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Popliteal Artery Aneurysms
- epidemiology, treatment and results

ANNE CERVIN
Abstract

Popliteal aneurysms (PA) are limb threatening, since the aneurysm thrombose and emboli from the aneurysm sac occlude the distal vessels, resulting in chronic or acute limb ischaemia. Open surgical repair (OSR) has been challenged by endovascular repair (ER), a minimal invasive technique. Little is known of long-term result, and comparisons of the methods have been difficult, since patients chosen for ER are mainly asymptomatic and have better outflow.

The overall aim of this thesis was to study epidemiology and risk factors to optimize patient selection and techniques for surgical treatment of PA.

Papers I and II: Data on all patients treated 2008-2012 (592 PAs in 499 patients) were analysed in the Swedish Vascular registry, Swedvasc. Patency was inferior after ER, in particular for patients with acute ischaemia. Nested in this cohort, a case-control study was performed, and the legs treated by ER (77) were matched, by indication, with twice the number treated with OSR (154). Medical records and radiologic images were collected and examined in a core-lab. In this matched cohort, the only independent risk factors for occlusion were ER and poor outflow. In a sub-group analysis of ER, risk factors for occlusion were acute ischaemia, poor out-flow, smaller stent graft diameter and elongation.

Paper III: Prevalence of PA was studied in men, screened for abdominal aortic aneurysm (AAA) and of sub aneurysmal aorta, 25-29 mm. Prevalence of PA was high, 14.2%, and correlated with dilatation of the iliac arteries.

Paper IV: Operations for ruptured PA (rPA) were identified in Swedvasc 1987-2012, medical records were reviewed. Compared with patients treated for other indications, they were 8 years older, had twice as large aneurysms (mean 64 mm) and many were treated with anticoagulants. The initial clinical picture was misleading.

In conclusion, when treating PA the preferred surgical technique is OSR with a vein graft. Anatomical features of the popliteal artery and outflow vessels affect outcome. These findings are important for future surgical decision making.

Keywords: Popliteal artery aneurysms, Endovascular, Open surgery, Outcome, Occlusion, Screening, Prevalence, Rupture

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urn:nbn:se:uu:diva-381534 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-381534)
To my family, who will always make sure that I keep track on what is most important in life.
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


II Cervin A, Acosta S, Hultgren R, Bjorck M, Falkenberg M. Favourable results after open compared to endovascular repair of popliteal aneurysm: a nested case-control study (Submitted manuscript)

III Cervin A, Bjorck M. Popliteal aneurysms are common among men with screening detected abdominal aortic aneurysms, and the prevalence is correlated with the diameters of the common iliac arteries. (Submitted manuscript)


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Cover pictures:
Front: Figuration of a popliteal aneurysm by Gunvor Pommer
Back: Imaging of a popliteal artery aneurysm
Contents

Introduction .................................................................................................................. 10
Anatomy ....................................................................................................................... 10
Epidemiology and Definition ....................................................................................... 10
Clinical manifestations of a popliteal artery aneurysm ............................................. 11
Indications for invasive treatment ............................................................................. 12
Surgical Treatment of PA ............................................................................................ 13
  Treatment of acute thrombosed PA ......................................................................... 13
  Definitive treatment by open surgery ....................................................................... 13
  Definitive treatment by Endovascular surgery ...................................................... 14
  Endovascular versus open repair ............................................................................ 15
Aims .............................................................................................................................. 16
Patients and Methods ................................................................................................. 17
  Study design ............................................................................................................ 17
  Registries ................................................................................................................. 17
    The Swedvasc registry .......................................................................................... 17
    SweAAA ............................................................................................................... 18
  Identification of patients and methods .................................................................. 18
    Paper I .................................................................................................................... 18
    Paper II ................................................................................................................. 20
    Paper III .............................................................................................................. 22
    Paper IV .............................................................................................................. 23
Ethical considerations ................................................................................................. 24
Statistics ..................................................................................................................... 25
Results ......................................................................................................................... 26
  Paper I ....................................................................................................................... 26
    The acute ischaemia group ................................................................................. 27
    The elective symptomatic group ........................................................................ 28
    The asymptomatic group .................................................................................... 29
    Open repair .......................................................................................................... 30
  Paper II ..................................................................................................................... 31
    Demographics, comorbidities and medication .................................................... 31
    Surgical details .................................................................................................... 31
    Anatomical characteristics .................................................................................. 31
    Outcomes ............................................................................................................. 31
Paper III .................................................................................................................. 35
Screening.................................................................................................................. 35
AAA vs SAA ............................................................................................................. 35
Popliteal artery diameter and popliteal aneurysms ................................................. 36
Correlations between vessel diameters and body surface area (BSA)..................... 37

Paper IV ................................................................................................................... 37
General discussion ................................................................................................... 40
Introduction .............................................................................................................. 40
Epidemiology of PA .................................................................................................. 41
Correlations between PA and vessel diameters in other segments ....................... 42
Results after treatment ............................................................................................ 42
Result after treatment with ER or OSR ................................................................. 45
Ruptured popliteal aneurysms ................................................................................ 48

Conclusions .............................................................................................................. 50

Future research on popliteal aneurysms ................................................................. 51
Epidemiology ........................................................................................................... 51
Timely intervention .................................................................................................. 51
Results after treatment with ER and OSR ............................................................. 51

Acknowledgements ............................................................................................... 53

Populärvetenskaplig sammanställning på svenska ................................................ 55

References .............................................................................................................. 58
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAA</td>
<td>Abdominal Aortic Aneurysm</td>
</tr>
<tr>
<td>ABI</td>
<td>Ankle Brachial Index</td>
</tr>
<tr>
<td>ALI</td>
<td>Acute Limb Ischaemia</td>
</tr>
<tr>
<td>BSA</td>
<td>Body Surface Area</td>
</tr>
<tr>
<td>CFA</td>
<td>Common Femoral Artery</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CIA</td>
<td>Common Iliac Artery</td>
</tr>
<tr>
<td>CLI</td>
<td>Critical Limb Ischaemia</td>
</tr>
<tr>
<td>CTA</td>
<td>Computer Tomography Angiography</td>
</tr>
<tr>
<td>CVL</td>
<td>Cerebral Vascular Lesions</td>
</tr>
<tr>
<td>DAT</td>
<td>Dual Antiplatelet Therapy</td>
</tr>
<tr>
<td>DSA</td>
<td>Digital Subtraction Angiography</td>
</tr>
<tr>
<td>DUS</td>
<td>Duplex UltraSound</td>
</tr>
<tr>
<td>DVT</td>
<td>Deep Venous Thrombosis</td>
</tr>
<tr>
<td>ER</td>
<td>Endovascular Repair</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>IQR</td>
<td>Inter Quartile Range</td>
</tr>
<tr>
<td>LELE</td>
<td>Leading Edge to Leading Edge</td>
</tr>
<tr>
<td>LLA</td>
<td>Linear by Linear Association</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>OR</td>
<td>Open Repair (paper I and IV)</td>
</tr>
<tr>
<td>OSR</td>
<td>Open Surgical Repair (paper II)</td>
</tr>
<tr>
<td>PA</td>
<td>Popliteal Artery Aneurysm (paper I, II and III)</td>
</tr>
<tr>
<td>PAA</td>
<td>Popliteal Artery Aneurysm (paper IV)</td>
</tr>
<tr>
<td>PTA</td>
<td>Percutaneous Transluminal Angioplasty</td>
</tr>
<tr>
<td>rPA</td>
<td>ruptured Popliteal Aneurysm</td>
</tr>
<tr>
<td>RRT</td>
<td>Renal Replacement Therapy</td>
</tr>
<tr>
<td>SAA</td>
<td>Sub Aneurysmal Aorta</td>
</tr>
<tr>
<td>SAT</td>
<td>Single Antiplatelet Therapy</td>
</tr>
<tr>
<td>SFA</td>
<td>Superficial Femoral Artery</td>
</tr>
<tr>
<td>SweAAA</td>
<td>Database created in Uppsala for follow-up of screening detected AAA</td>
</tr>
<tr>
<td>Swedvasc</td>
<td>Swedish vascular registry</td>
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<tr>
<td>TI</td>
<td>Tortuosity Index</td>
</tr>
</tbody>
</table>
Introduction

Popliteal artery aneurysms (PA) are limb threatening with potential for occlusion, embolisation and, uncommonly, rupture. It is an uncommon disease and studies are mainly based on small numbers of patients who underwent elective surgery, and the understanding of the mechanisms leading to complications is poor. The approach to this disease has been surrounded by controversies.

Anatomy

In a patient with normal anatomy, the popliteal artery is defined as from where the femoral superficial artery passes through the adductor hiatus (also named the Hunter’s canal in English literature) to where the vessel branches into the anterior tibial artery and the tibio-fibular trunk (T Petrên, Lärobok i anatomi, 1936). It passes through the popliteal fossa, which also contains the popliteal vein, the small saphenous vein, the common peroneal and tibial nerves, the posterior cutaneous nerve of the thigh, the genicular branch of the obturator nerve, connective tissue, and lymph nodes. This is a confined space due to tendons and muscles. Morphological changes of the vessel will occur during knee flexion. There are changes in length, curvature, angulation and torsion\textsuperscript{1, 2}. In healthy individuals, the movement of the vessel will be most pronounced in the areas of Hunter’s canal and at the origin of anterior tibial artery, areas where the vessel is more fixed.

Epidemiology and Definition

There are very few studies on prevalence of PA in the healthy population. In a paper from 2002 it was estimated to approximately 1% in men of, the age 65-80 years\textsuperscript{3}. There is no consensus how to define a PA and a number of definitions were suggested in different reports: 50% larger than a normal diameter\textsuperscript{3, 4}, 15 or 19 mm in diameter\textsuperscript{3, 5}, 50% larger than the adjacent vessel (i.e. the distal superficial femoral artery, SFA) or 50% larger than the contralateral, non-aneurysmal artery\textsuperscript{5, 6}. The problem is that it is unknown how the risk for future complications and growth are associated with these different definitions.
The number of PA repairs differ much between countries. An assessment of eight countries participating in the Vascunet collaboration, and having data on PA, showed a range of operations between 3.4 and 17.6 per million inhabitants per year during 2009-2012. This report also demonstrated the great differences in indications for surgery: emergent, elective symptomatic or asymptomatic. In Hungary, only 26% were elective, while in Australia the same figure was 86%.

Pseudoaneurysm is a dilation of an artery caused by injury to one or more layers of the artery. The popliteal artery can be injured during an accident (e.g. fracture or dislocation of the knee area) or secondary to surgical trauma (e.g. catheterisation or during knee surgery). It is important to single out the true aneurysms from the false ones, as the fundamental mechanisms for complications and choice of treatment, are different.

