques and pharmacological agents.(Comerota 2009, Kessel 2004, Robertson 2013, Walker 2009) Today, there is no *one* definitive treatment for ALI. Rather, a variety of modalities are available, including anticoagulation, open surgery, thrombolysis and other endovascular techniques.

Definition of acute limb ischaemia

The word ischaemia derives from the Latin words *ischo* that means restrain and *haima* that means blood. Ischaemia occurs when the blood supply is insufficient to meet the metabolic demands of the tissue. When the oxygen level within the tissue decreases below a critical level, the cells shift towards anaerobic metabolism and lipolysis, resulting in increased production of lactate.(Eliason 2009) Different types of cell can withstand the ischaemic state for different lengths of time before permanent damage and cell death occurs. The ischaemic insult is in fact an integral, an area under the curve, defined by depth and duration. In the lower extremities the nerve tissue is the most sensitive to ischaemic changes and permanent damage can occur after 4 to 6 hours of total ischaemia.(Blaisdell 2002, Duval 2014) ALI affects sensory nerves first, then motor nerves, resulting in the loss of sensation and muscle weakness, respectively. As ischaemia progresses, the skin and finally the muscles are affected.

ALI is an acute condition and most patients seek immediate medical attention after onset of the symptoms; however, the consensus definition of ALI includes patients with symptoms of ALI with a duration of less than 14 days.(Gerhard-Herman 2017)

Pathogenesis of acute limb ischaemia

Several pathologies can cause ALI, of which the most common are arterial embolism and acute arterial thrombosis. Other, less frequently occurring causes of ALI are occluded graft and stentgrafts, thrombosed popliteal aneurysm, dissection, trauma, iatrogenic injury, popliteal entrapment syndrome, cystic adventitia syndrome, endofibrosis and compartment syndrome. (Aboyans 2018)

Over 150 years ago, Virchow described a triad of abnormalities associated with thrombus formation. These alterations were abnormal blood flow or stasis, endothelial injury/vessel wall injury and hypercoagulability, or more simplified, flow, vessel wall and blood. These abnormalities, alone or in combination, still apply for the pathology underlying several of the aetiologies for ALI.(Bennett 2009)

The distinction between embolus and thrombosis can sometimes be difficult. Patient history, clinical presentation, examination, imaging and intraoperative findings can help the clinician to identify the most likely event, however.(Earnshaw 2001, O'Connell 2009)

Table 1. Clinical features that help to distinguish between embolus and thrombosis (Callum 2000)

Clinical features	Embolus	Thrombosis
Severity	Complete (no collaterals)	Incomplete (collaterals)
Onset	Seconds- minutes	Hours- days
Limb affected	Leg 3:1 arm	Leg 10:1 arm
Multiple sites	Up to 15%	Rare
Embolic source	Present (usually atrial fibrillation)	Absent
Previous claudication	Absent	Present
Palpation of artery	Soft, tender	Hard, calcified
Bruits	Absent	Present
Contralateral leg pulses	Present	Absent

Embolism

Embolism is the result of material passing through the arterial tree and obstructing a peripheral vessel, causing ischaemia distally. The embolus usually consists of clotted blood or atherosclerotic plaques.(Abbott 1982, Earnshaw 2013) Other biological substances (air, fat, bacterial debris or tumours), drugs or chemicals can also cause emboli.(O'Connell 2009)

Arterial emboli usually form within the heart (most commonly the left atrium) and are suspected in patients with untreated atrial arrhythmias.(Bjorck 2010) Arrhythmias predispose the heart to intracardiac clot formation, with subsequent release into the blood stream. Patients with chronic atrial fibrillation who are not anticoagulated have a 3% to 6% annual risk of thromboembolic complications.(O`Conell 2009) Paroxysmal atrial fibrillation can be difficult to diagnose because the patient may have a sinus rhythm on examination. Emboli can also arise from the heart's left ventricle as a result of acute myocardial infarction, when a dyskinekic part of the myocardium serves as a nidus for stagnant blood and clot formation. This mural thrombus can occur within hours after the myocardial infarction or can be delayed up to weeks after the event. (O`Conell 2009) Embolus secondary to myocardial infarction is a particularly dangerous cause of embolism. The patient has not only an ischaemic extremity but also a high risk underlying the medical condition(Earnshaw 2013, Norgren 2007) It has been suggested that 80-90% of all arterial emboli originate in the heart.(Abbott 1982)

An embolus can also take form in a proximal aneurysm, dislodge into the circulation and occlude a more distal vessel. A rare cause of embolus is paradoxical embolisation in patients with deep vein thrombosis and a cardiac septal defect.

The most common location for non-cerebral emboli is the lower limb. Emboli can occlude any artery; however, in the legs the common femoral and popliteal arteries are most commonly affected.(Earnshaw 2013) Emboli tend to adhere to bifurcations of vessels in which the lumen is narrowing and can potentially lead to more serious ischaemia.(Bjorck 2010)

Embolic ischaemia can be catastrophic because it often occurs in otherwise normal arteries, without any established collaterals. Typically, the patient presents with an acute white leg, including a complete neurosensory deficit.(Earnshaw 2013) The patients generally seek medical attention within hours after the start of the symptoms, which are often sudden and painful. The extension of the thrombus often causes complete obstruction of arterial outflow and embolic occlusions are progressive. The ischaemia worsens as secondary thrombus forms in regions both proximal and distal to the occlusion.(Earnshaw 2013)

Saddle embolus

Acute embolic occlusion of the aortic bifurcation is a rare but serious condition. The embolus terminates so as to "saddle" the aortic bifurcation, producing bilateral lower extremity obstruction that can have serious hemodynamic and metabolic consequences.(Busuttil 1983) The patients often have absent femoral pulses and appear marble white or mottled to the waist. They may

also present with paraplegia due to ischaemia of the cauda-equina, which can be irreversible. In an earlier era the major source for saddle emboli was rheumatic heart disease.(Webb 1988) Myocardial infarctions, often large with intramural thrombus in the left ventricle, are now the major source of large emboli that occlude the distal aorta. Although the incidence of embolism following myocardial infarction is less than 1%(Thompson 1970), the high prevalence of coronary artery disease makes this a common cause. Atrial fibrillation and other cardiac arrhythmias are other sources of large emboli and have been reported in 40-100% of patients with saddle emboli.(Busuttil 1983, Thompson 1970) Immediate revascularisation may restore lower limb perfusion, but many patients subsequently die from reperfusion injury in combination with their underlying cardiac condition.(Callum 2000)

Arterial thrombosis

An acute thrombosed arterial segment results from blood clotting within the artery itself. Nowadays, this is the most common cause of ALI in high-income countries. This condition is a consequence of progressive narrowing of the arterial lumen due to atherosclerotic stenosis.(Earnshaw 2001) Once a stenosis becomes critical, thrombus may develop on the stenotic lesion, leading to an acute arterial occlusion. An acute arterial thrombosis can also start as a rupture of an atherosclerotic plaque, an event causing platelet adhesion and activation of the clotting cascade and eventually formation of a clot. Virchow described the physiology underlying venous thrombosis formation as a disturbance of one of the factors in his famous triad: the wall, the flow and the blood.(Virchow 1877) This triad is also applicable to arterial thrombosis.

Atherosclerotic disease is a slowly progressive disorder and the tissue is therefore better preconditioned to withstand the ischaemic insult. The tissue slowly adapts to anaerobic metabolism and consumption of lipids rather than glucose. Furthermore, collaterals develop. Thus, the clinical presentation of thrombosis is often less dramatic than with embolisation and the patients have a longer duration of symptoms, often days, before seeking medical attention. Thrombosis can also occur rapidly, however, and cause acute occlusion with symptoms ranging from worsening of claudication to acute severe limb ischaemia with considerable pain.(Earnshaw 2013)

Atherosclerotic disease is a systemic disease in which the patient generally presents with a history of intermittent claudication and abnormal circulation in the contralateral limb.(Norgren 2007) A local plaque rupture or some physiological states associated with reduced perfusion of the lower extremi-

ties can be precipitating factors for the thrombotic event (*Table 2*).(Callum 2000, Earnshaw 2013)

Table 2.

Factors predisposing to acute thrombosis	
Cause	**Comment**
Dehydration	Hot weather, diabetes, infection, gastroenteritis, renal replacement therapy
Hypotension	Myocardial infraction, arrhythmia, heart failure, gastrointestinal haemorrhage, septic shock, multiple organ failure
Unusual posture or activity	Prolonged sitting, kneeling, sleeping when under influence of drugs or alcohol
Malignancy	Solid and haematological
Hyperviscosity	Polycythaemia, thrombocytosis
Thrombophilia	Protein C or S and antithrombin III deficiencies, activated protein C resistance, factor V Leiden, antiphospholipid syndrome

Occlusion of existing bypass and stentgraft

The availability of vascular surgery has increased in high- and medium-income countries, and as a consequence, the prevalence of existing bypass grafts has increased. Patients with acute occlusion of bypass and stentgrafts now constitute a frequent cause of ALI.(Earnshaw 2001)

Graft and stentgraft occlusions occur in patients with an already known and treated vascular disease. Graft occlusions in the first 6 weeks after bypass surgery is generally due to technical error or poor run-off. Most late occlusions result from intimal hyperplasia within the bypass, progressive disease of the inflow or run-off vessels. Graft thrombosis usually presents as an emergency, although it is occasionally preceded by increasing ischaemic symptoms, ranging from mild claudication to critical limb ischaemia (CLI).(Beard 2013) The diagnosis is usually easy and the cause is more likely to be thrombosis than embolism.(Earnshaw 2013)

Popliteal artery aneurysm

Popliteal artery aneurysm (PAA) is defined as an arterial segment with 1.5 times the diameter of a normal adjacent arterial segment or with a maximum diameter of >1.5 cm. The larger the aneurysm, the greater risk of complications (e.g., compression of surrounding veins and nerves, development of

thrombosis within the aneurysm or rupture).(Cervin 2018) PAAs are the most common peripheral aneurysms. The disease occurs almost exclusively in males (95%).(Ravn 2017)

PAAs are unlikely to rupture but are prone to thrombose when blood flow decreases. Thrombosed PAAs are often mistaken for acute arterial embolism.(Norgren 2007) The aneurysm can also generate emboli that can dislodge into the circulation and occlude one, two or three of the major calf arteries. This event generates an ischaemia that is more difficult to treat being that a great proportion of the distal arterial tree is occluded.(Bjorck 2010) ALI due to thromboembolism of a PAA needs urgent attention. Intra-arterial thrombolysis can improve arterial run-off flow in the lower leg before bypass surgery or endovascular stentgrafting can be performed.(Ravn 2007)

Because PAAs are bilateral in approximately 50% of the cases, detecting a prominent and broader pulse in the contralateral leg may be helpful in identifying the cause.(Norgren 2007) The presence of a PAA also increases the risk of having an aneurysm in the aorta, iliac or femoral arteries.(Ravn 2008) Treatment of PAAs differs greatly between countries(Bjorck 2014). In Sweden, treatments of PAAs has changed over time (Cervin 2015).

Clinical presentation and examination

ALI is defined as any sudden decrease in limb perfusion causing a potential threat to limb viability.(Aboyans 2018) The Society for Vascular Surgery and the international Society for Cardiovascular Surgery have published definitions of ALI based on clinical presentation of the affected limb. (Rutherford 1997) In a more recent publication, the guidelines for managing peripheral arterial diseases (PADs) from the European Society for Vascular Surgery (ESVS) and the European Society for Cardiology (ESC), this classification was verified as a valuable instrument for prognosis and treatment. (Aboyans 2018)(*Table 3*)

Ankle brachial index (ABI) is regarded as the first-line method to examine the extent of ischaemia of the affected limb. Systolic pressures are measured over the dorsalis pedis and posterior tibialis arteries with a Doppler probe and then divided with the highest brachial systolic pressure. An ABI <0.90 is associated with a 2-3-fold increased risk of cardiovascular death.(Aboyans 2018)

Table 3. Clinical categories of acute limb ischaemia (Rutherford 1997)

		Findings		Doppler signals	
Category	**Description/prognosis**	**Sensory loss**	**Muscle weakness**	**Arterial**	**Venous**
I. Viable	Not immediately threatened	None	None	Audible	Audible
II. Threatened					
a. Marginally	Salvageable if promptly treated	Minimal (toes) or none	None	Inaudible	Audible
b. Immediately	Salvageable with immediate revascularisation	More than toes, associated with rest pain	Mild, moderate	Inaudible	Audible
III. Irreversible	Major tissue loss or permanent nerve injury inevitable	Profound, anaesthetic	Profound, paralysis (rigour)	Inaudible	Inaudible

When a patient presents with ALI, it is important to quickly determine the severity of ischaemic injury. If the limb is immediately threatened, it is important to secure revascularisation to the tissue as soon as possible to reduce the risk of permanent injury and amputation. Imaging should not delay intervention.(Aboyans 2018) If the limb is viable and not immediately threatened, it is important to make a careful examination with imaging and optimise treatment and the circumstances for the patient.(Aboyans 2018, Bjorck 2010)

The classical findings of ALI may include the "6 Ps":

Pain. The abruptness and time of onset, its location and change in severity over time should be considered. The duration and intensity are important in the clinical decision-making process. For example, thrombolysis may be less effective for thrombosis of 2 weeks duration compared with newly formed thrombosis.(Palfreyman 2000) It is important to keep in mind that patients with diabetes can experience the pain differently because of neuropathy. (Norgren 2007)

Pallor. Changes in colour and temperature are common findings in ALI and are most useful when differing from the contralateral limb. Initially, the ischaemic limb is white and pale; however, if the ischaemia is prolonged, the limb develops a cyanotic colour. This change in colour is due to metabolites with a low pH that cluster in the tissue and induce vasodilatation. This, together with the restrained blood and desaturated haemoglobin, causes the

cyanotic colour. Cyanotic colour is a sign of a severe degree of ischaemia. (Lundberg 1999)

Poikilothermia. With the diminished blood flow the limb loses the ability to regulate temperature and become cold.(O´Conell 2009)

Pulselessness. The accuracy of pedal pulses are highly variable, but a palpable pulse can be helpful in excluding a more severe degree of ischaemia. Absence of a palpable pulse alone is not diagnostic of ALI. Doppler assessment should always be performed to determine whether a flow signal is present, as well as measurement of ankle blood pressure. Usually, very low pressure is obtained or the Doppler signal may be absent in patients with ALI. If performed correctly, the findings of absent flow in the foot arteries are highly consistent with a diagnosis of ALI and can also be helpful in defining the severity of ischaemia.(Rutherford 1997)

Paresthesia. The thin nerve fibres that transduce sensation of soft contact and vibration are the most sensitive to ischaemia.(Lundberg 1999) More than half of the patients with ALI present with numbness.(Norgren 2007) The distribution of numbness depends on the nerve involved but tends to be circular and more pronounced distally.(Lundberg 1999)

Paralysis. It first occurs as a consequence of ischaemic injury on the motor neurons and later to direct injury to the muscles. A muscle affected by ischaemia becomes tender and acquires an altered consistency. Usually, the patient does not present with complete paralysis: more common is a less obvious reduction in force and flexibility that is more pronounced distally.(Lundberg 1999)

The main question to be answered by the examination is the severity of the ALI, which is important for early surgical decision making.(Rutherford 2009) Three findings help separate whether the limb is viable or threatened. These findings are the presence of rest pain, sensory loss and muscle weakness.(Aboyans 2018, Norgren 2007)

Incidence and Epidemiology

Between 1965 and 1983, the incidence of ALI was 23/100,000 person-years in Uppsala, Sweden.(Ljungman 1991) No contemporary epidemiological data exist from Sweden prior to this investigation.

One century ago, life expectancy was considerably shorter than today and the prevalence of severe atherosclerotic disease was rare.(Earnshaw 2001) In those days, cardiac valve disease was the main cause of arterial embolism, which was related to rheumatic or congenital heart disease, but advances in the management of these patients have virtually eliminated this as a cause.(Abbott 1982, Tawes 1985) The incidence of ALI increases exponentially with age, with the highest age-specific incidence found among octogenarians.(Ljungman 1991). Two studies on acute thrombo-embolic occlusions of the superior mesenteric artery showed that the incidence was 8.6/100,000 person-years, increasing exponentially with age for both men and women. The incidence doubled per 5-year intervals, reaching a peak incidence of 217 (169–264) per 100,000 person-years in the age category 85 and above. (Acosta 2004, 2005) The age-specific incidence of embolic ALI probably increases in a similar pattern.

Nowadays, when life expectancy is longer and cardiac arrhythmia is the most common cause of embolic occlusion, it is not unusual that the embolus occludes an already atherosclerotic vessel.(Earnshaw 2013) These patients are often elderly with multiple comorbidities and symptoms of subclinical atherosclerotic disease. This condition makes treatment for ALI more complex and all vascular units should be familiar with both open and endovascular surgery to allow treatment decisions to be made on an individual basis.(Earnshaw 2004)

Treatment of acute limb ischaemia

ALI that is left untreated has a high mortality rate and there is a short window of time for action to save life and limb.(Earnshaw 2013) Once the clinical diagnosis is established, systemic treatment with unfractionated heparin should be given (unless contraindicated). This therapy can stop thrombus propagation and may provide an anti-inflammatory effect that decreases the ischaemia.(Gerhard-Herman 2017)

The method of revascularisation may differ depending on the severity of ischaemia, anatomic location and duration of the occlusion, aetiology of ALI and contraindications to endovascular or open surgery. If the limb is immediately threatened, revascularisation has to take place within hours.

ALI may be treated by:

- Anticoagulation alone
- Open surgical revascularisation – balloon catheter thromboembolectomy, bypass procedure or endarterectomy.
- Endovascular treatment – different modes of pharmacological thrombolysis, percutaneous thromboembolectomy, or both.
- Amputation

Anticoagulation alone

The initial goal of treating ALI is to stop the propagation of the occlusion and worsening of ischaemia by preserving the microcirculation, particularly in patients with emboli in which secondary thrombosis is common. Anticoagulation with unfractionated or fractionated low molecular weight heparin (LMWH) has no direct thrombolytic effect; its function is to merely stabilise the clot and prevent secondary thrombosis. Heparin occurs naturally in the body within mast cells. When released, it binds to and activates antithrombin III. When activated, antithrombin III binds to several factors in the coagulation cascade and inhibits those factors, thereby preventing further clot formation.(Rang 2012) Heparin may be given intravenously as a bolus dose of 5000 IE or calculated after bodyweight (500 E heparin/kg/24 hours). This action may be followed by continuous infusions of heparin titrated according to activated partial thromboplastin time (APTT), which should be two to three times above the reference value during therapy.

Use of anticoagulation alone implies that the limb is likely to remain viable or that other therapeutic options are limited. Anticoagulation for stable class I ischaemia (*Table 3*) can later be followed by intervention if collaterals do not become established.(Earnshaw 2013) Anticoagulation has been shown to improve results after embolectomy.(Campbell 2000) Patients with advanced malignancy are at increased risk of both arterial and venous thrombosis on account of hypercoagulability and endothelial damage. In cases of ALI these patients should, if possible, be treated conservatively with anticoagulation alone.(Tsang 2011)

Open surgical revascularisation

The Swedish surgeon, Einar Key, preformed and described one of the first embolectomy surgeries in 1913.(Key 1913) For many years, the embolectomy procedure was known as “The Swedish operation”.

After Fogarty et. al. described the embolectomy catheter for the remote removal of clot via a groin incision in 1963, surgery became the main treatment for ALI.(Fogarty 1963) Balloon catheter embolectomy may be successful, especially when intraoperative angiography is performed to ensure complete clot removal, which has led to increased use and a lower re-occlusion rate.(Zaraca 2012) Over the years, the pattern of disease has changed, however, and emboli now occur in patients with ischaemic heart disease (ICH), often in association with peripheral vascular disease. Thus, the embolectomy procedure has become more complicated in many cases with diseased arteries. Surgical embolectomy alone, without addressing the underlying atherosclerotic lesion, has been found to be a poor therapeutic option.(Zaraca 2012) Surgical bypass techniques are often required in this situation. Emergency lower extremity bypass for ALI is associated with increased rates of major in-hospital adverse events (including major amputation and death) compared with elective bypass surgery.(Baril 2013) There are several possible explanations for this, such as no surgical optimisation with acetylsalicylic acid and statins, smoking cessation, longer operative procedures with greater blood loss and more frequent use of prosthetic conduits.(Baril 2013)

Endarterectomy is rarely used for limbs with ALI but may be performed for *in situ* occlusion of the common femoral artery. To prevent narrowing of the common femoral artery, patch angioplasty closure is often used.(Kwolek 2013)

Endovascular revascularisation

Endovascular operations offer an expanding range of alternative treatments for ALI. They are a less invasive and can be performed even in elderly patients and in those with multiple comorbidities. Currently, available percutaneous endovascular procedures include catheter-directed thrombolysis, pharmacomechanical thrombolysis (PMT), catheter-directed thrombus aspiration and percutaneous mechanical thrombectomy.(Creager 2012, Karnabatidis 2011) These techniques clear the occluding thrombus from a peripheral artery with a minimally invasive approach, restore blood flow to the extremity and allow the identification of underlying lesions responsible for the occlusive event. Culprit lesions may then be addressed in a directed and less emergent fashion using open or endovascular procedures.

