

The use of prosthetic grafts in above-knee femoropopliteal bypass surgery

A clinical study of long-term results and risk factors for failure

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Professor emeritus Arne Trippestad, a pioneer in norwegian vascular surgery, developed a vascular registry for use in our department as the first of its kind in Norway. The registry was established in 1989 and contains now data of more than 16.000 open operations and endovascular procedures. Ole Martin Pedersen, Department of Cardiology, performed many of the duplex ultrasound controls in the surveillance program.

I want to express my deepest gratitude to my wife, Ann Brown, for her support and understanding and to our beloved children, Linnea, Sunniva and Jonas.

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List of publications

- I. Pedersen G, Hagala M, Laxdal E, Aune S. Local infections after above-knee prosthetic graft femoropopliteal bypass for intermittent claudication. *Surg Infect (Larchmt)*. 2004 Summer; 5(2): 174-9.
- II. Pedersen G, Laxdal E, Hagala M, Aune S. The impact of comorbidity on long-term results of above-knee prosthetic femoropopliteal bypass for intermittent claudication. *Int Angiol*. 2005 Sep; 24(3): 245-9.
- III. Pedersen G, Laxdal E, Hagala M, Amundsen SR, Dregelid E, Aune S. The impact of patient characteristics on long-term results of above-knee prosthetic femoropopliteal bypass for critical ischaemia. *Int Angiol*. 2005 Dec; 24(4): 349-54.
- IV. Pedersen G, Laxdal E, Amundsen SR, Dregelid E, Jonung T, Nyheim T, Aune S. Flow measurement before and after intragraft papaverine injection in above-knee prosthetic femoropopliteal bypass. *J Vasc Surg*. 2006 April; 43: 729-34.
- V. Pedersen G, Laxdal E, Aune S. The outcome of occluded above-knee femoropopliteal prostheses implanted for critical ischaemia. *Eur J Vasc Endovasc Surg*. 2006 Dec; 32(6): 680-5.

Abbreviations

ACE:	Angiotensin Converting Enzyme
COPD:	Chronic Obstructive Pulmonary Disease
CT:	Computer Tomography
DSA:	Digital Subtraction Angiography
HPS:	Heart Protection Study
HUV:	Human Umbilical Vein
IU:	International Units
LMWH:	Low Molecular Weight Heparin
MRI:	Magnetic Resonance Imaging
PCI:	Percutaneous Coronary Intervention
PTA:	Percutaneous Transluminal Angioplasty
PTFE:	Polytetrafluoroethylene
rt-PA:	Recombinant human tissue-type plasminogen activator
TASC:	Trans Atlantic Society Consensus
VAC:	Vacuum Assisted Closure

Abstract

Purpose

The purpose of this study has been to investigate the results of above-knee prosthetic femoropopliteal bypass surgery and to identify risk factors for complications and graft failure. The influence of comorbidity, degree of chronic leg ischaemia, preoperative angiographic run-off score and intraoperative flow measurements on long-term results were investigated. Furthermore, local infections and the outcome of treating occluded prosthetic grafts were studied.

Methods

Two-hundred-and-thirty-seven patients (156 men, 81 women) were subjected to 252 above-knee prosthetic femoropopliteal bypass operations at Haukeland University Hospital between Jan 1990 and Dec 2001. One hundred and forty-one graft implantations (129 patients) were done for intermittent claudication and 111 (108 patients) for critical ischaemia. Patient data were prospectively recorded in a database registry. Some data were supplemented from patients records. Occlusion dates, complications, re-operations including amputations, and mortality were also recorded. Patient characteristics, anatomical risk factors and intraoperative flow measurements were analysed for impact on results after surgery.

Survival, limb salvage and patency rates were analysed with the Product limit method and illustrated as Kaplan-Meier curves. The risk factors were subjected to univariate analysis using the log rank test for impact on survival, limb salvage and patency rates. Variables approaching significance were included in multivariate analysis performed with the Cox proportional hazard model.

Results

Paper I. Surgical site infection was recorded after 7.8 % of the operations and graft infection after 12 %. The risk of developing a local infection was significantly correlated with postoperative lymph fistula. Redo surgery was associated with graft infection. Graft infections caused by *Staph. Aur.* always warranted surgery, either local revision or graft excision.

Paper II. For grafts implanted for intermittent claudication, the assisted primary patency rates were 62 % at 2 years and 44 % at 5 years. The 5-year patency rate for smokers was 24 % versus 67 % for non-smokers ($p < 0.01$). A previous history of cerebral infarction was significantly associated with reduced graft patency. Preoperative s-creatinine > 125 mmol/L was significantly associated with reduced survival.

Paper III. The 30-day mortality rate of patients operated for critical ischaemia was 5.5 %. The 2- and 5-year survival was 72 % and 42 %, whereas the limb salvage rates at 2 and 5 years were 83 % and 73 %, respectively. The 2-year primary patency rate for smokers was 38 % versus 62 % for non-smokers ($p = 0.018$, hazard ratio 2.18). Smoking and tissue loss were significantly associated with reduced secondary patency.

Paper IV. Basal flow measurements were not related to patency. The 2- and 5-year patency rates for grafts with a papaverine flow < 500 ml/min were 48 % and 18 % compared with 66 % and 52 % for grafts with a papaverine flow ≥ 500 ml/min ($p = 0.012$, hazard ratio 2.6). Two and 5-year patency rates for smokers vs non-smokers were 44 % and 18 % vs 69 % and 54 %. Smoking ($p = 0.008$, hazard ratio 2.38) and poor run-off score ($p = 0.009$, hazard ratio 2.38) were independent risk factors for reduced patency. Poor run-off score did not correlate with low values of measured basal or papaverine flow.

Paper V. Half the 24 initial procedures to restore patency of occluded grafts originally implanted for critical ischaemia failed within a month. Outcome of second-

or third-time redo procedures were similar. Primary patency rates of all 55 redo procedures were 32 % at three months, 28 % at six months and 12 % at 12 months. The results of thrombectomy and thrombolysis were similar. Re-opened grafts additionally treated for an underlying anastomotic stenosis had significantly better patency, as compared with re-opened grafts without a pre-existing stenosis ($p = 0.027$, hazard ratio 2.813).

Conclusions

The results regarding survival, limb salvage and patency are comparable to previous reports. The results underline that a long observation period is necessary to achieve full overview of complications and the impact of risk factors.

Infectious complications after prosthetic femoropopliteal bypass in the study group were higher than previously reported. The results suggest that a selective approach should be taken towards excision of infected femoropopliteal prostheses according to the clinical presentation of the graft infection and the type of bacteriae involved.

A conservative attitude is recommended towards placing a prosthetic graft in the above-knee femoropopliteal position for intermittent claudication. The finding of reduced patency rates in patients with a history of a cerebral insult operated for intermittent claudication need further studies to be verified. Patients with intermittent claudication and renal impairment reveal poor survival, indicating renal impairment as a relative contraindication for surgical treatment. Smokers have inferior patency rates when operated for intermittent claudication as well as for critical ischaemia. Poor angiographic run-off score was also associated with inferior patency rates. These findings indicate that prosthetic femoropopliteal bypass is not very suitable for these groups of patients. Furthermore, the poor secondary patency rates of smokers as

well as for patients with tissue loss suggest that these patients may benefit from alternative treatment modalities to re-opening an occluded bypass.

A papaverine flow of < 500 ml/min is associated with reduced patency. Additional antithrombotic medication and frequent follow-up may be considered for these grafts. Redo procedures for occluded grafts originally implanted for critical ischaemia are of limited value and cannot be recommended except in cases with a proven graft-related stenosis. Other cases in need of re-intervention should be treated with either a new arterial reconstruction or an amputation.

Based on the findings in this study, the following issues must be evaluated when offering an above-knee prosthetic femoropopliteal bypass for chronic limb ischaemia: patient comorbidity, smoking, degree of ischaemia and angiographic run-off score. Careful selection of patients subjected to above-knee prosthetic bypass surgery for chronic ischaemia is mandatory to achieve the optimal gain of the operation.

1. Introduction

1.1 Re-occlusions and complications in infrainguinal vascular surgery

The durability of arterial reconstructions (both surgical and endovascular) performed below the groin is more limited (1-6) contrasted to that of reconstructions performed above the groin(7-9). Thus the anatomical region below the inguinal ligament constitutes an Achilles heel in vascular surgery.

The durability of vascular reconstructions is often reported in terms of patency. The term “patency” is explained in chapter 3.11.3. Limb salvage (3.11.2) and survival (3.11.1) are also often studied in vascular patients. Complications are less frequently reported despite the fact that these are well known to vascular surgeons.

The relatively large number of prosthetic femoropopliteal bypass operations performed at our department during the study period generated numerous complications and re-do procedures. Apparently, there was a need for scrutiny of the treatment policy and of the procedures related to the operations. This need for reevaluation initiated this study.

1.2 Femoropopliteal and systemic atherosclerosis

Arterial occlusions of the superficial femoral and the popliteal artery are common. Femoropopliteal atherosclerotic lesions may account for approximately 50 % of target lesions treated in a vascular clinic(10). However, this percentage may vary according to local treatment policy. Isolated femoropopliteal atherosclerotic lesions lead in most cases to intermittent claudication, whereas concomitant

significant lesions at other anatomical levels, i.e. multi-level disease, more often lead to critical limb ischemia(11).

Femoropopliteal occlusions are classified in four classes, TASC A-D, according to the Transatlantic Consensus Document (Table I, *Appendix*)(11). All cases included in the present studies were occlusions, either TASC-C or -D lesions.

