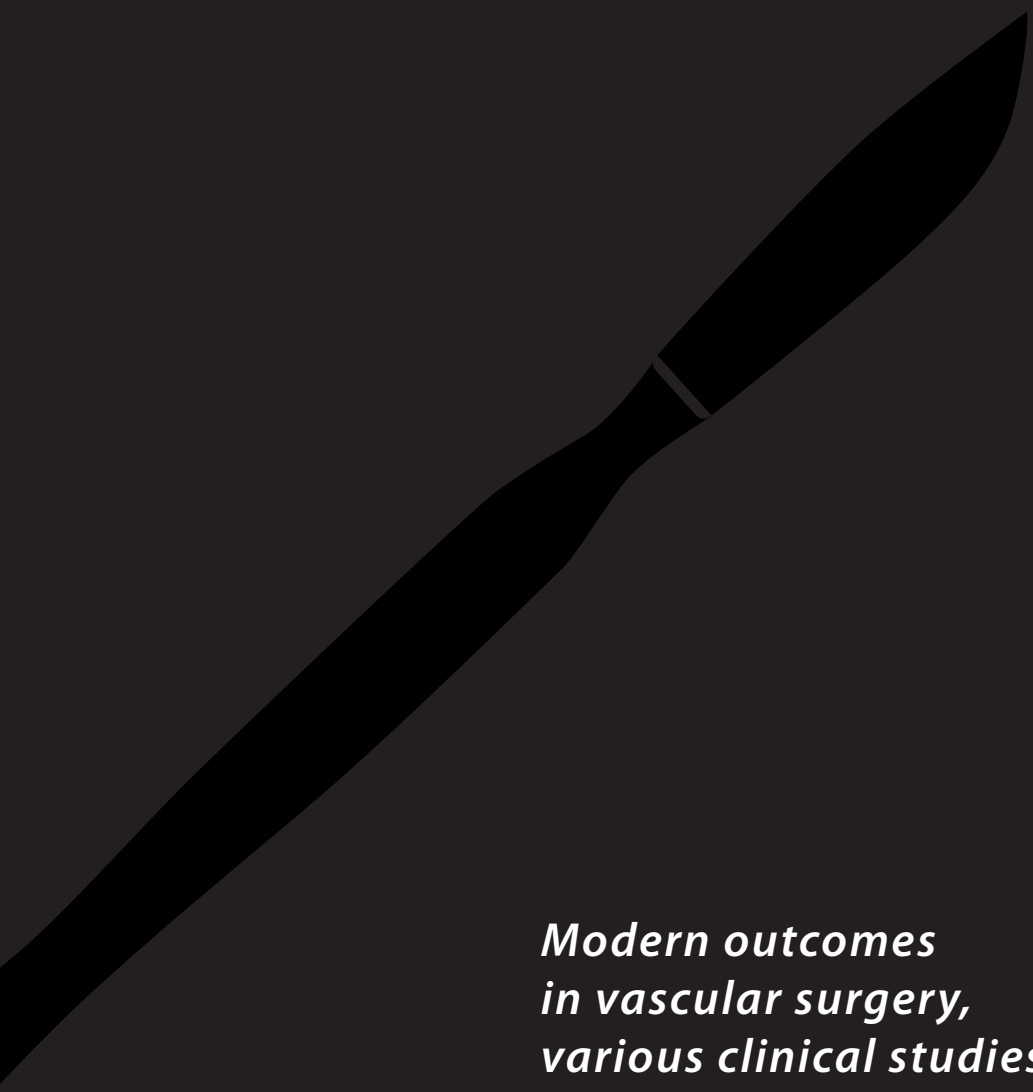

Modern outcomes in vascular surgery, various clinical studies

Jeroen Martinus Willem Donker

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MODERN OUTCOMES IN VASCULAR SURGERY, VARIOUS CLINICAL STUDIES

Moderne uitkomstmaten in de vaatchirurgie, verschillende klinische onderzoeken

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	Prof.dr. A. van Belkum
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CONTENTS: MODERN OUTCOMES IN VASCULAR SURGERY, VARIOUS STUDIES

Chapter 1

Introduction

INTRODUCTION

Peripheral Arterial Disease (PAD) is commonly caused by atherosclerosis of peripheral arteries. The prevalence of PAD is 3-10% in the modern population, and ranges up to 15-20% in the elderly population.[1-3] Patients with PAD can be treated either with exercise therapy, or with revascularization. In patients with critical limb ischemia there is an indication for a revascularization procedure, which can be performed by either a percutaneous transluminal angioplasty (PTA) or, when this is not possible (because of technical limitations, patient's co morbidities or lesion anatomy), by peripheral bypass surgery. Main outcomes of surgical vascular interventions include (graft) patency, limb salvage and surgery related morbidity and mortality.[4]

The graft of choice in peripheral bypass surgery is the autologous saphenous vein (ASV). However, a number of patients do not have a good quality ASV available to be used as a peripheral bypass graft [5, 6]. In these patients, there is a need for an alternative for the ASV graft. Commonly used prosthetic conduits are grafts made of expanded polytetrafluoroethylene (ePTFE). Patency rates of supragenicular ePTFE bypass grafts are comparable to autologous bypass grafts [7-9]. In contrast, ePTFE infragenicular and femorocrural bypass grafts perform worse than venous bypass grafts.

Refinements in the graft design, such as the addition of a venous Miller cuff or a St Mary booth at the distal anastomosis, have been advocated to improve the results of a prosthetic graft [10]. Alternatively, pre-cuffed ePTFE grafts were developed, which have specially designed cuff at the distal anastomosis, thereby optimizing flow. These grafts have comparable patency rates as ePTFE grafts with a venous cuff. [11]

As little is known on performance off these pre-cuffed grafts in the normal PAD population, we conducted a study to analyze pre-cuffed PTFE graft performance.

New techniques are also developed for the proximal anastomoses in addition to improvements on the distal anastomoses of peripheral bypass surgery.

The standard technique used for the proximal anastomosis in peripheral arterial surgery is with running monofilament non-resorbable sutures. Since 1997 there is a commercially available alternative technique, with non-penetrating titanium clips. The Vessel Closure System (VCS, Le Maitre Vascular Inc., Burlington, USA), has proven to increase patency of anastomoses in vascular access surgery. The use of the VCS system has also been advocated because of decreased anastomotic time, and its ease of use. [12] This could shorten clamping time of the artery and reduce per-operative limb ischemia.

In vitro research showed that the use of non-penetrating clips resulted in improved para-anastomotic compliance and reduction of intimal damage, compared with sutures. [13] Therefore, the use of clips for proximal anastomoses in vascular reconstructive surgery might help preserve endothelial function and structural integrity and could result in increased patency rates. There is very little known on performance of clipped anastomoses in PAD population

on the femoral arteries. Therefore we conducted a pilot study to assess the VCS safety in femoral artery anastomosis.

However main outcomes remain important, Quality of life (QoL) is increasingly considered a contributing outcome measurement of vascular interventions. It is an individual assessment of physical, psychological and social well-being that is based on the definition of health by the World Health Organization (WHO). [14] QoL incorporates a patient's individual perception of its disease and functioning. [15]

Patients suffering from PAD, who are not receiving treatment, cope with a deprived health status and QoL due to the effects of the disease and co morbid conditions.[15] However, improvements in both health status and QoL following peripheral bypass surgery have been observed at three months of follow-up. [16] We conducted a review of the literature to analyze QoL after vascular interventions, and analyzed midterm QoL scores in one of our previous study populations.

As the treatment of PAD is multidimensional and time consuming, an increasing number of vascular surgery units expand their care-teams with certified vascular Nurse Practitioners (NPs). These NPs have more time for each patient compared to the vascular surgeon. They work closely with a supervising vascular surgeon and assist in the multidimensional approach of patients' treatment and reducing and treating risk factors. The NPs follow up on patients and guides patients through treatments, for outpatient and inpatient care.[17] This could result in higher QoL scores, and lower anxiety and depression scores in patients guided by NPs. As there are no previous reports on QoL, anxiety and depression scores in patients guided by a vascular NP, we decided to study these effects in our vascular population before and after adding vascular NPs to our care team.

Every surgical interventions has a risk for complications. Some of these complications can be avoided, other complications can be diminished by optimal care taking.

For all complications, a reliable registration is very important. Registering complications gives an insight in the incidence and can show patterns of complications. These data could be used for diminishing the number of complications. The Dutch Association of Surgeons (ASN) has developed a national standardized system for the registration of complications to produce reliable information on surgical outcome and create a benchmark. [18] Complications are real time documented in this system by the physician who diagnoses the event. This form of registration is questioned by different authors for efficiency and objectivity.[19] One of the possible complications after surgery are surgical site infections, which are registered by surgeons or residents. Another way to register complications (in this case, surgical site infections) is by specially trained infection control nurses, of the department of medical microbiology, who have no direct connections to a surgical department. With the growing interest on the occurrence of complication, there is a need for determining the most reliable registration method.

In vascular surgery, surgical site infections are one of the most frequent diagnosed complications. A deep seated surgical site infection in vascular surgery can, with use of prosthetic grafts, lead to high morbidity and even be fatal. Decreasing the number of surgical site infections is therefore necessary.

Staphylococcus aureus nasal carriage increases a patient's risk for developing a health care-associated infection with this micro organism, at least after cardiac surgery, orthopedic surgery and in peritoneal dialysis. [20-24] Preoperative screening for nasal carriage and subsequent treatment of carriers with mupirocin and chlorhexidine reduces the risk for the development of hospital-acquired *S. aureus* infections by 79% for deep-seated infections and 55% for superficial infections. [25] Consequently, the mean duration of hospital stay is reduced in treated carriers by approximately 2 days. A cost benefit analysis shows that the strategy is cost-effective and saves lives. [26]

In vascular surgery little is known about the relation between nasal carriage of *S. aureus* and surgical site infections (SSI).

THESIS OUTLINE

The aims of this studies were to analyze both classic and modern outcomes in vascular surgery. Classic outcomes are; patency rates (primary, primary assisted and secondary), limb salvage and survival. Modern outcomes are; Quality of Life, the registration of complications, and new insights to diminish complications. Various clinical studies were performed to analyze these interests.

In **chapter 2**, we report patency rates, limb salvage rates and survival after peripheral bypass surgery with both autologous, as the new designed ePTFE (expanded polytetrafluoroethylene) pre-cuffed bypass graft. This graft has an especially designed cuff at the site of the distal anastomosis. The distal cuff has been advocated to increase patency rates by optimizing flow at the distal anastomosis, thereby increasing patency rates.

Chapter 3 presents our results of a pilot-study, assessing the safety and usability of the use of vascular clips in the construction of the proximal anastomosis. This technique is proven to be effective in the anastomosis in AV access surgery. We performed a randomized study to how these clips performed in the proximal anastomosis in peripheral vascular surgery.

In **chapter 4**, the literature will be reviewed concerning Quality of Life after treatment for peripheral arterial disease. We reviewed literature about QoL after walking exercise, percutaneous transluminal angioplasty, revascularization surgery and lower leg amputation.

Chapter 5 contains our results for mid-term (> 2 years) follow-up on QoL after peripheral vascular bypass surgery. In **chapter 6**, the effect of certified vascular Nurse Practioners (NPs) was studied on patients' QoL, anxiety and depression scores. We compared to groups, one

group with patients who were guided trough treatment by a vascular surgeon, and one group of patients who were informed and guided by NPs.

Chapter 7 reports on reliability of the registration of complications after vascular surgery. We compared two different database which registered surgical site infections (SSI's) after vascular surgery. One database was maintained by the surgical department. The other was maintained by infection control nurses from the department of Medical Microbiology. After comparing both databases an optimal registration program is described.

In an effort to establish improvement in the occurrence of SSI's after vascular surgery, we performed a study to analyze the relation between *Staphylococcus aureus* nasal carriage and SSI's. These results are presented in **chapter 8**.

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Chapter 2

Midterm results of autologous saphenous vein and ePTFE pre-cuffed bypass surgery in peripheral arterial occlusive disease

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ABSTRACT

Introduction

The graft of choice in lower limb bypass surgery is the autologous saphenous vein (ASV). However, a prosthetic graft is needed in the absence of an ASV. In such situations we used an ePTFE pre-cuffed Dynaflo® graft as supragenicular bypass or Distaflo® graft as infragenicular or femorocrural bypass. In respect to expanding possibilities of PTA (Percutaneous Transluminal Angioplasty), the indication for bypass surgery moved towards patients with advanced stages of peripheral arterial occlusive disease. For this reason, this study analyzed the current performances of these ePTFE grafts and ASV grafts with special attention to limb salvage.

Methods

In a retrospective study all patients were included who underwent peripheral bypass surgery between 2004 and 2008. Kaplan-Meier curves were used to express primary patency, secondary patency and limb salvage rates at one and three years. Log-rank tests were performed to compare graft types.

Results

A total of 272 grafts (ePTFE/ASV:110/162) were performed in lower limb bypass surgery. The mean follow-up was 20,3 months. The secondary 3-year patency rates were: for 78 supragenicular grafts (ePTFE/ASV:45%/94%)*, for 124 infragenicular grafts, (24%/74%)* and for 70 femorocrural grafts (26%/52%).

Limb salvage after 3 year was in the ePTFE group 59% vs ASV 78%.* (* $p < 0,05$)

Conclusion

In the current population of vascular patients where no PTA is possible and a peripheral bypass is necessary, the ASV remains the graft of first choice. However the pre-cuffed ePTFe graft is a good alternative, especially in cases of critical limb ischemia, in respect to an acceptable limb salvage rate.

INTRODUCTION

Selected patients suffering from severe peripheral arterial disease (PAD) might be treated with a peripheral bypass reconstruction. The graft of choice in lower limb bypass surgery is the autologous saphenous vein (ASV). However, a number of patients do not have good quality ASV available to be used as a peripheral bypass graft [1, 2]. In these patients, there is a need for an alternative for the ASV graft. Commonly used prosthetic conduits are graft made of expanded polytetrafluoroethylene (ePTFE). Patency rates of supragenicular ePTFE bypass grafts are comparable to autologous bypass grafts [3-5]. In contrast, ePTFE infragenicular and femorocrural bypass grafts perform worse than venous bypass grafts.

Refinements in the graft design, such as the addition of a venous Miller cuff or a St Mary booth at the distal anastomosis, have been advocated to improve the results of prosthetic graft [6]. Alternatively, Pannerton et.al. showed that pre-cuffed ePTFE grafts have comparable patency rates as ePTFE grafts with a venous cuff. [7]

In previously performed studies, including a randomized controlled trial, the patency rates of supragenicular positioned ePTFE and ASV grafts were compared to each other during the first two years [1, 2]. Since then, enhancements in technology such as the widespread introduction of percutaneous transluminal angioplasty (PTA) procedures, resulted in further reticence to construct a peripheral bypass. As a consequence, nowadays the indication for bypass surgery moves towards patients who suffer from advanced stages of PAD and who might cope with a compromised distal runoff. The effects of within patient population changes on the performance of peripheral bypasses is unknown.

We preferably use the ASV as the graft of choice in patients suffering from severe PAD in our hospital. In case of an absent ASV to be used as bypass graft, we currently use the ePTFE pre-cuffed Dynaflo® graft for supragenicular femoropoliteal bypass (SFPB) reconstructions and the Distaflo® for infragenicular femoropopliteal bypass (IFPB) and femorocrural bypasses (FCB) reconstructions.

The aims of this study were to analyze performance of ePTFE and ASV grafts in patients suffering from severe PAD at one and three years after surgery with special attention for limb salvage.

METHODS

Study design

A retrospective review was undertaken of the medical charts of all patients who underwent peripheral bypass surgery. All considered charts were from patients operated on between 2004 and 2008 due to severe PAD. The variables entered into a dataset were: baseline charac-

teristics including the Rutherford class, gender, age, smoking status and the presence of diabetes and associated co morbid conditions. In addition previous vascular interventions and data from the surgical work up were recorded. The revascularization related data included graft type and the position of the distal anastomosis. Follow up data consisted of all patency related information from the medical charts such as physical examinations, medical imaging and laboratory results.

Patients

Two groups of patients were considered by type of bypass. The groups consisted of patients who were revascularized either with pre-cuffed ePTFE bypass graft, or with an ASV bypass graft. Patients who had a missing ipsilateral ASV, were revascularized using the contralateral saphenous vein or the lesser saphenous vein if possible. The brachial veins however, were not considered to be used as a bypass graft.

Surgical work up

Prior to surgery, the vascular assessment included an ankle-brachial pressure index (ABI), a treadmill test, a venous and arterial duplex ultrasound (US) assessment and either a digital subtraction angiography (DSA) or a magnetic resonance angiography (MRA) scan. Patients were considered for pre-cuffed ePTFE graft if both ipsilateral and contralateral ASV, or the lesser saphenous veins were absent of unsuitable to be used as an autologous bypass graft. Judgment was based on a preoperatively performed ultrasound evaluation[8] or on findings following an open operative exploration if the ultrasound assessment was inconclusive.

Surgical procedure

Surgery was performed under general and/or spinal anesthesia. An autologous bypass was constructed using either a deep-tunneled reversed or an in-situ technique. A pre-cuffed ePTFE Dynaflo® (Bard Peripheral Vascular Inc., Tempe, AZ, USA) graft was used if the distal anastomisis was situated supragenicularily while a pre-cuffed Distaflo® (Bard Peripheral Vascular Inc., Tempe, AZ, USA) was used if the distal anastomosis was situated infragenicularily. All grafts were inplanted end-to-side. A routine Doppler assessment was performed before closure of surgical wounds. Patients underwent systemic heparinazation (5000 IE) during the operation.

Post-operative course and follow up

Oral anticoagulant administration (acenocoumarol) was initiated for a two year period or resumed post-operatively following autologous bypass surgery with a target International Normalized Ratio (INR) between 2.5 and 3.5 during the first two post-operative years[9, 10]. The use of acetylsalicylic acid (ASA) was initiated or continued postoperatively in patient who received an ePTFE graft (80mg daily). All follow-up examinations included an assessment of the distal pulses during interval visits. Patients with ASV grafts were routinely checked with Duplex US and an ABI at three months and at six months, followed by an ABI at two years. The follow up of patients with an ePTFE graft was restricted to a single Duplex US and ABI at three months, followed by an ABI at one and at three years. A Duplex US was performed as well on suspicion of graft related problems (such as the absence of pulses or deterioration in ABI) in all patients.

Statistical analysis

Patency was defined in conformity with the guidelines by Rutherford et al.[11] The last moment a graft was considered patent is defined by the last date on which the graft was proven to be patent. Beyond the last date of proof of patency the graft was considered lost to follow up. Limb salvage was defined as freedom from a major amputation in patients with critical ischemia only (Rutherford class 4-6).

Statistical analysis was performed with SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). Kaplan-Meier curves were used to express primary, primary assisted, secondary patency and limb salvage. These patency rates were calculated for supragenicular, infragenicular and femorocrural bypasses individually in both groups, as well as for limb salvage. In addition, due to imbalances at baseline of the revascularization indication, per Rutherford class patency rates were calculated.

Log rank tests were used to compare the results. A *P* value <0.05 was considered to show a significant difference.

RESULTS

A total of 272 grafts were used in revascularization of patients with peripheral bypass surgery in our hospital between 2004 and 2008. This consisted of 162 grafts of the ASV, while 110 grafts were a pre-cuffed ePTFE graft. In table 1, the baseline characteristics are listed. In addition the positions of the distal anastomosis are listed as well as the number of redo operations. Based on the Rutherford class, patients who underwent ePTFE peripheral bypass

surgery were affected more seriously than patients who underwent autologous bypass surgery.

As many ASV bypasses as pre-cuffed ePTFE bypasses were constructed supragenicularily. The ASV was used as a bypass graft in the majority of cases for infragenicular and femorocrural reconstructions. Table 2 shows a listing of the type of bypass used at each location.

Table 1. Baseline and surgical characteristics.