PAs are associated with multi-anerysm disesease. At presentation, bilateral PAs are present in 46-68% and concomitant AAA in 33-40%. Patients with bilateral PAs have a higher frequency of AAA than those with unilateral PA. Screening for AAA was launched in Sweden 2006 and have achieved nationwide coverage. In many centres, a measurement of the popliteal artery has become routine at re-examination of the enlarged aorta.

**Clinical manifestations of a popliteal artery aneurysm**

PA can cause acute limb ischaemia (ALI) or critical limb ischaemia (CLI) either by thrombosis/occlusion of the aneurysm itself, and/or by embolisation to the vessels below. Sometimes occlusion of both the aneurysm and the distal outflow vessels of the lower leg explain the acute onset. This is a very challenging situation. Depending on collaterals and the extent of occlusion, symptoms range between temporary pain from embolisation that resolves, to occlusion with sudden claudication or severe ALI that needs prompt revascularisation.

Little is known about ruptured PA (rPA). It is a rare event, and in the literature, only case reports are found, with the exception of two case series of six patients each. Large aneurysms can compress the adjacent vein which will cause a slowly increasing swelling of the lower leg and sometimes be the cause of deep venous thrombosis (DVT). Pressure from a large PA or hematoma in the popliteal space has been described to cause neurologic pain distally in the leg, adding to the diversity of symptoms, and the difficulty to set correct diagnosis.
Indications for invasive treatment

During the 1970’s and 1980’s, there was a debate if a conservative or a more aggressive surgical approach was appropriate for patients with asymptomatic PA. When presenting with acute ischaemic symptoms, there was a high frequency of amputations, 13-36%\textsuperscript{12, 20-22}. In earlier studies, patients with asymptomatic PA were more often managed conservatively and developed symptoms in 29-60%, see Table 1. There was, and still is, a higher risk of amputation in patients treated emergently (both in the acute setting and due to inferior patency at follow-up\textsuperscript{23-25}), and a more active approach was accepted. What criteria should justify intervention remained controversial. Size is easily measured and has some correlation with risk for thrombosis, but other mechanisms are poorly understood. Logically, size should reflect the risk of rupture. Rupture, however, is the indication for repair in only 2–4% of those treated\textsuperscript{13, 15} and little is known about this subgroup. In some studies, diameter less than 2 cm is associated with a lower incidence of complications (0–9%)\textsuperscript{21, 22, 26}. Acute complications in patients with small aneurysms were reported\textsuperscript{13, 27}. Galland and Magee, on the other hand, reported that a diameter \( \geq 3\) cm, in combination with a distortion of more than 45 degrees, was associated with ALI\textsuperscript{28}. Thus, the risk factors for acute complications of PA are not yet sufficiently investigated.

Table 1. Risk of amputation and complications after conservative management of asymptomatic PA

<table>
<thead>
<tr>
<th>Year of publication</th>
<th>No of PAs</th>
<th>Mean follow-up (months)</th>
<th>Major amputations N (%)</th>
<th>Complications (%)</th>
<th>Diagnostic method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gifford et al\textsuperscript{29}</td>
<td>1953</td>
<td>68</td>
<td>44</td>
<td>11 (16)</td>
<td>23 (33)</td>
</tr>
<tr>
<td>Wychulis et al\textsuperscript{20}</td>
<td>1970</td>
<td>94</td>
<td>41</td>
<td>3 (3.4)</td>
<td>27 (29)</td>
</tr>
<tr>
<td>Vermillon et al\textsuperscript{12}</td>
<td>1981</td>
<td>26</td>
<td>36</td>
<td>2 (7.8)</td>
<td>8 (31)</td>
</tr>
<tr>
<td>Szilagy et al\textsuperscript{23}</td>
<td>1981</td>
<td>28</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Whitehouse et al\textsuperscript{21}</td>
<td>1983</td>
<td>32</td>
<td>25</td>
<td>2 (6.3)</td>
<td>3 (9.4)</td>
</tr>
<tr>
<td>Anton et al\textsuperscript{25}</td>
<td>1986</td>
<td>13</td>
<td>66</td>
<td>2 (15)</td>
<td>4 (30)</td>
</tr>
<tr>
<td>Schellack et al\textsuperscript{26}</td>
<td>1987</td>
<td>26</td>
<td>37</td>
<td>0</td>
<td>2 (7.7)</td>
</tr>
<tr>
<td>Roggo et al\textsuperscript{10}</td>
<td>1993</td>
<td>45</td>
<td>50</td>
<td>2 (4.4)</td>
<td>45 (100)</td>
</tr>
<tr>
<td>Dawson et al\textsuperscript{30}</td>
<td>1994</td>
<td>42</td>
<td>64</td>
<td>3 (7.1)</td>
<td>25 (60)</td>
</tr>
</tbody>
</table>

DUS = duplex ultrasound; Ai= angiography; ClinEx = Clinical examination; OPm= per-operative measurement. Complications: occlusion, embolization, compression
Surgical Treatment of PA

When treating PA, in an acute, chronic or prophylactic setting, the intention is to exclude the PA from the circulation and restore adequate perfusion to the lower leg.

Treatment of acute thrombosed PA

The outcome, when treating acute thrombosed PA, is dependent on the outflow. If the vessels of the lower leg are occluded, outflow can be improved either by open embolectomy, or by catheter-led thrombolysis. The main goal is not to open up the PA, but to improve the run-off. Thrombolysis is effective in restoring outflow, as it affects both large and small arteries, as well as arteriolar and capillary beds. It is also possible to further improve the outflow by PTA if there is a stenosis. Some concern however, is the possible side effects of thrombolysis, the worst being intracranial haemorrhage or so-called trash foot from the thrombus in the reopened PA embolising to the arteries of the foot. If the ischaemia is severe, the effect of thrombolysis takes too long, and OSR must be performed promptly. Whichever method is used, the next step is definitive surgery to exclude the aneurysm, to prevent further embolisation, and to permanently restore circulation to the lower leg.

Definitive treatment by open surgery

The modern history of treatment of popliteal aneurysm starts in 1785 with John Hunter’s classical operation in London, UK, with proximal ligation of the aneurysm. In the early 20th century, endoaneurysmoraphy was described by Matas, in New Orleans, USA. In 1947, Blackmore presents a technique of using a vein inlay graft for the repair of arterial aneurysm, with a posterior approach in four legs. This remained the most commonly used technique throughout the 1950’s. In 1969 the medial approach, with bypass and proximal and distal ligation of the PA was first described in six patients. This method became, and remains, the most common operation.

Reports of aneurysmal sack growth, due to endoleak, led to re-evaluation of the posterior approach and it has regained in popularity. Comparing the results in patency after medial and posterior approach is complicated as the medial approach can be used when the aneurysm extends into the superficial femoral artery, above the adductor canal (Hunter’s canal), which is not feasible with the posterior approach. Evaluations, considering these aspects, have not shown any significant differences in patency rates, but a recent meta-analysis only comparing methods, advocates posterior approach.
Striking in these comparisons, however, is the inferiority of a synthetic graft compared with a vein. At three years, the patency was 67% vs. 87% in Kropman’s study, Huang reports 5-year secondary patency of 63% vs. 94% and these differences are enhanced when the indication for surgery is ALI.

There are occasional reports on a risk to develop vein graft aneurysms, counteracting the advantage of superior patency after having used a venous graft. The risk to develop vein graft aneurysms seems to be greater if the vein is duplicated or spiralized in order to address the difference in diameter between the often ectatic popliteal artery and the vein (unpublished data).

**Definitive treatment by Endovascular surgery**

Palmaz stents combined with a polytetrafluoroethylene graft was first used to treat an asymptomatic PA in 1994. As the technique has evolved, so have the stent grafts, and in the beginning of the 2000, the most commonly used stent graft was Hemobahn, (GORE®) a stent graft with high radial force and flexibility. The next generation was Viabahn endoprothesis (GORE®) with heparin bound to the inner surface, which has been the most commonly used stent graft in later studies.

In recent years, investigators reported results after endovascular treatment with stent grafts. There are great variations in how frequently those were used, between hospitals and countries. In Finland and Switzerland, according to the aforementioned Vascunet report, no stent graft was applied; whereas in Australia, the proportion was 35% and in Sweden 30%. The Society for Vascular Surgery Vascular Quality Initiative (SVS-VQI), a registry including 290 centres in the USA and Canada, reported an increase of endovascular repair from 35% in 2010 to 48% in 2013.

Questions remain about the durability of stent graft treatment for PAs, and in which patients endovascular treatment should be used. There is one randomised controlled trial (2005) that compared open and endovascular repair; it included 30 legs, and reported 100% secondary patency at one and three years of all assessed legs. It included patients with asymptomatic PAs with a high run-off score.

In recent years, larger studies of 50-134 legs were published and long-term results after treatment were reported. These studies report primary patency rates of 70–93% and secondary patency rates of 88-94% at one year. After two years, primary and secondary patency rates are between 76-79% and 86-90%, respectively and at three years, 60-82% and 79-88%, respectively. At two years of follow-up, most series include only half of the patients, and at three years only three studies evaluate half of the patients. In larger
series, with longer follow-up, the occlusion rate is high, 16-36%, but the amputation rate is low. Of the 27 occlusions in Golchehr’s study, 48% developed ALI. Thrombolysis was used in seven, four were converted to bypass and two were treated by embolectomy. There seems to be a learning curve, however, and better results over time are reported with newer stent grafts and dual antiplatelet therapy.

The studies are heterogeneous concerning the indication for surgery with a majority of asymptomatic PAs. Poor run-off (i.e. no run-off or only one open crural vessel) is reported consistently to be a risk factor for worse outcome after endovascular repair.

Endovascular versus open repair
Attempts have been made to identify when endovascular could be a better option than open repair. In a study from the US Medicare administrative database, including 2,962 patients, endovascular treatment showed no benefit in terms of mortality or cost, but was associated with more reinterventions over time.

A Markov model study suggested that even if open surgery with vein was the preferred strategy overall, patients at high risk for open surgery should be considered for endovascular repair. A more recent meta-analysis from 2017, including 14 studies, and >4500 PAs concluded that ER has a lower frequency of wound complications and shorter length of hospital stay compared with OSR, which is expected. This came with the cost of inferior primary patency, however, but no difference in secondary patency up to three years. However, in both studies, the groups of OSR and ER were not comparable in terms of indications or outflow, as patients chosen for ER had better outflow and were asymptomatic to a higher degree. Some data suggest that patency is inferior after emergent repair.
Aims

The overall aim of this thesis is to optimize patient selection and techniques for surgical treatment of PA.

