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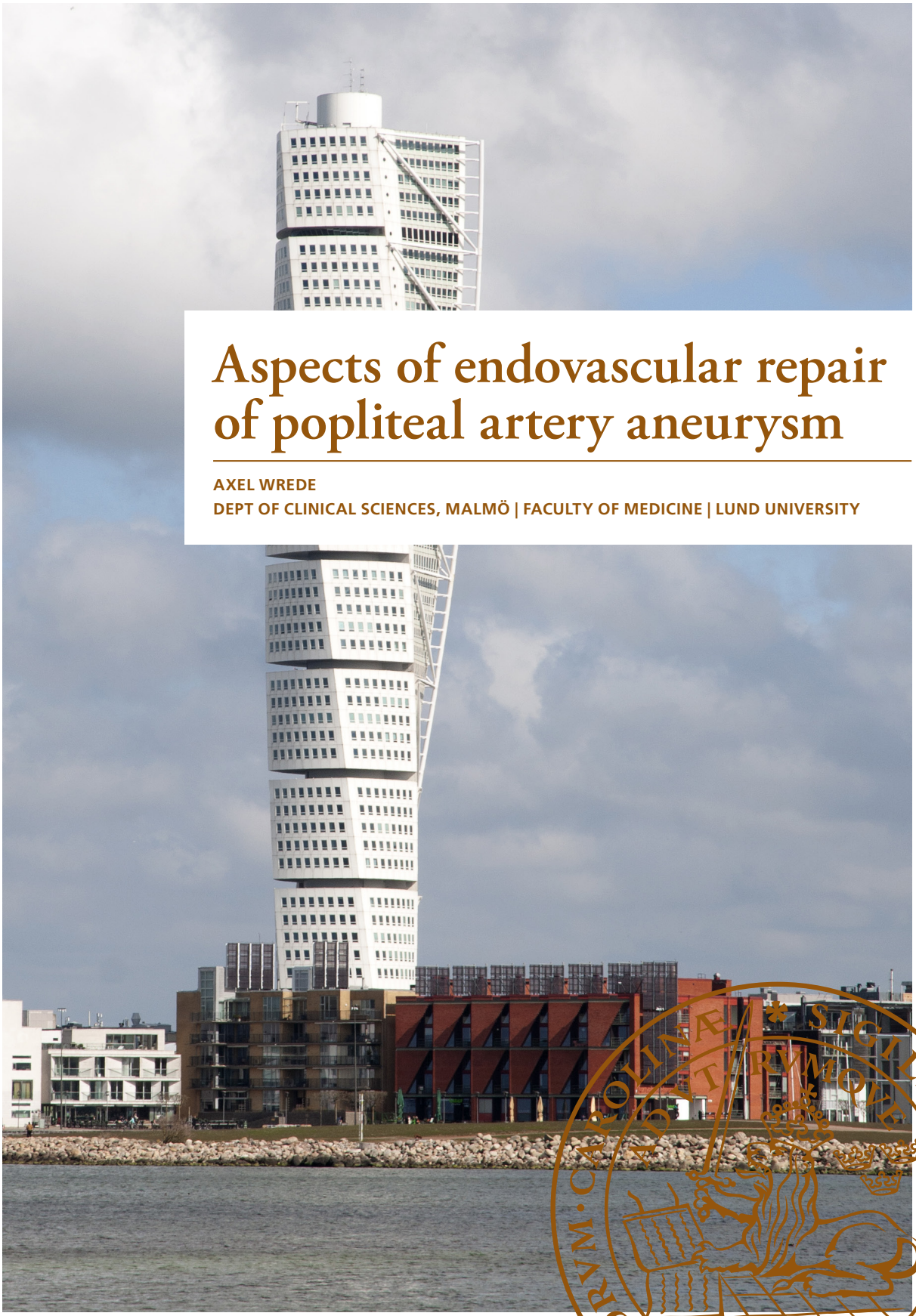
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Aspects of endovascular repair of popliteal artery aneurysm

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Aspects of endovascular repair of popliteal artery aneurysm

Axel Wrede



LUND
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DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on 9th of June at 01.00 pm at Lilla aulan, Medicinskt Forskningscenter, Jan Waldenströms gata 3, Malmö

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Organization: LUND UNIVERSITY Faculty of Medicine Department of Clinical Sciences, Malmö **Author:** Axel Wrede	**Document name: Doctoral dissertation** **Date of issue:** Sponsoring organization:

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Background: Although popliteal artery aneurysm (PAA) is a relatively rare disease, it carries the risk of causing thromboembolism in the lower limb leading to chronic and/or acute limb ischemia (ALI) and threatening the survival of the limb. There is an ongoing discussion if and when endovascular popliteal aneurysm repair (EPAR) should be offered over open popliteal aneurysm repair (OPAR).

Aims:

- To evaluate outcomes after OPAR and EPAR, in patients treated both electively (paper I) and due to ALI (paper II-III).
- To scrutinize anatomical and technical variables impact on stent-graft patency by scrutinizing adherence to Instruction For Use in patients receiving EPAR (paper IV).
- To investigate the presence and clinical significance of endoleak as well as long-term patency after EPAR using contrast-enhanced ultrasound (CEUS) (paper V).

Methods: All papers in the present thesis examine patients treated at Vascular Center, Skåne Univeristy Hospital, Malmö, Sweden. Retrospective data were collected from patients' medical charts after elective EPAR and OPAR between 2009-2017 (paper I), acute EPAR and OPAR between 2009-2019 (paper II) and all patients revascularized due to ALI between 2001-2018 (paper III). In paper IV, sizing criteria according to the IFU of Viabahn® endoprosthesis (W. L. Gore & Associates, Inc, Flagstaff, AZ, USA), maximal angulation and tortuosity index (TI) were scrutinized in pre- and peri-operative radiological images from all patients receiving EPAR between 2009-2019. In paper V, all patients included in paper IV with amputation-free survival were invited for follow-up examination including conventional ultrasound and CEUS. Endoleak was diagnosed by a core-lab consisting of three clinicians after analysis of all CEUS acquisitions.

Results: There was an increase in elective-to-acute repair ratio (p=0.014) as well as EPAR-to-OPAR ratio, both in elective (p=0.003) and acute (p=0.012) patients. In elective patients, EPAR was associated with higher major amputation-rate at one year (16% vs 0%, p=0.037) but fewer wound infections (0% vs 28%, p=0.003), major bleeding (4% vs 21%, p=0.046) and shorter in-hospital stay (median 2 vs 7 days, p<0.001). Patency at one year and amputation-free survival at follow-up were similar between patients receiving EPAR and OPAR, both in elective and acute patients. PAA was an independent risk factor for fasciotomy in patients revascularized due to ALI (OR 2.26; 95% CI 1.06-4.80, p=0.035). At least one deviation from IFU was present in 45/55 EPARs. Diameter difference >1 mm between overlapping stent-grafts was the only sizing criteria associated with lower primary patency at one year (43% vs 83%, p=0.004). TI and maximal angulation was not associated with loss of primary patency at one year. In an age-adjusted Cox regression model, TI (HR: 1.78/SD, 95% CI: 1.17-2.71, p=0.0071) and maximal angulation (HR: 1.73/SD, 95% CI: 1.018-2.95, p=0.043) were associated with combined major amputation/mortality at end of follow-up. Endoleak was detected in 16/31 EPARs. Aneurysms shrank in both aneurysms with and without endoleak (p=0.28) and there was no difference in patency at long-term follow-up between the two groups.

Conclusion: During the study period, use of EPAR has increased in the present vascular center. Although not being able to reproduce previous findings of inferior patency after EPAR compared to OPAR, the present thesis highlights the advantages of a minimal invasive technique as well as the risks. In patients presenting with ALI, PAA is an independent risk factor for fasciotomy. Deviations from IFU are common in patients receiving EPAR, though the clinical implications for these violations seem to be limited. Careful pre-operative planning should be carried out to avoid diameter difference >1 mm between overlapping stent-grafts. Prevalence of endoleak after EPAR was high, possibly owing to a superior sensitivity of CEUS compared to other imaging modalities. Use of CEUS is recommended for targeted examinations in case of aneurysm sac expansion after EPAR. Caution is warranted when interpreting and drawing conclusions from the present papers due to the limited study population.

Key words: Popliteal artery aneurysm, endovascular repair, vascular surgery, acute limb ischemia

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Aspects of endovascular repair of popliteal artery aneurysm

Axel Wrede



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Coverphoto: Turning Torso. In additon to being a symbol of Malmö, the tortuosity of the building and the external metal framework brings to mind both the popliteal artery and stent-graft, the two main actors scrutinized in papers of this thesis.

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“To know, is to know that you know nothing.”

- *Socrates*

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List of Papers

This thesis is based on the following papers, referred to in the text by their Roman numerals and reprinted with permission from thier respective publisher (paper I, II and IV) or copyright holders (study III and V).

Paper I

Wrede A, Wiberg F, Acosta S. Increasing the Elective Endovascular to Open Repair Ratio of Popliteal Artery Aneurysm. Vasc Endovascular Surg. 2018;52:115-23.

Paper II

Wrede A, Acosta S. Outcome of Open and Endovascular Repair in Patients with Acute Limb Ischemia Due to Popliteal Artery Aneurysm. Ann Vasc Surg. 2020;67:376-87.

Paper III

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

Paper IV

Wrede A, Lehti L, Eiberg JP, Acosta S. Adherence to instruction for use after endovascular repair of popliteal artery aneurysm. Vascular. 2022;30:276-84.

Paper V

Wrede A, Acosta S, Lehti L, Lorenzen US, Zielinski AH, Eiberg JP. Endoleak following Endovascular Repair of Popliteal Artery Aneurysm: Clinical Outcome and Contrast-Enhanced Ultrasound Detection. Int Angiol 2023; 42:26-32.

Abbreviations

AAA	Abdominal aortic aneurysm
ABI	Ankle-brachial index
ALI	Acute lower limb ischemia
CEUS	Contrast-enhanced ultrasound
CFA	Common femoral artery
CI	Confidence interval
CLTI	Chronic limb-threatening ischemia
CTA	Computed tomography angiography
DAPT	Dual antiplatelet therapy
DSA	Digital subtraction angiography
DUS	Duplex ultrasound
EPAR	Endovascular popliteal aneurysm repair
EVAR	Endovasular aneurysm repair
ePTFE	expanded polytetrafluoroethylene
ESVS	European Society for Vascular Surgery
GLASS	Global Limb Anatomic Staging System
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HR	Hazard ratio
ICD-10	International Classification of Diseases, 10th revision
IFU	Instruction for use
IQR	Interquartile range
KKÅ97	Swedish classification system of surgical procedures
MRA	Magnetic resonance angiography
OPAR	Open popliteal aneurysm repair
OR	Odds ratio
PA	Popliteal artery
PAA	Popliteal artery aneurysm

PAD	Peripheral arterial disease
PTA	Percutaneous transluminal angioplasty
RCT	Randomized control trial
SD	Standard deviation
SFA	Superficial femoral artery
SVS	Society for Vascular Surgery
TASC II	Trans-Atlantic inter-society consensus document II
TcPO2	Transcutaneous oxygen pressure
TI	Tortuosity index
Swedvasc	Swedish national registry for vascular surgery
US	Ultrasound
WIfI	Wound, Ischemia, foot Infection

Populärvetenskaplig sammanfattning

Arteria poplitea, eller knäveckspulsådern, är det blodkärl som för syresatt blod från låret till underbenet längs knäts baksida. Aneurysm, eller pulsåderbråck, innebär att en vidgning av artären bildar en så kallad bråcksäck som blodet behöver flöda genom. Uppstår ett åderbråck i knäveckspulsådern kallas detta för *poplitea aneurysm*, vilket utgör en av de vanligaste formerna av pulsåderbråck. Sjukdomen drabbar främst äldre män, där förekomsten uppskattas till 1% hos män över 65 år.

Det finns en stor samsjuklighet mellan att ha åderbråck i knäveckspulsådern och på stora kroppspulsådern i buken, så kallat bukaortaaneurysm. Sedan 2010 finns ett screeningprogram i Region Skåne där alla 65-åriga män bjuds in till ultraljudsundersökning av stora kroppspulsådern i buken. Hittas ett bråck på stora kroppspulsådern i buken vid screening utförs även ultraljudsundersökning i knävecken för att hitta eventuellt ytterligare pulsåderbråck.

Många upplever inga symtom från sitt åderbråck i knäveckspulsådern men sjukdomen innebär en ökad risk för att bilda blodproppar inuti bråcksäcken. Blodproppen inuti bråcksäcken tillväxer sakta och riskerar då orsaka stopp av knäveckspulsådern eller att delar av proppen lossnar och täpper igen mindre pulsådror utgående från knäveckspulsådern längre ner på underbenet, vilket i sin tur kan leda till syrebrist i underbenet eller foten. Graden av syrebrist beror på om stoppet är totalt, hur fort stoppet uppstått, var stoppet inträffar, och hur mycket blodförsörjning som finns via alternativa små pulsådergrenar (kollateraler) på underben och fot. I de fall då det blir plötsligt stopp i hela knäveckspulsådern måste blodflödet till underbenet återställas akut för att undvika irreversibla skador på underben och fot och behov av amputation. Musklerna i underbenet kan även ta skada när blodflödet återställs, då syretillförseln leder till att musklerna snabbt sväller och trycker på omgivande blodkärl och nerver. Man behöver då minska trycket genom att öppna musklernas höljen, så kallad *fasciotomi*. En mer gradvis tilltäppning av knäveckspulsådern eller pulsådrorna i underbenet kan i stället leda till mildare symtom så som smärta vid ökat syrebehov i vadmuskeln, till exempel vid gång.

När och hur patienter med åderbråck i knäveckspulsådern ska behandlas har länge debatterats inom kärlkirurgin. År 2021 utkom den amerikanska föreningen inom kärlkirurgi, Society for Vascular Surgery, med rekommendationer om att åderbråck i knäveckspulsådern med en diameter >20 mm bör behandlas, alternativt oberoende av storlek ifall patienten upplever besvär. Behandling utförs i huvudsak genom två olika tekniker, öppen kärlkirurgi eller endovaskulär behandling.

Vid öppen operation åstadkoms fortsatt blodflöde till underbenet genom att blodet leds runt bråcksäcken via en ven eller ett syntetiskt kärl som kopplas till pulsådern ovan respektive nedan om pulsåderbråcket, en så kallad by-pass. För att förhindra fortsatt blodflöde genom pulsåderbråcket får kirurgen knyta en knut runt om

knäveckspulsådern ovanför och nedanför bråcket. Detta är en relativt omfattande operation som oftast innebär att patienten behöver sövas. Endovaskulär behandling utförs däremot efter lokalbedövning i ljumsken. En så kallad *stentgraft* bestående av ett metall-nät täckt av en vätskeavvisande väv, placeras inuti blodkärlet genom bråcksäcken och förankras till den friska artären ovanför och under bråcket. Ibland behövs flera kärlproteser användas, som då måste överlappa varandra. På så sätt utesluts bråcksäcken från blodcirkulationen.

Den endovaskulära behandlingen är ett mindre kirurgiskt ingrepp jämfört med öppen operation, vilket borde innebära lägre risk för operationskomplikationer. På senare år har dock flera studier visat att kärlproteser i knäveckspulsådern riskerar att täppas igen av nya blodproppar efter endovaskulär behandling i högre utsträckning än en by-pass efter öppen operation.

Kvarvarande blodflöde utanför kärlprotesen i bråcksäcken efter behandling, så kallat *endoläckage*, förekommer hos patienter behandlade för åderbråck i knäveckspulsådern. I vilken omfattning läckande blodflöde utanför kärlprotesen i bråcksäcken förekommer och dess påverkan på bråcksäcken efter behandling har dock tidigare studerats i mycket ringa omfattning efter särskilt endovaskulär behandling.

Denna avhandling syftar till att utvärdera behandlingen av åderbråck i knäveckspulsådern hos patienter vid Kärlkirurgiska kliniken, Skånes Universitetssjukhus Malmö, och består av fem delarbeten;

- I delarbete I granskades journaler från patienter som genomgått planerad behandling av åderbråck i knäveckspulsådern mellan 2009 och 2017.
- I delarbete II granskades journaler från patienter som genomgått akut behandling av åderbråck i knäveckspulsådern mellan 2009 och 2019.
- I delarbete III granskades journaler från patienter som genomgått akut kärlkirurgisk behandling på grund av akut cirkulationsstopp till benen.
- I delarbete IV granskades journaler och röntgenbilder från patienter som behandlats endovaskulärt med kärlproteser för att jämföra hur väl ingreppen förhållit sig till de användar-instruktioner (*Instruction For Use*, IFU) som ges ut av kärlprotes-tillverkaren.
- I delarbete V undersöktes förekomsten av läckande blodflöde utanför kärlprotesen i bråcksäcken genom en kontrastförstärkt ultraljudsundersökning hos patienter som behandlats endovaskulärt med kärlproteser.

Sammanfattningsvis visade resultaten;

- En ökning av patienter som genomgått planerad behandling av åderbråck i knäveckspulsådern i förhållande till akut behandling. Andelen planerade behandlingar som utförts endovaskulärt har även ökat i förhållande till antal öppna operationer.
- Patienter som genomgått planerad endovaskulär behandling behövde oftare amputera en del av benet efter 1 års uppföljning jämfört med de som genomgått planerad öppen operation. Planerade endovaskulära behandlingar innebar dock lägre risk för sårinfektioner och blödningskomplikationer, samt kortare inneliggande sjukhusvistelse, jämfört med planerade öppna operationer.
- Patienter med syrebrist i benet på grund av akut propp till följd av åderbråck i knäveckspulsådern behövde oftare få muskelfacken i underbenet öppnade efter att cirkulationen förbättrats med kärlkirurgisk behandling än patienter med akut cirkulationsstopp i benet av annan orsak.
- En majoritet (82%) av alla endovaskulära behandlingar utfördes med minst en avvikelse från användar-instruktionerna. Det fanns ingen statistiskt säkerställd skillnad i utfall efter behandling mellan behandlingar utförda enligt användar-instruktioner eller ej. Vid fördjupad analys sågs dock att behandlingar som gjorts med överlappande kärlproteser med >1 mm diameterskillnad hade en ökad risk att täppas igen inom ett år.
- Läckande blodflöde utanför kärlprotesen i bråcksäcken hittades i en majoritet (52%) av alla patienter. Bråcksäcken krympte dock både hos patienter med och utan läckande blodflöde, och graden av storleksminskning påverkades inte av förekomst av eventuellt läckande blodflöde.

Resultaten i denna avhandling understryker vikten av att varje patient erbjuds rätt behandlingsmetod. De kortsiktiga fördelarna med endovaskulär behandling måste vägas mot ökade risker på sikt. Det är möjligt att endovaskulär behandling kan utgöra ett alternativ till öppen operation hos särskilt sköra patienter, medan flertalet förmodligen gynnas mest av öppen operation. Delarbete V visade även att läckande blodflöde utanför kärlprotesen i bråcksäcken efter endovaskulär behandling förekommer i högre utsträckning än tidigare rapporterat, men att betydelsen av dessa är begränsad. De slutsatser som kan dras från dessa studier begränsas dock av ett litet patientunderlag. Det behövs vidare forskning på större patientgrupper, eller helst en studie där patienter lottas till endera behandlingsmetod, för att bättre kunna vägleda val av behandlingsmetod.