Catheter-directed thrombolysis

Catheter-directed thrombolysis has become the preferred treatment in many vascular centres for the management of most viable or marginally threatened limbs. The procedure generally starts with atrial puncture of the common femoral artery in the non-affected leg and then a long thrombolysis catheter is advanced to the diseased artery and positioned in the occlusion. Multiple

side holes in the infusion catheter are often used to distribute the lytic agent throughout the thrombus. This procedure enables local deposit of a high concentration of thrombolytic therapy and a quicker clearance of the thrombus or embolus.(Kessel 2004)

The pharmacologic substance that is most often used is t-PA (tissue plasminogen activator). t-PA is an enzyme that naturally exists in the body, mainly produced by endothelial cells. t-PA is involved in degradation of blood clots and catalyses the transformation of plasminogen to plasmin. Plasmin is the most important enzyme in the breakdown of blood clots. The blood clot is stabilised by a meshwork of fibrin: plasmin breaks down the fibrin meshwork and degrades the thrombus. By local administration of t-PA, the dissolution of the occlusion is enhanced.(Chapin 2015, Rang 2012) The fibrin content of a thrombus appears to correlate to ischaemic time (Silvain 2011), which suggests that time is a factor affecting the stability and structure of the fibrin matrix. This observation is one explanation why an old thrombus is more difficult to dissolve with thrombolysis.

In the start of thrombolysis or continuously during thrombolysis, LMWH or heparin may be given to prevent pericatheter thrombosis and distal embolisation.

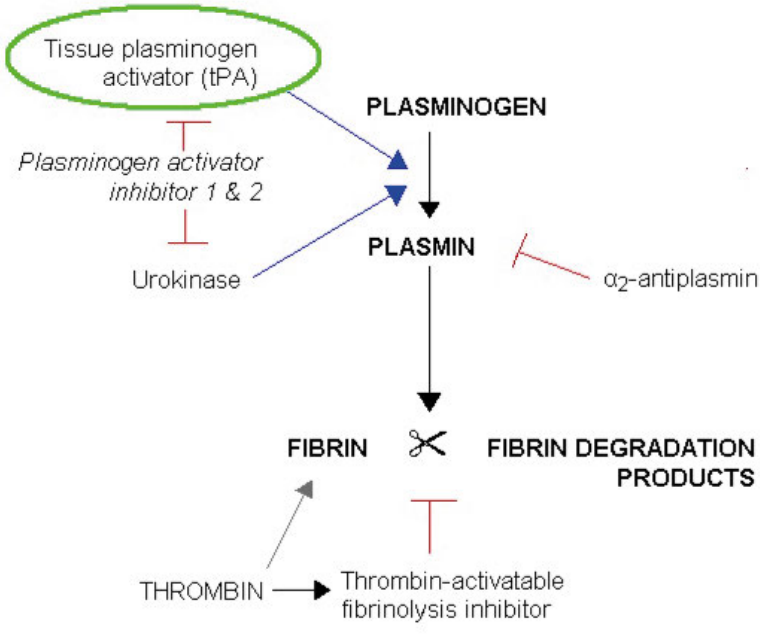

Figure 1. Schematic figure of clot degradation.(Banerjee 2004)

If a low-dose regimen is used, the administration of t-PA generally begins with a bolus dose, followed by several hours up to days with continuous infusions of smaller doses. The dose is decided individually depending on the duration and length of occlusion, grade of ischaemia and age of the patient.(Kuoppala 2008) High-dose and forced infusion techniques can also be used to deliver the thrombolytic therapy, which can achieve revascularisation faster; however, these techniques are associated with more bleeding complications.(Kessel 2004, Plate 2006)

During thrombolytic therapy, angiographic controls are performed. Generally, one or two controls during daytime are conducted based on previous angiographic findings, clinical status of the limb and occurrence of any bleeding complications.

A potential advantage of thrombolysis is that, unlike surgical embolectomy, which simply removes the occlusion from the large arteries, thrombolysis lyses clot in both large and small arteries and even in arteriolar and capillary beds.(Van den Berg 2010) Thrombolytic therapy gradually dissolves the clot. The low pressure and gradual reperfusion may reduce reperfusion injuries and compartment syndrome compared with open surgery.(Norgren 2007)

There are absolute and relative contraindications to thrombolysis that must be noted in the decision-making process, including recent surgery, prior haemorrhagic stroke, active internal bleeding, stroke or transient ischemic attack in the past year, or central nervous system neoplasm. (Kwolek 2013)

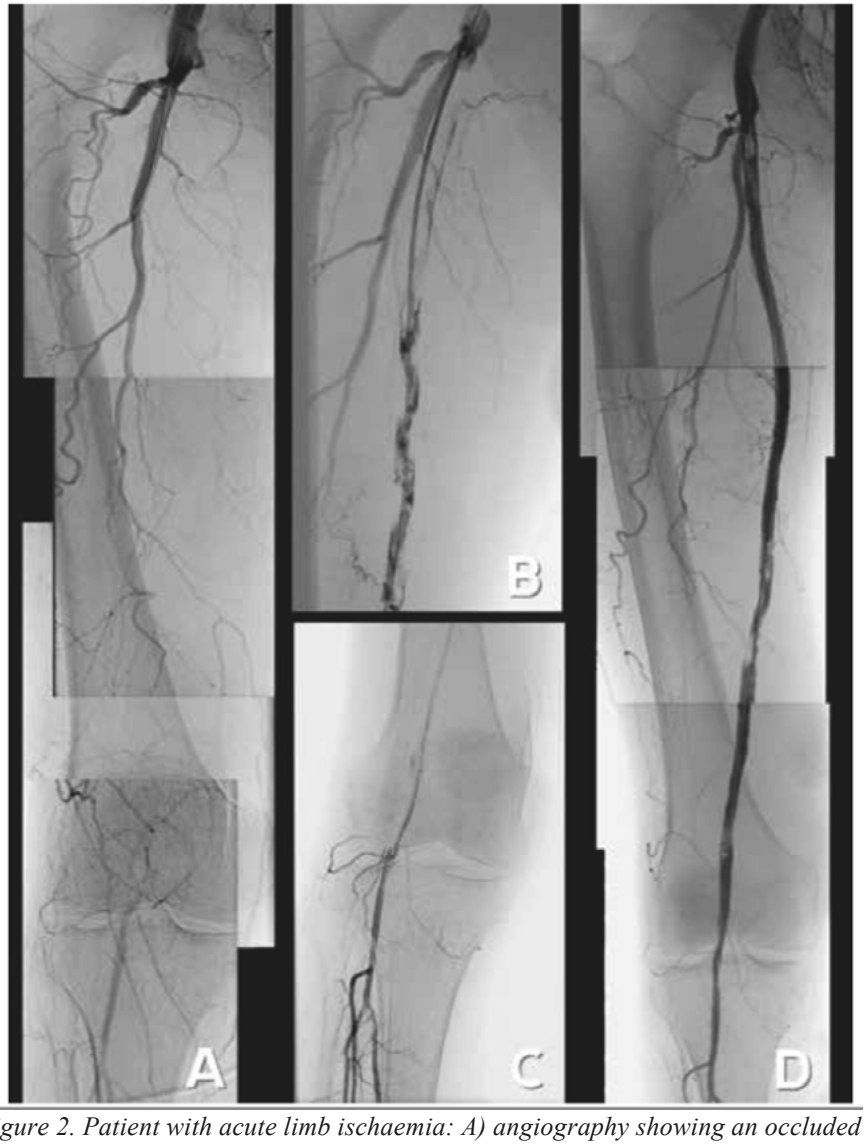

Figure 2. Patient with acute limb ischaemia: A) angiography showing an occluded superficial femoral artery, B) angiogram during recanalisation of the superficial femoral artery, C) angiogram after passing through occlusion demonstrating good run-off and D) post thrombolysis completion angiogram showing restoration of superficial femoral artery flow and good run-off.

Percutaneous mechanical thrombectomy techniques

Percutaneous mechanical thrombectomy techniques have become increasingly popular to further speed up revascularisation. These devices, used alone or as an adjunct to thrombolytic therapy, are designed to clear intra-

vascular thrombi by a combination of mechanical dissolution, thrombus fragmentation, aspiration or ultrasound accelerated techniques.

Rheolytic techniques involve jet-propelled fluid via a high-pressure catheter. The high-velocity turbulence causes lysis and the thrombus debris are aspirated through separate channels in the catheter.(Comerota 2009)

PMT is an increasingly popular method in patients with ALI. A catheter with distal and proximal balloons is inserted into the occluded vessel with t-PA infused between the two occluding balloons. The intervening catheter then assumes a spiral configuration with the insertion of a distribution wire and rotates at 1,500 rpm, spreading the t-PA and fragmenting the thrombus. (Comerota 2009)

Theoretically, PMT carries a greater risk than traditional thrombolysis with respect to endothelial injury secondary to the trauma induced by the device, as well as a risk for haemolysis.(Kasirajan 2002)

Leung and colleagues compared traditional thrombolysis with PMT in 283 patients with ALI in a propensity score-matched cohort.(Leung 2015) The group receiving PMT had a better immediate success rate (88 vs. 74%, p=0.021) and better 1-year amputation-free survival (87 vs. 72%, p=0.028). They concluded that PMT provides a rapid reperfusion to the extremity, reduces procedure time, has an acceptable risk profile and may be used even in patients with severe ischaemia and motor deficits (classified as Rutherford Class IIb) (*Table 3*). Other, smaller studies have also shown beneficial results for PMT in the context of ALI.(Byrne 2014, Gupta 2012, Hynes 2012)

Open surgery versus thrombolysis

In the mid-1990s five randomised control trials (RCTs) were performed to answer the question of the optimal treatment strategy for patients with ALI. Details from these RCTs are presented in *Table 4*. (Graor 1994, Nilsson 1992, Ouriel 1994, Ouriel 1996, Ouriel 1998)

Specifically, Ouriel et al.(Ouriel 1994) randomised 114 patients with ALI of less than seven 7 days duration to thrombolysis with urokinase or open surgery. At 1 year, the cumulative risk of amputation (18%) was equal in the two groups while thrombolysis was associated with a reduction in mortality. Thrombolysis was equally effective in those with embolic and thrombotic occlusions, but the survival benefit was greater for patients with emboli.

The Surgery versus Thrombolysis for Ischaemia of the Lower Extremity (STILE) trial(STILE 1994) randomised 393 patients with non-embolic lower

extremity ischaemia of less than six months duration to catheter-directed thrombolysis or surgical revascularisation. A higher percentage of patients randomised to thrombolysis had treatment failure at 30 days, defined as recurrent or ongoing ischaemia (54% vs. 26%). This circumstance led to premature termination of the trial. The majority of patients in the STILE trial had chronic limb ischaemia. Subsequent analysis, however, offered important insights. Patients presenting with ALI (symptoms <14 days) and who were randomised to thrombolysis had significantly better limb salvage (89% *vs.* 70%) and amputation-free survival compared to open surgery.

The Thrombolysis or Peripheral Arterial Surgery (TOPAS)(Ouriel 1996) randomised 213 patients with acute lower extremity ischaemia secondary to native arterial or bypass graft occlusion of less than 14 days duration to a variable dose of urokinase or surgery. Survival and amputation-free survival at 12 months were similar in the urokinase and surgical groups. These results were confirmed in a trial of 544 patients with ischaemia less than 14 days who were randomised to the optimal urokinase regimen or surgery.(Ouriel 1998) There was a trend towards a higher amputation-free survival among those randomised to surgery and significantly more bleeding in those randomised to urokinase.

An updated Cochrane review examined the cumulative results of available studies.(Berridge 2013) The pooled results of the randomised trials above showed a higher risk of bleeding (odds ratio [OR] 2.8; 95 confidence interval [CI] 1.7-4.6), stroke (OR 6.41; 95% CI 1.57-26.22) and distal embolisation (OR 8.35; 95% CI 4.47-15.58) in the thrombolysis group. Thrombolysis reduced the need for surgery required within 30 days (OR 5.37; 95% CI 3.99-7.22). There was no overall difference in amputation or death at 30 days or at 1 year between surgery and thrombolysis as first-line therapy. Based on available evidence, the Cochrane review could neither support nor reject the use of thrombolysis over open surgery for patients with ALI.

It is important to consider that the studies included in the Cochrane analysis were very heterogeneous in terms of aethology of the occlusion, duration of ischaemia and the thrombolysis protocol used (type of thrombolytic agent, dose and duration). The studies also used different reporting standards. Furthermore, given the fact that the most recent included study was published 20 years ago, it is unclear whether the results are applicable in a contemporary context. As previously mentioned, important technical advances in the endovascular field took place in the past two decades.

Table 4. Randomised controlled trials comparing thrombolysis with open surgery

Author /year	Patients (n)	Thrombolytic agent	Major bleeding <30 days (%)	Stroke <30 days (%)	Distal embolisation <30 days (%)	Amputation-free survival 1 year (%)
Nilsson /1992	20	High-dose t-PA 30mg/3h continuous heparin	0 vs. 0	0 vs. 0	9.1 vs. 0	Not reported
STILE /1994	393	High-dose t-PA 0.05mg/kg/h or urokinase continuous heparin	5.6 vs. 0.7*	1.2 vs. 0	Not reported	Not reported
Ouriel /1994	114	Urokinase continuous heparin	10.5 vs. 1.8	1.8 vs. 0	8.7 vs. 0*	75 vs. 52 *
Ouriel /1996 (TOPAS I)	213	Urokinase continuous heparin	39 vs. 30	2.1 vs. 0	Not reported	69 vs. 65
Ouriel /1998	548	Urokinase continuous heparin	12.5 vs. 5.5*	1.6 vs. 0*	13.2 vs. 0*	65 vs. 69.9
Meta-analysis Berrige /2013	1283		1.3 vs. 0*	8.8 vs. 3.3*	12.4 vs. 0*	*No statistical difference*

* $p<0.05$. All percentages are first given for thrombolysis versus open surgery.

Thrombolysis offers some advantages: First, it can be performed under local anaesthesia, which is less risky given that many patients with ALI are elderly and fragile with multiple comorbidities. Second, several experimental studies indicate that lytic therapy is less damaging to the endothelium compared with thrombectomy.(Reil 2000, Wengrovitz 1995, Whitley 1996) Third, if unsuccessful, thrombolysis can be followed promptly by surgical intervention, whereas the other way around is contraindicated.(Earnshaw 2013)

Primary amputation

For patients with irreversible ischaemia (Rutherford class III), amputation should be performed as the procedure of choice.(Rutherford 1997) Patients who have an insensate and immobile limb in the setting of prolonged complete ischaemia (>6 to 8 hours) are unlikely to have the potential for limb salvage.(Blaisdell 2002, Gerhard-Herman 2017) In addition, in this setting the reperfusion injury and circulation of ischaemic metabolites can result in multi-organ failure and cardiovascular collapse.(Gerhard-Herman 2017) It is

sometimes difficult to distinguish between Rutherford Class IIb and III in clinical practice, however, and at times patients in the borderline between these levels of ischaemia can be successfully revascularised.

Reperfusion injury

The reintroduction of oxygenated blood after a period of ischaemia can cause more damage than the ischaemia itself. The oxygenated blood generates high levels of reactive oxygen species (ROSs) within the cells. ROSs cause direct damage to the cell structures and also activate neutrophils, which migrate into the reperfused tissue causing further damage. For vascular injury to occur, neutrophils must be present and must adhere to the endothelium. The damaged endothelial cells become more permeable, resulting in efflux of plasma proteins and progressive interstitial oedema.(Callum 2000)

The risk of reperfusion injury correlates with the extent of the affected ischaemic tissue and the severity of the ischaemia. With more damaged tissue, the risk for systemic reperfusion injury increases. In patients with saddle embolus and bilateral complete occlusion of the lower extremities a large part of the body musculature is affected, and reperfusion injury is a frequent and serious threat that endangers the very survival of the patients.(Robinson 2016)

Local reperfusion injury

Limb swelling and compartment syndrome is caused by increased capillary permeability and oedema following reperfusion. The calf muscles are confined within tight fascial boundaries giving little room for expansion. Oedema in the calf muscles leads to increased interstitial pressure and impaired microcirculation. If this condition is left untreated, it results in muscle necrosis.(Blaisdell 2002, Callum 2000) The main risk factors for compartment syndrome are prolonged ischaemic time, the severity and extent of ischaemia, low degree of developed arterial collaterals, hypotension and young age.(Papalambros 1989) Fasciotomy should be considered for patients with class IIb ischaemia and for whom the time to revascularisation is >4 hours.(Gerhard-Herman 2017)

Symptoms of compartment syndrome are swelling and pain on squeezing the calf muscle or passive moving of the ankle. Palpable pedal pulses do not exclude the syndrome. The key to management is prevention through expeditious revascularisation and a low threshold for fasciotomy.

Systemic reperfusion injury

Acidosis and hyperkalaemia occur due to leakage from the damaged cells, which may cause cardiac arrhythmias and myoglobinaemia. Myoglobinaemia is nephrotoxic and can result in acute tubular necrosis and severe kidney injury. Acute respiratory distress syndrome may also develop and gastrointestinal endothelial oedema may lead to increased gastrointestinal vascular permeability and endotoxic shock.(Callum 2000, Eliason 2009)

Aims of the study

The overall aim was to study patients with ALI and examine treatment options and outcome. The specific aims were:

- To examine the outcome after intra-arterial thrombolysis, with or without continuous heparin infusion. (Paper I)
- To analyse long-term outcomes in patients with ALI treated with thrombolysis, in particular reinterventions, amputations and survival, as well as factors associated with these outcomes. (Paper II)
- To compare long-term outcomes after thrombolysis depending on the underlying aetiology of the ALI. (Paper II)
- To analyse outcome of all patients treated for ALI in Sweden during a 21-year period to understand time trends and compare different treatment strategies and revascularisation techniques. (Paper III)
- To compare the results after embolic and thrombotic occlusions resulting in ALI (Paper I, II and III)
- To study patients with acute aortic occlusion, in particular time trends and long-term survival. (Paper IV)
- To study time trends in survival for patients with ALI (Paper I, II, III and IV)

Methods

All papers included in this thesis are observational studies based on prospectively collected data, analysed in a retrospective design. All studies were approved by the Regional Ethics Committee in either Lund/Malmö (Paper I and II) or Uppsala/Örebro (Paper III and IV).

Swedvasc

The Swedish national registry for vascular procedures, the Swedvasc, has a nationwide coverage since 1994 and is based on prospectively collected data. The registry has been extensively validated, both internally and externally, showing a high validity of data.(Ravn 2007, Bergqvist 2007, Troeng 2008, Venermo 2015) Approximately 700-900 cases of acute lower limb ischaemia are treated annually and are registered in the Swedvasc.

Patients

The first two papers were performed as collaboration between the Universities/Regional hospitals of Uppsala and Malmö/Lund. The two hospitals had adopted different treatment algorithms for catheter-directed thrombolysis during the last decades. All patients receiving intra-arterial thrombolysis due to acute or sub-acute limb ischaemia between 2001 and 2013 at the two hospitals were identified. The hospital charts for included patients were analysed according to a predetermined protocol. Vascular imaging (computed tomography angiography, magnetic resonance angiography, perioperative angiography) were retrieved for included patients. If patients moved to other parts of Sweden during the follow-up period information about these patients were retrieved from local vascular surgeons regarding patency, re-interventions and amputations.

Patients were further divided into subgroups depending on the aetiology of the occlusion: native artery thrombosis, embolus, occluded popliteal artery aneurysm, and occluded grafts/stents/stentgrafts.

In the third paper the Swedvasc database was used to collect information regarding patients treated for ALI with occlusions below the infrainguinal ligament, between 1994 and 2014 (21 full years). ALI secondary to trauma, dissection, bleedings or graft infections were excluded, since the focus was on acute embolic or thrombotic arterial occlusions.

The fact that every Swedish citizen or permanent resident has a unique personal identification number (PIN) makes it possible to obtain accurate long-term outcome data in those registered. All deaths in Sweden are registered in the Population registry, and amputations are registered in the Inpatient registry. The combination of the Swedvasc database with the Population registry and the Inpatient registry made it possible to obtain complete follow-up data on mortality and amputations.

Patients with ALI were categorized into either open surgical or endovascular revascularization according to the type of primary procedure used to treat the acute ischaemic event. Patients treated with hybrid surgery (open and endovascular performed simultaneously) were classified as open. The patients in the endovascular group were thus exclusively treated with endovascular methods.

In the fourth paper the Swedvasc database was used to identify patients with ALI secondary to acute occlusion of the aorta (AAO). All patients with this serious condition that had been treated in Sweden between 1994-2014 were included. Patients treated for AAO secondary to trauma, dissection or graft infections were excluded. Accurate survival data were obtained by cross-linking the PIN with the national Population registry in January 2018.

