PERIPHERAL VASCULAR SURGERY

An appraisal of various clinical outcome measures

J. VAN DER SLEGT

Peripheral Vascular Surgery:

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J. van der Slegt

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Een evaluatie van verschillende klinische uitkomsten

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CHAPTER 1

General introduction

GENERAL INTRODUCTION

Peripheral arterial disease (PAD) includes a range of arterial syndromes causing obstruction of the arteries that supply the brain, visceral organs and the limbs (1). This thesis will focus on PAD of the abdominal aorta and lower extremity arteries which are frequently affected by atherosclerosis.

PAD affects a large proportion of the adult population with a total disease prevalence ranging between 3% and 10% and increases up to 20% for persons over 70 years of age (2, 3). Risk factors for developing PAD are in general the same as for developing atherosclerosis and includes age, male gender, hypertension, diabetes mellitus, smoking, dyslipidaemia, family history and homocystemia (2, 3).The presence of a multitude of risk factors increases the risk for PAD (2).

Clinical presentation can vary and depends on the severity of PAD. Repeated pain, discomfort or weakness during exercise of the lower legs which relieves after rest is typical for intermittent claudication (IC). Ischemic rest pain with or without ulceration or gangrene is seen in patients with critical limb ischemia (CLI). The diagnosis is based on an accurate history, non-invasive diagnostics (physical examination, ankle-brachial index (ABI) and duplex ultrasound) and, if indicated, followed by invasive diagnostics (contrast arteriography, Computed tomography arteriography and Magnetic resonance arteriography). A grading system, based on the Fontaine's and Rutherford classification is used for classifying the severity of PAD (Table 1) (1, 3, 4).

Although PAD is progressive in the pathological sense, its clinical course concerning the fate of the leg seems to be very stable (3). A major amputation is a relatively rare outcome in IC with amputation rates of only 1% and 3% over a 5-year period (3, 5). On the other hand, the fate of the leg is much more at risk at patients with CLI. The natural history of CLI is difficult to subscribe because most patients with CLI receive some form of treatment to retain the leg. In studies on selected patients with CLI having no treatment, 1-year amputation-rates varied between 16% and 54% (6, 7).

Despite the risk that cardiovascular events are strongly correlated to the severity of PAD, the mortality of most patients were rarely a direct result of PAD itself (3, 8-10). Most of these patients will die from the complications of coronary artery disease, cerebrovascular disease or non-vascular causes (3). The management of patients with PAD is therefore complex and requires a multidisciplinary approach to reduce risk factors leading to progression of generalized atherosclerosis and relieve symptoms.

Table 1. Rutherford's categories of peripheral arterial disease (4).

Grade	Category	Clinical description	Objective criteria
0	0	Asymptomatic	Normal treadmill or reactive hyperemia test
I	1	Mild claudication	Completes standard treadmill exercise; AP after exercise >50mmHg but at least 20 mmHg lower than resting value
	2	Moderate claudication	Between category 1 and 3
	3	Severe claudication	Cannot complete standard treadmill exercise*; AP after exercise <50mmHg
II	4	Ischemic rest pain	Resting AP<40mmHg, flat or barely pulsatile ankle of metatarsal PVR, TP < 30mmHg
III	5	Minor tissue loss: nonhealing ulcer, focal gangrene with diffuse pedal ischemia	Resting AP< 60mmHg, flat or barely pulsatile ankle or metatarsal PVR, TP<30mmHg
	6	Major tissue loss: extended above transmetatarsal level, functional foot no longer salvageable	Same as category 5

AP, ankle pressure; PVR, pulse volume recording; TP, toe pressure;*5 minutes at 2 mph (3.2 km/h) on a 12% incline.

The management of patients with less advanced stages of PAD is based on a restrained policy including preventative measures (e.g. statins and antiplatelet) and supervised walking exercise (11). However, invasive treatment options can be considered when supervised walking exercise fails or patients have more advanced stages of PAD like patients with CLI (1-3). Invasive treatment options include endovascular and surgical procedures. Although, endovascular procedures have positioned a prominent role in the modern vascular practice, surgical revascularisation might be indicated in selected patients with advanced stages of PAD (1-3).

Surgical revascularisation of infrainguinal lesions includes endarterectomy or bypass surgery (3). An endarterectomy might be considered in localized lesions. However, in complex- and mostly multilevel lesions a bypass is more suitable (femoropopliteal bypass (supragenicular or infragenicular) or femorocrural bypass) (3). The choice of conduit for peripheral bypass surgery can be an autologous- or a synthetic bypass (polytetrafluoroethylene (ePTFE) or polyethyleneterephthalate (Dacron®)). An autologous bypass is preferred over a synthetic bypass because of superior patency rates (12-18). In the absence of an adequate autologous vein, a synthetic bypass is a reasonable alternative.

A potential problem using ePTFE grafts is the formation of myointimal hyperplasia at the level of the distal anastomosis which can lead to loss of patency (19). To resolve this problem, further refinements were introduced like a venous Miller cuff or St. Mary boot (12). As these procedures

added complexity and increased operation time to the original procedure, pre-cuffed ePTFE grafts were developed which demonstrated comparable patency-rates (20, 21). Midterm results of these bypasses demonstrated the pre-cuffed ePTFE grafts a reasonable alternative compared to autologous grafts (22).

Besides the problems facing the choice of conduit in peripheral bypass surgery an even larger problem is seen in the treatment of patients with PAD. In general, surgical interventions performed in this particular patient group is associated with potentially severe adverse events influencing the outcome of peripheral vascular procedures.

Improving outcome of provided care is an important topic in today's medicine which is characterized by increased cost, individual patient awareness and the introduction of numerous diagnostic modalities and therapeutic strategies. Results can be used to detect shortcomings, evaluate new and old treatment modalities and initiate new research projects. Moreover this will increase transparency for physicians and hospitals.

AIM AND THESIS OUTLINE

The aim of this thesis is to evaluate the outcome of various clinical situations in the vascular clinic. The first part of this thesis evaluates the outcome of various vascular procedures. The focus of the second part of this thesis is on the prevention and treatment of SSI in patients with PAD.

Outcome after peripheral vascular surgery

The ABI is an important parameter to determine the stage of PAD and patency (3, 4, 23, 24). Performing a manual measure is considered time-consuming and operator dependent. An automated ABI-device could potentially lead to more reliable measurements with potential time-savings. The applicability of such a device for diagnosing PAD is already demonstrated in the general population (25-29). Unfortunately, studies of such a device in postoperative ABI measures are lacking. In **Chapter 2** the clinical applicability of an automated ABI-device is examined. Both manual and automated ABI measurements were compared in terms of reliability and time-performance.