Thesis at a glance

Paper	Aim	Methods	Main findings
I. Increasing the Elective Endovascular to Open Repair Ratio of Popliteal Artery Aneurysm	To evaluate time trends in treatment modality and to compare outcomes between EPAR and OPAR in electively treated patients.	Retrospective cohort study of 102 PAAs receiving either OPAR or EPAR, between 2009-2017. Focusing on 66 PAAs treated electively.	An increase in elective patients treated with EPAR compared to OPAR. Fewer wound infections and major bleeding as well as shorter in-hospital stay but higher major amputation-rate after one year in patients receiving EPAR.
II. Outcome of Open and Endovascular Repair in Patients with Acute Limb Ischemia Due to Popliteal Artery Aneurysm	To evaluate proportion of elective versus acute treatment for PAA since the introduction of the AAA-screening program. To evaluate risk factors for major amputation/mortality in patients with ALI.	Retrospective cohort study of 125 PAAs receiving either OPAR or EPAR, between 2009-2019. Focusing on 39 PAAs in 39 patients with ALI.	An increase in PAAs treated electively compared to acute during the study period. No difference in major amput/mortality between patients with ALI receiving EPAR or OPAR.
III. Risk Factors for Fasciotomy After Revascularization for Acute Lower Limb Ischaemia	To evaluate risk factors for fasciotomy and investigate risk factors associated with major amputation/mortality at one year after reperfusion due to ALI.	Retrospective observational study on 843 revascularizations for ALI between 2001-2018.	Independent risk factors for fasciotomy were Rutherford IIb, renal insufficiency, open vascular surgery and PAA, while patients with female gender and anemia had lower risk.
IV. Adherence to Instruction for Use after Endovascular Repair of Popliteal Artery Aneurysm	To evaluate adherence to the IFU in patients undergoing EPAR. A secondary aim was to evaluate factors associated with patency at one year.	Retrospective cohort study of 55 PAAs receiving EPAR. Pre- and perioperative imaging scrutinized in relation to IFU, tortuosity index and maximal PAA angle.	At least one deviation from IFU in 45/55 EPARs. Diameter size difference >1 mm between overlapping stent-grafts was associated with lower primary patency at one year.
V. Endoleak following Endovascular Repair of Popliteal Artery Aneurysm: Clinical Outcome and Contrast-Enhanced Ultrasound Detection	To investigate aneurysm sac growth, presence and classification of endoleak after EPAR using CEUS. Also, to investigate stent-graft patency at long-term follow-up in EPAR-treated patients.	Cross-sectional study of 31 PAAs in 26 patients receiving EPAR.Patients were examined by DUS, CEUS and clinical examination at end of follow-up. Core-lab analysis of CEUS acquisitions.	Endoleaks in 16/31 EPARs, and ten had type II endoleaks. Aneurysms shrank in both aneurysms with and without endoleak and there was no difference in patency at follow-up between the two groups.

ALI; Acute lower limb ischemia, CEUS; Contrast-enhanced ultrasound, DUS; Duplex ultrasound, EPAR; Endovascular popliteal aneurysm repair, IFU; Instruction for Use, OPAR; Open popliteal aneurysm repair, PAA; Popliteal artery aneurysm.

Introduction

Anatomy and definition

The popliteal artery (PA) is a direct continuation of the superficial femoral artery (SFA) distal to the adductor hiatus. It runs though the popliteal fossa, a restricted space on the posterior side of the knee also containing the popliteal and small saphenous vein, the tibial and common fibular nerves, lymph vessels and lymph nodes. Along its course, the PA gives rise to the genicular arteries and bifurcates below the knee into the anterior tibial artery and the tibiofibular trunk, which in turn branches into the posterior tibial artery and the fibular artery[1] (Figure 1). The PA is relatively fixed proximally at the adductor hiatus and distally at the origin of the anterior tibial artery, acting as hinge points when flexing the knee[2].

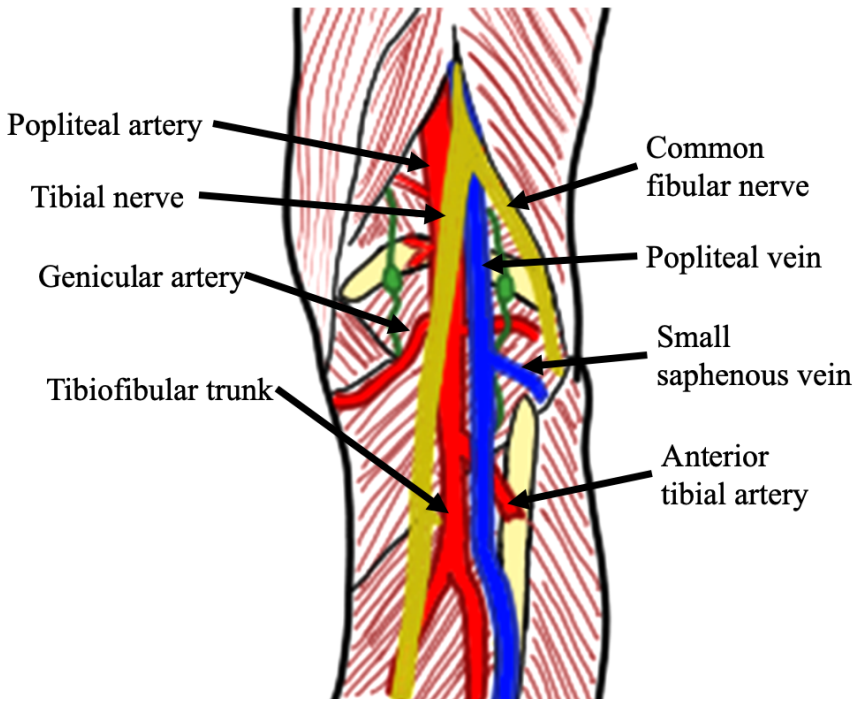


Figure 1. Illustration of the anatomical structures passing through the popliteal fossa, from a posterior view. Lymph nodes and lymph vessels are illustrated in green. ©Axel Wrede

The PA has a slightly cone-shaped profile, with wider diameter at its origin and narrower at the distal end[3]. Studies on the size of the PA in healthy individuals have reported a mean diameter between 0.5 to 0.9 cm[3-5]. Larger diameter has been reported to be related to higher age, larger body surface area and male sex[6].

Aneurysm constitutes a dilation of a blood vessel anywhere in the circulation. Arterial aneurysms are further divided into true aneurysms and pseudoaneurysms. A widening of the artery involving all layers of the vessel wall is considered a true aneurysm, whereas a pseudoaneurysm is in fact a contained hematoma constricted by a wall of connective tissue, often caused by trauma or loss of vascular graft anastomotic integrity[7]. A mycotic or infectious aneurysm is a third type of more rare aneurysms, which is caused by a bacterial, fungal or viral infection of the arterial wall[8].

There is no single established definition of when to consider the popliteal artery aneurysmatic. Instead, several different definitions have been used in previous studies on popliteal artery aneurysm (PAA): arterial diameter 150% of the normal diameter[9], diameter 150% of adjacent arterial segments[10, 11], diameter 150% of the contralateral PA[10], diameter ≥ 12 mm[11], diameter ≥ 15 mm[12] or diameter ≥ 20 mm[13].

Epidemiology

Not a great amount of research has been published on the epidemiology and natural history of PAA, although it is considered the most common type of peripheral arterial aneurysm[13]. Trickett et al. found a PAA, defined as arterial diameter ≥ 15 mm, in 1% of 1074 men aged 65-80 years[12]. The disease is far more common in men compared to women, with a 20:1 ratio[14, 15]. Having a PAA is associated with multi-aneurysm disease as bilateral PAA is present in 50% and abdominal aortic aneurysm (AAA) in 30-40% of patients treated for PAA[13, 15]. Conversely, reports show a prevalence of PAA in 10-15% of patients with AAA[10, 11].

A retrospective study reporting growth rates of 110 PAAs in 85 patients showed a mean aneurysm growth of 1.57 mm/year, with higher growth rate associated to larger aneurysm diameter and concomitant AAA[16]. Presence of mural thrombus within the aneurysm has also been reported as a predictor for higher growth rate[17].

Screening program for AAA

A screening program for AAA were initiated in Uppsala County, Sweden, in 2006 and has gradually reached national coverage[18]. In 2010, the screening program was implemented in Region Skåne, inviting all men at the age of 65 for an ultrasound examination of the abdominal aorta and has reached >80% compliance[19, 20]. There appears to be some evidence suggesting screening for AAA when a peripheral aneurysm is encountered[21]. Some authors advocate screening for PAA when an AAA is encountered due to the high prevalence of PAA in patients with AAA[11, 22].

However, questions have been raised regarding the cost-effectiveness of additional ultrasound screening for PAA in AAA screening program[23].

Historical milestones

Management of aneurysms has vexed surgeons for many centuries and was described by Galen in the second century as a pulsatile tumour that disappears when applied pressure[24]. In the third century, Antyllus proposed treatment of an PAA through ligation of the artery proximal and distal to the aneurysm followed by opening and emptying of the aneurysm sac. This, or some variation of this technique, remained the predominant approach to treat PAAs for one and a half millennia even though it often carried a fatal outcome[24, 25].

The next major advancement came in 1785 when John Hunter performed the "Hunterian operation" on a patient with PAA, by ligation of the artery at the end of the subsartorial canal (Hunters canal) and leaving the aneurysm sac untouched. Using this method, Hunter successfully avoided amputation in four out of five patients, seen as a great achievement[25].

A decade later, in 1888, Rudolph Matas introduced "endoaneurysmorrhaphy" as a new way of treating aneurysms. Through this technique, haemostasis is first attained by compression and elevation of the limb followed by dissection of the aneurysm sac. After any collaterals feeding the aneurysm have been ligated by suturing from within, the lumen of the aneurysm itself is "obliterated" by successive layered ligation of the aneurysm sac. The obliteration could either be complete, relying limb survival on collateral circulation, or "reconstructive" by leaving a patent channel within the aneurysm, allowing blood flow through the arterial segment[26]. Summarizing his career, Matas reported treatment of 40 PAAs by endoaneurysmorrhaphy, with a technical success rate of 95%[27].

The first account of a vein graft is attributed to José Goyanes, treating a PAA in 1906. The artery was ligated above and below the PAA followed by end-to-end anastomoses of the in-situ popliteal vein to the proximal and distal arterial segments[28]. Following years, repair using reversed saphenous vein graft to bypass the aneurysm was developed and described by Erich Lexer (1907), Hogarth Pringle (1913) and Bertrand Bernheim (1916)[29].

In 1947, Arthur Blakemore combined the endoaneurysmorrhaphy of Matas with a interposition vein graft, close to the posterior approach of popliteal aneurysm repair used today[30]. Until the 1960's, most PAA repairs were performed by surgery in the popliteal fossa[31]. The modern-day medial approach originates from the described operation by W. Sterling Edwards in 1969. The aneurysm itself was left unexposed but instead, ligation of the artery and anastomoses of vein bypass were performed through small incisions above and below the knee[32].

A new paradigm in the treatment of PAA, endovascular repair, was introduced in 1994. Marin et al. managed to implant a polytetrafluoroethylene graft through the aneurysm, sealing it to the proximal and distal arterial segments using bare-metal stents[33]. Since then, several so-called *stent-grafts*, combining a self-expanding stent with a luminal fabric lining, have been introduced and used to treat PAA[34].

Clinical presentation

In the literature, PAA has been referred to as a "sinister harbinger of sudden catastrophe" as the clinical presentation of PAA ranges from asymptomatic to intermittent claudication, chronic limb-threatening ischemia (CLTI) or acute lower limb ischemia (ALI)[32, 35, 36]. This result from turbulent blood flow within the aneurysm sac which increases risk of clotting of the blood leading to thrombosis of the PA or embolization to the crural arteries. Severity of ischemic symptoms is dependent on anatomic location of the occlusion and whether occlusion happen sudden or gradually over time as collateral arteries may to some extent compensate loss in blood flow in the original pathway[37]. ALI is defined as a sudden reduction in arterial blood flow with symptom duration < 2 weeks, that potentially threatens the survival of the limb, requiring emergent evaluation and management[37]. The Rutherford classification system is used to grade the severity of ALI and guide decision on further evaluation or intervention (Table 1)[38].

Table 1. Rutherford classification system of acute limb ischemia[38]

Category	Description/prognosis	Findings		Doppler signal	
		Sensory loss	Muscle weakness	Arterial	Venous
I. Viable	Not immediately threatened	None	None	Audible	Audible
IIa. Threatened – marginally	Salvageable if promptly treated	Minimal (toes) or none	None	Inaudible	Audible
IIb. Threatened – Immediatley	Salvageable with immediate revascularization	More than toes, associated with rest pain	Mild, moderate	Inaudible	Audible
III. Irreversible	Major tissue loss or permanent nerve damage inevitable	Profund, anestetic	Profund, paralysis	Inaudible	Inaudible

The sensory nerves are more sensitive to local ischemia than the motor nerves, why sensory loss develops earlier than muscle weakness. In case of severe ALI, the limb can become immediately threatened within a few hours. Clinical symptoms of ALI are described as the 6 Ps: pain, pallor, pulselessness, perishing cold, paraesthesia and paralysis (Figure 2)[39]. Rupture of the aneurysm is a rare event accounting for a couple of percentages of treated patients, predominantly in older patients with larger aneurysms (Figure 3)[40].



Figure 2. Doppler findings (A) and clinical examination (B) are cornerstones in diagnosis and grading of acute limb ischemia. ©Axel Wrede (A)/©Talha Butt/Stefan Acosta (B)

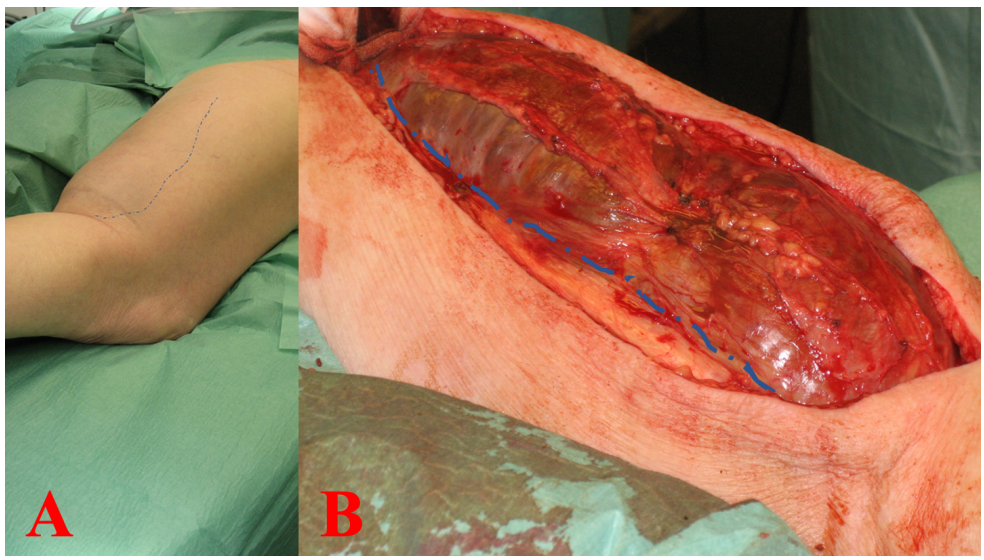


Figure 3. Ruptured popliteal artery aneurysm. The dotted blue line marks the lateral (A) and medial (B) margin of the hematoma. ©Stefan Acosta

Various classification systems for chronic limb ischemia have been developed, focusing on either clinical and/or diagnostic parameters. The first grading system was introduced in the 1950's by Fontaine et al. which stratifies patients according to clinical presentation only[41]. Rutherford et al. later added objective measurements in the form of treadmill test, ankle pressure and toe pressure to the criteria[38]. In 2014, the Wound, Ischemia and Foot Infection (WIfI) system was introduced by the Society for Vascular Surgery (SVS) which grades the limb by assessing extension

of tissue loss and local infection together with perfusion estimated by ankle-brachial index (ABI), toe pressure or transcutaneous oxygen pressure (TcPO2)[42].

Other systems for classification of PAD are based on anatomic distribution of stenotic/occlusive lesions, rather than clinical presentation. The Trans-Atlantic inter-society consensus document II (TASC II) system categorize severity of lesions in the aorto-iliac, femoro-popliteal and intra-popliteal regions[43], whereas the Global Limb Anatomic Staging System (GLASS) stage the vascular anatomy according to complexity of lesions in the target artery path planned for revascularization[44]. In both classification systems, endovascular revascularization is recommended for less complex lesions while open bypass surgery is recommended for more complex lesions. However, presence of a PAA is not accounted for in neither TASC II nor GLASS, and hence does not impact the recommendation for treatment modality.

Symptoms may also arise from compression of local structures by the aneurysm sac resulting in impaired venous blood flow causing lower leg swelling or even deep vein thrombosis, or nerve compression causing neurological symptoms[45, 46].

Indication for treatment

The Swedish National Registry for Vascular Surgery (Swedvasc) is a web-based registry with national coverage in Sweden[47]. In 2014, a separate module for prospective registration of PAAs were introduced. The indication for treatment in patients with PAA during 2021 and 2014-2020 are shown in Table 2[48]. A study from the Vascunet, a collaboration of population-based registries, recently reported that indications for treatment differ between different countries, with acute treatment ranging from 17.0% in Serbia to 31.0% in Norway[49]. Treatment modality and number of operations also varies among countries, as 58.1% of elective PAA were treated with endovascular repair in New Zealand compared to 0% in Denmark and Iceland, and 2.4 repairs/million inhabitants/year were performed in New Zealand compared to 19.3 in Sweden[49].

Table 2. Indication for treatment reported in Swedvasc. Modified from Swedvasc's annual report 2022 for operations in 2021[48].

Indication for treatment	2021 (%)	2014 – 2020 (%)
Asymptomatic	50.3	47.1
Chronic limb ischemia	13.6	16.3
Acute limb ischemia	21.1	25.2
Rupture	4.0	2.6
Other	11.1	8.8

When and how to treat PAA has been a controversial issue over the years and is still debated[50-52]. As PAAs often are asymptomatic at diagnosis, the risk of future symptoms and complications must be balanced against the peri- and postoperative

risks of repair. A systematic review by Beuschel et al. published in 2022 on the natural history of PAA reported that half of patients treated conservatively develop complications within five years, though the authors acknowledged that existing literature is limited and there is a low level of certainty[53]. Patients with PAA have worse outcome after acute compared to elective treatment in terms of patency, limb salvage and mortality[45, 54]. Timing of elective treatment has been based on the size of PAA diameter as reports have shown higher risk of ALI and rupture in larger aneurysms[40, 55, 56], though other studies have failed to reproduce this relation[57, 58]. Size does not seem to be the only prognostic factor for thrombosis however, as distortion $\geq 45°$ within the aneurysm[56], presence of mural thrombus[55] and poor distal runoff[59] have been described as risk factors for ALI.