Subgroups analyses were based on aetiology of the occlusion; saddle embolus, *in situ* thrombosis or occluded graft/stent/stentgraft, as documented by the treating surgeon. Information about the original surgery was retrieved and analysed for patients with occluded grafts/stent/stentgrafts. To analyse if the surgical volume at the treating centre affected outcome, the hospitals were separated into two groups, depending on if they had more or less than 20 cases of AAO during the study period.

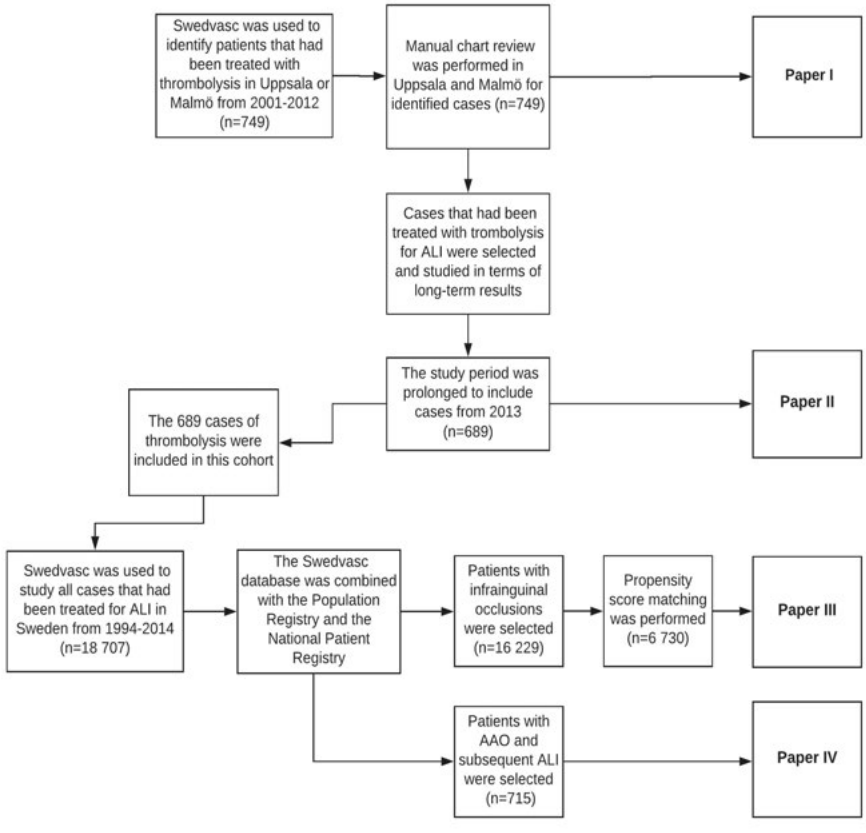

Figure 3. Flowchart of data collection

Table 5. Definitions

Definitions	
Acute Ischaemia	**Sudden decrease in or worsening of limb perfusion causing a potential threat to viability of the extremity. Symptoms for <14 days.**
Amputation	**Major amputation - defined as above the ankle.**
Anaemia	**Haemoglobin concentration <134 g/l in men and <117 g/l in women.**
ASA classification	**Classification of physical status according to the American Society of Anaesthesiology classification (ASA)(Owens 1978)**
Atrial fibrillation	**History of either chronic or paroxysmal atrial fibrillation.**
Cerebrovascular disease	**History of cerebral infarction, cerebral haemorrhage or transient ischaemic attack.**
Diabetes mellitus	**Dietary, oral or insulin treatment.**
Duration of symptoms	**From start of symptoms until the start of thrombolysis/surgery**
Hypertension	**Systolic blood pressure (BP) >140 mmHg or diastolic BP >90 mm Hg or antihypertensive medication.**
Ischaemic heart disease	**History of previous myocardial infarction, angina pectoris, coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI).**
Major bleeding	**Bleeding requiring blood transfusions, surgery, resulting in stroke or cessation of thrombolytic therapy.(Schulman 2010)**
Renal insufficiency	**Serum creatinine >105 µmol/l in men and >90 µmol/l in women.**
Supplementary procedures following the thrombolytic intervention	**Endovascular (aspiration of thromboembolic material, percutaneous transluminal angioplasty, stenting). Open (bypass, thromboembolectomy, other reconstruction) Hybrid (endovascular and open surgery).**

Statistics

In paper I, II and IV, primary and secondary outcomes were stratified and compared according to aetiology and in paper IV also by the operative procedure performed. Data management and statistical analysis were done with SPSS® software package (version 21.0 or 22.0) (IBM, Armonk, NY, USA). Variables associated with outcome were tested in univariate analysis, cross tabulation with the chi-square test for dichotomous variables and one-way ANOVA for continuous variables. Kendall's Tau-b analysis was used to analyse rank correlation between nonparametric variables. Survival distributions were analysed using Kaplan-Meier curves and the log-rank test. In paper I, variables associated (P<0.200) with bleeding complications, amputation or death were further tested in a multivariable analysis with binary logistic regression, with all variables entered into the model.

In paper I, significant associations were expressed in terms of ORs with 95% CIs. In paper II and IV, statistical significance was expressed as both P-values and 99% CI. P-values <0.01 were considered statistically significant after adjusting for multiple comparisons.

In paper III, all statistical analyses were performed using the SPSS® software package (version 22.0) or the *R* package mice (version 3.1.0). The Swedvasc database has a high completeness of registered procedures, with >95% of all vascular surgical procedures registered prospectively; however, full information on comorbidities at presentation is missing in some cases (9-12%). Multiple imputations to replace missing values in the database were performed using the R package mice. For each variable to be imputed, a prediction model was created. The model was determined by the variable type, predictive mean matching for numerical variables and logistic regression for dichotomous or proportional odds regression for ordinal variables. All other variables were used as predictors. This procedure generated 100 imputation sets. These imputations were analysed one at a time, pooling the results using Rubin's rules.(White 2011) This procedure is described in detail in the statistical appendix for Paper III.

Imputed values for smoking were post-processed to compensate for a believed over-registration of smoking patients in the registry. Calendar time was also used as a predictor for the variable "smoking" in that smoking habits have changed over the study period.

Missing values of aetiology for arterial occlusion were not random, however; this is because the latest Swedvasc edition simplified the questionnaire in favour of other registration aspects and removed the aetiology field. A manual chart review was performed at Uppsala University Hospital to compen-

sate for the missing values since the update. A total of 257 patients were identified as treated for ALI in Uppsala during the target period. This Uppsala cohort was used to create a model on how to impute these data for the remaining dataset.

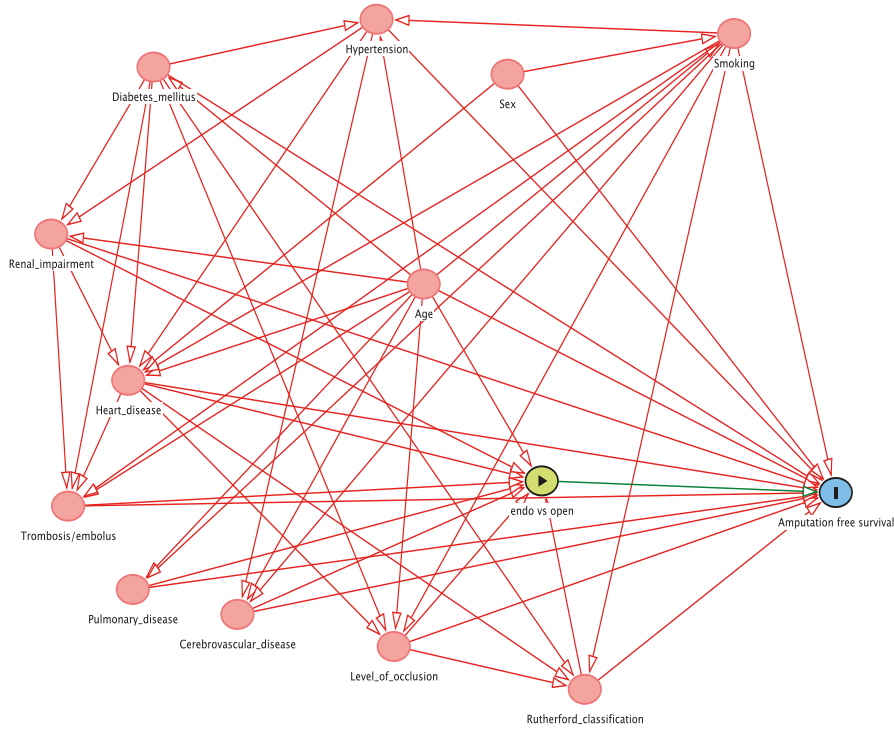

Figure 4. Directed acyclic graph (DAG)

The directed acyclic graph (DAG) method and our current knowledge were used to select suitable covariates.(Van der Weele 2007) A propensity score was constructed to control for treatment selection bias. The score included aetiology of the occlusion, period (1994-2000, 2001-2007, 2008-2014), patient age, level of occlusion, degree of ischaemia (Rutherford classification), heart disease, cerebrovascular event, renal impairment and pulmonary disease in the logistic regression model to predict probability that the patients would receive endovascular surgery. In the next step patients were 1:1 matched based on estimated propensity score (the propensity scores were not allowed to differ by more than 0.001 to be considered a match). The matches were exact in regards to aetiology of occlusion and period. Not all patients could be matched. Hence, unmatched patients were removed from subsequent analyses. Additional testing was performed to ensure that there were

no significant differences in demographics and comorbid characteristics. between matched groups.

Survival distributions for matched patients were compared using Kaplan-Meier curves and the log-rank test. Cox proportional hazard regression was used to identify risk factors for adverse events. Statistical significance was expressed as both *P*-values and 99% CIs. *P*-values <0.01 were considered statistically significant.

Results

Paper I

Totally, 749 thrombolytic procedures were included. The median age of the patients was 73 years and 47% were women. A majority of the patients presented with ALI (78.6%), whereas the other presented with CLI (12.3%) or claudication (9.1%).

At Uppsala University Hospital, the thrombolytic procedure generally started with a bolus dose of 4 mg t-PA, followed by 0.5 mg/h. At Malmö University Hospital, the procedure generally started with 1-2 mg/h for the first 4 h, followed by 0.5-1.0 mg/h. At the start of the endovascular procedure, all patients were given 5000 IU heparin intravenously. In Uppsala the patients received only this single bolus dose, whereas in Malmö it was followed by continuous infusions of heparin, adjusted according to APTT values aiming for two to three times the baseline value. When the results were analysed, it was clear that the patients in Malmö had received significantly more t-PA (mean 24 mg vs. 18 mg; P<0.001) during a shorter time (mean 23 hours vs. 27 hours, P=0.001).

Both hospitals registered all blood transfusions using the same unique personal identification number (PIN, the Swedish national identification number that is given to all permanent residents in Sweden). As a validation, all blood transfusions noted from hospital case records in Uppsala were verified with the blood transfusion registry (98.1% consistency was found). Both hospitals used the same haemoglobin concentration (80 g/l) as a cut-off point for administration of blood transfusions, but the final decision was based on the status of each individual patient (e.g., age, comorbidities).

The incidence of any bleeding complication was 21.4% in Uppsala and 36.7% in Malmö (P<0.001). Major bleeding was defined according to current consensus guidelines.(Schulman 2010) Major bleeding complications requiring blood transfusion occurred in 11.6% in Uppsala and 15.6% in Malmö (P=0.123). Bleeding complications necessitated discontinuation of thrombolysis in 5.0% in Uppsala and 6.3% in Malmö (P=0.473). The degree of distal embolisation or pericatheter thrombosis noted in hospital chart was not different between the two hospitals.

The most common site for any bleeding complication was the femoral access site: 15.7% in Uppsala *vs.* 28.6% in Malmö ($P<0.001$). Haemorrhage at distant sites was reported in 8.2% in Uppsala and 15.8% in Malmö ($P=0.002$). These haemorrhages involved the skin or subcutaneous tissue (40), the urinary tract (27), gastrointestinal tract (26), iatrogenic injury with the intra-arterial catheter (5) and brain (3).

When the material was further analysed, differences in case mix between the two hospitals were found. The four subgroups were native arterial thrombosis, embolus, occluded popliteal aneurysm and stent/stentgraft occlusions. The aetiology of arterial occlusions differed substantially between the two hospitals ($P<0.001$): thromboembolic occlusions and popliteal aneurysms were more common in Uppsala, whereas graft/stent/stentgraft occlusions were more common in Malmö. To address confounding factors multivariate analysis was performed (*Table 6*). Heparin was not found to be an independent risk factor for any of the adverse events tested in the multivariate analysis; nor was the total dose of t-PA. Heparin infusion was also not found to be a factor with a significant impact on the success rate of thrombolysis. Both the immediate success rate (80% in Uppsala vs. 81% in Malmö, P=0.595) and a 30-day amputation-free survival rate (83% in Uppsala vs. 84% in Malmö, P=0.689) were similar at the two hospitals.

Table 6. Multivariate analysis

	Variables	OR	95% CI	P-value
Any bleeding complication	PAA	2.24	1.15-4.39	0.018
	Treatment in Malmö	2.68	1.15-6.27	0.023
Major bleeding complication	Severe ischaemia	2.98	1.79-4.96	**<0.001**
	Anaemia	1.91	1.16-3.16	0.011
Fasciotomy	Severe ischaemia	2.94	1.65-5.26	**<0.001**
	Treatment in Upp-sala	6.50	2.31-18.5	**<0.001**
	Graft occlusion	2.72	1.25-5.91	0.012
	Total dose of t-PA	1.03/g	1.01-1.06	0.016
	PAA	2.81	1.03-7.67	0.044
Amputation <30 days	Embolus	0.30	0.14-0.66	**0.003**
	Age	1.03/year	1.01-1.06	0.014
	Anaemia	1.84	1.84-3.03	0.016
	Total dose of t-PA	1.03/g	1.01-1.05	0.016
	Severe ischaemia	1.89	1.12-3.19	0.018
Death <30 days	Cerebrovascular disease	3.82	1.53-9.57	**0.004**
	Renal insufficiency	3.86	1.50-9.96	**0.005**
	Severe ischaemia	2.88	1.30-6.79	0.015
	Age	1.06/year	1.00-1.11	0.046
Amputation or death <30 days	Anaemia	2.13	1.35-3.38	**0.001**
	PAA	3.28	1.54-6.99	**0.002**

Odds ratio (OR), confidence interval (CI), popliteal artery aneurysm (PAA). P-values ≥0.01 were considered trends. Bold numbers correspond to significant P-values.

Paper II

The study included 689 limbs (part of the cohort that was analysed in paper I was included in the present study) (*Figure 3*). Of the procedures, 316 (45.9%) were performed in women. The mean age of the patients was 72.0 (95% CI 71.1-72.9) years: men were younger than women (70.3 vs. 74.1 years, P<0.001).

The distribution of thrombolytic procedures between the aetiological groups was: graft/stent occlusions (39.8%), native artery thrombosis (27.7%), native artery emboli (25.1%) and occluded PAA (7.4%). The distribution of different degrees of ischaemia was similar in the aetiological groups (*Rutherford classification*). Adjuvant endovascular or open surgical procedures were common after thrombolysis (77.6%), but less so when the occlusion was embolic (67.1%, P=0.002).

Mean follow-up was 59.4 months (95% CI 56.1-62.7), during which 32.9% needed further reintervention, 16.4% underwent amputation without reintervention and 50.7% had no reintervention. The patients who had a reintervention-free survival were followed a mean of 74.1 months (95% CI 67.5-80.6) after thrombolysis. The need for reintervention during follow-up was 48.0% in the graft/stent occlusion group, 34.0% in the popliteal aneurysm group, 25.4% in the thrombosis group and 16.3% in the embolus group (P<0.001).

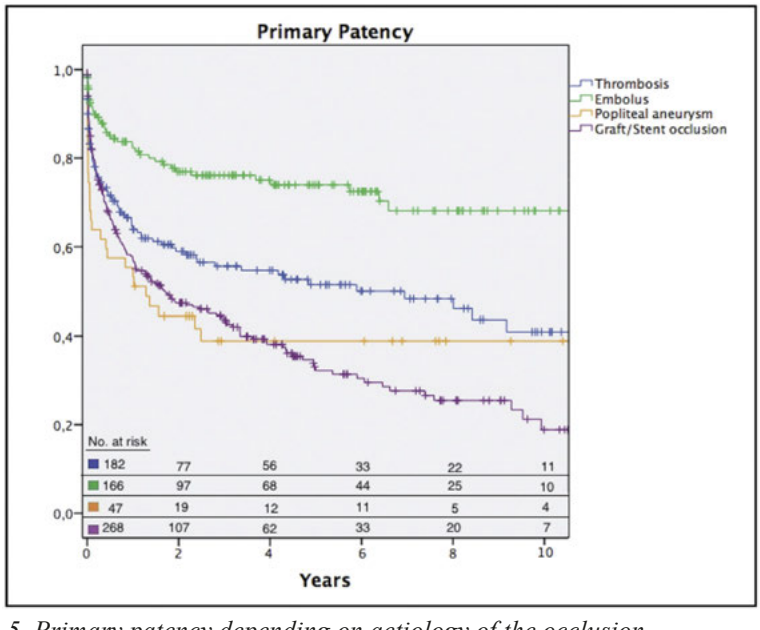

Figure 5. Primary patency depending on aetiology of the occlusion

The overall primary patency rates were 69.1% and 55.9% at 1 and 5 years, respectively. Primary patency at 5 years was higher in the embolus subgroup (83.3%, P=0.002) and lower in the occluded graft/stent subgroup (43.3%, P<0.001). Secondary patency rates were 80.1% and 75.2% at 1 and 5 years, respectively, with no difference between the subgroups.

Amputation rate was lower in the embolic subgroup, at 1 (8.1%) and 5 (11.1%) years, P=0.001. Survival was higher in the subgroup with occluded popliteal aneurysms at 5 years (83.3%, P=0.004). Amputation-free survival was 72.1% at 1 year and 45.2% at 5 years. Finally, amputation-free survival was lower in the occluded graft/stent subgroup at 5 years (37.9%, P=0.007).

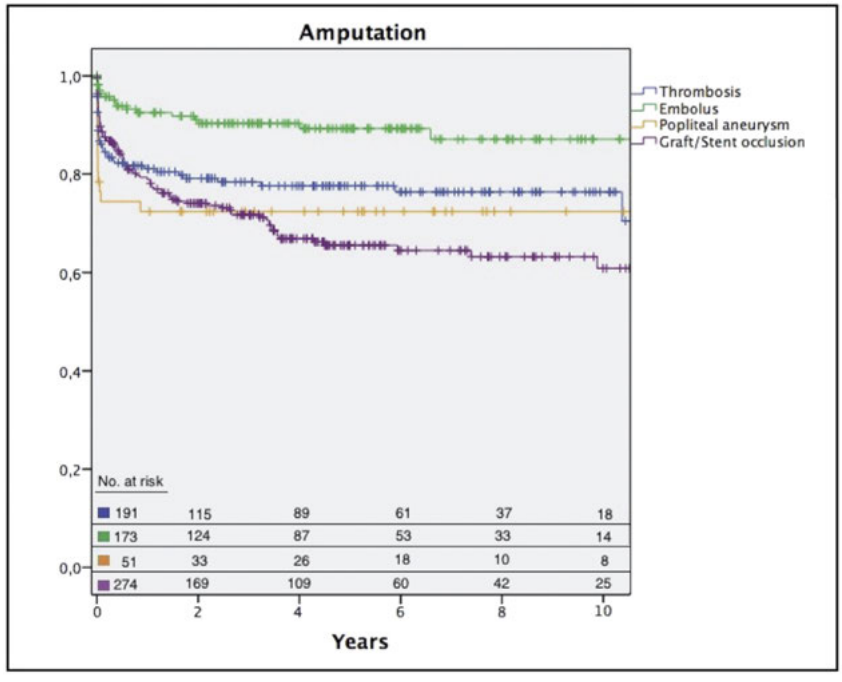

Figure 6. Amputation depending on aetiology of the occlusion.

Multivariate analyses were performed to identify risk factors for amputation, death and the combined variable amputation and/or death during 5 years after thrombolysis. The only risk factors identified were for death within 5 years: age (1.07/year; CI: 1.03-1.11, P<0.001), IHD (2.22; CI: 1.29-3.80, P<0.0019), preoperative anaemia (2.33; CI: 1.14-4.77, P=0.002) and atrial fibrillation (2.30; CI: 1.02-5.18, P=0.008). Continuous heparin infusion during thrombolysis or not was not associated with patency, amputation or death during any period.