As previously discussed, an autologous vein is the first choice of conduit for peripheral bypass surgery. Synthetic grafts are supposed to be inferior among others because of the change of anastomotic stenosis. Pre-cuffed ePTFE grafts are considered to mimic the natural state of the artery and to optimize flow at the distal anastomosis for improving patency rates. In **Chapter 3** the long-term outcome results of pre-cuffed ePTFE were compared to autologous vein bypass grafts used in patients with CLI.

Acute limb ischemia (ALI) is an acute and serious condition in which an artery of the lower limb is occluded. In general it is caused by an arterial embolism or thrombosis (30, 31). Rapid intervention is indicated to restore patency and limb salvage (23). Intervention options are surgical thromboembolectomy or intra-arterial thrombolysis. Thrombolysis has been gradually introduced since this is considered less invasive with comparable results as seen after thromboembolectomy (32-36). Insights on adverse events are lacking and need to be further specified. In **Chapter 4**, the outcome and adverse events after these two treatment options for patients with ALI are studied.

Prevention and treatment of SSI

A surgical site infection (SSI) is defined by the centers for disease control (CDC) and includes superficial incisional-, deep incisional- and organ/space SSI (37). SSI's are serious adverse events and can lead to reinterventions, morbidity and potential death after vascular surgery (38-40). Most importantly, SSI's are considered to be one of the most preventable adverse events (41). Therefore, reduction of these SSI's is very important in improving postoperative care of patients with PAD. This could be achieved by applying evidence based prevention protocols (42, 43). A bundle of care was developed by the Dutch hospital safety program to reduce these SSI's. In **Chapter 5** the implementation and effect of this bundle of care was evaluated.

A groin incision is also a risk factor for SSI development (44, 45). Additionally, re-interventions are frequently performed throughout the clinical course of a vascular patient. Multiple groin incisions could potentially lead to a high incidence of adverse events, such as a SSI. **Chapter 6** evaluates the effect of different groin incision intervals on SSI development after elective vascular procedures.

Besides preventing the occurrence of SSI's it is also important to manage a SSI. The management of a SSI in vascular surgery is challenging. Many treatment strategies have been suggested in the literature. Complete removal of the graft with extra-anatomic reconstruction, with in situ or antimicrobial-impregnated replacement, was traditionally considered as the 'golden standard' (46-48). More recently, the focus has shifted towards graft preservation and the previously mentioned strategies are considered to be associated with increased morbidity and mortality(49). Several successful graft preservation-strategies are mentioned like, muscle flaps and negative pressure wound therapies with or without muscle flaps (50-53). In **Chapter 7**, an observational study was performed of the treatment of all SSI after elective vascular surgery in patients with moderate to severe PAD in our clinic.

Finally, **Chapter 8** provides a summary of this thesis, a general discussion and future perspectives and **Chapter 9** provides the summary and discussion in Dutch.

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chapter
1

PART I

Outcome after peripheral vascular surgery

CHAPTER 2

The clinical applicability of an automated plethysmographic determination of the ankle-brachial index after vascular surgery

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ABSTRACT

An automated ankle-brachial index (ABI) device could lead to potential time-savings and more accuracy in ABI-determination after vascular surgery. This prospective cross-sectional study compared post-procedural ABIs measured by a manual method with ABIs of an automated plethysmographic method. Forty-two patients were included. No significant difference in time performing a measurement was observed (1.1 minutes, 95 % CI: -0.2 to +2.4; p = 0.095). Mean ABI with the automated method was 0.105 higher (95 % CI: 0.017 - 0.193; p = 0.020) than with the manual method, with limits of agreement of -0.376 and +0.587. Total variance amounted to 0.0759 and the correlation between both methods was 0.60. Reliability expressed as maximum absolute difference (95 % level) between duplicate ABI-measurements under identical conditions was 0.350 (manual) and 0.152 (automated), although not significant (p = 0.053). Finally, the automated method had a 34 percent points higher failure rate than the manual method. In conclusion based on this study, the automated ABI-method seems not to be clinically applicable for measuring ABI postoperatively in patients with vascular disease.

INTRODUCTION

The ankle-brachial index (ABI) is a widely used parameter for assessing the severity or progression of peripheral arterial disease (PAD) (1-4). Traditional manual measurements are carried out by a sphygmomanometer and a continuous wave Doppler. This method is considered difficult, time-consuming and operator dependent. An automated device could lead to potentially more reliable and easy to perform measurements. The applicability of such a device has already been described in the general population (5-9). Unfortunately clinical studies of such a device in postoperative ABI measures are lacking.
The objective of this study was to determine the clinical applicability of an automated ABI device. We compared the automated method with the manual method in terms of reliability (agreement and precision), time performance and failure rate in post procedural ABI measurement.

PATIENT AND METHODS

Study population

A prospective cross-sectional study was performed between September 2013 and February 2014. Patients aged 18 years or older were eligible for inclusion in this study after they underwent a vascular intervention. Patients with preoperatively proven non-compressible arteries (ABI ≥ 1.4 using the standard manual method) or patients unable to consent were excluded from this study.

Data collection

Patient characteristics were acquired by questionnaires from the consent form and patient records. Ankle-Brachial indices (ABIs) were obtained the first postoperative day by a manual- and an automated plethsmographic method (Dopplex® ABIlity, Huntleigh diagnostics, Inc) on the surgical ward. All measures were performed two-sided (the right side first), first by the manual method followed by the automated method on subjects in supine position. To mimic the daily practice the manual ABIs were obtained by trained operators and the automated ABIs by registered nurses. Time measures were obtained using a stopwatch.

Statistics

According to the protocol, 38 patients were needed to detect a correlation coefficient between the manual and automated method of 0.5 with 90 % power using a test size of 0.05 (2-sided).

Time performance

Time management between both methods was tested using the paired t-test.

Clinical applicability: agreement

The four repeated ABI-measurements (2 sides x 2 methods) were analyzed using linear mixed modeling. As fixed effects on ABI the mean difference between both methods and the effect of operation of the leg were estimated. The following random effects as components of total variance of ABI were considered: (i) between-subjects, (ii) side nested within subject, and (iii)) method nested within subject and side. The correlation coefficient between methods was calculated as the sum of the variance components (i) and (ii) and expressed as proportion of total variance (i) + (ii) + (iii). Limits of agreement (10) of the difference between both methods were calculated as the estimated fixed mean difference plus or minus 1.96 times the square root of twice the component (iii).