In 2021, the SVS published the first international clinical practice guidelines on PAA based on review of the existing literature and expert opinion, using the GRADE system for recommendations (Table 3[60])[61]. The guidelines recommend repair of asymptomatic patients with PAA diameter >20 mm or PAA diameter >30 mm in high clinical risk patients (grade 2C). Repair is also recommended regardless of PAA size in case of present mural thrombus and clinical signs of embolism or poor distal runoff (grade 2C).

Table 3. Grading of Recommendations, Assessment, Development and Evaluations (GRADE) used in SVS guidelines[60].

Strength of recommendation	Quality of evidence		
	Grade A	Grade B	Grade C
Grade 1	Strong recommendation, high quality of evidence	Strong recommendation, moderate quality of evidence	Strong recommendation, low quality of evidence
Grade 2	Weak recommendation, high quality of evidence	Weak recommendation, moderate quality of evidence	Weak recommendation, low quality of evidence

Vascular Imaging

Different imaging modalities are used to visualize clinically suspected PAAs, including digital subtraction angiography (DSA), magnetic resonance angiography (MRA), computed tomography angiography (CTA) and duplex ultrasound (DUS), each of which have its advantages and drawbacks.

DSA has traditionally been considered gold standard for vascular imaging of patients with lower limb ischaemia[62, 37]. However, DSA may fail to diagnose a thrombosed PAA or appropriately determine size of the aneurysm in case of extensive mural thrombus. Furthermore, DSA entails nephrotoxic contrast agent[63]. Use of carbon dioxide may be used instead to spare renal function[64], perhaps at the

expense of less accurate imaging of arterial anatomy. Due to a small but constant risk of procedure-related complications, DSA should not be offered diagnostically but only in connection with endovascular treatment. For pure diagnostics, the non-invasive modalities should be preferred: CTA, MRA and DUS.

DUS has shown good diagnostic performance of most arterial segments in patients with PAD[65]. It performs better in the assessment of the supra- compared to infragenicular arteries[66]. However, contrast-enhanced ultrasound (CEUS) has been reported to improve the diagnostic accuracy of pre-operative evaluation of lower leg arteries in patients with critical limb ischemia[67]. DUS is a non-invasive method that can be used bedside, but the diagnostic performance of ultrasound is considered user-dependent and might not always be available.

CTA is a non-invasive, generally available modality that allows rapid imaging of large parts of the vascular system with high diagnostic performance[68]. Besides accurate imaging of the lower extremity arterial tree, extravascular incidental findings may be both abundant and predictive for amputation-free survival in patients with ALI[69]. In cases with severe PAD with heavily calcified plaques and slow contrast flow, CTA imaging of the infrageniculate vasculature can be challenging[70]. Like DSA, CTA rely on ionizing radiation and nephrotoxic contrast.

MRA produces high-quality images with the possibility of 3D-reconstruction, as in CTA, but does not involve ionizing radiation or iodine contrast[68]. In addition, MRA might offer improved diagnostic accuracy in patients with very low flow and/or heavily calcified below-knee arteries. It is, therefore, often considered the preferred imaging modality for diagnosis and planning intervention, though longer examination times and often lower availability than CTA limit the use in patients with ALI[37, 71]. Usability might also be restricted due to contraindications in form of medical implants, claustrophobia or known allergy to gadolinium contrast agent.

Treatment of popliteal artery aneurysm

The main aim of definite repair of PAA is to ensure perfusion to the lower leg and prevent thromboembolism through either open popliteal aneurysm repair (OPAR) or endovascular popliteal aneurysm repair (EPAR) by excluding the aneurysm sac from the circulation.

Optimizing distal run-off

Local intra-arterial thrombolysis can be used either pre- or intraoperative in the acute treatment of a PAA to restore blood flow through a thrombosed aneurysm and/or embolized arteries in the calf or foot[72]. After local anaesthesia in the groin, arterial access is typically achieved after ultrasound-guided antegrade or retrograde puncture of the ipsilateral or contralateral common femoral artery (CFA),

respectively, followed by administration of fibrinolytic agent through a thrombolysis catheter positioned in the occlusion[73].

The primary intention for thrombolysis is not to open an occluded PAA, but to improve run-off before definite PAA repair by lysis of embolic occlusions of the calf arteries. Ravn and Björck reported that preoperative thrombolysis improved the run-off in 87% of PAA with ALI[74]. However, intra-arterial thrombolysis increases the risk of bleeding complications. In a study on 220 patients with ALI (of which 15 had PAA) receiving intra-arterial thrombolysis, 33% developed haemorrhage either at the introducer site or distant, including one case of fatal haemorrhagic stroke. In this series of patients, thrombolysis was discontinued prematurely in 6% due to haemorrhage[75].

Improving run-off and clearance of embolic calf arterial occlusions can also be performed by endovascular aspiration of embolus, pharmacomechanical embolectomy[76] and open tibial embolectomy by surgical exposure below knee[77, 78]. Stenosis of the calf arteries may also be treated by mainly endovascular angioplasty to improve run-off[76]. Pursuing endovascular options means that treatment can be continued at the endovascular laboratory facility, while switching to an open surgical technique means transferral to the operation theatres. In a few vascular centers, all operation facilities have been built to suit both endovascular and open surgical treatment, hybrid operation rooms, with no need for transferals between different facilities if there is a need to switch techniques.

The clinical practice guidelines by SVS[61] recommend that patients with ALI Rutherford I or IIa and impaired runoff should undergo preoperative thrombolysis or pharmaco-mechanical intervention (grade 1B). However, in case of more severe ischemia, patients may not benefit from the additional ischemic time during thrombolysis[79, 80]. In patients with ALI Rutherford IIb, prompt definite repair of the PAA with possible adjuncts is recommended (grade 1B).

Open popliteal aneurysm repair

Definite treatment by OPAR is accomplished through either a medial (Figure 4A) or posterior (Figure 4B) approach. In both cases, either an autologous vein graft or a synthetic graft is used as a conduit to direct the blood flow past the PAA.

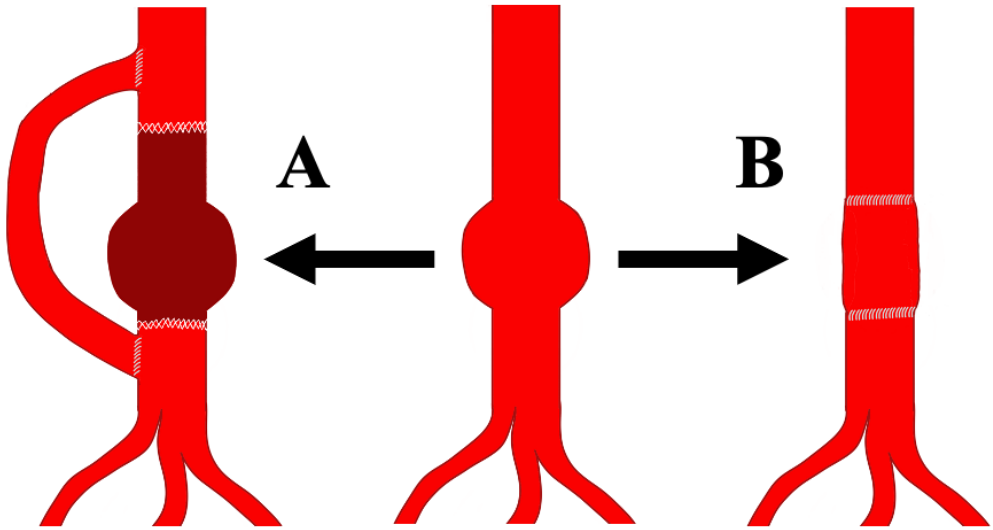


Figure 4. Schematic illustration of result after OPAR through medial approach (A) and posterior approach (B). ©Axel Wrede

Performing the medial approach, which is most used, the patient is put in the supine position, and an incision is made along the medial side of the leg. The same incision can be used to harvest the great saphenous vein and expose the arterial segments above and below knee. The great saphenous vein can be used either as a conduit after removing a long segment and then reversing it or as an in-situ conduit[81] after destroying the venous valves with a valvulotome. If the ipsilateral or contralateral great saphenous veins are absent or unusable, harvesting of lesser saphenous or cephalic veins could be considered before use of synthetic graft as bypass material[82]. The graft bypasses the aneurysm by running subcutaneously, or occasionally in smaller aneurysms, in a deeper anatomical or subfascial planes[83], from the distal CFA or SFA to the PA below the knee or connecting directly to one of the fibular or tibial arteries. Both proximal and distal anastomoses are usually end-to-side anastomoses but can also be end-to-end anastomoses. The PA is then ligated proximal and distal to the aneurysm.

The posterior approach is reserved for patients with PAA restricted to the popliteal fossa and no aneurysmal or ectatic adjacent arterial segments. The patient is put in the prone position, and an S-shaped incision over the popliteal fossa exposes the aneurysm. After isolation of surrounding nerves and veins, control of the artery is attained, and the aneurysm sac is opened. Bleeding from genicular branches is oversewn from within the aneurysm. An interposition, preferentially vein, graft is then sutured with end-to-end anastomoses to connect the proximal and distal PA (Figure 5).

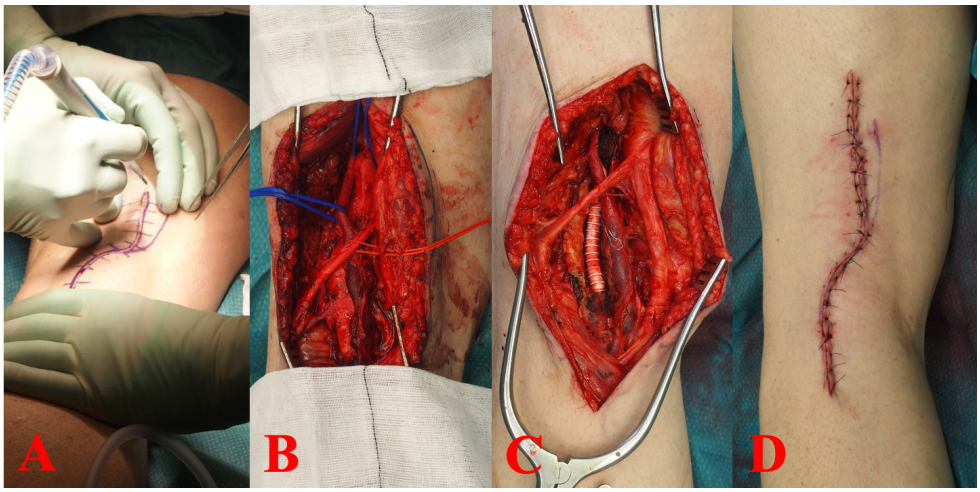


Figure 5. Open popliteal aneurysm repair through posterior approach. Access to the popliteal fossa is achieved via a S-shaped incision (A) followed by dissection and isolation of structures surrounding the artery (B). After the aneurysm sac is opened and genicular branches oversewn, an interposition graft (in this case a synthetic graft) is sutured with end-to-end anastomoses to the proximal and distal popliteal artery. ©Axel Wrede

Both medial and posterior approaches have shown excellent and comparable results regarding patency and limb salvage. Dorweiler et al. reported outcome of 206 PAAs treated with OPAR showing primary and secondary patency of 88.1% and 96.5%, respectively, and limb salvage of 96.9% at five years[84]. Graft material impact outcome after OPAR as vein grafts have shown superior patency to synthetic grafts, regardless of medial or posterior approach[14, 45, 49, 85]. Therefore, a single-segment great saphenous vein is advocated as a conduit[61].

Endovascular popliteal aneurysm repair

Definite treatment by EPAR is performed through intra-arterial deployment of an impermeable stent-graft with landing zones proximal and distal to the PAA, thus preventing circulation of the aneurysm sac (Figure 6). As in local intra-arterial thrombolysis, arterial access is gained via either the ipsi- or contralateral CFA and a guidewire is placed distal to the aneurysm. Hence, EPAR can easily be combined with adjunctive endovascular interventions such as thrombolysis, pharmacomechanical thrombectomy, aspiration or percutaneous transluminal angioplasty (PTA).

Currently, Viabahn® endoprosthesis (W. L. Gore & Associates, Inc, Flagstaff, AZ, USA), an expanded polytetrafluoroethylene (ePTFE) graft with heparin-coated luminal surface covered by an external nitinol stent, constitutes the stent-graft most used. Though, the manufacturer states in its Instruction For Use document that there

is “insufficient clinical and experimental data upon which to base any conclusions regarding the effectiveness of the GORE® VIABAHN® Endoprosthesis in applications where the endoprosthesis may experience repeated and extreme flexion, such as across the popliteal fossa”[86].

To plan the procedure and choose adequate stent-graft in terms of landing zone, stent-graft diameter and length, preoperative imaging by CTA or MRA and perioperative DSA is needed. After deployment, an angioplasty balloon is inflated within the stent-graft to smooth out any kinks and seal the landing zones. Postoperative antiplatelet therapy is usually prescribed in the form of dual antiplatelet therapy (DAPT, acetylsalicylic acid plus P2Y12 inhibitor) for 3-6 months followed by life-long single antiplatelet therapy.

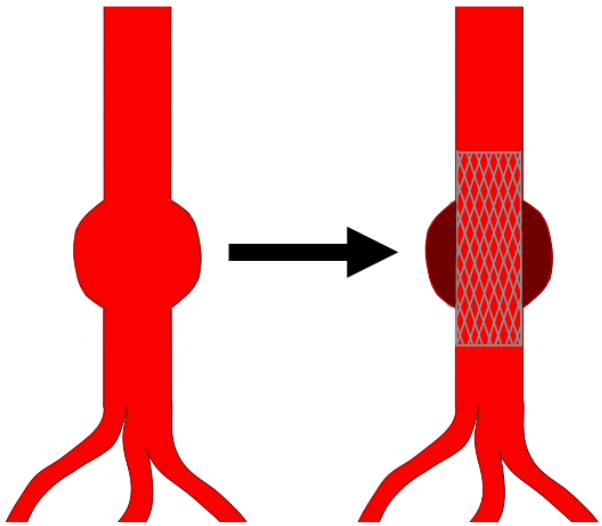


Figure 6. Schematic illustration of result after EPAR. The stent-graft coverage of the PAA will hopefully lead to a complete thrombosis (brown colored) of the aneurysm sac outside the stent-graft without endoleak and sac shrinkage with time. ©Axel Wrede

A report by Stupalkowska et al. on 64 PAAs, all receiving EPAR with Viabahn®, showed primary patency, secondary patency and limb salvage of 83%, 89% and 98%, respectively, after one year. After five years, primary patency, secondary patency and limb salvage were 67%, 75% and 93%, respectively[87]. Golchehr et al. reported similar patency rates at one and five years as well as 100% limb salvage in a series of 75 PAAs, half receiving Viabahn® and the other half receiving its predecessor Hemobahn®[88]. Segment coverage >20 cm[89], lack of post-operative DAPT[90], poor runoff[14, 91] and PA elongation[52] have been associated with lower patency after EPAR.

Endoleak

Endoleak, persistent blood flow within the aneurysm sac after repair, is a common complication after endovascular aortic repair (EVAR)[92-94]. There is no classification of endoleak specifically dedicated to PAA, instead classification has been used in the literature analogous to the classification of endoleak after EVAR (Table 4[95]).

In patients with endoleak after EVAR, prompt re-intervention is recommended for type I and type III endoleaks[21]. These conditions expose the aneurysm sac to high arterial pressures, possibly leading to aneurysm sac growth and risk of rupture[96]. Type II endoleak is by far the most common type of endoleak post-EVAR, though it resolve spontaneously in half of the patients, and <1% result in rupture due to low pressure, retrograde blood flow[97]. However, persistent type II endoleaks constitutes a risk for aneurysm sac growth and rupture[98, 99], and are therefore recommended to be subject for re-intervention if postoperative surveillance indicate continued growth[21].

Table 4. Classification of endoleak post-EVAR[95].

Type of endoleak	Definition
Type I - Ia - Ib	 Perigraft blood flow due to sealing failure at the proximal landing zone Perigraft blood flow due to sealing failure at the distal landing zone
Type II	Retrograde blood flow from collateral arteries
Type III	Endoleak through defect in graft fabric or dysjunction of overlapping stent-grafts
Type IV	Endoleak as a result of graft fabric porosity

Studies on PAA have described postoperative blood flow in the aneurysm sac after OPAR, or endoleak after EPAR, though prevalence and factors associated with endoleak have not received much attention in the literature. Reports on the incidence of endoleak differ widely, ranging from 0-38% and 0-20% after OPAR and EPAR, respectively[100]. Aneurysm sac expansion has been reported in >30% after OPAR through medial approach, with the risk of causing compressive symptoms[101, 102]. Reported data suggest that most treated aneurysms shrink after EPAR, though single cases of aneurysm sac growth related to endoleaks have been reported[89, 103, 104]. In OPAR, postoperative bloodflow in the aneurysm sac or "endoleak", occurs through retrograde blood flow of genicular side-branches (mimicking a type II endoleak) or failure to ligate the PA proximal or distal to the aneurysm (mimicking a type I endoleak). Literature suggests that endoleak is better prevented in OPAR through the posterior approach since this entails better ligation of patent genicular arteries[85, 105]. The SVS guidelines recommend surgical decompression for PAAs showing compressive symptoms or symptomatic aneurysm sac growth after repair (grade 1C)[61].

Fasciotomy

Reperfusion injury may happen upon revascularization to previous acute ischemic tissue, causing cell injury and oedema resulting in increased tissue pressure within muscle compartments enclosed by rigid fascia. Acute compartment syndrome occurs when the intra-compartmental pressure is high, >30 mm Hg[106], or when the local perfusion pressure (mean arterial pressure – intra-compartmental pressure) is <30 mm Hg[107]. At this point, arterial blood flow is restricted leading to tissue ischemia and possibly necrosis[7]. This is especially prone to happen in the calf after revascularization due to ALI, owing to tight fascias enveloping the muscle compartments. When suspecting or anticipating an acute compartment syndrome in the lower leg, emergency fasciotomy is achieved by longitudinal incisions of the fascias of the four anatomical compartments (Figure 7).