Specific aims were:
• To describe time trends in surgery of PA, (Paper I)
• To compare results after treatment depending on indication for surgery. (Papers I and II)
• To compare results after endovascular or open surgery. (Papers I and II)
• To identify risk factors influencing outcome after endovascular and open surgery (Papers I and II)
• To identify what anatomical features will have impact on outcome after endovascular surgery (Paper II)
• To study the prevalence of PA among patients with AAA and SAA (Paper III)
• To study the characteristics of patients with ruptured PA, comparing this small sub-group to the larger group of patients treated for PA with other indications than rupture (Paper IV)
Patients and Methods

Study design

The study designs of the four papers are summarized in Table 2. In Paper I, II and IV the patients were extracted from Swedvasc and supplementary data was acquired from case records and imaging. In paper III the patients and data were prospectively collected in SweAAA.

Table 2. Study designs of papers I, II, III and IV

<table>
<thead>
<tr>
<th>Design</th>
<th>Patients</th>
<th>Source</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper I Retrospective national cohort study</td>
<td>N 592 with PA</td>
<td>Swedvasc, cross-checked by a protocol</td>
<td>Contemporary results of treatment</td>
</tr>
<tr>
<td>Paper II Nested randomised case-control study</td>
<td>N 231 with PA</td>
<td>Medical records, radiologic imaging</td>
<td>Comparison of ER and OSR in matched groups</td>
</tr>
<tr>
<td>Paper III Prospectively collected population-based study</td>
<td>N 322 with AAA or SAA</td>
<td>SweAAA</td>
<td>Prevalence of PA and correlation to diameters of other vessels</td>
</tr>
<tr>
<td>Paper IV Retrospective national cohort study</td>
<td>N 45 with rPA</td>
<td>Swedvasc, medical records</td>
<td>Characteristics of rPA</td>
</tr>
</tbody>
</table>

Registries

The Swedvasc registry

The Swedish vascular registry, the Swedvasc, was created in January 1987, and since 1992 has registered more than 90% of open and endovascular vascular surgical procedures in Sweden\(^{55, 56}\). From 1994, patients operated on for PA could be singled out by the specific procedure code (PFG10). A large number of variables are registered prospectively such as preoperative risk factors, comorbidities, indication for surgery, anatomic in- and out-flow,
type of operation and graft. Survival, complications, patency, and amputations are registered at 30 days and one year.

In May 2008, the registry was thoroughly revised and specific modules were created for different standard operations, based on the indication for surgery. One such set of modules was created for infra-inguinal arterial procedures, with PA as one specific indication. All procedures for PA, open or endovascular, confined to the popliteal fossa or extending into the superficial femoral artery and/or the crural vessels are registered in this specific module.

Definitions of comorbidities were as follows; hypertension and diabetes were present if the patient were pharmacologically treated; CVD was if the patient had had a TIA, cerebral insult or bleeding; lung disease was symptomatic chronic obstructive pulmonary disease, emphysema or other chronic pulmonary disease; smoking habits at time of surgery; heart disease was earlier myocardial infarction, congestive heart failure, earlier heart surgery or endovascular intervention; renal dysfunction was defined as a serum creatinine >150mmol/l or on RRT (renal replacement therapy).

SweAAA
A general AAA screening program for 65-year-old men was introduced in Uppsala County 2006. Data from this program was prospectively collected in SweAAA, a registry of detected aortic aneurysms. Initially, only patients in Uppsala County were included, but with time, several other hospitals have joined. Each hospital has full control over their data. In Paper III, only data from the Uppsala cohort is used. At the time of inclusion, comorbidities, length, height, smoking habits and family history of aneurysmal disease is registered. A special module was created for patients with SAA (sub aneurysmal aorta), an aorta measuring 25-29 mm. These persons are followed with a control DUS after five years.

Identification of patients and methods

Paper I

Hypothesis: Treatment modalities have changed over time. ER and OSR do not have comparable outcomes. Do the outcomes differ depending on indications for surgery?

In Swedvasc, 668 interventions for PA were registered between May 2008 and May 2012. Dual registrations such as pre-operative thrombolysis followed by aneurysm repair were identified in Swedvasc and merged. Yet,
there were still questions if the registrations included pseudoaneurysms and reoperations? Were all the preoperative thrombolysis procedures registered? Were the patients operated on with medial or posterior approach? To validate the registry data and to enable analysis of the details mentioned above, a short questionnaire was created and sent to the 30 hospitals that had treated and registered the patients, and an additional case record analysis was performed. After cross-checking, 86 interventions were excluded or merged with other registrations (for details, see paper I) Ten non-registered interventions on PA during the designated period were identified and added (10/592, 1.7%), seven of which were performed on the contralateral leg. In all, 592 procedures remained, of which 99.1% were supplemented and crosschecked by the questionnaire. Analyses of outcome were carried out with regard to indication and treatment modality. Follow-up was at 30 days and one year. From this dataset, the case-controlled study of paper II was derived, and the small cohort of rPA was extracted and complemented for paper IV. See Figure 1.

**Figure 1. Flow chart over paper I, II and IV**

There was a previous publication on PA, using data from the Swedvasc from the years 1987 to 2002. First author of these publications was Hans Ravn who is also a co-supervisor for this thesis. Original data from this study was used for comparison in Paper I, and as source for data in paper IV.
Paper II

Hypothesis: Anatomical features of the aneurysmatic vessels could explain the different outcomes after ER and OSR.

From the original national cohort in paper I, 54 legs (9.1%) were excluded (for details see Paper II). After these exclusions, 528 legs treated for PA at 29 hospitals remained for analysis.

Seventy-seven PAs (15%) were treated with ER. Twenty-five had acute ischaemia, 10 other symptoms and 42 were asymptomatic. The remaining 454 PA were treated with OSR. To allow a detailed comparison of ER vs. OSR with a reasonable number of legs to analyse, a nested case-control study design was used. For three groups of PA treated with ER, each defined by the initial indication for the index procedure (acute ischaemia, symptomatic or asymptomatic), a corresponding group twice the size treated with OSR was randomly selected by a computer generated random permutation and choosing the first of the list of the randomly ordered legs. In total, 154 legs with matched indications constituted the OSR group.

Table 3. The number of PAs treated by ER and OSR in each group of indications in the case-control cohort

<table>
<thead>
<tr>
<th>Acute Ischaemia</th>
<th>Elective Symptomatic</th>
<th>Elective Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER 25</td>
<td>OSR 50</td>
<td>ER 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ER 42</td>
</tr>
</tbody>
</table>

For the 231 treated legs (77 ER, 154 OSR), medical records and radiologic images were requested from the hospitals. The images were sent to the core-lab in Gothenburg. Data on demographics, indications, procedural details, aneurysm diameter and medications were collected. Popliteal artery elongation was evaluated using preoperative imaging, including computer tomography angiography (CTA), Magnetic Resonance Imaging (MRI) and/or digital subtraction angiography (DSA). Supplementary late follow-up DUS examinations were requested from the hospitals having treated the patients, to evaluate patency. If no DUS or other imaging had been performed during follow-up, patency was assessed with clinical examination and ankle-brachial index (ABI).

Definitions
The duration of follow-up was defined as until the day when permanent occlusion was determined, or until the last date when the reconstruction was examined and found open. Primary patency was defined as a patent reconstruction without occlusion. Secondary patency was an occluded reconstruc-
tion that had been successfully reopened after one or more re-interventions. Conversion surgery was defined as OSR (in all cases a bypass) in a leg where a stent graft had previously been deployed.

Outflow was categorized into 0, 1, 2 or 3 open infrapopliteal vessels, with less than 50% stenosis, immediately before the index procedure.

Elongation and angulation of the popliteal artery was estimated by measuring tortuosity index (TI) and maximum angle$^{55}$ see Figure 2. Measurements were done in preoperative CTA datasets, when available, using the iNtuition, TeraRecon inc (Foster City, CA, USA) software. The TI was calculated by dividing the arterial centreline distance with the Euclidean distance from the exit of the Hunters canal to the origin of the anterior tibial artery. The maximum angle was measured in CTA and/or MRI images by rotating a volume rendering (VR) or maximum intensity projection (MIP) image of the popliteal artery until its most severe angulation was perpendicularly projected and measuring this angle in a 2-dimensional plane. In patients without preoperative CTA or MRI, maximum angle was measured in 2-dimensional DSA images using the OsiriX™ imaging software (Pixemo, Geneva, Switzerland), if such images were available. In cases with multiple angulations of the popliteal artery, the most pronounced angulation was chosen. TI was measured (using CTA) in 65 cases; maximum angulation was measured in 167 cases (using CTA in 75, MRI in 26 and DSA in 66).

Reproducibility was calculated by comparing with a second, blinded observer in 20 CTA and 15 DSA examinations. There was a significant correlation between the two estimates of popliteal artery elongation, TI and maximum angle (Spearman rho 0.786 (p<0.001)), and between observers (0.756 for TI (p <0.001) and 0.847 for maximum angle (p<0.001)). Since maximum angle was available in more patients than TI (167 vs. 65 legs), the maximum angle was chosen as a proxy to estimate popliteal artery elongation.
Figure 2. Images from the same patient in DSA and CTA. To the left, a DSA with measurements of maximum angle, 93°. To the right, Measurements of TI in Ter-aRecon: 1.27. The curved, thick, white line is the centreline; the straight, thin line is the Euclidean line.

Paper III

Aim: In patients with screening detected AAA and SAA, what are the prevalences of PA? Are there correlations between the existence of PA and diameters of other vessels?

The subjects registered in Uppsala SweAAA database from 2006 to 2017, because of a dilatation discovered during AAA screening, were included in the study. Patients with an infrarenal aorta measuring 30 mm or more were re-examined after one or two years, depending on size, and the maximum diameters of the common femoral (CFA), distal superficial femoral (SFA) and popliteal arteries were measured at the time of re-examination. Patients with an aorta measuring 25 to 29 mm were re-examined after 5 years, and the infrainguinal arteries were assessed simultaneously, as described above. Due to the difference in the interval to re-examination, those with AAA screened 2006 to 2017 and the subjects with SAA screened 2006 to 2013 were eligible for this study.
All arteries were measured with DUS by means of the leading-edge-to-leading-edge (LELE) principle, for details see Paper III.

**Definitions**

An aneurysm was defined as 50% larger than a normal artery in agreement with suggested standards for reporting on arterial aneurysms by the SVS/ISCS Ad Hoc Committee, 1991. Normal arterial diameter values are dependent on age, sex and body surface area (BSA). The cut-off value for iliac aneurysms was suggested to 20 mm and for the aneurysms of common femoral artery 15 mm, for details see Paper III. PA was defined as either an absolute diameter of 12mm, since normal values in the same age range between 7.2-8.9 mm, or 1.5 times the diameter of the adjacent distal SFA.

