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# Popliteal Artery Aneurysm

*Epidemiology, Surgical Management and Outcome*

HANS RAVN



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#### **Abstract**

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Even if popliteal artery aneurysm (PAA) is the most common peripheral aneurysm, no single surgeon or institution has enough patients to study this disease with appropriate scientific methods, and no population-based investigation exists.

PAA epidemiology, treatment, management, and outcome were studied in a population-based study of 571 patients (717 legs) primarily operated on for PAAs and 100 episodes of preoperative thrombolysis in Sweden between 1987 and 2002. Patients were identified in the Swedish Vascular Registry and case-records were reviewed. Information on amputation and survival was obtained for all patients, and 190 patients were re-examined with ultrasound, after mean 7.2 years (range 2-18)

Median age was 71 years; 5.8% were women. Patients with unilateral PAA had AAA in 28%, increasing to 38% when PAAs were bilateral. Crude survival was 91.4% at one and 70% at five years, significantly lower than among age and sex matched controls. The cumulative incidence for operation of PAA in Sweden was estimated to 8.3/million person year. One-year amputation-rate was 8.8 %, increasing to 11% after follow-up (7.2 years). Independent risk factors for amputation within one year were poor run-off, age, emergency procedure, and prosthetic graft. Run-off was improved by preoperative thrombolysis among 87% of legs, when acute ischemia. After surgical repair with a medial approach the risk of late expansion of the aneurysm was 33%, with a posterior approach 8% ,  $p=0.014$ . Among 190 re-examined patients, 108 (57%) had at least one additional aneurysm at index-operation, increasing to 131 (68%) at re-examination, the total number of aneurysms increasing by 42% (from 244 to 346).

Conclusions: Multiple aneurysms are common among patients operated on for PAA. Preoperative thrombolysis improves run-off and decreases the amputation-rate in PAAs with acute ischemia. Vein grafts do better than prosthetic grafts, especially when a long bypass is needed. Posterior approach, when possible, reduces the risk of late expansion. A complete examination of the aorto-iliac and femoro-popliteal arteries is warranted at the time of surgery. All patients should be kept under life-long surveillance in order to detect and treat newly developed aneurysms timely. Normal arterial segments should be re-examined after three years.

*Keywords:* popliteal artery aneurysm, thrombolytic therapy, acute ischemia, surgical technique, long-term outcome, surveillance

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# List of papers

This thesis is based on the following papers, which are referred to in the text by the Roman numerals given below (I-IV):

- I Ravn H, Bergqvist D, Björck M. Nationwide study of the outcome of popliteal artery aneurysms treated surgically. *Br J Surg* 2007;94:970-977.
  
- II Ravn H, Björck M. Popliteal Artery Aneurysm with Acute ischemia in 229 Patients. Outcome after Thrombolytic and Surgical Therapy. *Eur J Vasc Endovasc Surg* 2007;33:690-695. The abstract of paper II was also selected and published in *J Vasc Surg* 2007;45:1288.
  
- III Ravn H, Wanhainen A, Björck M. Surgical technique and long-term results after popliteal artery aneurysm repair: Results from 717 legs. *J Vasc Surg* 2007;46:236-243.
  
- IV Ravn H, Wanhainen A, Björck M. High risk to develop new aneurysms after surgery for popliteal artery aneurysm. A study based on 190 re-examined patients with a median follow-up of seven years. *Submitted*

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*Cover pictures:*

Front: John Hunter, painting by Reynolds

Back: Popliteal aneurysm specimen

The pictures were kindly provided by the Museums of the Royal College of Surgeons, London, UK.

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# Abbreviations

AAA	Abdominal aorta aneurysm
AK	Above knee
BC	Before Christ
BK	Below knee
CFA	Common femoral artery
CI	Confidence interval
CIA	Common iliac artery
CLI	Critical limb ischemia
CT	Computed tomography
Dist	Distal
DVT	Deep venous thrombosis
EAG	Endovascular approach group
FAA	Femoral artery aneurysm
IAA	Iliac artery aneurysm
MAG	Medial approach group
MRT	Magnetic Resonance tomography
NOMESCO	The NORdic MEDico Statistical COmmittee
OR	Odds ratio
PA	Popliteal artery
PAA	Popliteal artery aneurysm
PAG	Posterior approach group
Prox	Proximal
RR	Relative risk
SAS	Business Intelligence and Analytics Software
SFA	Superficial femoral artery
SHDR	Swedish hospital discharge register
SPSS	Statistical Package for the Social Sciences
Swedvasc	Swedish Vascular Registry
TFT	Tibiofibular trunk
US	Ultra sound
VRISS	Vascular registry in southern Sweden



# Introduction

## Definition

There is no consensus on how to define a popliteal artery aneurysm (PAA). Several definitions have been proposed, such as permanent localized dilatation of an artery having at least a 50% increase in diameter compared to the expected normal diameter of the artery in question [1] or a localized dilatation of the popliteal artery  $> 2$  cm in diameter or  $> 150\%$  of the normal proximal arterial calibre [2-5].

Arteriomegaly is a diffuse arterial enlargement involving several arterial segments with an increase in diameter of greater than 50% in comparison to the expected normal diameter while ectasia is characterized by dilatation less than 50% of the normal arterial diameter [1].

The popliteal artery diameter increases with age and growth. A gender difference also exists. It is possible to predict the normal popliteal arterial diameter if age, body size and sex are known and a nomogram based on ultrasound measurements of healthy individuals was published by Sandgren et al in 1998. [6].

## Historical notes

The management of PAA has engaged surgeons since 200 BC, when Antyllus described ligation of the aneurysm followed by packing the aneurysm sac, allowing it to heal by secondary intention [7]. In the last part of the 18th century the interest for PAA increased and several case reports on surgical management were published. They were all modifications of the methods of Antyllus, and most frequently ended up with amputation. The cause of PAA at that time was often infection or trauma of the popliteal fossa. The first successful surgical management of a PAA was reported by Sir John Hunter (1728-1793), "The Hunterian Operation 12<sup>th</sup> December 1785". John Hunter successfully treated a patient with a popliteal aneurysm by ligating the superficial femoral artery at the distal subsartorial canal (Hunters canal) and leaving the aneurysm intact. This departed radically from the principle of Antyllus. The patient recovered well. Fifteen months later the patient died of a remittent fever. John Hunter bought the leg from the widow and examined it seven days later. He found that the size of the PAA was appreciably reduced.

Hunter operated on four more patients, successfully in the sense that amputation was avoided in three [8]. His hypothesis was that collateral circuits in their natural state were endowed with a latent capability for taking the burden of supplying blood to the territory normally perfused by a major artery after ligation of that artery. *“I believe the circulation will always go on after the femoral artery is secured by ligation”* (John Hunter) [8].

In 1888, Rudolph Matas reported a new method to treat aneurysms, “endo-aneurysmorrhaphy” [9]. The first patient treated had a traumatic pseudoaneurysm of the brachial artery [7, 10], but Matas used this technique in several arterial segments and later distinguished between two different methods [10]. The obliterative endo-aneurysmorrhaphy consisted of obliteration of the lumen from within, as well as of the side-branches originating from the aneurysmal segment, and preservation of the extremity through its unharmed collateral circulation. This method was reported to still be used by some vascular surgeons in the 1980’s [9]. The second method consisted of resecting part of the aneurysm and re-suturing the arterial wall, thus maintaining blood-flow through the arterial segment. This later method is still being used when treating renal artery aneurysms. When Matas summarized his life-time experience he reported that he had repaired 42 PAAs with these two methods [10].

In the 1930’s the treatment of PAA with acute ischemia was carried out with preliminary lumbar sympathetic ganglionectomy followed in four weeks by an obliterative endoaneurysmorrhaphy. A small series followed this report [11, 12]. Linton described the natural history of the popliteal aneurysm and advocated early surgical intervention [12]. In 1947 Blackmore present a technique of vein inlay for the repair of arterial aneurysm in four legs [13] Following World War II and the early 1950’s, there was progress in the management. The most common treatment in the 1950’s was resection with interposition of an autogenous vein using a posterior approach to the popliteal space [13, 14]. In 1969, Edward described a technique of bypassing the aneurysm and ligation of the PAA immediately proximal and distal to the aneurysm through two small medial incisions above and below the knee joint. The aneurysm was left insitu. Resection of the aneurysm were reserved for patients with local symptoms in the popliteal space [15].

The first endovascular repair of a PAA was reported in 1994 [16]. Several case reports and relatively small series have been published about endovascular treatment of PAA [17]. The main problem with endovascular treatment for PAA has been the lack of an endograft with the necessary flexibility that is required in the knee joint. Long-term results may be jeopardized by stent-fractures. If the problems with flexibility and endurance are solved, endovascular treatment will become an alternative to the established open surgical treatments [18].

## Epidemiology

The popliteal artery is the most common site of aneurysm formation outside the abdominal aorta, accounting for more than 70% of all peripheral aneurysms [5, 19-21]. However, no single surgeon or institution has treated enough patients to study this disease with appropriate scientific methods. Incidence and prevalence is unknown, no population-based study was published.

Patients with a PAA, were reported to have an abdominal aortic aneurysm (AAA) in 35-40%, and a popliteal aneurysm in the contralateral leg in 50 % [2, 4, 5, 22, 23]. These prevalences are, however, based on small series and point prevalence studies at the time of diagnosing or operating on the PAA. Thus, no information on the long-term risk to develop new aneurysms was published.

From hospital series we know that PAA is more prevalent among men [5, 24, 25] and that the prevalences increase with age and peak in the sixth and seventh decades of life [5, 21].

## Clinical presentation

Frequently the PAA is first recognized after complications have occurred. In previously published case-series, the proportion of operated asymptomatic PAAs is one-third and symptomatic two-thirds [5]. The most prevalent acute symptoms are thrombosis of the aneurysm (40%) followed by distal embolization (25%). Rare symptoms are rupture as well as local symptoms such as venous thrombosis and neurological symptoms due to compression (<5%). Chronic thrombosis or distal embolization from the aneurysm leads to progressive occlusion of the crural vessels and results in sub-acute or chronic symptoms such as claudication, rest pain, tissue loss, blue toe syndrome and gangrene. Other chronic symptoms are venous congestion and local pain [5, 21, 26-30]. The asymptomatic PAA is often diagnosed accidentally during treatment of a symptomatic PAA in the contralateral leg.

## Diagnosis

The careful physical examination of the patient is a cornerstone in the diagnosis of popliteal aneurysm. PAA should be suspected when a prominent pulsation can be felt in the subsartorial or the popliteal fossa or if a pulseless mass is found behind the knee, especially if a normal or prominent pulse in the contra lateral knee is recognized. Clinical features include family history of aneurismal diseases, previous aneurysm repair or known aneurysms in other anatomical regions [5].

When a PAA is suspected an investigation to verify the diagnosis is warranted. Historically the golden standard was arteriography, but today it has been replaced by non-invasive investigations such as duplex ultrasonography, computed tomography or magnetic resonance imaging. These modalities also have the advantage of imaging not only the intra-arterial column but also the outer limit and the thrombosis.

The investigations can help the surgeon to plan the operative approach. In order to plan the procedure, the surgeon or endovascular interventionist needs information of the size of the arterial segments proximal and distal to the aneurysm and the distal run-off. Therefore a combination of diagnostic procedures may be required [5].

## Indications for treatment

There is consensus that symptomatic PAAs need treatment, because the risk of limb loss increases with the onset of symptoms [21, 28, 31-33].

The treatment of asymptomatic PAAs, however, is controversial [34]. Some argue that small asymptomatic aneurysms remain small for years without symptoms and treatment carries a risk of limb loss [35-38]. Others recommend aggressive repair of all PAA of whatever size and symptoms because it is associated with a low operative risk [21, 27, 33, 39]. All these arguments are based on retrospective surgical series, with the exception of one prospective study of PAA [4].

The prospective study was based on 32 patients with 44 asymptomatic PAAs over 5 years. Twenty two of the PAAs (50%) were thrombosed, 19 acutely. Thromboses of PAA were associated with distortion (above or below) of the aneurysm and conclude that there were important morphological differences between thrombosed and non-thrombosed PAAs. The authors suggested that this distortion should be an indication to operate on asymptomatic PAA [4, 40].

If a patient has multiple aneurysms without acute symptoms, an aortic aneurysm of significant size has the highest priority for treatment and PAA has the second priority because of its potential to threaten the viability of the limb. On the other hand, for technical reasons treating the PAA first may be a safer option. The PAA may thrombose during or immediately after AAA repair, resulting in acute ischemia in the postoperative period, a life-threatening complication. Femoral aneurysms seldom cause serious complications [41].