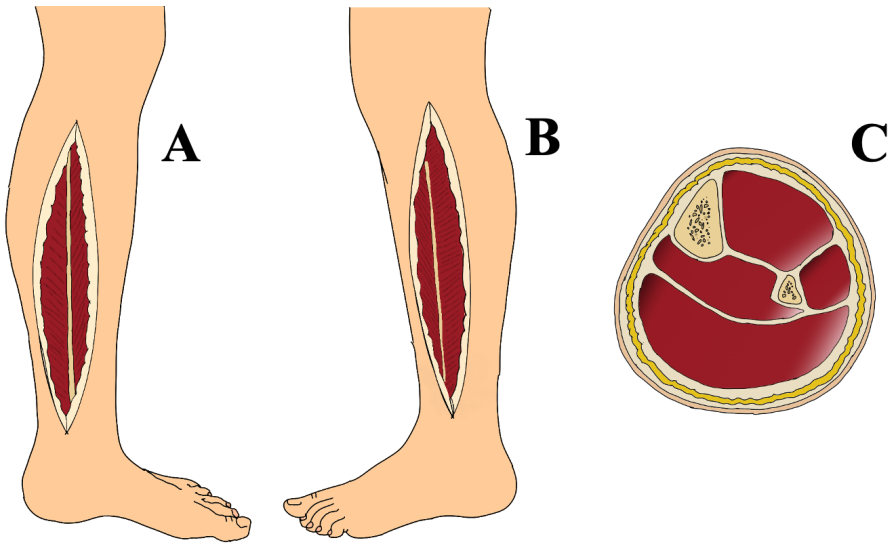


Figure 7. Illustration of double-incision fasciotomy of the left lower leg. The posterior compartments are accessed through a medial incision (A) while the anterior and lateral compartments are accessed through an anterolateral incision (B). The four muscle compartments are illustrated in a cross-sectional view of the lower leg (C). ©Axel Wrede

Amputation

Patients presenting with irreversible ischemia, Rutherford III, should undergo primary amputation according to the SVS guidelines (grade 1B)[61]. A correct amputation removes all infected and necrotic tissue and prevents reperfusion injury, while the level of amputation is determined by arterial perfusion for healing of the amputation stump, providing the patient with the longest possible functional limb[7].

Endovascular versus open popliteal aneurysm repair

According to a Cochrane review updated in 2019, only one small randomized control trial (RCT) on EPAR versus OPAR has been published[51]. This trial included 30 asymptomatic PAAs, 15 in each treatment arm, and could not identify any significant differences in primary patency at one year or secondary patency at three years. Though, the mean operation time and in-hospital stay were longer for OPAR than EPAR[108]. In 2013, the Open Versus Endovascular Repair of Popliteal Artery Aneurysm Trial (OVERPAR trial) was launched to randomize asymptomatic PAAs to OPAR or EPAR[109]. However, this trial was discontinued in 2017 after only being able to include six participants.

To date, OPAR is considered the gold standard for treating PAA, and the clinical practice guidelines by SVS recommend OPAR in patients with asymptomatic PAA, with a life expectancy ≥ five years and adequate saphenous vein (grade 2C). However, EPAR offers an appealing option due to its minimally invasive nature and should therefore be considered in patients with reduced life expectancy if intervention is indicated[61].

Aims

Main aims

To evaluate outcomes after OPAR and EPAR, in patients treated both electively and due to ALI, and to scrutinize anatomical and technical variables impact on stent-graft patency, as well as to investigate the presence and clinical significance of endoleak after EPAR.

Specific aims

Paper I: Evaluate time trends in treatment modality and to compare outcomes between EPAR and OPAR in elective treated patients.

Paper II: Evaluate the proportion of patients receiving elective versus acute treatment for PAA since the introduction of the AAA-screening program. Evaluate risk factors for major amputation, mortality, and combined major amputation/mortality after EPAR and OPAR in patients with ALI.

Paper III: Evaluate risk factors for fasciotomy after revascularization due to ALI. A secondary aim was to investigate risk factors associated with combined major amputation/mortality at one year in patients revascularized due to ALI.

Paper IV: Evaluate adherence to the IFU in patients undergoing EPAR. A secondary aim was to evaluate factors associated with patency at one year.

Paper V: Investigate aneurysm sac growth, presence, and classification of endoleak after EPAR using CEUS. The secondary aims were to investigate stent-graft patency and lower limb morbidity at long-term follow-up in EPAR-treated patients.

Methods

Setting

All studies included in this thesis (paper I-V) are based on data from patients treated at Vascular Center, Skåne University Hospital, Malmö, Sweden. The clinic is a tertiary referral center with a regional catchment population of 1.4 million inhabitants in Skåne County[110], as well as treating referred patients from neighboring counties in southern Sweden. The clinic has pioneered in endovascular therapy and has become a European center of excellence for the treatment of hypertension, including arterial disease[111, 112].

Study population

For paper I and II, patients treated for PAA were retrospectively identified by the International Classification of Disease, 10th revision (ICD-10) diagnosis code I72.4 (aneurysm of lower extremity artery). For paper III, patients undergoing revascularization due to ALI were retrospectively identified by the ICD-10 diagnosis codes I70.2 (atherosclerosis of native arteries of the extremity), I72.4 (aneurysm of lower extremity artery) and I74.0/1/3/5 (embolism and thrombosis of abdominal aorta/other and unspecified parts of aorta/arteries of the lower extremities/arteries of extremities, unspecified). In addition, patients were identified by the Swedish classification system of surgical procedures (KKÅ97) for endovascular therapy/thrombolysis (PDP 10, PDP 30, PDT 10, PDT 30, PDU 87, PET 10, PET 11, PET 12, PEU 87, PFT 10, PFT 30, PFT 87 and PFU 87) and for open vascular surgery (PDE 10, PDE 30, PDU 74, PEE 10, PEE 11, PEE 12, PEU 74, PFE 10, PFE 30, PFU 74 and PGU 74).

For papers specifically on PAA, start of inclusion was set to 1 January 2009. This date was chosen to make sure all patients eligible for AAA-screening were included and after the introduction of the Viabahn® stent-graft. For paper III, start of inclusion was set to 1 January 2001 to ensure a sizable study population. Data on patient characteristics, co-morbidities, intervention details and outcomes were collected from patients' electronical medical records and entered in a pre-specified database.

Ethics

All papers included in this thesis conform to the World Medical Association Declaration of Helsinki[113]. Paper III and V was approved by the Swedish Ethical Review Authority (Dnr 2020-00764 and 2020-00427, respectively). Written informed consent by study participants was waived for paper III in accordance with national legislation. Written informed consent were given by all study participants in paper V after receiving written and oral information about the study. Paper I, II and IV were considered clinical follow-up falling under the criteria of operational development and quality review and were approved by the Head of Unit at Vascular Center, Skåne University Hospital, Malmö.

Definitions

Acute limb ischemia is defined as a sudden decrease in arterial perfusion that may threaten the survival of the limb. Duration <14 days[37]. Classified as viable, marginally threatened, immediately threatened or irreversible ischemia according to the Rutherford classification[38] (Table 1, page 18).

Anaemia defined as haemoglobin concentration <134 g/l in men and <117 g/l in women.

Cerebrovascular disease defined as history of cerebral infarction, haemorrhage or transient ischaemic attack.

Claudication defined as history of muscle pain in the lower limb arising with exercise and dissolves by a short rest.

Diabetes mellitus defined as history of dietary, oral or insulin treatment.

Hypertension defined as use of antihypertensive therapy.

Index procedure defined as first attempt to treat PAA through either EPAR or OPAR.

Ischemic heart disease defined as history of previous myocardial infarction, angina pectoris, coronary artery bypass or percutaneous coronary intervention.

Major amputation defined as amputation above foot-level.

Major bleeding defined as bleeding requiring blood transfusion[114] or surgery.

Popliteal artery aneurysm defined as PA maximal diameter >15 mm >1.5 x the adjacent proximal/distal arterial segment.

Primary patency defined as patent arterial reconstruction after index procedure not needing re-intervention due to restenosis or occlusion.

Re-intervention defined as any endovascular or open surgical procedure performed after index intervention to adjust stent-graft or bypass failure.

Renal insufficiency defined as serum creatinine >105 mmol/l in men and >90 mmol/l in women.

Secondary patency defined as patent arterial reconstruction after re-intervention due to stenosis or occlusion, not needing conversion from EPAR to bypass surgery.

Smoking defined as current or previous use of tobacco cigarettes.

Successful thrombolysis defined as complete or partial lysis of thromboembolism that result in an improved run-off.

Pre-operative vascular imaging

Pre-operative imaging was performed using DUS, CTA and/or MRA. In CTA examinations, iodinated contrast agent used was Omnipaque (GE Healthcare, Chicago, IL, USA) 350 mg I/ml, total dose of 90 ml per examination, according to standard protocol. Systems used for CTA were either Siemens Somatom Definition Flash (Siemens Healthineers, Erlangen, Germany) or Canon Aquilion One (Canon Medical Systems, Otawara, Tochigi, Japan).

In MRA examinations, gadolinium contrast agent was Gadovist (Bayer, Leverkusen, Germany) 1 mmol/ml, total dose of 10 ml per examination, according to standard protocol. Systems used for MRA were either Siemens Magnetom Symphony 1.5 Tesla or Siemens Magnetom Avanto 1.5 Tesla (Siemens Healthineers, Erlangen, Germany).

According to standard protocol, both CTA and MRA scanning were done from the hemidiaphragms to the forefoot. In CTA, the leg was scanned in one projection from just below the groin to the forefoot. In MRA, the leg was scanned in two separate projections, one extending from groin to knee-level and one extending from knee-level to forefoot. All image acquisitions are stored and processed using Sectra IDS7 (Sectra AB, Linköping, Sweden).

Pre-operative DUS were used to assess arterial segments from the proximal SFA to the fibular and tibial arteries as well as availability of potential autologous vein graft. All examinations were performed using Logiq E9 ultrasound system and GE 9L transducer (GE Healthcare, Chicago, IL, USA).

Follow-up

Patients receiving either EPAR or OPAR are invited for routine follow-up, including clinical examination, ABI and duplex ultrasound (DUS) examination 30 days and one year after the index procedure. If there is no sign of complication after one year, the follow-up is terminated, and the patient is referred to his/her general practitioner.

For paper I, II and IV, the duration of follow-up was defined as the time from index procedure to either a major amputation of the treated limb, death or termination of follow-up determined for each study (Paper I; 30 April 2017, Paper II; 30 September 2019, Paper IV; 11 March 2020). Patients in paper III were followed one year after emergency revascularization. At termination of follow-up, medical records and the national population registry (Web-PASIS) were enquired for data on major amputation or death, respectively. All patients were considered to have amputation-free survival at end of follow-up if amputation or death had not been reported.

For paper V, duration of follow-up was defined as time from index procedure to time of contrast-enhanced ultrasound (CEUS) examination. Duration until loss of primary patency was defined as time from index procedure to examination showing stent-graft occlusion documented in the patient's medical records.

Papers

Paper I & II

Paper I & II are retrospective cohort studies investigating time trends and outcome of patients treated for PAA. Paper I mainly focuses on patients treated electively between 1 January 2009 and 30 April 2017, whereas paper II mainly focuses on patients with ALI due to PAA treated between 1 January 2009 and 1 February 2019. In both papers, patients were allocated to either the OPAR or EPAR group according to an "intention-to-treat" approach, i.e. a patient planned for EPAR would remain in this group even if intervention were converted to bypass surgery due to technical failure.

Patients with pseudoaneurysms, mycotic aneurysms, true aneurysms not engaging the popliteal artery and PAA treated before the study period were excluded. Management of true PAA within the study period not receiving either OPAR or EPAR was recorded but excluded from any statistical analyses.

Management and repair modality of patients included in paper I and II are outlined in Figure 8.

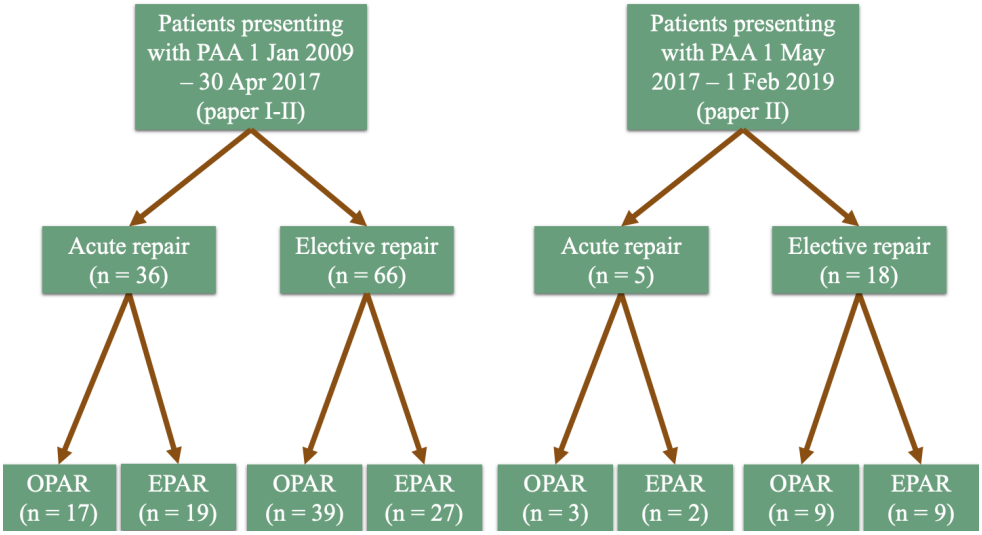


Figure 8. Patients included in paper I and II. EPAR; endovascular popliteal aneurysm repair, OPAR; open popliteal aneurysm repair, PAA; popliteal artery aneurysm.

To evaluate impact of the introduction of AAA screening on acute/elective PAA treatment ratio in paper I and II, patients were defined as eligible for PAA detection through AAA screening if invited to screening before the time of index procedure.

Paper III

Paper III is a retrospective study investigating factors associated with fasciotomy and major amputation/mortality at one year in patients revascularized for ALI, classified according to the Rutherford classification[38]. Decision to perform fasciotomy was based on the discretion of the treating surgeon and not based on any specific criteria. Indication for fasciotomy was considered therapeutic if clinical signs of compartment syndrome were present, and otherwise considered prophylactic.

Paper IV

Paper IV is a retrospective study investigating adherence to Instruction For Use (IFU) in patients treated with EPAR. The study population was derived from the study population in paper II, including all patients receiving EPAR. One PAA was

excluded due to not receiving any stent-graft due to technical failure, and one PAA was excluded due to absence of stored peri- or post-operative images. This resulted in a total of 55 EPAR-treated legs available for assessment. Primary endpoints were adherence to the IFU, primary patency after one year and combined major amputation/mortality during follow-up.

Instruction For Use

Placement of Viabahn® endoprosthesis in patients treated with EPAR was compared to the IFU provided by the manufacturer (W. L. Gore & Associates, Inc, Flagstaff, AZ, USA)[86]. All size measurements were performed in Sectra IDS7. Arterial diameter was measured on CTA or MRA images, whereas landing zones and stent-graft overlap were measured on peri-operative DSA images. Table 5 presents schematic illustrations of size measurement variables.

In addition to sizing criteria, the IFU declares that there should be at least one patent run-off vessel. All stenotic lesions should be covered with stent-graft, if pre-treated by PTA. If multiple stent-grafts are used, the stent-graft with larger diameter should be telescoped into the stent-graft with smaller diameter and there should be no overlap in the defined "No overlap zone". This constitutes a segment of the popliteal artery 3–7 cm proximal to the radiographic knee joint, which is most prone to arterial flexion and kinking upon knee flexion[2, 115] (Figure 9).

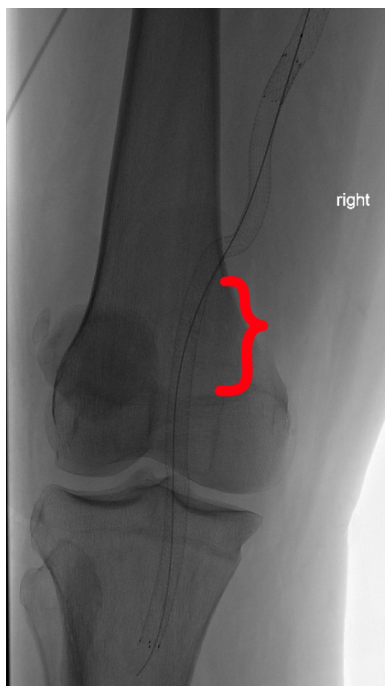
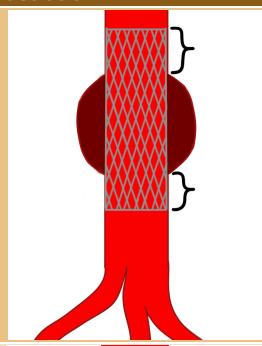
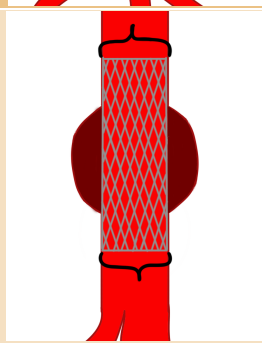
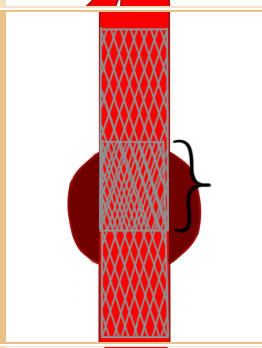
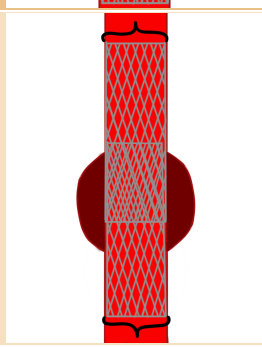


Figure 9. Peri-operative digital subtraction angiography image of endovascular popliteal aneurysm repair. Red line marks the "No overlap zone". ©Axel Wrede

Table 5. Illustration and description of size measurement variables according to Instruction For Use of Viabahn® Endoprosthesis[86]. Illustrations ©Axel Wrede.

Variable	Illustration	Description
Proximal and distal landing zone ≥20 mm		Stent-graft should have at least a 20 mm landing zone in the healthy artery, both proximal and distal to the aneurysm.
Proximal and distal oversizing 5-20%		The labeled diameter of the stent-graft should measure 5-20% larger than the diameter of the healthy artery at the proximal and distal landing zones.
≥20 mm overlap		When using multiple stent-grafts, there should be at least 20 mm overlap.
Diameter difference ≤1 mm between overlapping stent-grafts		When using multiple stent-grafts, the labeled diameter of overlapping stent-grafts should not differ more than 1 mm. Except when using a 13 mm diameter stent-graft to overlap a 11 mm diameter stent-graft.

Maximal angulation and tortuosity index

Maximal angulation of the popliteal artery was estimated on pre-operative CTA or MRA images in Sectra IDS7 after determining the arterial segment with most severe angulation by visual overview of 3D-reconstruction images (Figure 10A).

Tortuosity index (TI) was calculated from either CTA or MRA images in Aquarius (iNtuition Edition Ver.4.4.13.P5, TeraRecon, Inc, Durham, NC, USA) by dividing the length of the PA in centerline by the Euclidean line from the end of Hunter's canal to the branching of the anterior tibial artery[52, 116] (Figure 10B/C).