Up to 50 % of patients having symptomatic femoropopliteal atherosclerosis have concomitant symptomatic coronary disease and 10 % have cerebrovascular disease(12,13). Two thirds of patients with peripheral arterial disease die from coronary disease and 10 % from stroke(14). These facts clearly demonstrate atherosclerosis as a systemic disease.

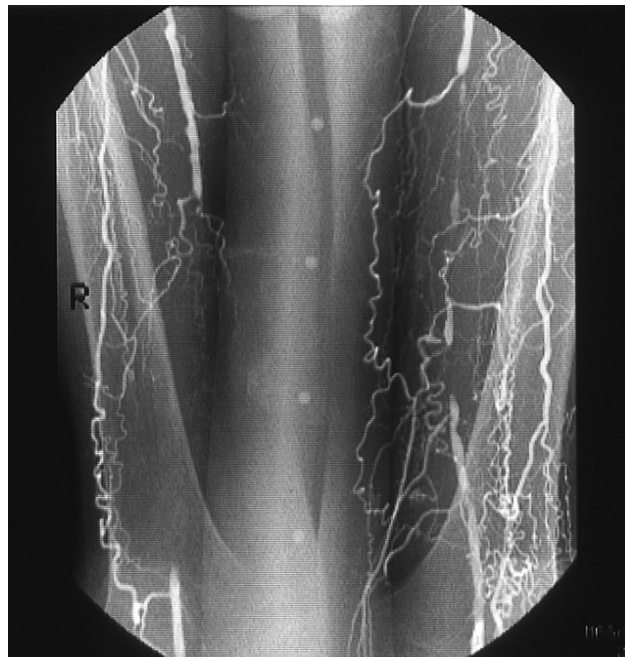


Figure 1. An angiogram demonstrating bilateral occlusion of the superficial femoral artery.

1.3 Peripheral bypass surgery: Historical background

Prosthetic grafts for use in peripheral bypass surgery were developed in the United States in the beginning of the 1950's. In 1952, Voorhees, Jaretzki and Blakemore's pioneering work with porous vinyon-"N"-prosthesis ushered the development of peripheral vascular surgery and the use of prosthetic grafts (15,16). In 1954, the nylon prosthesis was introduced by Edwards et al (17,18). Shortly thereafter, Edwards and Tapp devised the crimping process for arterial prostheses (18-20). However, the nylon grafts proved unsatisfactory because they lost up to 80 % of their tensile strength after experimental implantation. In 1956, the Teflon graft was developed. This graft proved to have a much longer tensile strength durability as compared with nylon(17,18). Concomitantly, the Dacron prosthesis (polyester) was found to be the most promising graft at that time, according to experiments performed on a number of materials by DeBakey et al (21,22). Based on these findings, the Dacron DeBakey vascular prosthesis was developed and introduced in January 1957.

The first prosthetic femoropopliteal bypass in Norway was performed in 1958, using the Edwards-Tapp's crimped nylon prosthesis. In 1964, the norwegian surgeon Karl Victor Hall reported dissappointing long-term results of 42 cases in which "the plastic graft" was used as bypass for femoropopliteal obstruction, concluding that these grafts were not suitable for this use (23).

In 1972, polytetrafluoroethylene (PTFE) (Gore-Tex[®]) wire insulation was first implanted in arteries and veins of dogs in Denver, Colorado(24). The PTFE-graft was subsequently modified including fibrillar arrangement, wall thickness, and pore size leading to the development of a vascular prosthesis with tissue ingrowth, viable neointima and acceptable patency rates.

During the years a variety of graft types of different materials have been manufactured followed by optimistic and promising reports of graft performance. However, several randomised controlled trials comparing different prosthetic grafts

concluded that the results were similar, i.e. no prosthetic graft material has been proven superior to the others (25,26).

The first prosthetic femoropopliteal bypass at Haukeland University Hospital was performed in 1975. The patient was a 66 year old male with intermittent claudication. The graft was made of non-impregnated polyester. Two months postoperatively, the graft was excised due to graft infection but amputation was not required. The patient died from a myocardial infarction two years later.

In many vascular clinics during the 1980's and 1990's, prosthetic femoropopliteal bypass surgery was standard treatment for occlusive arterial disease. After the introduction of the method at Haukeland University Hospital in 1975, the operation was only occasionally performed until 1990 when its use increased. The use of prostheses in above-knee femoropoplital bypass surgery reached a top in our department in 1995 (Figure 2).

During the years 1990 – 2001 a vein was used as conduit in only 27 above-knee femoropopliteal bypasses, as contrasted to the use of 252 prostheses during the same period. The annual number of prosthetic femoropopliteal bypass declined to a minimum after the year 2000 (Figure 2), and since then the preferred graft has been autologous vein. However, prosthetic femoropopliteal bypass is still used in selected cases. Therefore, the knowledge of risk factors for complications and failure after prosthetic bypass are still of value.

Current indications for the use of prosthetic grafts in the above-knee femoropopliteal position are discussed further in chapter 4.1.4.1 and 4.1.4.2.

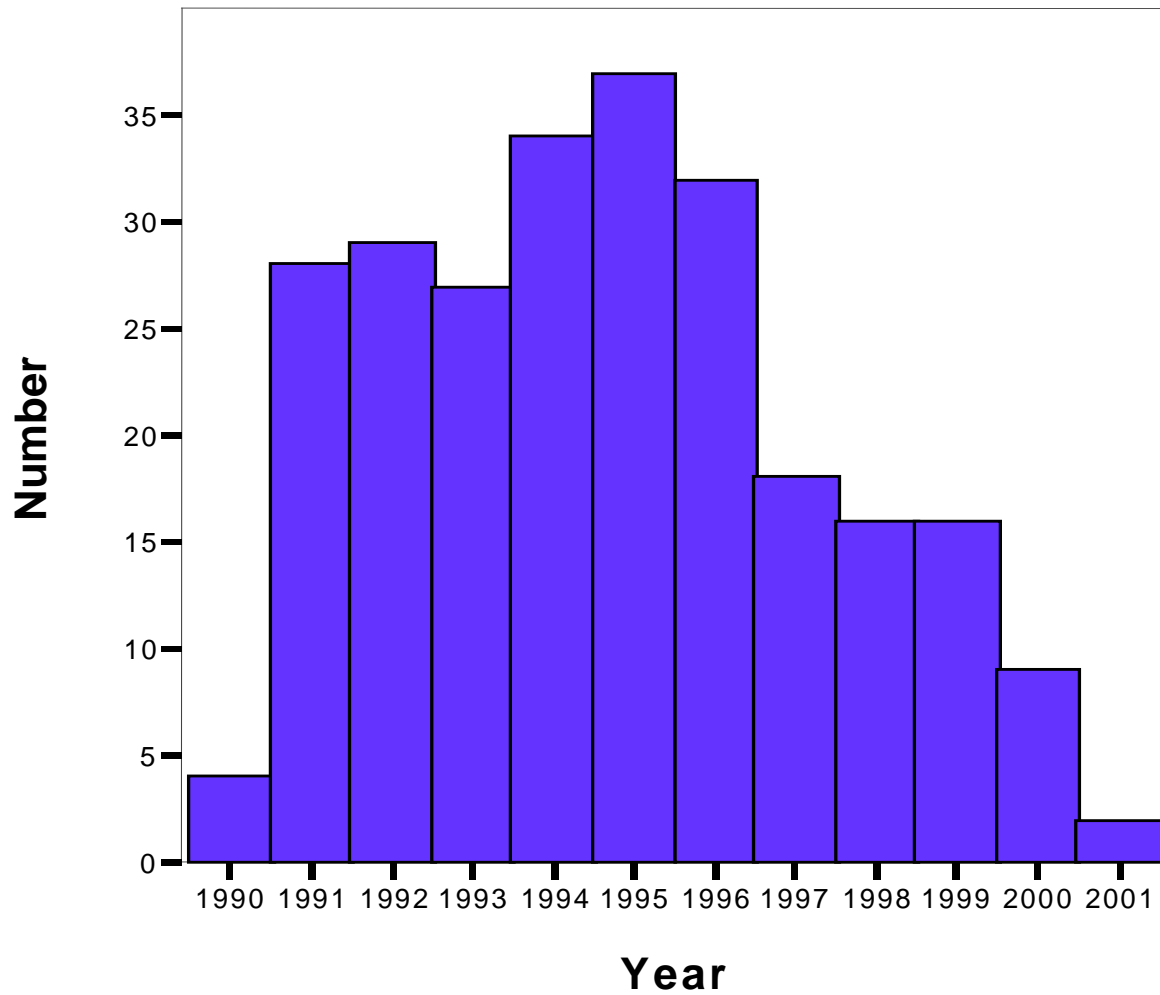


Figure 2. The annual numbers of above-knee prosthetic femoropopliteal bypass operations at Haukeland University Hospital 1990 – 2001.

2. Aims of the Thesis

The overall aim of this Thesis is to investigate the results of above-knee femoropopliteal prosthetic bypass and to identify risk factors for complications and graft failure. The aims of the studies in this Thesis are:

- Study I: to investigate the incidence of and to identify risk factors for surgical site infections and graft infections.
- Study II: to investigate the impact of comorbidity on long-term results of above-knee femoropopliteal prosthetic bypass for intermittent claudication.
- Study III: to investigate the impact of patient characteristics on long-term results above-knee femoropopliteal prosthetic bypass for critical ischaemia. Patient characteristics include comorbidity, degree of lower limb ischemia and preoperative angiographic run-off score.
- Study IV: to investigate the impact of intraoperative transit time flow measurements on short- and long-term results of above-knee femoropopliteal prosthetic bypass.
- Study V: to investigate the outcome of re-opening occluded prosthetic grafts implanted for critical limb ischaemia.