## Treatment

The primary aim of the management of PAA is to prevent thromboembolism and amputation. The secondary objective is to prevent aneurysm expansion, that can cause local compression symptoms and rupture [14, 25].

Acute surgery has been the preferred therapy for thrombosed PAA with ischemic symptoms, but the outcome is associated with reduced graft patency and an increased amputation rate compared with elective revascularization [28, 42, 43]. The acute management of thrombosed PAA is a challenge even for an experienced vascular surgeon. During the last four decades the technique of intra-arterial thrombolytic therapy in acute limb ischemia was developed and the number of treated patients increased. The thrombolytic therapy in acute limb ischemia is controversial [44]. Despite this lack of evidence, and the associated risks [45], intra-arterial thrombolysis is an established treatment modality of acute limb ischemia.

The first thrombolytic treatment of thrombosed PAA was reported in 1984 [46]. The aim for thrombolytic therapy is to improve the run-off in the acute thromboembolised leg and through this treatment improve the limb salvage after the subsequent operation of the PAA. Small series or case reports with thrombolytic therapy on PAAs with acute ischemia have been reported with improved results after intra-arterial thrombolytic therapy, administered both pre- and intra operatively [43, 46-49].

The surgical treatment has been the golden standard from the 1950s until today. There have been different approaches, but two dominate. First the posterior approach to the popliteal space with resection of the PAA, or rather opening the aneurysm, and use of an autogenous vein as interposition graft in an anatomical position, often with an in-lay technique [14]. Second, the medial and most commonly used approach, with ligation of the PAA proximal and distal through two small medial incisions above and below the knee joint [15]. True resection of the aneurysm was reserved for patients with local symptoms in the popliteal space.

Since the first case report in 1994 [16] the number of patients undergoing endovascular treatment has increased, and self-expanding stent, internally covered by ultra-thin polytetrafluorethylene graft were developed. Good flexibility and radial stiffness, as well as improved durability and less risk of stent fatigue fractures [18] may turn this into the preferred treatment of PAA in the future.

Each open surgical approach to the treatment of PAA has its advantages and disadvantages. When the posterior approach is used only a short graft is needed. Although the short saphenous vein may serve, often the long saphenous vein needs to be harvested, because of inadequate calibre of the short saphenous vein. This results in the need of a second incision, and sometimes the necessity to turn the patient during the procedure. Many surgeons prefer the medial approach because of easy harvesting of the long

saphenous vein and exposing of the femoral vessel through the same incision [5]. If the proximal limitation of the aneurysmal artery extends into the femoral segment, the medial approach is used either with the long saphenous vein as in-situ bypass or as a reversed vein bypass. A prosthetic graft can be used with both open approaches, when no adequate vein material is available. Some vascular surgeons may use a prosthetic graft even when venous material is available, with the rationale to revascularize the acutely ischemic limb more rapidly, to prevent future aneurysm formation in the graft, or based on other considerations.

## Outcome after PAA-repair

The natural history of untreated PAA is encumbered with high incidence of thromboembolic complications. These complications are associated with high amputation-rates, Table I. It can be noted that papers reporting low amputation-rates are small series from single-centres. Patients undergoing elective repair of PAA have a more favourable outcome. Five year primary graft patency rates are reported as 67-75% and secondary patency rates 90-95%, when asymptomatic PAA are included, Table II. The reported amputation-rates are high for patients treated with acute limb ischemia caused by a PAA, approximately 25% [27, 32]. These patients are often operated on acutely with urgent revascularization and emergent bypass grafting [24, 27]. The overall operative mortality for PAA repair is low [24].

The results of endovascular treatment for PAA over the last 5 years report varying rates of success, ranging from 47% to 75%, but the number of patients treated are small [24, 50, 51].

Table 1. *Risk of amputation after conservative management of asymptomatic PAA.*

Reference	No of legs	Mean follow-up (months)	Major amputation	
			N <sup>o</sup>	(%)
Gifford et al [72]	68	44	11	48
Wychulis et al [38]	94	41	3	11
Vermillion et al [27]	26	36	2	25
Szilagyi et al [2]	28	--	--	
Whitehouse et al [39]	32	25	2	67
Anton et al [28]	13	66	2	50
Schellack et al [37]	26	37	0	
Roggo et al [73]	45	50	4	
Dawson et al [74]	42	74	3	13
Lowell et al [30]	67	60	3	16
Varga et al [29]	58	22	1	6
Duffy et al [66]	10	36	0	
Davidovic et al [67]	7	--	0	
Mahmood et al [75]	7	--	0	

Table 2. *Elective repair of PAA, 5 years graft patency and limb salvage.*

Reference	No of PAAs	Graft patency	Limb salvage
Carpenter et al [32]	45	71 %	94 %
Dawson et al [52]	42	75 %	95 %
Shortell et al [31]	51	67 %	95 %

## Long-term survival

Survival rates are reduced when compared with age- and gender-matched controls. In a Dutch study, the overall survival for patients treated for PAA was clearly reduced when compared to the expected survival in the Dutch population individually matched for age and sex. The survival rate of patients was 35% at 10 years compared to 62% for the control group ( $p < 0.05$ ) [52]. Survival rates at 5 and 10 years were reported to be in approximately 60% and 40%, respectively [27, 28, 52]. The life expectancy is further reduced in patients with multiple aneurysms.

In a series of 42 patients with asymptomatic PAA (mean observation time of 18 months), 21 patients died. The causes of death are cardiovascular disease (47%), ruptured aortic aneurysm (9.5%), malignancy (9.5%) and other diseases (33%), [52]. Vermilion et al observed 102 patients and 33 died. They found a similar distribution of causes of death [27]. Both these studies are based on small numbers of events.

The patients treated for PAA have an increased prevalence of aortic, iliac, femoral and contralateral PAA. To prevent limb- or life- threatening complications, it is essential to detect and treat new aneurysms before they are complicated by rupture or thrombosis [24, 39, 52-54].

## Follow-up

Follow-up after treatment of a PAA focuses mainly on surveillance of the reconstruction. Normally, this implies ultrasound scanning during the first year after operation, and although routines differ between centres, the patient is often lost to a further follow-up after one year.

Whether a continued surveillance focused on development of new aneurysms, both contra-lateral and extra-popliteal, is warranted remains controversial. The prevalence of aneurysms in other anatomical positions, at different time-points, among patients operated on for unilateral or bilateral PAA is unknown. This information is crucial in order to establish an appropriate follow-up program for patients operated on for PAA.

## Swedvasc

The Swedish Vascular Registry [55] started in 1987 as a regional registry in the southern region of Sweden (VRISS). Since 1994 it has national coverage and includes all surgical centres performing vascular surgery. From 1994 more than 90% of vascular procedures (both open and endovascular) are registered prospectively.

The registry was extensively validated both internally and externally [56]. It was shown that core surgery, such as AAA repair [57, 58], carotid artery thrombendarterectomy [59-61] and femoro-popliteal bypass [58, 62] are reported in more than 90% and with great validity of data. The data from the registry corresponded well with the case records in a study on acute revascularization for occlusion of the superior mesenteric artery [63].

# Aims

The overall aim of this investigation was to study patients operated on for popliteal aneurysm, in a population-based study with respect to epidemiology, treatment, management and outcome.

Specific aims were:

- To study the epidemiology of popliteal aneurysm, including the prevalence of other associated aneurysm and outcome with special emphasis on long-term survival and risk-factors for amputation within one year of surgery. (paper I)
- To study the outcome of unselected treatment of PAA with acute ischemia in a population-based study. (paper II)
- To study how the introduction of thrombolytic therapy may have changed the management and outcome. (paper II)
- To study the importance of surgical approach, type of graft, anastomotic and ligation techniques used, on medium and long-term outcome. (paper III)
- To establish the long-term risk of amputation in patients operated for popliteal aneurysm. (paper III)
- To establish the risk of future expansion of surgically treated popliteal aneurysms. (paper III)
- To investigate the prevalences of aneurysms in other anatomical areas after long-term follow-up in patients previously treated for popliteal aneurysm. (paper IV)
- To establish recommendations for follow-up of patients operated on for popliteal aneurysm. (paper IV)

# Patients and Methods

## The Swedvasc registry

Since the start of the Swedvasc registry in 1987 vascular surgical procedures (both open and endovascular) has been registered prospectively and by November 2002, 110.000 procedures were included. A large number of variables are registered prospectively such as preoperative risk-factors, comorbidities, in-hospital stay, indication for surgery, anatomic in- and out-flow, type of operation and graft. Survival, complications, patency, re-operations and amputations are registered at 30 days and at one year. Each hospital with vascular profiling has a specific number in the registry.

## Patient selection

From 1987 to 1994 the procedure code according to the Nomesco classification for popliteal aneurysm was included in all peripheral aneurysm operations by the codes 8812 and 8809. From 1994 we could select patients operated on for popliteal aneurysm by the specific procedure code (PFG10). The procedure code together with anatomy of the inflow and the indication for surgery in Swedvasc was used to select the cases with popliteal aneurysm operations. We ended up with a list of 1231 interventions for infra-inguinal aneurysms.

All 42 institutions performing vascular surgery in Sweden participated, supplying the investigators with 1160 complete patient-files (94.2%). The principal investigator visited 27 hospitals analyzing 988 records in situ, 172 patient-files were photocopied and mailed to the investigator.

Among the 1160 interventions, 322 operations were on non-popliteal, mainly femoral aneurysms, 100 were pre-operative thrombolytic interventions, and 58 were miscellaneous procedures. When we scrutinized the patient records we identified 63 additional procedures in the contralateral leg that were reported to the Swedvasc, but the indication was reported to be ischemia without indicating the underlying PAA. Thus, we found 743 operations and 100 preoperative thrombolytic treatments for PAA among 593 patients. Twenty-six of these operations were redo operations in 22 patients, all in men. They were excluded from this thesis, since we focus on primary procedures, including their respective re-operations. In all, 141 of the 146

procedures in the contralateral leg (97%) were reported to the registry. In total, this thesis includes data on 717 legs primarily operated on for PAA among 571 patients, Figure 1.

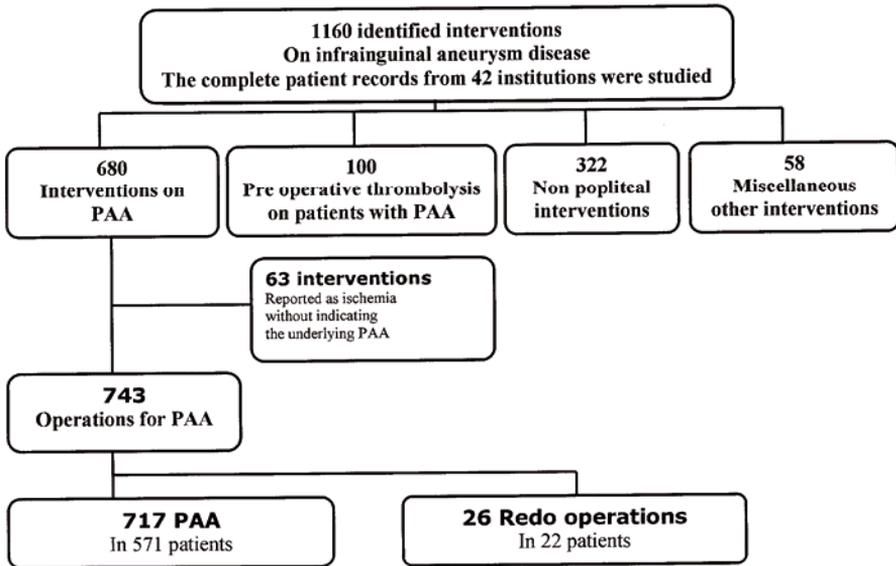


Figure 1.

## Data collection

### Variables collected from the patient records

The Swedvasc registry is divided into four sections for each vascular procedure.

1) Preoperative variables and patient identification. 2) Technical details about the open or endovascular procedure. 3) Follow-up at thirty days, including complications, patency and amputations. 4) Follow-up at one year, including patency and amputations. A protocol for each PAA operation was designed with the same sections, but with more detailed information.

From the patients' records information about aneurysms (operated or not operated on) in other anatomic regions and morphology of the operated PAA (size, proximal and distal extension, thrombosis in the aneurysm) were noted. The diagnosis of PAA was based on clinical examination together with some imaging technique in 680 legs (94.8%), on clinical examination only in 37 legs. Run-off distal to the popliteal aneurysm was evaluated by examining the number of patent crural vessels, in continuity from the popliteal artery to the ankle [30]. If the intervention was performed within 36 h

after presentation it was defined as acute, otherwise elective. Based on the information in the case-records, including results from different imaging techniques, we distinguished between acute ischemia from thrombosis of the PAA and acute ischemia from distal embolisation to the crural arteries. Detailed information on the operative techniques such as inflow, outflow, anastomotic technique, bypass anatomy, surgical approach, graft material and exclusion of the aneurysm were analyzed. The use of fasciotomy and Fogarty catheter during operation was also noted. Post-operative information on patency, amputation and death at 30 days and one year, respectively, were registered.