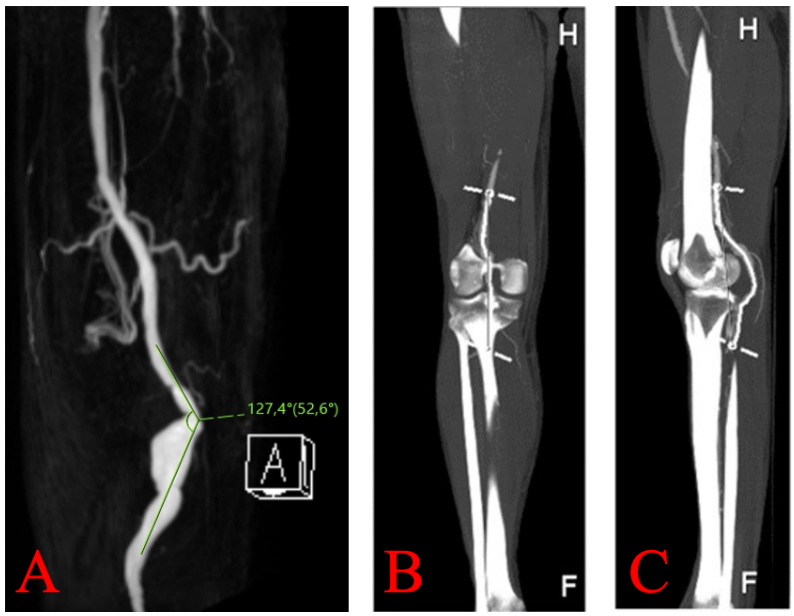


Figure 10. Maximal angulation of 52,6° shown on magnetic resonance angiography image (A). Tortuosity index of 1.2 measured in Aquarius in which the curved white line marks the centerline, and the straight grey line marks the Euclidean line of the popliteal artery (B/C). ©Axel Wrede

Paper V

Paper V is a cross-sectional cohort study investigating the prevalence of endoleak in patients treated with EPAR. During fall 2021, all patients included in paper IV were invited to participate in the study, except those deceased (n = 15) or having undergone re-intervention in the form of interposition grafting with the removal of aneurysm sac (n = 1) or major amputation of the treated leg (n = 4). This resulted in 31 EPAR-treated legs in 26 patients included and attending follow-up. Follow-up was conducted per a pre-specified protocol, including clinical examination of the lower extremities, ABI measurement and ultrasound examination, and CEUS. Details on the index procedure were collected from the database of paper IV. The

primary endpoint was endoleak detected on CEUS, and the secondary endpoint was primary patency during follow-up.

Ultrasound examination

All patients were examined by a single ultrasound sonographer with more than 20 years of experience in vascular ultrasound using the same US system and transducer (Logiq E9 and GE 9L transducer, GE Health Care, Chicago, IL, USA). Only the EPAR-treated leg was US scanned, except in patients receiving bilateral EPAR. Patients were examined in both supine and prone positions, as needed, for adequate visualization of the artery (Figure 11).

Scanning of the femoropopliteal arterial segment using conventional B-mode US and DUS were followed by assessment of stenosis or occlusion from the SFA to the tibiofibular trunk by DUS. Stenosis >50% of the artery diameter was considered significant and potentially hemodynamic important. According to team policy, this was defined as a peak systolic velocity ratio >2.0 (calculated as intra-stenotic peak systolic velocity divided by peak systolic velocity proximal to the stenosis)[66, 117].

The maximal PAA diameter was measured on-cart in transverse B-mode imaging with the patient in the prone position, from the adventitia leading edge of the posterior wall to the intima leading edge of the anterior wall[118, 119]. If no residual aneurysm sac were visualized, the maximal diameter was defined as the stent-graft diameter measured at follow-up. When analysing maximal diameter, diameter changes within ±3 mm were considered non-significant based on previous work on inter-operator reproducibility in post-EVAR surveillance[119].



Figure 11. Examination of the femoropopliteal segment by ultrasound with the patient in supine and prone position. ©Axel Wrede

Contrast-enhanced ultrasound

Patients were examined in the prone position using the built-in contrast mode of the US system. Intravenous US contrast agent (SonoVue®, Bracco, Milan, Italy) was administered as a bolus dose of 2 mL through a 20- or 22-gauge peripheral venous catheter in the antecubital fossa and subsequently flushed with 10 mL of saline solution (NaCl 0.9%). At the start of the CEUS examination, longitudinal visualisation of the stent-graft and aneurysm sac was kept until contrast arrival. Then, an examination of potential endoleak in the sac was performed in both longitudinal and transverse scan planes and saved as cine-loops for subsequent core-lab reading. Administration of contrast agent was repeated if necessary.

Core-lab reading

A core-lab consisting of three physicians, highly experienced in vascular US and CEUS, reviewed all US acquisitions. Reading was performed offline using dedicated software[120, 121] (MicroDicom Ltd, Sofia, Bulgaria). Diagnosis and classification of endoleak were made in a consensus-based process according to a predefined protocol.

Endoleak was only based on CEUS acquisitions and defined as contrast enhancement outside the stent-graft but within the aneurysm sac. Classification of endoleak was made analogous to the classification of endoleak following EVAR(Table 4, page 27)[95]. Synchronous contrast enhancement of the stent-graft and aneurysm sac was considered as either a type I or type III endoleak, whereas delayed contrast filling of the aneurysm was considered as a type II endoleak. Type IV endoleaks were not considered. The classification of endoleak after EPAR used are illustrated in Figure 12.

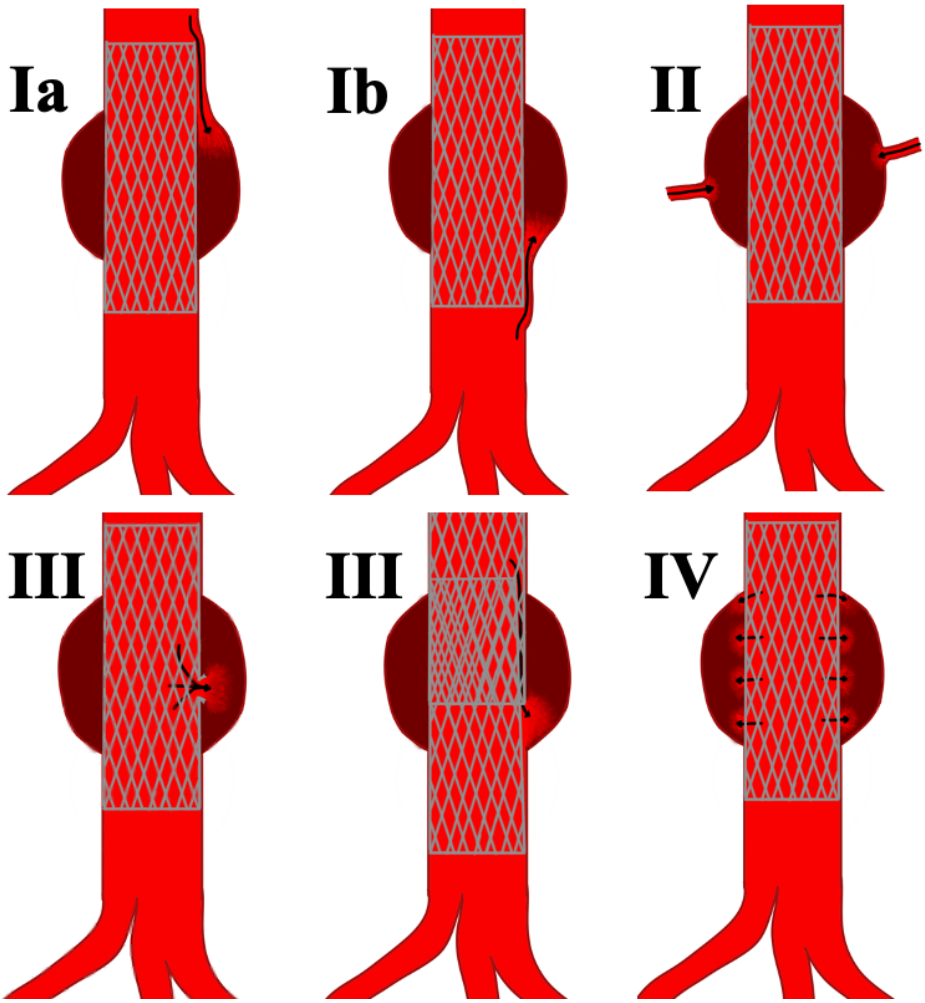


Figure 12. Illustration of definitions used for endoleak classification in paper V. Black arrows indicate direction of blood flow. ©Axel Wrede

Statistics

Data management and statistical analyses were performed in IBM Statistical Package for the Social Sciences (version 25.0 [Paper I, II and IV] or version 26.0 [Paper III and V], IBM, Chicago, IL, USA). In all papers, nominal and ordinal data were presented as frequencies together with percentages. Continuous data were presented as median together with either range or interquartile range (IQR). Pearson's χ^2 Test was used to evaluate differences between groups of nominal data but replaced by Fisher's Exact Test if the expected count were <5 in two or more

cells. Kendall's tau-b Test was used to evaluate time trends and differences between groups of ordinal data. Mann-Whitney U Test was used to evaluate differences between independent groups of continuous data.

In Paper IV, normal distribution of TI and maximal PAA angle were checked using the Kolmogorov-Smirnov Test. Both variables were found to have skewed distribution and were subsequently log-transformed.

In Paper I-II, difference in amputation-free survival between patients treated with EPAR versus OPAR was illustrated using a Kaplan Meier curve together with Life Tables and analysed using Log Rank Test. In Paper IV, the difference in amputation-free survival between patients treated within versus not within IFU was analysed using Log Rank Test.

Multi-variable Cox Regression analyses were performed in Paper I, II and IV, expressed by Hazard Ratio (HR) together with 95% confidence intervals (CI). Multi-variable logistic regression was performed in Paper III, expressed by odds ratios (OR) together with 95% CI. One variable was allowed to be included in the multi-variable analyses model per ten outcomes events[122]. In Paper I, analysis of major amputation/mortality at the end of follow-up in patients undergoing elective PAA repair was performed by including treatment modality (EPAR or OPAR), age, ischemic heart disease, and diabetes mellitus as covariates. In Paper II, analysis of major amputation/mortality at the end of follow-up in patients undergoing PAA repair due to ALI was performed by including variables initially associated to the outcome in a univariate analysis. In Paper III, analysis of major amputation/mortality at one year after revascularization of patients treated for ALI was performed by including variables initially associated to the outcome in a univariate analysis. In Paper IV, the associations between age-adjusted TI and age-adjusted maximal PAA angle, and major amputation/mortality at end of follow-up, were analysed by Cox regression.

In Paper V, Wilcoxon Signed-Rank Test was used to evaluate differences between groups of paired samples of non-parametric continuous data. Correlation between two groups of continuous data was evaluated with the Spearman's Rank Test.

For all analyses in all papers, no imputation of data was performed due to missing data. Instead, all available data was used for analyses and no patient were excluded due to missing data. A p-value < 0.05 was considered statistically significant for all analyses.

Results

Paper I & II

Patient characteristics

In paper I, 66 PAA in 55 patients received elective repair. The number of EPAR and OPAR were 27 and 39, respectively. Patients receiving elective EPAR were older than patients receiving elective OPAR (median 69 years [range 56-87] versus 66 years [range 48-81], p = 0.047). Before index intervention, ABI was higher in the EPAR compared to the OPAR group (median ABI 1.0 [IQR 0.9 – 1.2] versus 0.9 [IQR 0.7 – 1.1], p = 0.044), though there was no difference in the number of patent run-off vessels (Table 6, p = 0.13).

Table 6. Number of patent run-off vessels in limbs receiving elective popliteal aneurysm repair.

Run-off prior to index procedure	Endovascular repair (n = 27)	Open repair (n = 39)
Three patent arteries	18 (69)	22 (58)
Two patent arteries	6 (23)	4 (10)
One patent artery	2 (8)	11 (29)
None patent artery	0 (0)	1 (3)

In paper II, 41 PAA in 41 patients received acute repair. Two patients presented with ruptured PAA, both receiving EPAR. These patients were excluded from group comparisons, leaving 19 cases of EPAR and 20 cases of OPAR performed in patients with ALI. The etiology of ALI was thrombotic occlusion of the PAA in 26 cases (67%) and embolism to the calf arteries in 13 cases (33%). Patients with ALI receiving EPAR were older compared to those receiving OPAR (median 77 years [range 58-90] versus 64 years [range 42-81], p = 0.0058). The EPAR group had a higher prevalence of atrial fibrillation (32% versus 0%, p = 0.0063) and use of antithrombotic/anticoagulation therapy before the index procedure (68% versus 50%, p = 0.021), but lower prevalence of claudication before ALI compared to the OPAR group (16% versus 70%, p <0.001). There was no difference in the degree of ALI according to the Rutherford classification (Table 7, p = 0.36)

Table 7. Degree of acute limb ischemia according to the Rutherford classification in limbs receiving acute popliteal aneurysm repair.

Rutherford classification prior to index procedure	Endovascular repair (n = 19)	Open repair (n = 20)
I. Viable (%)	4 (21)	5 (25)
IIa. Threatened – marginally (%)	7 (37)	10 (50)
IIb. Threatened – immediately	8 (42)	5 (25)
III. Irreversible (%)	0 (0)	0 (0)

Main findings

Among 26 PAA in 22 patients eligible for AAA screening, five PAA in four patients (21%) received elective repair because of screening detection of AAA and subsequent screening of the popliteal arteries. Three PAA in three patients eligible for AAA screening underwent acute repair without prior detection from the screening program.

In paper I, there was an increase in the ratio of elective EPAR compared to elective OPAR throughout the study period (Figure 13).

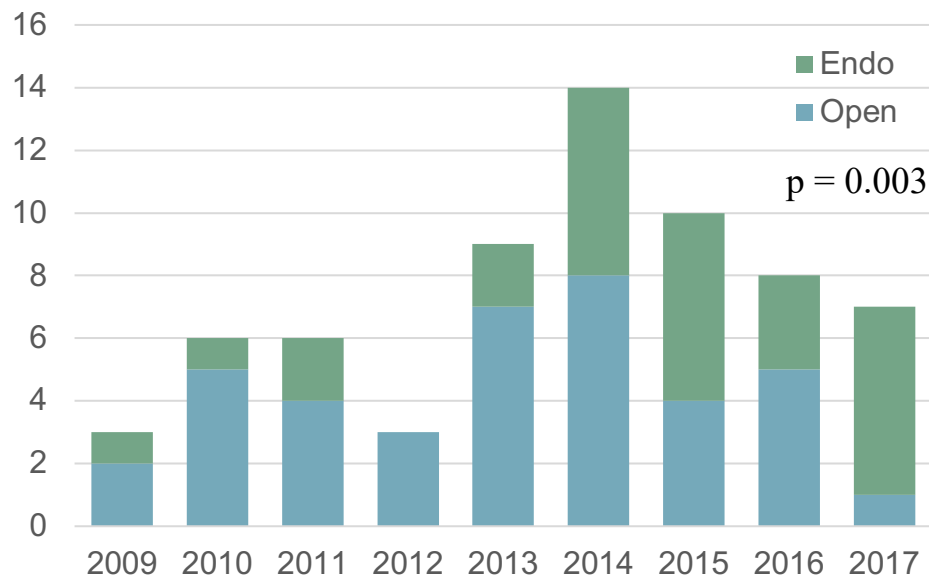


Figure 13. Graph showing numbers of popliteal artery aneurysms receiving elective endovascular (green) or open (blue) repair during the study period.

In paper II, there was an increase in the ratio of elective compared to acute repairs (Figure 14).

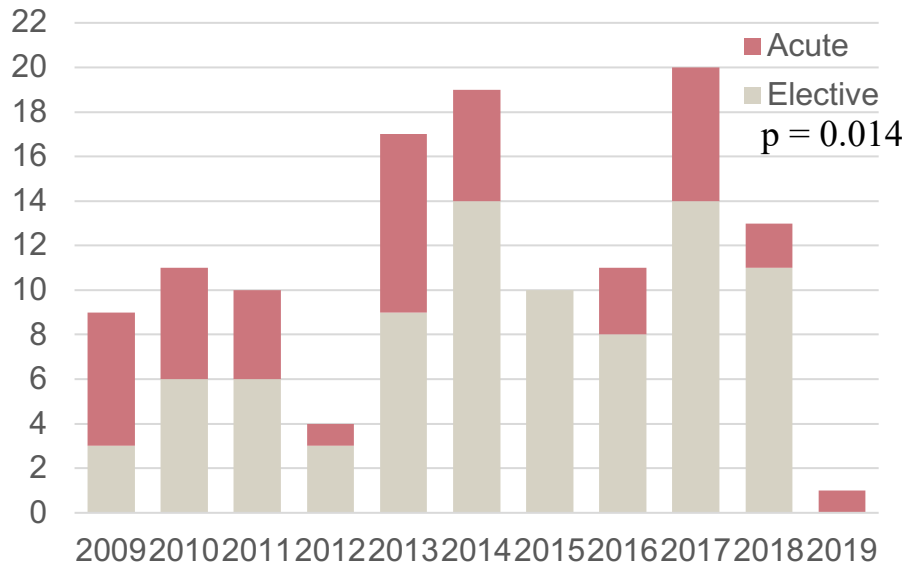


Figure 14. Graph showing numbers of popliteal artery aneurysms receiving elective (beige) or acute (red) repair during the study period.

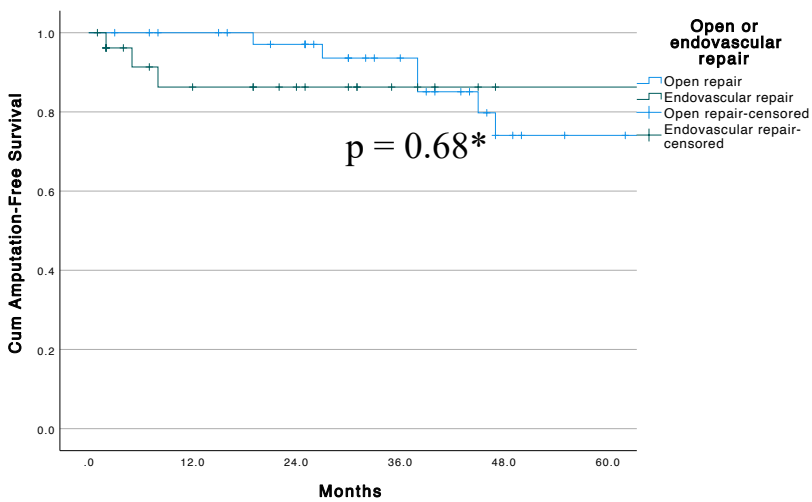
In paper I, the median follow-up time in the EPAR and OPAR groups were 24 months and 39 months, respectively ($p = 0.002$). In paper II, the median follow-up time in the EPAR and OPAR groups were 30 months and 63 months, respectively ($p = 0.17$). Post-operative complications and one-year outcomes after elective and acute PAA repair are outlined in Table 8. Patients with ALI received intra-arterial thrombolysis more often prior to EPAR than OPAR (74% versus 15%, $p < 0.001$). There was no case of intracranial bleeding associated with thrombolysis. Patients receiving adjunctive fasciotomy had a markedly longer median in-hospital stay compared to patient not receiving fasciotomy (40 versus 6 days, $p < 0.001$).

Table 8. Post-operative complications and one year outcome after elective and acute PAA repair.