3. Patients and Methods

3.1 Study design

The studies are based on prospectively recorded patient data in a vascular registry maintained by the department and supplemented with data from patient records. The data were retrospectively analysed.

3.2 Patients

The studies I-V include 237 patients (156 men, 81 women) subjected to 252 above-knee prosthetic femoropopliteal bypasses from Jan 1990 – Dec 2001. The patients were treated at the Surgical Clinic, Section for Vascular Surgery, Haukeland University Hospital, Bergen, Norway. No patients operated with femoropopliteal prosthetic bypass in the period were excluded.

For patients with vascular disease, Haukeland University Hospital serves as a primary hospital for 400.000 people and as a secondary and tertiary hospital for 800.000. No vascular surgery was done elsewhere in the primary uptake area during the study period.

3.3 Risk factors for complications and graft failure

3.3.1 Patient comorbidity. Patient comorbidities were defined as those prospectively recorded in the vascular registry.

3.3.1.1 Heart disease (Study I). Heart disease warranting treatment was considered significant and was recorded in the vascular registry. Thus,

coronary disease, valvular pathology, arrhythmia, congestive heart failure etc. were recorded as the same risk factor. No information about the function class of the patient was recorded. Symptomatic coronary disease was not specified in Study I. For studies II – V, information about coronary disease was extracted from the vascular registry. Coronary disease was recorded if the patient had had a myocardial infarction, a previous aortocoronary bypass or a percutaneous coronary intervention (PCI) or present angina pectoris. The coronary disease was not further classified.

3.3.1.2 Hypertension (Study I-V). Hypertension was recorded if medically treated. This definition was chosen when the vascular registry was established. The argument for not recording “untreated hypertension” is that measurements of high blood pressure without medication may represent falsely elevated blood pressure (“white coat hypertension”) due to a stress response in the patient (27).

3.3.1.3 Cerebrovascular disease (Study I – V). Cerebrovascular disease was defined as earlier history of cerebral insults. No distinction was made between major and minor strokes. It was not specified whether or not disability was present, which may have affected mobility.

3.3.1.4 Diabetes mellitus (Studies I – V). Both diabetes mellitus type 1 and type 2 were recorded as a risk factor if the condition was medically treated. No distinction was made between the two subgroups of diabetes mellitus. Thus, diet-controlled diabetes 2 was not recorded. Our definition of diabetes as a risk factor is debatable. Except s-glucose measurements, no screening investigations were done for detecting diabetes mellitus. Since 2005, we have routinely analysed HbA1c in all patients admitted to our clinic. In addition, S-Insuline is measured according to a protocol. The value of detecting diabetes mellitus in vascular patients is well documented (28,29).

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- 3.3.1.5 *Lung disease* (Study I). In study I, chronic lung disease was recorded. This information is inaccurate, since the patients had actually had COPD, which also was registered in the vascular database. This is corrected in study II – V.
- 3.3.1.6 *COPD* (Study II – V). Chronic obstructive pulmonary disease was recorded if the patient received medical treatment. The presence of COPD denotes a reduced respiratory status and this information is of importance since some of these patients are at high risk for surgery. The frequency of COPD is higher among smokers than non-smokers (30). COPD is not proven to affect results of peripheral vascular surgery. However, COPD may lead to secondary polycythaemia (31) and thus increased risk of thrombosis (32).
- 3.3.1.7 *Renal impairment* (Study I – V). This was defined as serum-creatinine above 125 $\mu\text{mol/L}$. The condition is known to increase the risk of atherosclerosis, inflammation, endothelial dysfunction and platelet activation (33). No distinction was made between patients with mild and moderate renal impairment or renal failure. Such a distinction may be of importance for grading risk. The association between renal failure and poor results of above-knee prosthetic femoropopliteal bypass is previously reported (34,35).

3.3.2 Smoking

The patient was classified as smoker if he had been smoking regularly within the last five years prior to surgery. This definition is debatable, but was chosen when the vascular registry was established. It has been reported that a quarter of the patients untruthfully claim having stopped smoking when examined with serum markers, especially s-isothiocyanate (36,37). Measurement of cotinine in urine has also been reported to be a reliable method for obtaining information on smoking status (38). However, the use of nicotine substitutes may be a confounder if laboratory analyses are chosen to

investigate smoking habits (39). We believe that patients are more prone to answer truthfully if they are asked if they have been smoking during the last five years as compared with smoking at the time of surgery. However, we regard smoking to be under-reported in the present material. Smoking status is an important preoperative information, since smoking puts patients at a higher risk for surgery and the results after surgery are correlated to the daily number of cigarettes postoperatively (36,40,41). According to a recently published meta-analysis, smokers have a three-fold increase in risk for graft failure after vascular surgery compared with non-smokers (42).

3.3.3 The degree of chronic leg ischemia

The degree of arterial insufficiency in the lower extremity can be stratified into four stages in non-diabetic patients according to the Fontaine classification (Table II, Appendix)(43).

3.3.3.1 *Intermittent claudication.*

Intermittent claudication (study I, II and IV) represents Stage 2 in the Fontaine classification. The patient experiences exercise-induced pain, numbness or fatigue in the muscles of the hip, thigh and/or calf. Typically, the symptoms disappear after rest, and then the patient is able to walk again. Exercise-induced ischaemia of the calf muscles is common in femoropliteal occlusive disease. In the present studies, intermittent claudication was described as “disabling” to the patient in many cases. The preoperative walking distance was referred in meters as reported by the patients. Thus, the exact walking distance was not described in meters as initial or absolute claudication distance. Since 2002, we have routinely performed treadmill testing in the outpatient clinic in order to obtain more detailed information. This diagnostic tool gives more liable information under standardised conditions (44).

3.3.3.2 *Critical ischaemia*

Critical ischaemia (study III, IV and V) was defined as either rest pain (Fontaine Stage 3) or tissue loss, i.e. ulcer or gangrene (Fontaine Stage 4) in agreement with the criteria in the Second European Consensus Document on Chronic Critical leg ischaemia (45). However, some cases with rest pain may not have had true critical limb ischaemia, due to the lack of Doppler toe pressure measurements in the present study (45). Toe pressure measurement was introduced in our department in 2001, and is now a routine investigation in the management of critical limb ischaemia. Toe pressure measurement is particularly important in diabetic patients and elderly patients in whom ankle pressure measurements may be overestimated in 5-15 % of cases due to tunica media sclerosis (46).

3.3.4 **Angiographic run-off score**

(Study III and IV). Run-off score was based on the number of patent crural arteries reaching the ankle, as seen on the preoperative angiogram. It was defined as good (> 1 patent artery) or poor (one patent artery or less). In study III, 45 out of 99 limbs had poor run-off score. In twelve cases the angiography was lost. In study IV, run-off score was recorded in 82 out of 87 cases. In three cases, the angiogram was missing at the time of the study and two operations were performed without a preoperative angiography.

3.4 Preoperative investigations

3.4.1 Clinical assessment. Patients whom the surgeon found to be fit for surgery were operated. There was no protocol for routine preoperative cardiac assessment.

3.4.2 Ankle-brachial pressure measurements. Ankle-brachial pressure measurements were done as standard preoperative assessment. A resting ankle-arm index < 0.9 was considered significant. This finding is diagnostic for the presence of peripheral arterial disease with a sensitivity of 95 % and a specificity of 99 % (47-49).

3.4.3 Digital Subtraction Angiography (DSA). DSA was routinely performed preoperatively. This was done with puncture of either common femoral artery. A catheter was then placed in the abdominal aorta by Seldinger technique (50,51). Contrast was injected and aortobifemoral angiography was performed.

3.5 Surgical procedures

3.5.1 Prosthetic above-knee femoropopliteal bypass (Studies I – V).

3.5.1.1 *Surgical technique.* All operations were done under epidural anesthesia. The surgical technique was uniform, with an end-to-side anastomosis between graft and native artery both proximally and distally (Figure 3). Distal end-to-side- anastomosis has been compared with end-to-end technique in a prospective randomised trial and the results of these two techniques were similar with respect to patency. However, in one study, major amputations after bypass failure were required more frequently for limbs with end-to-end anastomosis, probably due to occlusion of arterial branches cranial to the distal anastomosis when a distal end-to-end anastomosis is performed (52).

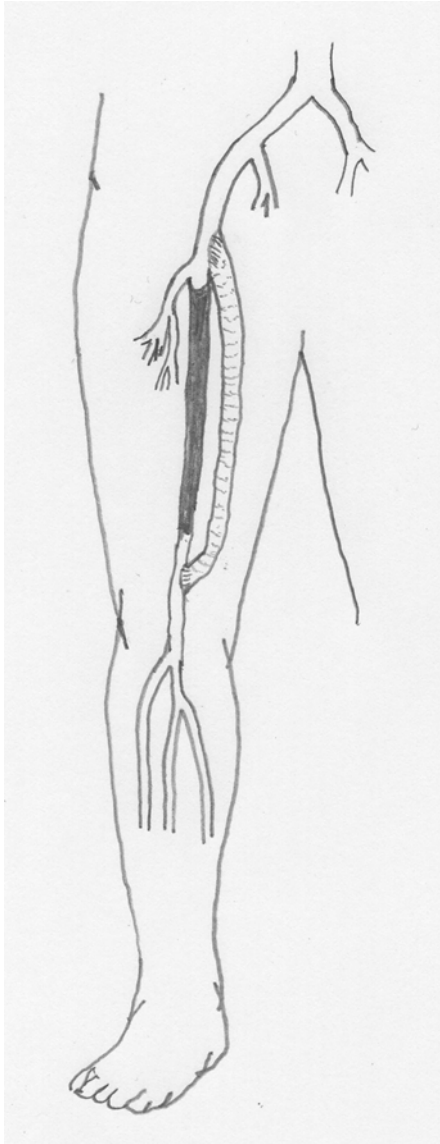


Figure 3. A polyester graft implanted as bypass from the common femoral artery to the above-knee popliteal artery in the right leg.