Clinical applicability: Precision

Linear mixed modelling was used to estimate the within-subject variance of the ABI from its observed left-right differences under either method and to test the null hypothesis that this variance was the same under both methods using a likelihood ratio test. This variance is built up from random measurement variability along with within-subject variability based on almost two simultaneous measurements within a subject. Of the former linear mixed model analysis we took the variance component (ii) to subtract it from the variance obtained from this mixed model analysis, so that the remaining variance is supposed to be completely attributable to the method used and to stand for the intrinsic precision of the method. In order to better compensate for potential bias due to missing values of ABI-measurements, adjustment was made for the following fixed effects in this analysis: method (manual/automated), left leg operated, right leg operated, gender, age, Rutherford score > 2 and current smoker.

Clinical applicability: ABI failure

For analyzing the probability of a measurement method not producing a valid ABI-value a dichotomous failure indicator was defined. This failure outcome variable with four repeated measurements within a subject was analyzed through generalized linear modeling (GENLIN). The generalized estimating equations method was used to account for the correlation between the repeated measurements within a subject. GENLIN with an identity link function was used for testing the difference in failure rate between both measurement methods. Given the presence of a valid manual measurement, GENLIN was used with a logit link function for analyzing the automated failure rate depending on the following explanatory variables: gender, current smoker, side, if the leg was operated, age and the value of the manual ABI measurement.

Statistical analyses were performed using the SPSS® software program version 20 (IBM, Armonk, New York, USA). P-values below 0•05 were considered to denote statistical significance.

RESULTS

Time performance

A total of 42 patients were included in this study (Table 1). The automated method took 9.3 minutes: 1.1 minutes shorter than the hand method (95 % CI: -0.2 to +2.4; p = 0.095).

Table 1. Patient characteristics (n = 42).

Characteristic			n (%)	
Gender (male/female)				
Male			31 (74)	
Female			11 (26)	
Risk factors				
Age			69 ±7.8	
Current smoker			38 (90)	
PAD (Rutherford class)				
≤ 2			13 (31)	
≥ 3			29 (69)	
Procedure				
Central			15 (36)	
Peripheral			27 (64)	
Raw ABI data				
Side	**Method**	**n**	**Mean ± SD**	**Median (range)**
Right	Manual	40	0.81 ± 0.28	0.82 (0.30-1.61)
	Automated	26	0.96 ± 0.26	0.96 (0.57-1.59)
Left	Manual	41	0.81 ± 0.26	0.87 (0.36-1.38)
	Automated	25	0.96 ± 0.29	0.86 (0.59-1.97)

Basic patient characteristics and study outcomes are presented as percentages, mean ± SD and median (range).

Clinical applicability: agreement

The automated method yielded a significantly higher mean ABI than the manual method (0.105, 95 % CI: 0.017 - 0.193; p = 0.020). Operation was associated with a significantly lower mean ABI (0.092; 95 % CI: 0.014 - 0.170; p = 0.022). After adjustment for these fixed effects, total variance was 0.0759 (ABI squared) and could be decomposed into: (i) 0.0302, (ii) 0.0156 and (iii) 0.0302. The correlation between both methods was 0.60. The limits of agreement of the difference (automated – manual) were -0.376 and +0.587 (Figure 1).

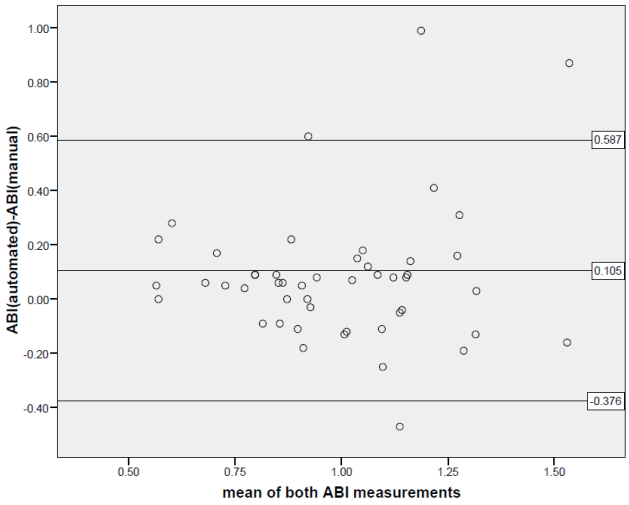

Figure 1. Bland-Altman plot for comparing ABI-measurements taken with the automated- and the manual method, based on 49 non-missing observations (23 subjects with both sides and 3 subjects with 1 side). Mean difference and lower and upper agreement limits are restricted maximum likelihood estimates obtained from linear mixed modeling applied to all 42 subjects.

Clinical applicability: precision

The within-subject variance of ABI based on left-right differences of the automated method was 0.0186 compared to 0.0315 of the manual method. However, this difference was not significant (chi-square with 1 df was 3.758, $p = 0.053$). Assuming the within-subject variance to be the same under both methods its estimate was 0.0273. Subtracting from these variances the pure within-subject component (ii) of 0.0156, we are supposed to get the intrinsic measurement variance (precision) of the methods: 0.0159 for the manual method and 0.0030 for the automated method, or 0.0117 assuming them to be equal. The absolute difference between duplicate ABI-measurements using the manual method in a patient under exactly the same conditions was maximally $1.96\times\sqrt{(2\times0.0159)}=0.350$ at the 95 % level. For the automated-method this maximum absolute difference was 0.152 and assuming identical variances of both methods was maximally 0.300.

Clinical applicability: ABI failure

The automated method had a failure rate of 34% points (95% CI: 18.7-49.5, $p < 0.0005$) higher than the manual method. The odds of the automated method not producing a valid ABI-value was significantly influenced by gender and the level of the manually-measured ABI-value. The

failure odds ratio of females to males was 10.74 (95 % CI: 1.78 - 65.0; p = 0.010). A 0.1 point decrease in the manually-measured ABI-value was associated with a failure odds ratio of 1.24 (95 % CI: 1.02-1.52; p = 0.035). These odds ratios were adjusted for the other variables in the model (current smoker, side, operation of the leg and age).

DISCUSSION

This present study demonstrated a moderate similarity between the measurements from the automated method and those from the standard manual method, although this might as well reflect the moderate reproducibility of ABI-measurements anyhow. The automated method seemed to have a higher intrinsic precision than the manual method, although this conclusion just did not reach significance. Also no substantial and significant time-savings were reached with the automated method. At last but not at least, in our group of patients the automated method demonstrated a large proportion of failing measurements especially in females and with lower manually measured ABI levels. In conclusion, the Dopplex® ABIlity seems not clinically applicable in postoperative ABI-measurement. Future technological refinements are necessary and this should be performed by independent researchers in an independent laboratory.