Characteristics	Pre-cuffed ePTFE group	ASV group
N	110	162
Sex, Male/Female (%)	70/40 (63.6/36.4)	116/46 (71.6/29.4)*
Age average (range)	71.8 (36.8-96.6)	69.1 (41.0-86.4)
Diabetes (%)	39 (35.5)	61 (37.9)
History of recent smoking (%)	56 (50.9)	82 (50.9)
Hypertension (%)	65 (61.9)	80 (52.6)*
Indication for revascularization (Rutherford Class)		
2 (%)	3 (2.8)	3 (1.9)
3 (%)	21 (19.4)	56 (34.6)*
4 (%)	46 (42.6)	46 (28.4)*
5,6 (%)	38 (35.2)	57 (35.2)
Location of distal anastomosis		
Supragenicular (%)	39 (35.5)	39 (24.1)
Infragenicular (%)	43 (39.1)	81 (50.0)
Femorocrural (%)	28 (25.5)	42 (25.9)
Primary/Redo (%)	83/27 (75.5/24.5)	145/17 (89.5/10.5)*

* Denotes a significant difference between ePTFE and ASV (P< 0,05)

Table 2. Percentage pre-cuffed ePTFE bypasses vs total performed bypasses.

Characteristics	Pre-cuffed ePTFE group	ASV group
Supragenicular (%)	39 (50%)	39 (50%)
Infragenicular (%)	43 (35%)	81 (65%)
Femorocrural (%)	28 (40%)	42 (60%)

Patency rates

All 1-year and 3-year patency rates, of both supragenicualar and infraganicular femoropopliteal and femorocrural bypass surgery are listed in Table 3. One-year and 3-year primary patency rates of supragenicular bypass were almost equal. However, significantly better 1-year and 3-year primary assisted and secondary patency rates of supragenicular ASV grafts were found in comparison to ePTFE grafts. All patency rates of autologous infragenicular

femoropoliteal bypasses were superior to corresponding ePTFE bypasses. No significant differences in patency rates could be detected between autologous and ePTFE femorocrural bypasses. However, a tendency of higher patency rates of autologous grafts was seen. Secondary patency rates of supragenicular and infragenicular bypasses, as well as patency rates of femorocrural bypasses are plotted in Figure 1 to 3. All significant differences maintained in a per Rutherford class analysis of patency rates.

Table 3. Patency rates.

Characteristics		Pre-cuffed ePTFE group			ASV group		
Mean follow up, months (range)		19.9 (<1–64.7)			20.5 (<1–63.3)		
Distal anastomosis	Patency	1-year	2-year	3-year	1-year	2-year	3-year
Supragenicular	Primary (%)	57	47	47	63	57	57
	Primary Assisted (%)	57	47	47	94*	94*	94*
	Secondary (%)	63	52	45	94*	94*	94*
Infragenicular	Primary (%)	34	13	13	63*	61*	55*
	Primary Assisted (%)	36	20	20	78*	75*	75*
	Secondary (%)	40	24	24	81*	74*	74*
Femorocrural	Primary (%)	28	28	19	42	42	42
	Primary Assisted (%)	28	28	19	42	42	42
	Secondary (%)	38	26	26	52	52	52
Limb salvage (%)		68	59	59	85*	78*	78*

*Denotes a significant difference between ePTFE and ASV (P< 0,05)

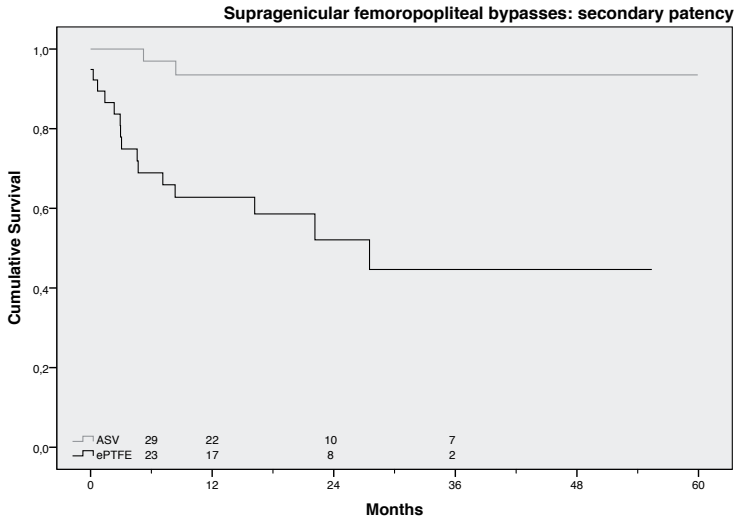

Figure 1) Kaplan-Meier curves representing secondary patency rates of supragenicular femoropopliteal bypasses.

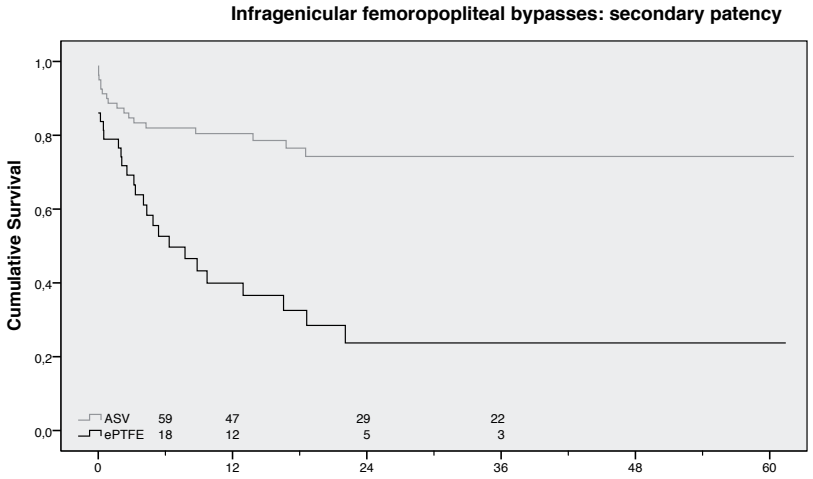

Figure 2) Kaplan-Meier curves representing secondary patency rates of infragenicular femoropopliteal bypasses.

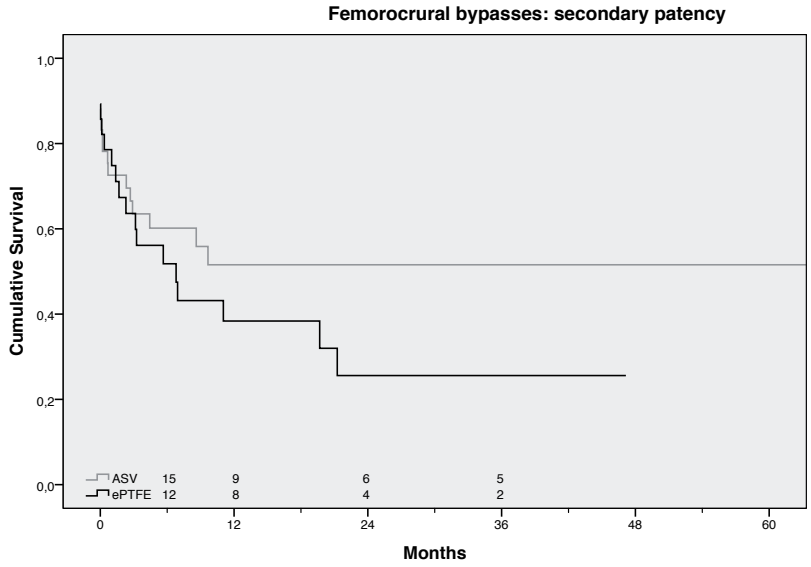

Figure 3) Kaplan-Meier curves representing secondary patency rates of femorocrural bypasses.

Limb salvage

One-hundred-eighty-six of a total of 272 grafts, were implemented in patients (ePTFE/ ASV:84/102) who suffered from chronic critical ischemia (Rutherford class 4-6). A significantly higher limb salvage rage was achieved in patients who underwent autologous bypass sur-

gery (Figure 4). These significant difference also maintained in a per Rutherford class analysis of limb salvage. The pre-cuffed ePTFE limbsalvage rates are 68 % after one year of surgery, and 59% after three years of surgery.

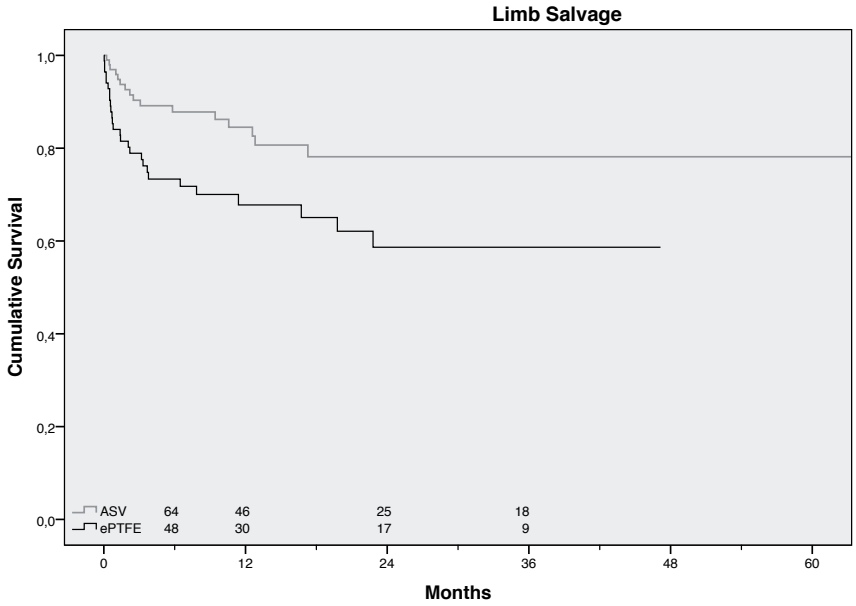

Figure 4) Kaplan-Meier curves representing limb salvage.

DISCUSSION

The autologous vein still offers superb performances in peripheral bypass surgery in comparison to prosthetic conduits. In this study patency rates of both autologous and ePTFE peripheral bypass grafts were compared to each other. Especially infragenicular autologous bypasses performed significantly better than ePTFE grafts. Performances of autologous grafts were comparable to previously performed studies[1], at least for secondary patency. A 77% 2-year secondary patency rate for supragenicular autologous bypass grafts was reported meta-analysis performed by Klinkert et.al.[1]

Alternatively, prosthetic grafts can be used in the absence of a suitable vein to be uses as a bypass graft. Over the years several artificial graft types were introduced, such as Dacron and ePTFE. In the meta analysis performed by Roll et all, nine randomized controled trials were included to analyze the performance of Dacron versus PTFE grafts [12]. No significant differences could be detected between primary patency of both graft types.

One of the explanations for lower PTFE patency rates was the mismatch in compliance between the relatively stiff prosthetic graft and the native artery. In combination with iatrogenic injury caused by suturing the anastomosis, this is thought to induce neointimal hyperplasia and therefore stenosis at the distal anastomosis. Enhancements in cuff-design led to improvement of prosthetic graft performance. Miller described the first widely used vein cuff in 1984, which improved patency results from 29% to 57% after three years. [13]

Similar results have been achieved by the Taylor patch and St. Mary´s boot. This all led to the development of a pre-cuffed (e)PTFE graft, which performance was comparable with a venous cuffed (e)PTFE. [7]

However, ePTFE patency rates from this study underperformed in comparison to other recently published studies. This study´s infragenicular and femorocrural patency and limb salvage results, compared to literature are listed in table 4.

Table 4. Reported patency rates of infragenicular ePTFE Distaflo® bypasses by this study and previous studies.

				1-year patency rates			
Study	Reference Nr.	N (Nc)	Follow up (months)	Primary (%)	Secondary (%)	Femorocrural primary (%)	1-year limb salvage (%)
Alcocer et al	16	35 (30)	15.2	51	53	nr	75
Fisher et al	17	(30b)	10.4	39	nr	20b	50
Panneton et al	7	47 (35)	14	52	53	nr	72
Bellosta et al	18	12 (12)	22.5	nr	31c	31c	nr
Oderich et al	19	40 (25)	25.7	70	nr	nr	97
Gulkarov et al	14	52 (24)	12	65.1	80.4	44.4 (63.2d)	85.3
Donker et al	—	71 (28)	19.9	31.5	39.1	28 (38d)	67.6

N = number of Distaflo® bypasses, Nc = number of femorocrural Distaflo® bypasses, nr = not reported, b study reports patency data only for 20 femorocrural Distaflo® bypasses, c 4-year secondary patency, d secondary patency.

In both this and the study by Gulkarov et.al.[14], a large percent of patients were included who suffered from chronic critical ischemia. However, in the latter study superb patency rates are presented compared to ours. A possible explanation could be, that we analyzed bypass performances rather than patients. Several patients are thus included double as illustrated by the redo bypass procedures. Another explanation could be that we set very strict patency definitions, based on Rutherford et.al. [11], to determine graft patency.

Only a small number of femorocrural bypasses were included in this study. As a consequence, we could not prove the superiority of the ASV graft over the ePTFE graft. In the absence of alternatives, performing pre-cuffed ePTFE femorocrural bypass surgery can be considered justifiable.

When we compare our pre-cuffed ePTFE results to other grafts, like the Heparin bounded ePTFE graft, the Heparin bounded grafts show higher patency rates.

Daenens et.al study showed very impressive patency rates with Heparin bounded synthetic bypasses [15], however their study contains very few autologous grafts, so in our opinion their results are hard to compare to our results.

For patients who require a peripheral bypass, but who do not have a suitable ASV or other vein to be used as bypass, a pre-cuffed ePTFE bypass offers reasonable alternatives. Also there is a fairly acceptable limb salvage rate for pre-cuffed ePTFE bypasses.

CONCLUSION

The ASV remains the bypass of first choice, because of the higher patency rates and better limb salvage. However, in patients in whom the autologous saphenous vein is absent or unsuitable, the pre-cuffed ePTFE graft seems to be an appropriate alternative.

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Chapter 3

Anastomoses in the common femoral artery, vascular clips or sutures? A feasibility study

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ABSTRACT

Introduction

The Vessel Closure System is commercially available since 1997. This clip system has proven to be successful for vascular anastomoses in access surgery. There is little experience with the VCS in peripheral vascular surgery.

Materials and Methods

A trial was performed for patients with peripheral arterial disease, which required either a femoral artery endarterectomy or a peripheral bypass procedure. Patients were randomized in two groups; a VCS group, in which the proximal anastomoses were made with VCS clips and a control group in which both anastomoses were made with prolene. Outcomes were; speed of anastomosis and patency. Adverse events were monitored.

Results

In the VCS group, 12 patients received VCS clips. In the control group, 12 patients underwent vascular reconstruction with sutures. In the VCS group the mean speed of anastomosis was 1.9 mm/min, where the mean speed in the control group was 2.5 mm/min. This was not significantly different. ($P = 0.096$). After a follow-up of 12 months, there was no difference in patency. In the VSC group, two serious adverse events took place which required emergency surgery.

Conclusion

The use of VCS in anastomosis in the femoral artery is not faster than running prolene sutures and in our small sample size, two serious adverse events in the VCS group were observed. These results do not support the further use of vascular clips in peripheral vascular surgery.

INTRODUCTION

The standard technique used for the anastomosis in peripheral arterial surgery is with running monofilament non-resorbable sutures. Since 1997 there is a commercially available alternative technique, with non-penetrating titanium clips. The Vessel Closure System (VCS, Le Maitre Vascular Inc., Burlington, USA), has proven to increase patency of anastomoses in for vascular access surgery.[1] The use of the VCS system has also been advocated because of decreased anastomotic time, and its ease of use.[1] This could shorten clamping time of the artery and reduce per-operative limb ischemia.

In vitro research showed that the use of non-penetrating clips resulted in improved para-anastomotic compliance and reduction of intimal damage, compared with sutures. [2] Therefore, the use of clips for vascular anastomoses might help preserve endothelial function and structural integrity.

Because results in access surgery are positive, and results in peripheral arterial surgery are limited, we started a pilot study on the use of vascular clips in patients with peripheral arterial disease.

The aim of this study was to compare the VCS with running monofilament sutures in femoral anastomoses in patients who required either a femoropopliteal bypass graft, or a femoral artery endarterectomy and a vascular patch.

METHODS

Study Design

Patients with Rutherford stage 3 or more, who were planned to undergo either a peripheral bypass or a femoral artery endarterectomy were recruited from our outpatient clinic. They were randomized between the VCS system and sutured anastomosis. Between 2009 and 2010 we planned to include 20 patients in the pilot study. While the trial was running, there was some early loss to follow-up because of early mortality not caused by surgery. For this reason we adjusted the inclusion to 24 patients in order to maintain a reasonable number of anastomoses to analyze during one year.

Randomization was performed by a closed envelope system, after patients signed a written informed consent agreement.

The primary outcome measure was speed of anastomosis during the operation.

The length of the anastomosis in centimeters and the time it cost to construct the anastomosis with either the VCS clips or with running sutures in minutes were noted in a case form by the vascular surgeon. The time of anastomosis was defined as the moment of the first suture until release of the circulation and timed by the circulating nurse during surgery.

The secondary outcome was patency of the bypass or endarterectomy, as defined by Rutherford et al[3].

One of our vascular surgeons followed a training for the use of the VCS clip applier, this surgeon trained our other surgeons on handling of the VCS.

Surgical work up

Prior to surgery, the vascular assessment included an ankle-brachial pressure index (ABI), a treadmill test, a venous screening by duplex ultrasound (US) assessment and a magnetic resonance angiography (MRA) scan.

Surgical procedure

Surgery was performed under general and/or spinal anesthesia. An autologous bypass was constructed using a deep-tunneled reversed or an in-situ technique. In case the autologous saphenous veins were absent, or inadequate, a pre-cuffed ePTFE Dynaflo® (Bard Peripheral Vascular Inc., Tempe, AZ, USA) graft was used if the distal anastomosis was situated above the knee while a pre-cuffed Distaflo® (Bard Peripheral Vascular Inc., Tempe, AZ, USA) was used if the distal anastomosis was situated below the knee. All grafts were implanted end-to-side in the femoral artery.

A femoral artery endarterectomy was performed by an longitudinal arteriotomy. The defect in the femoral artery was closed with a bovine pericardium patch. (Vascu-Guard, Biovascular Inc., Saint Paul, MN, USA)

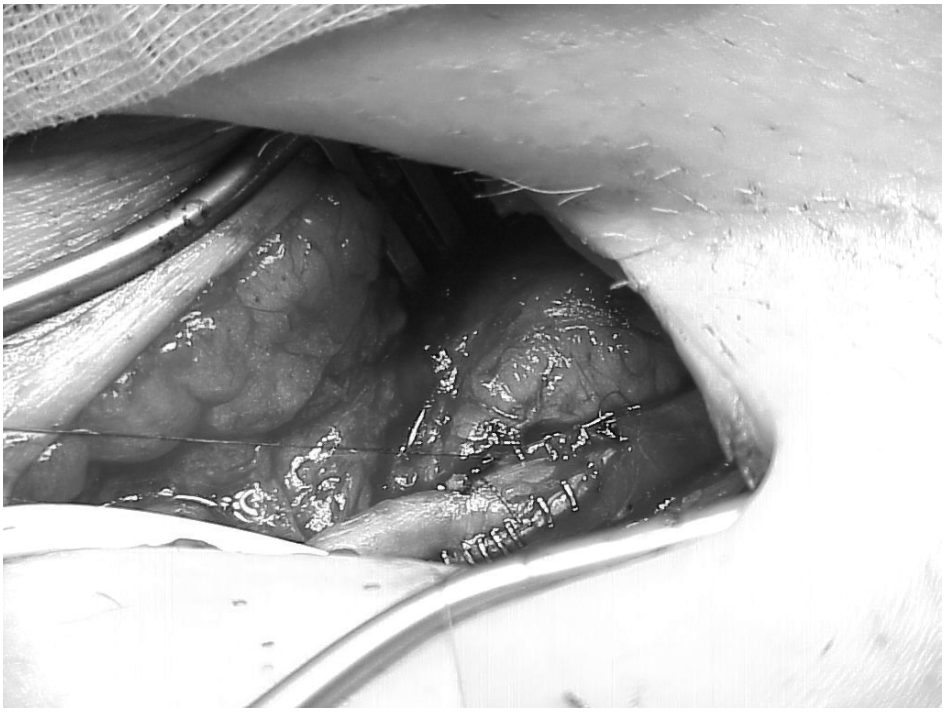
In the VCS group, the proximal anastomosis, or patch in case of a femoral endarterectomy procedure, was made with clips, by using the Vessel Closure System, as advised by the LeMaitre and described in Balar et al.[4] (Picture 1)

VCS were applied by use of the applicator, all clipped anastomosis were made with size Large clips.