When correlations were evaluated between different arterial segments, the largest diameter of the left and right sides were used for comparison in the CIA, CFA, SFA and the popliteal artery.

There were missing values in the measurements of CIA (10.6%), CFA (18.0%), and the popliteal artery (16.8%), in most cases because the person had not yet been re-examined.

**Paper IV**

*Aim: This subgroup of patients with PA has only been described in small case series. The aim was to compare a larger cohort with those treated for other indications*

In Paper I, only 13 patients treated for rPA were found. In the publications of Ravn H et al another 24 of 717 legs treated for PA 1987-2002 (3.2%) were registered as operated on for rPA. An extraction from the Swedvasc for the interval years 2002-2008, added another 12 patients with rPA. The patients treated for rPA from these three time intervals were joined into one cohort. Information in the registry was supplemented with a review of all medical records, retrieved from the hospitals in charge of the patients. For details, see Paper IV. One double registration and four pseudo aneurysms were excluded, leaving 45 patients treated for rPA in this cohort.

To put the characteristics of rPA into context, a comparison with PA treated for other indications was performed, using original data from the two previously described nationwide studies.
Ethical considerations

For Paper I, approval was obtained from the Regional ethics committee of Uppsala accounting for the nationwide study of validated registry data. In preparation for Paper II and IV, all patients were asked for informed consent by letter, and those who declined were excluded from these papers. In 2016 the Swedish National Ethics committee (Centrala Etikprövningsnämnden) decided to waive informed consent for retrospective review of case-records in clinical research. Unfortunately, this new interpretation of Swedish law, adapting it to the International situation, had not yet taken place at the time when the project was initiated.

For the original data (used in Papers I and IV), basis for the publications by Ravn H et al\textsuperscript{13}, ethical approval was obtained in 2003, from all the nine Regional Ethics Committees, according to the system of ethical scrutiny at that time. For the patients treated 2002-2008 (Paper IV), a supplementary ethics application was made for retrieval of case-records. For Paper III, the study was approved by the Regional Ethics committee of the Uppsala-Örebro region. All patients (AAA) and subjects (SAA) gave informed consent.
Statistics

In all papers, data management and statistical analyses were done using the software package SPSS version 20.0 to 24.0 (IBM SPSS, Inc.).

Distribution of categorical data was evaluated by Fischer’s exact test or Chi-square test as appropriate. A trend in ordinal data was evaluated by p-value for linear by linear association (LLA). Normal distribution was visually assessed by histogram and Q-Q-plots, and evaluated by the Kolmogorov-Smirnov test. Comparisons of continuous data were made by students T-test if normally distributed, if not, with Mann-Whitney U-test. Correlations between continuous variables were evaluated with Pearson coefficient if normally distributed, if not, with Spearman rho. ANOVA test was used to compare differences between multiple subgroups and Tukey’s range test was used for inter group comparisons. Levene’s test was used to test normal distribution and if homogeneity was violated, it was adjusted for with the Brown-Forsythe test. The Kaplan-Meier method was used to analyse time to event (primary and secondary patency) and Cox proportional hazard regression model to estimate the unadjusted and adjusted hazard ratio (HR) with 95% confidence interval (CI).

All tests were two-tailed. In Paper I, p-values <0.01 were considered significant, adjusting for multiple comparisons, whereas p-values <0.05 were considered a statistical trend. In Paper II – III, p-values of <0.05 were considered significant.
Results

Paper I

There were 592 interventions (in 499 patients) during the four years, resulting in an incidence of 15.7 operations/million person years (compared to 8.3 during 1994-2001). The distribution over the four years is seen in Figure 4.

Figure 4. Distribution of treatment for PA May 2008 to May 2012

Of the 592 PAs, 187 (31.6%) were treated emergently and 405 (68.4%) electively. Four subgroups were created based on the indication for treatment, see Figure 5.
Background characteristics, such as age, comorbidities and sex, did not differ between the groups of acute ischaemia, symptomatic and asymptomatic, but the patients treated for rPA were older and had more heart disease (p = 0.013 and 0.005, respectively). The groups of acute ischaemia, symptomatic and asymptomatic were analysed regarding surgical technique and outcome.

There were no differences in background characteristics between OSR and ER in the acute ischaemia group. In both the elective symptomatic and asymptomatic groups, however, those treated with ER were older compared to those treated with OSR, 78 versus 68 years (p=0.006) and 74 versus 68 years (p<0.001), respectively.

The acute ischaemia group
Of the 174 treated for ALI, 118 received pre-operative thrombolytic treatment, and 92 of those (78%) improved their outflow. Nine patients with ALI had incomplete treatment, the blood-flow was not restored: eight of those had no benefit from thrombolysis, and all were either amputated or dead within one month. Including the incompletely treated group, the total number of amputations was 17/170 (10%) at 30 days and 20/159 (13%) at one year. Primary and secondary patency, amputation, death and amputation free survival at 1 year among those operated on with OSR and ER are given in Table 4.
Table 4. *Outcome after treatment of popliteal aneurysm with acute ischaemia depending on treatment modality*

<table>
<thead>
<tr>
<th>Total nr</th>
<th>Open repair</th>
<th>Stent graft</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>165</td>
<td>138</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>N/Total*</th>
<th>%</th>
<th>N/Total*</th>
<th>%</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary patency, 1 year</td>
<td>89/113</td>
<td>78.8</td>
<td>9/21</td>
<td>42.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Secondary patency, 1 year</td>
<td>99/114</td>
<td>86.8</td>
<td>10/21</td>
<td>47.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Amputation &lt;1 year</td>
<td>8/117</td>
<td>6.8</td>
<td>4/23</td>
<td>17.4#</td>
<td>0.098</td>
</tr>
<tr>
<td>Death &lt;1 year</td>
<td>6/138</td>
<td>4.5</td>
<td>4/27</td>
<td>14.8</td>
<td>0.037</td>
</tr>
<tr>
<td>Amputation-free survival, 1 year</td>
<td>109/122</td>
<td>89.3</td>
<td>19/25</td>
<td>76.0</td>
<td>0.070</td>
</tr>
</tbody>
</table>

* The total number varies because of some missing data.
# The total number of amputations did not increase between 30 days and one year, but two patients died, and two were lost to follow-up.

Within 1 year, five of the patients originally treated with ER, were converted to OSR. Four bypasses were patent at 8 months to 1 year, information on long-term outcome after the conversion was missing in one.

In 116 of the bypasses a vein graft was used (89.9%), in 13 a synthetic graft (10.1%) and in nine patients this information was missing. At one year, secondary patency with a vein graft was 91% (87/96) compared with 56% (5/9) among those who had a prosthetic graft (p=0.002).

**The elective symptomatic group**

Of 405 elective operations, 105 were symptomatic, and 103 of those underwent complete treatment of the PA. The main symptoms were claudication (40/103, 38.8 %), rest pain (29, 28.2%), ischaemic ulcer (22, 21.4%), venous compression or thrombosis (5, 4.9%) and micro embolism (2, 1.9%). Out-
comes one year among those operated on with OSR and ER are given in Table 5.

**Table 5. Outcomes after treatment of symptomatic popliteal aneurysm depending on treatment modality**

<table>
<thead>
<tr>
<th></th>
<th>Total nr</th>
<th>Open repair</th>
<th>Stent graft</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>103</td>
<td>90</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Primary patency, 1 year</td>
<td>60/74</td>
<td>81.1</td>
<td>4/7</td>
<td>57.1</td>
</tr>
<tr>
<td>Secondary patency, 1 year</td>
<td>64/74</td>
<td>86.5</td>
<td>6/7</td>
<td>85.7</td>
</tr>
<tr>
<td>Amputation &lt;1 year</td>
<td>7/81</td>
<td>8.6</td>
<td>0/9</td>
<td>0</td>
</tr>
<tr>
<td>Death &lt;1 year</td>
<td>5/90</td>
<td>5.6</td>
<td>1/13</td>
<td>7.8</td>
</tr>
<tr>
<td>Amputation-free survival, 1 year</td>
<td>73/83</td>
<td>88.0</td>
<td>9/9</td>
<td>100</td>
</tr>
</tbody>
</table>

*The total number varies because of some missing data.

One in the ER-group was converted to an open bypass, and remained patent. Two of the stents were multi-layer stents; one occluded after 4 months, was reopened with thrombolysis and relined with a covered stent graft. The other remained open at one year.

**The asymptomatic group**

Of the 300 asymptomatic legs, 55 (18.3%) were treated with ER and 245 (81.7%) with OSR. Outcomes at one year among those operated on with OSR and ER, are given in Table 6.
Table 6. *Outcomes after treatment of asymptomatic popliteal aneurysm depending on treatment modality*

<table>
<thead>
<tr>
<th></th>
<th>Total nr</th>
<th>Open repair</th>
<th>Stent graft</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>300</td>
<td>245</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>N/Total*</td>
<td>%</td>
<td>N/Total*</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Primary patency, 1 year</td>
<td>186/209</td>
<td>89.0</td>
<td>31/46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary patency, 1 year</td>
<td>200/214</td>
<td>93.5</td>
<td>41/49</td>
<td>0.026</td>
</tr>
<tr>
<td>Amputation &lt;1 year</td>
<td>2/220</td>
<td>0.9</td>
<td>1/50#</td>
<td>0.507</td>
</tr>
<tr>
<td>Death &lt;1 year</td>
<td>3/242</td>
<td>1.2</td>
<td>3/55</td>
<td>0.045</td>
</tr>
<tr>
<td>Amputation-free survival, 1 year</td>
<td>216/221</td>
<td>97.8</td>
<td>48/52</td>
<td>0.048</td>
</tr>
</tbody>
</table>

* The total number varies because of some missing data.
# The total number of amputations did not increase between 30 days and one year, but three patients died, and two were lost to follow-up.

Among those treated with ER, one was converted to a bypass within a month and another two within a year. Two of these were examined and found patent after one year. Two legs were treated with multi-layer stents, none of which was patent at late follow-up.

**Open repair**

Vein grafts were used in 87.6% (395/451), and had significantly better results both overall and in the subgroups at one year. Primary and secondary patency at one year was 87% and 93% for venous and 70% and 73% for prosthetic bypass (p-values 0.002 and <0.001), respectively. A posterior surgical approach was used in 20.8% (121/581), had better patency at 30 days (p-0.007) and a trend towards lower amputation risk at one year (p-0.012).
Demographics, comorbidities and medication

Patients treated with ER were older than those treated with OSR, 73 (46-89) vs. 68 (42-102) years (p-0.001), and had pulmonary disease more often, 17.4 vs. 5.9% (p-0.012). Patients in the ER group were more often treated with dual antiplatelet therapy (DAT) or anticoagulants (p<0.001). There were no significant differences between groups in concomitant aneurysms (aortic, iliac, femoral and contralateral popliteal), in aneurysm diameters, number of outflow vessels prior to surgery, or percentage treated with thrombolysis (for details, see Table 1, Paper II).