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CHAPTER 3

The current position of pre-cuffed ePTFE bypass grafts in peripheral vascular surgery

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ABSTRACT

Objective: Long-term results of pre-cuffed expanded polytetrafluoroethylene (ePTFE) grafts used for peripheral bypass surgery are lacking. The aim of this study was to obtain the long-term outcomes of pre-cuffed ePTFE grafts compared with autologous saphenous vein (ASV) grafts used in patients with peripheral arterial disease (PAD).

Methods: A single-institution retrospective study of pre-cuffed ePTFE and ASV graft performances in patients with PAD was undertaken between January 2004 and December 2012. Five-year primary patency, secondary patency, and limb salvage rates were determined by Kaplan-Meier analyses.

Results: A total of 467 bypass grafts were included in this study (169 pre-cuffed ePTFE grafts and 298 ASV grafts). Secondary patency rates of ePTFE vs ASV at 1 and 5 years, respectively, were as follows: for 134 supragenicular femoropopliteal bypasses, 60% and 27% vs 89% and 85% ($P < .05$); for 190 infragenicular femoropopliteal bypasses, 40% and 25% vs 86% and 79% ($P < .05$); and for 84 femorocrural bypasses, 30% and 14% vs 50% and 50% ($P < .05$). Five-year limb salvage rates of ePTFE vs ASV for supragenicular femoropopliteal bypasses were 82% vs 94% ($P = .16$); for infragenicular femoropopliteal bypasses, 41% vs 92% ($P < .05$); and for femorocrural bypasses, 43% vs 64% ($P = .06$).

Conclusions: ASV bypasses are still the first-choice conduit in peripheral bypass surgery performed in patients with PAD. Pre-cuffed ePTFE bypasses are acceptable alternatives in the absence of adequate autologous vein.

INTRODUCTION

The autologous saphenous vein (ASV) is widely accepted as the first choice of conduit in peripheral bypass surgery. Because of impaired quality or previous use of the ASV for vascular or cardiac surgery, synthetic grafts like expanded polytetrafluoroethylene (ePTFE) have been demonstrated to be acceptable alternatives. Especially in supragenicular femoropopliteal bypass surgery, patency rates are acceptable for ePTFE bypass reconstruction (1-3). Patency rates of infragenicular femoropopliteal and femorocrural bypasses are still worse in ePTFE grafts compared with ASV (4).

Adjunctive procedures like the venous Miller cuff and St. Mary boot, which mimic the natural state and improve distal flow dynamics, have been developed to improve ePTFE patency rates (5, 6). As these procedures added complexity and increased operation time to the original procedure, pre-cuffed ePTFE grafts were developed. These bypasses demonstrated patency rates comparable to those of ePTFE grafts refined with venous cuffs (7, 8).

As mentioned in an earlier report from our clinic (9), we preferably use ASV grafts for peripheral bypass surgery in patients with peripheral arterial disease (PAD). If that is not applicable, a pre-cuffed ePTFE Dynaflo graft (Bard Peripheral Vascular Inc, Tempe, Ariz) is used in supragenicular femoropopliteal bypass reconstructions, and a pre-cuffed ePTFE Distaflo graft (Bard Peripheral Vascular Inc) is used in infragenicular femoropopliteal bypass and femorocrural bypass reconstructions.

During the past decades, technical development of endovascular procedures like percutaneous transluminal angioplasty has led to an increased use of minimally invasive treatment options for patients with less severe stages of PAD and less complex arterial lesions(10-12). This has shifted the indication for peripheral bypass surgery toward a more severe stage of PAD. Previously reported patency and limb salvage rates are potentially not applicable for contemporary clinics (2). Our previous report demonstrated acceptable midterm results of pre-cuffed ePTFE grafts with respect to limb salvage(9). However, the long-term results of pre-cuffed ePTFE grafts are lacking. The aim of this study is to analyse long-term results up to 5 years of pre-cuffed ePTFE and ASV grafts in patients with moderate to severe PAD, with special attention to limb salvage and adverse events.

METHODS

Study design

Between January 2004 and December 2012, all consecutive patients having peripheral bypass surgery for moderate to severe PAD (Rutherford class 3-6) were retrospectively reviewed. Inclusion criteria were use of autologous venous or pre-cuffed ePTFE bypass grafting. Patients who underwent peripheral vascular revascularization by combined venous or other bypass graft material (standard PTFE or Dacron®) were excluded from analyses.

Basic characteristics like age, gender, Rutherford classification, diabetes, arterial hypertension, and smoking status were retrieved from patients medical charts. Previous vascular interventions and data from surgical work up like ankle-brachial index (ABI), TASC-scores and number of open crural arteries, were recorded. Patency rates were determined by information from medical charts, such as physical examination, medical imaging, and laboratory results. Death was confirmed through the COMPET&T database from the company T&T Eindhoven.

Before surgery, patient workup included ABI, treadmill test, and magnetic resonance angiography or, when that was not applicable, digital subtraction angiography. Autologous bypass grafting was intended in all patients. Pre-cuffed ePTFE bypass grafts were considered when the ASV or lesser saphenous vein in both the ipsilateral and contralateral leg were absent or unsuitable (diameter <2 mm) for bypass grafting. This was determined by standard ultrasound evaluation (13) or, if ultrasound was inconclusive, on the basis of perioperative exploration.

Surgery was performed under general or spinal anesthesia. Before clamping, all patients received an intravenous dose of 5000 international units of heparin. All anastomoses were made end to side. Autologous bypass grafting was performed with either deep-tunneled reversed or in situ techniques. Pre-cuffed Dynaflo grafts were used in supragenicular femoropopliteal bypasses, and pre-cuffed Distaflo or pre-cuffed minicuff Distaflo grafts were used in infragenicular femoropopliteal and femorocrural bypasses. Routine Doppler assessment was performed before wound closure.