	Elective EPAR (n = 27)	Elective OPAR (n = 39)	p-value	Acute EPAR (n = 19)	Acute OPAR (n = 20)	p-value
Wound infections (%)	0 (0)	11 (28)	0.003	0 (0) (n = 19)	3 (15)	0.23
Major bleeding complications (%)	1 (4)	8 (21) (n = 38)	0.046	5 (26)	11 (55)	0.069
In-hospital stay (days [median; range])	2 (1-5)	7 (4-27)	<0.001	6 (3-68)	8 (4-65)	0.080
Primary patency at one year (%)	16 (84) (n = 19)	33 (94) (n = 35)	0.33	8 (57) (n = 14)	16 (80)	0.15
Secondary patency at one year (%)	-	-	-	12 (86) (n = 14)	16 (80)	1.00
Major amputation at one year (%)	3 (16) (n = 19)	0 (0)	0.037	0 (0)	3 (15)	0.23
Mortality at one year (%)	0 (0)	0 (0)	-	5 (26)	0 (0)	0.014

EPAR; Endovascular popliteal aneurysm repair, OPAR; Open popliteal aneurysm repair

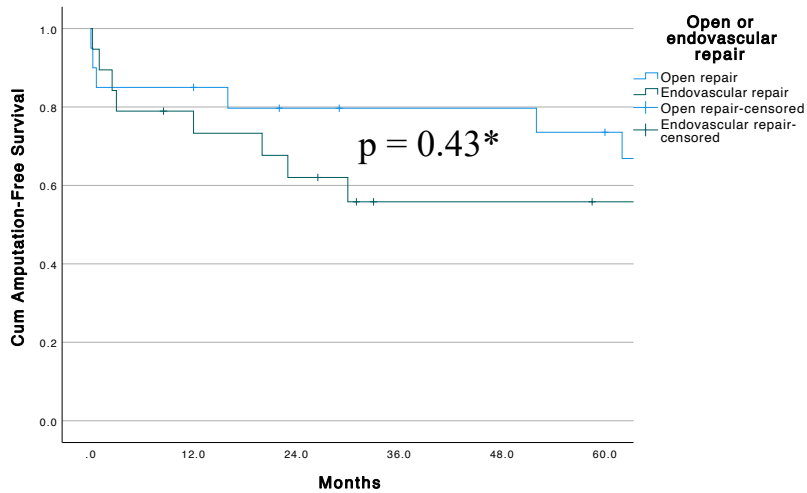
There was no difference in amputation-free survival between patients receiving elective OPAR and EPAR (Figure 15, p = 0.68). In a multivariable Cox regression analysis including treatment modality (EPAR/OPAR), age, ischemic heart disease, and diabetes mellitus, only age (HR: 1.12, 95% CI: 1.02-1.24; p = 0.022) remained as an independent risk factor for decreased amputation-free survival.



Patients at risk:							
	39	36	32	23	12	9	Open
	27	17	13	7	3	3	Endovascular

Figure 15. Kaplan Meier curve and Life Tables illustrating amputation-free survival in patients receiving elective open and endovascular popliteal aneurysm repair. *Log rank test.

Patients with ALI receiving EPAR compared to OPAR had comparable primary and secondary patency rates and major amputation rates at 30 days and one year follow-up. At one year after the index procedure, there was a higher mortality in the EPAR compared to the OPAR group (26% versus 0%, p = 0.014). There was no difference in amputation-free survival during follow-up between the EPAR and OPAR group (Figure 16, p = 0.43).



Patients at risk:							
	20	17	14	13	13	12	Open
	19	14	11	7	7	6	Endovascular

Figure 16. Kaplan Meier curve and Life Tables illustrating amputation-free survival in patients with acute limb ischemia receiving open and endovascular popliteal aneurysm repair. *Log rank test.

In univariable analyses, atrial fibrillation, hypertension and AAA were associated with the combined variable major amputation and mortality at the end of follow-up. After adding these potential risk factors in a multivariable Cox regression analysis, atrial fibrillation was the sole independent risk factor for combined major amputation and mortality (HR: 6.4, 95% CI: 1.9 – 21.6, p = 0.003). When scrutinizing this finding, all patients with atrial fibrillation (n = 6) were deceased without undergoing major amputation at the end of follow-up.

Paper III

Main findings

Fasciotomy was performed in 84 (10%) out of 843 legs revascularized due to ALI, 28 out of 394 female patients and 56 out of 449 male patients. For all patients, the median age at revascularization was 72 years (IQR 61 – 77), though higher in female compared to male patients (75 years [IQR 68 – 82] versus 70 years [IQR 61 – 77], $p < 0.001$). Diagnostic and treatment factors associated with fasciotomy in univariate analysis are outlined in Table 9.

Table 9. Univariate analysis of factors associated with fasciotomy.

	Fasciotomy (n = 84)	No fasciotomy (n = 759)	p-value
Admittance 2001-2009 (%)	6	94	
Admittance 2010-2018 (%)	13	87	< 0.001
Female (%)	7	93	
Male (%)	12.5	87.5	0.009
Renal insufficiency (%)	46	30.5	0.004
Anemia (%)	19	28	0.070
Symptom duration (hours [median; IQR])	24 (9 – 72)	48 (19 – 120)	< 0.001
ABI at admission (median [IQR])	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.11)	< 0.001
Rutherford Iib (%)	75	32	< 0.001
Bilateral arterial occlusion (%)	24	5	< 0.001
PAA thromboembolism (%)	18	6.5	< 0.001
Primary endovascular treatment (%)	36	74	< 0.001
Primary open vascular treatment (%)	62	23	< 0.001

ABI; Ankle-brachial index, IQR; Interquartile range, PAA; Popliteal artery aneurysm

A PAA was the etiology for ALI in 64 (8%) of all patients, 59 male patients (13%) and five female patients (1%), respectively ($p < 0.001$). The proportion of patients with PAA and diabetes mellitus was lower than those PAA without diabetes mellitus (3% versus 9%, $p = 0.007$). Age was not lower in patients with and without PAA (median age 71 [IQR 61-78] versus 72 [IQR 65-80], $p = 0.11$). Thrombotic occlusion of the aneurysm was the cause of ALI in 72% and distal embolization in 28%.

The proportion of patients with PAA thromboembolism was higher among those undergoing fasciotomy than those not undergoing fasciotomy (18% versus 6.5%, p

<0.001). Thromboembolism from PAA had a combined major amputation/mortality at one year of 25%, similar to the entire cohort of patients (27.5%; p = 0.64).

Factors associated with fasciotomy in a multi-variable logistic regression model are presented in Table 10.

Table 10. Multi-variable logistic regression analysis of factors associated with fasciotomy.

	Multi-variable logistic regression	
Variable	OR (95% CI)	p-value
Admittance 2010 – 2018 versus 2001 – 2009	1.92 (1.09 – 3.39)	0.024
Primary open versus endovascular surgery	3.43 (1.97 – 5.98)	< 0.001
Female gender	0.43 (0.24 – 0.76)	0.004
Anemia	0.43 (0.22 – 0.83)	0.012
Renal insufficiency	1.77 (1.04 – 3.01)	0.034
PAA thromboembolism	2.26 (1.06 – 4.80)	0.035

CI; Confidence interval, OR; Odds ratio, PAA; Popliteal artery aneurysm

Fasciotomies were defined as prophylactic in 44 cases (53%) and therapeutic in 40 cases (47%). Factors associated with prophylactic and therapeutic fasciotomy are outlined in Table 11.

Table 11. Factors associated with prophylactic or therapeutic fasciotomy after revascularization due to acute limb ischemia.

	Timing of fasciotomy		
	Prophylactic (%)	**Therapeutic (%)**	**p-value**
Primary open surgery	75	25	<0.001
Primary endovascular surgery	4	96	<0.001
Rutherford IIb	64	36	<0.001
Renal insufficiency	67	33	0.031
Major amputation/mortality at one year	69	31	0.013

Patients undergoing fasciotomy had a longer in-hospital stay (median 28 days [IQR 13 – 51] versus 6 days [IQR 4 – 11], p < 0.001) and more major bleeding complications (48% versus 20%, p < 0.001) than those not undergoing fasciotomy.

At one year after revascularization, mortality was higher among patients receiving fasciotomy than those not (29% versus 15%, p = 0.001). In comparison, there was a non-significant association in major amputation at one year between the two respective groups (22% versus 14%, p = 0.067).

Factors associated with higher combined major amputation/mortality at one year in a multi-variable logistic regression analysis are presented in Table 12.

Table 12. Multi-variable logistic regression analysis of factors associated with combined major amputation/mortality at one year after revascularization due to acute limb ischemia.

	Multi-variable logistic regression	
Variable	OR (95% CI)	p-value
Female gender	1.44 (1.00 – 2.08)	0.049
Cerebrovascular disease	1.86 (1.23 – 2.82)	0.003
Anemia	1.84 (1.24 – 2.73)	0.002
Foot/leg ulcers	2.47 (1.46 – 4.18)	0.001
Rutherford lib	2.43 (1.66 – 3.56)	< 0.001
Infra-inguinal occlusion	1.62 (1.07 – 2.46)	0.024
Major bleeding	1.94 (1.30 – 2.90)	0.001
Fasciotomy	1.94 (1.11 – 3.40)	0.021

CI; Confidence interval, OR; Odds Ratio

Paper IV

Main findings

At least one deviation from IFU was found in 45 (82%) out of 55 EPAR. Distal oversizing greater than 20% was the single most common deviation from IFU (40% of all EPAR), followed by a diameter difference >1 mm between overlapping stent-grafts and the presence of overlap in the "No overlap zone" (both present in 31% of all EPAR). Deviations from IFU are shown in Figure 17.

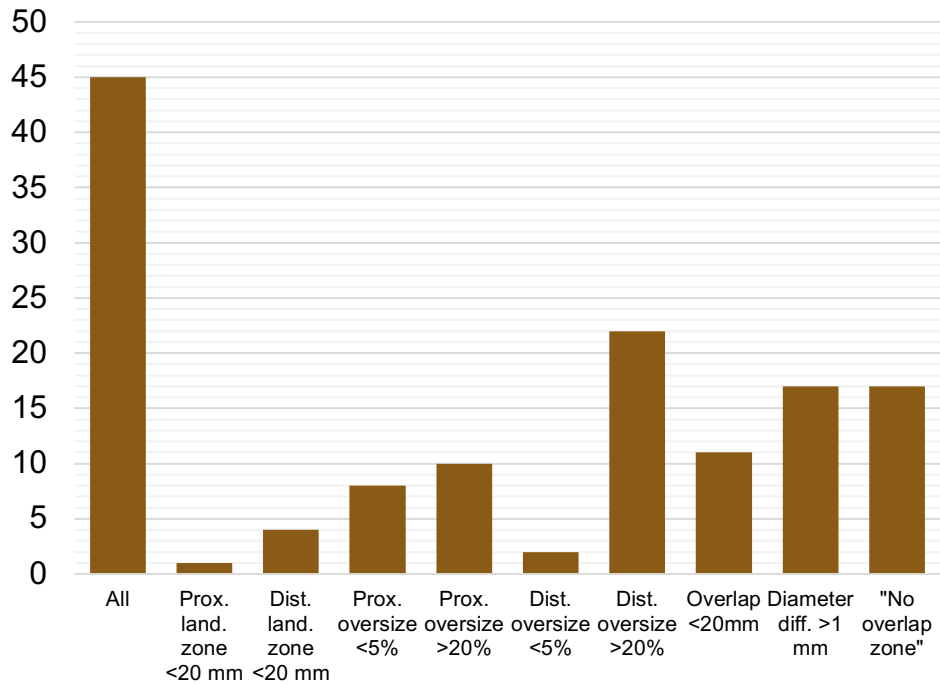


Figure 17. Graph showing number of endovascular popliteal aneurysm repair not adherent to one or more Instruction For Use criteria.

There were no demographic differences in patients with PAA treated within and not within IFU. Intra-arterial thrombolysis was used in 14 PAA (25.5%) and PTA was performed in 11 PAA (20%) before stent-grafting. Dual-antiplatelet therapy was prescribed at discharge after 31 (56%) of all EPAR. PAA and procedure characteristics are described in Table 13.

Table 13. PAA characteristics and number of stent-grafts used at index procedure

	Consistent with IFU (n = 10)	Not consistent with IFU (n = 45)	p-value
Acute repair (%)	2 (20)	18 (40)	0.23
ABI prior to index procedure (median; IQR)	1.0 (0.8 – 1.3) (n = 7)	0.93 (0.36 – 1.1) (n = 38)	0.13
Maximal aneurysm diameter at index procedure (mm [median; IQR])	24 (21 – 36)	30 (21 – 40)	0.73
Tortuosity index (median; IQR)	1.08 (1.06 – 1.08)	1.08 (1.05 – 1.13) (n = 43)	0.31
Maximal angulation (median; IQR)	46 (27 – 64)	40 (27 – 57)	0.45
Number of stent-grafts used (median; range)	1 (1-2)	2 (1-3)	0.11

Median follow-up time was 53 months and 44 months for EPAR within and not within IFU, respectively (p = 0.38). There was no difference in amputation-free survival during follow-up between patients treated within and not within IFU (p = 0.48).

The overall primary patency rate was 72% at one year after the index procedure. There was no difference in primary patency rate at one year between EPAR performed within and not within IFU (80% versus 70%, p = 0.53). When analysing each IFU criteria independently, EPAR performed with a diameter difference >1 mm between overlapping stent-grafts was associated with lower primary patency at one year (43% versus 83%, p = 0.004). There was no association between either TI or maximal angulation and primary patency at one year (p = 0.41 and p = 0.62, respectively).

In univariable analysis, acute procedures (p = 0.042), age >75 years (p = 0.0016), atrial fibrillation (p = 0.0025), abdominal aortic aneurysm (p = 0.0055), anaemia (p = 0.00030), TI >1.1 (p = 0.019) and maximal angulation >60° (p = 0.0025) was associated with combined major amputation and mortality at end of follow-up. In an age-adjusted Cox regression model, TI (HR: 1.78 per SD, 95% CI: 1.17 – 2.71, p = 0.0071) and maximal angulation (HR: 1.73 per SD, 95% CI: 1.018 – 2.95, p = 0.043) were associated with combined major amputation and mortality.

Paper V

Main findings

Endoleak was detected in 16 (52%) of 31 EPAR-treated legs examined with CEUS (Figure 18). Classification of CEUS detected endoleak was type I (n = 3), type II (n = 10), type III (n = 1) and indeterminate (n = 2).

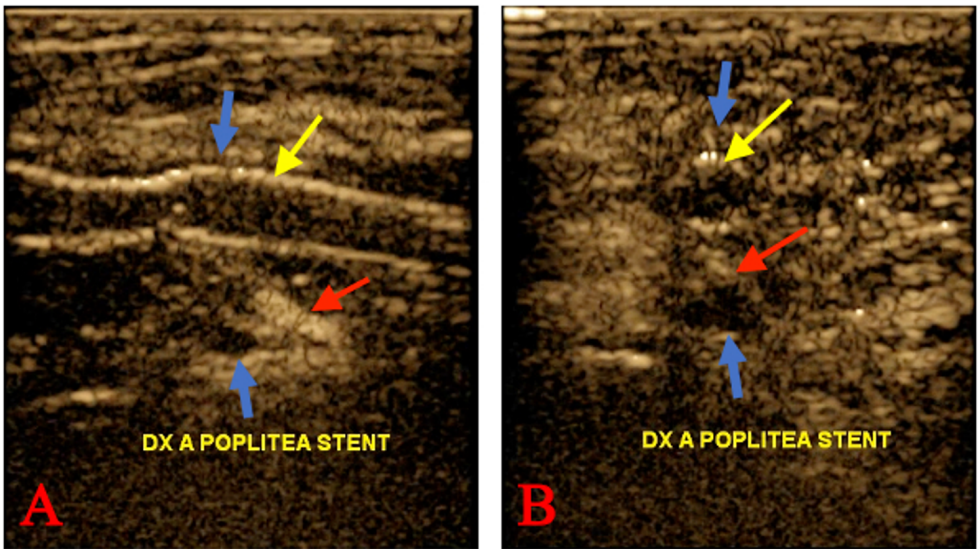


Figure 18. Contrast-enhanced ultrasound images of a type II endoleak in longitudinal (A) and transversal (B) projections. Contrast enhancement (red arrow) is visible within the aneurysm sac (blue arrow). The stent-graft (yellow arrow) is occluded. ©Axel Wrede

Median follow-up time was 57 months for all patients, 70 months and 55 months for patients with and without endoleak, respectively (p = 0.92). Re-intervention before the CEUS examination was more common in PAA without endoleak than PAA with endoleak (40% versus 6%, p = 0.037). There was no association between aneurysm diameter and the presence of endoleak (Table 14, Figure 19).

Table 14. Comparison of number of stent-grafts and maximal aneurysm diameter between patients with and without endoleak

	Endoleak (n = 16)	No endoleak (n = 15)	p-value
Follow-up (months [median; range])	70 (33 – 143)	55 (35 – 142)	0.92
Number of stent-grafts used (%)	One – 8 (50) Two – 8 (50) Three – 0 (0)	One – 9 (60) Two – 2 (13) Three – 4 (27)	0.86
Maximal aneurysm diameter at index procedure (mm [median; range])	22.5 (17 – 55)	25 (15 – 40)	0.89
Maximal aneurysm diameter at follow-up (mm [median; range])	21.5 (6 – 43)	17 (7 – 37)	0.18
Maximal aneurysm diameter difference (%)	Increase – 1 (6) Stationary – 5 (31) Decrease – 10 (63)	Increase – 0 (0) Stationary – 2 (13) Decrease – 13 (87)	0.093

Maximal aneurysm diameter decreased in both aneurysms with (median maximal aneurysm diameter difference -6 mm [range -14 – 4 mm], p = 0.005) and without endoleak (median maximal aneurysm diameter difference -8 mm [range -29 – 1 mm], p <0.001).

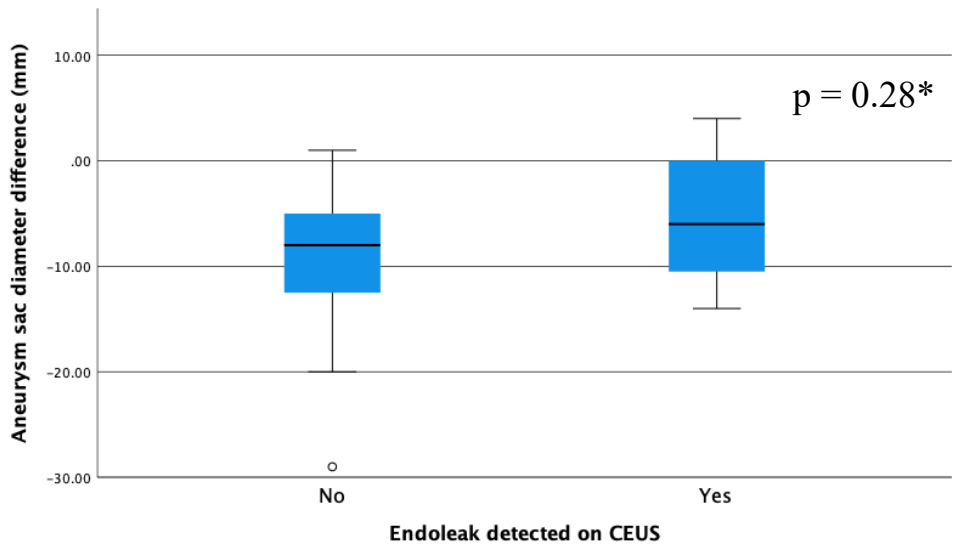


Figure 19. Maximal aneurysm diameter difference between index procedure and follow-up. Thick black line marks median value (-8 mm for aneurysms without endoleak and -6 mm for aneurysms with endoleak on contrast-enhanced ultrasound). CEUS; Contrast-enhanced ultrasound. *Mann-Whitney U test.