The study was divided into three time-periods: 1987-1993, 1994-1997 and 1998-2002.

## Thrombolysis

We identified 132 patients who were treated with thrombolysis, 100 were treated with preoperative thrombolytic therapy and later operated on either simultaneously or electively and 32 legs were treated with intraoperative thrombolysis. The thrombolysis was performed as a regional intra-arterial catheter procedure in all patients. The 100 preoperative thrombolytic treatments transformed 59 open surgical procedures from acute to elective operations. An operation performed > 24 hours after completion of thrombolytic therapy was defined as elective.

## Cross-checking against the national population registry

Every Swedish citizen has a unique identity-code and this code is used as identification code in Swedvasc. In January 2005 data were cross-checked against the national population registry, resulting in 100% accurate survival data and we found that 337 patients were alive at that time.

## Cross-checking for amputations

Date of amputation and complications were prospectively registered in the Swedvasc registry and these data were cross-checked against the complete patient records. Limb loss was considered an end-point for the leg if it underwent an amputation above the ankle during the first postoperative year. All 337 patients alive in January 2005 were invited to participate in a telephone interview, 240 (71%) accepted and were asked if they had been amputated. The surgeons responsible for the Swedvasc at the local hospitals checked all remaining 331 patients for information on amputation in orthopaedic case-records.

## Validation of the Swedvasc

Procedure codes for operations are reported from all hospitals to the Swedish Hospital Discharge Register (SHDR), used for reimbursement. The numbers were compared with the Swedvasc numbers in the years 1998, 2000 and 2001. Patients are often operated on bilaterally, and therefore we validated registration of contralateral operations. In all, 141 of the 146 procedures in the contralateral leg (97%) were reported to the registry.

Detailed patient records gathered information regarding 94% of the limbs at 30 days and 90% at one year. It was possible to supplement data on all patients lost to follow-up through either telephone interview or by cross-checking the orthopaedic files for amputation, resulting in great validity regarding limb-loss.

## Telephone inquiry

A telephone interview with patients was made in the spring of 2005 and 240 patients participated. They were asked about smoking, medication, family history of aneurysmal diseases, amputation, aneurysm operation in other regions or on the contralateral knee, as well as symptoms from the operated leg.

## Re-examination

The patients were also offered a re-examination, 196 patients with 246 operated legs accepted. However, four of them were not included in the study because of a primary operation for PAA, but for a redo procedure, and another 2 patients were not re-examined with ultrasound or CT, Figure 2. A majority of those who refrained from participating in the interview or re-examination were either severely aged, diseased or suffered from dementia.

The re-examination was carried out at 38 local hospitals. The principal investigator together with the same experienced ultrasound technician from the vascular laboratory at Uppsala University Hospital examined 162 patients by visiting the local hospitals, another 24 patients were examined by a local vascular surgeon and an ultrasound technician. Two patients were re-examined with computer tomography (CT). The bypass was examined for flow, aneurysm formation and stenosis. The operated PAA was evaluated for size and flow in the aneurysm sac.

The patients were screened for aneurysm in other regions at re-examination, and the presence of aneurysms was defined as described in Table 3. We noted the size of the infrarenal aorta, the common iliac arteries, the common femoral arteries and the contralateral popliteal artery. If we

found an undiagnosed aneurysm in the patient, it was reported to the local vascular surgeon to be treated or included in the local aneurysm surveillance program. If the patient had been operated on for any aneurysm after the popliteal aneurysm operation (index operation) it was noted.

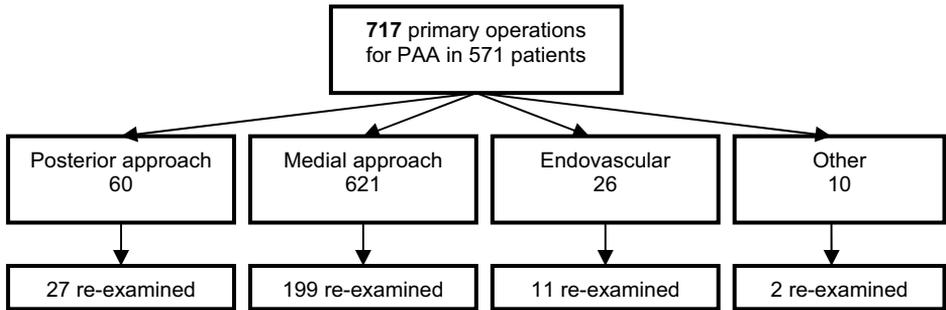


Figure 2. Re-examination of 239 legs.

Table 3. Definition of aneurysm at re-examination

	Diameter of the vascular segment mm	Indication for vascular treatment mm
AAA	≥ 30	≥ 50
CIA	≥ 20 or 50% larger than the contralateral side	≥ 30
CFA	≥ 15	≥ 20
PAA	≥ 15	≥ 20 or ≥ 15 with mural thrombus

## Ethics

The study was approved by all nine Regional Ethics Committees in Sweden. According to the administrative rules of the Swedvasc, each patient is inquired regarding informed consent prior to registration. It is extremely rare that consent is not given. Patients who die during treatment are registered without consent, in accordance with Swedish law.

## Statistics

Statistical evaluation of data was carried out with a computer software package (SPSS PC version 11.0-13.0). Survival analysis was performed with the SAS-software (paper I).

Differences in proportions were evaluated using the Chi-square test or Fisher's exact test (when frequencies of events were  $<5$ ) for nominal variables and Kendall's tau-b test for ordinal variables. Student's t-test was used to evaluate differences in continuous variables (paper I-IV).

Risk-factors were evaluated with odds ratio (OR) and 95% confidence intervals (CI). Variables identified as significant risk-factors for amputation with univariate analysis were entered into a multivariate logistic regression analysis (paper I). To estimate the odds ratio (OR) for risk factors associated with multi-aneurysmal disease – after adjustment for gender, age, hypertension, smoking, 1<sup>st</sup> degree relative with aneurysm, and follow-up time – with multi-aneurysmal disease (or no additional aneurysm) as dependent variable, these variables were entered into a logistic regression model (paper IV). Separate models were analyzed for new AAA (or no AAA) and new contralateral PAA (or no contralateral PAA) as the dependent variables, where only subjects at risk were included. Thus, those with an AAA or PAA operated on prior to- or known at the index operation were excluded for the respective analysis. Bilateral PAA was included in the model when the risk to develop AAA was analysed, and the presence of AAA when the risk to develop contralateral PAA was analysed.

Relative survival was calculated by comparing the patients with normal Swedish population with the same gender and age during the same calendar time. Survival between groups of patients was compared with Cox regression (paper I).

Kaplan-Meier plots of cumulative limb salvage were calculated, censoring for deaths and end of follow-up. Comparisons of limb salvage were made by log rank test (Chi-Square) and Cox regression models adjusted for gender, age, surgical approach, graft used, distal anastomotic technique and whether the operation was elective or acute (paper III).

# Results

## Epidemiology - Paper I

Papers I and II were based on data from the Swedvasc registry, the retrospective review of the patients' case-records, the interviews and the validation of amputation data through a specific review of orthopaedic case-records. Data from the re-examinations were not available when these papers were written, but were included in Papers III and IV.

Among 571 patients operated on (717 legs), 33 were women, 5.8% (95% CI 3.9-7.7). Thirty eight legs were operated on female patients, 5.3%. Median age was 71 years (range 18-94), 71 years (18-94) for men and 74 (22-92) for women. The incidence of operative reconstruction of PAA during the period 1994-2001 was estimated at 8.3 per million person years.

## Symptoms

Two hundred and nineteen legs (30%) were asymptomatic, 494 (69%) were symptomatic, and four had missing data regarding symptoms. Women were more often operated on for symptomatic disease (84.2% vs 68%,  $p=0.046$ ). Treatment was performed acutely in 264 limbs (37%). The distribution of preoperative symptoms, the correlation between symptoms and whether treatment was acute are illustrated in Table 1, paper I.

## Distribution of extra popliteal aneurysms

When the index PAA was operated on, 266 patients (46%) had bilateral PAAs: 28 were operated on prior to the study period, 146 during the study period and 92 were not operated on before 2004. The time span between the index and contralateral operations varied: 73.3% were operated on within one year, 91.8% within three years and 97.9% within five years. The aneurysms were more often symptomatic in the first operated legs 79.0%, than in the contralateral leg, 27.0%, Figure 2 paper I. The distribution of extra popliteal aneurysms at the time of the index operation is given in Table 4.

Table 4. *Location of extra popliteal aneurysms at the time of the index operation*

Location	Unilateral PAA*		Bilateral PAAs*		P
	(300 patients) N <sup>o</sup>	%	(264 patients) N <sup>o</sup>	%	
AAA	84	28.0	99	37.5	=0.016
IAA	25	8.3	32	12.1	=0.136
FAA	28	9.3	37	14.0	=0.082
Other location	4	1.3	4	1.5	=0.855

\*Seven patients had missing data regarding the contralateral leg at the time of the index operation.

## Outcome

At 30 days 5.7% of the limbs were amputated, 12.2% had ischemic symptoms, 3.7% had other symptoms (neurological impairment, haematoma, seroma, wound rupture or infections), 72.6% were asymptomatic, and in 5.8% detailed information on symptoms were missing. The patencies at 30 days and one year are given in Table 5.

Table 5. *Primary and secondary patencies at 30 days and one year*

	30 days		Patency	One year		Patency
	N <sup>o</sup> of legs	%	%	N <sup>o</sup> of legs	%	%
Primary open reconstruction	639	89.1	90.9*	534	74.5	85.4*
Secondary open reconstruction	9	1.3	92.2*	8	1.1	86.7*
Occluded reconstruction	55	7.6		83	11.6	
Dead	9	1.3		49	6.8	
Missing data on patency	5	0.7		43	6.0	
Total	717			717		

\* Graft patency was calculated on living patients available to follow-up

Table 6. *Amputation-free survival and Limb salvage rate at 30 days and one year*

	30 days		One year	
	N <sup>o</sup> of legs	%	N <sup>o</sup> of legs	%
Living with intact limb	668	93.2	614	85.6
Patient dead with intact limb	8	1.1	40	5.6
Amputated	40	5.6	54	7.5
Amputated and dead	1	0.1	9	1.3
Missing data	0		0	
Total	717		717	
Limb salvage rate		94.3		91.2
Amputation-free survival		93.2		85.6

Limb salvage rate and amputation-free survival are given in Table 6. There were no missing data on survival or amputation.

An error appeared in paper I that I did not recognize prior to E-publication. In “Outcome”, the second paragraph, it is written: “One year

after surgery 703 (98.0 per cent) of the 717 operated limbs were available to follow-up, etc....” All this information is correct except the time-period, it should have been written: “Thirty days after surgery...etc”.

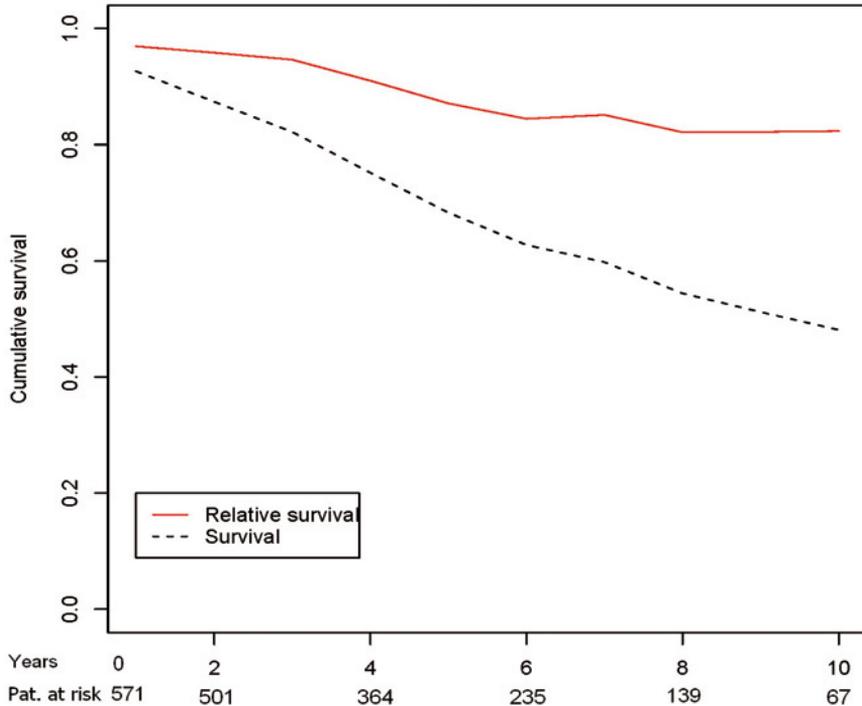
Risk factors for amputation within one year after surgery are given in Table 7. To adjust for confounding a multivariate analysis was performed with logistic regression.