The control group received suture closing technique (Prolene, Ethicon, Johnson and Johnson, Somerville, New Jersey, USA) of the proximal anastomosis, or patch in case of a femoral endarterectomy procedure.

In case of a distal anastomosis in patients receiving bypass surgery, it was performed with running sutures in both groups.

A routine doppler assessment was performed before closure of surgical wounds. Patients underwent systemic heparinization (5000 IE) during the operation. After anastomosis construction, the anastomosis was visually inspected for several minutes, to evaluate anastomotic bleeding. If necessary an extra suture, or clip in the VCS group, was placed until the anastomosis was completely dry. No Heparin antagonists were administered (eg Protamine).



Picture 1. Anastomosis at the Common Femoral Artery, performed with Vascular Clips.

Post-operative course and follow up

Oral anticoagulant administration (acenocoumarol) was initiated or resumed post-operatively following autologous bypass surgery with a target International Normalized Ratio (INR) between 2.5 and 3.5 during the first two post-operative years[5, 6]. The use of acetylsalicylic acid (ASA) was initiated or continued postoperatively in patient who received either an ePTFE graft or patients after a femoral artery endarterectomy (80mg daily). All follow-up examinations included an assessment of the distal pulses during interval visits. All patients were routinely checked with duplex ultrasound and an ABI at three months, at six months and at one year post surgery.

The proximal anastomosis was closely monitored with duplex for signs of occlusion or stenosis.

Statistical analysis

For all patients, the speed of the proximal anastomosis was calculated, and an independent samples t-test was performed. A *P*-value < 0,05 was considered significant. Statistical analysis was performed with SPSS 19.0 software (SPSS Inc., Chicago, IL, USA).

Ethics

Our study protocol was approved by a regional Medical Ethical Committee, as well as our own MEC.

RESULTS

Between 2009 and 2010, 24 patients were included. The VCS group consisted of 12 patients, 10 of whom underwent bypass surgery (9 autologous saphenous vein, 1 ePTFE graft) and 2 patients underwent a femoral artery endarterectomy.

The control group consisted of 12 patients, 8 of whom underwent a femoral artery endarterectomy, and 4 patients underwent bypass surgery (3 autologous saphenous vein, 1 ePTFE graft).

The mean age in the VCS group was 73 years (48-83 yr) and in the control group 71 years (51-80 yr). (Table I)

Table 1. Baseline characteristics.

Characteristics	VCS group	Control group
N	12	12
Sex, Male/Female (%)	7/5 (58%)	12/0 (100%)
Age average (range)	73 (48-83) years	71 (51-80) years
Number of bypasses	10	4
Number of Femoral artery endarterectomies	2	8
Rutherford classification		
3	2	7
4	5	2
5 and 6	5	3

In one VCS patient the arterial wall was deemed unfit for clips because of calcification, so the surgeon decided to use sutures.

The average speed (mm/min) in the VCS group was 1.9 mm/min, while the average in the control group was 2.5 mm/min. This was not a statistically significant difference ($P > 0,05$). (Table II) In the VCS group one patient died after one year of follow-up. There were also three occluded bypass grafts in the VCS group. No stenoses were detected in the other anastomoses during follow-up.

In the control group were three deceased patients after one year of follow-up, there was also one occluded bypass graft. Mean follow-up was 11.3 months.

Table 2. Anastomosis speed.

Characteristics	Control group	VCS group
Mean Speed (mm/min) (SD)	2.5 (0.81)	1.9 (0.84)

P-value = 0.096

None of these deaths were directly related to the performed surgery. Three patients died of cardiac failure and possible myocardial infarction. One patient died after an ischemic cerebrovascular accident.

In one VCS patient, there was a major complication of a anastomosis rupture because of a clip malfunction, which needed a surgical reintervention. This was reported as serious adverse event to the medical ethic committee.

One VCS patient needed a surgical reintervention because of an acute thrombosis of the superficial femoral artery, one day after femoral artery endarterectomy, because of a distal intima laesion, which was not fixed adequately by the placed clips.

DISCUSSION

The VCS has been used previously in the creation of vascular anastomoses at different anatomical locations, for access surgery, transplant surgery and in small numbers for peripheral vascular surgery[1, 4, 7] Multiple studies showed advantages of vascular clips in access surgery[1, 8-14], however the benefits of vascular clips in peripheral arterial surgery is less clear. Several small series showed reasonable patency rates when using clips, and a possible faster anastomotic time.[4, 13, 15] Despite initial promising results, we found no other publications since 2001 on the subject. In order to improve results of peripheral vascular surgery we hypothesized that the VCS could create a more durable anastomosis than running prolene sutures. Before conducting a large randomized control trial, we aimed to establish whether the VCS clips were safe and easy in use for anastomoses at the femoral artery, in a pilot study.

We included patients after both peripheral bypass surgery as well as after femoral endarterectomies, because we assumed that the technique of applying an anastomosis at the femoral artery, would not differ between both procedures. At least for our outcomes of anastomosis speed and patient safety. We are aware that patency rates between both procedures are not very comparable.

In this study, three people already had a complete occlusion of their proximal anastomoses within one year. The time needed for applying the anastomoses was not significantly different from the control group. However, a faster applied anastomosis means less clamping time, the time needed for the anastomosis is still only a part of the complete time of surgery, and therefore clamping time is not only dependant on the speed of the anastomosis. Our preliminary results did not meet our expectations. Although the initial technical success rate

was high, significant complications occurred in the VCS group that could be attributed to the use of clips. The presumed higher speed of anastomosis could not be confirmed. In fact, average speed was lower in the VCS group.

There were two serious adverse events in the VCS group; in one patient the clipped anastomosis ruptured, causing major bleeding from the femoral artery. In another patient an acute thrombosis of the superficial femoral artery had occurred. As we could not determine any benefits from the use of clips in the proximal anastomosis, we concluded the safety of the use of VCS clips in peripheral vascular surgery is not proven, and we will not continue with a large randomized control trial.

In conclusion, because of the two serious adverse events, the costs of the disposable clip appliers, and the lack of any positive results of the use of vascular clips, we dispute the safety of the use of VCS on the Femoral artery.

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Chapter 4

Review: Quality of life in peripheral vascular surgery

Submitted

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ABSTRACT

Introduction

Vascular intervention studies generally consider patency, limb salvage and operative morbidity and mortality as primary outcomes. However, Quality of life (QoL) is increasingly considered an important patient-oriented outcome measurement of vascular interventions. In this review, the existing literature was analyzed to determine the effect of different treatments on QoL for patients suffering from either claudication or critical limb ischemia (CLI).

Methods

A review of the literature was undertaken in the Medline library. Terms used were "Peripheral Vascular Diseases"[MeSH] AND "quality of life"[MeSH] (251 results) and "Peripheral arterial disease" [MeSH] AND "Quality of Life" (36 results).

Results

A total of 21 articles described results on QoL in patients suffering from PAD, in relation to exercise therapy, percutaneous transluminal angioplasty (PTA), or surgical treatment. The follow-up duration ranged from 1 month to 11 years. Patient populations were exclusively claudicants in studies analyzing the response to exercise therapy, and both claudicants and CLI in the remaining interventions. In respect to significant heterogeneity, pooling of the data was not performed.

QoL was analyzed after conservative treatment, endovascular treatment and surgical intervention. Invasive treatment generally results in better QoL scores (at a maximum of 2 years of follow-up), compared with non-invasive treatment. In patients with limb ischemia, successful revascularization improves QoL scores, while failed procedures or lower limb amputations decrease QoL. A study with a follow-up of 11 years showed patient' QoL scores were reduced.

In patients with critical limb ischemia very little is known on QoL after amputation.

Conclusion

Increase in QoL scores can be found for any intervention performed for PAD. However, there is scarce information on long term QoL after vascular intervention.

INTRODUCTION

Peripheral Arterial Disease (PAD) is commonly caused by atherosclerosis of peripheral arteries. The prevalence of PAD is 3-10% in the current population, and ranges up to 15-20% in the elderly population.[1-4] PAD is categorized by the Rutherford Classification.[5] Rutherford classifications 1 to 3 are used for patients suffering from intermittent claudication. These patients can be treated either with exercise therapy or revascularization.[1]

In patients with critical limb ischemia, Rutherford classifications 4 to 6, the need for intervention is inevitable, which can either be performed by a percutaneous transluminal angioplasty (PTA), peripheral bypass surgery or, when this is technically not possible, primary amputation or palliation.[1] Typically, reported outcomes of vascular interventions include walking distance, patency rates, limb salvage rates and operative mortality. [5] However, these outcomes may and reflect a physician-oriented view on results.

Quality of life (QoL) is increasingly considered an important outcome of vascular interventions.[2, 6] It is an individual assessment of physical, psychological and social well-being that is based on the definition of health by the World Health Organization (WHO).[7] QoL incorporates a patient's individual perception of its disease and functioning.[8] Patients suffering from PAD frequently cope with a deprived health status and QoL due to the general effects of the disease and co-morbid conditions.[8] In this perspective, QoL is a patient-oriented way of evaluating results and may provide a better-balanced estimate of the impact of a certain intervention for patients.

There are reviews available on different topics of QoL in vascular surgery. However, these are mostly outdated and they assess only a small spectrum of QoL in vascular surgery.

We decided to conduct a systematic literature review to analyze the effect of exercise therapy, endovascular procedures, and surgical interventions on the QoL of patients suffering from lower limb ischemia.

METHODS

This review is based on a search in the Medline library, which was accessed by the PubMed search engine on December 31th 2011. The search was based on both Medical Subject Headings [MeSH] and normal search terms and was performed by the first author, aided by the librarian.

Terms used were "Peripheral Vascular Diseases"[MeSH] AND "quality of life" [MeSH] (251 results), and "Peripheral arterial disease" [MeSH] AND "Quality of Life" (36 results). Only abstracts published in English were included. All titles and abstracts were read, and all articles which were not concerning QoL in peripheral vascular surgery were excluded. QoL was defined as outcome, either primary or secondary, and had to be assessed with a valid questionnaire.

All relevant articles were read completely, and possible references were included and read as well. This resulted in 21 articles which described results on QoL after peripheral vascular procedures. For detailed information on search strategy, see figure 1.

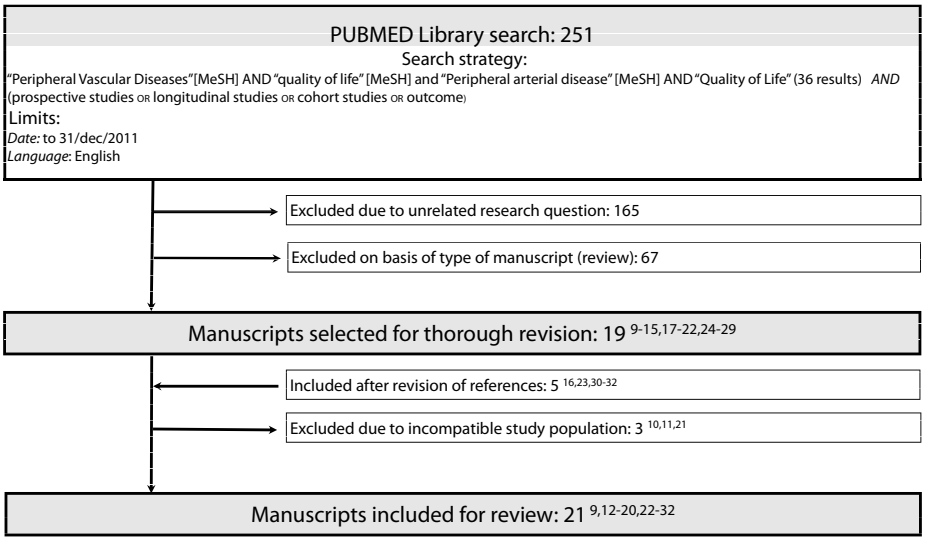

Figure 1) Detailed search strategy information.

Inclusion criteria

All papers that reported QoL scores after any intervention in PAD were included. QoL had to be assessed with a questionnaire. Only articles published in English were included. Papers had to be published before December 31th 2011.

QoL assessment

There are many different questionnaires that assess patients' QoL. There are generic QoL questionnaires like the WHOQOL and the EQ-5D questionnaires, disease specific questionnaires like the VascuQoL questionnaire and the Walking Impairment Questionnaire (WIQ), or health status questionnaires like the SF-36 and RAND-36 questionnaires.

RESULTS

A total of 21 studies were included. These were distributed by type of intervention as follows: QoL after exercise therapy (N=5); QoL after endovascular procedures (N=11); QoL after surgical revascularization (N=13) and QoL after major lower limb amputation (N=2).

Many studies have analyzed and reported QoL results after all different types of vascular treatment, in either patients suffering from intermittent claudication [9-16], or patients with threatening lower limb ischemia[17-21], or studies with both groups of patients[22-32]. There are studies comparing endovascular treatment with bypass surgery[9, 12, 18, 19, 24, 28], studies comparing endovascular therapy with exercise therapy[9, 14], studies comparing autologous bypass surgery with PTFE bypass surgery[22] and studies analyzing QoL after a single intervention[13, 15-17, 20, 21, 23, 25, 27, 29-33].

QoL after exercise therapy

Five articles assessed QoL in patients after exercise therapy. [9, 13-16]. All articles assessed QoL in patients suffering from intermittent claudication.

Exercise therapy, both supervised as unsupervised, resulted in increment in QoL, at a maximum of 24 months of follow-up. However, results of supervised exercise therapy were better, compared to the unsupervised exercise therapy.[13]

Patients receiving invasive treatment (both endovascular as surgical reconstruction) showed more increment in QoL than patients who only received exercise therapy.[14] For detailed information on studies analyzing QoL after exercise therapy see table 1.

QoL after endovascular procedures

Eleven articles assessed QoL in patients after endovascular procedures.[9, 12, 14, 18, 19, 23-25, 28, 31, 32]

For patients suffering from intermittent claudication, an increase in QoL could be expected up to 2 years of follow-up[14].

Patients with critical limb ischemia also showed increased QoL up to 36 months of follow-up, after endovascular treatment. [18]

The difference in QoL between patients suffering from critical limb ischemia versus patients suffering from intermittent claudication remains unclear, as different papers report in contrast to each other.[24,25]

A study analyzing QoL in critical limb ischemia patients after endovascular procedures, bypass surgery and secondary amputations stated that achieving limb salvage was related to better QoL. [19]

Table 1. Change from baseline in quality of life after exercise therapy.

Article	Year	N Start/ end	Questionnaires	Female (%)	Age+	Degree of ischemia	Follow-up months	Supervised?	Outcome	Mean Change	P value
Curie et al.	1995	78/ 78	SF-36	24	68	Claudicant	3	No	Physical function Physical role Pain Vitality	3 (95% CI: 0 – 6) 5 (95% CI: -3 – 12) 7 (95% CI: 2 – 11) 3 (95% CI: -1 – 7)	0,2 0,25 0,005 0,1
Nicolai et al.	2010	102/83	SF-36	44	67	Claudicant	12	No	Physical function Physical role Pain Vitality	6.6 ± 18.5 4.8 ± 49.4 3.9 ± 26.6 –3.9 ± 18.7	<0,001 0,71 0,36 0,05
Nicolai et al.	2010	202/169	SF-36	33	66	Claudicant	12	Yes	Physical function Physical role Pain Vitality	12.3 ± 18.3 16.6 ± 45.2 13.4 ± 24.5 –0.6 ± 17.5	<0,001 <0,001 <0,001 0,46
Nordanstig et al.	2011	101/72	SF-36	36	68	Claudicant	24	Yes	Physical function Physical role Pain Vitality	0,46* 0,17* 0,44* 0,07*	<0,05 NS <0,05 NS
Fakhry et al.	2011	142/95	SF-36 / VascuQoL	36	68	Claudicant	12	No	Physical function Physical role Pain VascuQoL total score	6.88 (95%CI: 2.85–10.91) 8.89 (95%CI: 0.57–17.21) 6.55 (95%CI: 1.54–11.56) 0.45 (95%CI: 0.21–0.69)	<0,05 <0,05 <0,05 <0,05
Fakhry et al.	2011	75/ 75	SF-36 / VascuQoL	41	67	Claudicant	12	Yes	Physical function Physical role Pain VascuQoL total score	12.68 (95%CI: 7.33–18.03) 5.93 (95%CI: -4.7-416.61) 9.67 (95%CI: 3.85–15.49) 0.60 (95%CI: 95%CI: 0.28–0.91)	<0,05 NS <0,05 <0,05
Gardner et al.	2001	31/ 28	SF-36	11	71	Claudicant	6	Yes	Physical score Mental score	0 +4	NS NS
Gardner et al.	2001	30/ 24	SF-36	8	70	Claudicant	6	No	Physical score Mental score	-1 0	NS NS

+ mean or median; * Effect size (difference in mean values between baseline and 2 years per SD at baseline) NS – not significant

Only articles reporting treatment specific, before and after data are listed.

Table 2. Change from baseline in quality of life after endovascular treatment.

Article	Year	N Start/ end	Questionnaires	Female (%)	Age+	Degree of ischemia	Follow-up months	Outcome	Mean Change	P value
Curie et al.	1995	74/ 74	SF-36	28	73	Claudicant	3	Physical function Physical role Pain Vitality	18 (95% CI: 12 – 24) 19 (95% CI: 8 – 30) 17 (95% CI 11 – 24) 8 (95% CI: 4 – 12)	<0.001 <0.005 <0.001 <0.05
Nordanstig et al. **	2011	100/86	SF-36	38	68	Claudicant	24	Physical function Physical role Pain Vitality	0.89* 0.68* 1.16* 0.15*	<0.05 <0.05 <0.05 NS
Johnson et al.	1997	26/ 19	DomainQ	42	76	Critical	12	Pain Barthel ADL score Mobility	-3 0.14 1	<0.01 <0.05 <0.05
Dippel et al.	2006	44/ 44	Walking impairment Questionnaire	41	70.3	CL 88% CR 12%	12	WIQ score	7405 (95% CI 6555 – 9245)	<0.0005
Kalbaugh et al.	2006	54/ 52	SF-36	NR	Pop: 64.5 Gr NR	Claudicant	12	Physical function Physical role Pain	9.2 7.0 7.2	<0.0001 0.0001 <0.0001
Kalbaugh et al.	2006	30/ 18	SF-36	NR	Pop: 64.5 Gr NR	Critical	12	Physical function Physical role Pain	2.9 0.7 11.2	0.30 0.85 0.0009
Egberg et al.	2010	56/ 41	EQ-5D CLAU-S	49	68	CL 85% CR 15%	12	EQ-5D index CLAU-S score Total	0.19 18	0.0019 <0.0001
Forbes et al.	2010	224/132	SF-36 EQ-5D VascuQol	43	NR	Critical	12***	EQ-5D index Physical function Physical role Pain VascuQoL score	0.3 10.91 19.85 23.89 1.74	NR NR NR NR NR

Table 2. Change from baseline in quality of life after endovascular treatment (continued).