Among all patients attending the follow-up examination, primary patency was 55%, and secondary patency was 61%. There was an association between patients treated with multiple stent-grafts and loss of primary patency (p=0.031; Table 15).

Table 15. Comparison of number of stent-grafts and maximal aneurysm diameter between patients with and without primary patency at follow-up.

	Primary patency (n = 17)	Loss of primary patency (n = 14)	p-value
Follow-up (months [median; range])	83 (33 – 143)	55.5 (43 – 142)	0.54
Number of stent-grafts used (%)	One – 12 (71) Two – 4 (24) Three – 1 (6)	One – 5 (36) Two – 6 (43) Three – 3 (21)	0.031
Maximal aneurysm diameter at index procedure (mm [median; range])	22 (17 – 40)	27.5 (15 – 55)	0.52
Maximal aneurysm diameter at follow-up (mm [median; range])	17 (9 – 23)	19.5 (6 – 43)	0.97
Maximal aneurysm diameter difference (%)	Increase – 1 (6) Stationary – 4 (24) Decrease – 12 (71)	Increase – 0 (0) Stationary – 3 (21) Decrease – 11 (79)	0.55

Discussion

Increase in elective to acute repair ratio

There was an increase in elective-to-acute repair ratio between 2009 – 2019. The overall proportions of elective and acute repairs during this period were 67% and 33%, respectively. The proportion of acute repairs (ALI or rupture as an indication for treatment) is slightly larger compared to what has been reported from the Swedvasc registry between 2014 – 2020 (28%)[48] and the Vascunet collaboration 2012 – 2018 (27%)[49]. Although the proportion seems relatively close to the national Swedvasc registry, the difference is more pronounced when comparing figures to other countries in the Vascunet report, where the proportion of emergent repair were <20% in Malta, New Zealand, Serbia and Switzerland. Concordant with the present thesis, the Vascunet report also showed a decrease in the proportion of patients treated for ALI over time, from 30% to 24% between start and end of the study.

Underlying driving factors towards increasing elective repair is not fully clear. Since elective compared to acute PAA repair have better outcomes[45, 54], early repair in often asymptomtatic patients with PAA is advocated. In the present thesis, the increase in elective-to-acute repair ratio did not seem to be heavily impacted by more asymptomatic patients identified via the AAA screening program, as only five PAA repairs were performed because of screening detection over a nine-year period. Also, as Sweden were the only country having enrolled a nationwide AAA screening program at the time the latest Vascunet report was published, this cannot explain the increase in elective repairs also present in other countries. Instead, more patients with none to mild symptoms from a PAA might be detected because of an overall increase in radiological examinations. Given the high probability of co-existence of having a concomitant AAA and PAA, patients already included in AAA surveillance programs may have their PAA detected at a routine exam. It could also be speculated that introducing various national and international registries and collaborations on PAA has raised awareness of the disease among clinicians, thus promoting detection and elective repairs.

Increase in endovascular to open repair ratio

Paper I and II showed an increase in EPAR-to-OPAR ratio, both among patients treated elective and acute. At the present vascular center, the decision on treatment

modality is based on the discretion of the treating vascular surgeon. Unfortunately, the reasoning behind this decision was often not well documented in the patients' medical records. Since the first clinical practice guidelines, issued by the SVS in 2021[61], was published well after the end of patient inclusion of paper I and II (2017 and 2019, respectively) it would not have guided the decision on treatment modality for patients included in this thesis.

Increase in the use of EPAR has also been described in the Society for Vascular Surgery Vascular Quality Initiative (SVS-VQI), reporting on asymptomatic patients treated between 2010 – 2013 from 290 vascular centers in North America[123], as well as reports from the Swedvasc registry[45]. In addition to the appeal of choosing a less invasive treatment option, factors influencing this shift might be practical rather than based on reported outcome results. Reduced surgical capacity, partly due to shortage of scrub nurses[124], and consequently long waiting time for patients to receive OPAR might be reduced by offering EPAR.

Endovascular versus open popliteal aneurysm repair

The lack of RCTs comparing outcomes after EPAR and OPAR means there is limited high-quality evidence to build guidelines and recommendations[51]. Attempts on new RCTs have proven difficult, even when only asymptomatic patients are included[109]. Including symptomatic patients or patients presenting with ALI would be even more challenging, why the comparison of EPAR and OPAR will have to rely on non-randomized data for the foreseeable future.

In 2013, Hogendoorn et al.[125] presented a Markov decision model comparing OPAR with great saphenous vein graft, EPAR and conservative treatment in asymptomatic patients. Main outcome was quality-adjusted life-years (QALY). Results favoured OPAR but shifted towards EPAR if 30-days mortality risk were >6% for OPAR or if primary patency at five years were >80% after EPAR. Interestingly, for patients aged >95 years or with a life expectancy of <1.5 years, conservative treatment showed highest QALY. However, as acknowledged by the authors, the results rely on the pool of published outcome data that may change in the future, and values for QALY had to be extrapolated from patients with PAD or AAA which may not be the true values for patients with PAA.

In the last decade, several population- or registry-based studies comparing EPAR and OPAR have been published, increasing the knowledge base through larger numbers of patients/limbs available for comparison. However, since these studies are based on non-randomized data, it is important to note the underlying differences between the two groups as patients receiving EPAR are typically older and have more co-morbidities[45, 123] but present with less ischemic leg symptoms[14, 103] compared to patients receiving OPAR.

Eslami et al. published results of 169 EPARs and 221 OPARs in asymptomatic patients treated between 2010-2013 from the Vascular Quality Initiative, a prospective registry including 290 vascular centres in North America. A Cox regression analysis adjusting for confounders showed higher risk of combined major adverse limb event and mortality as well as loss of primary patency after EPAR, however, there was a very high loss to follow-up in the EPAR group[123].

Cervin et al. published data from the Swedvasc registry on patients receiving EPAR (n = 95) and OPAR (n = 473) between 2008-2012. This included both elective and acute patients. Patients receiving OPAR had superior primary and secondary patency rates, and this difference was even more pronounced in patients presenting with ALI. However, there was no difference in amputation rates at one year[45]. In 2021, Cervin et al. published a comparison between EPAR (n = 77) and OPAR (n = 154) from the same cohort, this time matched on the indication for treatment. Adjusting for indication, hazard ratio (HR with 95% confidence intervals) for occlusion and permanent occlusion after EPAR was 2.69 (1.60 – 4.55) and 2.47 (1.35 – 4.50), respectively, compared to OPAR. Poor outflow, defined as >50% stenosis in all three calf arteries before repair or after preoperative thrombolysis if performed, had a HR for occlusion and permanent occlusion of 3.03 (1.26 – 7.27) and 4.68 (1.89 – 11.62), respectively[52].

Grip et al. reported results from the Vascunet on >3000 limbs treated between 2012-2018 showing one-year patency of 84.0% and 78.4% for OPAR and EPAR, respectively[49]. Data from the POPART registry, a collaboration of German-speaking countries, on 662 OPARs and 106 EPARs between 2014-2019 showed overall patency of 83.2% and 74.2% at one year, respectively. However, follow-up data were only available in half of the patients included, and there was no report on amputations after one year[14].

Patency and major amputation/mortality

Poor run-off has been suggested as a risk factor for loss of patency, especially in patients receiving EPAR[54, 91, 126]. In paper I, number of patent run-off vessels were similar between patients receiving elective EPAR and OPAR. Further, in paper II, degree of ALI according to Rutherford classification was similar between patients receiving acute EPAR and OPAR.

In paper I and II, primary patency at one year were higher after OPAR compared to EPAR in patients receiving elective or acute repair (94% versus 84% and 80% versus 57%, respectively). Although differences did not reach statistical significance, these are comparable to findings in previously published studies[84, 87]. While primary patency in patients receiving EPAR due to ALI was low, the proportion of acute patients receiving EPAR was high compared to other studies, associated with the endovascular profile of the present vascular center. However, secondary patency at one year in patients receiving OPAR and EPAR due to ALI

was 80% versus 86%, respectively, and no patient in the EPAR group underwent major amputation. This raises the question if EPAR should be considered for patients who are not fit for general anaesthesia, extensive vascular surgery or do not have a suitable autologous vein conduit, but who are candidates for repeated vascular interventions needed to maintain patency.

Among electively treated patients, four EPAR-treated (15% of all elective EPAR, three within one year and one after six years follow-up) and none OPAR-treated legs underwent major amputation. On the contrary, among patients undergoing PAA repair due to ALI, three OPAR-treated (15% of all acute OPAR, all three within one year) and none EPAR-treated legs underwent major amputation. These findings may seem paradoxical, but differences are more likely to result from chance and small group sizes rather than reflecting an underlying superiority of OPAR in elective repair and EPAR in acute repair.

There was no difference in combined major amputation/mortality between EPAR and OPAR, neither in elective patients nor patients with ALI. Though patient characteristics between patients receiving EPAR and OPAR were similar in many aspects, older patients were selected for EPAR in elective and acute repairs, which should negatively impact overall mortality, as shown by the multivariable Cox regression analysis in paper I.

Complications and in-hospital stay

Wound complications should be lower after EPAR compared to OPAR, but there seem to be few comparative reports examining this issue[54, 127]. In paper I, patients receiving elective EPAR had fewer wound infections and major bleeding complications than patients receiving elective OPAR, supporting the notion that EPAR might be suitable for fragile patients in an elective setting. In patients treated for ALI due to PAA, major bleeding rate was not significantly higher after OPAR compared to EPAR (55% versus 26%), highly likely explained by a type II statistical error, and a higher use of intra-arterial thrombolysis in patients receiving acute EPAR.

Reports on in-hospital stay show that the length of stay is shorter for EPAR compared to OPAR[36, 81, 128]. In our study populations, in-hospital stay was shorter for patients receiving elective EPAR than elective OPAR. However, there was no difference in in-hospital stay after EPAR and OPAR in patients with ALI. Complicating factors after revascularization, such as fasciotomy, greatly impacted in-hospital stay. This finding was replicated in paper III, showing median in-hospital stay more than four times longer in patients receiving fasciotomy than in patients not.

Popliteal artery aneurysm, acute limb ischemia and fasciotomy

In paper II, a high risk of fasciotomy was found in patients treated for ALI due to PAA. This was further investigated in paper III where ALI due to PAA was found to be independently associated with a higher risk of fasciotomy compared to having ALI of other etiologies. A possible explanation for this association could be a high proportion of onset of sudden thromboembolism with no or mild PAD before occlusion, and reduced existence of collateral blood flow, in patients with ALI due to PAA.

This likely explanation was supported by the lower proportion of diabetes mellitus in patients with PAA in paper III. It is well-known that patients with diabetes mellitus have a more extensive distal arterial occlusive disease with a high prevalence of long tibial occlusions compared to those without diabetes mellitus[129]. The preference of anatomical distribution of PAD to the lower leg in individuals with diabetes mellitus may reduce the effect of acute revascularization, making them less susceptible to acute compartment syndrome.

Further, PAA was predominantly found in male patients in paper III, and female patients was shown to have a lower risk of undergoing fasciotomy after revascularization for ALI after adjusted analysis. Although speculative, smaller muscle mass may be protective towards reperfusion injury and acute compartment syndrome. Therefore, compared to men, female patients may benefit more from active monitoring rather than prophylactic fasciotomy after emergency revascularization due to ALI[130]. The condition may also be poorly recognised in females.

Instruction For Use – does it matter?

Evaluation of the IFU has not received much attention in the literature. Hellwig et al.[131] scrutinized the eligibility of EPAR according to the IFU. The study was conducted by retrospective analysis of preoperative vascular images in 61 consecutive PAAs, both asymptomatic and symptomatic, all having received OPAR. In total, 38% of PAAs were deemed ineligible for EPAR based on IFU criteria. In addition, Zimmermann et al.[132] found 35% of PAA to be ineligible for EPAR based on either lack of adequate landing zones or no patent run-off artery.

In paper IV, at least one deviation from the IFU was found in a vast majority, 82%, of all EPAR procedures. A total of 92 individual deviations from the IFU were made in 55 PAA receiving EPAR, the most common being a distal oversizing >20%, present in 40% of all procedures. This high degree of deviations might be related to the endovascular profile of the present vascular center, attempting an endovascular approach even in case of unfavorable anatomy.

No difference in primary patency was seen between patients treated within and not within the IFU, either at one year after index procedure in paper IV or at follow-up in paper V. This raises the question if IFU are too strict, or if some IFU criteria might have higher impact on outcome than others, and hence are more important to adhere to. In paper IV, procedures using overlapping stent-grafts with >1 mm diameter difference were associated with lower primary patency at one year. Since stent-grafts with larger diameter should be telescoped into smaller stent-grafts, it could be speculated that a too large diameter difference would lead to inadequate expansion of the larger stent-graft at the overlap zone, promoting turbulent blood flow and edge stenosis. However, this association might also be a proxy for underlying mechanisms affecting stent-graft patency, such as anatomical variations, which needs to be clarified in future studies.

The IFU also states that patients should "not have a large difference in vessel diameter proximal and distal to the aneurysm to help minimize numerous device overlaps in points of flexion", however no cut-off value is specified, why this analysis was not incorporated in the analysis of EPARs in paper IV. In previous studies different cut-off values have been suggested, ranging from 2 – 5 mm[54, 133, 134]. In case of proximal-to-distal vessel diameter difference >2 mm, appropriate oversizing at landing zones according to IFU will be difficult while maintaining ≤1 mm diameter difference of overlapping stent-grafts. To do this, at least three stent-grafts will be needed, associated with lower primary patency according to the results from paper V. Several overlapping zones also increases the risk of overlapping within the "No overlap zone" and has previously been reported to increase risk of stent-graft fracture by Tielliu et al.[135]. However, stent-graft fractures were not explicitly investigated in our material, and primary patency at one year was not associated with overlap within the "No overlap zone" in paper IV.

While paper IV did not detect any differences in outcome between the groups treated within versus not within IFU, the results suggests that adherence to some IFU criteria may be more important than others. For example, although too large oversizing was present in 40% of all procedures, it was not associated with primary patency at one year. In contrast, procedures using overlapping stent-grafts with >1 mm diameter difference had lower primary patency. These findings warrant further scrutiny in a larger population and, if replicable, should help guide clinicians in procedural planning.

Introducing a tapered stent-graft to match the cone-shaped profile of the PA could minimize the number of stent-grafts of different diameters needed to accomplish adequate seals. Although some tapered stent-grafts are available on the market, none are indicated for use in peripheral arteries. As outcome after EPAR is suggested to be associated to number of stent-grafts used and inappropriate stent-graft diameter difference, it could be speculated that using a tapered stent-graft might improve outcomes in patients with PAA.

Stent-graft at the knee bend – is it a good idea?

Reports on patency rates after EPAR varies greatly between different studies[14, 87], which might suggest that there is a steep learning curve for this technique[36]. Patient selection may also impact outcomes as results are inferior in symptomatic patients compared to asymptomatic patients.

When analysing both elective and acute EPAR in paper IV, primary patency was 72% at one year. However, long-term patency after EPAR was evaluated in paper V only in patients attending the follow-up examination. The results showed primary and secondary patency of 55% and 61%, respectively, at a median follow-up time of almost five years, excluding patients who had died or undergone major amputation.

An unexpected finding was the low percentage of patients receiving DAPT at discharge after EPAR, which could have had a negative impact on patency rates[90]. Nevertheless, when analyzing primary patency at one year of all patients receiving EPAR in paper IV, there was no difference between patients receiving DAPT or not. Possible explanations for this could either be that patients not receiving DAPT instead received single antithrombotic or anticoagulation therapy that were just as effective (as patients who were prescribed NOAC/warfarin prior to EPAR continued with this treatment rather than switching to DAPT), or that the effect of DAPT were negligible in our rather small study population.

Notably, ABI were for the most part relatively good at follow-up examination in paper V, even in patients with loss of primary patency, though lower than in patients with patent stent-graft. Almost half of the patients with loss of primary patency reported claudication at follow-up, though no patient presented with rest pain or foot ulcers. This fact indicates a development of collateralization around the popliteal occlusion over time in patients with occluded stent-grafts, protecting them against more severe symptoms.

Kropman et al.[136] investigated the impact of knee flexion and extension on PAA lumen and angulation using CTA. When flexing the knee joint 90°, the PAA lumen decreases and the angulation of the popliteal artery increases at both its proximal and distal end, changes that were even more pronounced in larger PAAs. As these factors impact the hemodynamics of the popliteal artery or PAA, they might increase degree of turbulent blood flow and risk of thromboembolism. Since patients treated with EPAR have their arterial reconstruction passing through the PAA, the stent-grafts will still be subjected to these changes which will not be the case after OPAR. The authors therefore suggested that pre-operative knee flexion and extension CTA could be used in selection of patients for EPAR.

Supporting this issue, Cervin et al. [52] found an association between maximal angulation and loss of patency in patients receiving EPAR, after adjusting for

indication and stent-graft diameter. These results could not be replicated in paper IV. However, maximal angulation and TI of the PA were both associated with combined major amputation and mortality at one year after the index procedure. Since measurements were made on CTA or MRA images with the knee fully extended, the dynamic changes in angulation and tortuosity upon bending the knee could not be studied.

In paper V, there was an association between the number of stent-grafts used at index procedure and patency at follow-up examination. This finding could be contingent on the association between longer stent-graft coverage and loss of primary patency shown by Piazza et al. [89], owing to a higher risk of stent-graft kinking at knee flexion. However, contradicting this theory, Zaghloul et al. [126] reported no association between either number of stent-grafts or length of coverage and major adverse limb event-free survival. Interestingly, coverage with stent-grafts below knee were associated with lower three-year major limb event-free survival[126], an analysis not performed in paper IV or V.

As shown in the present thesis and previous reports, there are complicating factors associated with an arterial reconstruction crossing the knee bend. Native arterial tortuosity, dynamic changes upon knee flexion, and maybe also large arterial diameter discrepancy between beginning and end of the PAA, are challenges for endovascular repair. In addition, patency of these reconstructions is often impeded by poor run-off, contributing to low blood flow and increased risk of thrombosis. However, the influence of each of these factors are difficult to determine. Future prospective and registry studies should rely upon pre-specified anatomical, functional and flow characteristic variables and patency. To improve patient selection and treatment outcomes after EPAR, a collaboration between scientists and industry companies producing stent-grafts is necessary.

Based on the present thesis and current literature, EPAR should be seen as a complementary treatment alternative to OPAR if adequate autologous vein graft is absent, especially in frail, elderly patients with favourable anatomy and acceptable run-off. Suggestions for patient/modality selection are presented in Figure 20. Adjunctive interventions to optimize distal run-off should be considered both in patients receiving EPAR and OPAR. Patient preference should also guide treatment decisions based on information of risks and benefits for each treatment modality.