Based on the Dutch Bypass Oral Anticoagulants or Aspirin (BOA) trial, postoperative anticoagulant administration (acenocoumarol) was initiated for a 2-year period after autologous bypass surgery, followed by acetylsalicylic acid (ASA) (14, 15). After pre-cuffed ePTFE bypass grafting, ASA was administered. No warfarin was administered after any of the procedures. Follow-up after ASV bypass surgery included routine duplex ultrasound and ABI at 3 months, 6 months, 1 year, and 2 years after the initial procedure, followed by ABI every subsequent 2 years. Follow-up after ePTFE bypass surgery was restricted to duplex ultrasound and ABI examination at 3 months, 1 year, and 2 years after the initial procedure (9, 16). ABI was measured every subsequent 2 years. All other interim duplex ultrasound examinations

were performed after suspicion of graft-related problems. Interventions were performed on the basis of high-grade stenosis (peak systolic velocity ratio > 2.5); evidence comprised flow in the bypass or graft thrombosis. The primary end point was graft patency after 5 years, divided into primary patency, primary assisted patency, and secondary patency according to the definition of Rutherford (17). Patency dates were recorded at the last visit at which the bypass was proved open. The definition of limb salvage was freedom from having a major amputation in patients who had critical ischemia (Rutherford class 4-6).
Adverse events per procedure were recorded until 1 month after discharge of the primary procedure and defined according to the Association of Surgeons of the Netherlands. Total follow-up was performed until October 2013.

Statistical analysis.

Statistical analysis was performed with SPSS 20.0 software (SPSS Inc, Chicago, Ill). Continuous variables were analyzed by a Student t-test, and categorical variables were analyzed by c2 analyses and Fisher exact tests for smaller samples. Survival rates were produced with Kaplan-Meier survival curves with log-rank tests for comparison. Results were compared with a P value < .05 to show significant differences.

RESULTS

A total of 467 peripheral bypass grafts were included between January 2004 and December 2012. Basic patient characteristics are listed in Table I. In general, the indications for peripheral bypass grafting were based on moderate to severe PAD. Of these 467 grafts, 169 ePTFE grafts (36%) and 298 ASV grafts (64%) were used. Significantly more patients with Rutherford class 3 had undergone venous grafting compared with ePTFE (28% vs 15%; P < .05). In the ePTFE group, significantly more procedures were a repeated procedure (31% vs 11%; P < .05).
Preoperative patient characteristics are listed in Tables 2 and 3. In more than 50% of the bypasses, the indication for surgery was based on multiple femoropopliteal lesions (TASC D: ePTFE 62% and venous 60%). In two patients, pre-procedural information about open crural arteries was missing. Significantly more ePTFE bypasses were placed in legs having one open crural artery (59 ePTFE [35%] vs 79 ASV grafts [27%]; P < .05).

Table 1. Patient basic characteristics.

Characteristics	Total (N=467)	Pre-cuffed ePTFE (N=169)	ASV (N=298)	P-value
Mean age (range)		73,0 (41,0-92,7)	70,1 (36,8-96,5)	
Gender				0,17[a]
Male		108 (64%%)	209 (70%)	
Female		61 (36%)	89 (30%)	
Risk factors				
History of smoking		125 (74%)	230 (77%)	0,43[a]
Diabetes		66 (40%)	112 (38%)	0,72[a]
Hypertension		109 (72%)	187 (63%)	0,49[a]
Rutherford classification				
Rutherford 2		1 (1%)	4 (1%)	0,66[b]
Rutherford 3		25 (15%)	82 (28%)	0,00[a]
Rutherford 4		69 (41%)	101 (34%)	0,13[a]
Rutherford 5, 6		74 (44%)	112 (38%)	0,19[a]
Distal anastamosis				
Supragenicular		45 (27%)	89 (30%)	0,46[a]
Infragenicular		67 (39%)	123 (41%)	0,73[a]
Crural		57 (34%)	86 (29%)	0,27[a]
Primary/redo status		52 (31%)	32 (11%)	0,00[a]

ASV, Autologous saphenous vein; ePTFE, expanded polytetrafluoroethylene. ePTFE = expanded polytetrafluoroethylene; [a]Pearson χ^2-test; [b]Fisher's Exact Test.

Table 2. Pre-operative patient characteristics.

	Total (N=467)	Pre-cuffed ePTFE (N=169)	ASV (N=298)	P-value
TASC II femero-popliteal				
TASC A		3 (2%)	6 (2%)	1,00[b]
TASC B		8 (5%)	15 (5%)	0,89[a]
TASC C		53 (31%)	97 (33%)	0,79[a]
TASC D		105 (62%)	180 (60%)	0,71[a]
Number of open crural arteries[c]				
3		46 (28%)	100 (34%)	0,18[a]
2		52 (31%)	109 (37%)	0,24[a]
1		59 (35%)	79 (27%)	0,05[a]
0		10 (6%)	10 (3%)	0,18[a]

ASV, Autologous saphenous vein; ePTFE, expanded polytetrafluoroethylene; TASC II, TransAtlantic Inter-Society Consensus Document II. [a]Pearson χ^2-test. [b]Fisher exact test. [c]Two missing bypasses for number of open arteries.

Table 3. Percentages pre-cuffed ePTFE vs vein uses in the total study population.

Characteristics	Pre-cuffed ePTFE	ASV
Supragenicular (%)	45 (34%)	89 (66%)
Infragenicular (%)	67 (34%)	123 (66%)
Femerocrural(%)	57 (40%)	86 (60%)

ASV, Autologous saphenous vein; ePTFE, expanded polytetrafluoroethylene.

Patency

Primary, primary assisted, and secondary patency rates in supragenicular and infragenicular femoropopliteal bypass grafts and femorocrural bypass grafts were in favor of ASV compared with ePTFE (Table 4). Five-year primary patency rates for ePTFE and ASV in supragenicular femoropopliteal bypass grafts were 25% and 60%; in infragenicular femoropopliteal bypass grafts, 8% and 54%; and in femorocrural bypass grafts, 9% and 50% ($P < .05$). Secondary patency rates were also in favor of ASV compared with ePTFE in all three anatomic sites. Five-year secondary patency rates for ePTFE and ASV in supragenicular femoropopliteal bypass grafts were 27% and 85%; in infragenicular femoropopliteal grafts, 25% and 79%; and in femorocrural grafts, 14% and 50% ($P < .05$) (Table 4; Figs 1-3).

Table 4. Patency rates expressed in percentages (%).

Characteristics		Pre-cuffed ePTFE			ASV		
Mean follow-up months (range)		28,8 (<1-112)			36,1 (<1-116)		
Anatomic site	Patency	1 year	2 years	5 years	1 year	2 years	5 years
Supragenicular	Primary	56[d]	42[d]	25[d]	68[d]	60[d]	60[d]
	Primary assisted	59[d]	45[d]	27[d]	87[d]	82[d]	82[d]
	Secondary	60[d]	47[d]	27[d]	89[d]	85[d]	85[d]
Infragenicular	Primary	34[d]	18[d]	8[d]	65[d]	60[d]	54[d]
	Primary assisted	36[d]	22[d]	11[d]	79[d]	77[d]	74[d]
	Secondary	40[d]	31[d]	25[d]	86[d]	81[d]	79[d]
Femorocrural	Primary	24	24	9	39	39	18
	Primary assisted	24[d]	24[d]	9[d]	45[d]	43[d]	30[d]
	Secondary	30[d]	27[d]	14[d]	50[d]	50[d]	50[d]

ASV, Autologous saphenous vein; ePTFE, expanded polytetrafluoroethylene. Patency rates are expressed in percentages. [a]Log-rank, $P < .05$. All standard errors were less than 10%.