Article	Year	N Start/ end	Questionnaires	Female (%)	Age+	Degree of ischemia	Follow-up months	Outcome	Mean Change	P value
Bosch et al.**** Gr 1	1999	143/ 143	EQ-5D Rand 36	29	59	Mostly claudicant	24	Physical function Physical role Pain EQ-5D index	35 75 33 0.24	NR NR NR NR
Bosch et al.**** Gr 2	1999	136/ 136	EQ-5D Rand 36	27	60	Mostly claudicant	24	Physical function Physical role Pain EQ-5D index	40 100 45 0.20	NR NR NR NR

+ mean or median; * Effect size (difference in mean values between baseline and 2 years per SD at baseline) NS – not significant; NR – not reported ** data is for invasive treatment group (PTA + surgery)

*** 12 months follow-up was selected, because of very little follow-up at 36 months (original study endpoint)

**** study consistend of two groups, first underwent PTA + Stent, second one underwent PTA only.

Only articles reporting treatment specific, before and after data are listed.

One case-control study reported that both intermittent claudication patients as critical limb ischemia patients cope with a deprived QoL score compared to matched healthy control subjects. [28]

Endovascular treatment can increase QoL, even for chronically occluded superficial femoral arteries [23]. For detailed information on studies analyzing QoL after PTA see table 2.

QoL after surgical revascularization procedures

Thirteen articles assessed QoL in patients after surgical revascularization procedures. [9, 12, 14, 17-20, 22, 24, 27-30]. Surgical revascularization improved QoL in both patients suffering from intermittent claudication as critical limb ischemia, at least for two to three years after surgery. The increment in QoL achieved by a surgical revascularization intervention was significantly better compared to walking exercise. [9, 14]

Little is known about the long-term effect of endovascular or surgical reconstructive interventions on patients' QoL.

Only one prospective study analyzed results after more than 2 years of follow-up, after both endovascular as surgical reconstructive procedures.[18] They showed an increment in QoL for both procedures after 3 years of follow-up.

A case control study[28] showed that QoL scores of patients after both endovascular and surgical reconstructions (mean 3.5 yrs for surgery, 2,7 years for PTA), were lower, compared to healthy subjects.

One study analyzed long term follow-up results (mean follow-up 11 years) after reconstructive surgery[29], they reported decrement in QoL scores for patients treated with surgical reconstructions. Especially patients who experienced an adverse event during the follow-up period scored lower on QoL. For detailed information on studies analyzing QoL after surgical revascularization see table 3.

QoL after major lower limb amputation

Two articles assessed QoL in patients after major lower limb amputation. [19, 33]

Achieving limb salvage in patients with critical ischemia resulted in an overall better QoL compared to patients who underwent lower limb amputation[33].

A case control study showed that the reported QoL of amputees is significantly lower compared to healthy control subjects.[33] Especially for those who were living in an institution and not in their own homes.

QoL scores in the domain of pain significantly improved (up to 1 year of follow-up) for both patients who underwent unilateral (decrement in pain score with 5 point on a 0-10 scale) or bilateral (decrement in pain scores with 6 point on a 0-10 scale) amputation ($P < 0,01$).

Table 3. Change from baseline in quality of life after surgical reconstructive treatment.

Article	Year	N start/ end	Questionnaires	Female (%)	Age+	Degree of ischemia	Follow-up months	Outcome	Mean Change	P value
Curie et al.	1995	34/ 34	SF-36	32	67	Claudicant	3	Physical function Physical role Pain Vitality	18 (95% CI: 15 – 26) 16 (95% CI: 1 – 30) 17 (95% CI 6 – 27) 9 (95% CI: 2 – 17)	<0.002 <0.05 <0.01 <0.05
Engelhardt et al.	2008	89/ 47	SF-36	28	71	Critical	24	Physical function Physical role Pain Vitality	20 11 21 10	<0.001 NS <0.001 NS
Johnson et al.	1997	44/ 35	DomainQ	42	71	Critical	12	Pain Barthel ADL score Mobility	-3 0.05 1	<0.01 <0.01 <0.001
v Hattum et al.	2011	482/ 53	EQ-5D Rand-36	29	73	Cladicant 72% Critical 28%	Mean 132	EQ-5D index Physical function Physical role Pain Vitality	-0.16 (95% CI: -1.9 – -0.27) -20 (95% CI: -30 – -9) -15 -1 -7	0.004 0.001 NS NS NS
Ozturk et al.	2012	101/ 93	WHOQOL	26	69	Claudicant 34% Critical 66%	3	Physical domain General QoL	+10.0 0.14	<0.0005 0.078
Wohlgemuth et al.	2008	74/ 74	SF-36	NR	57.7	Claudicant 30 Critical 70%	18	Physical function Physical role Pain Vitality	17 38 57 22	<0.05 <0.05 <0.05 NS
Nguyen et al.	2006	1404/ 732	VascuQol	36	69	Critical	12	VascuQol score Pain	2.27 2.7	<0.0001 <0.0001
Forbes et al.	2010	228/ 119	SF-36 EQ-5D VascuQol	38	NR	Critical	12**	EQ-5D index Physical function Physical role Pain VascuQoL score	0.34 14.35 18.4 28.07 1.77	NR NR NR NR NR

+ mean or median; * Effect size (difference in mean values between baseline and 2 years per SD at baseline) NS – not significant; NR – not reported ** 12 months follow-up was selected, because of very little follow-up at 36 months (original study endpoint)

Only articles reporting treatment specific, before and after data are listed.

Mobility scores were not significantly different from baseline, where ADL scores significantly improved with 2 points, one year after unilateral amputation. [19]

DISCUSSION

Our systematic review, involving approximately 4400 patients subjected to supervised walking therapy, revascularization or amputation revealed that for every performed intervention in PAD, some degree of increase in QoL scores was observed. However, this improvement varies significantly depending on the type of population (intermittent claudication vs. critical limb ischemia), the intervention performed and the type of QoL scoring method used. QoL scores also varied significantly with the duration of follow-up, which suggests that QoL in patients with PAD is very dynamic and multifactorial.

For patients suffering from intermittent claudication, walking advice itself can increase QoL scores as demonstrated by Nicolai et al. However, supervised walking exercise results in better QoL scores. Nordanstig et al. and Currie et al. reported increased QoL scores after walking exercise. They also stated that QoL could be further improved after invasive treatment with either endovascular intervention or surgical treatment.

In patients suffering from lower limb ischemia, endovascular treatment can result in improved QoL scores. A few studies analyzed the difference in QoL between endovascular and surgical intervention. They all showed increased QoL scores, but a significant difference between both treatments was not found. This suggests that the decision for treatment modality should not be based on QoL, which is similar after both types of intervention.

Surgical reconstructive intervention will increase patients' QoL scores, at least for short term analyses. The long term analysis, reported by van Hattum et al.[29] showed that the increment in QoL scores may not be everlasting, and QoL scores may deteriorate at long term follow-up.

Very little is known on QoL after major lower limb amputation. Only two studies assessed QoL after this type of intervention. Johnson et al[19] stated that QoL of patients suffering from lower limb ischemia is higher in patients who underwent successful revascularization compared to patients who underwent primary or secondary amputations.

Remes et al.[33] stated that PAD patients who received lower extremity amputation have lower QoL scores, compared to healthy control subjects. How PAD patients QoL relates to other chronically illnesses is unclear. This study only analyzed QoL after amputation and compared these scores to a healthy control subject, not evaluating QoL change over time.

There are several problems we encountered while working on our study. Firstly, QoL was analyzed with different questionnaires. The SF-36 (and the Rand-36) are more health status questionnaires, and not real QoL questionnaires. This is a subtle difference. A study performed by Breek et al.,[8] showed there is a discrepancy between QoL scores and health

status scores. Patients who scored relatively high on one scale, could easily score very low on the other. Therefore, it is hard to compare studies with different questionnaires in a reliable way. Health status questionnaires should generally not be used for assessing patients' QoL. Best results can be achieved by using either a general QoL questionnaire or a disease specific QoL questionnaire. In this review we used the term QoL even for studies that used health status questionnaires, because they presented their results as QoL scores. However, this is not absolutely accurate.

Also, the duration of follow-up in the included studies varied significantly, this makes results hard to compare. Moreover, the number of included patients in many studies is small, which may lead to type-II errors. Finally, no studies were randomized and most were retrospective observational studies. There may be significant publication bias in the included studies, as positive results are more likely to be reported and published.

In conclusion, QoL may benefit from all types of interventions performed in patients with PAD. However, increment is not homogeneous and depends on the studied population, type of intervention, scoring method and duration of follow-up. Little is known on long term follow-up QoL after vascular intervention. Only a small number of studies analyzed QoL in patients who underwent lower limb amputation. These studies were not specifically designed to analyze the effect of lower limb amputation on QoL scores before and after surgery.

Randomized studies are required to provide evidence of the true benefit of intervention in patients with PAD.

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Chapter 5

Midterm follow-up of quality of life following peripheral bypass surgery

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ABSTRACT

Introduction

Peripheral bypass surgery is an important treatment option for patients with peripheral arterial disease.

Short term results of Quality of life (QoL) after peripheral bypass surgery showed an increase in QoL at 3 months. Little is known on QoL at more than 2 years of follow-up. This study was performed to analyze QoL at midterm follow-up and overall survival after peripheral bypass surgery.

Methods

This study was part of a randomized control trial in which intermittent pneumatic compression was compared with compression stockings in the treatment of edema after bypass surgery.

Patients completed a QoL questionnaire before surgery, 14 days and 3 months postoperatively and at least 2 years after the original operation.

A survival analysis was performed to calculate survival for both the autologous and the PTFE group.

Results

The original study consisted of 93 patients, QoL midterm follow-up was achieved for 42 patients. QoL scores at midterm follow-up were comparable with the pre-operative baseline scores for both the Autologous group and the PTFE group. 3-year survival rates were 75% in the autologous group, versus 54% in the PTFE group.

Conclusion

Although peripheral bypass surgery significantly increased QoL 3 months after surgery, midterm follow-up showed a return to baseline scores.

No significant difference was found in survival between autologous and PTFE grafts.

INTRODUCTION

Peripheral Arterial Disease (PAD) is commonly caused by atherosclerosis of peripheral arteries. The prevalence of PAD is 3-10% in the current population, and ranges up to 15-20% in the elderly population.[1-3] Patients with PAD can be treated either with exercise therapy, or with revascularization. In patients with critical limb ischemia there is an indication for a revascularization procedure, which is either performed by a percutaneous transluminal angioplasty (PTA) or, when this is not possible (because of technical limitations, patient's co morbidities or lesion anatomy), by peripheral bypass surgery. Main outcomes of surgical vascular interventions include graft patency, limb salvage and operative mortality. [4]

Quality of life (QoL) is increasingly considered an important outcome measurement of vascular interventions. It is an individual assessment of physical, psychological and social well-being that is based on the definition of health by the World Health Organization (WHO).[5] QoL incorporates a patient's individual perception of its disease and functioning.[6] A generic QoL assessment instrument which has been satisfactorily used in patients suffering from cardiovascular disease is the World Health Organization Quality of Life assessment instrument (WHOQOL).[5, 7] The original WHOQOL-100, as well as an abbreviated version (WHOQOL-BREF) are reliable and have proven to be sensitive in detecting a change in QoL after surgery.[8, 9]

Patients suffering from PAD, who are not receiving treatment, cope with a deprived health status and QoL due to the effects of the disease and co morbid conditions.[6] However, improvements in both health status and QoL following peripheral bypass surgery have been observed at three months of follow-up.[9] Limb threatening ischemia which is treated with bypass grafting, shows an increase in QoL, especially on physical function, bodily pain, mental health and social function, at two years after treatment.[10-12]

In an earlier published article concerning short term effects of peripheral bypass surgery, we showed a significant increased QoL at three months, for both supragenicular and infragenicular bypass surgery at least for the physical domain.[9] As PAD is an ongoing disease, it is likely that beneficial effects on QoL are limited over time.

Recent studies report long term QoL in patients with PAD is decreased, compared to short term follow-up and compared to age matched healthy subjects.[13, 14]

As recent studies showed a discrepancy on long term results, we decided to analyze our population for QoL at 2 years of follow-up.

Aim of this study is to investigate if the beneficial effects of bypass surgery on QoL are still present at midterm follow-up.

As recent published studies reported a high number of lost to follow-up in patients suffering from PAD, we calculated survival for both the autologous as well as the PTFE group.

METHODS

Trial Design

A Single-centre randomized control trial (RCT) was performed to study the effects of intermittent pneumatic compression (IPC), compared to compression stockings (CS), as a treatment method of edema following peripheral bypass surgery. [15, 16] The effects of therapy on the formation and decreasement of edema, as well as detailed study information have been described in detail elsewhere. [15, 16]

Patients were enrolled between August 2006 and September 2009, midterm follow-up was investigated September 2011.

Original inclusion criteria

All patients suffered from PAD Rutherford category 3,4,5 and 6 on principal lower limb vessels or crural vessels as defined by the international (TASC II) consensus criteria.[3] None of the patients were eligible for endovascular treatment. There was an unobstructed iliac inflow and there was sufficient outflow through at least one crural vessel based on duplex, digital subtraction angiography (DSA) or magnetic resonance angiography (MRA) findings gathered pre-operatively.

Original exclusion criteria

Patients suffering from severe cardiac failure (NYHA class-III and IV) were excluded. Patients with known deep vein thrombosis or pulmonary embolism on admission were not included. Patients who demanded hemodialysis due to severe renal impairment were excluded. So were patients who experienced pre-existent limb edema due to severe liver failure (Child-Plugh score B and C), venous insufficiency, endocrinology diseases or who experienced manifest edema caused by medication. Patients with large ulcers (> 3 cm^2) on the plantar aspect of the foot or who had undergone amputations that would compromise the fit of the IPC pad were excluded. Further exclusion criteria were known malign diseases, enrolment in other trials and mental inability to understand the contents of the trial.

Approval was granted by both a nationally recognized medical ethical committee and the hospital's medical ethical review committee. All patients who participated in this study gave written informed consent.

Surgical Procedure

All patients underwent supragenicular or infragenicular femoropopliteal bypass surgery. Whenever possible, autologous grafting was performed. [17, 18] Alternatively, an expanded polytetrafluoroethylene (ePTFE) pre-cuffed Dynaflo® (Bard Peripheral Vascular Inc., Tempe, USA) graft for supragenicular femoropoliteal bypass reconstructions and the Distaflo® (Bard Peripheral Vascular Inc., Tempe, USA) for infragenicular femoropopliteal bypass reconstructions was used.

The 1:1 randomization to either IPC or CS was performed in a stratified way by bypass graft type, constituting two surgery groups (strata): Autologous and PTFE.

QoL Assessment

Patients were asked to complete the WHOQOL-BREF assessment questionnaire the day before surgery, and two weeks and three months after surgery.

In September 2011, all remaining patients who were originally included in our study, were attempted to be contacted and were asked to complete another WHOQOL-BREF questionnaire.

The WHOQOL-BREF is an abbreviated version of the WHOQOL-100. [5, 7] The WHOQOL-BREF consists of 26 questions of which 24 questions assess the domains: Physical health (7 questions), Psychological health (6 questions), Social relationships (3 questions) and Environment (8 questions). Each question has a five-point (1-5) Likert scale. The two remaining questions assess overall perceived health and make up the facet global QoL. Scoring of the various QoL domains was based on instructions of the WHO.[19] Following those instructions the four specific domain scores were essentially obtained by averaging the relevant questions and rescaling the averages towards a 0-100 scale, aligning such that higher scores represent a better QoL. The global QoL was left untransformed and kept a 1-5 scale after averaging.

For analysis of the development of patients' QoL across time, all four measurements were used.

Statistical analysis

Statistical analysis was performed with SPSS 16.0 software (SPSS Inc., Chicago, IL, USA).

Survival analysis of the time-to-death (in months) since surgery was performed using Cox-regression, stratified by bypass graft (autologous or PTFE), with the following explanatory variables: edema treatment (IPC or CS), age and gender. In order to test the effect of bypass graft on mortality we performed un unstratified Cox-regression with bypass graft as an explanatory variable rather than as stratification factor in the model. For illustrative purposes Kaplan-Meier curves were drawn based on product-limit estimates of the survival

probabilities, with the crude difference in survival between the two bypass grafts tested using the log-rank test.

Analysis of each of the QoL domains was performed using linear mixed modeling applied to the four repeated measurements of each domain. The following explanatory variables were considered: time (as categorical variable with four levels), bypass stratum (autologous or PTFE), edema treatment (IPC or CS), the stratum-by-treatment interaction, age at baseline (as continuous variable) and gender. Interest was in the evolution in time of each QoL domain, adjusted for stratum-by- treatment, age and gender. For that purpose we estimated the adjusted mean changes from baseline by specifying the appropriate contrasts in the model. A restricted maximum likelihood estimation method (REML) was used in order to deal with missing observations as properly as possible. No structure was imposed on the (co)variances of the four repeated measurements. We also performed an overall test (likelihood ratio test) of the interaction of time with stratum and treatment, for which we used a significance level of 0.01 per domain, in order to be sure that the overall significance level across all five domains of the WHOQOL does not exceed 0.05 (Bonferroni correction). Although we will report significant time-interactions in the results, the adjusted mean changes from baseline as presented derived from the simple model without those interactions. The reason for this presentation lies in our interest to focus on the time-behavior of the domain scores, which even in case of time-interactions can still be considered to be validly estimated in the simple model as an average time-behavior across the four stratum-by-treatment subgroups.

A possible non-response selection in respondents to the fourth QoL-measurement was analyzed using logistic regression analysis for investigating the dependency of the binary outcome non-response (yes/no) on the following baseline characteristics: bypass graft, treatment, age gender, QoL-domain scores and circumference of the affected lower leg.

RESULTS

Between August 2006 and September 2009, 101 patients were included in our study to undergo femoropopliteal bypass grafting due to severe PAD. In early follow-up 8 patients were lost due to either death or lower limb amputation before day 14 post-operatively and were excluded from the analysis. A total of 93 bypass grafts were analyzed in 92 patients, as one patient was included in both strata, having a autologous graft in one leg, and a PTFE one in the other.

In September 2011, 31 patients were deceased, leaving 61 patients available for a midterm QoL-measurement.

Of those patients, eight were irretrievable for the investigators and considered lost to follow-up. These patients were still alive according to hospital records. Another eight patients

refused to complete another questionnaire. Therefore, 46 patients participated in the mid-term follow-up of QoL. Two patients had too much missing values for the questionnaire to be analyzed. One patient was included in both strata, with an autologous bypass graft on one side and a PTFE graft on the other side. Only the autologous bypass data of this patient was included in the statistical analyses. One patient was excluded for analysis after answering the questionnaire, because her mental state was considered insufficient to fully understand the questionnaire. This resulted in 42 patients who completed the WHOQOL-BREF with a valid score. Figure 1 shows the study design.

Considering the pattern of missing values of WHOQOL-BREF across all four time points, it appeared that 87 of the 92 patients (95 %) had at least one valid QoL-measurement and 71 patients (77 %) had not more than one missing observation, of whom 24 (26 %) completed all four observations.