Surgical details

In OSR, by-pass was done with a medial approach in 116/154 (75.3%) of the legs. A posterior approach was used in 38 (24.7%). Vein grafts were used in 126 (82%).

In ER, all stent grafts were Viabahn (GORE® VIABAHN® Endoprosthesi). The mean number of stent grafts per leg was 2.15 (range 1-5). The mean total length of stent grafts per leg was 220 mm (range 100-550 mm) (data from 70 legs). The median diameter, of the most proximal stent graft, was 8 mm (range 5-13) and of the distal stent graft 7 mm (range 5-11) (72 legs).

Anatomical characteristics

The median maximum angle for all legs with PA was 45° (range 17-110°, IQR 32-61°). There was no difference in maximum angle between legs treated with ER (43°) vs. OSR (48°) (p-0.251).

Outcomes

Primary and secondary patencies of the popliteal reconstruction were significantly better after OSR compared to ER. The risks of any occlusion and of permanent occlusion were HR 2.741 (CI 1.683-4.463) and 2.407 (CI 1.384-4.185), respectively. Most occlusions occurred within the first year, see Figure 6.
Figure 6. Kaplan Meier curves over primary and secondary patency after endovascular and open surgery

In a cox regression, unadjusted analysis, there were no associations between risk for occlusion and age, concomitant aneurysms, diameter of aneurysm, anti-platelet or anti-coagulation medication, nor with popliteal elongation, Table 7.
Table 7. Cox log regression analysis for occlusion or permanent occlusion

<table>
<thead>
<tr>
<th></th>
<th>Occlusion*</th>
<th></th>
<th>Permanent occlusion*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Bilateral PA</td>
<td>0.81 (0.48-1.37)</td>
<td>0.422</td>
<td>0.87 (0.48-1.56)</td>
<td>0.631</td>
</tr>
<tr>
<td>N=210</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant AAA</td>
<td>1.18 (0.71-1.95)</td>
<td>0.524</td>
<td>0.78 (0.45-1.37)</td>
<td>0.385</td>
</tr>
<tr>
<td>N= 198</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter PA</td>
<td>1.01 (0.99-1.03)</td>
<td>0.629</td>
<td>1.01 (0.99-1.03)</td>
<td>0.370</td>
</tr>
<tr>
<td>N= 189</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAT or AC</td>
<td>1.16 (0.68-1.97)</td>
<td>0.578</td>
<td>0.90 (0.49-1.69)</td>
<td>0.752</td>
</tr>
<tr>
<td>N= 187</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum angle</td>
<td>1.01 (0.99-1.02)</td>
<td>0.369</td>
<td>1.01 (0.99-1.02)</td>
<td>0.280</td>
</tr>
<tr>
<td>N =167</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.01 (0.98-1.03)</td>
<td>0.725</td>
<td>1.02 (0.99-1.05)</td>
<td>0.234</td>
</tr>
<tr>
<td>N=231</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical technique ER/OR</td>
<td>2.74 (1.68-4.46)</td>
<td><strong>&lt;0.001</strong></td>
<td>2.41 (1.38-4.19)</td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td>N=231</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outflow 0 or 1 to 3</td>
<td>2.16 (0.93-5.05)</td>
<td><strong>0.074</strong></td>
<td>3.34 (1.41-7.94)</td>
<td><strong>0.006</strong></td>
</tr>
<tr>
<td>N=191</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Occlusion is defined as loss of primary patency. Permanent occlusion is defined as an occlusion that was not possible to reopen permanently.

#HR= hazard ratio; DAT=dual antiplatelet therapy; AC=anticoagulation

In an adjusted cox regression analysis, both poor out-flow (0-vessels) and ER were independent risk factors for occlusion (poor out-flow HR 3.03 (1.26-7.27), p=0.013), ER HR 2.69 (95% CI 1.60-4.55, p<0.001) and permanent occlusion (poor outflow HR 4.68 (1.89-11.62), p<0.001), ER 2.47 (1.349-4.504), p=0.003).

The number of open crural vessels (1,2 or 3) did not matter as long as at least one vessel was open.

Early mortality within one month did not differ between groups but mortality beyond one year was higher in the ER group. Amputations during follow-up did not differ between ER and OSR, but within a year, there were 14 (of 77) treated with thrombolysis in the ER vs 3 (of 154) of the OSR. Over time,
there were eleven conversions to bypass surgery in the ER, with no amputations in this subgroup at follow-up.

Variables affecting occlusion (loss of patency) in ER are given in Table 8.

Table 8. Univariable sub-group analysis of endovascular repair with cox log regression

<table>
<thead>
<tr>
<th></th>
<th>Occlusion*</th>
<th></th>
<th>Permanent occlusion*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (CI)</td>
<td>p-value</td>
<td>HR (CI)</td>
</tr>
<tr>
<td>Indication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergent/elective N 77</td>
<td>2.94 (1.45-5.97)</td>
<td><strong>0.003</strong></td>
<td>4.16 (1.79-9.67)</td>
</tr>
<tr>
<td>Medical therapy DAT, AC/SAT N 71</td>
<td>0.81 (0.38-1.72)</td>
<td>0.585</td>
<td>1.36 (0.58-3.22)</td>
</tr>
<tr>
<td>Number of open outflow vessels 0/1-3 N 73</td>
<td>14.39 (3.46-59.92)</td>
<td><strong>&lt;0.001</strong></td>
<td>53.18 (7.92-356.91)</td>
</tr>
<tr>
<td>Maximum angle N 70</td>
<td>1.01 (0.99-1.02)</td>
<td>0.288</td>
<td>1.01 (0.99-1.03)</td>
</tr>
<tr>
<td>Stent diameter# N 72</td>
<td>0.71 (0.54-0.93)</td>
<td><strong>0.014</strong></td>
<td>0.66 (0.48-0.91)</td>
</tr>
<tr>
<td>Stent length N 70</td>
<td>1.02 (0.96-1.07)</td>
<td>0.553</td>
<td>1.02 (0.96-1.08)</td>
</tr>
</tbody>
</table>

*Occlusion is defined as loss of primary patency. Permanent occlusion is defined as an occlusion that was not possible to reopen permanently, 11 of those underwent open surgical bypass.

The distal, smaller diameter was used for this analysis. DAT= Dual antiplatelet therapy; AC= Anticoagulation; SAT=Single antiplatelet therapy

Indication and stent graft diameter were correlated (p<0.001). Patients undergoing emergent procedures had a median diameter of 6.5 mm of their stent grafts (range 5-8 mm), and those undergoing elective procedures 8 mm (range 5-11). There was no correlation between maximum angulation and indication (p=0.190), or with stent graft diameter (Spearman rho 0.108, p=0.391).

To explore risk factors for occlusion, an adjusted cox regression model was performed. Maximum angle was included due to clinical observations. Three patients with 0 in outflow were not included as this was an obvious, independent risk factor and in two patients, it was not possible to measure maximum angulation. There were 25 occlusions in the remaining 62 patients. The
model included stent graft diameter, indication and maximum angle. Diameter had a HR of 0.70 (CI 0.49-0.98, p=0.039), indication a HR of 1.74 (0.71-4.10, p=0.203) and max angulation a HR of 1.02 (1.00-1.03, p=0.030). In an equivalent analysis for permanent occlusion (62 patients and 18 events), stent graft diameter had a HR of 0.67 (0.43–1.04, p=0.072), indication a HR of 2.74 (0.97 – 7.74, p=0.057) and maximum angle a HR of 1.02 (1.00- 1.05, p=0.040). The low number of events makes this latter analysis underpowered, however.

Paper III

Screening

From 2006 to 2017, 23,422 men in the Uppsala region were invited to AAA screening at the age of 65 (men born 1941 to 1952). Those who accepted were 19,820 (compliance 84.6%).

The number with AAA was 173 (0.9%) and the number with SAA was 205 (1.0%). Of the SAA, 149 subjects were eligible for the study, as they were examined 2006-2013, and had had the possibility of being reexamined, including peripheral vessels.

AAA vs SAA

The group with AAA differed from SAA in BSA (body surface area), 2.14 (CI 2.100-2.177) vs 2.088 (CI 2.059 – 2.116), p=0.050. The AAA group had higher proportion of current smokers 70/173 (40.5%) vs 43/149 (28.9%), p=0.013. There were no differences in comorbidities or the presence of a first-degree relative with AAA. The frequencies of concomitant aneurysms are seen in Table 9.
Table 9. Frequency of concomittant aneurysms in different arterial segments among 322# persons with AAA or SAA

<table>
<thead>
<tr>
<th>Aneurysm</th>
<th>ALL</th>
<th>AAA(173#)</th>
<th>SAA (149#)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIA, N (%)</td>
<td>28/289 (9.7%)</td>
<td>22/157 (14.0%)</td>
<td>6/132 (4.5%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Bilateral CIA, N (%)</td>
<td>6/28 (21.4%)</td>
<td>5/22 (22.7%)</td>
<td>1/6 (16.7%)</td>
<td>1.000</td>
</tr>
<tr>
<td>CFA, N (%)</td>
<td>17/267 (5.3%)</td>
<td>11/146 (7.5%)</td>
<td>6/121 (5.0%)</td>
<td>0.457</td>
</tr>
<tr>
<td>Bilateral CFA, N (%)</td>
<td>4/17 (23.5%)</td>
<td>2/11 (18.2%)</td>
<td>2/6 (33.3%)</td>
<td>0.584</td>
</tr>
<tr>
<td>PA, N (%)</td>
<td>38/268 (14.2%)</td>
<td>23/145 (15.9%)</td>
<td>15/123 (12.2%)</td>
<td>0.483</td>
</tr>
<tr>
<td>Bilateral PA, N (%)</td>
<td>11/38 (28.9%)</td>
<td>8/23 (34.8%)</td>
<td>3/15 (20.0%)</td>
<td>0.470</td>
</tr>
</tbody>
</table>

*Not all patients were examined in all arterial segments.

*P-values refer to comparisons between AAA and SAA; AAA=Abdominal aortic aneurysm (≥30mm); SAA=Subaneurysmal aorta (25-29mm); CIA=common iliac artery aneurysm; CFA=common femoral artery aneurysm; PA=popliteal artery aneurysm.

Popliteal artery diameter and popliteal aneurysms

The mean and median diameter of the popliteal artery was 9 mm (CI 8.76 – 9.32), and 9 mm (range 5-50 mm), respectively.