3.5.1.2 *Prosthetic material.* The majority of 108 PTFE-grafts were Gore-Tex[®] (W.L.Gore & Associates, Flagstaff, Ariz, USA) and most of the 144 polyester-grafts were Unigraft[®] (B Braun, Melsungen, Germany). However, a small number of grafts from other manufacturers were used during the study period. PTFE grafts were used during the first four years of the study period, and polyester grafts were used latterly. The first polyester grafts used in our department were non-impregnated. However, the vast majority of the polyester grafts were impregnated. In study IV, the graft diameter was 6 mm in 68 (78 %) cases and 8 mm in 19 cases (22 %).

3.5.1.3 *Heparin before clamping.* Before 1999, rheomacrodex was given intravenously to prevent arterial thrombosis during surgery. After 1999, heparin (5000 IU) was administered intravenously before the common femoral artery was clamped. The Heparin dosage given is in agreement with established practise in Scandinavia. A subtherapeutic dosage may have been given in some cases, especially in obese patients. Alternatively, a weight-based heparin protocol may be administered.

3.5.1.4 *Antithrombotic prophylaxis.* LMWH 2500 IU daily was administered subcutaneously to low- and medium-risk patients whereas high-risk patients received a dosage of 5000 IU daily.

3.5.1.5 *Antibiotic prophylaxis.* From 1990 to 1999, prophylaxis of cefuroxime 1.5 g was administered intravenously three times during the day of surgery with the first dosage given at induction of anaesthesia. From 1999, the antibiotic was changed to 2 g of cephalotin given in a similar way.

3.5.2 Reoperative/redo surgery. Reoperative surgery was defined as a new prosthetic bypass in cases with previous graft failure and was considered and analysed as a risk factor (Study I). A total of 17 cases underwent reoperative surgery. All of these were done for intermittent claudication. Surgical redo procedures were defined as re-opening occluded grafts. This was done surgically by an incision over the distal graft. The graft was incised and the thrombectomy was performed with a rubbered or un-rubbered graft thrombectomy catheter.

3.5.3 Revisions for anastomotic stenoses. After graft thrombectomy, the area of the anastomoses was assessed intraluminally. Anastomotic revision was done in all cases found to have an anastomosis-related stenosis.

3.5.4 Revisions for infections. The choice of surgical treatment is dependent on whether the whole graft was infected or only part of it, and of the clinical response to the antibiotic treatment. Revision for graft infection was defined as surgical revision of the tissue surrounding the graft but leaving the graft in situ.

3.5.5 Graft excision. (Study I) Excision of the graft was defined as complete removal of the graft. Excision of infected grafts was performed in selected cases with or without graft replacement.

3.5.6 Amputation. (Study I, III and V). Major amputations were recorded. Major amputations were defined as above-knee, through-knee and below-knee amputations. Thus, minor amputations as toe and forefoot amputations were not recorded. No cases were treated with Syme's operation.

3.6 Endovascular procedures

3.6.1 Percutaneous transluminal angioplasty (PTA)

PTA (studies II-V) is a minimally invasive technique for angiographically guided vascular interventions, first described by Dotter and Judkins in 1964 (53), in which the angioplasty was performed with coaxial catheters. Gruntzig et al developed a catheter with a central balloon, which is the method still used today (54,55). By the use of Seldinger technique, a balloon-catheter is inserted into the artery over a guidewire and inflated at the arterial lesion, with the intent to increase the internal diameter. This treatment method is typically applied on stenoses and short occlusions (< 3-4 cm). In the present study, PTA was done for significant graft-related stenotic lesions (> 50 % lumen reduction). All of these stenoses were localised at the distal anastomoses.

3.6.2 Intraarterial thrombolysis

(Study III and V). Intraarterial thrombolysis was done selectively for graft thrombosis. Selection criteria for choice of treatment were not clearly defined. However, patients unfit for thrombolysis according to the recommendations of the Working Party on Thrombolysis in the Management of Limb Ischaemia were selected for thrombectomy (56). The procedures were performed with crossover technique. The catheter was placed with continuous release of the thrombolytic agent into the proximal portion of the thrombus. The catheter was distalised as the thrombus dissolved. Until April 1997 Streptokinase (40 000 IE/hour) was routinely used as thrombolytic agent. Thereafter, recombinant human tissue-type plasminogen activator (rt-PA) was preferred. A bolus dose of 5 mg was injected into the thrombus, followed by a continuous infusion (1.5 mg/hour). Cases complicated with distal embolisation were managed with further thrombolysis or endovascular aspiration. Percutaneous transluminal angioplasty (PTA) after thrombolysis was done in cases with a significant stenotic lesion at the distal anastomosis. In the present studies, there were no cases with significant stenoses in the proximal anastomoses.

3.7 Transit time flowmetry

3.7.1 Theoretical background and principles

The first transit time flowmeter was described by Franklin et al (57) and Plass (58), but the theoretical basis for transit time flow measurement was described by Drost in 1978 (59). The transit time flow probe consists of two small piezoelectric crystals, one upstream and one downstream, mounted in a common tip that can be placed around the vessel without constricting it (Figure 4). The front of the probe is flat, and a small metallic reflector bracket

is mounted opposite the crystals. Each crystal can produce a wide ultrasound beam covering the entire vessel diameter. The transit times are measured for an ultrasound pulse signal emitted from the upstream crystal to arrive at the downstream crystal via the reflector and for a signal from the downstream crystal to reach the upstream electrode via the reflector. Since ultrasound travels faster when it is transmitted in the same direction as flow, a small time difference (Δt) for the two signals as expressed in a shift of phase (down to picosecond values) can be determined. All blood flow velocity components are detected by the wide ultrasound beam, and transit time determinations are sampled at all points across the vessel diameter, so the measurement of volume blood flow is theoretically independent of the blood flow velocity profile due to this integration procedure (60).

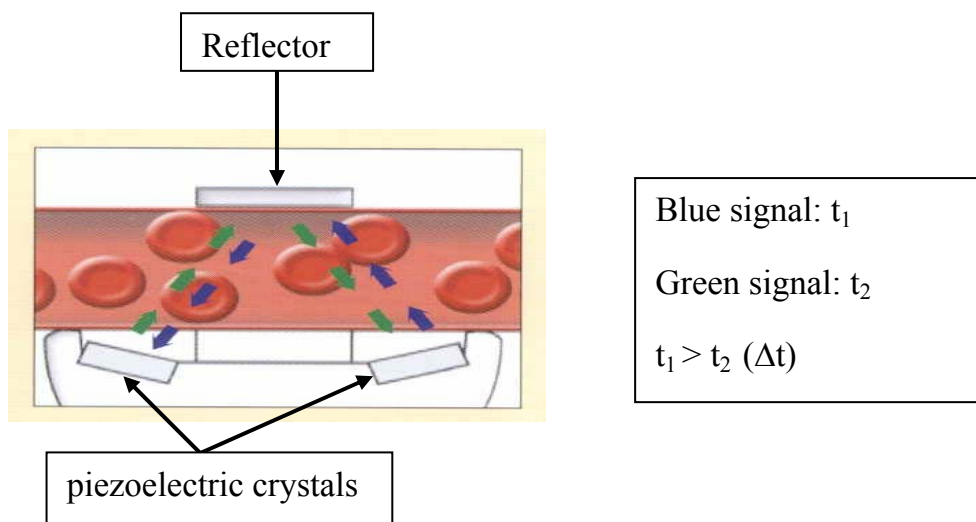


Figure 4. A transit time flow probe with two small piezoelectric crystals, mounted in a common tip placed around the vessel.

3.7.2 Validity and reliability

Transit time flowmetry has been demonstrated to be a reliable method with reproducible results (61-63). This method does not have the major disadvantages that characterise the previous methods for blood-flow

measurements; electromagnetic flowmetry and the Doppler flowmetry. In electromagnetic flowmetry, the measurement is influenced by the hematocrit, the vessel wall thickness as well as the angle between the probe and the vessel. The flow signal is unstable and the flowmeter has to be recalibrated continuously (64). The Doppler flowmeter is sensitive to the alignment between probe and vessel. This is not the case for transit time technique, but acoustic fluid (gel, blood or saline water) must be present between the probe and the vessel to ensure good acoustic coupling.

3.7.3 Clinical relevance

The method has been widely used in vascular surgery since its introduction in 1983(61). The clinical value of using transit time flowmetry is described by Lundell(65). Low values of blood-flow measurements has been reported to be predictive of early graft occlusion in infrainguinal bypass bypass surgery (66-70). A flow of ≤ 50 ml/min has been associated with failure of above-knee prostheses (69,70). Low levels of maximum capacity flow, i.e. the peak flow after intragraft injection of papaverine) have also been reported to be predictive of reduced graft patency in vein grafts (66). The relationship between papaverine flow and femoropopliteal prosthetic graft patency has not been reported previously.

3.7.4 Limitations of flowmetry in prosthetic bypass surgery

Blood flow in prostheses can only be measured indirectly with transit time flowmetry, by measuring flow in inflow or outflow arteries. This is due to the attenuation of Doppler signals in air trapped inside the prosthesis wall (60). Outflow can be measured by placing the probe distally to the reconstruction, which was done in most cases in the present studies. Alternatively, inflow can

be measured by placing the probe proximal to the reconstruction. In the present study, this was done in cases with technical difficulties in placing the probe around the popliteal artery. In these patients, the profunda femoral artery was clamped while measuring flow in the common femoral artery. If a proximal part of the superficial femoral artery was open, a higher flow volume than the actual graft flow may have been recorded. Likewise, flow measurements in the popliteal artery may not have reflected the actual graft flow volume in the femoropopliteal graft. Because the anastomoses in the present series were created end-to-side, some degree of retrograde flow from the popliteal artery may have occurred in some patients. If this was the case, the recorded flow was lower than the actual graft flow.