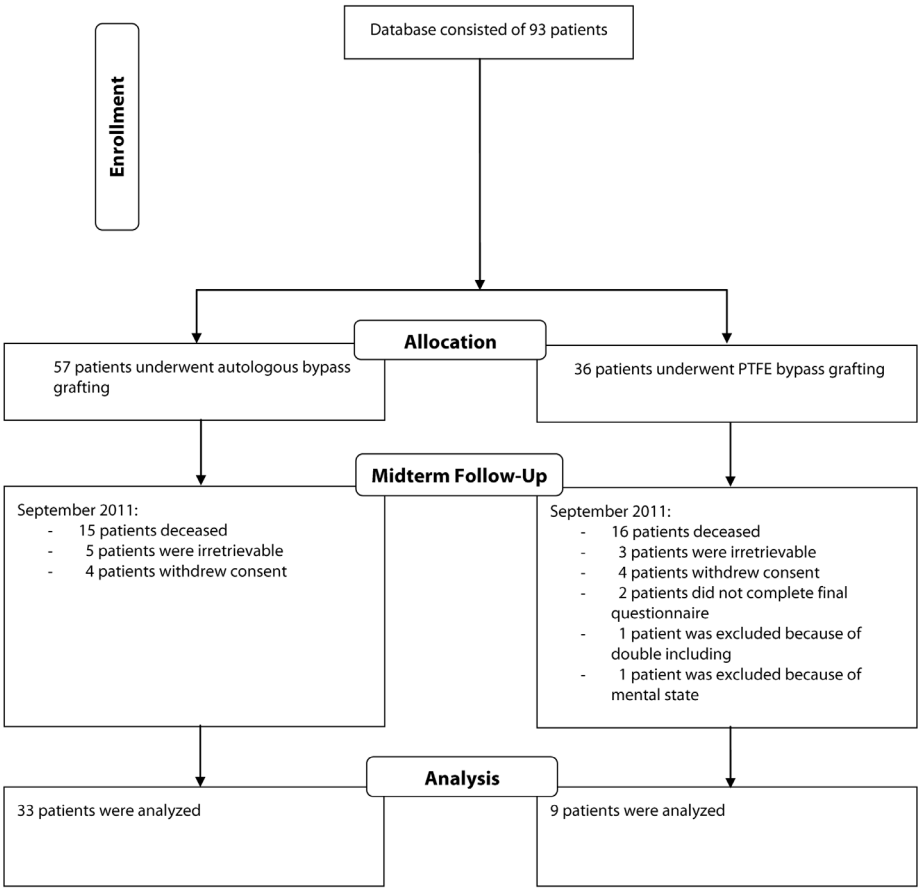

Figure 1) Trial profile.

Baseline characteristics are listed in Table 1, were Total is the baseline group, >2 year are all remaining patients in September 2011 and >2yearQoL are all patients who completed the midterm follow-up questionnaire. Table 2 shows patients characteristics, broken down by bypass type and allocated treatment.

Of the 42 patients who were analyzed for QoL, only 2 patients had undergone lower limb amputation. Both patients were in the PTFE group.

Table 1. Baseline characteristics.

Characteristic	Total N = 93	>2year N = 62	>2yearQoL N = 42
Mean age, years (SD)	70 (10)	68 (9)	68 (7)
Pre-operative Rutherford classification			
3 n/(%)	32 (34)	28 (45)	22 (51)
4 n/(%)	28 (30)	19 (31)	13 (30)
5 and 6 n/(%)	33 (36)	15 (24)	8 (19)
Sex, male/female (%)	69/24 (74/26)	50/12 (81/19)	35/8 (81/19)
Diabetes n/(%)	37 (40)	24 (39)	16 (38)
Autologous/PTFE (%)	57/36 (61/39)	42/20 (68/32)	33/10 (77/23)

Table 2. Baseline characteristics IPC vs CS trial.

Characteristic	Autologous		PTFE	
	CS (28)	IPC (29)	CS (19)	IPC (17)
Mean age, years	69	67	72	71
Rutherford classification				
3 n/(%)	11 (39)	13 (45)	6 (32)	2 (12)
4 n/(%)	10 (36)	5 (17)	5 (26)	8 (47)
5 and 6 n/(%)	7 (25)	11 (38)	8 (42)	7 (71)
Sex, male/female (%)	23/5 (82)	22/7 (76)	13/6 (68)	11/6 (65)

Non response analysis

As 50 patients out of the total of 92 did not participate in the fourth QoL-measurement, a logistic regression analysis was performed to determine which factors affected non-response. It appeared that the proportion of non-response to the fourth QoL-measurement was significantly higher in the PTFE group compared to the autologous group ($P = 0.020$). In this analysis we adjusted for age, treatment, gender, circumference of the affected lower leg at baseline and the five QoL-domain scores at baseline, which variables separately and simultaneously did not significantly contribute to the logistic regression model for explaining non-response (overall p = 0.12). Death could not explain the higher non-response rate in the PTFE-stratum. The proportions of deaths among non-respondents were similar in the autologous and PTFE-

strata: 15/24 and 16/26 respectively (p = 1.00). We conclude that patients in the autologous stratum responded significantly better to the fourth QoL-measurement than patients in the PTFE-stratum, which seems to be a mere effect of bypass type that we could not attribute to other variables or find another explanation for.

Survival

All patients were included in the survival analyses, using death and time-of-death since surgery as outcomes. We observed 15 deaths in a total follow-up of 2026 person-months in the autologous group (57 patients) and 16 deaths in 1045 person-months in the PTFE group (35 patients). One-year survival was 89% (product-limit estimate) in the autologous group, versus 83% in the PTFE group. Three-year survival was 75% in the autologous group versus 54% in the PTFE group. Overall three-year survival was 67%. (P:0.048 Log-Rank test) (Table 3). Survival data are plotted in figure 2. Patients at risk at subsequent time points are illustrated in the figure as well.

Table 3. Survival probabilities.

Characteristic	Autologous* N=57	PTFE* N=35	Overall N=92
One-year survival (%)	89	83	87
Two-year survival (%)	79	71	76
Three-year survival (%)	75	54	67

Survival probabilities (product-limit estimates). *P-value 0.048 (Log-rank test).

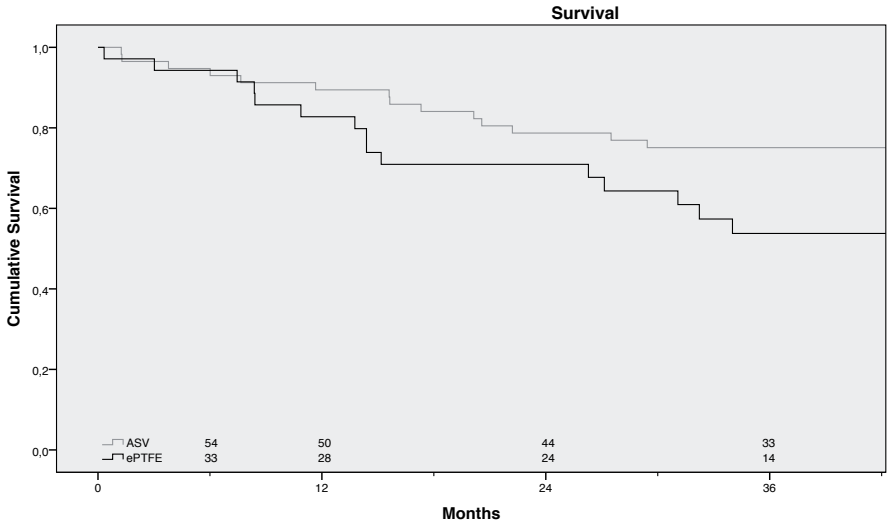

Figure 2) Patients' survival data.

Table 4. Raw domain scores.

		Autologous data			PTFE data		
Domain		**Mean**	**N (participants)**	**SD**	**Mean**	**N (participants)**	**SD**
Physical health	baseline	52.1	48	13.6	47.0	28	11.9
	14 days (stockings/pump)	54.8/59.7	23/24	15.3/16.2	57.9/52.6	17/14	14.2/17.9
	3 months (stockings/pump)	60.7/65.7	21/26	17.5/15.7	58.3/50.4	12/9	13.6/13.9
	> 2 years (stockings/pump)	56.7/61.7	18/15	18.7/14.3	55.4/34.6	4/5	28.3/21.6
Psychological health	baseline	72.2	48	16.2	64.9	28	13.4
	14 days (stockings/pump)	67.4/71.7	23/24	14.8/17.8	66.5/63.4	17/14	13.1/17.7
	3 months (stockings/pump)	67.3/73.4	21/26	15.7/14.5	65.6/55.6	13/9	11.7/15.0
	> 2 years (stockings/pump)	64.6/75.3	18/15	13.7/10.9	66.7/47.9	4/5	29.1/18.4
Social relationships	baseline	67.0	48	19.8	66.5	27	16.7
	14 days (stockings/pump)	63.9/69.4	23/24	19.0/21.2	69.8/66.4	16/14	19.5/16.4
	3 months (stockings/pump)	63.1/71.7	21/25	19.5/23.7	62.8/49.5	13/9	18.8/13.9
	> 2 years (stockings/pump)	60.2/65.3	18/15	20.9/20.4	79.2/30.6	4/5	16.0/18.0
Environmental	baseline	67.7	48	14.7	65.7	27	12.8
	14 days (stockings/pump)	69.4/71.5	23/24	14.5/17.3	68.9/62.9	17/14	15.8/17.4
	3 months (stockings/pump)	68.9/71.2	21/26	12.9/16.4	66.3/61.1	13/9	16.0/11.6
	> 2 years (stockings/pump)	69.6/67.9	18/15	11.3/12.4	66.4/54.9	4/5	15.4/16.5

Raw data of the various WHOQOL-BREF domains. The domains have a 0-100 scale.

A Cox proportional hazard survival analysis, stratified by bypass graft type, did not show a significant effect of treatment: the mortality rate ratio of IPC to CS was 1.07 (95 % CI: 0.52-2.20; p = 0.86), adjusted for age and gender. Only the effect of age was significant: the mortality rate increases by 8 % per year of age at baseline (95 % CI: 2.9-13.3 %; p = 0.002). Taking graft bypass type as explanatory variable in an unstratified Cox-regression along with treatment, age and gender resulted in a non-significant mortality rate ratio of PTFE to autologous of 1.51 (95 % CI: 0.73-3.12; p = 0.27).

QoL analysis

Descriptive statistics of the QoL-domains are presented in Table 4 by time as observed in the patients of the four groups considered (two bypass types by two treatments).

The estimated results of linear mixed modeling are presented in Table 5 as mean changes from baseline (with 95 % confidence intervals) and as mean levels by time, adjusted for bypass-stratum, edema treatment, the stratum-by-treatment interaction, age and gender. The restricted maximum likelihood procedure used is known to yield estimates that are properly corrected for missing observations. Out of the 92 patients, 87 contributed to the analysis.

Only on the physical domain a significant evolution ($p < 0.0005$) was found over time at the 0.01 level using F-tests. The physical domain scores show a significantly increasing QoL after 14 days and 3 months[9].

At long term follow-up this increased QoL score on the physical domain was not present any longer.

On psychological (p = 0.33), social (p = 0.059), environmental (p = 0.38) and general (p = 0.011) domains no significant effect of time was found at the 0.01 level.

The social domain was the only domain on which the effect of time was significantly different (p = 0.002) between the four stratum-by-treatment conditions, using a chi-square likelihood ratio test with 9 degrees-of-freedom. Particularly in the PTFE-bypass group undergoing pump treatment a strong decrease in social domain score was seen. However, the estimated time-effects as presented for the social domain (and also for the other domains) represent the properly averaged effects across the four stratum-by-treatment conditions, adjusted for age and gender. For the other domains there was no suspicion that their evolution in time was modified by stratum and treatment: physical p = 0.49; psychological p = 0.086; environmental p = 0.18; general p = 0.095.

Figure 3 shows the estimated adjusted means per domain for the physical health, psychological health, social relationships and environmental domains.

Table 5. QoL.

Domain		Adjusted means	Change from baseline	p-value	95% CI for change from baseline	
					lower	upper
Physical health	baseline	50.0	—	—	—	—
	14 days	56.8	6.8	<0.0005*	3.8	9.8
	3 months	59.9	10.0	<0.0005*	7.0	12.9
	> 2 years	54.0	4.0	0.12	-1.1	9.2
Psychological health	baseline	68.7	—	—	—	—
	14 days	67.6	-1.1	0.40	-3.5	1.4
	3 months	67.4	-1.3	0.30	-3.7	1.2
	> 2 years	64.7	-4.0	0.081	-8.5	0.5
Social relationships	baseline	66.0	—	—	—	—
	14 days	66.6	0.6	0.71	-2.5	3.6
	3 months	63.9	-2.1	0.28	-6.0	1.8
	> 2 years	59.2	-6.9	0.029	-13.0	-0.7
Environmental	baseline	66.4	—	—	—	—
	14 days	68.5	2.1	0.15	-0.8	5.1
	3 months	67.8	1.4	0.40	-1.9	4.7
	> 2 years	65.5	-0.9	0.64	-4.7	2.9
General QoL (1-5)	baseline	3.43	—	—	—	—
	14 days	3.57	0.14	0.047	0.00	0.27
	3 months	3.57	0.14	0.078	-0.02	0.29
	> 2 years	3.22	-0.22	0.12	-0.49	0.06

*Estimated means and mean changes from baseline of the various WHOQOL-BREF domains by time under study, adjusted for study, treatment, age and gender, resulting from linear mixed modeling. The domains have a 0-100 scale, except for the general domain, which has a 1-5 scale. * A significant difference is defined by a* P-*value < 0.01.*

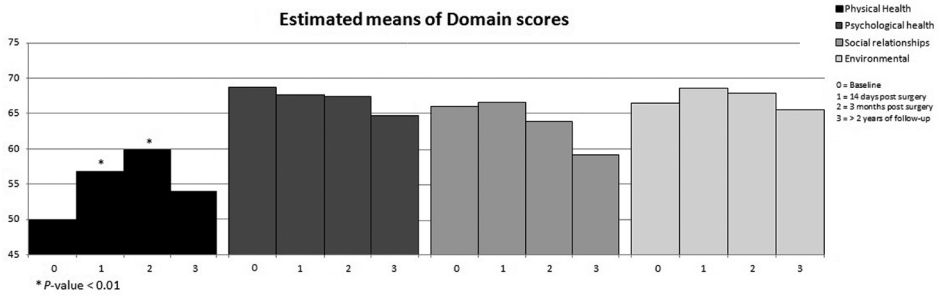

Figure 3) Estimated means of the WHOQOL-domain scores

DISCUSSION

An important result in our study is that the increase in short term QoL on the physical domain in patients who underwent peripheral bypass surgery is not consistent after a mean follow-up of 33 months. The results found with our last WHOQOL-BREF questionnaire showed no significant change compared to baseline QoL.

It seems that the gained increase in QoL after bypass surgery is of a temporarily nature.

A prospective trial performed by Aquarius et al., showed a significantly increased QoL, after one year of follow-up in patients diagnosed with peripheral arterial disease.[10] However, this study followed patients from the first time they visit the outpatient clinic, until one year later. Some patients were only treated with exercise therapy, some underwent a percutaneous transluminal angioplasty (PTA) and only a small number (13) were treated with bypass surgery. Therefore, this report gives no information of QoL after peripheral bypass surgery. Another prospective trial performed by Nguyen et al., addressed QoL after bypass surgery for critical limb ischemia only and found a significant improvement of QoL after one year of follow-up.[12] As they only followed patients with critical limb ischemia, there results are not applicable for the whole population of vascular patients.

A long-term QoL study, performed by Remes et al., showed a decrease in QoL after peripheral bypass grafting. At a mean follow-up of 2.7 years, patients who underwent revascularization (either treated with PTA or with surgical interventions) scored lower on QoL compared to case control group. [14] However, this study did not compare QoL in patients before and after surgery, but only analyzed QoL 2,7 years later. Therefore a benefit of intervention, could not be determined.

A prospective trial, performed by Engelhardt et al., on QoL 2 years after infragenicular bypass surgery showed an increased QoL on multiple domains, however for most domains the effect was slowly decreasing over time.[11] In this study, only patients treated for chronic limb ischemia were analyzed. And therefore, results are not completely comparable to a more diverse patient population. The used questionnaire was the Short Form 36, which should be interpreted as a health status questionnaire. Effects in changes in health status do not necessarily correspond to changes in QoL.

A recently published study by van Hattum et al, showed a decrease in QoL in patients after 11 years of follow-up, even in patients who were advent free, and coped with a patent graft.[13] As this study followed patients at a mean of 11 years, relatively few people were still alive and could participate in their QoL analyses. With a relatively large number of patients lost to follow-up, long term QoL is hard to determine in vascular patients. Their results are in concordance with ours.

This study was part of a RCT comparing IPC with CS for both autologous peripheral bypass grafting and PTFE bypass grafting. As in autologous bypass grafting the long-term results (90

days) of IPC vs Cs shows no significant difference [16], and in PTFE bypass grafting no significant difference between IPC and CS were found at all. [15] We are convinced that there is no influence of IPC vs Cs on long-term QoL or survival.

Three-year mortality rates were 25% for autologous bypass grafts and 46% for PTFE grafts, overall three-year mortality rate was 33% for both groups combined.

Such survival rates are not unusual as recently reported by Bradbury et al.[20]

The biggest limitation to our study, is the high rate of missing data on the last QoL measurement. Unfortunately more than half of the original included people were not able to participate in the last QoL analysis. The main reason for this was death.

As the WHOQOL-BREF questionnaire was able to detect a difference in QoL scores on the short term, we are convinced this questionnaire is suitable for use in vascular patients. However, there are more suitable QoL questionaires available for use in vascular patients. As long as a questionaire is designed for measuring QoL scores, and is proven to be effective in vascular surgery, it should be suitable. However, use of health status questionaires, like the SF-36 and familiar, questionaires, should be avoided, as research showed that health status is not reliable converted in QoL in vascular patients.[6]

Conclusion

Although peripheral bypass surgery significantly increases QoL at 2 weeks and 3 months after surgery, this is lost after midterm follow-up. Therefore, there is no midterm increased QoL benefit after bypass surgery. Quality of life as outcome, seems to have no relation with classical outcome measurements, such as graft patency, mortality and limb-salvage.

For a broader analysis of QoL in vascular patients, in different treatment groups, we have started a prospective study to analyze QoL in the elderly vascular patient, with critical limb ischemia.

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Chapter 6

A novel finding: the role of nurse practitioners in vascular surgery and the relation to quality of life, anxiety and depression scores

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ABSTRACT

Background

An increasing number of vascular surgery units expand their team with nurse practitioners (NP) to optimize patient care. There are no previously performed studies which assessed the influence of NPs on patients' Quality of life (QoL), anxiety and depressive symptoms levels.

Objective

The transition in care-taking from surgeon to NP in the vascular surgery unit of our hospital facilitated the comparison of both groups.

Methods

A prospective study was undertaken to analyze the NPs effects on QoL, anxiety and depressive symptoms scores. Two groups were analyzed, a group of patients treated by a vascular surgeon alone (surgeon group), and a group of patients treated by a NP supervised by a vascular surgeon (NP group). Patients completed the WHOQOL-Bref, STAI-State and CES-D questionnaires before and after intervention.

Results

214 patients were included in our study. Within groups there was a significant increase in physical QoL, with 5.2 points in the surgeon group and 4.4 points in the NP group. There was a significant decrease in anxiety scores, i.e., -3.8 points in the surgeon group and -5.4 points in the NP group. No differences were found for depressive symptoms. Between groups, no differences were found.

Conclusions

The same improvements were found for QoL and anxiety scores in both groups.

So vascular NPs are competent to explain procedures and guide patients through vascular interventions.

INTRODUCTION

Peripheral Arterial Disease (PAD) is commonly caused by atherosclerosis of peripheral arteries. The prevalence of PAD is 3-10% in the total population and 15-20% in the elderly population.[1-3] Comorbid risk factors, such as hypertension, hypercholesterolemia, smoking status and diabetes need to be established. These factors make the treatment of PAD multidimensional and time consuming. For this reason, an increasing number of vascular surgery units expand their care-teams with certified vascular Nurse Practitioners (NPs) who have more time for each patient than the surgeon. These NPs work closely with a supervising vascular surgeon and assist in the multidimensional approach of patients' treatment and reducing and treating risk factors. The NPs follow up on patients and guides patients through treatments, for outpatient and inpatient care.[4] Main outcomes of surgical vascular interventions include graft patency, limb salvage and operative mortality.[5] Increasingly, quality of life (QoL) is considered as an important outcome measurement for describing the quality of care.[1, 6] It is a patient oriented outcome measurement, based on an individual assessment of physical, psychological and social well-being that is based on the definition of health by the World Health Organization (WHO).[7] QoL incorporates a patient's individual perception of its disease and functioning.[8]

To our knowledge, no prior studies have examined the effects of NPs in vascular surgery on patients' QoL, anxiety and depressive symptoms scores. Therefore, we performed a study comparing the effect of a NP supervised by a vascular surgeon with a vascular surgeon alone on PAD patients' QoL, anxiety and depressive symptoms scores after treatment.