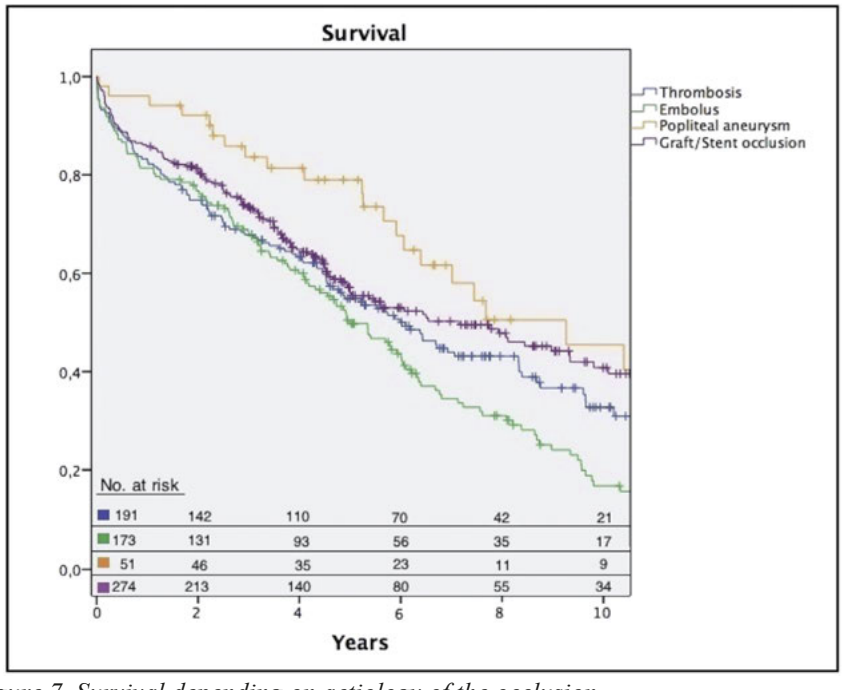

Figure 7. Survival depending on aetiology of the occlusion.

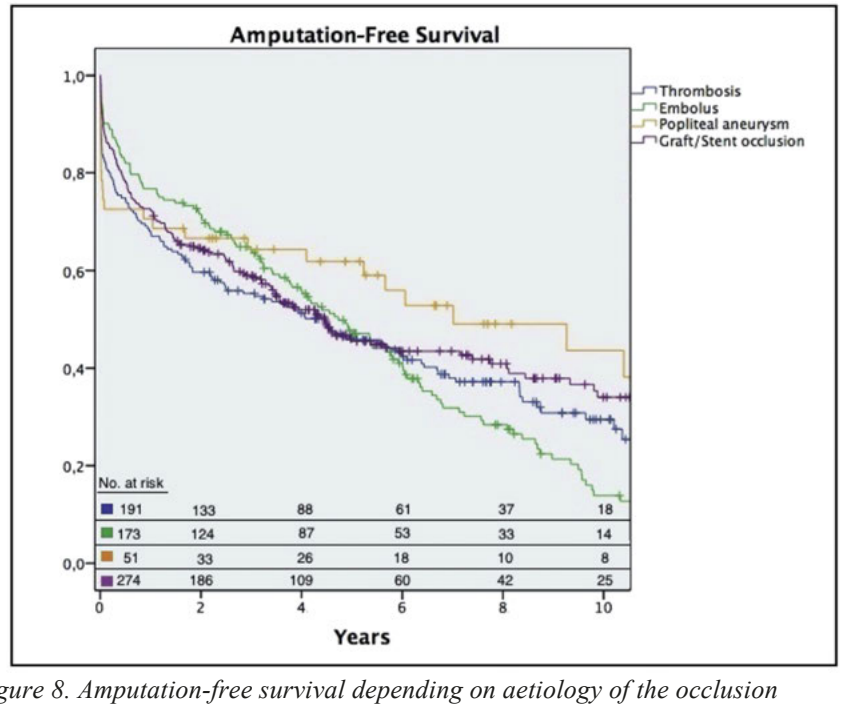

Figure 8. Amputation-free survival depending on aetiology of the occlusion

Paper III

In all, 16,229 treatments of ALI in 13,308 unique patients were identified. Of those 16,229 treatments, 7,276 (44.8%) were performed in eight University hospitals while the remaining were done in county or district hospitals. Mean follow-up was 51.6 months (99% CI 50.5-52.7).

Before propensity score matching, there were differences between the open surgery and endovascular groups on several baseline variables (*Table 7*). More specifically, patients treated with open surgery were older, had more severe ischaemia, more proximal occlusions and more often had a history of IHD, cerebrovascular disease and renal or respiratory insufficiency, whereas male sex, smoking, hypertension and diabetes were more common among patients treated with endovascular surgery. After propensity score matching, 3,365 patients in each treatment group remained: the results hereafter focus entirely on comparing those patients.

Patient characteristics appear in *Table 7*. Mean age was 74.7 years (71.7 for men, n=3,533 and 78.9 years for women, n=3,197). After propensity score matching, the only remaining difference was a higher prevalence of diabetes mellitus in the endovascular group (23.8% vs. 20.0%, P=0.002) (*Table 7*).

In the open surgery group 61.3% underwent thrombectomy/embolectomy, 25.6% bypass surgery and 13.1% thromboendarterectomy. In the endovascular group 49.9% underwent thrombolysis alone, 31.7% thrombolysis with stent and/or percutaneous transluminal angioplasty (PTA) and 18.4% stent/PTA/subintimal angioplasty. Hybrid interventions when both endovascular and open surgery were used were classified as open surgery and represented 7.5% of the open surgery group. Thus, the patients in the endovascular group had received exclusively endovascular treatment, whereas some patients in the open surgery group had been treated with hybrid techniques.

Any complication 30 days after surgery occurred in 31.3% of the patients after open surgery and 22.6% after endovascular treatment, P<0.001. Bleeding complications occurred in 5.0% after open surgery and 7.1% after endovascular revascularisation, P=0.02. Perioperative stroke occurred in 0.2% after open surgery and 0.4% after endovascular surgery, P=0.19. Other complications (e.g., fasciotomy, myocardial infarction, stroke) were also similarly distributed between the two groups (*Table 8*). The overall 30-day patency rate was 78.6% in the open group and 83.0% in the endovascular group, P<0.001.

The amputation rate at 30 days was 8.2% after open surgery and 7.0% after endovascular revascularisation, P=0.11. After open surgery and endovascular surgery, the 30-day mortality rate was 11.1% in the open surgery group and 6.7% in the endovascular revascularisation group, P<0.001. Amputation-free survival was 82.1% after open treatment and 87.5% after endovascular surgery, P<0.001. The same pattern was observed at 1-year post-surgery: similar amputation rates but superior survival and amputation-free survival were observed after endovascular surgery (*Table 8*), with a 1-year death risk of 28.6% in the open surgery group and 20.2% in the endovascular group, P<0.001. This risk difference corresponds to a numbers needed to treat (NNT) of 12 patients to prevent one death within the first year.

Table 7. Baseline characteristics before and after propensity score matching

	Before propensity score matching		
	Open surgery	Endovascular treatment	P-value
Number of cases	9,736	6,493	
Age	75.7 (75.3-76.0)	74.4 (74.1-74.8)	<0.001
Sex (female)	50.2 (48.9-51.5)	46.5 (44.8-48.0)	<0.001
Period (7 years)			
- **1994-2000**	35.3 (34.1-36.6)	24.1 (22.7-25.5)	<0.001
- **2001-2007**	27.3 (26.1-28.5)	27.9 (26.4-29.3)	0.413
- **2008-2014**	37.4 (36.1-38.7)	48.0 (46.4-49.6)	<0.001
Indication			
- **Thrombosis**	43.3 (42.0-44.6)	69.4 (67.0-70.9)	<0.001
- **Embolus**	52.8 (51.5-54.1)	28.2 (26.8-29.6)	<0.001
- **Popliteal aneurysm**	3.9 (3.4-4.4)	2.4 (1.9-2.9)	<0.001
Rutherford classification			
- **I**	9.3 (8.6-10.1)	16.9 (15.7-18.1)	<0.001
- **IIa**	26.0 (24.8-27.1)	51.6 (50.0-53.2)	<0.001
- **IIb**	62.9 (61.7-64.2)	31.3 (29.8-32.8)	<0.001
- **III**	1.8 (1.4-2.1)	0.2 (0.0-0.3)	<0.001
Level of occlusion			
- **Femoral**	77.1 (76.0-78.2)	37.5 (36.0-39.1)	<0.001
- **Popliteal**	16.4 (15.5-17.4)	50.7 (49.1-52.3)	<0.001
- **Below popliteal**	6.4 (5.8-7.1)	11.8 (10.7-12.8)	<0.001
Smoking			
- **Current**	23.2 (22.1-24.3)	24.8 (23.5-26.2)	0.026
- **Previous**	14.6 (13.7-15.6)	18.6 (17.3-19.8)	<0.001
- **Never**	62.2 (60.9-63.5)	56.6 (54.9-58.2)	<0.001
Comorbidities			
- **Hypertension**	57.8 (56.5-59.1)	61.7 (60.2-63.3)	<0.001
- **Diabetes mellitus**	20.1 (19.1-21.1)	23.1 (21.8-24.5)	<0.001
- **Heart disease**	64.1 (62.9-65.4)	54.2 (52.7-55.8)	<0.001
- **Cerebrovascular events**	25.8 (24.7-26.9)	17.6 (16.4-18.9)	<0.001
- **Renal impairment**	11.3 (10.5-12.1)	7.7 (6.9-8.6)	<0.001
- **Pulmonary disease**	16.1 (15.1-17.1)	13.1 (12.0-14.2)	<0.001

	After propensity score matching		
	Open surgery	Endovascular treatment	P-value
Number of cases	3,365	3,365	
Age	74.5 (74.0-75.1)	74.8 (74.3-75.3)	0.420
Sex (female)	46.2 (44.0-48.4)	48.8 (46.6-50.1)	0.071
Period (7 years)			
- **1994-2000**	27.0 (25.0-29.0)	27.0 (25.0-29.0)	1.00
- **2001-2007**	28.2 (26.2-30.2)	28.2 (26.2-30.2)	1.00
- **2008-2014**	44.8 (42.6-47.0)	44.8 (42.6-47.0)	1.00
Indication			
- **Thrombosis**	63.7 (61.6-65.8)	63.7 (61.6-65.8)	1.00
- **Embolus**	34.1 (32.0-36.2)	34.1 (32.0-36.2)	1.00
- **Popliteal aneurysm**	2.2 (1.5-2.9)	2.2 (1.5-2.9)	1.00
Rutherford classification			
- **I**	13.7 (12.2-15.2)	14.5 (12.9-16.1)	0.381
- **IIa**	42.2 (40.0-44.4)	41.9 (39.7-44.1)	0.838
- **IIb**	43.9 (41.8-46.0)	43.3 (41.1-45.5)	0.671
- **III**	0.2 (0.1-0.3)	0.2 (0.1-0.2)	0.830
Level of occlusion			
- **Femoral**	59.9 (57.8-62.0)	60.6 (58.4-62.8)	0.565
- **Popliteal**	29.6 (27.6-31.6)	29.7 (27.7-31.7)	0.945
- **Below popliteal**	10.5 (9.2-11.9)	9.7 (8.3-11.0)	0.329
Smoking			
- **Current**	24.1 (22.3-26.0)	25.2 (23.3-25.2)	0.418
- **Previous**	18.1 (16.3-19.9)	17.6 (15.9-19.3)	0.706
- **Never**	57.8 (55.6-60.0)	57.2 (55.0-59.4)	0.665
Comorbidities			
- **Hypertension**	59.9 (57.7-62.1)	61.9 (59.7-64.0)	0.171
- **Diabetes mellitus**	20.0 (18.2-21.8)	23.8 (21.9-25.7)	**0.002**
- **Heart disease**	57.2 (55.0-59.4)	57.2 (55.0-59.4)	0.972
- **Cerebrovascular events**	18.9 (17.1-20.6)	19.1 (17.4-20.8)	0.867
- **Renal impairment**	8.3 (7.1-9.5)	8.1 (6.9-9.3)	0.790
- **Pulmonary disease**	14.3 (12.7-15.9)	14.5 (13.0-16.1)	0.798

Numbers correspond to per cent (99% confidence intervals) or mean (99% confidence intervals). Bold numbers correspond to significant P-values after propensity score matching.

Table 8. Outcomes in the matched cohort by treatment status

	Total	Open surgery	Endovascular treatment	P-value
Number of cases	6730	3365	3365	
30 days				
-Patency	80.8 (79.6-82.0)	78.6 (76.8-80.4)	83.0 (81.4-84.6)	**<0.001**
-Fasciotomy	6.4 (5.6-7.2)	7.5 (6.3-8.7)	5.4 (4.4-6.4)	0.014
-Myocardial infarction	2.9 (2.3-3.5)	3.1 (2.4-3.9)	2.6 (1.9-3.3)	0.342
-Stroke	1.7 (1.3-2.1)	1.4 (0.9-1.9)	2.1 (1.5-2.8)	0.077
-Amputation	7.6 (6.7-8.4)	8.2 (7.0-9.4)	7.0 (5.9-8.1)	0.113
-Death	8.9 (8.0-9.8)	11.1 (9.7-12.5)	6.7 (5.6-7.8)	**<0.001**
-Amputation-free survival	84.8 (83.5-85.8)	82.1 (80.3-83.7)	87.5 (86.0-88.9)	**<0.001**
1 year				
-Amputation	14.3 (13.2-15.4)	14.8 (13.2-16.4)	13.8 (12.3-15.3)	0.320
-Death	24.4 (23.1-25.7)	28.6 (26.6-30.6)	20.2 (18.4-22.0)	**<0.001**
-Amputation-free survival	65.7 (64.2-67.2)	61.6 (59.4-63.7)	69.9 (67.9-71.9)	**<0.001**

Cox regression analyses reveal the same pattern at 30 days, 1 year and 5 years post-surgery (*Table 9*). The endovascular group had lower mortality rates (HR 0.78, 99% CI 0.70-0.86) and superior amputation-free survival (HR 0.82, 99% CI 0.75-0.90) at 5 years post-treatment.

Table 9. Endovascular treatment versus open surgery in relation to hazard ratios (HRs) for amputation and death

	Open surgery (n=3365) HR	Endovascular treatment (n=3365) HR	99% Confidence interval	P-value
30 days				
- **Amputation**	1.0 (reference)	0.843	0.65 - 1.10	0.10
- **Death**	1.0 (reference)	0.579	0.45 - 0.74	<0.001
- **Amputation and/or death**	1.0 (reference)	0.669	0.56 - 0.81	<0.001
1 year				
- **Amputation**	1.0 (reference)	0.922	0.76 - 1.12	0.27
- **Death**	1.0 (reference)	0.661	0.57 - 0.77	<0.001
- **Amputation and/or death**	1.0 (reference)	0.730	0.65 - 0.83	<0.001
5 years				
- **Amputation**	1.0 (reference)	1.01	0.85 - 1.19	0.94
- **Death**	1.0 (reference)	0.781	0.70 - 0.86	<0.001
- **Amputation and/or death**	1.0 (reference)	0.819	0.75 - 0.90	<0.001

A landmark analysis was performed starting 1 year after the index operation to interpret the remaining effect of the intervention. When time censoring was set at 5 years, no statistically significant difference was found in risk of adverse events after endovascular surgery: amputation (HR 1.45, 99% CI 0.96-2.17; P=0.019), death (HR 0.90, 99% CI 0.78-1.04; P=0.066) and amputation and/or death (HR 0.96, 99% CI 0.83-1.12; P=0.485).

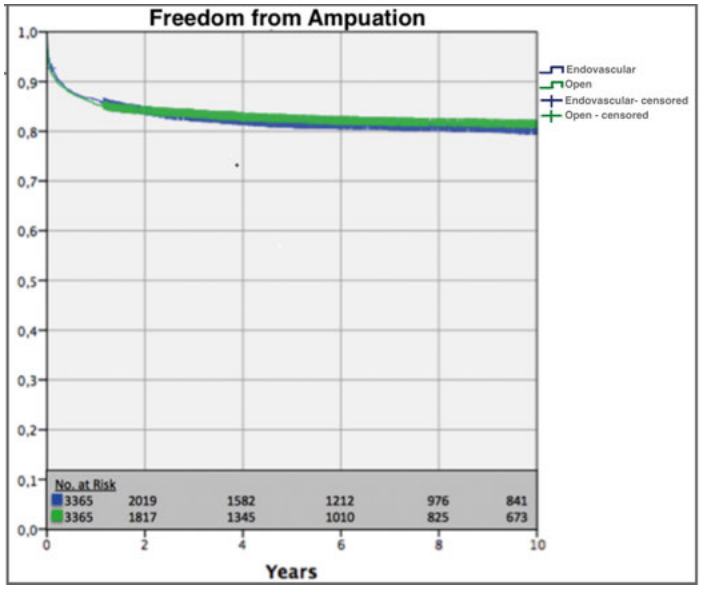

Figure 9.

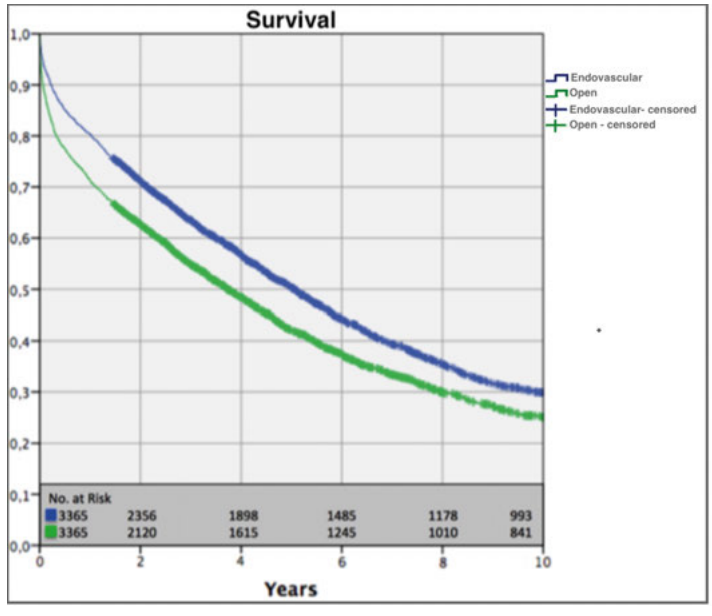

Figure 10.

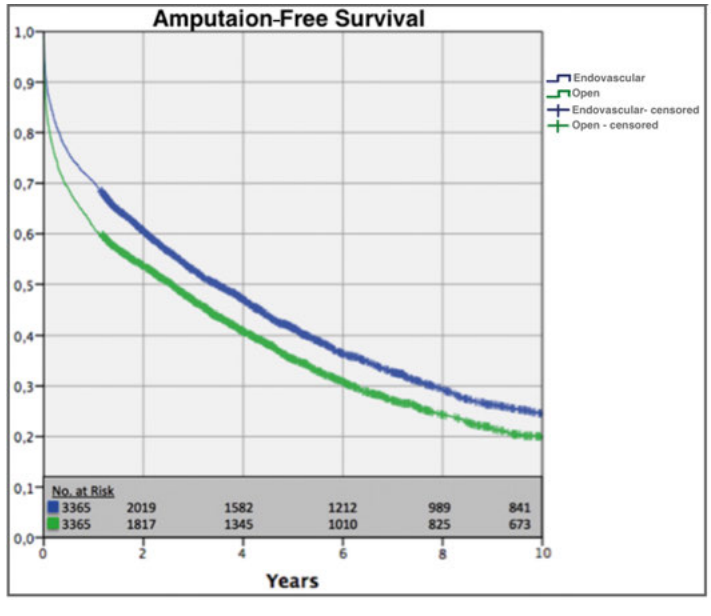

Figure 11

Figure 9 depicts similar freedom from amputation curves up to 10 years after the intervention for the two treatment groups (log-rank, P=0.32). *Figure 10* gives survival curves (log-rank, P<0.001) and *Figure 11* expresses the amputation-free survival curves (log-rank, P<0.001). The survival curves

reveal a difference in mortality rates between the treatment groups during the first year of follow-up. Thereafter, the mortality rates were similar.

In a sensitivity analysis amputation-free survival after endovascular and open surgery was investigated by type of occlusion (*Figure 12*). The superiority in amputation-free survival was higher after endovascular compared with open surgery, irrespective of whether the ALI was caused by embolic or thrombotic occlusion (log-rank, P<0.001).

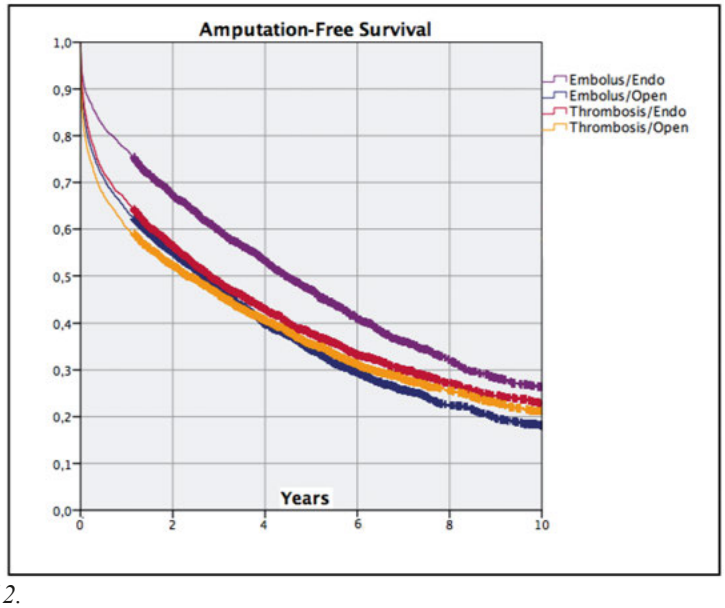

Figure 12.