3.7.5 Definitions

Basal flow: The flow measurement after declamping, before injection of papaverine.

Papaverine flow: The peak flow, i.e. the maximum capacity flow, after injection of papaverine.

3.7.6 The use of flowmetry in the present study

A transit time Doppler flowmeter (CardioMed 1000, Medi-Stim AS, Oslo, Norway) was used for blood-flow measurements. The probes were precalibrated by the manufacturer and the measurement error was less than 10 %. Flow was measured with the probe placed around the popliteal artery below the distal anastomosis. Where lack of exposure prohibited flow measurement of the popliteal artery, flow was measured in the common femoral artery while clamping the profunda femoral artery. Flow was measured before and after a 40 mg intragraft injection of papaverine.

3.8 Antiplatelet medication

Aspirin 160 mg daily was given postoperatively on a permanent basis if tolerated. No other antithrombotic agent was given. Whether or not the patients were compliant to this medication was not investigated.

3.9 Complications

3.9.1 Registered complications were recorded in the database registry. A selection was made as listed below. Occlusion and death within 30 days of surgery were recorded according to the suggested standards for reporting (71). Local complications (lymphatic complications, surgical site infections, graft infection) and general complications (myocardial infarction, stroke, death within 30 days) were registered. In addition, all graft infections during follow-up were recorded (Study I).

3.9.2 Lymphatic complications.

Lymphatic fistula was defined as at least two days of persistent leakage of clear fluid from the incision (72), whereas a *lymphocele* was diagnosed in cases with a subcutaneous fluid collection in the absence of hematoma or a surgical site infection (72).

3.9.3 Local infections.

Szilagyi's clinical classification of infection was applied (73).

Grade 1. Surgical site infection confined to dermis.

Grade 2. Infection of the subcutaneous tissue without involving the graft.

Grade 3. Graft infection was diagnosed in cases with a tender, erythematous, pulsatile mass overlying the prosthetic material, and in cases with exposed graft, or if there was persistent drainage from a sinus tract close to the prosthetic material.

3.9.4 Occlusion within 30 days.

Graft occlusion occurring within 30 days of surgery was considered a complication and was recorded accordingly. Early graft occlusion is usually due to technical failure or subjection of non-eligible patients for bypass surgery (74).

3.9.5 Death within 30 days.

This information is regarded reliable in the studies of this thesis, since the mortality data were obtained from The Registrars Office for Death and Birth.

3.10 Follow-up and endpoints

3.10.1 Protocol for follow-up

Follow-up was done with duplex scanning, ankle-brachial pressure measurement and clinical assessment 1, 3, 6 and 12 months after surgery and annually thereafter. New procedures during follow-up warranted a new follow-up protocol.

3.10.2 DSA.

Angiography was performed as preoperative diagnostic work-up in cases in need for intervention.

3.10.3 Endpoints

3.10.3.1 *Paper I:* Surgical site infection or graft infection.

3.10.3.2 *Paper II:* The primary occlusion or death.

3.10.3.3 *Paper III:* The primary occlusion, the terminal occlusion, major amputation, death.

3.10.3.4 *Paper IV:* The primary occlusion.

3.10.3.5 *Paper V:* The primary occlusion, terminal occlusion, major amputation.

3.11 Statistics

3.11.1 Survival

Mortality data on the operated patients were obtained from The Registrars Office of Birth and Death. Death rate tables were obtained from a national database registry, Statistics Norway (75), and used to calculate the survival of a demographically matched population (i.e. the expected survival).

In cases with more than one operation per patient, the calculation of survival was based on the time of the first operation. Observed survival was compared with that of a demographically matched population. The relative survival was defined as the ratio of the observed survival to that of the expected. The Mantel-Haenschel test was applied to analyse the difference between observed and expected survival (76).

3.11.2 Limb salvage.

Limb salvage was defined as freedom from major amputation.

3.11.3 Patency.

The diagnosis of graft occlusion was based on duplex scanning or angiographic findings. The occlusion date was defined as either the time of verification of occlusion or recurrence of symptoms. The decision to reopen occluded grafts was based on the surgeon's opinion on the possibility and importance of salvaging the graft.

3.11.3.1 *Primary patency.* Primary patency was defined as freedom from occlusion without any procedures done on the graft.

3.11.3.2 *Primary assisted patency.* This was defined as freedom from occlusion. Treatment of stenotic lesions may or may not have been performed.

3.11.3.3 *Secondary patency.* Secondary patency was defined as an open graft which may have been subjected to one or more re-opening procedures.

3.11.4 Analyses of survival, limb salvage and patency

3.11.4.1 *Analyses of survival, limb salvage and patency rates.* These analyses were carried out with the Product-limit method. The computations are performed each time a defined event happens, i.e. death, amputation or graft occlusion. The survival rates are presented as Kaplan-Meier curves where the decreasing survival rate is illustrated stepwise. The numbers of cases still at risk are indicated along the curves. This method is recommended for such analyses in vascular surgery (77).

3.11.4.2 *Univariate analyses.* Univariate comparison of rates between subgroups was done with the log rank test. This test is a non-parametric method for testing the null-hypothesis that the groups compared are samples from equal populations with respect to survival, limb salvage or patency.

3.11.4.3 *Multivariate analyses.* Multivariate analyses of the association between risk factors and survival, limb salvage and patency rates were performed with the Cox proportion hazard model (77).

Cox' method is a "semi-parametric" approach – no particular distribution is assumed for the survival times, but an assumption is made that the effects of the different variables on survival, limb salvage or patency are constant over time and are additive. The intercorrelation of variables included in the analysis is explored, accounting for variable observation times. In the present context it means calculation accounting for the relative impact of concurrent diseases and other risk factors on survival, limb salvage or patency. Interpreting a Cox model involves exploring the coefficient for each explanatory variable. A positive regression coefficient (β) for an explanatory variable means that the hazard is higher, and thus the prognosis worse for higher values. Conversely, a negative regression coefficient implies a better prognosis for a higher value. The hazard ratio is $\text{Exp}(\beta)$.

3.11.5 Categorical data

The Fisher exact test was applied for comparison of categorical data. This test is considered more accurate than the standard Chi square test, especially for small sample sizes (78).

3.11.6 Continuous data

The Student t-test was used to compare continuous data. The t-test is appropriate when you have continuous values in two groups and wish to test the difference of means (79). The Student's t-test is a parametric test assuming a normal distribution. In this study, mean age differences between men and women are compared.

3.11.7 Software program

For paper I and II, the software "Statistica 6.0" (Statsoft, Inc., Tulsa, OK, USA) was used for statistical computations. For paper III – V, the software "SPSS for Windows 13.0" (SPSS Inc. (2004), Illinois, USA) was used.

3.11.8 Statistical significance

Differences were considered statistically significant at $p < 0.05$.

4. General discussion

4.1 General discussion

4.1.1 Reporting standards.

Suggested standards for reports dealing with lower extremity ischemia were published in 1986 in Journal of Vascular Surgery (71). In 1997, a revised edition of recommended standards was published (80).

According to these, quite a number of issues need to be addressed: the degree of lower limb ischemia, outcome criteria, risk factors (comorbidity, run-off), death and complications. Grafts used should be reported with graft material, manufacturer, graft diameter and coating of the graft. Furthermore, operative techniques (anastomoses etc.) should be described. Thus, of the five studies in the present Thesis, study IV only satisfies the suggested standards.

4.1.2 Treatment options for femoropopliteal occlusive disease

4.1.2.1 *Medical treatment.* Modern medical treatment of lower limb ischemia consists of smoking cessation, systematic exercise and modification of risk factors for atherosclerosis including specific medication. This treatment may be described as “best medical treatment”. All patients with peripheral arterial disease should receive best medical treatment. This is documented below in this chapter.

4.1.2.1.1 **Smoking** is discussed in 3.3.2. It is mandatory that smokers receive information on the great benefit of smoking cessation, i.e. the

magnitude of smoking as a risk factor for poor results after femoropopliteal bypass surgery.

4.1.2.1.2 **Excercise.** Randomised controlled trials have proven that systematic exercise improves walking distance significantly in patients with intermittent claudication. According to a meta-analysis of such studies, walking distance may be improved approximately 150 % by 30 minutes walking exercise minimum three times per week (81). Thre preventive effect of exercise on risk of cardiovascular events is an extra bonus of this treatment (82,83).

4.1.2.1.3 **Medication.** Aspirin is effective in preventing thromboembolic disease and patients with peripheral atherosclerosis should therefore receive a daily dosage of aspirin (84-87). Patients with have aspirin-intolerance should receive clopidogrel instead (86). Treatment with ACE-inhibitors reduces the risk of cardiovascular events by 25 % per year in patients with peripheral vascular disease (88,89). According to the HPS-study, the same reduction in cardiovascular morbidity can be achieved with the use of statins (90). Statins are reported to reduce inflammation in atherosclerotic plaques as well as plaque-thickness (91). Use of statins has also been proven to improve walking capacity in claudicants (92,93). Patients with chronic limb ischaemia would thus benefit from a triplet basis medication: an antiplatelet agent, an ACE-inhibitor and a statin. This medication regimen has been standard treatment in our department since 2002.

Antithrombotic medication following bypass surgery is discussed in 4.1.3.