METHODS

Study Design

We conducted a prospective study to analyze the effect of NPs on patients QoL, anxiety and depressive symptoms scores before and just after vascular intervention.

Two groups were defined. In the surgeon group patients were only seen and treated by a vascular surgeon. The inclusion period was from October 2009 until December 2009.

In the NP group, patients were diagnosed by a vascular surgeon and then referred to a NP for treatment explanation and guidance through treatment. The inclusion period was from January 2010 until April 2010.

The formation of these groups was possible during the time that the vascular surgeon unit of our hospital was in the process of employing NPs to attend the patients to partly relief the surgeons of that task. Patients were allocated naturalistically to either group depending on the availability of a NP, there being no self-selection of patients.

All patients gave written informed consent.

Inclusion criteria

All patients diagnosed with PAD who were planned to undergo one of the following, elective, vascular interventions: central reconstructions for both abdominal aortic aneurysms and occlusive disease (endovascular (EVAR) and open), peripheral reconstructive procedures (autologous and polytetrafluoroethylene (PTFE) bypass surgery, endarterectomies of the femoral artery), endarterectomies of the carotid artery and Percutaneous Transluminal Angioplasty (PTA).

Exclusion criteria

Patients who needed urgent vascular surgery, patients with malignant diseases and patients who were not capable of answering the questionnaires were excluded from the study.

QoL, anxiety and depressive symptoms scoring

Patients were asked to complete the WHOQOL-BREF, STAI-state and CES-D questionnaires the week before intervention and at the first outpatient clinic follow-up visit after the intervention.

The WHOQOL-BREF is an abbreviated version of the WHOQOL-100. [7, 9] The WHOQOL-BREF consists of 26 questions of which 24 questions assess the domains: Physical health (7 questions), Psychological health (6 questions), Social relationships (3 questions) and Environment (8 questions). Each question has a five-point (1-5) Likert scale. The two remaining questions compose the overall facet general QoL and global QoL. Scoring of the various QoL domains was based on instructions of the WHO.[10] Following these instructions the four specific domain scores were essentially obtained by averaging the relevant questions and rescaling the averages towards a 0-100 scale, aligning such that higher scores represent a better QoL. The global QoL was left untransformed and kept a 1-5 scale after averaging. The reliability and validity of this questionnaire are good. [9]

The STAI-state is a reliable and valid 20-item questionnaire that assesses momentary anxiety. The range of scores is 20-80, the higher the score, the greater the anxiety is.[11]

The CES-D assesses depressive symptoms in patients. The range of scores is 0 – 60. [12] The reliability and validity of the CES-D are found to be good.[13]

Statistical analysis

Statistical analysis was performed with SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). A P-value <0.05 was considered statistically significant.

Analyses of each of the QoL domains as well as for the anxiety and depressive symptoms scores, were performed using linear mixed modeling. The following explanatory variables were considered: the age at baseline (as continuous variable), gender, performed intervention and indication to intervention. Interest was in the changes of scores at each QoL domain, anxiety score or depressive symptoms score, adjusted for age and gender, across time.

As this is a non-randomized study, the following explanatory co-variables were considered as potential confounders along with time (before/after) and treatment (NP/surgeon): age at baseline (as continuous variable), gender, performed intervention (6 categories) and indication to intervention (5 categories). The restricted maximum likelihood procedure used to estimate the coefficients of the linear mixed model is known to appropriately deal with missing values on one of both measurements of the outcome variables. No structure was imposed on the residual (co)variances. Special interest lied in the time-by-treatment interaction: do patients' scores change differently in time between NP-care and surgeon-care while adjusting for age, gender, indication and intervention?

RESULTS

A total of 214 patients was eligible to be included in the study. The surgeon group contained 81 patients and the NP group consisted of 133 patients. One hundred and six patients (49%) were included for PTA, 34 patients (16%) were included because of peripheral reconstructive surgery, 36 patients (17%) for carotid endarterectomies, 32 patients (15%) for abdominal aortic aneurysm surgery (11 open reconstructive and 21 endovascular) and six patients (3%) were included for central occlusive reconstruction. Baseline characteristics of patients in the two groups are shown in table1.

Table 1. Baseline characteristics of all included patients.

Characteristics	Surgeon group (n=81)	NP group (n=133)
Male/Female (% male)	56/27 (69)	98/35 (74)
Age: mean (in years) ±SD	67.9 ±9.6	67.9 ±10.0
Interventions N (%)		
PTA	48 (59)	58 (44)
Peripheral reconstructions	13 (16)	21 (16)
Carotid endarterectomy	9 (11)	27 (20)
AAA open reconstruction	6 (7)	5 (4)
AAA EVAR	4 (5)	17 (13)
Central occlusive reconstruction	1 (1)	5 (4)

Table 2. Raw mean scores and SD's on QoL, anxiety and depression scales.

Questionnaire		Surgeon group [N]		NP group [N]	
		t0	t1	t0	t1
QoL					
	Physical health	56.9 ±17.8 [51]	63.4 ±16.3 [60]	59.0 ±17.7 [78]	63.8 ±17.8 [89]
	Psychological health	69.5 ±14.0 [52]	71.4 ±11.1 [60]	69.3 ±13.1 [78]	71.2 ±13.1 [88]
	Social relationships	72.6 ±18.8 [52]	71.0 ±15.8 [60]	70.8 ±16.1 [78]	71.5 ±16.0 [89]
	Environmental	72.8 ±11.3 [52]	71.7 ±11.7 [59]	72.1 ±12.1 [78]	72.0 ±13.9 [88]
	General QoL	3.46 ±0.72 [52]	3.69 ±0.67 [60]	3.63 ±0.70 [78]	3.71 ±0.68 [89]
Anxiety	STAI	39.7 ±12.7 [56]	36.1 ±9.6 [62]	41.1 ±13.5 [85]	35.3 ±11.5 [95]
Depressive symptoms	CES-D	11.7 ±9.2 [53]	11.0 ±8.5 [58]	13.9 ±8.3 [82]	12.3 ±8.7 [90]

Scales for Physical health, Psychological health, Social relationships and Environmental are 0-100.
Scale for General QoL is 1-5. Scale for STAI-state is 20–80. Scale for Ces-D is 0-60.
[N] number of valid scores

Descriptive statistics of all instrument scores in either group at either time are presented in table2.

These data were inserted in the statistical analyses, which corrected the time and treatment effects for possible confounding by intervention, age, gender and intervention indication. The number of patients actually included in the linear mixed modeling analysis was the number that completed at least one of both measurements of the instrument and had no missing values on the explanatory variables. These numbers were 170 out of 214 for the QoL-domains and CES-D, and 175 out of 214 for the STAI-state.

In the surgeon group, the physical domain showed a significant mean increase in QoL after treatment (P=0.029). All other QoL domains showed no significant change from baseline. Depressive symptoms scores showed no significant change from baseline. Patients' mean anxiety scores were significant lower after treatment (P=0.023). (table3a)

In the NP group, scores on the physical QoL domain increased after treatment (P=0.026), while all other domains and depressive symptoms showed no significant change from baseline.

Patients' mean anxiety scores were significant lower after treatment (P<0.0005). (table 3b)

At both times, there were no significant differences in mean QoL, anxiety and depressive symptoms scores between the two groups.

The mean increase in the physical domain in the surgeon group was 5.2, compared to 4.4 in the NP group, which gives a non-significant difference in mean increase between groups of 0.8 (95% CI: -5.3 to +6.8; P:0.80) in favor of the surgeons. The mean decrease in state-anxiety was 3.8 in the surgeon group compared to 5.4 in the NP group, giving a non-significant difference in mean decrement of 1.6 (95% CI: -2.6 to + 5.8; P:0.45) in favor of the NPs.

None of the differences in mean changes between surgeon and NP were found to be significant. (Table 4)

Table 3a. Estimated means and mean change from baseline for the various WHOQOL-bref domains, STAI-state and Ces-D scores in the surgeon group adjusted for age, gender, indication and intervention.

		Adjusted means	Change from baseline	p-value	95 % CI for change from baseline	
					Lower	Upper
Physical health	Baseline (t0)	58.5	—	—	—	—
	t1	63.7	5.2	0.029	0.55	9.85
Psychological health	Baseline (t0)	69.6	—	—	—	—
	t1	70.9	1.2	0.44	-1.89	4.34
Social relationships	Baseline (t0)	72.2	—	—	—	—
	t1	70.6	-1.6	0.45	-5.84	2.62
Environmental	Baseline (t0)	73.1	—	—	—	—
	t1	71.7	-1.4	0.38	-4.43	1.70
General QoL	Baseline (t0)	3.48	—	—	—	—
	t1	3.66	0.17	0.079	-0.02	0.37
STAI-state	Baseline (t0)	40.2	—	—	—	—
	t1	36.5	-3.8	0.023	-6.99	-0.52
CES-D	Baseline (t0)	12.0	—	—	—	—
	t1	11.1	-0.9	0.48	-3.14	1.42

Scales for Physical health, Psychological health, Social relationships and Environmental are 0-100.
Scale for General QoL is 1-5. Scale for STAI-state is 20–80. Scale for Ces-D is 0-60.

Table 3b. Estimated means and mean change from baseline for the various WHOQOL-bref domains, STAI-state and Ces-D scores in the NP group adjusted for age, gender, indication and intervention.

		Adjusted means	Change from baseline	p-value	95 % CI for change from baseline	
					Lower	Upper
Physical health	baseline	59.0	—	—	—	—
	t1	63.4	4.4	0.026	0.55	8.3
Psychological health	baseline	70.3	—	—	—	—
	t1	71.3	1.1	0.43	-1.57	3.68
Social relationships	baseline	71.4	—	—	—	—
	t1	71.3	-0.1	0.93	-3.69	3.39
Environmental	baseline	72.0	—	—	—	—
	t1	71.7	-0.3	0.83	-2.88	2.30
General QoL	baseline	3.64	—	—	—	—
	t1	3.72	0.08	0.34	-0.08	0.24
STAI-state	baseline	40.7	—	—	—	—
	t1	35.3	-5.4	< 0.0005	-8.01	-2.69
CES-D	baseline	13.8	—	—	—	—
	t1	12.2	-1.5	0.11	-3.40	0.35

Scales for Physical health, Psychological health, Social relationships and Environmental are 0-100.
Scale for General QoL is 1-5. Scale for STAI-state is 20–80. Scale for Ces-D is 0-60.

Table 4. Estimated mean changes between baseline and t1 on the various WHOQOL-bref domains, STAI-state and Ces-D scores, both groups compared, adjusted for age, gender, indication and intervention.

Questionnaire		Surgeon group	NP group	Difference in mean	p-value	95 % CI for difference in mean	
						Lower	Upper
QoL							
	Physical health	5.2	4.4	0.77	0.80	-5.28	6.83
	Psychological health	1.2	1.1	0.17	0.93	-3.90	4.25
	Social relationships	-1.6	-0.1	-1.46	0.60	-6.97	4.06
	Environmental	-1.4	-0.3	-1.08	0.60	-5.09	2.94
	General QoL	0.17	0.08	0.10	0.46	-0.16	0.35
Anxiety	STAI	-3.8	-5.4	1.60	0.45	-2.59	5.78
Depressive symptoms	CES-D	-0.9	-1.5	0.67	0.66	-2.29	3.62

DISCUSSION

Thus far are no reports available about QoL, anxiety and depressive symptom scores in patients treated and guided by a (vascular) NP. We wanted to establish whether NPs would influence patient oriented outcome measurements differently than vascular surgeons themselves.

QoL on the physical domain did increase in both groups after treatment while anxiety scores significantly decreased after treatment. However no differences between both groups were found.

The increased QoL on the physical domain, was about 5 points. This is in concordance with previously performed studies on QoL after bypass surgery, in which a short term QoL results were investigated. The authors found an increased QoL 14 days after peripheral bypass surgery of about 5 points, and even more increased QoL scores at 3 months of follow-up (10 points).[14]

Very few studies have investigated the beneficial effects of NPs in addition to an already existing care team. Recently, Finn et al. described the results of adding NPs to a discharge team. They state that the discharge process improved by many aspects, but no change in readmissions were observed[15].

It seems to be quite difficult to assess the actual benefits of adding NPs to an existing team.

Conclusion

We conclude our vascular NPs, at least for patients' QoL, anxiety and depression scores, perform equally to the vascular surgeons. This shows that they are capable of explaining intervention procedures to patients, and their guidance through treatment is comparable to those of vascular surgeons.

Practice implications

Since NPs partly relieve vascular surgeons, we see this as a large benefit. As the number of patients submitted to a vascular clinic is growing, NPs can lower the vascular surgeons workload and lower costs at the same time, without losing quality of care.

Future research should focus on patients' satisfaction with care. More studies are needed to adequately determine the role and effect of NPs in vascular surgery.

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Chapter 7

The registration of complications, a comparison between two different methods in vascular surgery

Accepted: Surgical Infections

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ABSTRACT

Introduction

Complication registration is an important instrument to measure quality of healthcare. A reliable registration is dependent on definitions, case-finding method and registration. The aim for this study is to compare two different registration methods for surveillance of surgical site infections in one clinic.

Methods

All patients who received surgical treatment on the abdominal aorta, or peripheral vascular procedures, between march 1st 2009 and march 1st 2010, were included from both the surgical database and the microbiology database.

The surgical database scored positive for surgical site infection in case of; positive wound swab, the need for wound drainage, or when antibiotic treatment was needed.

The Microbiology department used criteria from the Centers for Disease Control and Prevention (CDC). They based their score on; redness, heat, swelling or pain around the wound within 30 days after the procedure, and the presence of a positive swab, drainage of the wound, or pus after a diagnostic puncture.

Results

The surgical complication database included 218 patients, 20 of which had a surgical site infection (9.2%). The microbiology database included 236 patients, 33 of which had a surgical site infection (14%). The databases were merged and all infections were ascertained by an expert team. The surgical database had a sensitivity for surgical site infections of 57%, whereas the microbiology database scored 93% sensitivity. ($P < 0.05$)

Conclusion

Medical doctors registered less reliable in comparison with trained infection control practitioners. This raises questions regarding comparability of infection rates between institutes to judge the quality of hospital care.

INTRODUCTION

Surgical complications are one of the most used outcome measures in hospitals.

The definition of complications has changed over time, from events directly related to surgery to a much wider combination of factors which can be relevant in surgical outcome.[1-3] The Dutch Association of Surgeons (ASN) has developed a national standardized system for the registration of complications to produce reliable information on surgical outcome and create a benchmark. [4] Complications are real time documented in this system by the physician who diagnoses the event. This form of registration is questioned by different authors for efficiency and objectivity.[5] One of the possible complications after surgery are surgical site infections, which are registered by surgeons or residents. Another way to register complications (in this case, surgical site infections) is by specially trained infection control nurses who have no direct connections to a surgical department. In our hospital, there are two different methods of registering surgical site infections in vascular surgery. The first is the vascular surgical complication database, in which we document complications according to the definition and classification system of the ASN. Besides the surgical registration system, the department of Microbiology and Infection prevention performs a surveillance of surgical site infection by infection control nurses. The aim of this study is to compare both registries used in our hospital for the incidence of surgical site infections after vascular surgery.

METHODS

All patients who underwent elective or urgent vascular surgery, either aortic or lower limb arterial surgery, between March 1st 2009 and March 1st 2010 were analyzed in both databases. The surgeon or resident were responsible for the registration in the surgical database. Surgical site infection was scored in case of clinical manifestations of infection (areas of redness, heat, swelling or pain around the wound), in case of the need for wound drainage, or when antibiotics were needed. For registering complications, all the charts of vascular patients were fitted a new form, on which different types of complications could be scored prospectively. All vascular patients admitted to our hospital were included in this registration. Surgical site infections were registered both during clinical period, as well as at the out-patient clinic, and documented in the patient file and afterwards entered in an electronic database file. (Microsoft Access).

The Microbiology and Infection Prevention database scored surgical site infections based on the criteria from the Centers for Disease Control and Prevention (CDC). The main criteria are the presence of: redness, heat, swelling or pain around the wound within 30 days after the initial procedure, and the presence of a positive culture, drainage of the wound, or pus after a diagnostic puncture. Patients were included based on the planning list of the operat-

ing theatre and were followed prospectively for the development of a surgical site infection. The medical records were searched for the presence of the criteria mentioned above. Post-discharge surveillance was performed until 30 days after the surgical procedure. The microbiology and infection prevention department documented complications in a SPSS database. Patients who met our inclusion criteria were selected from both databases, based on operation code and operation date.

The patients were matched and merged into one aggregated database.

All patients with a discordant score in the two databases were reviewed by an expert team consisting of a surgeon and medical microbiologist who had not been involved in the initial assessment. They used the above mentioned criteria of the CDC.

Statistical analysis was performed with SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). The Fisher Exact Test was used to calculate statistical significance. A *P*-value < 0.05 was considered to be statistically significant.

RESULTS

The surgical database contained a total of 218 patients, of which 20 (9,2%) had a surgical site infection (table 1). After aorta surgery there were 7 surgical site infections (n=127), after peripheral vascular surgery there were 13 surgical site infections (n= 91).

In the Microbiology database 236 patients were included, 33 (14%) of which scored positive on surgical site infection (table 1). After aorta surgery there were 14 surgical site infections (n=133), after peripheral vascular surgery there were 19 surgical site infections (n= 103).

Because of the discordant number of patients in both databases, we merged both databases into one, thus analyzing only patients who were present in both databases.

For the 28 patients present in the surgical database, but absent in the microbiology database, no infection was scored. The microbiology database contained 45 patients that were not included in the surgical database and in this population 2 surgical site infections were present.

Table 1. Infection rates.

	Surgical	Microbiology
total patients (n)	218	236
number peripheral surgery (%)	91 (42)	103 (44)
number aortic surgery (%)	127 (58)	133 (56)
number of surgical site infections (%)	20 (9,2)	33 (14)

After merging both databases, 191 matching patients were found and in 155 no infection was scored. In 15 patients an infection was documented in both databases.

For patients (n= 21 (11%)) who had discordant results the patients' charts were reviewed by the researcher, surgeon and medical microbiologist who where blinded to the initial scores. After revision, of the 191 matching patients, there were 161 patients without an infection and 30 patients scored positive on infection. (table 2) (Figure 1 shows the dataflow). These

Table 2. After chart revision.

	SurgicalDB infection positive	SurgicalDB Infection negative
Microbiology DB infection positive	15	13
Microbiology DB infection negative	2	161

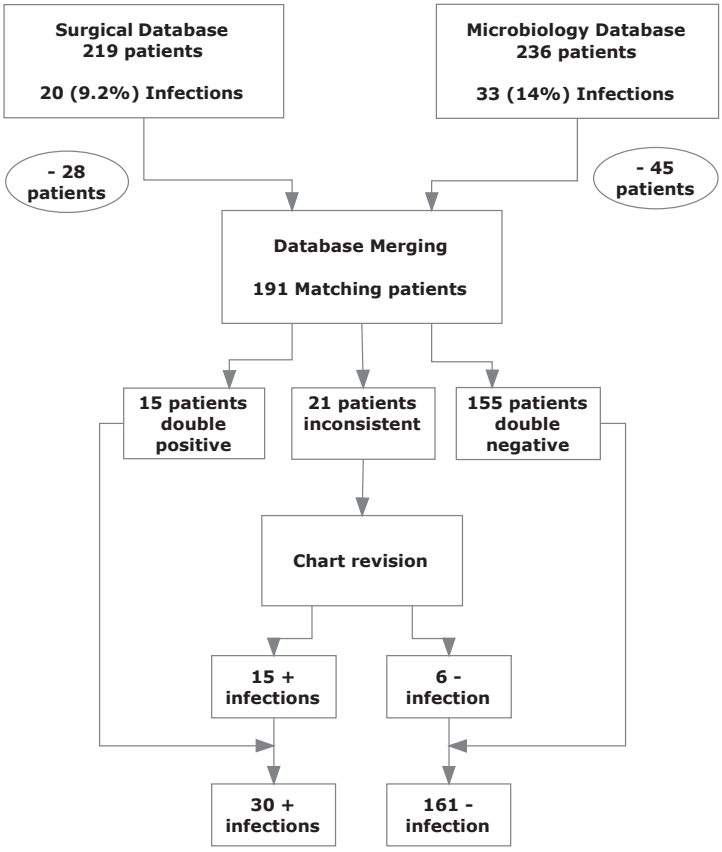

Figure 1) Study dataflow.