During the study period, a shift towards more endovascular treatment for ALI was observed (including the whole cohort before propensity score-matching). In the first year of the study period endovascular treatment represented 19.4% of all surgeries, whereas in the last year endovascular treatment represented 47.3% (*Figure 13*).

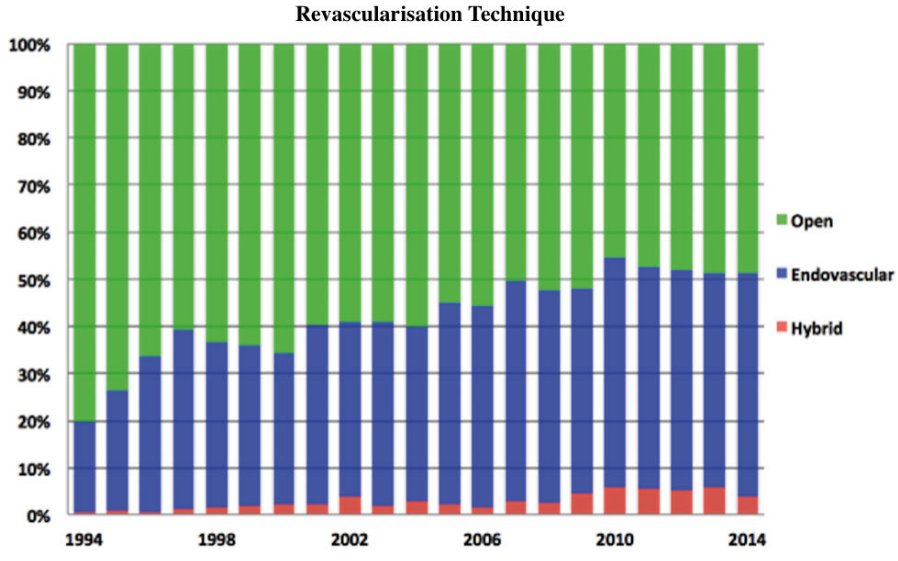

Figure 13. Revascularisation technique over time

The 30-day amputation rate was 6.3% in the first period (1994-2000), 7.4% in the second period (2001-2007) and 8.3% in the third period (2008-2014). When comparing the first and last periods, there was an increase over time, P<0.001). In contrast, mortality rates 30 days after treatment decreased over time from 14.8% in the first period to 11.7% in the second period to 8.8% in the last period (p<0.001). The incidence of postoperative myocardial infarction within 30 days from intervention decreased from 3.5% in the first period to 1.9% in the last (P<0.001). Amputation-free survival at 30 days after surgery improved over the study period from 80.1% in the first period to 82.3% in the second period and 84.0% in the third period (P<0.001) (*Figure 14*).

One year after surgery a similar pattern was observed. The amputation rates increased from 11.2% in the first period to 15.2% in the last period (P<0.001). Survival rates improved from 67.4% to 75.5% (P<0.001). Amputation-free survival increased from 60.5% in the first period to 65.0% in the last period (P<0.001) (*Figure 14*).

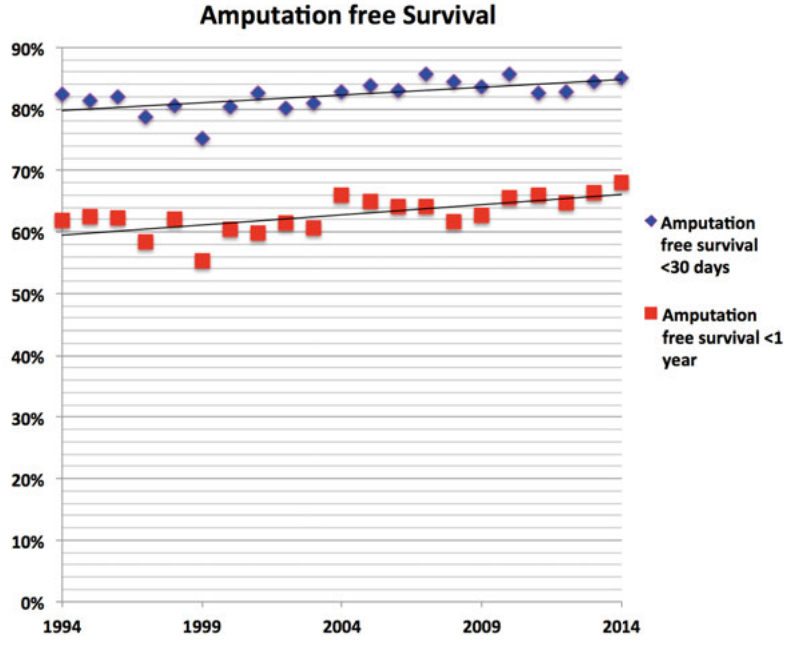

Figure 14.

After paper III was submitted and accepted in the British Journal of Surgery, some additional analyses were preformed to examine whether surgery volume, and thereby the experience of treating ALI, affected the outcome. A total of 42 hospitals had surgically treated patients with ALI during the study period. Hospitals were divided into three groups depending on whether the average yearly surgical volume was <10 cases, between 10 and 20 cases or >20 cases of ALI per year. The distribution of surgical volumes and outcomes is listed in *Table 10*. As can be seen in *Table 10,* there were no significant differences between the groups; however, there was a trend towards better outcome for patients treated at hospitals with lower surgery volume. When long-term outcomes were assessed with Kaplan Meier analyses (death, amputation and amputation-free survival were examined), this trend had disappeared and all three groups showed similar results.

Table 10. Outcome depending on yearly surgery volume.

	Surgery volume			
	<10 cases	**10-20 cases**	**>20 cases**	P-value
Number of hospitals	15	9	18	
30 days				
- Death	10.6%	10.9%	11.8%	0.255
- Amputation	7.3%	6.3%	7.7%	0.034
- Amputation-free survival	82.9%	84.0%	82.0%	0.037
1 year				
- Death	25.5%	27.2%	28.8%	0.034
- Amputation	12.8%	12.2%	13.7%	0.065
- Amputation-free survival	65.2%	64.9%	62.4%	0.014

Paper IV

In all, 715 cases of AAO in 673 patients were identified in Sweden from 1994-2014. This figure corresponds to a yearly incidence of 3.7 cases of AAO per million inhabitants. Of the 715 cases, 361 were women (50.5%). Age ranged from 38-96 years with a median of 70.0 years. AAO was due to *in situ* thrombosis in 458 patients (64.1%), saddle embolus in 152 (21.3%) and occluded graft/stent/stentgraft in 105 (14.7%). Patients were followed for a mean time of 5.2 years after the acute episode (SD 5.5).

In the group with occluded grafts/stents/stentgrafts, 34 patients (32.4%) had occluded grafts after previous open surgical repair for abdominal aortic aneurysm (AAA), 19 (18.1%) had occluded stentgrafts after previous endovascular aneurysm repair (EVAR), 19 patients (18.1%) had an occluded aorto-bi-iliac bypass and 11 (10.4%) had occluded aortic stents. Some patients previously had an axillary-bifemoral bypass due to chronic aortic occlusion; these occluded in 22 patients (21.0%), resulting in acute bilateral limb ischaemia. The graft/stent/stentgrafts occluded after a median of 19.3 months (range 0.2-197) from original surgery.

At presentation, most patients had severe bilateral ischaemia (81.2%) with a mean ABI of 0.08 (SD 0.18) of the affected limbs.

Regrettably, information on comorbidities of registered patients in the Swedvasc is not complete in this cohort, where the frequency of missing data varies from 5-40% for different comorbidities (40% of the data are missing on smoking history). Available information on status at presentation and comorbidities are presented in *Table 11*. A Kendall's Tau-b analysis was performed to further study the correlation between type of occlusion and smoking habits. The analysis revealed a positive correlation between smoking and graft/stent/stentgraft occlusions (τ_b=0.159, P<0.001)

Table 11. Preoperative characteristics and comorbidities

	Total	***In situ* Thrombosis**	**Saddle embolus**	**Occluded graft/stent /stentgraft**	P-value
Number of cases	**715**	**458**	**152**	**105**	
Age	**69.7 (68.6-70.9)**	**68.6 (67.2-69.9)**	**74.3 (72.4-77.2)***	**66.8 (63.8-69.5)**	<0.001
Female sex	**50.5 (45.5-54.5)**	**50.2 (44.4-55.6)**	**62.1 (52.6-72.6)***	**33.4 (22.6-46.2)***	<0.001
Period (7 years)					0.126
- 1994-2000	**29.7 (25.0-34.4)**	**31.2 (26.1-37.3)**	**30.0 (20.5-41.0)**	**20.5 (10.4-32.6)**	0.137
- 2001-2007	**32.0 (28.0-37.0)**	**33.3 (28.2-39.4)**	**33.3 (24.1-44.5)**	**22.7 (12.5-35.9)**	0.002
- 2008-2014	**38.3 (33.1-43.5)**	**35.4 (29.3-42.5)**	**36.7 (26.5-47.9)**	**56.8 (44.0-70.2)***	
Bilateral limb ischaemia	**81.2 (77.0-86.4)**	**75.9 (69.8-82.0)***	**91.3 (85.2-97.4)***	**82.2 (70.1-93.3)**	<0.001
Smoking					
- Current	**63.2 (58.1-69.3)**	**69.1 (62.0-75.3)**	**42.3 (28.1-48.5)***	**63.0 (46.0-79.0)**	<0.001
- Previous	**2.9 (1.1-6.0)**	**2.2 (0.5-5.7)**	**2.6 (0.4-8.0)**	**7.4 (0.5-18.1)**	0.110
- Never	**33.9 (28.8-40.0)**	**28.8 (22.7-36.9)**	**55.1 (40.0-70.3)***	**29.6 (14.4-46.8)**	<0.001
Previous vascular surgery	**50.1 (44.0-56.3)**	**49.5 (42.3-57.8)**	**30.0 (18.8-43.2)***	**100 ***	<0.001
Comorbidities					
- Hypertension	**56.6 (50.2-63.0)**	**55.4 (48.2-63.6)**	**52.2 (38.1-66.3)**	**73.3 (55.2-89.4)**	0.049
- Diabetes mellitus	**17.1 (13.0-22.2)**	**17.0 (12.0-22.0)**	**13.3 (4.1-23.5)**	**24.5 (10.4-43.6)**	0.249
- Heart disease	**59.5 (53.1-65.9)**	**53.8 (47.6-62.0)**	**78.9 (68.8-88.0)***	**57.1 (40.0-76.2)**	<0.001
- Cerebrovascular event	**19.4 (14.2-24.6)**	**17.7 (12.5-24.9)**	**27.2 (16.1-40.3)**	**14.9 (2.8-29.0)**	0.096
- Renal impairment	**11.2 (7.1-15.3)**	**10.2 (6.0-15.4)**	**11.4 (3.3-20.5)**	**17.0 (3.0-31.0)**	0.389
- Pulmonary disease	**20.4 (16.0-28.8)**	**18.5 (12.3-25.7)**	**17.0 (7.0-29.0)**	**38.3 (20.1-57.5)***	0.005

Numbers correspond to per cent (99% confidence intervals.) or mean (99% confidence intervals). The right column with P-values is based on ANOVA of all three groups. * $P<0.010$ when comparing this group with the other two groups.

Patients with AAO due to saddle embolus were older, more often women, few had a history of smoking, a small number had undergone previous vascular surgery and a majority had a known heart disease compared with the patients in the other groups (*Table 11*). Patients with occluded graft/stent/stentgrafts were more often men, it was more common during the last study period and they had more pulmonary disease (*Table 11*). The frequency of patients with saddle embolus did not change during the study period, whereas graft/stent/stentgraft occlusions increased with a simultaneous reduction in the proportion of *in situ* thrombosis (*Figure 15*.) The total incidence of AAO did not change during the study period (range 2.7-5.0 cases/million person-years).

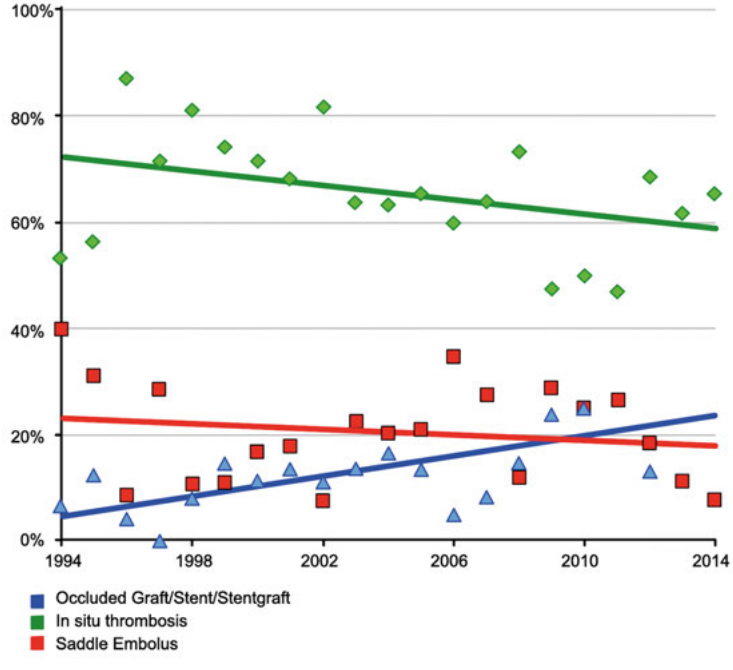

Figure 15. Proportion of the subgroups during the study period

All patients registered in the Swedvasc had received some type of revascularisation. The most common method for revascularisation was thromboembolectomy (32.0%), thrombolysis (22.4%), axillary-bifemoral bypass (18.9%) and aorto-bi-iliac/bifemoral bypass (18.2%) (*Figure 16*). There were differences in choice of revascularisation techniques depending on the aethology of the occlusion. These data are presented in *Table 12*.

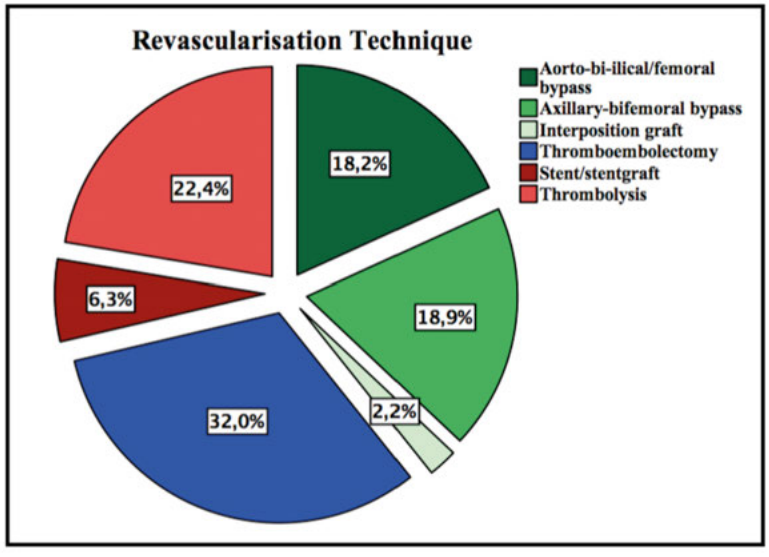

Figure 16. Revascularisation technique

Table 12. Methods of revascularisation

	Total	*In situ* thrombosis	Saddle embolus	Occluded graft/stent /stentgraft	P-value
Number of cases	715	458	152	105	
Aorto-bi-iliac/femoral bypass	130 (18.2)	112 (24.5)*	11 (7.2)	7 (6.7)	<0.001
Axillary-bifemoral bypass	135 (18.9)	100 (21.8)	9 (5.9)*	26 (24.8)	<0.001
Interposition graft	16 (2.2)	10 (2.2)	2 (1.3)	4 (3.8)	0.411
Thromboembolectomy	229 (32.0)	99 (21.6)	96(63.2)*	34 (32.4)	<0.001
Graft/stent/graftstent	45 (6.3)	32 (7.0)	11 (7.2)	2 (1.9)	0.134
Thrombolysis	160 (22.4)	105 (22.9)	23 (15.1)	32 (30.5)	0.013

Values in parentheses are percentages. *P<0·010 when comparing this group with the other two groups

In 67.0% of the cases the revascularisation procedure was performed without any complications during hospital stay (bleedings, infections, re-operations or fasciotomy). The most frequent complications were re-occlusion (12.5%) and infection (8.4%); of those, 6.2% were superficial wound infections and 2.2% deep infections with systemic manifestations. Other complications are described in *Table 13*. There were no differences in the frequencies of complications in the three subgroups; nor were there any differences in the frequencies of complications between the open surgery and endovascular group.

Table 13. Outcome after revascularisation

	Total	***In situ* Thrombosis**	**Saddle Embolus**	**Occluded graft/stent /stent graft**	P-value
Number of cases	**715**	**458**	**152**	**105**	
Complications					
- Re-occlusion	**12.5 (8.0-17.2)**	**12.3 (7.2-17.4)**	**10.8 (4.6-19.8)**	**17.8 (4.9-32.0)**	0.495
- Infection	**8.4 (5.5-12.5)**	**7.6 (4.2-12.4)**	**9.7 (2.5-18.9)**	**11.1 (0.0-26.1)**	0.656
- Bleeding	**6.2 (4.0-8.8)**	**5.3 (2.2-9.4)**	**8.6 (2.4-18.0)**	**6.7 (1.1-18.2)**	0.510
- Distal embolisation	**3.4 (1.2-6.5)**	**3.7 (1.0-6.9)**	**3.2 (0.0-8.8)**	**2.2 (0.0-9.2)**	0.880
- Local nerve injury	**1.8 (0.0-4.6)**	**2.3 (1.2-5.4)**	**1.1 (0.0-5.8)**	**0.0 (0.0-0.0)**	0.462
- Intestinal ischaemia	**1.6 (0.0-3.2)**	**1.0 (0.0-3.3)**	**2.2 (0.0-7.1)**	**4.4 (0.0-15.6)**	0.203
Fasciotomy	**7.5 (4.4-11.6)**	**7.9 (4.1-12.0)**	**6.5 (1.4-14.6)**	**6.3 (0.0-17.6)**	0.852
30-day follow-up					
- Myocardial infarction	**6.4 (3.3-9.5)**	**6.4 (3.1-10.7)**	**7.4 (1.2-15.6)**	**4.3 (0.0-12.2)**	0.768
- Major stroke	**1.1 (0.0-2.3)**	**0.6 (0.0-2.7)**	**2.1 (0.0-7.1)**	**2.1 (0.0-10.2)**	0.378
- Amputation	**8.6 (5.1-11.7)**	**9.4 (5.2-14.5)**	**6.2 (1.0-13.4)**	**8.2 (0.0-20.4)**	0.605
- Death	**19.9 (16.5-23.2)**	**18.6 (14.4-23.8)**	**30.9 (22.6-41.0)***	**9.5 (3.2-18.6)***	<0.001
- Amputation-free survival	**74.0 (69.0-79.1)**	**74.4 (68.0-80.8)**	**67.0 (54.8-79.0)**	**85.1 (70.0-98.3)**	0.064

Numbers correspond to per cent (99% confidence intervals.) or mean (99% confidence intervals). *P<0·010 *vs.* other groups.

Thirty days after surgery, 142 of the patients (19.9%) were deceased and among the survivors 74.8% underwent follow-up examination by a vascular surgeon. However, the survival data were complete during all follow-up. Within 30 days from surgery, 6.4% of the patients had suffered from myocardial infarction and 1.1% from major stroke. Amputation was required in 8.6% of the cases within the first month after surgery.

The mortality rate was higher in the group with AAO because of saddle embolus and lower after occluded graft/stent/stentgrafts (*Table 13*). This difference remained after adjustment for baseline differences in a Cox regression model adjusting for differences in age and sex. The difference in mortality remained after combining patients with embolus and thrombosis into one group (21.6%, P=0.004). Hospitals were separated into two groups depending on whether they had more or less than 20 cases of AAO during the study period. No difference in mortality or amputations was found in low- versus high-volume centres (P=0.901).

There was a reduction in the 30-day mortality rate over time (*Figure 17*). Mortality was 25.0% in the first study period, 20.5% in the second (2001-2007) and 15.3% in the third (2008-2014) (p=0.008 when comparing the first and third periods).

During the follow-up (mean 5.2 years), 45 patients (6.3%) required reoperation of the aorta or a bypass graft. The reoperations were performed at a median of 12.6 months from the index operation (range 0.3-133). The most common types of reoperation were thromboembolectomy (16 cases, 35.6%), aorto-bi-iliac/femoral bypass (11 cases, 24.4%) and placement of stents in the aorta or bypass grafts (7 cases, 15.6%). There was no difference in the need of reinterventions between the aetiological groups (P=0.180). Reoperations were needed more frequently if the index operation had been thrombolysis (P=0.003), where 11.3% of the patients needed additional surgery after a median time of 8.2 months (range 0.3-104) after thrombolysis. Patients who required reoperations had lower mortality than the rest of the patients, both at 30 days (4.4% vs. 20.9%, P=0.007) and at 5 years after surgery (17.8% vs. 61.2%, P<0.001).