4.1.2.2 *Endovascular treatment.*

4.1.2.2.1 PTA. PTA can be used for treatment of arterial stenoses and short (3-4 cm) occlusions. This method is not suitable for treatment of long lesions due to low technical success rate and poor patency and should be reserved for TASC-A and -B lesions (94).

4.1.2.2.2 Subintimal angioplasty. This technique was first describe by Bolia et al. in 1990 (95). In 1994, the same group published long-term results, suggesting subintimal angioplasty as a useful alternative to bypass surgery (96). The common femoral artery is punctured on the ipsilateral side. Subintimal entry is achieved by pushing a 5 French straight angiography catheter into the lesion. The occluded segment is then traversed with a .035`` hydrophilic guidewire (Terumo). The tip of the guidewire is looped during the passage and followed by a 5 French straight catheter. After reentry at the distal end of the lesion, the subintimal passage is dilated with either a 5 or 6 mm balloon angioplasty catheter. A few centres have reported good results using subintimal angioplasty (97-100). However, patients in these studies often had intermittent claudication and follow-up has not always been with duplex (4). Other centres have experienced poorer results after subintimal angioplasty (4,101). It appears that this treatment method is only successful in the hands of few.

4.1.2.2.3 Metal stents. Metal stents became commercially available in the early 1990's. Many trials have been performed to investigate the results of treatment with stents for femoropopliteal occlusive disease. The results reported are often in terms of 12-monts patency rates of 50 – 60 % (102,103). These results are not superior to treatment with PTA alone

(104). In our department, a stent is used only for salvaging a technical unsuccessful PTA due to recoil or dissection. The outcomes of these salvaging procedures have been proven similar to PTA and stent as a primary procedure (105).

4.1.2.2.4 Absorbable metal stents. Biodegradable stents basically made of magnesium have been used in treating infrapopliteal lesions with acceptable short-term results. This stent permits the use of MRI in follow-up after the stent has been absorbed (106). Long-term results are lacking, but this stent may have a potential in treating atherosclerotic lesions in the superficial femoral and popliteal artery.

4.1.2.2.5 Drug-eluting stents. Drug-eluting stents became available for use in peripheral vascular surgery in 2003. Basically, the stent has an inner coating in which a slow-releasing drug is deposited. Examples of drugs used for this purpose are sirolimus and tacrolimus. Drug-eluting stents were expected to improve performance compared with the metal stents available on the market for some years. This optimism was based on the promising reports on drug-eluting stents in the coronary arteries. However, randomised controlled trials have revealed patency in the same range as for metal stents without the drug coating (107,107). Furthermore, drug-eluting stents do not seem effective in treating in-stent restenosis (108).

4.1.2.2.6 Hemobahn[®]/Viabahn[®]. These devices are long metal stents with an inner covering of PTFE. Initially, this device was manufactured as Hemobahn[®]. In 2004, the device was slightly modified, and the name was changed to Viabahn[®]. Long occlusions are supposed to be the primary indication for covered stents in femoropopliteal occlusive disease. A one-year patency rate of 58 % has been reported in a feasibility study (109). As for subintimal angioplasty, good results seem

to be achieved only in the hands of the few, which may explain the not so widespread use of the technique.

4.1.2.2.7 Other endovascular treatment methods. Publications do exist of treatment methods such as the excimer laser (110) and endovascular atherectomy (111) for infrainguinal atherosclerotic lesions. Furthermore, endovascular cryotherapy (112) and brachytherapy (113) has been used in combination with PTA. However, none of the above-mentioned methods are proven effective and their use is not widespread.

4.1.2.3 *Surgical treatment.*

4.1.2.3.1 Bypass surgery. In these procedures, a vein or a prosthetic graft is used as conduit. The technique for prosthetic graft bypass is described in 3.5.1. Vein grafts may be used either in situ or in the reversed fashion. Veins must have good quality in order to be accepted as conduit in bypass surgery. Vein bypass is somewhat more time-consuming as compared with prosthetic bypass. A more detailed presentation of vein grafting is considered beyond the scope of this thesis.

4.1.2.4 Open endarterectomy of the superficial femoral artery. This treatment option is seldom used, although acceptable long-term results have been reported for lesions localised in the adductor canal (114). Thus, this method should be remembered as an alternative for selected cases with critical limb ischaemia, in which other treatment options not are available.

4.1.2.5 Remote endarterectomy (ring-stripping a.m. Moll). This procedure is carried out with a groin incision only, with open access to the common femoral artery. The atherosclerotic plaque is removed by the use of a modified ring stripper, cutting the intima at the distal end. The

procedure includes placement of a covered stent at the end of the endarterectomy (115). This method has been reported with acceptable results up to 18 months (116). However, remote endarterectomy is not in widespread use, and acceptable results have only been reported from a few centres. Thus, it appears that this method, like subintimal angioplasty and Hemobahn[®]/Viabahn[®], works well in the hands of few only.

4.1.3 Antithrombotic therapy after bypass surgery

Antiplatelet agents improve graft patency, especially for prosthetic grafts (117). Patients with aspirin intolerance should therefore receive clopidogrel (117). Warfarin has been reported to have an effect in preventing occlusion in infrainguinal vein grafts, but not in prosthetic grafts(118). Long-term injection of heparin was in 1988 proven to reduce neointimal hyperplasia in an animal study(119). In 1994, results came forth from a trial where 200 femoropopliteal bypasses were randomised to either three months treatment with subcutaneous low-molecular-weight heparin (LMWH) or low-dose aspirin and dipyridole (120). After 12 months, patency was 87 % in the LMWH-group and 72 % in the antiplatelet group. The difference was statistically significant. However, the publication of these results did not alter clinical practice. In our department, LMWH is given for four weeks after surgery in cases believed to be at high risk for occlusion.

4.1.4 Choice of treatment for femoropopliteal occlusive disease – conservative treatment, endovascular treatment or bypass surgery?

4.1.4.1 *Intermittent claudication.* Invasive treatment for intermittent claudication has hitherto not been found to improve survival of patients with peripheral atherosclerosis. However, a secondary health effect on cardiac function might occur in some patients due to improved walking capacity. Treatment of intermittent claudication may enhance quality-of-life but to a variable extent. The effect seems unrelated to the initial and absolute claudication distances, but more to in which manner the condition affects the patient. Therefore, patients need to be evaluated individually. There is a need for more studies on how quality-of-life actually is affected by intermittent claudication (121).

For intermittent claudication caused by lesions in the femoropopliteal segment, there is consensus on a conservative strategy (122-124). This is due to the benign nature of intermittent claudication, with an amputation risk of approximately 1 % per year (125,126). In fact, even very low complication rates after intervention may lead to an amputation risk exceeding that of the natural history.

Subintimal angioplasty has limited durability, but performs better when done for intermittent claudication as compared with critical ischaemia (4,97). Subintimal angioplasty is accepted in our department as the first treatment option for severely disabled claudicants with unilateral disease. However, the patients must have had a stable disease and been on medical treatment for at least six months. In cases with a failing subintimal angioplasty, bypass is done on patients with severely disabling intermittent claudication. Autologous vein is preferred over prosthesis as conduit in above-knee femoropopliteal bypass in our department, and prostheses are used only when a suitable vein is lacking.

4.1.4.2 *Critical ischaemia.* A recently published randomised controlled trial comparing endovascular treatment with bypass surgery for critical ischemia (BASIL) revealed long-term results (i.e. > 2 years) in favour of bypass surgery (127). The results from this study indicate that bypass should be preferred to endovascular procedures for patients with life expectancy beyond two years. Bypass-surgery-first and PTA-first strategy was associated with similar outcome in terms of amputation-free survival up to two years after treatment. In the short term (< 12 months), surgery was more expensive than angioplasty. Patients with critical leg ischaemia are often elderly with extensive comorbidity, and open surgery might not always be an option. Thus, the two treatment modalities, endovascular treatment versus bypass surgery, appear in many cases not to be two competitive but rather complementary treatments options.

At Haukeland University Hospital, subintimal angioplasty is preferred as the treatment choice for critical limb ischaemia in cases with anatomically suitable lesions. Duplex assessment of the reconstruction is performed within a week, due to the low patency rates of subintimal angioplasty. In cases of a failed subintimal angioplasty, a femoropopliteal vein bypass is the next step. Prosthetic bypass is only done in cases lacking suitable vein.

4.1.5 Graft-types for bypass

4.1.5.1 *PTFE.* Polytetrafluorene (Goretex[®]) prostheses were used during the first four years of the studies included in this Thesis. PTFE is manufactured with and without circular rings to support and maintain an

open lumen in cases with low diameter, low flow or substantial external pressure forces.

- 4.1.5.2** *Polyester.* Polyester graft was the preferred conduit for prosthetic bypass in our department from 1994 until now. Polyester grafts may be knitted or woven, and impregnated or not. The majority of prostheses in the present study were of polyester (dacron) and most of them were impregnated, except during the first years of the study.
- 4.1.5.3** *Human umbilical vein (HUV).* HUV-grafts are reported to have long-term patency rates in the same range as autologous vein (128). However, a main disadvantage of HUV is the formation of aneurysms, which may occur in 20 % at five years (129).
- 4.1.5.4** *Modifications of prosthetic grafts.* Some prostheses are manufactured with an additional external or internal layer, for instance a gelatin-layer or an external covering. PTFE-grafts are now available with an inner layer containing immobilised heparin. Polyester grafts are also available with silver-impregnation and some grafts may be soaked in antibiotics before implantation, for instance rifampicin, provided there is a gelatin coating for deposition and binding of the drug.
- 4.1.5.5** *Autologous vein.* Vein as conduit may be used *in situ* or in the *reversed* fashion. Preferably, the great saphenous vein is used. However, the lesser saphenous vein, the Giacomini vein or even veins from the upper extremity may be used with acceptable long-term results (130-132).
- 4.1.5.6** *Autologous artery.* An excised occluded artery may be used as bypass after ring stripping, for example the superficial femoral artery.
- 4.1.5.7** *Homologous artery or vein.* Arteries and veins have been harvested from donors of transplant organs and used as conduits in peripheral vascular reconstructions (133). Alloveins harvested during varicose vein

stripping have also been used (134). However, the use of homografts in peripheral vascular surgery is an ethical dilemma, especially since prosthetic grafts are readily available. Therefore, the use of homografts is not considered acceptable practice in peripheral vascular surgery.