Limb salvage and survival

Limb salvage was based on 356 patients suffering from critical limb ischemia (Rutherford class 4-6). Limb salvage after 5 years was significantly higher in the ASV group (82% vs 49%; $P < .05$). No significant difference was seen in limb salvage for supragenicular femoropopliteal (82% vs 94%; $P = .16$) and femorocrural (43% vs 64%; $P = .06$) bypasses.

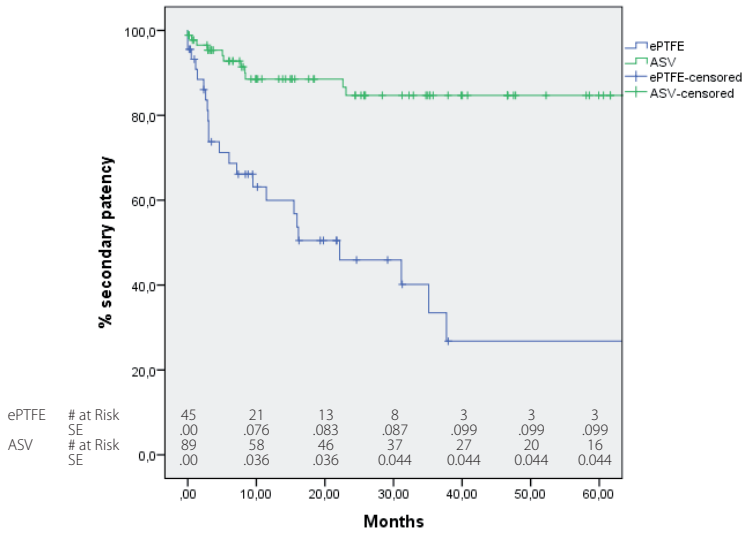

Figure 1. Kaplan-Meier curves representing secondary patency rates of autologous saphenous vein (ASV) and expanded polytetrafluoroethylene (ePTFE) supragenicular femoropopliteal bypasses (log-rank, P = .000). SE, Standard error.

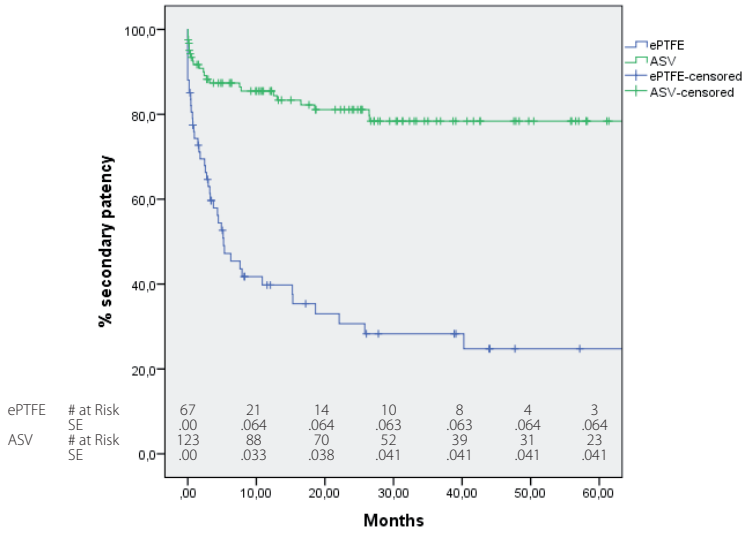

Figure 2. Kaplan-Meier curves representing secondary patency rates of autologous saphenous vein (ASV) and expanded polytetrafluoroethylene (ePTFE) infragenicular femoropopliteal bypasses (log-rank, P = .000). SE, Standard error.

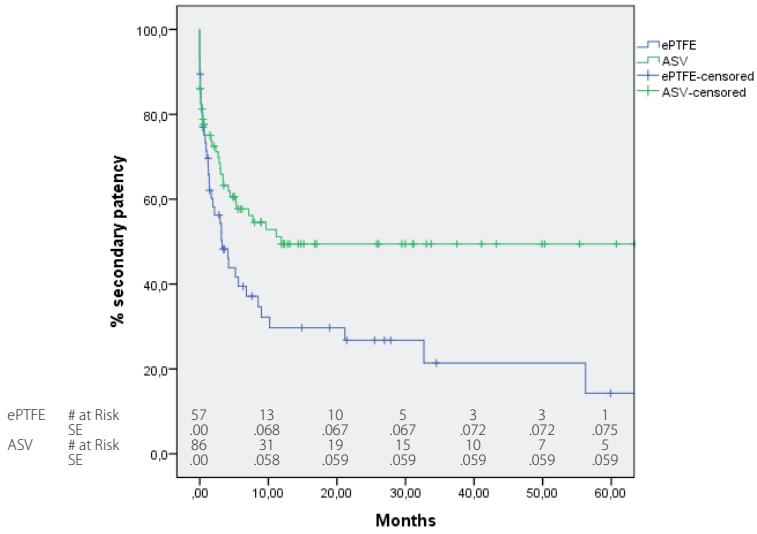

Figure 3. Kaplan-Meier curves representing secondary patency rates of autologous saphenous vein (ASV) and expanded polytetrafluoroethylene (ePTFE) femorocrural bypasses (log-rank, P = .012). SE, Standard error.