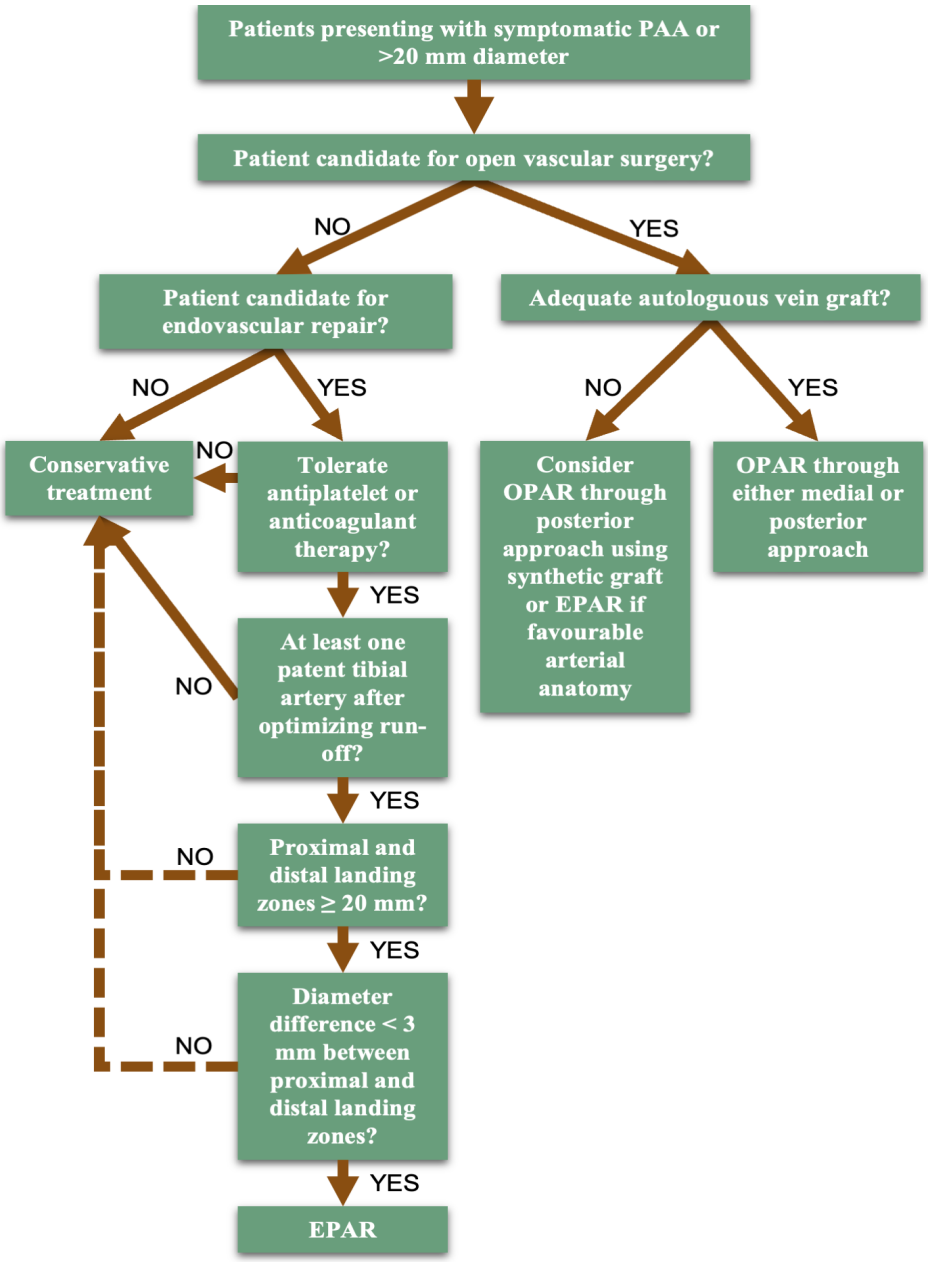


Figure 20. Flowchart of suggested treatment selection for patients presenting with symptomatic popliteal artery aneurysm or aneurysm diameter >20 mm. Inadequate length and diameter difference of proximal and distal landing zones could be seen as relative contraindications and should be weighed against risk of conservative treatment. Additional factors may impact suitability for endovascular repair such as arterial tortuosity and length of aneurysmatic disease, but needs further investigation and are not accounted for in this model. EPAR; Endovascular popliteal aneurysm repair, OPAR; Open popliteal aneurysm repair, PAA; Popliteal artery aneurysm.

Endoleak after endovascular popliteal aneurysm repair

Several studies have reported post-operative aneurysm sac expansion after OPAR, suggested to be a consequence of retrograde blood flow from collaterals, described as type II endoleaks[101, 137]. In theory, endoleak after OPAR could also arise from incomplete proximal or distal ligation of the popliteal artery, analogous to a type I endoleak. Symptoms due to post-operative aneurysm sac expansion include local pain, swelling, venous congestion and neurologic impairment[102] and in rare cases even rupture[138, 139].

The results from paper V in the present thesis showed an unexpectedly high prevalence of endoleak after EPAR, present in half of re-examined aneurysms, compared to data from the existing literature[89, 140, 141]. A possible contributing factor for increased endoleak detection could be superior sensitivity of CEUS compared to other examinations, mainly DUS, that has been used in previous studies. As an ultrasound contrast agent gives off a signal different to both tissue echoes and blood flow, it increases the signal-to-noise ratio[142].

In patients receiving EVAR, CEUS has shown a superior sensitivity for detecting type II endoleak compared to rotational angiography[143], as well as superior sensitivity and specificity compared to DUS[144]. In a systematic review of 1773 post-EVAR patients, Harky et al. demonstrated a superior sensitivity and comparable specificity for endoleak detection using CEUS compared to CTA[145]. It has therefore been suggested that CEUS should be used for post-EVAR surveillance, especially in patients where a non-nephrotoxic contrast agent is indicated[146].

The literature on CEUS examination in patients with PAA is scarce. However, Schwarze et al.[147] presented their experience of diagnostic evaluation using CEUS in patients with PAA (eight untreated, four having received OPAR and one EPAR). A type I endoleak was seen in one CEUS examination after OPAR, because of incomplete proximal and distal ligation of the popliteal artery, which could not be visualized on DUS. Ucci et al.[148] reported use of CEUS in routine post-operative surveillance in 25 PAA endovascularly treated with a multilayer flow modulator. Though not having endoleak as an endpoint, complete aneurysm sac thrombosis was seen in 93% and freedom from aneurysm sac expansion was 100%.

In paper V, freedom from aneurysm sac expansion was 97%. Although the single PAA showing aneurysm sac expansion at follow-up also had a type II endoleak, maximal aneurysm diameter difference between index procedure and follow-up was similar between PAAs with and without endoleak. In fact, the majority of PAAs in both groups had a decrease in maximal aneurysm diameter. Since there was no association between endoleak and aneurysm sac expansion, the importance of detecting these endoleaks can be questioned. It could be argued that CEUS is redundant in routine follow-up after EPAR but proposes a useful tool for endoleak detection in patients where DUS indicates post-operative aneurysm sac expansion.

While paper V provides a momentary cross-sectional view of the prevalence of endoleak in patients treated with EPAR, the persistency and long-term fates of these endoleaks remain unknown. Endoleaks post-EVAR, mainly type II endoleaks, are known to often resolve spontaneously without intervention[149]. This temporal relation has not been studied in patients with endoleak after EPAR and cannot be answered from the present thesis. However, since median time from index procedure to re-examination for patients with endoleak was almost six years, the shortest being 33 months, it could be argued that these endoleaks are persistent.

Methodological considerations

Limitations

Normal distribution was not assumed for continuous variables because of the small sample sizes, why Mann Whitney-U test was performed when comparing two independent groups instead of, for example, Student's t-test. While the Mann Whitney-U test allows us to identify difference in mean rank between two groups, it does not account for the difference in mean value which is an interesting aspect in addition to a statistically significant p-value.

Due to skewness in maximal angulation and TI, log transformation of these variables was performed prior to entering the age-adjusted Cox regression model. The results of these analyses are therefore presented as increase in Hazard Ratio per standard deviation, which might be difficult to interpret or transfer to a clinical setting. It is possible that the level of skewness would decrease in a larger study population, allowing for this analysis to be performed without prior log transformation.

The number of statistical analyses performed and the chosen significance threshold of $p < 0.05$ introduces risk of type I statistical error. That is, the risk of wrongly detecting a difference that does not exist in the general population, thus rejecting a true null hypothesis. Analysing a small number of patients receiving EPAR and OPAR also comes with a risk of type II statistical error, thus not rejecting a false null hypothesis. Therefore, each analysis must be interpreted critically and cautiously, most often seen as steppingstones for further research.

Unfortunately, completion knee flexion angiograms after EPAR were rarely available in the present study population due to local practice. Therefore, impact of knee flexion on arterial morphology after stent-graft deployment could not be analyzed. When predefining objectives in prospective studies, assessment of completion knee flexion angiograms, would be one of those issues to study.

Confounding

Although retrospective studies have the strength of being able to collect relatively large amount of real-world data in a short space of time, this study design cannot determine causality between exposures and outcome because of possible confounding factors. Adjustments for possible confounders between PAA repair and outcome through multi-variable analyses were limited due to the small study population. As discussed above, results from univariate analysis needs to be interpreted very carefully and validated in future studies, preferably in randomized trials or studies with possibility for adjusted analyses.

In paper IV, only one variable, in addition to treatment within IFU/not within IFU, were possible to enter into the multi-variable regression model because of too few outcome events. Age at index repair was chosen as this was thought to have the highest association with the outcome combined major amputation/mortality during follow-up, as suggested in paper I. As in all studies, it is important to be aware of possible residual confounding, factors not entered in the regression model or not even studied.

Information bias

Detailed routine follow-up data were limited to one year, due to current practice at the vascular center guided by Swedish Society for Vascular Surgery recommendation. Data on stent-graft or by-pass patency beyond one year after index procedure were available only if vascular examination had been performed due to clinical set-back. Patients with loss of patency without developing symptoms or simply not seeking medical attention could have been misinterpreted as having a patent PAA repair. However, long term follow-up data after re-examination are presented on patients in paper V. Data on major amputation and mortality were thought to be reliable in the patients' medical records and Web-PASIS, respectively, even though routine follow-up of the treated PAAs were lacking.

Missing values might pose a form of bias if some data are structurally missing, i.e. non-randomly distributed. Missing values resulted from the retrospective study designs due to incomplete patient medical records registration. In all papers included in this thesis, no imputation of missing values was performed, instead, all available data was used for analysis and no patient was excluded because of missing values. The degree of missing values in different patient groups has not been investigated in the present papers. However, one might suspect a higher degree of missing values in patients receiving acute compared to elective PAA repair. Since these groups were analysed separately in paper I and II, this should not impact the comparison between EPAR and OPAR, but could be a source of bias when analysing both acute and elective EPAR together in paper IV and V.

Selection bias

Due to the retrospective study design of paper I-III, there is an inherent selection bias in these studies. Study populations in all three papers were based on patients identified through assigned diagnosis/procedure codes, meaning that patients with PAA and/or ALI not receiving any of the specified codes would be missed. Also, as the present vascular center is one of several hospitals in Skåne County that treats patients with vascular diseases, patients treated for PAA and/or ALI at one of the other hospitals would not be included.

In paper I and II, reason for selecting either EPAR or OPAR was not well documented in most patients' medical charts. Although inclusion was made of consecutive patients, 12 and 15 patients presenting with PAA did not receive neither EPAR nor OPAR in paper I and II, respectively. Documented reasons for not offering PAA repair were often poor prognostic factors such as high burden of comorbidities and poor run-off. It is possible that offering PAA repair to these patients would alter the results of subsequent analyses. As the study population of paper IV and V are drawn from paper I and II, the same selection bias applies to these studies.

Similar risk of bias is present in paper III since the decision to perform fasciotomy were based on the discretion of the treating physician. As there was no routine for measuring intra-compartmental pressure, decision on therapeutic fasciotomy was guided by clinical symptoms. Thus, patients with acute compartment syndrome but mild symptoms or lower ability to mediate their symptomatology may have been missed. There could also be patient groups in which clinicians for some reason are more hesitant to perform fasciotomy. Half of the fasciotomies performed in paper III were labelled prophylactic, with a clear predominance in patients receiving primary open vascular surgery as opposed to endovascular revascularization. While fasciotomy can be performed in junction to open vascular surgery, it demands transfer to the operating theatre from the endovascular laboratory in patients receiving endovascular revascularization, why this finding might be explained by practical reasons rather than actual incidence of acute compartment syndrome.

Strengths

Paper I and II gains strength from the separate analysis of elective and acute PAA repairs, respectively. Several previous studies presenting results after PAA repair mix elective and acute repair[81, 150], which complicate interpretation of results as patients have a worse outcome after acute compared to elective repair.

Paper III gains strength from the large cohort and the relative high frequency of fasciotomies performed, allowing for multivariate adjustments in the Cox regression analysis.

The proportion between patients receiving EPAR compared to OPAR was relatively even, possibly owing to the endovascular profile of the present center. In addition, the single center study design allowed for in-depth scrutiny of medical charts, including pre- and perioperative images, which might not always be the case in registry-based studies. This was essential for evaluating adherence to IFU after EPAR in paper IV.

Median follow-up of almost five years in patients receiving EPAR was a strength in paper V as data on long term outcomes are scarce in the literature. The use of CEUS was possible due to access to advanced ultrasound system with built-in contrast mode. Accuracy of diagnosis and classification of endoleak were strengthened using consensus-based core-lab decision. Inter-operator for CEUS and inter-modality reproducibility between CEUS and ultrasound was not performed in paper V. It was simply not planned for, and based on studies in EVAR surveillance after AAA[144, 151, 152] and team experience, a consensus-based approach of endoleak detection and categorization was used.

Conflict of interests

No part of this thesis has been subject for external founding. Results have been submitted for publication without prior approval from anyone else than the authors of each paper. All papers included have been published through peer-review process.

Conclusion

- During the study period, the proportion of elective repair and use of EPAR has increased in the present vascular center. This does not seem to be a direct effect of the introduction of the AAA-screening program.
- Patency at one year was similar after EPAR compared to OPAR. Elective EPAR was associated with higher major amputation at one year compared to elective OPAR. There was no difference in amputation-free survival or combined major amputation/mortality between EPAR and OPAR, either in patients treated electively or due to ALI.
- In elective PAA repair, EPAR compared to OPAR was associated to fewer wound infections and major bleeding complications, as well as shorter in-hospital stay.
- In patients presenting with ALI, PAA was an independent risk factor for fasciotomy. However, PAA was not associated with combined major amputation/mortality at one year after revascularization.
- Deviations from IFU were common in patients receiving EPAR, though there was no difference in primary patency at one year between patients treated within or not within IFU. Diameter difference >1 mm between overlapping stent-grafts was associated with lower primary patency at one year.
- In patients receiving EPAR, higher maximal angulation and TI were associated with combined major amputation/mortality in an age-adjusted Cox regression model. Maximal angulation and TI were not associated with loss of primary patency at one year.
- Prevalence of endoleak after EPAR was high, probably owing to a superior sensitivity of CEUS compared to other imaging modalities. Compared to those without endoleak, endoleak did not influence aneurysm sac shrinkage. Number of stent-grafts used at index procedure was associated with lower primary patency at long-term follow-up.

Future aspects

Timing of PAA repair

The timing of PAA repair is still a topic for debate as risk factors for asymptomatic aneurysms to progress and cause ALI or rupture is not fully understood. Rupture is associated with aneurysm size, as shown by Cervin et al.[40], however, smaller aneurysms also have a risk of causing thromboembolism[16]. As shown in paper I, even elective repair in asymptomatic patients come with the risk of potentially severe complications such as major amputation following occlusion of the reconstruction, which should be weighed against the risk of conservative surveillance.

The papers included in this thesis can only account for patients with PAA treated at the present vascular center, which turned out to be slightly above 100 over a decade. Given the estimated prevalence of 1% in men >65 years of age[12], and the regional catchment population of 1.4 million for this vascular center, one could suspect the patients with PAA included in this thesis to represent the tip of an iceberg. Further studies are needed to investigate the natural history and risk factors for developing symptomatic PAA to improve treatment selection in asymptomatic patients.

Role of medical therapy

Data on optimal medical therapy for the prevention and improving outcomes after PAA repair are lacking. In general, optimization of atherosclerotic risk factors through smoking cessation, statins and antiplatelet therapy are advocated, though extrapolated from recommendations on PAD management[61].

Importance of cardiovascular risk factor management is also stressed in the clinical practice guidelines for AAA, both pre- and post-intervention, though no specific drug has been proven effective in prevention[21]. Use of metformin has been associated with slower aneurysm growth in patients with AAA[153]. Several ongoing RCTs are aiming to further investigate this relation[154-156]. If results from these trials provide evidence for metformin therapy in patients with AAA it could be suspected that this would also benefit patients with PAA, given the high similarity of the two diseases. Use of metformin for prevention of PAA could therefore be a topic for future studies.

Today, EPAR is only recommended for patients who tolerate post-operative DAPT, suggested to be associated with higher patency[90]. Dual pathway inhibition (DPI), combining an antiplatelet drug and an anticoagulant drug (acetylsalicylic acid plus low-dose rivaroxaban), has emerged in recent years as an alternative antithrombotic therapy. Two recent RCTs have compared treatment with DPI to acetylsalicylic acid after revascularization in patients with PAD. The COMPASS trial showed a risk reduction for major adverse limb events (acute/chronic limb ischemia or amputation) for patients receiving DPI[157], followed by the VOYAGER trial showing a risk reduction for major adverse limb and cardiovascular events[158], as well as ALI[159], in patients receiving DPI, regardless of concomitant use of P2Y12 inhibitor[160]. Though, the effect of DPI has not been examined in patients treated for PAA. It would be interesting to investigate if DPI could provide a way to improve outcome after PAA repair, and if there would be a difference in benefit after EPAR compared to OPAR.

Role of ultrasound in patients with PAA

Ultrasound is an effective imaging modality for PAA detection and preoperative diameter surveillance. Further, CEUS can be used for assessing run-off[67] and is effective in detecting endoleak after repair, as shown in paper V. Use of three-dimensional (3D) CEUS has been suggested to improve the accuracy endoleak classification [161] and have a superior sensitivity compared to CTA after EVAR[162]. In addition, CEUS have an excellent assessment of pedal and calf arteries in patients with PAD[163]. Preoperative workup and postoperative endoleak detection in patients treated for PAA could be a natural expansion of the indication for 3D CEUS but has yet to be evaluated.

Although not applied in any of the patients included in the present thesis, intravascular ultrasound (IVUS) has been proposed as a method for perioperative artery/stent sizing and reducing the use of nephrotoxic contrast agent during endovascular procedures[164]. Some studies have reported use of IVUS in patients receiving EPAR, suggesting that this may improve choice of stent-graft dimensions fitted to the proximal and distal landing zones[165, 166]. The potential benefit of IVUS during EPAR needs to be addressed in a larger cohort.

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