4.1.6 Prosthetic graft diameter

Whether or not graft diameter influences the results of above-knee prosthetic bypass has been studied previously. Three-year results from a prospective, randomised multi-center trial comparing PTFE and polyester grafts were published in 1997 (1), and five-year results were published in 2000 (25). The three-year patency rates for small (< 7 mm) and large grafts (> 7 mm) were 60 % and 80 % respectively. Grafts with diameter less than 7 mm also had inferior patency at five years compared to grafts with diameter above 7 mm. However, the difference was found to be sex-dependant. The five-year primary patency rates for men with small and large grafts were 37.9 and 69.1%, respectively. Similar comparisons for women revealed five-year patency rates of 45 % for both small and large grafts.

Since 1997, 8 mm grafts have been used as standard size for above-knee femoropopliteal prostheses at Haukeland University Hospital, except for cases with small-caliber arteries, usually women, in which 6 mm grafts were chosen. Before 1997, 6 mm grafts were mainly used. Thus, the majority of the grafts in the present study are 6 mm. It is not known if the use of larger grafts in men would have influenced the results in the present study.

4.1.7 The use of above-knee prosthetic femoropopliteal bypass

4.1.7.1 *Graft type.* In the present studies, 144 were polyester and 108 were PTFE. There were no differences in results between the graft types, nor were there any differences in the distribution of complications. The same finding has been reported previously (1,26). Mathisen et al demonstrated that PTFE was more prone to platelet aggregation on the luminal surface as compared with polyester (135). However, this remains to be proven in a clinical setting.

4.1.7.2 *The use of femoropopliteal grafts at Haukeland University Hospital.* The total numbers of femoropopliteal bypasses performed at Haukeland University Hospital during the study period was 388, of which 279 were above-knee bypasses and 109 were below-knee. In above-knee femoropopliteal bypass, a vein was used as conduit in 27 cases, whereas prosthesis was used in 252 cases. For below-knee femoropopliteal bypass, an autologous vein was used in 75 cases, HUV in two cases, a composite graft in 13 cases and a prosthetic graft in 19 cases.

4.1.7.3 *Time trends.* The yearly number of prosthetic bypass procedures inclined to a peak in 1994-1995 and then declined (Figure 2). The reduction in yearly operations is concomitant in time with the introduction of subintimal angioplasty in our department, which was in 1997. From 1997 throughout 2001, a total of 124 femoropopliteal subintimal angioplasties were done.

4.1.7.4 *Prosthetic grafts versus autologous vein.* Similar results for prosthetic grafts versus autologous vein used as conduit in the above-knee position have been reported (136). However, a metaanalysis published in 2004 concluded that vein is superior to prosthesis in the femoropopliteal above-knee position (137).

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- 4.1.7.5** *Sparing the saphenous vein.* Sparing the saphenous vein for later coronary bypass has been used as an argument for using prosthetic grafts. However, only 1 % of patients undergoing infrainguinal bypass surgery will later need the vein for this or other purposes (138).
- 4.1.7.6** *Advantages and disadvantages of prosthetic grafts.* The main advantages of prosthetic grafts are that they are readily available for use and that the operation becomes less time-consuming as compared with vein bypass. The main disadvantages are the susceptibility to infection and the limited durability with respect to patency.
- 4.1.7.7** *Impact of flow on the fate of femoropopliteal prostheses.* In the present study (Paper IV), basal flow was not related to patency but papaverine flow was. High-flow reconstructions like aortoiliac or aortofemoral bypass have good long-term results, whereas infrainguinal bypass operations have limited durability. An experimental study revealed that high-flow arterial reconstructions develop less intimal hyperplasia than low-flow reconstructions do and conversion from a low-flow bypass to a high-flow bypass in a baboon model showed regression of neointimal hyperplasia (139).

4.1.8 Graft surveillance.

The results in studies III and V indicate a possible gain from surveillance and that a long observation period is necessary to achieve full overview. A possible gain from graft surveillance has been reported previously. A randomised study revealed significant better patency of grafts subjected to a duplex surveillance program due to detection of stenoses subsequently successfully treated (140). However, surveillance of vein grafts has been reported not to improve limb salvage in another randomised study (141).

The majority of occluded grafts in the present study were not identified with significant graft-related stenotic lesions. Occlusion may be attributed to the thrombogenicity of the prostheses, but also to risk factors influencing patency, as demonstrated in the present studies. Perhaps grafts with stenoses of less than 50 % lumen diameter reduction are prone to graft occlusion, and that these stenoses should be more liberally revised. However, data to prove this are not available.

The results in the present studies underline the need of a long observation period to achieve full overview. Examples are late graft infections in Study I and the increasing difference in patency over time between smokers and non-smokers (Study III and IV).

5. Results and discussion of specific papers

5.1 **Paper I. Local infections after above-knee prosthetic femoropopliteal bypass for intermittent claudication.**

5.1.1 Results. Local infections were found during follow-up in approximately 20 % of the operations, surgical site infection in 8 % and graft infection in 12 %. Lymphatic complications were recognised after 13 % of the operations. The risk of developing a local infection was significantly correlated with postoperative lymph fistula, and reoperative surgery was associated with graft infection. Graft infection caused by *Staphylococcus aureus* always warranted surgery, either local revision or graft excision.

5.1.2 Discussion. The infection rate in this study is higher than several previous reports. The high infection rate is partly explained by the wide definition of infectious complication applied in this study and by the long observation period, revealing four very late graft infections. The results suggest a conservative attitude towards prosthetic femoropopliteal bypass for intermittent claudication.

5.2 **Paper II: The impact of comorbidity on long-term results of above-knee prosthetic femoropopliteal bypass for intermittent claudication.**

5.2.1 Results. The five-year survival was 77 %, which is significantly lower than the survival of a demographically matched population (85 %). Preoperative serum-creatinine > 125 µmol/l was significantly associated with reduced survival ($p < 0.01$). The assisted primary patency rates

were 62 % at two years and 44 % at five years. The five-year patency rate for smokers was 24 % versus 67 % for non-smokers ($p < 0.01$). A previous history of a cerebral infarction was significantly associated with reduced graft patency ($p = 0.02$).

5.2.2 Discussion. Smokers should be treated more conservatively due to their inferior patency rates. In contrast to what was seen in non-smokers, the grafts in smokers continued to occlude beyond eighteen months postoperatively and the difference between patency rates of grafts in smokers and non-smokers increased with time. The reduced graft patency rates of patients with a preoperative history of a cerebral insult need further studies to be verified.

5.3 Paper III: The impact of patient characteristics on long-term results of above-knee prosthetic femoropopliteal bypass for critical ischaemia.

5.3.1 Results. The 30-day mortality rate was 5.5 %. The 2- and 5-year survival was 72 % and 42 %, respectively. Twenty-seven limbs were subjected to major amputations during follow-up. The limb salvage rates at 2 and 5 years were 83 % and 73 %. The 2 and 5-year assisted primary patency rates for smokers were 38 % versus 62 % for non-smokers. Smoking and tissue loss were significantly associated with reduced secondary patency rates on multivariate analysis.

5.3.2 Discussion. The 5.5 % 30-day mortality rate (six patients) may be reduced by a more careful selection of patients for surgery. Five patients died from a coronary infarction and one from a cerebral stroke. This suggests a possible benefit from preoperative cardiac assessment, or at least a troponine assessment. Smokers had inferior patency rates. As demonstrated in study II, the difference between patency rates of grafts

in smokers and non-smokers increased with time, but in this study the difference became apparent after one year postoperatively.

5.4 Paper IV: Flow measurement before and after intragraft papaverine injection in above-knee prosthetic femoropopliteal bypass.

5.4.1 Results. Basal flow measurements were not related to patency. The 2- and 5-year patency rates for grafts with a papaverine flow < 500 ml/min were 48 % and 18 % compared with 66 % and 52 % for grafts with a papaverine flow \geq 500 ml/min. These differences were statistically significant ($p = 0.012$, hazard ratio 2.6). Two- and 5-year patency rates for smokers vs non-smokers were 44 % and 18 % vs 69 % and 54 %. The patency rates for patients with poor vs good run-off were 42 % and 27 % vs 69 % and 31 %. Smoking ($p = 0.008$, hazard ratio 2.75) and poor run-off score ($p = 0.009$, hazard ratio 2.38) were found to be independent risk factors for reduced patency rates. Poor run-off score did not correlate with low values of measured basal or papaverine flow.

5.4.2 Discussion. Additional antithrombotic medication and frequent follow-up for grafts with a papaverine flow < 500 ml/min may be considered. The inferior patency of smokers and patients with poor run-off indicate that prosthetic bypass is less suitable for these groups of patients.

5.5 Paper V: The outcome of occluded above-knee femoropopliteal prostheses implanted for critical ischaemia.

5.5.1 Results. The one-year patency rate for redo procedures was 12 %. Cases in which a pre-existing anastomotic stenosis was identified and treated fared significantly better, although only 4/10 of these cases were alive with open graft one year postoperatively.