In all subjects, there were 49 PAs in 38 persons. Thus they were bilateral in 11/38, 28.9%, and 14.2% had a PA in any leg. In eleven arteries, the popliteal artery was 1.5 times larger than the distal SFA, and in seven of those the diameters of the popliteal arteries were also ≥12 mm. Eight subjects (3.0%) had at least one PA with a diameter ≥15 mm, and 6 (2.2%) with a diameter of ≥20 mm. Surgery after examination was performed on five patients (six legs). In two, occluded aneurysms were found, but with moderate symptoms that did not require intervention.

There was no difference in comorbidities between those with or without PA, except for fewer smokers in the group with PA, 26.3% vs 34.8%, p=0.030. Those with PA had a first-degree relative with an AAA in 23.7% (9/38) vs 10.3% (23/224) in those without PA, p=0.030.
The mean diameters of the iliac arteries were larger among patients with PA compared with those without PA, 17mm vs 15mm (p=0.001), as were the CFA diameters, 13mm vs 11mm (p<0.001), and the SFA diameter, 12mm vs 9mm (p=0.001), Figure 7. There was no significant difference in diameter of aorta in those with or without PA (p=0.459).

Figure 7. The maximum diameter of the iliac artery, depending on if the patient had a PA or not.

Correlations between vessel diameters

There was no correlation between aortic diameter and popliteal artery diameter (Spearman rho -0.26, p=0.717) while there were significant correlations between popliteal artery diameters and the diameters of CIA (Spearman rho, 0.289, p<0.001), CFA (Spearman rho 0.486, p<0.001) and SFA (Spearman rho 0.681, p<0.001).

Paper IV

To calculate the proportion of patients operated on for rupture we used the time-periods 1987-2002 and 2008-2012, under which we had complete data on the total number of repairs (1304) as well as the number of those who had been operated on for rupture (33): the proportion was 2.5 %.
Clinical characteristics in patients with ruptured and non-ruptured popliteal aneurysms were compared. Patients with rPA were eight years older, 77.7 versus 69.7 years (p<0.001) and had more lung and heart disease (p=0.003 and 0.023) compared with those with PA treated for other indications. The maximum diameter of the PA was assessed in 38 patients, by computed tomography (N=17), ultrasound (16), magnetic resonance imaging (2), and perioperative measurement (3). The mean maximum diameter was 63.7 mm, range 25 to 200. There was no correlation between age and diameter (Pearson r= 0.046, p=0.777). The diameters were compared with the diameters of 513 non-ruptured PAs treated 1987-2002\textsuperscript{11}, that had a mean diameter of 30.9 mm, p<0.001.

![Ruptured popliteal artery (rPA) diameter](image)

**Figure 8.** Ruptured popliteal artery (rPA) diameter

Twenty-two patients (49%) were treated with anticoagulants at the time of surgery for rupture, nineteen with oral anticoagulants and three with low molecular weight heparins. Among those, seven had their treatment initiated within two months prior to the diagnosed rupture because of suspicion of deep venous thrombosis (DVT). Seven patients presented with critical limb ischaemia. No patient was in severe shock at presentation. Almost half of the patients (18/42, 43%) presented the same day as they had debut of symptoms, another eleven, in all 29/42 (69%) within a week after onset.
The initial diagnosis was rPA in only eight cases (17.8%), half of whom had a known diagnosis of PA. Twenty-seven patients (60%) had a preliminary diagnosis of DVT or a Baker’s cyst. Bleeding because of minor trauma or anticoagulants was suspected in seven (15.6%). In the remaining three, no preliminary diagnosis could be identified. All patients had swelling, and in twenty (44.4%), the whole leg was affected.

Most patients were operated on by open surgery through the medial approach. Fasciotomy was performed in twelve (26.7%), and four (8.9%) were amputated on at 30 days. Of these, three presented with both ischaemia and rupture. At one year, 26 were alive (57.8%) and of the 22 that were examined, reconstructions were patent in 20 (91%).

*Figure 9.* A CTA taken of a ruptured PA. To the left a sagittal plane, to the right a coronal plane. The arrow indicates a bulb at the location of the rupture
General discussion

Introduction

Optimal treatment of PA is controversial. Complications of PA include ALI due to distal embolisation and thrombosis of the PA, compression of adjacent veins and nerves, as well as rupture with extravasation. Patients treated emergently for PA, most often for ALI, have higher risks for amputation and death compared to those who undergo elective surgery\(^{13, 23, 39}\). It is of clinical importance to diagnose PAs and intervene timely before complications.

It is a relatively uncommon disease, and the majority of studies are either from single centres, presenting a small cohort with detailed reports, or registry studies, with larger cohort, but lacking details.

There are several outstanding issues. What is the prevalence, related to the issue how a PA should be defined? How do PAs correlate to other aneurysms? What indication for surgery is justifiable? In many centres, the indication for prophylactic surgery is a diameter of 2 cm with thrombus\(^{39, 46, 59}\). However, the diameter should rather reflect the risk for rupture, and the mechanisms behind the most common complications of occlusion or embolization are not fully investigated. That brings into question if the outcome after treatment of asymptomatic PAs is transmittable to PAs with acute complications or if it becomes a comparison between two fundamentally different cohorts. Finally, the question if ER and OSR have comparable outcomes and if there are risk factors associated with the choice of method, not accounted for.

In this thesis, two registries have been used to identify the patients with PA; SweAAA, with prospectively collected data within a screening program, with the intent to explore the questions of prevalence and correlation to other aneurysms. Swedvasc was used to identify patients treated for PAs in a national cohort. The data has been evaluated with two different levels of details. In paper I, data was validated by a protocol with aim to study time trends and outcomes after treatment with different surgical techniques. The size of the national cohort enabled us to evaluate outcome based on indication. The result from paper I, led to the nested case-controlled study Paper II, aiming to address confounders that may affect both the decision to chose ER
or OSR, as well as results of treatment. From Swedvasc it was possible to identify the patients, and collect medical records to explore the characteristics in detail of the very rare group of rPA. These patients constitute the basis of paper IV, shedding some light on the risks for rupture in perspective to other indications.

Epidemiology of PA

In the cohort of screening detected AAA and SAA in Paper III, 14.2% of the examined persons had at least one popliteal aneurysm of any size, 3.0% \( \geq 15 \text{ mm} \) and 2.2% \( \geq 20 \text{ mm} \).

Comparing with other cohorts using equal definitions of PA, it is 3 times as frequent, as the prevalence of 1% in a population of men 65 to 80 years old, screened for PA (definition \( \geq 15 \text{ mm} \)). In cohorts of patients clinically diagnosed with AAA (thus, not screening detected and larger), the prevalence was 7.6% in a study with the definition of a dilation of 1.5 the adjacent normal vessel or the contralateral normal vessel and 19% with the definition of \( \geq 12 \text{ mm} \) in diameter.

A number of definitions were suggested in different reports: 50% larger than a normal diameter, 15 or 19 mm in diameter, 50% larger than the adjacent vessel (i.e., the distal SFA) or 50% larger than the contralateral, non-aneurysmal artery. The latter of these definitions has an obvious shortcoming since almost half of the PAs are bilateral. The problem is also that it is unknown how the risk for complications and the growth are associated to these different definitions.

We have used the combined definition of 12 mm in diameter and/or 1.5 times the adjacent vessel. This investigation has the advantage of being population based, and the strength of being a longitudinal cohort study, enabling us to address the issues of risk for complications in a future follow up study.

The incidence of treatment for PA was studied in Paper I. In a previous analysis Ravn et al reported an incidence of PA repair of 8.3 million person years in 1994-2001 in Sweden, compared with 15.7 per million person years during 2008-2012, a doubling of the surgical activity. There are great international differences in surgical activity for PA, and in the Vascunet report from 2014, Sweden had the highest activity of the eight countries studied. These differences may also be explained by registration practices, however.
Swedvasc is the only vascular registry that has a dedicated module to register procedures for PA.

The proportions of patients operated on for acute ischaemia had not changed over time (29.4 vs. 31.5%). Thus, a change in the indications for surgery did not seem to have taken place. A more reasonable explanation is either a true increase in the prevalence of PA or an increased detection rate. The Swedish AAA screening program had reached a more than 99% population coverage in 2014. Many vascular centres perform a routine ultrasound examination on a newly detected AAA, but that cannot account for the symptomatic PAs. Improved imaging routines and higher awareness of the disease, may result in a thrombosed PA being detected more frequently in a patient with ALI.

Correlations between PA and vessel diameters in other segments

In this cohort of men with a screening detected AAA or SAA, there was no correlation between aortic diameter and PAs, neither in the AAA nor in the SAA groups, nor when correlating to the exact diameter as a continuous variable. The occurrence of PA was, however, correlated to the diameter of the CIAs. The correlation between PA and aneurysms in CFA is well known, but the correlation to diameter and aneurysms of the CIAs in men is, to the best of our knowledge, a novel finding. In a recent study on women with AAA, however, a similar correlation was found. Women with CIA aneurysms had infrainguinal aneurysms in 40%, those without only in 1.6%. Other studies suggest that peripheral aneurysms are associated with larger vessels in several arterial segments, as a subgroup, not necessarily directly correlated to AAA.

In this study, the mean diameter of SFA in the subjects without PA, 8.9 mm, is comparable to normal values of popliteal artery in subjects without aneurysmal disease at all. An observation, even if the group is small, is the higher degree of first-degree relatives among those with PA (24% vs 10% among those with AAA or SAA without PA). This finding supports the hypothesis that patients with infrainguinal or common iliac aneurysms might form a specific subgroup, in which hereditary factors are more important.

Results after treatment

Results after OSR for PA are well studied. Independent risk factors for occlusion and amputation are emergency procedures and the use of prosthetic
bypass grafts. There is a risk for wound complications, especially after emergency procedures, but operative mortality is low, even in high-risk patients. Excellent four-year secondary patency rates of 84-97% have been reported. However, OSR is depending on availability of good conduits for by-pass. As the population considered for invasive treatment is becoming older and more fragile, there are benefits with a minimally invasive procedure, as long as the outcomes are comparable.

There were reports on ER of PA and it seemed to have become a more frequent method in Sweden. With the intent to study changes in and results after different surgical treatments, the national study in Paper I was initiated.

The results after OSR were generally quite good. One reason is certainly the frequent use of vein grafts, almost 90%, the importance of which has been demonstrated previously. The use of vein graft was associated with better patency in all the subgroups, but the patients with ALI benefitted most from this choice of bypass. In the small subgroup, treated med a prosthetic bypass, primary and secondary patency were 30% respectively 55% at one year, underlining the importance to use vein, whenever possible.