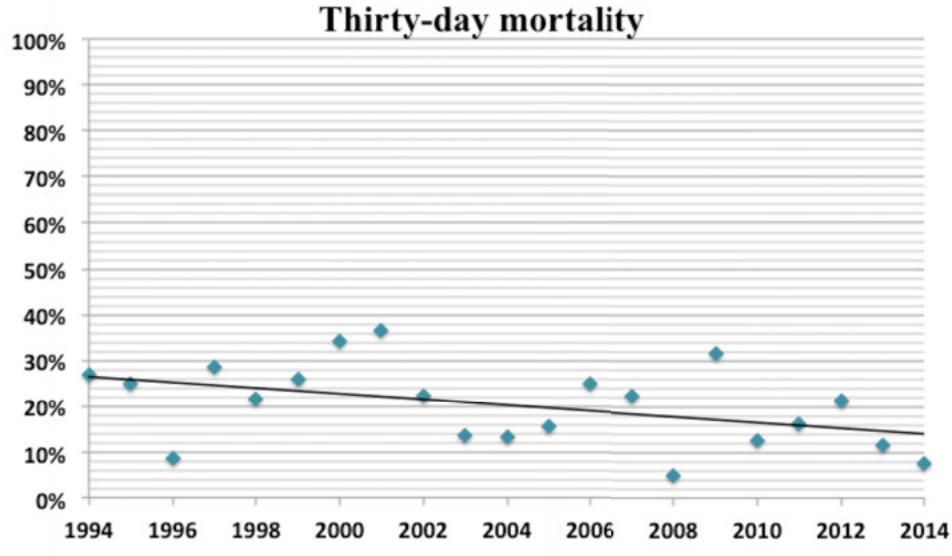

Figure 17. Thirty-day mortality rate

Figure 18 displays survival curves up to 10 years after the intervention for the three aetiological groups (log-rank, $p<0.001$). The survival curves show a difference between the groups in the early postoperative period. Thereafter, the group with saddle embolic occlusions continues to have an inferior survival throughout the follow-up. No difference in long-term survival was found in the low- and high-volume centres (log-rank, $P=0.701$).

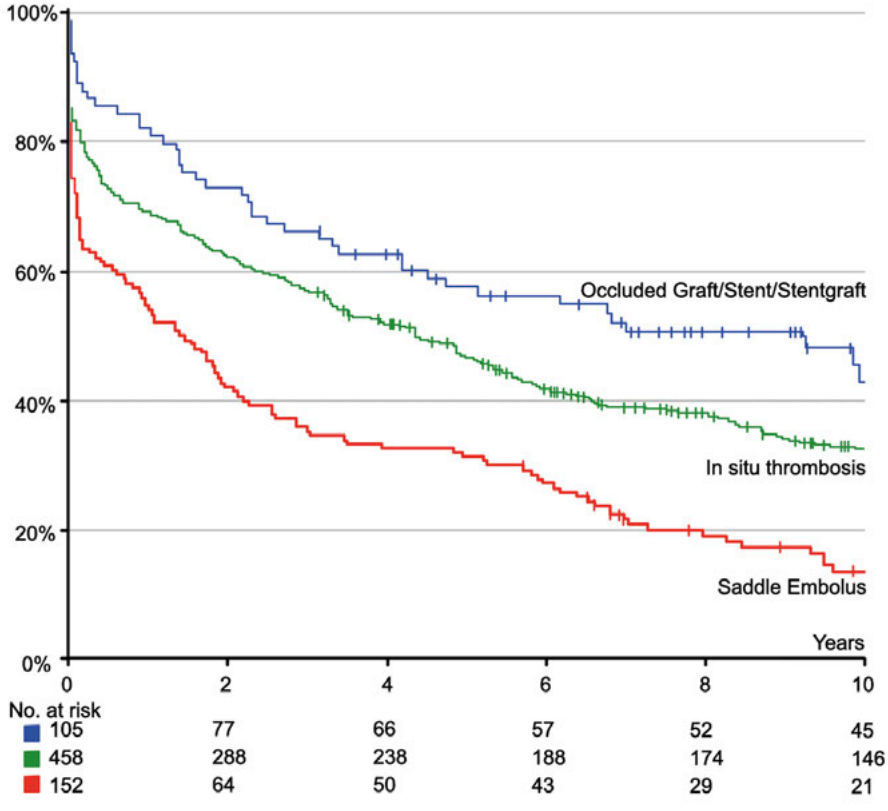

Figure 18. Kaplan-Meier survival curves.

General discussion

The first study offered an opportunity to evaluate two treatment strategies of intra-arterial thrombolysis, with or without continuous heparin. The success rates for the two hospitals with the two treatment strategies were similar at 30 days for limb salvage and survival. When the patient cohort was further studied, differences in patient selection between the two hospitals were found, namely patients in Malmö were younger and had different underlining aetiology to the ischaemic insult. The difference in case mix underlines the value of the multivariate analysis given that a direct comparison between hospitals could have led to misleading conclusions regarding the optimal treatment strategy. Continuous heparin administration was not a factor with significant impact on any of the events tested for in multivariate analysis. This result is in accordance with that from the only randomised study in this field, where continuous heparin infusion did not result in a significant benefit.(Berridge 1990)

Heparin is a potent drug with a relatively narrow therapeutic interval; an overdose can have devastating consequences for the patient. To avoid such a mishap from occurring continuous heparin infusions require repeated monitoring of APTT values and adjustment of the infusion rate. The patients treated in Malmö were monitored in intensive care, whereas patients in Uppsala were monitored in a high-dependency unit. If the use of continuous heparin infusions during thrombolysis does not offer any advantages, as paper I indicates, time and resources can be spent in a more efficient way. Although the study did not include a proper health economic evaluation, it is rather obvious that continuous heparin infusion is associated with an increased cost.

Some studies have indicated that t-PA not only disturbs haemostasis and has a fibrinolytic effect, t-PA may also affect the coagulation system and has a direct anticoagulant effect in a dose-dependent manner.(Stehling 2008, Stewart 2003) t-PA converts plasminogen to plasmin and plasmin degrades plasma fibrinogen and factor VIII. Relatively high doses of t-PA are needed for depletion of these clotting factors and disruption of the coagulation cascade, however. Although more studies in this area are needed, the findings of this study suggest that the anticoagulant effect of heparin might not be as important for the total effect of thrombolysis as previously thought. The mild

anticoagulant effect of t-PA may be sufficient to prevent secondary clotting during thrombolysis.

The dose-dependent effect of t-PA has been verified by other studies demonstrating that higher dosages of t-PA accelerate the thrombolysis and achieve faster restoration of blood flow, a potential advantage for patients with acute ischaemia. On the other hand, faster thrombolysis with a higher dose of t-PA is counterbalanced by a higher rate of bleeding complication.(Braithwaite 1997, Plate 2006)

Many clinicians are concerned about the risk of bleeding associated with intra-arterial thrombolysis. Local bleeding from the arterial puncture site was common (30.3% of total episodes), but most of the reported bleeding episodes in the first study were mild and could be managed without surgical intervention. Some episodes of bleeding required blood transfusion (13.9%) or thrombolysis to be discontinued (5.7%). Stroke has occurred in 1–2% of the procedures in previous larger studies.(meta-analysis by Semba 2000) In paper I, which included 749 thrombolytic procedures, there were only three cases (0.4%) with intracranial haemorrhage. A previous study reported an even higher bleeding complication rate (47%) but was also accompanied by a higher success rate (86%)(Swischuk 2001). One study reported bleeding complications to be associated with a lower amputation rate(Kuoppala 2008), suggesting that it is important to accept minor bleeding complications to achieve optimal limb salvage; however, the results of the Uppsala/Malmö study do not support that finding.

In some countries thrombolysis is seldom used to treat embolic occlusions. The rationale behind this decision is the belief that thrombolysis is relatively ineffective against the organised thrombus present in most peripheral emboli.(Callum 2000) The present study suggests the opposite. In Sweden, there is a tradition to treat even embolic occlusions with thrombolysis. It should be noted that in paper I embolic occlusions represented 21.5% of the total. The embolus group had a success rate above average (81.4%) and a lower amputation rate at 30 days (5.7%). In multivariate analysis, however, the only significant factor associated with amputation within 30 days was embolic occlusion with an OR below 1 (OR 0.30).

The only independent risk factor for major bleeding complication during thrombolysis was severe ischaemia, which is an important and novel finding. The group of patients with severe ischaemia and motor deficits represented 20.7% of the total cohort in paper I. This group had a lower success rate compared with the rest of the cohort (73.5% vs. 83.5%, P=0.005). Patients with severe ischaemia had similar age and pre-surgical comorbidities, except for a higher rate of renal insufficiency (42.9% vs. 30.4%, P=0.004) and of

atrial fibrillation (37.0% vs. 27.0%, P=0.015). Particularly noteworthy is that the group with severe ischaemia received a similar amount of t-PA (20.6 mg vs. 21.2 mg, P=0.671) during a similar treatment time (24.1 hours vs. 25.8 hours, P=0.459) compared with those with less severe ischaemia. The results from this study suggest that patients with severe ischaemia and motor deficits are especially vulnerable to thrombolysis. In this study there was no comparator, however, and hence they may have been vulnerable to open surgery as well.

In the multivariate analysis treatment at Uppsala was found to be an independent risk factor for fasciotomy. There are several possible explanations for this observation. In Uppsala the thrombolytic procedures had longer duration compared with Malmö (26.7 hours vs. 23.2 hours). This longer duration resulted in a longer time before reperfusion was established and possibly a greater ischaemic injury to the tissues with greater risk for reperfusion injury and the need for subsequent fasciotomy. Several studies have reported results contradicting this theory. A Cochrane meta-analysis showed that high dose regimens and forced infusions reduce the duration of thrombolysis, but is associated with higher risk for reperfusion injury and bleeding complications compared with low-dose regimes.(Kessel 2004) Slow and gradual reperfusion seems to be the most circumspect way to reperfuse the tissue. Possibly, there is an optimal reperfusion pace in which the risk for reperfusion injuries and bleedings are balanced against the risk for permanent ischaemic injury? More studies are needed to investigate an optimal reperfusion pace.

Another reason for the higher fasciotomy rate in Uppsala might be linked to the use of heparin. Heparin is a substance that naturally exists in the body within mast cells. Heparin not only affects the coagulation system but also has anti-inflammatory properties.(Rang 2012) Because many of the inflammatory mediators are generated by the act of clotting, anticoagulation will have an additional benefit by decreasing the inflammatory response. (Blaisdell 2002) It is possible that heparin supresses the inflammation in response to reperfusion injury and hence reduces the need for subsequent fasciotomy.

Finally, the increased risk for fasciotomies at Uppsala might be due to different treatment traditions at the two hospitals. The Uppsala team might perform fasciotomy with wider indications? This issue is difficult to study, even with a prospective study design, and in this retrospective analysis proved impossible to investigate.

To compare treatment strategies between two hospitals is not ideal, largely because there are many potential confounders. Indeed, as shown in this study

a difference in patient selection between the two hospitals was demonstrated. To compensate for this potential confounder multivariate analysis was performed. Ideally, the question of whether continuous heparin infusion during thrombolysis has any benefits or disadvantages should have been studied in a randomised control trial (RCT).

Power calculations of a potential RCT showed that to detect a difference in major bleeding complications with a power of 0.9 and a significant level of 0.01 a sample size of 4,368 patients would be needed. During this 10-11-year study, 749 patients received thrombolysis at the two hospitals. To collect a sample size of 4,368 patients at these hospitals would take approximately 55-60 years, which would not be a feasible time frame for this study. A better study design would have been to include more hospitals. Yet, including more hospitals carries the risk of further differences in treatment strategies (though in an RCT potential confounders are addressed).

The present authors thought that the setup of the present study with multivariable analysis under the circumstances described above was the best way to answer the question of the possible effects of continuous heparin infusion.

One of the limitations of paper I is the way in which the aetiology of the occlusion was identified. The distinctions between the subgroups were made by investigating four sources: hospital charts, radiological images, Swedvasc registration and diagnostic codes from hospital stay. For stent/graft occlusions and PAA, the aetiology was relatively obvious and clearly documented in hospital charts. The distinction between thrombotic and embolic occlusions can sometimes be difficult, however. For most patients, the responsible surgeon had documented the aetiology after amalgamation of important factors such as patient history, symptoms, presence of an embolic source and angiographic images (see *Table 1,* page 14). When classification was problematic or missing in hospital charts, two of the authors (OG and MB) carefully studied hospital charts and radiologic images and discussed the case until consensus was achieved.

There is no gold standard for validation of the documented aetiology, which makes it difficult to address this question in an objective way. As a validation, an independent vascular surgeon at Uppsala hospital was asked to study some of the cases where it was difficult to classify aetiology. Of the 15 cases included in this validation, a consistency of 14/15 (93%) was found.

Paper I included patients treated with thrombolysis between 2001 and 2012. In this patient cohort 65.1% were prescribed acetylsalicylic acid (ASA) treatment regularly before the ischaemic episode. Only 15.1% of the patients were prescribed warfarin.

During the past two decades, major advancements in the treatment of cardiovascular diseases have been made. Today, secondary prophylactic treatment is routinely used for patients with known atherosclerosis in Sweden. (Aboyans 2018, Smith 2006) A combination of ASA and statins is a common treatment for patients with PAD. The introduction of direct oral anticoagulants (DOACs also called NOACs) has influenced the treatment of patients with cardiovascular disease. The DOACs are set to replace vitamin K antagonists (principally warfarin), heparin and LMWH as the leading antithrombotic prophylaxis in several surgical and medical settings.(Blann 2016, Sardar 2015)

This change in medical treatment for patients with PAD raises several questions pertinent to thrombolytic treatment in the future. As the use of DOACs increases, more patients presenting with ALI will be on DOAC treatment. Surgical procedures under DOAC treatment can be scheduled at the beginning of the next dosing interval or omitted in patients with low/minimal risk of bleeding, so that only 2-3 DOAC doses are not administered. In patients with moderate and high risk of bleeding, there should be a DOAC break of 24-48 hours prior to surgery to allow a corresponding decay of the active metabolite. Vascular surgery is generally classified as causing moderate to high risk of bleeding.

Patients with ALI are in need of urgent surgical treatment. Antidotes for some of the DOACs already exist and a universal reversal agent is in development.(Balla 2017) In the meantime how will DOAC treatment affect thrombolysis? Will the risks for bleeding complications be considered too great? Will we see a reduction in thrombolytic treatment for these patients? Will double treatment (thrombolysis + remaining effect of DOAC) affect the results of thrombolysis?

The second paper presents a first time opportunity to investigate the long-term results after thrombolysis for different subgroups, depending on the underlying cause of ALI.

Data on long-term follow-up after thrombolysis are scarce in the international literature. While there are a few studies that include a 5-year follow-up (*Table 14*), the differences in study populations in these studies make comparisons between the studies difficult.

Table 14. Studies including a 5-year follow-up after thrombolysis

Author	Aetiology of ischaemia	Number of patients	Type of ischaemia	Secondary patency at 5 years (%)
(Hess 1987)	Emboli	59	ALI mixed with claudication	89.5
(Hess 1987)	Thrombosis	254	ALI mixed with claudication	58.8
(Conrad 2003)	Vein grafts, only successful thrombolysis	49	*Not known*	65
(Sebastian 2010)	Native occlusions, only successful thrombolysis	20	*Not known*	70
(Sebastian 2010)	Graft/stent occlusions, only successful thrombolysis	16	*Not known*	75
Grip (Paper II)	Thrombosis, emboli, PAA and graft/stent	689	ALI	75.2

In the entire cohort of Paper II a little over half (50.7%) did not require any surgical reintervention or amputation in their remaining lifetime or at the end of follow-up (mean74.1 months). Thrombolysis, if followed by an intervention tailored to prevent a recurrence of the ALI, transforms an emergent into an elective situation.

Previous studies have reported thrombolysis to be a successful method for revascularisation in ALI, especially for occluded grafts/stents/stentgrafts. (Palfreyman 2000) This argument is consistent with the results of Paper I, where this subgroup had a high success rate at 30 days and at 1 year. Yet, after 5 years, this subgroup had an unfavourable primary patency, amputation rate and amputation-free survival. In multivariate analysis graft/stent/occlusions showed a trend as a risk factor for amputation within 5 years (P=0.011).

When studying long-term results after thrombolytic treatment for the subgroup with occluded grafts/stents/stengrafts, the combination of the treatments is presented. Short-term results after thrombolysis are more likely to

reflect results linked to the thrombolytic treatment, whereas long-term results will be combined with results from the surgery addressing the underlying cause.

It has been suggested that endothelium alterations in vein grafts and the development of a thin prothrombotic layer in synthetic grafts could explain failure after thrombolysis.(Conrad 2003) Some surgeons promote *de novo* bypass in patients with a thrombosed graft rather than thrombolysis.(Conrad 2003)

The patients with embolic occlusions had a higher immediate success rate (86.7%), as well as a better primary patency at 5 years. Embolic patients who were still alive at 5 years of follow-up had a lower amputation rate compared with the other groups. The favourable outcome for limb salvage in the embolic group is explained by these patients having cardiac rather than vascular disease, although some will have both.(Earnshaw 2013) Patients with embolic occlusions were older, had more atrial fibrillation and renal insufficiency, which explains their higher mortality. Furthermore, a possible explanation for the low rate of reinterventions might be the age and comorbidities in this patient cohort, which would influence the surgeon to take the decision to abstain from surgery owing to the slim chances of success.

Occluded PAA had the lowest primary and secondary patency rates. The poor patency rate after thrombolysis for occluded PAA might be explained by incomplete run-off clearance of fresh and/or old embolic clots. This subgroup, however, had the best amputation-free survival rate at 5 years and the highest survival rate after 5 years. These latter findings are explained by this group being younger, presenting with a low rate of diabetes and having more collaterals because of the progressive occlusion of the crural arteries, secondary to embolisation. Most of the thrombolytic procedures were followed by durable open surgical repair of the aneurysm. Thus, although the short-term outcome in this subgroup was inferior in terms of limb salvage, the opposite was true for long-term outcome.

Unfortunately, paper II is lacking information on the cause of death for the participating patients. In the general population in Sweden approximately 1/3 of all deaths are caused by cardiovascular diseases. During the study period, death caused by cardiovascular diseases decreased from 45.0% in 2001 to 35.0% in 2015 (Cause of Death Registry, National Board of Health and Welfare 2018). Death caused by cardiovascular diseases in the patient cohort in this study is expected to be considerably higher than in the general population because all of the patients already had manifestations of severe cardiovascular disease. The reasons for the general decrease in cardiovascular death are multiple and include improvement in secondary prophylactic

treatment and new anticoagulation treatments, which were discussed in the previous section. The introduction of fast tracks for patients' with typical symptoms of cardiovascular diseases have reduced the time to efficient treatment. Moreover, improvements in invasive treatments have also contributed to the decreased death rate in cardiovascular diseases (Anderson 2017, Wong 2016).

A majority of the patients included in paper II suffered from mild to moderate ischaemia (Rutherford class I: 16.5%, class IIa: 58.9%). Only 24.3% of the patients presented with an immediate threatened limb (Class IIb). It is possible that patients with the most severe ALI were offered other kinds of treatment and thus were excluded from this study. This fact may have contributed to the favourable outcome after thrombolysis shown in this study. The previous recommendation for immediate threatening limb ischaemia has been prompt surgical revascularisation because of the relatively long time needed for revascularisation with thrombolysis.(Hirsch 2006) To determine a more complete picture of the best way to treat patients with ALI we decided to include all patients in the third study presenting with ALI, irrespective of treatment.

In **the third study** the results revealed similar amputation rates between endovascular treatment and open surgery in patients with ALI. However, endovascular treatment proved superior to open surgery regarding survival. No previous large-scale population-based observational study had been published and no RCT in recent decades has compared endovascular treatment with open surgery in the treatment of ALI. The results from paper III indicate that one life can be saved during the first year after treatment if the primary treatment were changed from open to endovascular in 12 patients (NNT=12).

In the mid-1990s, three large RCTs were performed to address the optimal treatment strategy for patients with ALI. These studies are discussed in more detail in the introduction (page 27-29). A Cochrane database meta-analysis of the studies (Berridge 2013) concluded that there was no overall difference in limb salvage, death or amputation-free survival at 30 days or at 1 year. A limitation of this meta-analysis is the low precision of the estimates. Furthermore, therapy has markedly improved in recent decades.

Wang and colleagues (Wang 2016) concluded in an evidence summary review, comparing open end endovascular revascularisation (including also retrospective studies) that endovascular revascularization should be the first-line treatment for ALI. This was based on equivalent results in terms of amputation and amputation-free survival, and lower mortality and morbidity

after endovascular revascularisation. They, however, acknowledge a higher need for future interventions in the endovascular cohort.

Paper III compares first-line endovascular treatment with open surgery. There was a trend towards more bleeding complications associated with endovascular treatment. The risk of the most devastating bleeding complication (i.e. stroke/intracranial haemorrhage) was low, however, and equally distributed between the two groups.