Three time periods were analyzed: 1987-1993 (160 operated limbs), 1994-1997 (259) and 1998-2002 (298). The amputation rates were 13.7%, 9.7% and 5.4%, respectively (p=0.003). When only patients treated acutely (<36 hours) were analyzed (264 legs), amputation occurred in 25.4%, 16.8% and 12.0% respectively (p=0.035). The overall amputation rate within one year was 8.8%.

Table 7. Risk factors for amputation within one year

Risk factor	N° amputations/ N° of legs at risk	Amputation %	Unadjusted Odds Ratio (95% CI)	Adjusted** Odds Ratio (95% CI)	P ***
All patients	63/717	8.8			
Elective treatment	18/453	4.0	1*		
Acute treatment	45/264	17.0	5.0 (2.8-8.8)	2.7 (1.3-5.5)	=0.006
Asymptomatic	4/221	1.8	1*		
Symptomatic	59/492	12.0	7.2 (2.6-20)	2.9 (0.8-10.8)	=0.11
Run-off:2-3 vessels	27/535	5.0	1*		
Run-off:0-1 vessel	29/103	28.2	7.4 (4.1-13)	4.5 (2.3-8.5)	<0.001
Age ≤ 70	16/353	4.5	1*		
Age > 70	47/364	12.9	3.1 (1.7-5.6)	2.2 (1.1-4.4)	=0.02
Vein graft	33/531	6.2	1*		
Prosthetic graft	27/174	15.5	2.8 (1.6-4.8)	2.9 (1.5-5.5)	=0.001

\* Control group \*\* Logistic regression model including all risk factors stated in the table, \*\*\* p-values refer to likelihood-ratio test, multivariate analysis.



*Figure 3.* Relative and crude survival among 571 patients operated on for PAA. Relative survival was calculated by comparing the patients with normal Swedish population of the same gender and age during the same calendar time.

The absolute (crude) survival was 98.8% at 30 days, 91.4% one year and 70.0% at five years, Figure 3. The relative survival compared with normal Swedish population of the same gender and age during the same calendar time was decreased by 3.1% (95% CI: 0.9-5.3) at one, 11.9% (7.8-18.0) at five, and 17.7% (8.4-27.0) at ten years. Patients operated on emergently had an increased mortality, compared to those operated on electively, RR 1.59.

## Acute treatment of PAA – Paper II

Treatment was performed acutely in 264 legs. Twenty-nine legs were treated acutely with surgery because of rupture (24) or local symptoms (5). The management of the remaining 235 legs in 229 patients was divided into two groups, Figure 4. The sizes of PAA, ages, and amputation rates in the two groups are given in Table 8.

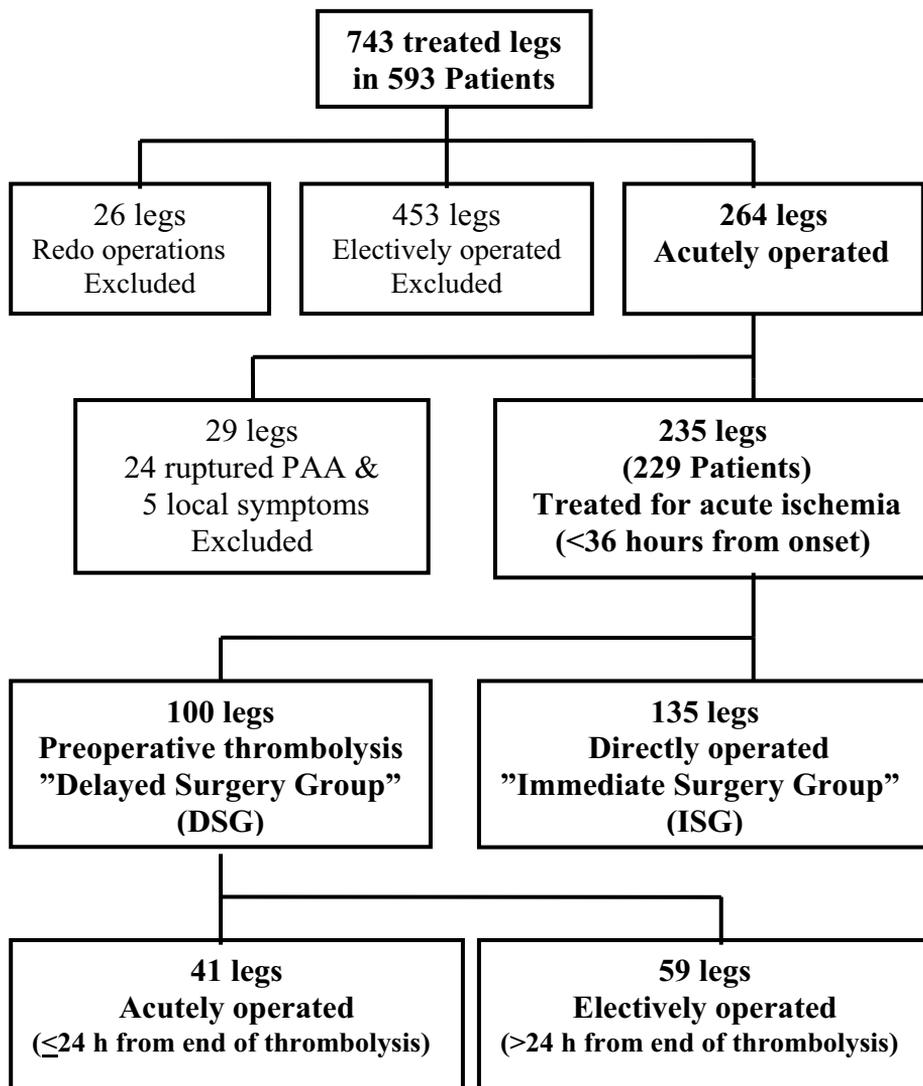


Figure 4. Distribution of the 235 legs into two groups, 1: DSG, Delayed Surgery Group and 2: ISG, Immediate Surgery Group.

Table 8. Difference between DSG and ISG regarding age, aneurysm size and one year amputation-rate

	DSG	ISG	p
Size (mean)*	27 mm	37 mm	<0.001
Age (mean)	66.8 year	71.6 year	<0.001
Amputation	7 %	27 %	<0.001

\*The size of the PAA was measured in 144 legs.

## Operative technique

In the ISG 125 legs were operated on with a medial and four with a posterior approach. In the DSG 80 legs were operated on with a medial, eleven with a posterior and seven with endovascular approach. Eight legs were operated on with other miscellaneous techniques.

Vein-grafts were used more often in the DSG (93%) than in the ISG (70%). Within the group operated on with a medial approach (Median Approach Group, MAG) the use of prosthetic graft was lower in the DSG compared to the ISG, 6.3% vs. 25%,  $p < 0.001$ , and within the group operated on with a posterior approach (Posterior Approach Group, PAG) the use of vein was higher in the DSG compared to the ISG, 91% vs. 50%,  $p < 0.001$ .

Fasciotomy, primary or secondary, was performed in 30% in the ISG and 11% in the DSG,  $p < 0.001$ . Fasciotomy rates increased in the ISG over time, but not in the DSG.

## Outcome

The effect of the preoperative thrombolysis was evaluated by the change in run-off. It was possible to review the angiograms both before and after the thrombolysis in 84 legs (84%). The run-off was improved in 87% and unchanged in 13%.

In the DSG there was a non-significant trend towards a lower amputation-rate (5.1%) among those operated on electively after completion of thrombolysis compared to those who were operated on emergently (9.8%),  $p = 0.14$ . When the three time-periods were compared for all legs, a trend towards decreasing amputation-rates was observed,  $p = 0.06$ , Table 9. Amputation without prior fasciotomy decreased over time.

Table 9. *Proportion of delayed surgery, amputation-rates, and frequency of amputation without fasciotomy, during three time periods.*

	1987-1993	1994-1997	1998-2002	p
Delayed surgery	18%	41%	59%	<0.001
Amputation rate	28%	17%	14%	0.06
Amputation without fasciotomy	79%	59%	33%	0.02

## Surgical technique used on 717 legs operated on for PAA – Paper III

The surgical approach most commonly used was the medial (Medial Approach Group, MAG, 87%), followed by the posterior (PAG, 8.4), endovascular (EAG, 3.6) and other miscellaneous approaches (1.4%).

The miscellaneous group consisted of; exploration, thromboembolectomy and a single extra-anatomic bypass to the anterior tibial artery through a lateral approach, and were not included in the analysis.

Information on the precise proximal and distal extension of the aneurysm was available in 656 legs (92%). The proximal extension of the aneurysmal arterial segment was within the popliteal artery in 545 (83%) and the superficial femoral artery in 111 (17%). The distal extension was within the popliteal artery in 635 (96.8%), the tibiofibular trunk (TFT) in 17 (2.6%) and a crural artery in four (0.6%).

The inflow and outflow anatomy of the open surgical reconstructions (681 legs), depending on approach and graft type, are given in Table 10.

There were no significant differences between PAG and MAG concerning age, gender or distribution between acute and elective treatment. In the PAG 37 (62%) aneurysms were operated on with an interposition graft with endo-aneurysmorrhaphy, 21 (35%) with a bypass, and two (3.3%) with resection and direct anastomosis. PAG was only practiced in 22 centres during the study period. In MAG shorter bypasses were reconstructed with a reversed vein-graft more frequently (70%), while longer bypasses more often were reconstructed with an in-situ technique (70%).

Table 10. *Type of graft, in- and outflow in 673\* legs operated on for PAA with a posterior or medial approach*

	Posterior approach		Medial approach		
	Vein reversed N (%)	Prosthetic graft N (%)	Vein in-situ N (%)	Vein reversed N (%)	Prosthetic graft N (%)
Total	38	22	184	314	115
<b>Inflow</b>					
CFA	--	--	87 (47)	12 (4)	19 (17)
SFA prox	--	--	49 (27)	16 (5)	12 (10)
SFA dist	5 (13)	3 (14)	32 (17)	168 (53)	39 (34)
PA AK	33 (87)	19 (87)	16 (9)	118 (38)	45 (39)
<b>Outflow</b>					
PA BK	36 (95)	20 (91)	113 (61)	227 (88)	96 (83)
TFT	1 (2.5)	--	23 (13)	26 (8)	11 (10)
Crural vessel	1 (2.5)	2 (9)	48 (26)	11 (4)	8 (7)

\* This information was missing in 8 operated legs.

## Patency

Graft patency at 30 days, one year and at the time of re-examination, depending on surgical approach and graft type, among the 681 legs in the PAG and MAG, are given in Table 11.

The frequency of claudication reported at re-examination was similar in MAG and PAG (37.0% vs. 37.9%,  $p=0.933$ ), as well as among those operated on with a vein or prosthetic graft (38.7% vs. 33.3%,  $p=0.501$ ).

In the EAG five legs were occluded within 30 days and six within one year. Among them, two underwent thrombolysis, but re-occluded and the patients suffered claudication. Two were converted to a bypass which both re-occluded resulting in claudication.

Table 11. *Primary patency, at different time-points, depending on surgical approach and graft type after open surgery of 681 legs with PAA*

	Vein graft %	Prosthetic graft %	$p^*$
<b>30 days</b>			
PAG	92	86	=0.664
MAG	94	87	=0.016
$p^{**}$	=0.498	=1.0	
<b>One year</b>			
PAG	85	81	=0.719
MAG	90	72	<0.001
$p^{**}$	=0.374	=0.584	
<b>At re-examination</b>			
PAG	90	57	=0.101
MAG	84	69	=0.098
$p^{**}$	=0.743	=0.661	

\* Refers to Fisher's exact Test, comparing graft-type within the posterior or medial approach groups. \*\* Refers to Fisher's exact Test, comparing the posterior or medial approach groups, within the subgroups with the same graft-type.