5.5.2 Discussion. The results were disappointing. Some patients may benefit from a redo procedure if a stenotic lesion is known prior to graft occlusion. All other patients with a need for intervention should be treated with a new arterial reconstruction or amputation.

6. Conclusions

From this study the following conclusion might be drawn:

- The results regarding survival, limb salvage and patency correspond with previous reports.
- A long observation period is necessary to achieve full overview of complications and of the impact of risk factors on the results.
- Infectious complications after prosthetic femoropopliteal bypass were higher than in previous reports.
- A selective approach should be taken towards excision of infected femoropopliteal prostheses, and surgical treatment should be individualised according to the clinical presentation of the graft infection and the type of bacteriae involved.
- A conservative attitude is recommended towards above-knee prosthetic femoropopliteal bypass for intermittent claudication.
- Smokers have inferior patency rates when operated for intermittent claudication as well as for critical ischaemia, indicating that prosthetic femoropopliteal bypass is not very suitable for smokers.
- The reduced graft patency rates of patients with a history of a cerebral insult operated for intermittent claudication need further studies to be verified.
- Patients with intermittent claudication and renal impairment reveal poor survival, indicating renal impairment as a relative contraindication for surgical treatment of intermittent claudication.

- The poor secondary patency rates for smokers as well as for patients with tissue loss suggest that these patients may benefit from alternative treatment modalities instead of reopening an occluded bypass.
- Papaverine flow of < 500 ml/min is associated with reduced mid- and long-term patency rates of above-knee femoropopliteal prosthetic bypass.
- Additional antithrombotic medication and frequent follow-up may be considered for grafts with a papaverine flow less than 500 ml/min.
- The inferior patency rates of patients with poor run-off indicate that prosthetic bypass is less suitable for these patients.
- Redo procedures for occluded grafts originally implanted for critical ischaemia are of limited value and cannot be recommended except in cases with a proven graft-related stenosis. Other cases in need of re-intervention should be treated by amputation or a new arterial reconstruction.
- When offering an above-knee prosthetic femoropopliteal bypass as treatment, the following must be evaluated: patient comorbidity, degree of ischaemia, affection on quality-of-life and anatomical-pathological considerations as the atherosclerotic lesion and the angiographic run-off score.

Risk factor	Reduced patency
Smoking	+++
Papaverine flow < 500 ml/min	++
Critical ischaemia vs intermittent claudication	++
Poor run-off score	++
Tissue loss vs rest pain	+
Preoperative cerebral insult	+

Table III. Table III demonstrates the relationship between studied risk factors and reduced patency of above-knee prosthetic femoropopliteal bypass.

7. Future perspectives

The findings in this study suggest that the following topics might be studied in order to improve the results of above-knee prosthetic femoropopliteal bypass surgery:

- 7.1 *Therapeutical advances in antithrombotic medication.* A possible effect of additional platelet inhibition on patency might be studied in a randomised trial, i.e. aspirin + placebo versus aspirin + clopidogrel. This would be of particular interest for the subgroups with poor results such as low flow grafts, smokers, critical ischaemia, poor run-off and tissue loss. An ongoing study (the CASPAR-study) investigates this.
- 7.2 *Advances in risk modification.* Smoking cessation has the greatest potential for graft patency improval. Varenicline (nicotine acetylcholine receptor agonist) is reported to give better results with respect to smoking cessation as compared with bupropione (142). The impact of active anti-smoking therapy might be subjected to clinical investigation in peripheral bypass surgery. Since the study period (i.e. after 2001), medical treatment of atherosclerosis has been implemented as standard treatment in vascular surgery whether patients are operated on or not. Whether or not such anti-atherosclerotic treatment would have affected the results in the present study is not known. The possible benefit of preoperative cardiological assessment in improving the results after peripheral bypass surgery might be tested in a clinical trial. Advances in detection of and management of diabetes mellitus may also improve results after peripheral bypass surgery. As discussed previously, we are currently investigating this in a prospective trial at Haukeland University Hospital.

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- 7.3 *More aggressive treatment of graft-related stenoses.* It is not obvious that a 50 % lumen diameter reduction in the anastomotic region is a clear-cut indication for anastomosis-revision. Graft-related stenoses less than 50 % might have the potential to cause graft occlusion. This may be studied in a clinical trial, although such a trial might be difficult to organise due to the low number of these operations performed.
- 7.4 *Development in graft engineering.* The subgroups with even the best results after above-knee femoropopliteal bypass surgery demonstrate the need for grafts with better performance. Reports with promising results after using a new PTFE-graft with an interior coating of immobilised heparin have been published (143-145). However, these are only observational studies on selected patients. External scaffolding has been proven effective in experimental studies (146,147). Recently, a PEG-hirudin/iloprost coating was proven effective in prevention of intimal hyperplasia formation in a canine model(148).
- 7.5 *Studies on Quality-of-life.* This would be particularly helpful in selecting patients for surgery and it might influence indications for intervention in the future. However, the indication for prosthetic femoropopliteal bypass would probably still be severe disabling intermittent claudication in cases lacking vein, unless progress in graft engineering with substantially improved graft performance will occur.
- 7.6 *Vacuum Assisted closure (VAC).* VAC gives the opportunity for in-situ treatment of graft infection (149). This treatment alternative may reduce the need for surgical procedures, especially graft excision, in cases with graft infection (149).
- 7.7 *Advances in endovascular techniques and devices.* Improvements in devices for endovascular treatment might enhance results of these procedures, and perhaps reduce the need for surgical treatment.

8. Strengths and weaknesses

8.1 Strengths

- 8.1.1 *Prospectively recorded data.* Most of the data analysed were prospectively registered in a database.
- 8.1.2 *Surveillance program.* All cases entered a protocol for regular follow-up which included duplex ultrasound and ankle-brachial pressure measurement. This allows an acceptable precision in determining the time of events.
- 8.1.3 *Sample size.* Two-hundred-and-fifty-two prostheses implanted on 237 patients constitute a relatively large material.
- 8.1.4 *Surgical technique.* The creation of anastomoses during graft implantation was uniform. This reduces the possibility of variations in surgical technique influencing the results.
- 8.1.5 *PTA of graft-related stenoses.* The definition of success of PTA performed on a graft-related stenosis was based on the evaluation of completion angiography. However, these cases entered a new follow-up protocol including duplex investigation, ensuring that residual stenoses were not present.
- 8.1.6 *Long follow-up.* The long follow-up period in studies I – IV provides a true picture of complications and patency rates.
- 8.1.7 *Accuracy of mortality data.* The use of data from the Registrars office for births and deaths leaves a high degree of accuracy.

8.2 Weaknesses

- 8.2.1 *Retrospective analyses.* Studies I – V are retrospectively analysed. Thus, selection bias may influence results. Furthermore, the case series is uncontrolled.
- 8.2.2 *Single-center experience.* Usually single-center studies do not include large scale number of patients, which may be the case in multicenter studies.
- 8.2.3 *Preoperative investigations.* Preoperative assessments were based upon statements made by the patients, ankle-brachial pressure measurements and angiography. Treadmill testing of patients with intermittent claudication and toe pressure measurements in patients with critical ischaemia have been used during the later years. This allows a more objective evaluation.
- 8.2.4 *Sample size.* The small sample size and few events, especially in study I and V, may be considered a weakness.
- 8.2.5 *Postoperative medication.* There are no data confirming the use of aspirin postoperatively. The only information given is that aspirin was administered to all patients except in cases with aspirin intolerance. Whether or not the patients were compliant to this medication and how this may have influenced the results are not known.

9. Errata

Paper I

In study I, chronic lung disease was recorded. This information is unaccurate, since the patients had COPD, which was actually registered in the vascular database. This is corrected in study II – V.

Paper II

None errors have been detected in this paper.

Paper III

Page 2, line 20: "All operations were done by specialist in vascular surgery". This is not correct due to the fact that some of the operations were performed by surgeons-in-training.

Page 3, Graft patency, third paragraph: "The association between smoking and reduced secondary patency was also significant in univariate analysis ($P = 0.20$, log rank test)". The p-value is incorrect. The correct p-value is 0.020.

Paper IV

Abstract, line 1 and 2: “The 2- and 5-year patency rates for grafts with a papaverine flow \leq 500 ml/min....” should be corrected to: “...a papaverine flow $<$ 500 ml/min.

Patients and Methods, 1. Paragraph: Numbers of 6 and 8 mm grafts: Numbers should be reversed.

Paper V

Abstract, results, line 1: “restored” should be replaced with “restore”.

10. Appendix

Type	Anatomical lesions
TASC-A	1. Single stenosis < 3 cm, not at the origin of the superficial femoral artery or at the distal popliteal artery
TASC-B	2. Single stenosis 3-5 cm, not involving the distal popliteal artery 3. Heavily calcified stenoses < 3cm 4. Multiple lesions < 3 cm (stenoses or occlusions) 5. Single or multiple lesions in the absence of continuous tibial run-off to improve inflow for distal surgical bypass
TASC-C	6. Single stenosis or occlusion > 5 cm 7. Multiple stenoses or occlusions, each 3-5 cm, with or without heavy calcification
TASC-D	8. Complete common femoral artery or superficial artery occlusions, or complete popliteal and proximal trifurcation occlusions

Table I. Morphological stratification of femoropopliteal atherosclerotic lesions according to the TASC document (11).

Stage	Clinical presentation
Stage 1	No symptoms
Stage 2	Intermittent claudication
Stage 3	Rest pain due to critical ischaemia
Stage 4	Tissue loss (ulcer or gangrena)

Table II. Fontaine classification of lower limb ischemia in non-diabetic patients.

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