30 patients were considered the "true" positive patients with a surgical site infection, after review by the expert panel.

Of all patients who scored positively for a surgical site infection, 13 patients were only scored in the microbiology database.

Of all 13 patients, who were not positively scored in the surgical database, 10 infections occurred after patients were discharged. However, all 10 patients with surgical site infection, were readmitted to the hospital for proper diagnosis en treatment. That meant that they could have been detected by the surgical registration method as well.

The Surgical database sensitivity for a surgical site infection was 57% and the sensitivity in the microbiology database was 93%. ($P < 0.001$)(Table 3)

Table 3.

	N/N	%
Surgical Sensitivity	17/30	57 *
Surgical Specificity	158/161	98
Microbiological Sensitivity	28/30	93 *
Microbiological Specificity	158/161	98

* $P < 0{,}001$ (Fisher Exact Test)

DISCUSSION

This study shows that surgical site infections are scored more reliable by infection control nurses than by medical doctors.

One of the explanations for this result could be, data managers are focused on registering complications from a medical chart, to an electronic database. Registration is performed for clinical patients, as well as patients who are in follow-up at the out-patient clinic.

Whereas for doctors, the registration of a complication is one of the many aspects of his job. Doctors recognize complications, treat them, explain them to patients and document them in the patients' medical chart. Registration (in a complication registration), unfortunately, is for a patient the least concerning part of the doctors job. Therefore documentation of complications, either on a paper form, or in an electronic database, is easily overlooked.

As doctors have to recognize and register not only possible surgical site infections, but all the complications which could possibly occur after surgical intervention, the maintenance of a complication database is more work, compared to the infection prevention nurse, who only documents surgical site infections. This might be, at least partially, an explanation for our results. Sensitivity rates for the other complications registered in the Surgical database are hard to calculate, as there are no other registrations to compare these with. Therefore it is almost impossible to calculate the 'true' values for comparison.

Discordant results after combining both databases are partly explained by the way the registration was performed. Some patients received multiple and different operations, as we selected patients by operation codes from our databases, the right code must be noted in the database. This was not always the case, some patients were listed only with a different code, which fell not in our inclusion operation codes. Therefore this patient was not included from one database, however, if the other database registered the right code, it was included from the other database. For calculating sensitivity and specificity rates we needed a true value of surgical site infections after vascular surgery, which we could compare to the results from each database. As the real true value is not known, we made our own reference with the true infections. After discussion in our expert panel meeting, a decision was made on which patients really had underwent a surgical site infection, and which did not. This was done, retrospectively, based on al prospectively registered information.

The missed infections in the vascular database occurred almost all after the patient's discharge. However, every patient with a surgical site infection, which was not recorded in the vascular database, was admitted to the hospital again, and received the appropriate care.

The surgical registry failed to establish the number of surgical site infections after vascular surgery, because this complication was not properly registered into the database by the care team. As most surgical site infections occurred after patients discharge, especially the outer-patient-clinic registration is unreliable. A possible improvement for this problem, could be assigning a specially trained data-manager, to register all complications in a database.

Surgical site infection after vascular surgery is a frequent complication associated with increased morbidity and significant additional costs [6-17]. Therefore adequate registration is necessary, so evaluation in time is adequate and reliable.

As more states in the United States of America are mandatory in reporting their Healthcare associated infections [18], the reliability of the used registration method is becoming more and more important.

When in one hospital, in one surgical department, two different registrations methods produce such different values, it is clear that published results are more dependent on the type of registration, than they are on the quality of healthcare.

Best result will be obtained when surgeons and the department of Microbiology and Infection prevention work together in identifying and registering all surgical site infections.

Our center now uses a scheduled meeting with a vascular surgeon, a medical microbiologists and a trained infection control nurse. Here every possible surgical site infection is discussed and registered, to produce a reliable database.

Considering the reports in literature, with an incidence for surgical site infections from 4% to 43 %, [6-17] our surgical site infections score seems acceptable.

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Chapter 8

Evaluation of Staphylococcus aureus nasal carriage screening before vascular surgery

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ABSTRACT

Introduction

Staphylococcus aureus is the most important pathogen in the development of surgical site infections (SSI). Patients who carry *S. aureus* in the nose are at increased risk for the development of SSI in cardiothoracic and orthopedic surgery. In these populations it has been shown that the risk for SSI can be substantially reduced by eradicating *S. aureus* carriage. For vascular surgery the relation between nasal carriage and surgical site infections has not been clearly investigated. For this reason we performed this study to analyze the relation between *S. aureus* nasal carriage and SSI in our vascular surgery population.

Methods

A prospective cohort study was undertaken, including all patients undergoing vascular surgery between January first 2010 and December 31th 2010. Before surgery patients were screened for *S. aureus* nasal carriage using a PCR technique. The presence of SSI was recorded based on criteria of the CDC.

Results

Screening was performed in 224. Of those, 55 (24.5%) were positive, 159 (71.0%) were negative and 10 (4.5%) were inconclusive. In the screened vascular population 4 *S. aureus* SSI occurred in the 55 carriers compared with 6 in 159 non-carriers (p=0.24). A stratified analysis revealed a 10-fold increased risk in nasal carriers undergoing central reconstruction surgery (3 *S. aureus* SSI in 20 procedures versus 1 in 65 procedures in non-carriers, p=0.039).

Discussion

In patients undergoing central reconstruction surgery nasals carriers are at increased risk for the development of *S. aureus* SSI. These patients will probably benefit from perioperative treatment to eradicate nasal carriage.

INTRODUCTION

Staphylococcus aureus nasal carriage increases a patient's risk for developing a health care-associated infection with this micro organism, at least after cardiac surgery, orthopedic surgery and in peritoneal dialysis. [1-5] Preoperative screening for nasal carriage and subsequent treatment of carriers with mupirocin and chlorhexidine reduces the risk for the development of hospital-acquired *S. aureus* infections by 79% for deep-seated infections and 55% for superficial infections. [6] Consequently, the mean duration of hospital stay is reduced in treated carriers by approximately 2 days. A cost benefit analysis shows that the strategy is cost-effective and saves lives. [7]

In vascular surgery little is known about the relation between nasal carriage of *S. aureus* and surgical site infections (SSI).

For this reason we conducted a prospective analysis of *S. aureus* nasal carriage in patients undergoing vascular surgery and the occurrence of surgical site infections.

METHODS

A prospective cohort study was performed on all patients who underwent elective vascular surgery between January 1st 2010 and December 31th 2010 in the Amphia Hospital, Breda, The Netherlands.

Operations included were; central reconstructions for both abdominal aortic aneurysms and occlusive disease (endovascular (EVAR) and open), peripheral bypass procedures (autologous and PTFE), endarterectomies of the femoral and carotid artery, embolectomies and Artero-venous access procedures.

Patients were screened on the day that they were admitted to the vascular surgery department of the Amphia hospital in Breda. Screening was performed using a dry, sterile swab, which was rotated four times in each nostril. The swab was placed in saline and centrifuged. Part of the sample was processed for polymerase chain reaction (PCR) on the presence of *S. aureus*, and part was inoculated onto a blood agar plate, to allow nasal and infecting strains to be compared in case a surgical site infection did occur.

The GeneXpert MRSA/SA Assay (Cepheid, Sunnyvale, CA) is a real-time PCR-based method, which identifies *S. aureus* and also can differentiate whether a *S. aureus* is a Methicillin-susceptible (MSSA) or Methicillin-resistant (MRSA).[8-11]

Patients were followed prospectively for the development of Surgical site infections (SSI) which were defined according to the criteria of the Centers for Disease Control. [12]

The main criteria are the presence of: redness, heat, swelling or pain around the wound within 30 days after the initial procedure, and the presence of a positive culture, drainage of the wound, or pus after a diagnostic puncture. When prosthetic material had been used the

follow up was extended up to one year. Infections were differentiated between superficial, deep seated and organ based infections.

Screening was performed as part of the infection control strategy of the Amphia hospital using non-invasive sampling. Approval of the medical ethical committee and informed consent were not applicable.

A stratified analysis was performed for patients with central vascular surgery, as we expected a possible difference for the importance of nasal carriage between patients suffering from peripheral arterial occlusive disease (PAOD) and patients suffering from central diluting vascular disease.

Patients suffering from PAOD have a gradient of lower limb ischemia, which ranges from impaired walking distance, due to inappropriate blood flow to the lower limbs (intermittent claudication), to critical limb ischemia. In those patients hypo perfusion of the lower limbs often results in ischemia or even ischemic ulcers. These ulcers may be colonized with pathogens, which may be introduced into the surgical wound. This may alter the role of nasal carriage as there is an additional source of *S. aureus* in the patient.

Statistical analyses was performed with SPSS software v 19.0 (SPSS Inc., Chicago, IL, USA), the Fisher exact test was used to determine significance.

A multivariate analysis was performed for evaluation of several other known risk factors on the development of SSI's. Chi-square test was used to determine significance.

A *P*-value <0,05 was considered significant.

RESULTS

As shown in table 1, 224 patients were included. There were a total of 17 SSI's, 13 of which were superficial, and 4 where deep seated SSI's. The PCR of nasal swabs showed that 159 (71.0%) were negative for *S. aureus*, 55 (24.6%) were positive and 10 (4.5%) were inconclusive because of inhibition of the amplification reaction. In 214 patients with conclusive results, there were 16 surgical site infections, 10 of which were caused by *S. aureus* and 6 by other pathogens.

The incidence of surgical site infections in nasal carriers of *S. aureus* is 4 out of 55 (7.3%), whereas the incidence in non-carriers is 6 out of 159 (3.8%)(RR=1.9, 95%CI 0.5-7.5).

A stratified analysis was performed for central reconstruction surgery, peripheral bypass surgery and other procedures as shown in Table 2. In peripheral bypass surgery 2 *S. aureus* surgical site infections occurred in patients who did not carry *S. aureus* (n=45) and no infections in Patients who carried *S. aureus* (n=17) (*P*>0.05).

Table 1. Baseline and surgical characteristics and surgical site infections caused by *S. aureus.*

Characteristics			
N	224		
Sex, Male/Female (%)	171/53 (76.3/23.7)		
Age mean (SD)	70 (10.1)		
Type of Surgery N/(%)		N° of SSI's (%)	N° of *S. aureus* SSI (%)
Aortic open repair	52 (23)	6 (11)	3 (6)
Aortic endovascular repair	38 (17)	1 (3)	1 (3)
Femoral endarterectomy	34 (15)	3 (9)	3 (9)
Peripheral bypass surgery			
Autologous bypass	42 (66)	2 (5)	1 (2)
PTFE bypass	22 (34)	4 (18)	1 (5)
AV access surgery	14 (6)	0 (0)	0 (0)
Peripheral embolectomy	4 (2)	1 (25)	1 (25)
Carotid endarterectomy	18 (8)	0 (0)	0 (0)
Total	224 (100)	17 (8)	10 (4)

Table 2. Relation between *S. aureus* carriage and surgical site infections caused by *S. aureus.*

Surgery type	*S. aureus* SSI-rate (%)	RR	95% CI	P-value*
Central reconstructions (n=90)				
Non-carriers (n=65)	1 (1,5)			
Carriers (n=20)	3 (15)	9.8	1.1-88.6	0.039
Inconclusive (n=5)**	0			
Other procedures (n=134)				
Non-carriers (n=95)	5 (5)			
Carriers (n=35)	1 (3)	0.5	0.1-4.4	0.480
Inconclusive (n=5)**	0			

* Fisher exact test; **Inconclusive screening results were not used for analyzation

In the central reconstruction surgery population, there was 1 surgical site infection in patients who did not carry *S. aureus* (n=65), this SSI occurred after an aortoilliac bypass procedure because of occlusive disease, and there were 3 infections with *S. aureus* in Patients who carried *S. aureus* (n=20), 1 SSI after an EVAR procedure, 1 SSI after open aneurysm repair and 1 after an aortoilliac bypass procedure because of occlusive disease (RR=9.8, 95%CI 1.1-88.6, P=0.039).

A multivariate analysis including 3 other risk factors known from the literature for the development of surgical site infections, did not alter the effect of nasal carriage (Table 3).

Table 3. Relation to *S. aureus* carriage and surgical site infections caused by *S. aureus*.

	S. aureus SSI-rate	RR	95% CI	P-value
Central reconstruction (n=85)				
non-carriers	1/65			
carriers	3/20	9.75	0.94-242.31	0.039
Peripheral bypass surgery (n=62)				
non-carriers	2/45			
carriers	0/17	na	na	1.000
Other procedures (n= 67)				
non-carriers	3/49			
carriers	1/18	na	na	1.000

DISCUSSION

Our study shows that surgical site infections in vascular surgery occur relatively frequent and that the majority (62%) are caused by *S. aureus*. Especially the central reconstructions and the peripheral bypass procedures have a relatively high incidence of surgical site infections, compared to, for example, carotid endartectomies and AV access procedures.

Overall there is no significant relation between nasal carriage of *S. aureus* and the occurrence of surgical site infections. However, a stratified analysis on patients who underwent abdominal aortic surgery shows a significant association. The effect in this group is comparable to what has been found previously in cardiothoracic and orthopedic surgery.[1-3, 5]

In other vascular procedures no significant effect was found. The infections in this group mainly occurred in peripheral procedures of patients with occlusive disease. Patients with occlusive vascular disease cope with insufficient blood flow to at least one of the, mostly lower, limbs. This insufficient blood flow is often associated with ischemic disease, e.g. gangrene of non healing ulcers. As this wounds can be infected or colonized prior to surgery with a large scale of different pathogens, this could limit the role of *S. aureus* nasal carriage. In our study no significant effect after peripheral vascular surgery was found. However, for one patient who was positive for *S. aureus* nasal carriage and who developed a *S. aureus* SSI, accidently a sample of both the nasal swab as well as a wound swab were available for typing. This showed that the two trains were identical. Considering the small number of patients and the frequent presence of wounds before surgery we consider the role of nasal carriage in peripheral vascular surgery unresolved.

All *S. aureus* strains were methicillin susceptible and no MRSA was found which reflects the low rate of MRSA in Dutch hospitals. Also all strains were mupirocin susceptible. Potentially administration of mupirocin could reduce the risk of nasal carriage.[6] A cost effectiveness analysis showed that treating every patient with *S. aureus* eradication therapy, without screening for nasal carriage is the most cost-effective way for preventing surgical site infec-

tions.[7] However, as recent studies reported mupirocin resistant MRSA strains[13, 14], it should only be used in proven MSSA and MRSA carriers to limit the risk for development of further resistance.

Based on the results of this study we conclude that *S. aureus* carriers who undergo central reconstructive surgery have a significant higher risk for the development of SSI which can be decreased by perioperative eradication of *S. aureus* in nasal carriers.[6]

This is important because infection with *S. aureus* after aortic reconstructions is related to severe complications and a high mortality rate.

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Chapter 9

General discussion and summary

GENERAL DISCUSSION

With the increasing incidence[1, 2] of PAD and the further development of minimal invasive treatment options, the role of vascular surgery is changing. In contrast to classical outcomes, like patency and limb salvage rates, new outcomes are increasing in popularity. In addition, new techniques are developed for increasing graft performance. For example, changes on the distal anastomosis and new techniques on how to perform a proximal anastomosis.

Chapter 2 describes our results from a comparative study on the newly developed pre-cuffed ePTFE bypass graft. Despite the newly designed distal cuff, the patency rates of the autologous grafts, especially for infragenicular bypass grafting, were significantly better compared with the pre-cuffed ePTFE grafts. So, the autologous vein still offers superb performances in peripheral bypass surgery in comparison to prosthetic conduits. For patients who require a peripheral bypass, but who do not have a suitable ASV or other vein to be used as bypass, a pre-cuffed ePTFE bypass offers reasonable alternatives. Also there is a fairly acceptable limb salvage rate for pre-cuffed ePTFE bypasses. When we compare our pre-cuffed ePTFE results to other grafts, like the Heparin bounded ePTFE graft, the Heparin bounded grafts show higher patency rates.

Daenens study showed very impressive patency rates with Heparin bounded synthetic bypasses [3], however their study contains very few autologous grafts, so in our opinion their results are hard to compare to our results. For determining the optimal non autologous graft in peripheral bypass surgery, a prospective trial comparing both the pre-cuffed ePTFE grafts and the Heparin bounded grafts is necessary.

A new technique for the proximal anastomosis is investigated in **chapter 3**. The use of non-penetrating, titanium clips in vascular surgery has been advocated to reduce clamping time of the artery, reduce intimal hyperplasia, due to the non-penetrating characteristics of the clips, and increase patency rates. [4] However, little was known on the use of clips on the femoral artery. We therefore conducted this pilot study, to assess the safety of the clips on the proximal anastomosis in peripheral vascular surgery. We included patients after both peripheral bypass surgery as well as after femoral endarterectomies, because we assumed that the technique of applying an anastomosis at the femoral artery, would not differ between both procedures. At least for our outcomes of anastomosis speed and patient safety. We are aware that patency rates between both procedures are not very comparable.

The time needed for applying the anastomoses was not significantly different from the control group. Our preliminary results did not meet our expectations. Although the initial technical success rate was high, significant complications occurred in the VCS group that could be attributed to the use of clips. There were two serious adverse events in the VCS group; in one patient the clipped anastomosis ruptured, causing major bleeding from the femoral artery. In another patient an acute thrombosis of the superficial femoral artery had occurred. As we could not determine any benefits from the use of clips in the proximal anas-

tomosis, we concluded the safety of the use of VCS clips in peripheral vascular surgery is not proven, and we will not continue with a large randomized control trial.

Chapter 4 shows the results of a review, conducted on QoL in peripheral vascular surgery. On short term follow-up, all interventions resulted in increased QoL scores. However, on long term follow-up very little is known. Only one study assessed QoL on real long term, and showed a decrease in QoL scores[5]. However, as long term follow-up results in high number of lost to follow up, the long term effect of intervention in vascular surgery remains uncertain.

Another problem is the use of different questionnaires, which makes it hard to compare results between studies. Most importantly, many studies use health status questionnaires, instead of QoL questionnaires. This can make the interpretation and comparison of their results very difficult as health status does not necessarily relates to QoL.[6]

In **chapter 5** the results for QoL on midterm follow-up after peripheral bypass surgery are presented. An important result in our study is that the increase in short term QoL on the physical domain in patients who underwent peripheral bypass surgery is not consistent after a mean follow-up of 33 months. The results found with our last questionnaire showed no significant change compared to baseline QoL scores. It seems that the gained increase in QoL after bypass surgery is of a temporarily nature. This study was part of a RCT comparing pneumatic compression (IPC) with compression stockings (CS) for both autologous peripheral bypass grafting and PTFE bypass grafting. As in autologous bypass grafting the long-term results (90 days) of IPC vs CS shows no significant difference [7], and in PTFE bypass grafting no significant difference between IPC and CS were found at all. [8] We are convinced that there is no influence of IPC vs Cs on long-term QoL or survival. Analyzing treatment effect on QoL in PAD patients is hard to establish. As PAD is multifactorial, and occurs mostly in the elderly patients, co-morbidities have a large influence on the QoL scores, both before, and after treatment. As showed a study by Breek[9], not only the walking limitation affects the QoL scores of PAD patients. Cardiovascular co-mobidities, as well as other leg problems (eg lower back, hip or knee problems) have a significant influence on QoL scores. In our new designed, prospective study on QoL scores in the elderly PAD population, patients are classified by use of the Possum score.