## Expansion

The risk of expansion after operation was higher in the MAG (57/174, 33%) than in the PAG (2/24, 8.3%),  $p=0.014$ . Among the 57 legs in the MAG that had expanded their PAA, 20 had expanded 1-4 mm, sixteen 5-9 mm and 21  $\geq 10$  mm. Among those with expansion  $\geq 10$  mm the mean diameter was 45 mm (range 30-95) and the mean expansion was 17 mm. The two expanded PAA in the PAG had expanded 7 mm to 19 and 39 mm, respectively. Fifty of the 57 legs with expanding PAA in the MAG (88%) were symptomatic at re-examination. The most common symptoms were local pain, swelling and neurological impairment, and they were more common the greater the ex-

pansion rate,  $p=0.023$ . When analyzing all re-examined legs, the 60 with expanding PAA more often had claudication (50 vs. 33%,  $p=0.023$ ) as well as local symptoms as described above (70 vs. 53%,  $p=0.022$ ), compared to the 179 legs without expansion of the PAA. Eight legs (all in the MAG) were re-operated on for local symptoms caused by expansion of the PAA prior to re-examination, after a median follow-up of 12.5 months (range 5-79). These eight grafts were all patent prior to, as well as after the re-operation, and no leg was amputated. In the subgroup with short bypasses in MAG 11.6% were operated on without or with distal ligation only, whereas 88.4% were ligated both proximally and distally. There was no difference in risk of future expansion between PAG and MAG with short bypass,  $p=0.321$ . Analyzing the bypasses with outflow from the CFA or the proximal SFA (195 legs) as many as 42% were operated on without or with only distal ligation. Thus, the surgeons decided to refrain from proximal ligation more often when performing a long bypass. Among these legs, 51 were re-examined and the frequency of expansion was 30.4% among those ligated and 40.0% among those not ligated,  $p=0.544$ .

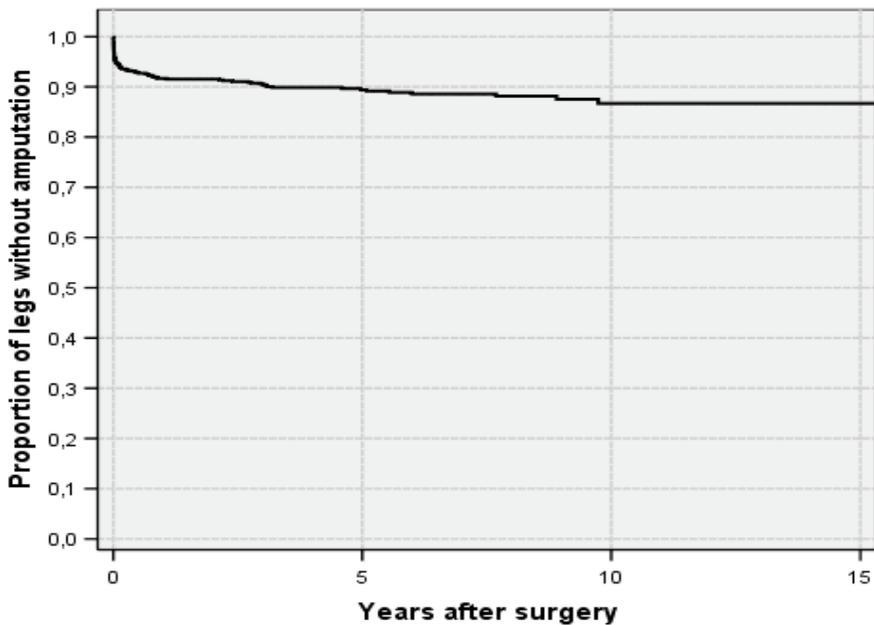
## Amputation rate

Until re-examination or end of follow-up for other reasons, 80 of 717 legs were amputated above or below the knee (11%). Seventy-nine percent (63/80) of the amputations were performed within one year and the amputation rate within one year was 8.8%. Amputation-rate within one year was higher in the acutely than in the electively treated group (21 vs. 4 %,  $p<0.001$ ), Table 5 paper III. Overall limb salvage-rate is shown in Figure 5.

In the MAG vein grafts did significantly better than prosthetic grafts, log rank (Chi-Square) 14.6,  $p<0.001$ . This difference in amputation-rate remained when legs amputated within 30 days were excluded, log rank 15.4,  $p<0.001$ , while no difference was observed when all legs amputated within one year were excluded, log rank 0.992,  $p=0.319$ . No difference in amputation rate was found between vein and prosthetic graft in the PAG,  $p=0.623$ . Among the legs reconstructed with vein grafts, there was no difference between in-situ and reversed veins. The EAG was too small to permit a meaningful comparison, but results were similar to those of the PAG.

A Cox regression model revealed a significant and independent association between long-term amputation-rate and age, odds ratio (OR) 1.06/year,  $p<0.001$ , emergency procedure compared to elective procedure OR 2.67,  $p<0.001$ , and prosthetic graft compared to vein graft OR 2.02,  $p=0.008$ , while gender, surgical approach and anastomotic technique were not associated with long-term amputation-rate. The observed association between amputation-rate and emergency procedure was lost when legs amputated within 30 days were excluded, while age and prosthetic graft retained the associa-

tion, OR 1.05/year,  $p=0.008$  and OR 3.09,  $p=0.001$  respectively. When legs amputated within one year were excluded the association between amputation and age, as well as between amputation and prosthetic graft, were lost, OR 1.04,  $p=0.098$  and OR 1.89,  $p=0.223$  respectively.



Number at risk 717

369

93

7

*Figure 5.* Kaplan-Meier plot of limb salvage-rate over 15 years among 717 legs operated on for PAA.

The median time from operation to amputation of the 17 legs amputated after one year was 3.1 years (range 1.1-9.8). The frequency of late amputation was 3.7% (2/54) in the PAG and 2.6% (15/571) in the MAG. Among the legs which underwent late amputation, five were treated with preoperative thrombolysis because of acute ischemia, the other 12 had been operated on electively.

## Re-examination of 190 patients – Paper IV

It was possible to re-examine 190 patients (among them seven women, 3.7%), 239 legs operated on. The median age at the index operation was 63 years (18-84) and at re-examination 71 years (29-91). The median time-span from index operation to re-examination was seven years (2.9-18.7).

The number of patients with multiple aneurysms (at least one aneurysm in addition to the index PAA) at the index operation was 108 (57%), which increased to 131 (69%) at follow-up. The distribution of extra-popliteal aneurysm and PAA in the contralateral leg at index operation and re-examination is given in Table 12.

Between index operation and re-examination the total number of aneurysms increased with 41.8%. The risk of developing additional aneurysms at different time-points after the operation for PAA is given in Table 13. Among the 117 extra-index aneurysms that were diagnosed at re-examination 61 (52.1%) required operation (for definition see Table 3). Among the 72 new aneurysms, not previously detected but identified during re-examination 32 (44.4%) needed repair.

Among the 82 patients who had an isolated PAA at the index-operation, 23 developed new aneurysms during follow-up, and 59 did not. Those who did develop new aneurysms during follow-up were older at the index operation, mean age 64.0 versus 59.7 years,  $p=0.004$ . Among these 23 patients, no one developed or was operated on for a new aneurysm within three years. Nine patients, however, had their extra-index aneurysm detected during the fourth or fifth years of follow-up.

Of 108 patients with known extra-index aneurysms at the primary operation, eight were re-examined within three years. Among them, two were without any new aneurysm, five had been operated on for an aneurysm known at the index-operation and one patient had been operated on for an FAA not detected at the primary operation. After three years of follow-up the number of aneurysms requiring surgery continued to increase, Table 13.

## Factors associated with the development of AAA

Thirty-four AAAs developed during follow-up in 139 patients with no AAA or history of AAA-repair at the index operation, 24.5%. In a univariate analysis bilateral PAA at index operation was significantly associated with the development of AAA,  $p=0.004$ , while gender, age, hypertension, smoking, heredity and follow-up time were not. In a logistic regression model bilateral PAA retained this association after adjustment for all other factors, OR 2.96 (95 CI 1.26-6.98),  $p=0.013$ .

Table 12. *Prevalence of multiple aneurysms at index-operation and at re-examination in 190 patients operated on for PAA*

N° of additional aneurysms	All aneurysms at index operation		All aneurysms at re-examination	
	N°	%	N°	%
None	82	43.2	59	31.1
One	47	24.7	41	21.6
Two	21	11.1	26	13.7
Three	19	10.0	25	13.2
Four	13	6.8	24	12.6
Five	2	1.1	8	4.2
Six	6	3.2	7	3.7
Total N° of patients	190		190	
Total N° of aneurysm	244		346	
N° of affected re-gions *	N°		%	
	N°	%	N°	%
Only index PAA	82	43.2	59	31.1
One extra region	54	28.4	43	22.6
Two	28	14.7	40	21.1
Three	18	9.5	28	14.7
Four	8	4.2	20	10.5
Total N° of patients	190		190	

\* Four possible regions were evaluated: The aortic, iliac, femoral and contralateral popliteal regions

Table 13. *Risk of developing additional aneurysms at different time-points\*\* after operation for PAA*

	At index-				
	Operation	3 years*	5 years*	7 years*	10 years*
Patients at risk	190	177	131	82	26
% with operated extra-index aneurysm#	22.1	41.2	46.6	48.8	57.7
% with detected, non-operated, extra-index aneurysm*	34.7	15.8	13.0	12.2	7.7
% with operated or detected extra-index Aneurysm	56.8	57.0	59.6	61.0	65.4

\* This time-period was defined as the time between index operation and re-examination, when a non-operated aneurysm was detected

# This time-period was defined as the date between the index-operation and the date an extra-index aneurysm was operated on, prior to re-examination.

## Factors associated with multi-aneurismal diseases

Of all 190 patients, 131 had a history of or developed additional aneurysms at any site during follow-up. Age ( $p=0.004$ ) and hypertension ( $p=0.012$ ) were significantly associated with multi-aneurysmal diseases in a univariate analysis, while gender, smoking, heredity and follow-up time were not. In a logistic regression model after adjustment for all other factors age (OR 1.1/year,  $p=0.003$ ) and hypertension (OR 2.1,  $p=0.041$ ) retained the association and, in addition, follow-up time (OR 1.1/year,  $p=0.036$ ) was significantly associated with multi-aneurysmal diseases.

# General discussion

Although PAA is the most common aneurysm after AAA, most vascular centres will only see a few cases each year. Consequently, most previous reports on PAA are small retrospective studies from single institutions [32, 64-68], and only one prospective multi-centre study has been published [29]. This thesis is an observational study, based on prospectively reported data from the vascular institutions in Sweden, supplemented by review of patient records and re-examination of most patients who were fit at the time of the study. The study is the largest ever on PAA.

A crucial issue throughout this study has been whether the validity of the register is sufficient to permit conclusions. The Swedvasc registry has been extensively validated previously, and core surgery, such as AAA-repair [57, 58], carotid artery thrombendarterectomy [59, 60], and femoro-popliteal bypass [58] were reported in more than 90% and with great validity of data. In the present study complete records were retrieved in 94%. Of all 146 patients, who underwent bilateral operations, 141 (97%) were reported to the registry. The validity of the reporting of cases was further supported by the fact that 15-38% more patients were recorded in the Swedvasc than in the SHDR. In conclusion, missing patients or legs having undergone operation are uncommon, and selection bias is a minor problem in this investigation.