One year after the intervention and onwards, the two survival curves were parallel, indicating that the propensity score match was successful in addressing confounding and selection bias. The difference in effects of the two acute treatments is likely to be more pronounced close to the intervention. The landmark analysis was performed to interpret the remaining effect of the treatment 1-year post-intervention. Time censoring at 5 years revealed that there was no significant difference in risk of adverse events after endovascular revascularisation. Still, early amputation rates were similar between the treatment groups though there was a trend towards a higher rate of late amputation in the endovascular group. However, results from the landmark analysis should be interpreted with caution being that the covariate balance achieved by the propensity score matching might no longer be accurate because patients with a follow-up shorter than 1 year were excluded from this analysis. The amputation rate might have been affected by the competing risk phenomena of death: only living patients are considered for amputations and survival was better in the endovascular group, leaving more patients at risk of amputation.

We hypothesised that the advantage of endovascular treatment could be more pronounced in patients with a thrombotic occlusion, where the endovascular techniques have emerged the most, but the subgroup analysis showed the opposite (*Figure 12*). The ultimate advantage of the less invasive technique seems to be in the most vulnerable group with embolic occlusions.

There are several possible explanations for the favourable outcome after endovascular treatment for patients with ALI. First, it can be performed under local anaesthesia, which is convenient because many patients with ALI are elderly and fragile with multiple comorbidities.(Earnshaw 2013) Second, endovascular treatment includes accurate angiographic imaging, localisation of the underlying disease and a more directed and potentially more definitive therapeutic approach.(Van den Berg 2010)

Several studies have verified that initial thrombolytic therapy reduces the need for subsequent surgical treatment.(Ouriel 1996, STILE 1994) In paper II, we found that less than half of the patients needed subsequent revasculari-

sation after thrombolysis. If unsuccessful, endovascular treatment can be promptly followed by surgical intervention, whereas the opposite order is contraindicated.(Earnshaw 2013) A noteworthy observation from the STILE trial was the fate of patients who failed the primary intervention. More specifically, patients who had failed open surgery had more than twice the risk of major amputation than those who underwent unsuccessful thrombolysis. (STILE 1994)

For patients with severe ischaemia and motor deficits (Rutherford class IIb), previous recommendations have been prompt surgical revascularisation because of the relatively long time required for revascularisation with thrombolysis.(Hirsch 2006) Emergency lower extremity bypass for ALI, however, is associated with increased rates of serious in-hospital adverse events, major amputation rates and mortality compared with elective bypass surgery.(Baril 2013)

In recent years several endovascular solutions have evolved with the introduction of percutaneous mechanical thrombectomy, aspiration and rheolytic techniques. Percutaneous mechanical devices enhance the surgeon's ability to remove thrombus quickly, resulting in lower doses of thrombolytic agents and reducing the time to reperfusion.(Comerota 2009) Some studies indicate that when rapid reperfusion is needed, percutaneous local mechanical thrombectomy, with or without thrombolysis, may be used in a safe and efficient way, even in patients with severe ischaemia and motor deficits. (Byrne 2014, Gupta 2012, Hynes 2012, Leung 2015) Endovascular treatment may also serve as a valuable first-line approach, which later in elective settings can be followed by surgical treatment when patient and circumstances are optimised.(Ravn 2007)

This strategy has already been implemented in Sweden, as shown in this nationwide population-based study. A sizable proportion of the patients treated with endovascular methods had severe ischaemia with neurological symptoms (Rutherford class IIb). Many of those with the most severe ischaemia (Rutherford class III) were excluded in the propensity score matching procedure because most were treated with open surgery, which might still be the preferred treatment for this patient group, i.e. assuming that they were to be vascularised at all. For most, primary amputation remains the treatment of choice for these patients, but there are borderline cases when distinguishing between Class IIb and III may be difficult.

During the study period, a shift towards more endovascular and hybrid revascularisation techniques was observed (*Figure 13*). During the same period, amputation-free survival increased, which was mostly affected by the improvement in the survival rate. Patients with ALI are known to have high

morbidity and mortality.(Hynes 2012, Earnshaw 2013) Although mortality is still high, it is improving and even more patients might survive in the future with an increased proportion of endovascular treatment (*Figure 13*). Because patients with ALI often have multiple comorbidities, survival is also affected by improvements within other specialties, particularly cardiology. As discussed previously in the discussion, death in cardiovascular diseases is decreasing in Sweden. Changes in demographics (e.g., reduced tobacco consumption and other lifestyle changes) may also improve survival. According to the Swedish Board of Health and Social Welfare (report from 2016), the frequency of Swedes that regularly smoke decreased from 23.5% in 1994 to 10.8% in 2014.

The main purpose of study III was to compare outcome after endovascular and open surgery for all patients with ALI in Sweden. The primary focus was not to compare different aetiologies, even if variables such as thrombosis, emboli and PAA had to be included in the propensity score analysis to create comparable groups. However, information on whether it was a native artery occlusion or an occluded graft/stent/stentgraft was not included. The rationale for this decision is that re-occlusions can be registered in the Swedvasc Registry in different ways, either as a re-operation after more or less than 30 days with different types of registration depending on time since index surgery or it can be registered as a new operation. The Swedvasc Registry recommends that a second operation in the same anatomical segment is registered as a reoperation, but if the in-flow or out-flow is affected and treated, a new operation is registered. The patient cohort was considered too large (>16,000 operations) to permit a manual study of all patients' hospital charts to properly validate the aethology. To avoid this potential confounder the authors concluded not to include a variable whether it was a native artery occlusion or a stent/graft occlusion because this information is not readily available in the registry. This is a limitation of study III.

Furthermore, this study did not include analysing angiographic images. Potentially, patients treated with endovascular approaches could have had shorter occlusions that may have affected the favorable outcome in this group. However, information about the anatomical location of the occlusion, severity of ischaemia (Rutherford classification) and ABI were available from the Swedvasc. McNamara and colleagues have previously demonstrated strong correlation between the clinical degrees of ischaemia and the angiographic patterns of occlusion.(McNamara 1995) Together, we feel that these variables compensate for the drawback associated with the absence of angiographic images and therefore the risk for this potential bias is considered low.

Another limitation of this study is the observational design. A pseudo-randomisation creating comparable groups with propensity score matching was used. Yet, in certain aspects our approach has produced results that are more useful than those that would be expected from a RCT.(Rothwell 2005, Rothwell 2007) Most RCTs recruit only a small proportion of patients in the population with the disease of interest, sometimes <1% and usually <10%.(Bergqvist 2007, Rothwell 2005) Recruited patients often differ from those not recruited for age, sex, ethnic origin, social class, educational status and severity of disease, as well as in their willingness to be randomised.(Bergqvist 2007, Rothwell 2005) By creating a rigorous population-based study that included all patients with ALI in Sweden over a 21-year period, we avoided such selection restrictions. For example, 41.4% of the patients treated in this study were aged >80 years (and 8.5% were >90); it is well-known that patients >80 years are often excluded from many trial protocols used in vascular disease.(Rothwell 2005) Even after the propensity score match, this age distribution was intact (38.9% >80 years and 7.0% >90 years). The data on the effect of the intervention on the whole population also facilitate more complete assessments of the effects of the intervention on health economics and public health.(Bergqvist 2007, Rothwell 2007) Exceedingly high study costs for RCTs often require important external funding, which is an additional limiting factor that could be mitigated when studies are performed within a registry setting such as the Swedvasc Registry.(Mani 2018)

One of the key benefits of randomised experiments for estimating causal effects is that the treated and control groups are guaranteed to be only randomly different from one another on all background covariates, both observed and unobserved.(Stuart 2010) A propensity score is a single score (a number between 0 and 1) that represents the probability of receiving a treatment, conditional on a set of observed covariates. The goal of creating a propensity score is to balance covariates between individuals who did and did not receive a treatment (in this case two types of treatment), making it easier to isolate the effect of one treatment.(Garrido 2014) It is important to keep in mind that propensity score matching cannot adjust for non-available variables or unobserved differences between groups. The Swedvasc Registry did not include a variable for the anatomical complexity of the operation, which thus remains as a possible residual confounder. It is also important to consider which variables to include in the propensity score and check for balance before and after matching (this information is provided in the statistical appendix on page 17-19).

We matched patients from the two groups pairwise (1:1 matching) based on the estimated propensity score. The propensity score was not allowed to differ by more than 0.001 to be considered a match. There was no hierarchy

between variables included in the propensity score, although the match had to be exact for the "indication" and "period" variables.

Many statisticians and epidemiologists are now considering propensity score matching to be a useful tool to account for observed differences between treated and comparison groups to isolate the effect of a treatment on a health outcome.(Garrido 2014, Stuart 2010)

In recent years multiple imputation has gained popularity as a powerful statistical tool for handling missing data (Hayati Rezvan 2015, Mackinnon 2010) and is starting to be recommended by journal reviewers (Ware 2012). Statistical analyses that exclude individuals with missing data result in estimates with less precision compared with the analysis of all individuals and, more importantly, may lead to selection bias. Applying statistical methods that handle missing data may reduce the bias and increase the precision of the obtained estimates.(Wood 2004) It is important to note that imputed values produced from an imputation model are not intended to be "guesses" as to what a particular missing value might be; rather, this modelling is intended to create an imputed data set that maintains the overall variability in the population while preserving relationships with other variables. The main interest with multiple imputations is to preserve important characteristics of the data set as a whole (e.g., means, variances, regression parameters). Creating imputes is merely a mechanism to deliver an analysis that makes use of all possible information.

When using multiple imputation, it is recommended to include descriptions of missing data, stating the missing data assumptions for the statistical approach selected for handling the missing data and performing sensitivity analyses for the method chosen to handle situations when there is a large proportion of missing data.(Wood 2004) All this information can be found in the statistical appendix related to paper III.

Multiple imputation is a highly contemplative process when deciding on which variables to include in the analysis. All authors discussed and evaluated each variable independently before inclusion: included variables can either become imputed or function as predictors for imputation of other variables, or both simultaneously. The imputation process is then running in a circular model, creating 100 imputation sets. The imputations were analysed one at a time, pooling the results using Rubin's rules.(White 2011) This complex procedure reduces the risk of bias.

Although multiple imputation is appealing and relatively easy to implement in standard statistical software, it can introduce bias if not carried out rigorously.(Lee 2012) To avoid this problem and to learn more about this statisti-

cal method we engaged a statistician to help with the multiple imputations and propensity score matching.

As previously discussed, the distinction between thrombosis and embolus can sometimes be difficult, especially with an ageing population that has often established atherosclerotic disease of the arteries. When a patient presents with both lower limb atherosclerosis and a source of embolus (e.g., atrial fibrillation), not only the classification but also the treatment becomes complex.(Earnshaw 2013) Modern endovascular techniques might even be more appropriate in this difficult clinical situation, as was shown in the subgroup analysis in *Figure 12*.

As described in the statistical section, a manual chart review of 257 patients was performed at Uppsala University Hospital to create a model on how to impute missing aetiology data. This manual chart review also functioned as a validation of the aetiology data (page 15-16 in the statistical appendix). A validation histogram was performed. In the histogram concentrated distributions correspond to the correct imputations being equally spread out among the patients, whereas distributions with a large mass close to 0 or 100 would mean that the imputation consistently identifies the same set of patients for an imputed value. The latter is preferable.

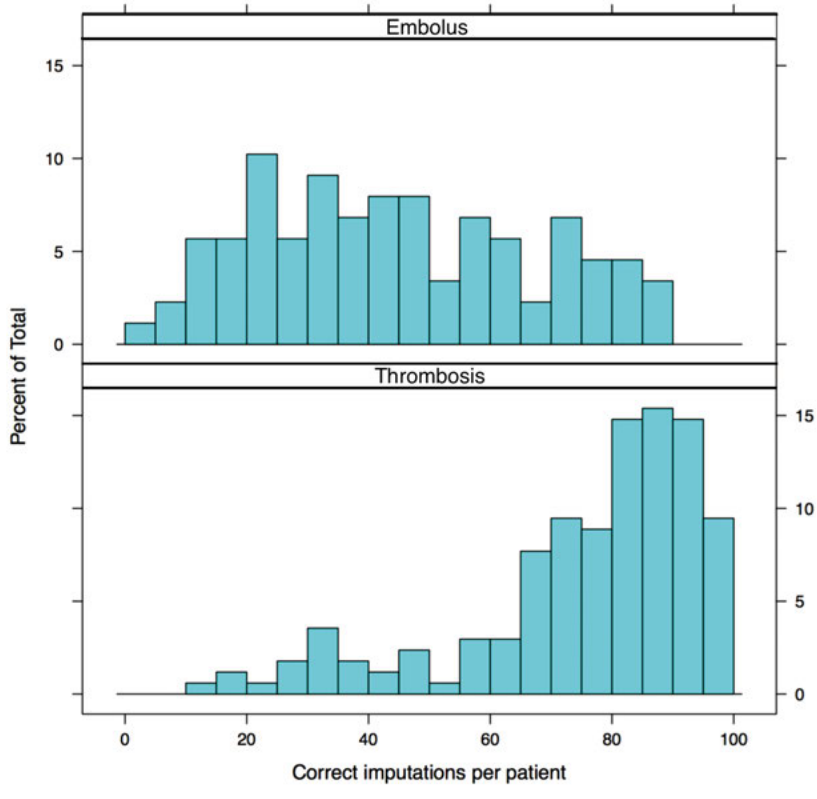

Figure 19. Validation histogram showing correct imputations per patient

This histogram shows the number of correct imputations per patient. A total of 100 imputation sets were created to establish a robust adjustment to the missing data. The imputation model was effective in predicting thrombosis, whereas prediction of emboli was inferior.

Paper IV focused on AAOs with subsequent ALI. AAO is a rare condition and previous studies are largely based on case reports and case series of modest size, with most of them published several decades ago.(Busuttil 1983, Dossa 1994, Littooy 1986, Surowiec 1998) Paper IV is, to our knowledge, the largest study published in this field and demonstrates that AAO is still a rare, but very serious, condition.

The most common cause of AAO in paper IV was *in situ* thrombosis of pre-existing aortoiliac atherosclerosis and the next most common cause was aortic saddle embolus. A study on aortic saddle embolus published in 1983 (Busuttil 1983) postulated that the incidence of saddle embolus would increase over time secondary due to increased age of the population, use of prosthetic heart valves and improved care of cardiac patients. During the 21-

year study period of paper IV, no such increase in incidence of saddle embolus was observed. On the contrary, the incidence of saddle emboli was relatively unaltered over the study period (*Figure 15*). The study instead showed a shift toward *in situ* thrombosis rather than embolism as the most common aetiology of AAO. Dossa et al.(Dossa 1994) reported that 65% of 46 cases of AAO between 1953 and 1993 were embolic; the frequency of thrombotic AAO increased with each decade. Surowiec et al.(Surowiec 1998) reported that between 1985 and 1997, 48% of the 33 cases were embolic. In paper IV, only 21.3% of the cases with AAO were caused by an embolus. This finding is consistent with the findings from two recently published studies, (Crawford 2014, Robinson 2016) reporting embolic occlusions in 8.3% and 28% of their patients. This shift in aetiology may reflect a growing population of elderly with advanced aortoiliac atherosclerosis. It may also be a result of improved secondary prevention of cardio-embolic events with anticoagulation for patients with acute myocardial infarction, atrial fibrillation and/or valvular heart disease.

Another notable finding in paper IV is the observed increase over time in graft/stent/stentgraft occlusions leading to AAO and subsequent limb ischaemia. ALI is a serious complication after AAA repair and remains a challenging crisis in vascular surgery. Occlusions and limb ischaemia after AAA repair are fortunately a rare complication with reported frequencies of <2%, although they are associated with worse overall outcome.(Behrendt 2017) The increased use of EVAR has led to a decrease in postoperative morbidity and shorter hospital stay. Nevertheless, EVAR is burdened with a high frequency of lower limb ischaemic complications, also seen after open aortic surgery.(Maldonado 2004) The EVAR 1 trial reported a 3–4 times higher rate of graft-related complications or reinterventions in the EVAR group compared with open aortic surgery.(Greenhalgh 2010) Ischaemic complications related to EVAR have significantly decreased over time, however, as the issue of limb occlusions was acknowledged and new generation stent grafts are typically manufactured with flexible and more kink-resistant limbs.(Behrendt 2017) Yet, in a recent publication from the UK (the IMPROVE trial) the authors found that randomised patients with ruptured AAA between OR and EVAR, graft/stentgraft occlusion were more common after EVAR both within 90 days and between 90 days and 3 years.(Powell 2018)

Previous reports have shown that graft occlusions are most common within the first 3 months after the procedure.(Woody 2004) In paper IV, however, graft occlusions occurred at a median time of 12.9 months after EVAR and 68.4 months after open AAA repair. This difference may be explained by the fact that this study has longer (and perhaps also more complete follow-up regarding reinterventions) than previous investigations.

Previous studies have concluded that the procedure of choice to treat AAO should be bilateral transfemoral thromboembolectomy.(Busuttil 1983, Littooy 1986, Surowiec 1998) A major advantage of balloon catheter thromboembolectomy is that laparotomy can be avoided in most cases, which is an enormous advantage, especially with respect to frail patients that have embolic occlusions secondary to myocardial infarctions. Thromboembolectomy is also possible to perform under local anaesthesia.(Busuttil 1983, Littooy 1986, Surowiec 1998) In paper IV, thromboembolectomy was the most commonly used method of revascularisation, representing 32% of all procedures. If this fails to re-establish circulation, some other emergent treatment should be pursued. In this situation some authors advocate that aorto-bi-iliac/bifemoral bypass is the operation of choice, provided that the patient is otherwise healthy and the ischaemic time has been minimal.(Littooy 1986, Surowiec 1998) In high-risk patients an extra-anatomic bypass procedure, such as an axillary-bifemoral bypass, is indicated because of the increased mortality associated with laparotomy.(Littooy 1986) The proportions of aorto-bi-iliac/bifemoral bypasses and axillary-bifemoral bypasses were almost identical in the present study (18.2% vs.18.9%).

Paper IV also shows that endovascular therapy in AAO is becoming more prevalent. Thrombolytic therapy, often in combination with PTA and/or stenting, represented 22.4% and stenting alone 6.3% of the procedures. Thrombolytic therapy may also be the preferred treatment for patients with hypercoagulable states because this subset of patients responds poorly to surgical intervention despite normal arteries and good cardiac function. (Shapiro 1981) Reoperations were more common if the patients were treated with thrombolysis. The frequency was 11.3% after thrombolysis compared with an overall frequency of reoperations of 6.3%. Some of these reoperations may have been planned, however, because a treatment of the underlying cause of the AAO often can follow thrombolysis to prevent recurrence. Such a reintervention can be performed in a semi-elective setting.

Because rhabdomyolysis is a known complication for AAO patients, some authors advocate avoidance of endovascular treatment with additional contrast to reduce the risk of renal insufficiency (Crawford 2014). In paper IV, there was no difference in the frequency of any complication during hospital stay in open and endovascular treatment when comparing the different treatment modalities and that included the need for renal replacement therapy.

Overall 30-day mortality during the 21-year study period was 19.9%. Previous studies reported in-hospital or 30-day mortality rates varying from 21-52%.(Babu 1995, Busuttil 1983, Dossa 1994, Littooy 1986) The two more contemporary studies reported mortality rates of 24% and 31%(Crawford

2014, Robinson 2016) Their conclusion was that mortality continues to be high for patients with AAO. This conclusion could be verified in our population-based study that included not only large centres of excellence but also all hospitals of different types performing vascular surgery in an entire country. However, a gradual reduction of the mortality was observed over time and was only 15.3% during the final 7-year period. As discussed previously, the reason for this improvement is probably multifactorial and includes advancement in surgical techniques, routinely used secondary prophylactic treatment, introduction of new oral anticoagulants, advancement in other related specialties, changes in awareness and possibly demographics (e.g., the possibility of more fit elderly patients).

The fact that patients who required reoperations had better survival compared with patients who did not need a reoperation, might be explained by competing risk: Patients that deceased in the early postoperative period never had the opportunity to undergo a reoperation, whereas patients that survived longer could undergo a reoperation if required.

The results from paper IV suggest a flexible approach to treating AAO when it comes to which kind of treatment to use. A variety of techniques (open aortic surgery, extra-anatomic bypass and endovascular procedures) were applied. The decision regarding treatment strategy should be based on the type of occlusion, the patient's anatomy, physiologic state and comorbidities, as well as the tradition and experience at the treating centre.(Aboyans 2018)

Competing risk

One of the primary outcomes studied in this thesis is amputation-free survival, describing time to death or major lower limb amputation, whichever occurs first. Because the goal with any type of intervention for ALI is to save both limb and life, this is an adequate outcome to measure. Both Kaplan-Meier estimates and Cox regression analyses were used to calculate amputation-free survival. In analyses of amputation-free survival there was no distinction between the two events and the *rate* and *risk* are equal because of the one-to-one correspondence.(Andersen 2012) The censored cases are "truly censored" (lost or end of follow-up). For the censoring to be correct, it needs to be independent of the outcome, implicating that patients who are censored at a given time point would have had the same future prognosis (i.e. they are neither 'sicker' nor 'healthier') as those who remained in the study beyond that time point.(Wolbers 2014)

Because amputation-free survival only addresses the event that occurs first, all results for amputations and death are reported separately throughout the thesis so that readers can interpret all this information. The mortality rates

presented are all-cause mortality rates and are not exposed to any competing risk: because you can only die once, the *rates* and *risk* are equal. This is not true, however, for the amputation rates in which the risk of death is a competing risk (only living patients are at risk of amputation). Some studies have shown that standard survival analysis (Kaplan-Meier and Cox regression) methods overestimate the risk of amputation in this patient population, where the risks of amputation and death are not independent of one another and where most patients have a high risk of death from old age and multiple comorbidities.(Heikkila 2018) Patients that die without amputation are censored from the analysis. This censoring, however, does not discriminate between "truly censored" cases in which the patients are still at risk of amputation and cases that are censored because of death. This lack of discrimination may lead to an over-estimation of amputation risk. Consequently, it is important to clarify "numbers at risk" so that this information is accessible.