Three-year mortality rates were 25% for autologous bypass grafts and 46% for PTFE grafts, overall three-year mortality rate was 33% for both groups combined. A Cox proportional hazard survival analysis, stratified by bypass graft type, did not show a significant effect of treatment: the mortality rate ratio of IPC to CS was 1.07 (95 % CI: 0.52-2.20; p = 0.86), adjusted for age and gender. Only the effect of age was significant: the mortality rate increases by 8 % per year of age at baseline (95 % CI: 2.9-13.3 %; p = 0.002). Taking graft bypass type as explanatory variable in an unstratified Cox-regression along with treatment, age and gender resulted in a non-significant mortality rate ratio of PTFE to autologous of 1.51 (95 % CI: 0.73-3.12; p = 0.27).

Such survival rates are not unusual as recently reported by Bradbury et al.[10]

Chapter 6 shows our results on the introduction of Vascular Nurse Practitioners (NPs) in relation to patients QoL scores, anxiety and depression scores. Thus far are no reports available about QoL, anxiety and depressive symptom scores in patients treated and guided by a (vascular) NP. In this study the goal was to establish whether NPs would influence patient oriented outcome measurements differently than vascular surgeons themselves.

QoL on the physical domain did increase in both groups after treatment while anxiety scores significantly decreased after treatment. However no differences between both groups were found.

The increased QoL on the physical domain, was about 5 points. This is in concordance with previously performed studies on QoL after bypass surgery, in which a short term QoL results were investigated. [11] It seems to be quite difficult to assess the actual benefits of adding NPs to an existing care team.

In **chapter 7** our results for registering surgical complications are presented. The mean outcome of this investigation is that surgical site infections are scored more reliable by infection control nurses than by medical doctors. The missed infections in the vascular database occurred almost all after the patient's discharge. However, every patient with a surgical site infection, which was not recorded in the vascular database, was admitted to the hospital again, and received the appropriate care.

As most surgical site infections occurred after patients discharge, especially the outer-patient-clinic registration is unreliable. A possible improvement for this problem, could be assigning a specially trained data-manager, to register all complications in a database.

Surgical site infection after vascular surgery is a frequent complication associated with increased morbidity and significant additional costs [12-23]. Therefore adequate registration is necessary, so evaluation in time is adequate and reliable.

As more states in the United States of America are mandatory in reporting their Healthcare associated infections [24], the reliability of the used registration method is becoming more and more important.

When in one hospital, in one surgical department, two different registrations methods produce such different values, it is clear that published results are more dependent on the type of registration, than they are on the quality of healthcare.

Best result will be obtained when surgeons and the department of Microbiology and Infection prevention work together in identifying and registering all surgical site infections.

Our center now uses a scheduled meeting with a vascular surgeon, a medical microbiologists and a trained infection control nurse. Here every possible surgical site infection is discussed and registered, to produce a reliable database.

In **chapter 8** we analyzed the effect of *S. aureus* nasal carriage on the incidence of surgical site infections with this pathogen. The outcomes were; the majority of SSI's are caused by *S. aureus*, and that, at least for central reconstructions, there is an increased risk for occurrence

of *S. aureus* based SSI's in positive carriers. The effect in this group is comparable to what has been found previously in cardiothoracic and orthopedic surgery.[25-28]

Based on the results of this study we conclude that *S. aureus* carriers who undergo central reconstructive surgery have a significant higher risk for the development of SSI which can be decreased by perioperative eradication of *S. aureus* in nasal carriers.[29]

This is important because infection with *S. aureus* after aortic reconstructions is related to severe complications and a high mortality rate.

CONCLUSIONS

Chapter 2 In patients without a suitable ASV (or other vein), the pre-cuffed PTFE bypass graft is a reasonable alternative, which results in an acceptable limb salvage rate.

Chapter 3 The VCS clip system has not proven its safety on anastomoses on the femoral artery.

Chapter 4 Little is known on Long Term follow-up QoL after vascular intervention. Randomized studies are required to provide definitive evidence of the true benefit of intervention in patients with PAD.

Chapter 5 Although peripheral bypass surgery significantly increases QoL at 2 short term follow-up, this is lost after > 2 years of follow-up. Therefore, there is no midterm increased QoL benefit after bypass surgery. Quality of Life as outcome (at least at > 2 years of follow-up), seems to have no relation with classical outcome measurements, such as graft patency, mortality and limb-salvage.

Chapter 6 Vascular NPs, at least for patients' QoL, anxiety and depression scores, perform equally to the vascular surgeons. This shows that they are capable of explaining intervention procedures to patients, and their guidance through treatment is comparable to those of vascular surgeons. Therefore NPs can lower the vascular surgeons workload and lower costs at the same time, without losing quality of care.

Chapter 7 A reliable complication registration is very important on improving quality of care. However, trained data managers produce a more reliable database in comparison to medical doctors.

Chapter 8 Pre-operatively eradicating nasal carriage of *S. aureus* in patients who have to undergo central reconstructive surgery may decrease the number of surgical site infections in this population. Thereby lowering patients morbidity and costs.

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Chapter 10

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DISCUSSIE EN SAMENVATTING

Gezien de incidentie van perifeer arterieel vaatlijden (PAV) toeneemt[1, 2] en er steeds meer nieuwe technieken worden ontwikkeld voor de behandeling van vaatlijden op minimaal invasieve manieren is de rol van de chirurgische interventies aan het veranderen. Als aanvulling op de klassieke uitkomstmaten, zoals patency en limb salvage, is er ook steeds meer aandacht voor nieuwe, patiëntgebonden uitkomsten.

Daarnaast zijn ook de chirurgische interventies aan doorontwikkeling onderhevig.

Zo blijven er doorontwikkelingen verschijnen van de distale anastomoses van kunststof bypasses en is er aandacht voor nieuwe technieken bij het aanleggen van de proximale anastomoses.

Hoofdstuk 2 toont onze resultaten van een vergelijkende studie naar de nieuw ontwikkelde kunststof bypass, met een voorgevormde distal cuff. Ondanks deze cuff, blijken de patency waarden van de autologe bypasses, zeker voor aansluiting onder het niveau van de knie, significant beter. Concluderend blijft de autologe bypass nog steeds de techniek van eerste keus bij perifere bypass chirurgie. Daarentegen is bij patiënten die geen geschikte vene hebben voor een autologe bypass, de kunststof bypass met voorgevormde cuff een redelijk alternatief. Zeker op het gebied van limb salvage. Naast de kunststof bypasses met een cuff, zijn er ook kunststof bypasses met een speciale Heparine coating. Wanneer we onze resultaten vergelijken met een studie naar de Heparine gecoate bypasses, blijken de laatste mogelijk tot betere patency waardes te resulteren.

Een studie door Daenens laat indrukwekkende patency waardes zien voor een Heparine gecoate bypass[3], maar aangezien in deze studie erg weinig autologe bypass operaties zijn verricht, maakt het 1 op 1 vergelijken van onze resultaten lastig. Om met zekerheid uit te zoeken welke kunststof bypass superieur is in patiënten met PAV is een prospectieve, gerandomiseerde studie nodig.

In **hoofdstuk 3** wordt een nieuwe techniek beschreven voor het aanleggen van de proximale anastomose in perifere vaatchirurgie. Het gebruik van niet penetrerende, titanium clips zou zorgen voor kortere tijdsduur voor het aanleggen van de anastomose en daardoor zorgen voor een kortere klem tijd, tevens zouden de clips het optreden van intima hyperplasie moeten reduceren en daardoor de patency waarden verhogen.[4] Echter voor het gebruik van deze clips op de femoraal arteriën is weinig bekend. Daarom is een haalbaarheidsstudie verricht om te beoordelen of de clips op de femoraal arteriën veilig te gebruiken zijn.

In een studieverband werd een klein aantal patiënten gerandomiseerd voor het aanleggen van de anastomose middels clips. Het ging om zowel perifere bypass operaties, alsmede endarteriectomiën van de femoraal arteriën. Hiervoor is gekozen omdat de techniek middels clips in beide groepen goed vergelijkbaar is, ondanks het verschil in patency waardes tussen beide procedures. Er was geen significant verschil in de snelheid van het aanleggen van de anastomoses. Daarnaast bleken de clips, hoewel het technische resultaat per operatief

goed was, op langere termijn toch tekortkomingen hadden. In de clip groep traden twee ernstige complicaties op, doortoedoen van de clips. In één patiënt scheurde post operatief de anastomose uit, resulterend in een bloeding uit de femoraal arterie. Bij een andere patiënt trad een acute occlusie op van de aangelegde anastomose, door een niet gefixeerde intima flap. Beide patiënten hadden acuut een her operatie nodig. Gezien deze resultaten durven we de veiligheid van de clips op de femoraal arteriën niet te garanderen. Als gevolg hiervan zal er geen groot gerandomiseerd onderzoek worden opgezet.

Hoofdstuk 4 beschrijft de resultaten van een review naar de literatuur betreffende de Kwaliteit van Leven (KvL) na interventies vanwege PAV. Op korte termijn resulteren alle interventies naar een stijging van KvL, maar over lange termijn resultaten blijkt weinig bekend te zijn. Slechts één grote studie analyseerde de lange termijnresultaten voor KvL na perifere bypass chirurgie, en laat dalende KvL waardes zien.[5] Aangezien het na lange termijn analyseren van KvL in oudere patiënten tevens zorgt voor een grote hoeveelheid uitvallende deelnemers, zijn de resultaten moeilijk te interpreteren. Er blijft veel onduidelijkheid over de lange termijn resultaten naar KvL in PaV.

Daarnaast is ook de grote diversiteit tussen verschillende vragenlijsten naar KvL een probleem om resultaten van verschillende onderzoeken goed te vergelijken.

Daarnaast blijken veel studies vragenlijsten te gebruiken die een gezondheidstoestand analyseren en geen KvL. Dit maakt interpretatie van deze resultaten erg lastig en vergelijking tussen studies bijna onmogelijk, aangezien gezondheidstoestand scores niet gerelateerd kunnen lijken te worden aan KvL scores.[6]

In **hoofdstuk 5** presenteren wij onze resultaten naar KvL op de middellange duur na perifere bypass chirurgie. Een belangrijke uitkomst is dat de op korte termijn verhoogde KvL, op de middellange duur niet meer detecteerbaar is. De gevonden KvL waardes bij ons laatste meetmoment laten geen significant verschil meer zien met de waardes bij start van de studie. Het blijkt dat de toegenomen KvL waarden na perifere bypass chirurgie slechts van korte duur is. Deze studie was onderdeel van een gerandomiseerde trial naar het effect van een voetpomp, in vergelijking met steunkousen, ter behandeling van post operatief oedeem na bypasschirurgie. Aangezien de resultaten van voetpomp behandeling na autologe bypass operatie geen verschil laten zien na 90 dagen[7] en in de kunststof groep überhaupt geen verschil tussen beide behandelingen is aangetoond [8] zijn we ervan overtuigd dat zowel de voetpomp behandeling, als de steunkous behandeling geen invloed heeft op de KvL of overleving. Het bestuderen van een behandelingseffect op KvL, is zeker voor patiënten met PaV lastig te onderzoeken op de lange termijn. Het ziektebeeld is multifactorieel, en treft over het algemeen de oudere patiënten, die een uitgebreide comorbiditeit kunnen hebben.

Zoals aangetoond is in een onderzoek van Breek[9], hebben niet alleen belemmeringen van PaV invloed op de KvL, maar ook is er een significante invloed van andere ziektebeelden die deze patiëntengroep vaak heeft (zoals gewrichtsproblemen). Daarnaast blijken ook cardiovasculaire comorbiditeit een significante invloed te hebben op de KvL waardes van patiënten

met PaV. In een nieuwe studie naar KvL voor oudere patiënten lijdend aan PaV, die onlangs door ons is opgezet, zullen we hiervoor patiënten classificeren middels de Possum score. De drie-jaars mortaliteit was 25% voor patiënten die een autologe bypass operatie hadden ondergaan, en 46% voor patiënten na een kunststof bypass operatie.

De gemiddelde drie-jaars mortaliteit was 33% voor beide groepen samen. Een multivariate analyse toonde alleen een significante invloed van hogere leeftijd op de mortaliteit. Er werd geen significant verschil aangetoond op basis van bypass type. Overlevings en mortaliteit cijfers als deze zijn niet ongebruikelijk, gezien de uitkomsten van Bradburry.[10]

Hoofdstuk 6 toont de resultaten van ons onderzoek naar de invloed van de invoering van Nurse Practitioners, op patiënt scores voor KvL, angst en depressie. Tot nu toe waren hierover geen onderzoeken beschreven. In deze studie was het doel om aan te tonen welke invloed de invoering van NP's had op patiëntgebonden uitkomstmaten. De KvL verbeterde in beide groepen na behandeling, de angst en depressie scores verminderde na behandeling. Echter tussen beide groepen kon geen significant verschil worden aangetoond.

Op het fysieke domein, steeg de KvL met ongeveer 5 punten, dit is in overeenstemming met eerder gepubliceerde artikelen naar de invloed van behandeling van PaV op KvL scores op korte termijn.[11] Het blijkt erg lastig te zijn, om de toegevoegde waarde van NP's aan een behandelteam te bewijzen.

In **hoofdstuk 7** worden de resultaten gepresenteerd van een studie naar de registratie van complicaties. De belangrijkste uitkomst is dat artsen complicaties minder nauwkeurig registreren als speciaal getrainde buitenstaanders. De meest gemiste complicaties traden op na het ontslag van patiënten. Echter, elke patiënt die na ontslag een wondinfectie kreeg, was hiervoor wel behandeld op de polikliniek of op de spoed eisende hulp. Het probleem is niet het missen of onderkennen van het optreden van een complicatie, maar het registreren van deze complicatie. Met name in de poliklinische setting, blijkt dat de registratie onbetrouwbaar is. Wij menen dat met de toevoeging van speciaal getrainde personen, die als taak hebben om complicaties te registreren en analyseren, dit probleem kan worden ondervangen. Het optreden van complicaties, met name post operatieve wondinfecties, is geassocieerd met toegenomen morbiditeit en extra kosten[12-23].

Hierom is een adequate registratie noodzakelijk, om zo de kwaliteit van zorg te bewaken, en veranderingen in tijd aan het licht te stellen. Met de toegenomen druk, mede vanuit overheden en zorgverzekeringen om complicatie cijfers te openbaren, is een betrouwbare registratie van het allergrootste belang. Wanneer in één ziekenhuis, twee verschillende registratie databases een dusdanig verschil tonen, is de vraag wat de betrouwbaarheid zal zijn, wanneer cijfers tussen verschillende ziekenhuizen worden vergeleken.

De meest betrouwbare registratie van post operatieve wondinfecties kan worden verkregen, wanneer de afdelingen heelkunde en medische microbiologie gaan samenwerken aan de registratie.

In ons ziekenhuis is nu een multidisciplinair overleg ingesteld, waarin zowel een vaatchirurg, als een medisch microbioloog en een adviseur infectie preventie gezamenlijk de registratie van post operatieve wondinfecties voor de vaatchirurgie documenteren. Op deze wijze menen wij een betrouwbare registratie database te kunnen opzetten voor post operatieve wondinfecties na vaatchirurgie.

In **hoofdstuk 8** werd de relatie bestudeerd tussen neusdragerschap van *S aureus* en het optreden van wondinfecties met deze bacterie na vaatchirurgie. De belangrijkste uitkomsten waren; de meerderheid van alle wondinfecties na vaatchirurgie wordt veroorzaakt door de *S. aureus*. Daarnaast is voor in ieder geval centrale vaatoperaties een significant hoger risico op het ontwikkelen van een post operatieve wondinfectie voor patiënten met een positief neusdragerschap. Deze relatie komt overeen met de eerder gevonden relatie binnen de cardiothoracale chirurgie en de orthopedische chirurgie.[24-27]

Gebaseerd op deze resultaten concluderen wij dat dragers van een *S. aureus* die een centrale vaatoperatie moeten ondergaan een significant hoger risico hebben op het ontwikkelen van een post operatieve wondinfectie. Dit verhoogde risico zou mogelijk kunnen worden verlaagd met een preoperatieve eradicatie van het dragerschap.[28]

Dit is een belangrijke uitkomstmaat gezien wondinfecties met een *S aureus* na centrale vaatoperaties zijn gerelateerd aan ernstige complicaties en een toegenomen mortaliteit.

CONCLUSIES

Hoofdstuk 2 Voor patiënten die geen geschikte vene hebben om als bypass te dienen, vormt de kunststof bypass met voorgevormde cuff een redelijk alternatief gezien de limb salvage resultaten.

Hoofdstuk 3 Het VCS clip system heeft niet kunnen overtuigen dat het veilig gebruikt kan worden bij anastomoseringen op de femoraal arteriën.

Hoofdstuk 4 Voor de lange termijnresultaten is er weinig bekend over de KvL in PaV. Prospectieve, gerandomiseerde studies zijn nodig om eenduidig bewijs te leveren naar KvL in PaV.

Hoofdstuk 5 Ondanks dat perifere bypass chirurgie op de korte termijn resulteert in toegenomen KvL, is dit effect na >2 jaar niet meer aan te tonen. KvL lijkt geen relatie te hebben met de klassieke uitkomst maten, als patency en limbsalvage.

Hoofdstuk 6 Nurse practitioners hebben geen invloed op de KvL, angst en depressie scores van patiënten met PaV. De begeleiding en uitleg, gegeven door NP's stellen patiënten even-

veel gerust, als die van de vaatchirurgen zelf. Hiermee kan de toevoeging van NP's aan het behandelteam de werklasten van de chirurg verminderen, zonder aan kwaliteit van zorg in te leveren.

Hoofdstuk 7 Om de kwaliteit van zorg te verbeteren is een betrouwbare complicatieregistratie van groot belang. Echter levert een speciaal getraind, onafhankelijk persoon een betrouwbare registratie op, in vergelijking met artsen zelf.

Hoofdstuk 8 Preoperatief eradicatie therapie voor neusdragerschap van *S. aureus* bij patiënten die een centrale vaatoperatie moeten ondergaan kan mogelijk het aantal postoperatieve wondinfecties verminderen. Daarbij zullen de morbiditeit, evenals de kosten van de gezondheidszorg afnemen.

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PUBLICATIONS

J.M.W. Donker, J. de Vries, G.H. Ho, F.B. Gonçalves, S.E. Hoeks, H.J.M. Verhagen, L. van der Laan. Review: Quality of life in peripheral vascular surgery. Submitted

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CURRICULUM VITAE

Jeroen Martinus Willem Donker was born on february 22nd 1984 in Rotterdam.

After graduation from high school at Marnix Gymnasium in Rotterdam in 2003, he started medical studies at Erasmus University Rotterdam. During his study he developed an increasing interest in surgery. He followed an internship at the Department of Surgery at the Amphia hospital, Breda.

At this point, he started research in vascular surgery. After obtaining his medical degree (January 2010), he took up a surgical residency at the Amphia hospital, in Breda. Research activities were expanded during his residency and formed a basis for his PhD project under supervision of prof.dr. H.J.M Verhagen, Erasmus University Rotterdam, prof.dr. J.A.J.W Kluytmans, Vrije Universiteit Amsterdam and dr. L. van der Laan, Amphia hospital Breda. This resulted in this thesis.

In January 2013 he started as a resident in training for surgeon at the Amphia hospital under supervision of dr. L van der Laan and dr. B.P.L. Wijnhoven, ErasmusMC, Rotterdam.