## Incidence

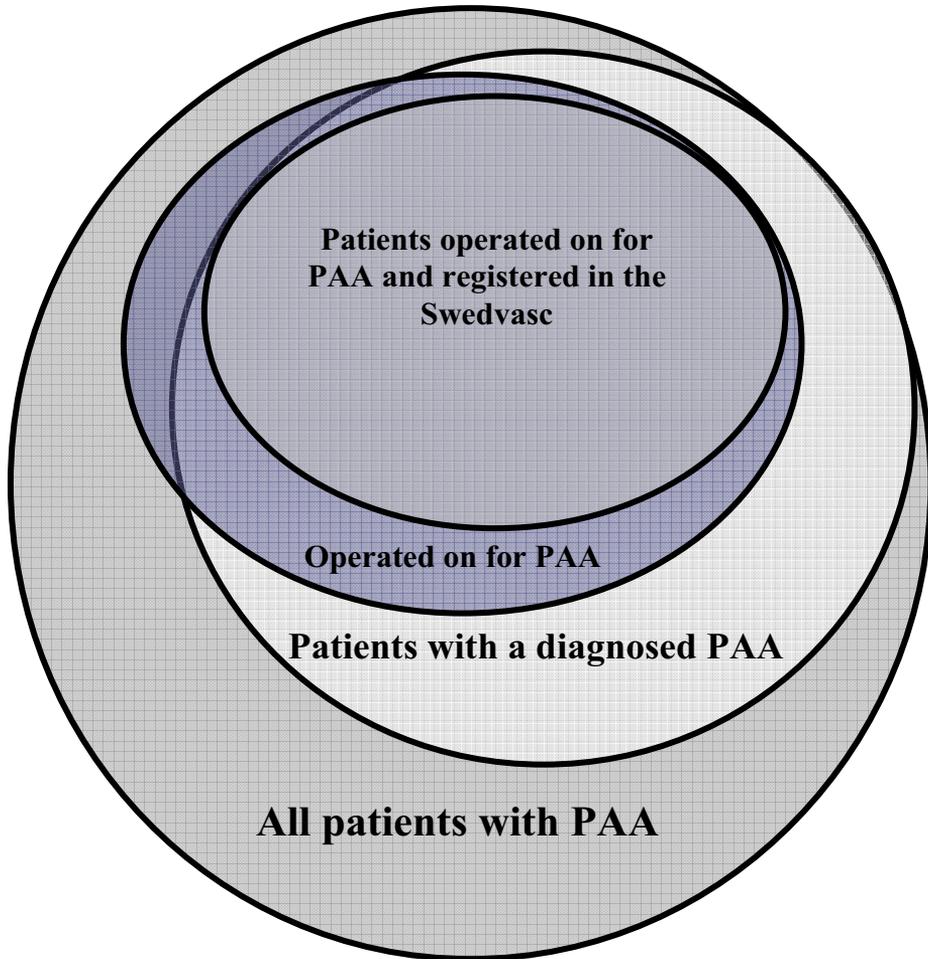
From the present data the incidence of surgical repair of PAA was estimated to 8.3/million person years or 75 operations per year in Sweden. This is, however, most likely a slight underestimation, because not all operated PAAs are registered in Swedvasc, but maybe only 90%, Figure 6. The true prevalence of PAA remains unknown, since no population-based studies exist, and to carry out such a study seems to be very difficult. Screening for PAA was tested as part of an AAA screening program [69], and the conclusion was that it was not cost effective to screen for PAA since a PAA was found in less than 3% of men with a small AAA and not at all in men with a normal aorta. This is in accordance with the results of Sandgren et al, who found the prevalence of popliteal aneurysms to be 3% (4 of 158) in patients with AAA. Other investigators have tried to determine the incidence of lower extremity aneurysms in hospitalized patients, but they conclude that

extra-aortic aneurysms were infrequent in this cohort [70], and furthermore not representative of the entire population.

PAA is often undetectable on physical examination and liberal ultrasound investigation has been suggested [71]. Many patients with a PAA present symptoms of acute or chronic leg ischemia. We found 63 legs, contralateral to a leg operated on for PAA, which had been operated on with a bypass and registered in the Swedvasc registry with the indication leg ischemia, but the underlying cause of PAA was not registered. When these case-records were scrutinized it was verified that the vascular surgeons had diagnosed underlying PAAs, though they were not registered as such in the Swedvasc. Another situation, that we were unable to address with the study design of this investigation, is when the patient presents with acute or chronic ischemia and an occlusion of the popliteal artery is diagnosed with angiography only. In this situation the surgeon responsible for the patient never realizes the PAA causing the ischemia, which consequently remains undiagnosed. A more extensive diagnostic examination of the ischemic legs with ultrasound, CT or MRT results in a more frequent detection of PAA.

Other situations when the PAA may be undetected is in patients where an amputation is performed without vascular examination of the leg prior to the amputation, or in symptomatic PAA causing claudication, but where the patient and/or the doctor find no indication for surgery. Although we lack data to support such a statement, it is reasonable to assume that patients were examined with ultrasound, CT or MRT more frequently during the latter part of the study period.

These problems are illustrated in Figure 6.



*Figure 6.* A schematic illustration of the prevalence of PAA

In this study all the 190 re-examined patients donated blood for research. This blood-bank is a valuable asset for future research on PAA and multi-aneurysmal disease.

## Outcome

Untreated PAA is encumbered with a high incidence of thromboembolic complications. Results from several small single centre studies indicate that these complications are associated with high amputation-rates (0 to 67%) [2,

27-30, 37-39, 66, 67, 72-75]. This study focused on patients who underwent surgery for their PAAs. Patients undergoing repair have more favourable outcome [5].

Amputation after PAA repair was one of the endpoints in this study. Paper I focused on the amputation rate at 30 days and within one year, paper III on long-term outcome, including the amputation rate. The amputation rate decreases throughout the study period, from 14% before 1993 to 5.4% after 1998. Within 30 days 5.7% of the patients were amputated and 8.8% within one year. After one year an additional 2.4% (N=17) of the patients were amputated. The majority of amputations thus occurred within one year. The observed amputation rate was in accordance with previously published studies [5]. Independent risk factors for amputation within the first year were poor run-off, emergency procedure, a prosthetic bypass and age, while no independent risk factor for late amputation was identified in this study. However, despite the size of the study and the long follow-up period, the number of late amputations (after one year) was limited (n=17), making it prone to type II statistical error.

Long-term survival was reduced in patients with PAA compared with the age- and sex-matched normal population, Figure 3. These findings are similar to previously published studies [5, 27, 28, 52]. Although this was not yet studied in this cohort of patients, Dawson reported that survival is further reduced in patients with multiple aneurysms [52] and one reason to follow this population more closely after repair of the PAA, is to detect life threatening additional aneurysms, in particular AAAs.

Primary patency at 30 days, one year and at re-examination among patients operated on with a bypass (N=681) are presented in Table 10. There was an advantage of vein over prosthetic graft in patients operated on with a medial approach, Figure 2B in paper III. This difference was, however, only valid for the long bypasses, while no such difference was observed among patients operated on with a short bypass. This lack of difference among the patients operated on with a short bypass may, however, be the result of a type II statistical error, since the PAG was small. It may also be explained by confounding factors such as differences in run-off and in the frequency in which prosthetic grafts were used, between the groups. Previously published investigations have found that reconstructions performed for aneurysmal diseases are more durable than reconstructions performed for occlusive diseases [5, 28, 52], explaining why a greater number of patients may be needed to show a difference between the groups, thus supporting the possibility of a type II statistical error.

In paper III it was possible to compare the aneurysm size at the primary operation with that at the re-examination in 210 legs. Expansion of the excluded PAA sac was not uncommon and much more frequent in MAG than in PAG (33% vs. 8.3%,  $p=0.014$ ). The symptoms of expansion were claudication and local symptoms, and 14% of the legs with expansion in the MAG

underwent re-operation for symptoms related to the expansion. Even patients who did not undergo re-operation suffered from claudication and local symptoms more often when an expansion was present, compared to those without expansion. This indicates that exclusion of the aneurysm sac to prevent future expansion may be an important aim of the surgical procedure when operating on patients for PAA. This complication seen after surgery on PAA is similar to the endoleak type II after endovascular repair of AAA, and in this aspect a posterior approach offers an obvious advantage.

## Acute treatment

In paper I, emergency procedure was found a risk factor for amputation in patients with PAA, and a subgroup analysis of legs with acute symptoms of PAA was performed in paper II. Of 264 legs with acute symptoms, the cause was thrombo-embolism in 235. The remaining 29 legs, 24 with rupture and 5 with local symptoms, were operated on directly and were not included in the analysis.

The selection of patients to either preoperative thrombolysis with delayed surgery (DSG) or to immediate surgery (ISG) is a complex process. The patients in the DSG were younger and had smaller PAA with significantly poorer run-off prior to therapy, while some of the patients in the ISG did not require thrombolysis because of good run-off preoperatively. Inadequate information on the severity of ischemia, such as sensory and motor function loss, is a limitation of this investigation. It is possible, and even likely, that the patients in the ISG had neurological impairment necessitating immediate revascularisation more often than the patients in the DSG. It can be concluded, however, that the two groups were very different in their preoperative characteristics.

The use of thrombolysis increased during the study period, table 8. Thrombolysis is not an independent therapy for PAA, but a supplement to surgical repair, either pre- or perioperatively. Thrombolysis attacks several of the observed risk factors for amputation. The run-off improves (87%) and acute treatment may be converted to elective treatment (59%). These factors may explain the decreased amputation rate in patients treated with preoperative thrombolysis. Perioperative thrombolysis was, however, less effective. In this study 31% later underwent amputation. In these patients the intraoperative thrombolysis is performed in the acute situation when surgery is needed because of the threat of immediate limb loss. The leg has lost the motor function and an irreversible ischemia is imminent.

Thrombolytic therapy in general has been controversial because of the risk of haemorrhagic complications [45, 76]. The risk of embolization into the distal vessels has been an argument against the use of preoperative

thrombolysis [77]. Other investigators have concluded that thrombolytic therapy given to this patient group is safe, given that well-known contraindications are restricted [36, 43, 47-49, 75, 78, 79]. All previous publications were on small groups of patients, including between 3 and 15 cases, precluding scientific conclusions. In this larger study on 100 patients no serious haemorrhagic side-effect occurred in the patients treated with preoperative thrombolysis. They were all independently registered in Swedvasc as a thrombolysis and we feel confident in the conclusion that preoperative thrombolysis is safe and results in improved run-off.

Poor run-off was the strongest risk factor for amputation. In paper III an analysis was made on acutely versus electively operated patients. We found that the risk of amputation within one year was significantly lower in the electively operated group, 4% vs. 21%,  $p < 0.001$ . Preoperative thrombolysis transformed 59% of the patients with acute ischemia into elective patients, since the acute ischemia was eliminated, and the run-off improved. In the ISG some of the legs were operated on because the local surgeon was satisfied with the run-off prior to surgery. It cannot be ruled out that in some of these legs, run-off could have been further improved if they had been treated with preoperative thrombolysis, maybe avoiding amputation? The complex decision-making between ISG and DSG is difficult to study in a retrospective study-design, and this is a limitation of the study, already discussed above.

We observed that fasciotomy was more frequent in the ISG, furthermore the use of fasciotomy increased over time, offering an alternative explanation to the observed improvement of results. Fasciotomy, performed timely in selected cases, is fundamental to minimize the risk of limb-loss.

An additional factor that may explain the observed reduced amputation rate is that the patients are more likely to have been treated by vascular specialists during the later time-period.

Theoretically, another possible explanation to the observed improved results over time is that patients in the later time-period with irreversible ischemia more often were treated with primary amputation. It does seem more likely, though, that the higher degree of subspecialisation would result in a more aggressive revascularisation. Unfortunately we lack data on patients undergoing primary amputation, leaving the discussion of these potentially important factors to speculation only.

## Surgical technique

Surgical management of PAA aims at avoiding thromboembolism, limb dysfunction associated with nerve and vein compression, and amputation [75]. The surgical strategy depends on several factors, including the configuration of the aneurysm, in- and outflow, elimination of embolic sources and

prevention of continued enlargement of the aneurysm [5]. The leading treatment has been open surgical repair (either medial or posterior), while endovascular repair has only been used in the last ten years and long-term results of this procedure are not yet available [50, 80].

The medial approach [2, 15, 24, 81], was the most frequently used procedure in this study (87%) The approach allows easy access to distal arteries and enables vein harvesting from the same incision and position. The MAG should be used as first choice whenever a long bypass is needed such as when the SFA has atherosclerotic stenosis, aneurismal dilatation or when there is a CFA or SFA aneurysm. In the present study 195 legs (27%) were operated on with a medial approach because of at least one of these conditions, and among these 34 legs (17%) underwent an associated reconstruction of a CFA aneurysm. With this approach the aneurysm sac has to be ligated proximally and distally. There is, however a risk for continued expansion from patent side branches, which may explain the observed high rate of expanded aneurysms at the re-examination in this group (33%). Other studies report similar expansion rates after long-term follow-up [82-85], with the exception of Box et al [86] who found an expansion rate after a follow-up of median 18 months (6-48) of only 6% after medial approach. They concluded that a meticulous ligation technique gave these favourable results. The small sample size of this study (N=17 legs), in combination with a short follow-up, offers an alternative explanation, however.

With the posterior approach, all vessels can be ligated [87] and a short interposition graft with end-to-end anastomoses can be used [2, 14, 64, 75, 88]. In most patients it is possible to find a vein of good quality suitable for a short bypass. In an elective situation the run-off is often better in aneurysmal disease than in legs operated on for occlusive disease, and the diameters of the arteries are often larger [27, 28]. These factors may explain the increased use of prosthetic graft in the PAG in this study. We found no significant difference in patency between vein and prosthetic graft in PAG. This lack of difference may be the result of a type II error, however, since there were only 38 and 22 legs in the two groups, respectively, and the absolute patency-rates were inferior in the prosthetic reconstructions. The expansion rate in the PAG was only 8.3% and significantly lower than in the MAG in this study. The high frequency of symptoms necessitating re-operation in legs with expansion of the excluded aneurysm shows that the risk of expansion after PAA repair is an important issue to consider in the selection of surgical approach. In Sweden only 22 centres (52%) operated on patients with PAAs using both posterior and medial approach. There seems to be a need to train vascular surgeons in the posterior technique so that patients can be offered the optimal surgical procedure, "tailor-made" for their specific pathology.