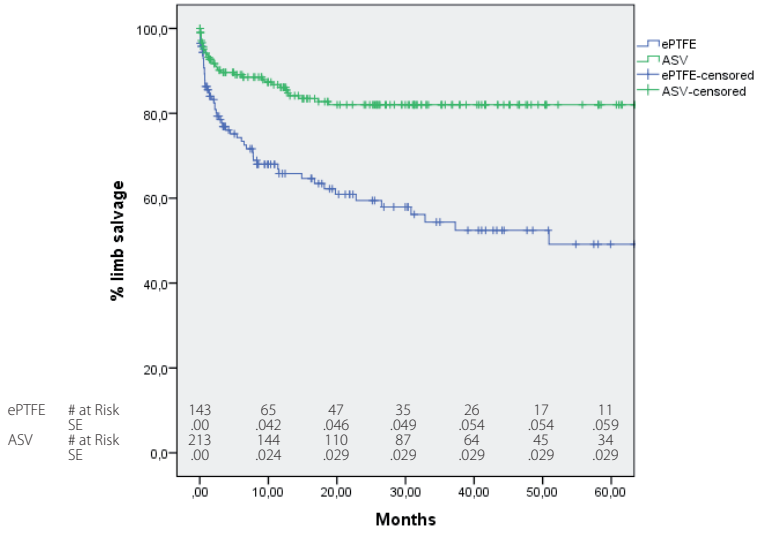

Figure 4. Kaplan-Meier curves representing limb salvage of autologous saphenous vein (ASV) and expanded polytetrafluoroethylene (ePTFE) bypasses (log-rank, P = .000). SE, Standard error.

Table 5. Limb salvage expressed in percentages (%).

Characteristics	Pre-cuffed ePTFE			ASV		
Distal anastomosis	1 year	2 years	5 years	1 year	2 years	5 years
Supragenicular	82	82	82	94	94	94
Infragenicular	69[a]	59[a]	41[a]	95[a]	92[a]	92[a]
Femerocrural	54	48	43	72	64	64
Overall	66[a]	60[a]	49[a]	86[a]	82[a]	82[a]

ASV, Autologous saphenous vein; ePTFE, expanded polytetrafluoroethylene. Limb salvage rates are expressed in percentages. [a]Log-rank, P < .05.

Limb salvage was significantly higher in the ASV group for infragenicular femoropopliteal bypasses compared with ePTFE grafts (92% vs 41%; P < .05) (Table 5; Fig 4). For 5-year survival, see Fig 5. After 5 years, significantly more patients were still alive after ASV bypass graft procedures compared with pre-cuffed ePTFE bypass graft procedures (ePTFE 56% vs ASV 67%; P < .05).

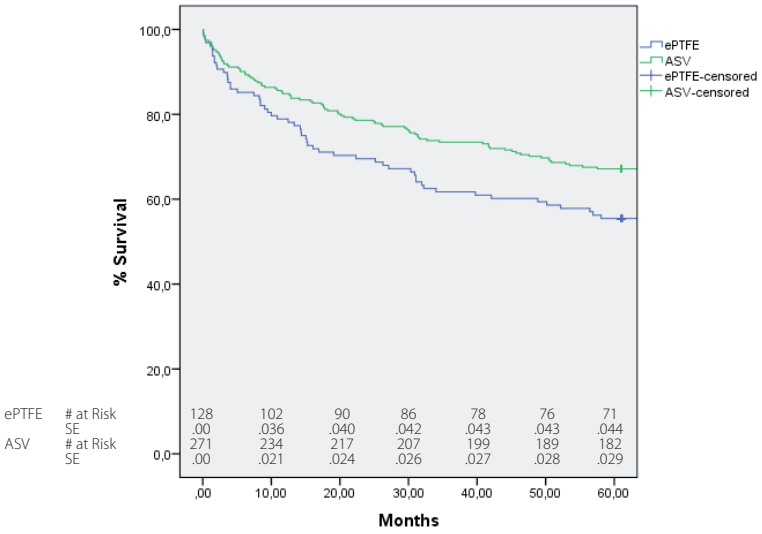

Figure 5. Kaplan-Meier curves representing survival of autologous saphenous vein (ASV) and expanded polytetrafluoroethylene (ePTFE) bypasses (log-rank; P ¼ .02). SE, Standard error.

Adverse events

As listed in Table VI, a total of 159 adverse events were registered after all primary procedures. Significantly more adverse events were observed after ePTFE compared with ASV bypass grafting (40% vs 30%; P < .05). No particular adverse event was significantly different between both groups. Most adverse events were related to the surgical procedure (surgical site infections: ePTFE 18%, ASV 17%; hemorrhages: ePTFE 11%, ASV 15%; compartment syndromes, ePTFE 1%, ASV none). The 30-day mortality was 3% for both groups.

Table 6. Adverse events occurred after primary procedure.

Characteristics	Total (N=467)	Pre-cuffed ePTFE (N=169)	ASV (N=298)	P-value
Adverse events per procedure		70 (41%)	89 (30%)	0,01[a]
Minor Events				
Urine tract infection		4 (2%)	2 (1%)	0,20[b]
Bladder retention		2 (1%)	2 (1%)	0,62[b]
Decubitus		-	4 (1%)	0,30[b]
Surgical Events				
Wound infection		30 (18%)	50 (17%)	0,79[a]
Wound necrosis		3 (2%)	2 (1%)	0,36[b]
Seroma		4 (2%)	3 (1%)	0,26[b]
Hemorrhages		11 (7%)	15 (5%)	0,53[a]
Compartment syndrome		2 (1%)	-	0,13[b]
Systemic				
Myocardial infarct		4 (2%)	8 (3%)	0,84[a]
Decord compression		6 (4%)	5 (2%)	0,22[b]
Arrhythmia		2 (1%)	4 (1%)	1,00[b]
Hypovolemic shock		-	1 (0%)	1,00[b]
Pneumonia		5 (3%)	4 (1%)	0,30[b]
Respiratory insufficiency		5 (3%)	2 (1%)	0,10[b]
CVA		1 (1%)	2 (1%)	1,00[b]
Neurological		2 (1%)	3 (1%)	1,00[b]
Acute renal failure		2 (1%)	5 (2%)	1,00[b]
Diarrhea		3 (2%)	2 (1%)	0,36[b]
Ileus		-	1 (0%)	1,00[b]
Delier		5 (3%)	4 (1%)	0,30[b]
Mortality				
Within 30 days		5(3%)	8 (3%)	0,86[a]

ASV = Autologous saphenous vein; ePTFE = expanded polytetrafluoroethylene; CVA = cerebrovascular accident. [a]Pearson χ^2-test; [b]Fisher's exact test.

DISCUSSION

This study confirms ASV grafts to be the first choice of conduit in peripheral bypass surgery, with better 5-year patency and limb salvage rates compared to pre-cuffed ePTFE grafts (2, 18). When an ASV graft is not applicable, pre-cuffed ePTFE grafts used in supragenicular femoropopliteal bypass surgery demonstrate acceptable short-term patency results and 5-year limb salvage rates comparable to those of ASV grafts. Pre-cuffed ePTFE grafts used for infragenicular femoropopliteal and femorocrural bypass grafting demonstrate poor short- and long-term results but are considered acceptable alternatives when ASV grafts are not available.