Kaplan-Meier survival estimates should not be used for risk estimation in the presence of competing risks. The survival analyses used to describe amputation only describes amputation rates and should not be confused with the risk of amputation.

Swedvasc

The Swedvasc Registry was used for identification or collection of data in all of the papers in this thesis. For paper I and II, the local Swedvasc Registry was employed to identify patients that had been treated in Uppsala during the period of interest, whereas Malmö had a separate endovascular registry that was thought to be more reliable. Thereafter, a manual chart review was performed for all patients included in the studies. Papers III and IV consist of information collected from the Swedvasc database combined with information from the Swedish Population Registry and the Swedish Patient Registry.

The Swedvasc Registry has been externally validated (for completeness, comparing with other databases), showing that more than 95% of all vascular operations have been registered prospectively.(Lees 2012, Troeng 2008, Venermo 2015) The registry has also been internally validated (for accuracy of data).(Bergqvist 1998, Kragsterman 2006, Ravn 2007, Bergqvist 2007).

Some explicit benefits that can be gained by the use of Swedvasc are as follows: It is an easy way to identify patients with a specific vascular surgical treatment or disease with high accuracy. In paper III, Swedvasc offers a unique opportunity to study a large population-based cohort of unselected patients. In paper IV, it was possible to study patients and treatments for a rare disease where it otherwise would have been difficult to collect a purposively large patient cohort.

There are also some drawbacks with the use of registry data. The Swedvasc database has been updated a few times when variables have been adjusted. This updating process results in several separate databases that have to be merged into one to enable analysis. As already mentioned, the latest Swedvasc edition simplified the variable set for ALI in favour of other registration aspects (in particular, AAA, carotid procedures and PAD) and removed the distinction between embolus and thrombosis (although PAA was registered even more specifically in a separate module).

One further limitation that has already been mentioned in the discussion is the documentation in Swedvasc of the aethology causing the occlusion. It is most often the responsible (the most experienced) surgeon who registers the aetiology in the Swedvasc Registry at the same time as the surgeon dictates the operative report. Thus, it is not an administrator or a nurse as in many other quality improvement registries. The assessment is based on an overall evaluation of the patient, including radiologic imaging of the arteries, patient history (e.g., history of claudication if the patient has atrial fibrillation, recent history of myocardial infarction involving the left ventricle) and intraoperative findings.

The description of the variable “heart disease” changed in the update of Swedvasc in May 2008: from this edition of Swedvasc, “atrial fibrillation” is no longer included in the variable “heart disease”. This change explains the drop in frequency of heart diseases that can be seen between 2007 and 2009.

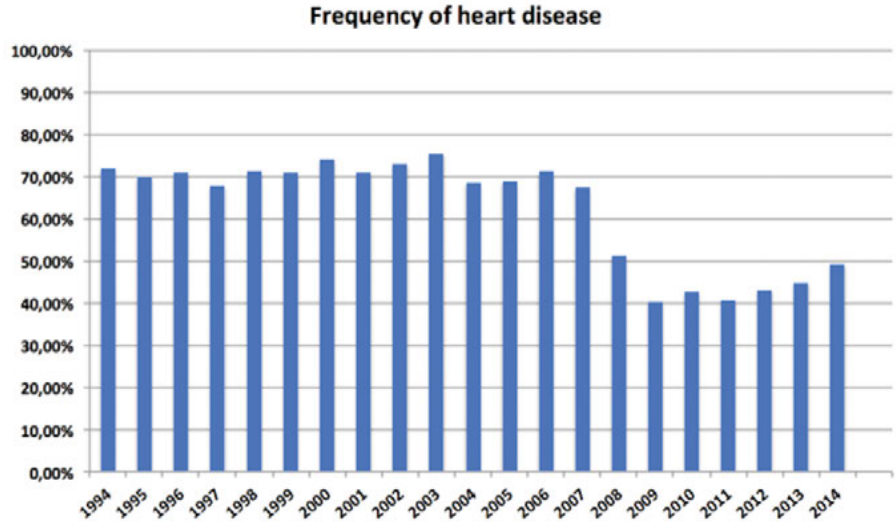

Figure 20.

The change in the definition of heart disease is not believed to have affected any of the primary or secondary outcomes. After the propensity score matching in paper III, the frequency of heart disease was equal between the two treatments groups and the times were also equally distributed. Irrespective of this, the frequency of cardiovascular disease-related death has decreased in Sweden during the past two decades.(Cause of Death Registry, Dödsorsaksregistret, Socialstyrelsen 2018)

Conclusions

- Paper I compared the results from thrombolysis with and without continuous heparin infusions in 749 thrombolytic procedures and concluded that both treatment strategies were equally successful in achieving revascularisation, with acceptable complication rates for both strategies. Continuous heparin infusion during intra-arterial thrombolysis offered no advantage.

- Thrombolysis achieved good medium- and long-term clinical outcome, which reduced the need for open surgical treatment in most patients. More than half of the patients in paper II did not require any surgical reintervention or amputation in their remaining lifetime or until the end of follow-up after a mean of 74.1 months.

- Long-term outcome differed between the aetiological groups. Five years after thrombolysis, the group with occluded graft/stent/stentgrafts had inferior amputation-free survival, whereas occluded PAAs had better survival and embolic occlusions had better amputation rates.

- In paper III, primary endovascular treatment of ALI was associated with significantly better short-term survival and amputation-free survival compared with primary open revascularisation.

- Embolic occlusions below the aortic bifurcation that were treated with endovascular revascularisation have a favourable outcome, as demonstrated in paper I, II and III.

- Paper IV showed that the mortality after AAO remains high but has improved over time. The proportion of AAO secondary to occluded graft/stent/stentgrafts increased over time, which is a result of the endovascular shift in treating aortic diseases. In addition, the proportion secondary to native artery thrombosis decreased, which might be a result of improved smoking habits.

- Both short- and long-term survival was found to improve over time for patients with ALI, as confirmed in paper I, II, III and IV.

Future aspects of revascularisation for ALI

The lack of a modern consensus for recommendations for the treatment of ALI has led to variability in treatment practises, which partly grounds the background to the studies in this thesis. The European Society of Vascular Surgery has initiated a process of developing clinical practice guidelines for the treatment of ALI to be published in late 2019. It is with great anticipation that I and others look forward to seeing how these guidelines will affect the treatment of ALI in the future.

ALI is a condition threatening both limb and life. Thankfully, intensive research to improve the treatment for these patients is conducted globally at several innovative research institutes.(Comerota 2009) Researchers in the Netherlands are currently investigating whether it is possible to enhance the effect of thrombolysis by the use of microbubbles as a carrier for fibrinolytic agents.(Ebben 2015, Nederhoed 2017) Microbubbles target and adhere to the thrombus. Theoretically, it would be possible to deliver the thrombolytic medication locally following simple intravenous injection and thereby making thrombolytic treatment less invasive on the one hand, and more precise on the other. An even further acceleration of clot lysis can be achieved by using ultrasound contrast agents.

The ultrasound waves alter the morphology of fibrin, allowing greater penetration and surface exposure of the fibrinolytic agent, which would accelerate the lysis process.(Tiukinhoy-Laing 2007, Wissgott 2007) The Dutch studies have showed promising results of combining intravenously administered microbubbles with locally applied ultrasound in animal models in acute peripheral arterial occlusion.(Ebben 2015, Nederhoed 2017)

Other researchers focus on developing a new class of pharmacologic lytic agents that acts directly on the thrombus (not via the plasminogen enzyme system). These agents appear to act more rapidly than traditional plasminogen activators and are immediately neutralised upon entering the systemic circulation.(Marder 2012, Shlansky-Goldberg 2008)

Revascularisation by itself does not ensure successful outcome in patients with ALI, and especially patients with AAO in which large body parts are affected. Paradoxically, many patients die as a consequence of the reperfusion injury that occurs after revascularisation of one or both acutely ischaemic limbs. Experimental studies have shown promising results for controlled reperfusion after acute ischaemia with reduced manifestations of reperfusion injury.(Beyersdorf 2009, Vogt 1996) To further reduce the mortality associated with ALI and AAO future research efforts should be directed towards the ability to modulate ischaemia, reperfusion injury and cascades of physiologic insults.

Populärvetenskaplig sammanfattning

Årligen drabbas hundratals personer i Sverige, både män och kvinnor, av plötsligt cirkulationsbortfall i ett eller båda benen. Detta kallas akut ischemi och orsakas av en blodpropp i något av de större syreförsörjande kärlen i benen. Det uppstår då en skadlig syrebrist i vävnaden nedströms om blodproppen, ett tillstånd som är akut och som utgör ett hot mot både liv och lem. För att rädda benet och patienten krävs att blodproppen avlägsnas så att cirkulationen återställs. Personer som drabbas av akut extremitetsischemi är ofta äldre med flera andra sjukdomar i bagaget som man måste ta hänsyn till vid val av behandling. Idag finns det nämligen flera olika behandlingsalternativ att tillgå.

Traditionellt sett har dessa patienter behandlats med öppen kirurgi, då man kirurgiskt avlägsnat blodproppen på en sövd patient. Under de senaste decennierna har dock nya och möjligen skonsammare behandlingsalternativ utvecklats. Genom att enbart göra en punktion i ett ytligt blodkärl kan man via kärlsystemet ta sig fram till blodproppen och med hjälp av olika verktyg avlägsna blodproppen, samlingsnamnet för den här typen av ingrepp är *endovaskulär kirurgi*. *Trombolysbehandling* är ett sådant behandlingsalternativ som innebär att man lokalt i blodproppen lägger en slang och deponerar en hög koncentration av ett propplösande läkemedel. Behandlingen kräver bara ett litet ingrepp och kan utföras i lokalbedövning. Då patienten inte behöver var sövd innebär det en mindre påfrestning för kroppen och även skörare individer kan komma ifråga för behandling jämfört med öppen kirurgi. En nackdel är dock att det kan ta längre tid att återställa cirkulationen än med öppen kirurgi. Trombolysbehandling är heller inte riskfritt, en fruktad komplikation som kan uppstå är blödning, särskilt hjärnblödning. Detta gör att patienterna kräver noggrann övervakning under behandlingen som därför är behäftad med en del arbete och kostnader.

Syftet med studierna var att kartlägga patienter med akut extremitetsischemi för att öka kunskapen om denna patientgrupp samt att studera olika behandlingsalternativ. Studierna bygger på journalgenomgång av inkluderade patienter och/eller registerdata från det svenska kärlkirurgiska registret.

I den första studien jämförde vi resultaten efter trombolysbehandling med och utan samtidig tillförsel av ett blodförtunnande läkemedel, heparin. Samtidig administrering av ett blodförtunnande läkemedel kan potentiellt förstärka effekten av trombolysbehandling men samtidigt öka risken för blödningskomplikationer. Det finns inga större studier som undersökt detta och det saknas entydiga behandlingsriktlinjer för trombolysbehandling, vilket gör att olika sjukhus har utvecklat olika rutiner.

Vår studie visade att båda behandlingsstrategierna hade likvärdiga resultat gällande grad av lyckad behandling, amputationer, död och amputationsfri överlevnad. Det fanns en trend som pekade mot mer blödningskomplikationer vid samtidig administrering av blodförtunnade läkemedel. Detta gjorde att vi drog slutsatsen att tillförsel av blodförtunnande läkemedel under trombolysbehandling inte ger några fördelar för resultatet av behandlingen och att tid och resurser därför kan användas på bättre sätt.

I den andra studien tittade vi på långtidsresultaten efter trombolysbehandling. De flesta tidigare studier gällande trombolysbehandling har presenterat resultat för 1-månad och ibland 1-års uppföljning. Vi ville nu studera hur resultaten efter trombolysbehandling ser ut på lång sikt och hur vanligt det är att patienterna behöver ytterligare kirurgi i aktuellt kärlområde (hur länge kärlen förblir öppetstående). Materialet delades även in i mindre grupper beroende av vilken bakomliggande sjukdom som orsakat blodproppen, detta för att studera hur det påverkar långtidsresultatet av trombolysbehandling.

Resultaten från studien visade att trombolysbehandling har goda medel- och långtidsresultat. Färre än hälften av patienterna var i behov av ytterligare behandling under resterande livstid eller under uppföljningstiden (medel 6,2 år). Behandlingsresultaten skilde sig åt beroende av bakomliggande orsaken till blodproppen, något som bidrar med ny information och som bör värderas då man väljer behandlingsstrategi för olika patientkategorier.

På 90-talet publicerades tre randomiserade kontrollstudier som visade på minst likvärdiga resultat för trombolysbehandling som för öppen kirurgi. Sedan publiceringen av dessa studier har den endovaskulära tekniken dock utvecklats mycket. Bilddiagnostiken av blodproppen har förbättrats, utrustningen och tekniken har förfinats och idag används inte heller samma propplösande läkemedel som användes i dessa studier. Motsvarande större randomiserade studier som jämför öppen kirurgi med den förbättrade endovaskulära tekningen saknas.

I den tredje studien ville vi göra en större nationell registerstudie och inkludera alla patienter som behandlats för akut extremitetsischemi i hela Sverige under en 21-års period för att kunna jämföra resultaten efter öppen och en-

dovaskulär behandling. I denna studie inkluderades mer än 16 000 patienter och avancerade statistiska metoder användes för att skapa jämförbara grupper.

Resultaten från den tredje studien visade att patienterna som behandlats med endovaskulär behandlingsteknik hade samma risk för amputation men signifikant bättre korttidsöverlevnad jämfört med öppen kirurgi. Vi tolkade resultatet så att den endovaskulära, mindre invasiva metoden, är bättre för dessa ofta gamla och svårt sjuka patienter.

I det fjärde delarbetet i avhandlingen studerades patienter med akut blodpropp i aorta (Stora kroppspulsådern). När proppen sitter högre upp i kärlsystemet stänger den av cirkulationen till båda benen samtidigt. Tillståndet är ovanligt och mycket allvarligt, patienter med detta tillstånd har en mycket hög dödlighet då stora delar av kroppen drabbas av akut syrebrist och celldöd. Eftersom tillståndet är ovanligt har det varit svårstuderat och de studier som finns i området inkluderar bara ett fåtal patienter. Det fjärde arbetet är en observationsstudie där vi studerade en större patientgrupp med akut propp i aorta än som någonsin tidigare studerats, total 715 patienter. Syftet var att öka kunskapen om detta ovanliga tillstånd samt att studera behandlingsalternativ.

Studien visade att dödsiffran för den här patientkategorin är fortsatt hög, men ändå har förbättrats de senaste decennierna. Stopp i tidigare kärlrekonstruktioner blir en allt vanligare orsak till akut propp i aorta, detta troligtvis sekundärt till att aortasjukdom allt oftare behandlas med endovaskulära metoder.

Sammanfattningsvis så har studierna i denna avhandling visat att endovaskulära behandlingstekniker för akut extremitetsischemi blir allt vanligare, och med fördelaktiga resultat. Framförallt påverkar val av behandlingsmetoden överlevnaden för denna sköra patientkategori. Under de senaste decennierna har både kort- och långtidsöverlevnaden förbättrats för patienter med akut extremitetsischemi.

Acknowledgment

I would like to express my sincere gratitude to all those who have contributed to this thesis. I would like to extend special appreciation to:

Professor **Martin Björck,** for your great work ethic and being a superb supervisor. You have introduced me to the field of medical research and been an awesome inspiration with your commitment, enthusiasm and sharp intellect. After our meetings, I invariably felt a wave of new energy and desire to delve into the information-rich and objective world of scientific research. You have not only been invaluable to this thesis work but also to my future medical and scientific career. When we did not discuss science, you generously shared many of your personal stories from around the globe. Thus, in your company there was never a boring moment.

My co-supervisor and head of the section of Vascular Surgery Professor, **Anders Wanhainen,** thank you for your never-ending support and constructive criticism. Your valuable comments often made me see problems in a new perspective. Thank you for being a great leader of the vascular team.

Professor **Stefan Acosta,** for intriguing scientific discussions, sound advice and excellent comments. I would also like to extend my thanks for allowing me to use your office while working on the project in Malmö.

My co-authors, **Monica Kuoppala, Jonas Åkeson, Karl Mikaëlsson** and **Lars Lindhagen,** for your valuable contributions to the studies that made up this thesis. Thank you for increasing the overall quality of the work and the very engaging and thoughtful discussions about science and statistics.

Lars Lindhagen for being a very competent statistician and introducing me to advanced statistical methods.

The Swedvasc Registry, my gratitude goes out to all those wonderful people that work with the registry and to all vascular surgeons that diligently register each and every patient. Your work enabled the studies to be carried out and greatly enhanced their quality.

Claes Juhlin, former head of the Department of surgery at Uppsala University Hospital, and **Kristiina Kask**, present head of the department, and **Per Hellman**, head of the Department of surgical sciences, for providing me with resources and conditions to complete this thesis.

The financial support from **Bergholm's fund**, **Makarna Eriksson's fund**, **Swedvasc's research fund** and from **ALF-Uppsala:** your contributions made this work possible.

Camilla Hartman at UCR. Anyone that has requested data from a national registry knows that this is a complex procedure that takes time. Thank you, Camilla, for your help and effort to make this a smooth and relatively speedy process.

My colleagues, **Kevin Mani, Gustaf Tegler, Christer Ljungman, Baderkan Hassan, Achilleas Karkamanis, Marek Kuzniar, Demos Dellagrammaticas, Jon Unosson, Jacob Eriksson, Kalle Sörelius** and **Tina Hellgren**. Thank you for your help, support, tender counsel, friendship, joyful moments and for helping me to better understand just how amazing vascular surgery can be.

Leslie Shaps, for your expertise in the English language and improving the manuscripts of this thesis.

Faud Bahram, for your competence in graphic design and providing the wonderful cover picture.

My **colleagues and the staff** at the Department of Surgery at Uppsala University Hospital and vascular unit for providing continuous support and encouragement.

Världens bästa **Mamma Annette**, utan dig hade det inte blivit mycket av den här avhandlingen eller av mig överhuvudtaget. Tack för det oändliga engagemang och tid som du har lagt ned på att få rätsida på mig. Det finns inte ord nog för att beskriva vad du betyder för mig, du är min största förebild och min bästa vän.

Pappa Dan. Det är nog inte fel att säga att den här boken började med dig. För det var när jag som liten fick följa med dig till ditt lab. hela denna spännande värld av forskning öppnades för mig. Och våra äventyr med fallskärmshopp, resor, dykning och klättring har gett mig modet som ibland krävs för att våga påbörja något sånt här. Och du har inspirerat mig i flera av mina livsval Tack för det!

Mina storebröder **Jonathan** och **Fredrik** som har lärt mig innebörden av uttrycket ”tough love”. Att växa upp med ert kärleksfulla beskydd har gett mig skin på näsan, men också det självförtroende och den trygghet som gjort mig till den person jag är idag.

Min **Mormor Christina.** När man i Spanien säger att en person ”vuxit upp utan en mormor”, då menar man att det är skrytsam person, som aldrig hört någon annan skryta om den. Och jag förstår så väl vad som saknats. För min mormor har från den dagen som jag föddes alltid har varit mitt största fan. Hon har alltid överöst mig med kärlek och talat om för mig hur fantastisk jag är och att det inte finns något som jag inte kan klara av. Med sådan support är det inte konstigt om man kommer långt!

Familjerna **Grip** och **Gryth** för stöd, kärlek och support.

Robin Ström Mörnås som stöttat mig under en stor del av arbetet med den här avhandlingen. Du har alltid uppmuntrat och trott på mig samtidigt som du tagit bort mycket av bruset omkring mig så att jag kunnat fokusera på forskningen. Du har betytt väldigt mycket för mig. Tack!

Fredrik Vedung för viktig vänskap och roliga stunder. Tack för hjälp med illustration av omslaget och figurer i avhandlingen.

Mina fantastiska tjejkompisar **Sofia, Mikaela, Jenny, Liv, Maja** och **Katharina** som alltid kan få mig att skratta. Ni har bidragit med så mycket kärlek och livsenergi i livets ljusa, som såväl mörka, stunder.

Hundarna **Domino** och **Furbo,** och katten **Lakriz** som alltid har bidragit med villkorslös kärlek och sett till att jag tagit välbehövliga pauser.

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