Endovascular repair with transfemoral endoluminal stent graft deployment is an alternative to open surgical repair [16, 89]. The first endovascular

PAA repair was reported in 1994 [16], and at the same time the first endovascular procedures for PAA were registered in the Swedvasc. In this study, 3.6% of all PAA repair was performed with endovascular technique. Four centres performed 81% of these procedures, and we regarded these 26 endovascular PAA repairs as a pilot experience of a new technique. Studies comparing endovascular technique with open surgical technique were published lately showing similar patency rates [18, 90, 91]. However, only small groups of patients (N=15-30) with predominantly asymptomatic aneurysms were studied. A major problem when comparing open repair with endovascular repair is the selection of patients, including run-off, age, and the position of the PAA in the popliteal fossa. The advantages of endovascular technique, quicker recovery and shorter hospital stay, must be weighed against possible late complications, such as endoleak type II and stent fractures causing thrombosis. Careful follow-up is necessary to determine the durability of the endoluminal stent graft in relation to the open technique. Long-term outcome must be evaluated before endovascular repair can be recommended as a standard treatment [5], unless the patient has a short life-expectancy.

## Multiple aneurysm disease

PAA accounts for more than 70 % of all peripheral aneurysms [5, 19, 20]. In this study the median age of the patients was 71 years (range 18-94). In a previous review based on 29 reports published between 1980 and 1995, including 1673 patients with 2445 PAAs, the prevalence was found to increase with age and peaked in the sixth- and seventh decades of life [5]. In the same review 50% of the patients had bilateral PAAs, 37% had an AAA, and it was estimated that PAA occurs in 6-12% of patients with AAA. In paper I we found a high prevalence of extra-popliteal aneurysm in patients operated on for PAA and it increased in patients with bilateral PAAs. This finding is in accordance with previous reports [39, 52-54].

Most published reports on PAA have focused on the management and outcome [39, 52-54]. Follow-up programmes have been focused on the surveillance of the vascular reconstruction and often the patient has been lost to follow-up after one year. The risk to develop new aneurysms after PAA-repair was basically unknown. There is no consensus on the need and design of a surveillance programme after PAA-repair. The 190 patients re-examined in this study had 244 aneurysms at the index operation which increased by 102 to 346 aneurysms at re-examination. The 102 aneurysms developed in 74 patients after a median follow-up of seven years. This indicates that if early detection of aneurysm is aimed at, e.g. before limb- or life-threatening complications occur, it is important to include other locations than the operated PAA in a life-long surveillance programme.

In the present study age, hypertension and follow-up time were independently associated with multi-aneurysm disease. This has been shown by Dawson et al in previous reports on long-term surveillance [5, 52]. It is not clear, not even after this larger investigation, whether the two cohorts of patients with either isolated PAA or with multiple aneurysms, represent one or two separate diseases. The patients with isolated PAAs were younger and had shorter follow-up time, which may indicate that the patients have been studied at different stages of disease. Only 59 patients of 190 did not develop additional aneurysms, neither at the time of the index operation nor after follow-up.

All patients with hypertension were on medical treatment, but no information on the blood pressure was available, nor on the compliance of the treatment. It is therefore difficult to evaluate the possible patho-physiological impact of anti-hypertensive treatment on preventing the development of new aneurysms in this study. It makes sense, however, to treat hypertension in any patient with aneurysmal disease.

The presence of bilateral PAAs at the index operation was independently associated with a later development of AAA. This finding is in accordance with the only previously reported study [5]. However the presence of an AAA at index operation was not associated with later development of a PAA in the contralateral leg. This indicates that bilateral PAAs are a stronger marker for generalised aneurysmal diseases than the combination of one PAA and an AAA.

Within the first three years after the index operation for PAA only one new aneurysm was operated on in the multiple aneurysms group and no new aneurysms requiring surgery developed in the group with isolated PAA at the index operation. This implies that, patients with isolated PAA at index operation could have a re-examination every three years in arterial segments previously found normal. This interval may, however, be too long for patients with multiple aneurysm disease. Some authors have suggested that patients older than 65 years or with hypertension should be in life-long surveillance programs after PAA-repair [5, 52]. Our study supports this recommendation, but with our present knowledge it would seem risky not to include younger patients with isolated PAA in a life-long surveillance program. Obviously, the meaning of “life-long” is not literal, but is meant as long as the patient is fit for surgery. A suggested surveillance programme is described in Figure 7.

A limitation of this study was that the thoracic aorta was not studied, which would have required a CT-examination. The high prevalence of additional aneurysms indicates that a CT-examination may be appropriate to rule-out a thoracic aortic aneurysm, at least once, preferably at the index operation. In younger patients, this examination might even need to be repeated. The CT-examination was not included in the suggested surveillance programme in Figure 7, since we lack data to give recommendations on this

issue. However, studies are in progress to elucidate this potentially important aspect of the disease.

A further limitation is that no information on the prevalence of aneurysms, nor the causes of death were available on the 234 patients who had died before January 2005. Among the survivors, 240 (71%) underwent a telephone interview but only 190 (56%) a complete re-examination including ultrasound or CT. In cohort studies it is essential to analyse and report patients lost to follow-up. The present study is not a true cohort study, although data obtained at index operation were registered prospectively in the Swed-vasc. Non-attenders to re-examination were older than attenders, and since age was a risk factor for multiple aneurysm disease in this population it is likely that non-attenders would have had an even higher prevalence of additional aneurysms, had they been examined.

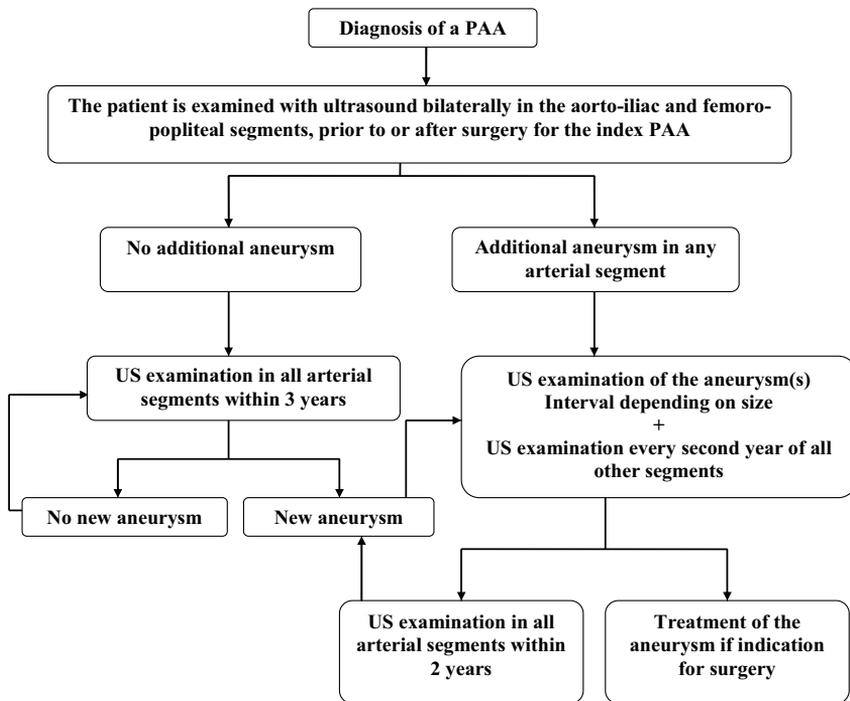


Figure 7. A suggested surveillance programme for patients operated on for PAA

# Conclusions

In patients with PAA multiple aneurysms are common, particularly in patients with bilateral PAAs. Relative survival is substantially decreased compared with the general population. Risk factors for amputation within one year were poor run-off, prosthetic graft, emergency procedure and age.

The treatment of PAAs with acute ischemia was selected into different treatment modalities in a complex manner. A trend towards a decreased amputation-rate during the study period was associated with increased use of preoperative thrombolysis and fasciotomy.

The use of thrombolysis has increased over time, and enables to transform an acute into an elective situation. Preoperative thrombolysis improves run-off and is associated with a lower amputation rate, although a cause effect cannot be verified, since the patients undergoing immediate and delayed surgical treatment are different in their pre-operative characteristics.

The surgical approach depends on the extension of the PAA. The type of graft depends on the length of the bypass and availability of vein. Vein do better than prosthetic grafts, especially in long bypasses. The length of the bypass and the approach had more impact on future expansion than the ligation technique used.

The risk of late amputation is low. No independent risk factor for late amputation was identified.

The risk of late expansion is high and associated with relevant symptoms. When a short bypass is used, the posterior approach has a lower risk of expansion, and this technique should be considered the first choice

The risk to develop of multiple aneurysms is high, increasing with hypertension, age and follow-up time. The risk to develop AAA is higher among patients with bilateral PAAs.

All patients, regardless of age or other risk factors, should be kept under life-long close surveillance in order to detect and treat newly developed aneu-

rysms timely. Normal arterial segments should be re-examined after a minimum of three years.

# Future perspectives on continued research on PAA disease

## Ruptured PAA

In this study only 24 patients with ruptured PAA were identified (3.4%). Other studies have shown a frequency of 1.4% [5]. With a new search in Swedvasc from 2002 to 2007 on ruptured PAAs it should be possible to identify 40-50 ruptured PAAs, and to describe this sub-group of patients more in detail.

## Women and PAA

Thirty-three women with 38 legs (5.3%) were identified in this study, and with a new search in Swedvasc from 2002 to 2007 it should be possible to identify approximately 50 women operated on for PAA and give more details regarding aneurismal disease in women.

## Re-examination of the 59 patients with no additional aneurysms

Only 59 subjects out of 190 who were re-examined had not developed additional aneurysms. Whether the two cohorts of patients with isolated PAA or multiple aneurysms represent two separate diseases is not clear. Subjects with isolated aneurysms were younger and had shorter follow-up time, indicating that patients may have been studied at different stages of disease. We intend to re-examine these patients after another five years to address this issue.

## Thoracic aortic aneurysms

A preliminary study to evaluate the prevalence of thoracic AA with CT-examination in 50-100 patients has been designed.

## Blood samples

Blood samples from the 190 re-examined patients are stored in a blood-bank in Örebro, Sweden to be used in future studies of etiological and pathophysiological markers

# Populärvetenskaplig sammanfattning

## (Summary in Swedish)

Pulsåderbräck (aneurysm) innebär en utvidgning av blodkärlet. Vanligast är de som sitter på stora kroppspulsådern (aortaaneurysm) och som vid bristning förorsakar 700-1000 dödsfall per år i Sverige. Näst vanligaste lokalisationen av ett aneurysm är pulsådern bakom knäet (poplitea). Till skillnad från aortaaneurysm, brister popliteaaneurysm (förkortas PAA, Poplitea Artär Aneurysm) sällan (1-2%). Däremot riskerar levrat blod i bräcket att orsaka en blodpropp (trombos), vilket ofta leder till en akut cirkulationsnedsättning i benet. Om det inträffar är det bråttom och risken är stor att det slutar med en amputation av benet. Obehandlat har en patient med ett trombotiserat PAA en risk att behöva genomgå en amputation på cirka 80-90 %.

Orsaken till att vissa människor utvecklar aneurysm är bara delvis känd. Sjukdomen drabbar oftare rökare och ses mestadels hos män. Det är oklart hur ofta kvinnor drabbas och om de i så fall drabbas på ett likartat sätt som männen. Hälften av patienterna har sjukdomen i båda benen, och ungefär 1/3 har ett samtidigt aortaaneurysm. Ungefär 1/3 av patienterna med PAA har inga symptom, och upptäcks först i samband med akut trombotisering.

PAA är en ovanlig sjukdom som inte ses särskilt ofta av den enskilde kirurgen och därmed är svår att undersöka vetenskapligt. De publikationer som finns i litteraturen omfattar som mest 147 PAA. Genom det svenska kärlregistret [55], världens första nationella kvalitetsregister inom kärlkirurgi som startade 1987, har jag haft möjlighet att studera sjukdomen hos ett unikt stort antal patienter. I Swedvasc hade över 120 000 kärlkirurgiska ingrepp registrerats mellan 1987 och november 2002, varav jag kunde hitta 743 PAA operationer. Av dessa var 717 primära ingrepp på 571 patienter och 26 var reoperationer på 22 patienter fördelat på 42 sjukhus i Sverige. Vid en efterundersökning 2005 var 337 patienter fortfarande i livet och av dem accepterade 190 att ingå i en efterundersökning. Med ultraljud undersöktes patienternas tidigare opererade PAA, andra benets poplitea, stora kroppspulsådern, bäcken- och ljumskkärlen. Patienterna deltog även i en telefonutfrågning. Mitt avhandlingsarbete består av fyra olika analyser av denna, världens hittills största, samling av patienter opererade för PAA.