No difference was shown in patency rates between the medial or posterior approaches in any of the sub-groups, but adding the groups together, there was an advantage with the posterior approach. The comparison is not altogether fair, however, as in most centres patients chosen for the posterior approach have less extensive aneurysmal disease. This results in a possibility to use shorter interposition grafts. On the other hand, these are indications that the posterior approach is preferable if anatomical and patient features are suitable. The posterior approach will also decrease the risk for late expansion due to a phenomenon similar to type II endoleak after EVAR for AAA. This is a late complication and could not be expected to affect the result within a year, which was the follow-up period in paper I.

In the two largest published studies comparing ER with OSR to date, indications were markedly different between the groups. Leake et al. (76 ER, 110 OSR) had 24.5% legs with ALI in the OSR group compared to only 9.2% in the ER group. Pulli et al. (134 ER, 178 OSR) had three times as many legs with ALI in the OSR group. Furthermore, run-off was significantly worse in legs treated with OSR in both studies. In spite of this, primary patency still significantly favoured OSR, even though secondary patency rates were comparable. A recent meta-analysis from 2017, including 14 studies and 4,500 operated PAs, concluded that ER had lower wound complications and shorter length of hospital stay. This came at the cost of inferior primary patency, but no significant difference in secondary patency up to three years was found. The only published randomized study comparing OSR vs. ER was
small, 30 patients, and included only asymptomatic PA. No significant differences were found in primary or secondary patency rates.\textsuperscript{43}

The national cohort included 592 legs treated for PA of which 581 had definitive surgical treatment and was large enough to analyse outcome after ER an OSR based on indication. Outcome in the asymptomatic group were significantly inferior for the ER, both in primary and secondary patency at one year, but figures of 67% primary and 84% secondary patency were still comparable with results form other reports. The differences in outcomes in those with ALI were more alarming, however. The outcome in patency in the OSR group was somewhat less than in the asymptomatic group (secondary patency 87% vs. 94%) was expected, but secondary patency after ER was 48% vs. 87% in OSR (Figure 10), and there even was a trend for a higher amputation rate. Results would have been even worse for ER, had not five patients been converted to OSR between 30 days and 1 year, since these patients went on to do well without re-occlusion or amputation.

\begin{figure}[h]
\includegraphics[width=\textwidth]{figure10.png}
\caption{Primary and secondary patency in percentage at one year, distributed by indication and surgical technique}
\end{figure}

The difference in outcomes was not explained by case selection; there were no differences in background characteristics between those operated on with OSR or ER in the ALI group. In the asymptomatic group, the patients chosen for ER were older and had more heart disease, but had otherwise no significant differences in comorbidities. All numerical trends disfavoured ER, even in the asymptomatic group. These ominous results had not been reported previously. At the time, there were several studies\textsuperscript{43-45, 70, 71} looking at stent graft treatment, but mainly with small numbers and a majority of asymptomatic patients. Long-term results were seldom reported.
Performing research on registry data has advantages and limitations; it makes it possible to assemble a large database on a relatively uncommon disease, but data will be lacking in detail. What were the reasons for the inferior result after ER? Could data on important details such as size and thrombus of the PA, the anatomy of the run-off vessels, elongation, diameter of vessels and postoperative medication account for some of the results? Were there confounders not yet identified? A confounder in this context is a factor that both affect the choice of treatment (OSR or ER) and the results. To answer these questions a case control study, nested in the national cohort, were initiated (Paper II).

**Result after treatment with ER or OSR**

After matching for indication (Paper II), the groups of ER and OSR differed only in age, lung disease and higher degree of DAT in the ER group. There was no difference in outflow. Compared with other studies, the proportion of patients treated for ALI was high, 32%, which effected outcome, in particular after ER.

In comparable groups, a primary endovascular strategy for treatment of PA had an almost 3-fold increase in risk for postoperative occlusions compared to OSR, and 2.4 times risk for permanent occlusion. In addition to OSR, patency was associated with the presence of at least one open outflow vessel.

In the combined cohort, age, concomitant aneurysms and aneurysm diameter did not affect outcome. Neither did popliteal elongation, in the combined cohort, adjusting only for surgical technique and outflow. An adjustment for other anatomical features, such as vessel diameter, was not possible as we did not have this data in enough patients in the OSR group. As expected, poor outflow (defined as at least 50% stenosis in all three crural vessels) had an independent impact on outcome. An outflow of more than one vessel did not further affect outcome, which was somewhat surprising. Perhaps spending many extra hours in thrombolysis, trying to open multiple outflow vessels, might be reconsidered, in particular if the risk for the patient is high. The only other independent risk factor for occlusion in the combined cohort, was ER.

The number of amputations did not differ between ER and OSR. There were however, a high proportion of redo thrombolysis in the ER group, 18% (14/77) at one year. Eleven patients (14%) primarily treated with ER were subsequently converted to OSR with good results. One could argue that
primary ER works if supplemented with future reinterventions, but this comes at a cost, and a risk.

In the ER group, a small stent graft diameter and ALI were significantly associated with risk for occlusion. The importance of the diameter is in line with previous observations after stent graft treatment for chronic occlusive disease in the SFA. In a study from 2015, diameter <7 mm predicted loss of patency\textsuperscript{72}. Plausible reasons for this may be an increased risk of oversizing the stent grafts in smaller vessels\textsuperscript{73} and more severe consequences of edge stenosis at the proximal or distal ends. In studies on stent graft treatment of occlusive lesions in SFA, edge stenosis is common and associated with acute thrombosis\textsuperscript{74, 75}. With flexion of the knee, conformational changes will lead to shortening, twisting and kinking of the vessel. In a small CTA study of patients with PA, flexion of the knee led to significant lumen reduction and increase of vessel angulation\textsuperscript{76}. In our study, the median diameter of occluded stent grafts was 7mm and 8 mm for stent grafts that stayed patent. Although a small absolut difference, it was highly significantly different between the groups, indicating that in patients with smaller popliteal arteriers adjacent to PA, outcome after ER is particularly poor. It was not possible to evaluate oversizing from the available imaging.

In the ER group, patency was significantly associated with max angulation/vessel elongation in an analysis adjusted adjusted for stent graft diameter and indication. Although it should be emphasized that the statistical power of this association was relatively weak, with 25 events in 62 patients, it highlights an interesting potential mechanism for poor patency after ER, since many aneurysms are characterized by an increase in both vessel diameter and length. As a possible consequence of elongation, a distinct kink at the end of stentgraft was seen in some images from first procedure \textit{(Figure 11)}. 
Figure 11. Showing the right leg of a patient who was treated with a stent graft. A final DSA was made with the knee in 90° flexion and there was a pronounced kinking directly distally of the graft. The reconstruction occluded after six weeks. To open up the crural vessels, the patient was first treated with thrombolysis, followed by a bypass with vein. The arrows indicate the edge of the stent graft.

In others, with less elongation, there were no apparent kink at the initial procedure, but still, over time, an edge stenosis developed, and was revealed after thrombolysis of the occlusion. It is possible, that small diameter of the vessel, risk for oversizing, elongation and conformational changes at flexion are all factors, independent or synergetic, that will increase the risk for occlusion and/or edge stenosis in patients with PA, treated with stent grafts.

An unexpected finding was the strong correlation between smaller diameter of stent graft and treatment for ALI. In the adjusted analysis in the sub-group of ER, stent diameter remained a significant risk factor for occlusion, but indication did not. To what degree these two variables overlap is not discernable in this study, but the observed correlation of small vessel diameter with risk for occlusion warrants further investigation.

This case-control study has strengths and limitations. The main contribution compared to previous studies is the analysis of anatomical and procedural
features, in comparable groups. The fact that the study is based on a population based cohort reduces the risk of bias, which is otherwise a main weakness of any case-control study. Although the patients were registered prospectively in a registry, with a module dedicated to treatment of PA, detailed case history and imaging were collected retrospectively. Inevitably there were some missing data in the retrospective part of the study. Furthermore, patients were treated at 29 hospitals during 2008-2012, reflecting daily clinical practice at that time. The Viabahn stentgraft was modified in 2009, with contour shaped edge, possibly reducing the risk of edge stenosis.

The results from Paper I were evaluated for confounders and the main result was confirmed, since OSR had superior outcomes for treatment of PA. The main reasons for this were the anatomical features of the popliteal vessels and outflows, that had severe impact after ER, but were of less importance after OSR.

Ruptured popliteal aneurysms

In other aneurysm diseases the major concern is the risk of rupture, which also guides the indication for treatment. In patients with PA, this is an uncommon event and little is known about this sup-group. The largest cohorts before this investigation, were published 1953 and 1962, including 16 and 11 patients respectively. In neither of these studies were specific characteristics of patients with rPA described, and pseudoaneurysms after trauma were also included. A small group of six rPA, from a cohort of 89 patients treated for 124 PAs, was described in detail. The main finding was that the clinical presentations varied, with different and often incorrect preliminary diagnoses, a finding that was verified in Paper IV.

In this paper, it was clear that the usual indication of 2 cm in diameter for prophylactic surgery, is not correlated with risk for rupture. The mean diameter of rPA was were 63.7, mm, twice as large as those who had surgery for other indications. The patients with rPA were 8 years older than those treated for non-ruptured PA and had more comorbidities, but there was no correlation between age and diameter.

PAs may reach a diameter diameter of 10 cm without rupturing, and yet six ruptured in this series despite having a diameter of only 30-40 mm. It is known that even small-diameter aneurysms sometimes rupture. In Finland, 8 per cent of ruptured AAA were below 55 mm in diameter. In a multinational study, 6 per cent of internal iliac artery aneurysms were smaller than 4 cm at the time of rupture. Thus, factors other than size...
influence the risk for rupture. In this serie, two of the aneurysms were probably infected during sepsis, resulting in rapid expansion and rupture. Infection has been associated with a high risk of rupture in AAA. An unexpected finding was that almost half of the patients were on anticoagulants at time of the rupture. Most had been treated for a long time and the anticoagulation may explain why the aneurysms grew so large without thrombosis and embolisation, that would have resulted in ALI. In others, swelling of the leg associated with a contained rupture, may have been misinterpreted as a DVT. This was most likely the case in four patients who had their anticoagulation treatment initiated within two months of the diagnosis and treatment of rPA.

PAs usually rupture into the popliteal space/fossa, confined by muscles and tendons. The main symptoms were often pain and swelling, which lead to the misdiagnosis of DVT or Baker’s cyst (the preliminary diagnosis in 60%) and delay in treatment. Compression of the popliteal vein and development of DVT, are well known complications of large PAs, but 20 (44%) of the patients with an rPA presented with a swelling of the entire leg, which should not to be expected of a local compression in the popliteal space.

The result after surgery were quite good, given the challenge of this rare condition and the old age of the affected patients. Among those who survived one year, all but two reconstructions were patent. Of the four patients who needed an amputation, three presented with both ischaemia and rupture, obviously a difficult situation. But even if the patients got through the operation, survival at one year was only 58%, reflecting that this is a fragile cohort.