## Delarbete I.

I delarbete I beskrivs operation för PAA i Sverige. Dessutom studerades amputationsfrekvensen det första året efter operation och långtidsöverlevnaden. Av 571 patienter var 538 män (94,2%). 266 patienter hade dubbelsidigt PAA (46%). Ett samtidigt aortaaneurysm sågs hos 28% vid enkelsidigt PAA och hos 38% vid dubbelsidigt PAA. Storleken av PAA var i genomsnitt 30 mm, det största 15 cm.

Inom 30 dagar efter operationen amputerades 5,7% av patienterna och inom ett år var 8,8% amputerade. Amputationsfrekvens inom ett år minskade över tiden, från 14% före 1993 till 5,4% efter 1998. Antalet fungerande blodkärl i underbenet (run-off) påverkade amputationsfrekvensen. Patientens egen ven var bättre att använda än konstgjort material (kärlprotes) vid operationen. Användning av trombolys (propplösande medicin givet direkt i kärlet genom en tunn slang) kunde förbättra run-off och därmed minska amputationsfrekvens (se delarbete II).

Långtidsöverlevnaden hos patienter opererade för PAA var lägre än hos befolkningen i övrigt. Efter ett år var överlevnaden 3,1% lägre, efter fem år, 12,9% lägre och efter 10 år 17,7% lägre än hos en normalbefolkning med samma ålders- och könsfördelning. Patienter som opererades akut hade sämre överlevnad än patienter som opererades planerat (elektivt).

## Delarbete II.

I delarbete II analyserades patienter som behandlats akut pga. trombotisering. Hos 229 patienter identifierade i registret, behandlades 100 ben initialt med trombolys och 135 ben opererades direkt.

Av dem som behandlades med trombolys blev 41 ben senare akutopererade (mindre 24 timmer efter trombolysavslutning) och 59 opererades planerat. Trombolysbehandling förbättrade avflödet (run-off) avsevärt och amputationsfrekvens var 7% i gruppen som fått trombolys jämfört med 27% i gruppen som opererades direkt. Trombolys förvandlade således akuta till planerade operationer, med bättre resultat som följd. Amputationsfrekvensen minskade även sannolikt genom ökad frekvens fasciotomi (klyvning av bindvävshinnorna i underbenet).

## Delarbete III.

I delarbete III analyserades operationstekniken som användes när patienterna opereras för PAA. Största andelen (87%) blev opererad med en medial approach (tillgång via insidan av benet), posterior approach användes i 8,4% (tillgång bakifrån), endovaskulär behandling i 3,6% (via blodbanan med hjälp av katetrar) och övrigt i 1,4%. Jämförelser gjordes mellan medial och posterior tillgång och mellan olika bypassmaterial. Vid medial tillgång var

vengraft bättre än kärlprotes, vid posterior tillgång sågs däremot ingen skillnad. Patienter som var opererade med medial tillgång hade ökad frekvens av fortsatt tillväxt av det tidigare opererade aneurysmet (33%) jämfört med de som hade opererats bakifrån (8,4%).

## Delarbete IV.

I delarbete IV analyserades förekomsten av multipla aneurysm och utvecklingen av nya aneurysm hos 190 patienter som efterundersöktes efter i medeltal 7 år (2-18) efter operationen för PAA. Vid den ursprungliga operationen för PAA hade 56,8% av patienterna ett aneurysm någon annanstans (andra sidans poplitea, ljumskpulsådern, bäckenkärlet eller aortan). Vid efterundersökningen hade andelen ökat till 68,9%. Bland patienterna som bara hade ett isolerat PAA vid primäroperationen utvecklade 28% ett nytt aneurysm under uppföljningstiden. Patienterna som inte utvecklade något nytt aneurysm var yngre. Riskfaktorer för multipla aneurysm var ålder och hypertoni (högt blodtryck), medan kön, ärftlighet och rökning inte hade någon betydelse. Utveckling av aortaaneurysm efter operation för PAA var vanligare om patienten hade dubbelsidiga PAA och om uppföljningstiden var längre. Utifrån resultaten i delarbete IV kunde vi för första gången föreslå rekommendationer för ett uppföljningsprogram, baserat på vetenskapliga fakta.

## Sammanfattning

Denna avhandling har främst bidragit till att visa att patienter som opereras för PAA har hög risk för att utveckla nya aneurysm på andra ställen i kroppen, varför regelbundna efterundersökningar med ultraljudsteknik rekommenderas så länge patienten lever och är tillräckligt frisk för att kunna opereras. Trombolysbehandling kan förvandla akuta situationer till planerade och genom förbättrat avflöde minska risken för amputation. Ven graft är bättre vid operation från benets insida, speciellt vid lång bypass. Bakre operation har, om möjlighet finns, fördelen att risken för fortsatt tillväxt av det exkluderade aneurysmet minskar.

# Populærvidenskabelig sammenfatning

## (Summary in Danish)

Pulsårebrot (aneurysme) er en lokal udvidelse af et blodkar. Hyppigst forekommende er de aneurismer, som findes på den store kropspulsåre (aorta), og som ved bristning (ruptur) forårsager 700-1000 dødsfald per år i Sverige. Den næst mest almindelige lokalisering af aneurismer ses på pulsåren bag ved knæet (poplitea). Forskellen fra aortaaneurysmet er, at popliteaaneurysmet (PAA, Popliteal Artery Aneurysm) sjældent brister (1-2%). Derimod findes der risiko for, at blodet størkner i aneurysmet og forårsager en blodprop (trombose). Dette medfører ofte akut koldbrand i benet. Behandlingen er akut, men på trods af dette er risikoen for amputation af benet stor. En ubehandlet patient med tromboseret PAA har en risiko for at amputation af benet på 80-90%.

Årsagen til at nogle mennesker udvikler et aneurysme er kun delvist kendt. Sygdommen findes oftest iblandt rygere og hos mænd. Det er uklart, hvor ofte kvinder rammes af denne sygdom, og om de rammes på samme måde som mændene. Halvdelen af patienterne har sygdommen i begge ben og cirka 1/3 har et aortaaneurysme samtidigt. Omkring 1/3 af patienterne med PAA har ingen symptomer og sygdommen opdages først ved den akutte trombose.

PAA er en sjælden sygdom, som ikke ses så ofte af den enkelte kirurg, og som derved er svær at dokumentere videnskabeligt. De største publicerede studier, omfatter højst 147 tilfælde med PAA. Gennem det svenske kar register [55], som er verdens første nationale kvalitetsregister inden for karkirurgi, med start i 1987, har jeg haft mulighed for at studere sygdommen på et unikt stort antal patienter. I Swedvasc er der registreret over 120 000 karkirurgiske indgreb mellem 1987 og november 2002. Jeg fandt 743 PAA operationer. De var fordelt på 42 sygehuse i Sverige og omfattede 717 primære indgreb på 571 patienter, og 26 re-operationer på 22 patienter. Ved en efter undersøgelse i 2005 var 337 af patienterne fortsat i live, og af disse var 190 villige til at deltage i en efterundersøgelse. Ved hjælp af ultralyd undersøgte patienternes tidligere opererede PAA, det modsatte bens poplitea, aorta, bækken- og lyske karrene. Patienterne deltog desuden i et telefoninterview. Mit afhandlings arbejde består af fire forskellige analyser af materialet. Det er til dato verdens største samling vedrørende patienter opereret for PAA.

## Delarbejde I

I delarbejde I beskrives operationer for PAA i Sverige over et forløb på 15 år, fra 1987-2002. Desuden studeredes amputationsfrekvensen i løbet af det første år efter operationen og langtidsoverlevelsen. Af 571 patienter var 538 mænd (94,2%) og 33 kvinder. Tohundredeogfireogtre havde dobbeltsidigt PAA (46%). Et samtidigt aortaaneurysme fandtes hos 28% af patienterne med ensidigt PAA og hos 38% med dobbeltsidigt PAA. Størrelsen af PAA var i gennemsnit 30 mm (15-150).

Inden for 30 dage efter operationen fik 5,7% af patienterne amputeret benet og i løbet af det første år havde 8,8% fået foretaget amputation. Amputationsfrekvensen mindskedes i løbet af perioden fra 14% før 1993 til 5,4% efter 1998. Antallet af fungerende blodkar i underbenet (run-off) påvirker amputationsfrekvensen, og patientens egne kar (vener) var bedre end kunstigt materiale (kar proteser) ved valg af bypass materialer til operationen. Brug af trombolyse (blodprop opløsende medicin givet direkte i karet gennem en tynd slange) kunne forbedre run-off og dermed mindske amputationsfrekvensen (se delarbejde II).

Dødeligheden var højere hos patienter som var opereret for PAA end hos befolkningen i øvrigt. Efter et år var dødeligheden 3,1% højere, efter fem år 12,9% højere og efter 10 år 17,7% højere end hos en normalbefolkning med samme alders- og kønsfordeling. Patienter, som blev opereret akut, havde dårligere overlevelses prognose end patienter, hvor operationen var planlagt (elektivt).

## Delarbejde II

I delarbejde II analyseredes de patienter, som var blevet behandlet akut pga. trombose. Af 229 patienter som fandtes i registeret, fandt man 100 ben som blev behandlet initialt med trombolys og 135 ben som blev opereret direkte.

Blandt de, som behandlede med trombolyse, blev 41 ben senere akut opereret (mindre end 24 timer efter trombolys afslutningen) og 59 elektivt opereret. Trombolysen forbedrede run-off betydeligt, og amputationsfrekvensen var 7% i gruppen som havde fået trombolys sammenlignet med 27% i gruppen, som blev opereret direkte. Trombolysen kunne således ændre akutte operationer til planlagte operationer med et bedre resultat til følge. Amputationsfrekvensen faldt også gennem en forøget frekvens af fasciotomier (spaltning af muskelhinderne i underbenet).

## Delarbejde III

I delarbejde III analyseredes operations teknikken som blev anvendt på patienterne opereret for PAA. Største delen (87%) blev opereret med en medial approach (adgang via indersiden af benet), hos 8,4% anvendtes posterior approach (adgang bagfra i knæet), og hos 3,6% anvendtes endovascular behandling (via blodbanen ved hjælp af et kateter under røntgen gennem lysning) og hos 1,4% gennemførtes andre behandlingstyper. En sammenligning blev foretaget mellem medial og posterior approach. Derefter gennemførtes en sammenligning inden for hver gruppe ud fra bypass materialet. Ved medial approach var egne kar (vene graft) bedre end kunstigt materiale (kar protese). Ved posterior approach fandtes derimod ingen forskel. Patienterne, som var opereret med medial approach, havde en øget frekvens af tilvækst i det tidligere opererede aneurysme (33%) sammenlignet med patienter opereret med den posteriore approach (8,4%).

## Delarbejde IV

I delarbejde IV analyseredes forekomsten af multiple aneurysmer, og udviklingen af nye aneurysmer hos 190 patienter, som blev efterundersøgt mellem 2-18 år efter operationen for PAA (gennemsnitstid 7år). Ved den oprindelige operation for PAA havde 56,8% af patienterne et aneurysme ud over det opererede PAA (modsatte bens poplitea, lyske pulsårene, bækken karrene eller aorta). Ved efterundersøgelsen var andelen med aneurysme steget til 68,9%. Otteogtyve procent af de patienter som kun havde det PAA som de var opereret for udviklede et nyt aneurysme i løbet af opfølgningstiden. De patienter som ikke udviklede noget nyt aneurysme var aldersmæssigt yngre. En anden risiko faktorer var hypertension (højt blodtryk), mens køn, arvelighed og rygning tilsyneladende ikke havde nogen betydning. Udviklingen af aortaaneurysm efter operation for PAA var associeret med dobbeltsidigt PAA og opfølgningstiden. Ud fra resultatet i delarbejde IV anbefales et fortsat opfølgningsprogram, baseret på videnskabelige fakta, hos patienter opereret for PAA.

## Sammenfatning

Denne afhandling har først og fremmest bidraget ved at vise, at patienter som er opereret for PAA har højere risiko for at udvikle nye aneurysmer på andre steder i kroppen. Derfor anbefales regelmæssige undersøgelser med ultralyds teknik i resten af patientens levetid. Trombolysebehandling kan i visse tilfælde forvandle akutte operationer til planlagte og gennem forbedret run-off mindske risikoen for amputation. Anvendelse af patientens egne kar er bedre end anvendelse af kunstigt materiale specielt i tilfælde med behov

for en lang bypass. Posterior approach er, om muligt, at foretrække for derved at mindske den fortsatte tilvækst i det tidligere opererede aneurysme.

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