The limitations of this study is in the small numbers of this rare event, that makes it prone to type II statistical error. Furthermore, a long time interval was studied and imaging and clinical pathways may have changed over time, leading to more accurate diagnosis, although no such changes were seen in this small cohort.
Conclusions

OSR with vein is the preferred technique in the treatment of PA. Anatomical features of the popliteal vessel and the outflow will impact results after ER negatively, but less so when treatment is performed with OSR.

- The number of operations for PA almost doubled in 2008 – 2012 compared with 1994-2001, while the indications remained the same (Paper I).
- The surgical technique changed in favour of posterior approach with OSR, and of ER (Paper I).
- The use of vein graft predicted better outcome overall, but in particular in those with acute ischaemia. Posterior approach should be considered first choice, whenever feasible (Paper I).
- The outcomes after emergent procedures were less successful than after elective surgery, in particular after ER (Papers I and II).
- ER had inferior results compared with OSR, in all subgroups in the national cohort (Paper I and Paper II). Apart from ER, the only other independent risk factor for occlusion in the combined cohort was poor outflow (Paper II).
- Anatomical risk factors for occlusion in the ER subgroup were poor outflow, smaller stentgraft diameter and elongation (Paper II).
- A high prevalence of PA among subjects with screening detected AAA and SAA was found (Paper III).
- Patients with rPA were 8 years older than those treated for non-ruptured PAs. The aneurysms were twice as large and the initial clinical picture was misleading, resulting in frequent delays in diagnosis. The immediate outcome after surgery was good; however there was a high risk of death within a year (paper IV).
Future research on popliteal aneurysms

Epidemiology

There is a need for a consensus definition of PA and follow-up studies to see how this correlates to future growth and complications. As of now, the definition varies in different papers. We have used the combined definition of 12 mm in diameter and/or 1.5 times the adjacent vessel. A follow-up study would be valuable to see how this and other definitions correlate to further dilatation, need of surgery and future complications, in particular ALI, CLI and claudication.

The correlation between PA and aneurysms in CFA is well known\(^5,\ 62\), but the correlation to diameter and aneurysms of the CIAs in men is a novel finding. The correlation with the diameter of the CIAs, and the lack of correlation with the degree of aortic enlargement, supports the hypothesis that patients with infrainguinal aneurysms or aneurysms in CIA, might form a specific subgroup, in which hereditary factors are more important\(^8\).

Timely intervention

This thesis cannot answer the important question what indication is justifiable for prophylactic surgery of a PA. The diameter of 2 cm as indication is clearly not directly correlated to risk for rupture, and how it would affect the risk for occlusion or embolisation, was not investigated. In general we have mainly studied patients treated for PA, and those under surveillance were only studied in Paper III. The heterogeneity in result between different subgroups of indication brings forth the question what other factors will contribute to risk for complications. The unexpected finding of the strong correlation between ALI and small stent graft diameter needs to be explored. Flexion of the knee, elongation and conformational changes in the vessel, could have hemodynamic consequences\(^7\). These factors could have independent or synergetic effects that need to be investigated. A better understanding of these factors would enable a more tailored prophylactic treatment, and better understanding of the most suitable techniques.
Results after treatment with ER and OSR

In this theses, the examination of anatomical features, influencing results after ER and OSR, gives strong indications that these factors are of great importance to achieve good results after surgery for our patients. However, these features have not been evaluated before and other studies would be called for to confirm and further elaborate on the findings.

Minimal invasive techniques are preferable in some patients, given that the results are good. It is possible that ER can be improved by technical development, or by selecting this treatment to well-defined subgroups of patients. Results need to be thoroughly investigated, however before treatment is propagated outside of the context of clinical trials.
Acknowledgements

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Poplitea aneurysm, PA (bräck på pulsåden i knävecket) är det vanligaste bräcket på kärlen ute i kroppen. Trots det, är det en relativt ovanlig sjukdom som är svår att studera på ett enskilt sjukhus. Studier som tidigare publicerats är ofta från enstaka center med få patienter beskrivna i detalj, eller registerstudier med många patienter men översiktligt beskrivna. Förekomsten av PA i befolkningen och hur det hänger ihop med bräck på andra kärl finns det lite kunskap om.

PA kan ge komplikationer i form av ocklusion (stopp i flödet i pulsåden) eller embolier (blodproppar som åker längre ner i underbenet), med risk för otillräckligt blodflöde som kan leda till amputation. De kan också brista (rupturera), men det är mycket ovanligt och det finns därför mycket litet beskrivet om den gruppen. PA behandlas både akut och i förebyggande syfte hos symptomfria patienter. Indikationen för förebyggande åtgärd är en diameter på 2 cm, men mekanismerna som leder till ocklusion eller embolier är inte klarlagda.


Det har dock har varit svårt att värdera resultatet av behandlingen med de olika metoderna. De studier som finns är ofta från enstaka center och har en övervikt av icke symptomgivande PA till skillnad från studier av öppen kirurgi. För behandling med stentgraft har man valt patienter med bättre anatomiska förutsättningar, som tex bättre avflöde. Långtidsstudier sak-
nas. Samma process som gör att kärlret vidgar sig, kan också leda till en för- 
längning av kärlret, en slingrighet, men om det påverkar resultaten efter 
behandling är inte studerat.

Syftet med avhandlingen var att undersöka resultat efter öppen respektive 
endovaskulär behandling av PA och kartlägga vilka orsaksfaktorer som spe-
lar roll när man väljer behandlingsmetod. Vi ville undersöka förekomsten av 
PA och även beskriva vad som kännetecknar de få patienter som drabbas av 
rupturerat PA (rPA).

I det svenska kärlregistret (Swedvasc) registreras åtgärder utförda av kärl-
kirurser på nationell nivå. I den första studien (Paper I) gjorde vi ett utdrag 
från Swedvasc av de som behandlats för PA maj 2008 till maj 2012, fyra år. 
Registreringar dubbel-kontrollerades med ett kort protokoll och samman-
taget var 592 behandrade ben registrerade (499 patienter). Av dessa behand-
lades 95 med stentgraft. Resultat, i form av öppetstående graft, var betydligt 
sämre för stentgraft, vilket blev än tydligare när analysen gjordes i under-
grupper beroende på indikation. I gruppen akut ischemi behandlade var 48% 
de apa endovaskulärt behandlade öppetstående vid ett år, att jämföra med 
87% av de öppet opererade. I gruppen med icke symptomgivande PA, var 
motsvarande resultat 84% för EB och 94% för öppet opererade. Det primära 
öppetståendet i denna grupp var 67% (EB) jämfört med 89% (öppen kirurgi), 
dvs en stor andel fick ocklusioner som krävde reoperation.

Fördelen med registerdata är att kunna samla en stor grupp för analys av 
en ovanlig sjukdom. Nackdelen är att det saknas data om orsaksfaktorer, som 
anatomi, avflöde, medicinsk behandling och diameter. I syfte att analysera 
dessa detaljer, påbörjades en fall-kontrollstudie utgående från den nationella 
kohorten (Paper II). Efter att ha tillfrågat patienterna om deltagande, något 
som etikprövningsnämnden krävde vid denna tidpunkt, återstod 77 PA 
behandlade endovaskulärt: 25 för akut ischemi, 10 symptomgivande och 42 
icke symptomgivande. Ur gruppen med öppen kirurgi, lottades en 
kontrollgrupp baserad på indikation, två gånger större än den som behandlats 
med EB. Sammantaget 77 EB och 154 öppet opererade, 231 ben hos 212 
patienter. För dessa patienter begärde vi in journalkopior angående beha-
dling och uppföljning. Vi efterfrågade även en sen uppföljning med ultraljud 
från respektive sjukhus. Röntgen undersökningar som var gjorda innan eller i 
anslutning till behandling länkades till Sahlgrenska Universitetssjukhuset, 
Göteborg. Där analyseras avflöde, knickbildning på kärlret, slingrighet och 
andra anatomiska egenskaper som skulle kunna påverka resultaten.

Det visade sig att i en kohort, matchad för indikation, var det nästan tre ggr 
ökad risk för att ett stentgraft skulle ockludera jämfört med efter öppen ki-
rurgi. Vissa stentgrafter kunde åtgärdas med lokal propplösande behandling 
(trombolys) men det var 2,4 gånger förhöjd risk för att stentgraftet skulle
Förbli varaktigt stängt jämfört med efter öppen kirurgi. Av de stentgrafter som som var stängda, var det några patienter som endast fick fönstertitstursjuka, hos dem gjorde man ingen ytterligare åtgärd. Elva patienter fick så uttalade besvär av sänkt blodflöde till underbenet att de fick reopereras med öppen kirurgi. Resultaten efter reoperationerna (dvs de som konverterades till öppen kirurgi) var goda och ingen behövde amputeras under uppföljningstiden. Riskfaktorer för ocklusion i gruppen behandlade med EB var akut indikation, dåligt avflöde, mindre diameter på stentgraftet och uttalad slingrighet av kärllet.

Förekomsten av PA hos 65 åriga män med vidgad aorta studerades i Paper III. Screening för abdominellt aorta aneurysm, AAA (bräck på stora kroppspulsådern) påbörjades 2006 i Uppsala. I ett register (SweAAA) samlades alla de med AAA (30 mm eller mer i diameter) och även de med subaneurysmala aortor (SAA), 25-29 mm i diameter. Både aorta och kärlen på benen (i ljumskn, läret och i knävecket) mättes med ultraljud vid en efterundersökning som utfördes efter 1-2 år för de med AAA och efter 5 år för de med SAA, totalt 322 män. Ett PA definierades som minst 12 mm i diameter och/eller 1.5 gånger ökad storlek jämfört intilliggande kärl. Av de undersökta hade 14.2 % minst ett PA enligt definitionen ovan, många av dem var vidgade i båda knäartärerna (29%). Hos 3.0% vad PA ≥15 mm och hos 2.2 % ≥20mm. Det fanns inget sammanhang mellan PA och diameter på aorta, men däremot till vidden på iliaca communis (bäckenartären).

För att studera rPA (de PA som brister och blöder, en ovanlig händelse) gjorde vi ett ytterligare utdrag från Swedvasc och fick ett samlat nationellt material på dem som behandlats för rPA 1987 – 2008, totalt 45 patienter (Paper IV). Det visade sig att jämfört med de som behandlas av andra orsaker (Paper I), var patienterna betydligt äldre (8 år), och bräckten var dubbelt så stora (i medeltal 64 mm). Nästan hälften hade pågående behandling med blodförtunnande läkemedel och handläggandet blev fördöjd eftersom symptomen var lätta att misstolka, och de flesta patienter fick först en felaktig diagnos.

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