Many reports demonstrating acceptable midterm results are published in the literature (9, 19, 20). Also, our previous report demonstrated acceptable short-term outcome of ePTFE bypass grafts especially with respect to limb salvage (9). The present study, by demonstrating comparable results, did not change this conclusion.

A recently published study of long-term results from pre-cuffed ePTFE vs ASV bypasses demonstrated better 5-year secondary patency rates of infragenicular femoropopliteal bypasses of 51% vs 84% compared with our results (18). Limb salvage after infragenicular femoropopliteal bypasses also demonstrated better results (79.4% vs 83.3%; not significantly different). The 5-year rates of pre-cuffed femorocrural ePTFE vs ASV grafts for secondary patency (22.1% vs 50.6%) and limb salvage (22.1% vs 50.6%) were comparable to our results. The choice of conduit could be a potential explanation for these differences because this was based on the preference of the attending surgeon in their series.

To improve patency rates, heparin-bound ePTFE (HePTFE) grafts were introduced. Daenens et al (16) demonstrated impressive patency rates of below-knee HePTFE bypasses, with equal primary patency rates for HePTFE and vein grafts (83% vs 80%). In later reports, the superiority of HePTFE grafts was invalidated by no significant difference between HePTFE and ePTFE grafts (21, 22). The explanation of this difference could be the large number of HePTFE bypasses (69%) included in the Daenens study, in contrast to the small number of ASV grafts (31%).

Our antithrombotic regimen was based on the BOA trial demonstrating that the use of anticoagulants for more than 2 years after ASV bypasses does not attain better patency rates (14). The use of anticoagulants after synthetic bypass grafting did not attain better patency rates compared with ASA monotherapy and resulted in more postoperative adverse events like major bleedings. On this basis, we assume that our antithrombotic regimen had no attributable effect on our patency rates.

Adverse events until 1 month after discharge were registered from medical charts. Most events were wound related but not significantly different between both procedures. Because

most procedures were performed on patients with a mean age of more than 70 years, the probably underestimated prevalence of postoperative delirium (3%) is therefore worth mentioning. Postoperative prevalence of delirium up to 42% is known in the literature (23) and because of the consequences like prolonged recovery time, extra nursing care, longer intensive care unit stay, and higher complication rates (24) this could be an interesting topic for future prospective studies.

Pre-cuffed ePTFE grafts were frequently used in patients with an advanced stage of PAD and also in repeated procedures, demonstrating that pre-cuffed ePTFE grafts were used in a more disadvantaged situation compared with ASV grafts. This could be an explanation of why we obtained these worse patency outcomes after these bypass grafts. This was also demonstrated in previous reports in which ePTFE demonstrated obligatory results because of the absence of an autologous vein (4). This should be taken into account in interpreting our results.

Our study has limitations because of its retrospective design, which should be considered in interpreting the results. We acknowledge that because of multiple medical problems related to severe PAD, it was difficult to retain a large patient population during 5 years of follow-up. Five-year results, especially for femorocrural bypasses, were therefore based on less patients. We also acknowledge that there could be an underestimation of the total amount of adverse events during follow-up because we registered only the adverse event from the primary procedure. Adverse events after secondary procedures were not registered but are also important to be taken into account because these procedures will happen during follow-up. Finally, our results were obtained from a large population of peripheral bypasses based on a patient population with moderate to severe PAD.

CONCLUSION

In a population with more patients suffering severe PAD, ASV bypass grafts are the first choice of conduit. Pre-cuffed ePTFE bypasses used in infragenicular femoropopliteal and femorocrural bypass surgery are still acceptable alternatives in the absence of adequate autologous vein. For improvement of the patency rates in infragenicular femoropopliteal and femorocrural bypasses, future research has to be performed on alternative procedures or other bypass conduits.

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CHAPTER 4

Adverse events after treatment of patients with acute limb ischemia

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ABSTRACT

Background: To assess the outcome and the occurrence and consequences of adverse events (AEs) after treatment of acute limb ischemia (ALI).

Methods: Retrospective analysis on intra-arterial thrombolysis (group I) and thromboembolectomy (group II). Outcome measures were primary patency and limb salvage rates. AEs and consequences were registered during admission and 30 days after discharge.

Results: A total of 238 procedures were included (group I, 173 vs. group II, 65). The primary patency (P = 0.144) and limb salvage rates (P = 0.166) were not significantly different between both groups. A total of 195 AEs were registered. Most AEs were procedure related and resulted in surgical reintervention (77% vs. 76%). Some AEs resulted in irreversible physical damage (15% vs. 25%) and death (6% vs. 12%).

Conclusions: Both, intra-arterial thrombolysis and thromboembolectomies are adequate therapies; however, they result in a wide variety of AEs resulting in serious morbidity and even death.

INTRODUCTION

Acute limb ischemia (ALI) generally occurs after an acute arterial occlusion of an extremity mostly due to an arterial embolism or thrombosis(1, 2). Accurate and adequate clinical recognition is essential to improve limb salvage, reduce morbidity, mortality and to maintain quality of life(3).

Surgical thromboembolectomy has been the standard procedure for ALI for a long period (4). Since the last 2 decades, intra-arterial thrombolysis demonstrated comparable outcome results to thromboembolectomy(5-9) and has become the preferred choice of treatment in patients with ALI(3).

Arguments for thrombolysis instead of surgery were the less invasive character of the treatment with decreased risk of perioperative adverse events (AEs). However, reports about post-procedural AEs of both procedures are in our opinion scarce, outdated and mostly focussed on haemorrhages (10, 11).

AEs are one of the key issues in outcome measurement resulting in prolonged hospital stay and/or reinterventions, eventually leading to increased health care costs (12). Outcome measures are important since intra-arterial thrombolysis is considered to be a relatively safe procedure, although the indications for intra-arterial thrombolysis and thrombectomy are different.

The aim of this study was to assess the occurrence and consequences of AEs after both procedures. Secondary outcome parameters were patency and limb salvage.

MATERIAL AND METHODS

Patients

All consecutive procedures performed in patients with ALI were retrieved from a database based on operation codes corresponding to intra-arterial thrombolysis or thrombectomies between January 2008 and December 2012. The included procedures were divided into two groups; group I: patients treated with intra-arterial thrombolysis, and group II: patients treated with thromboembolectomy. Combined procedures (thrombolysis/thrombectomy followed by other vascular procedures), procedures performed within 6 weeks after the last elective vascular procedure or procedures performed on patients with more than 6 weeks complaints were excluded from this survey (Figure 1).

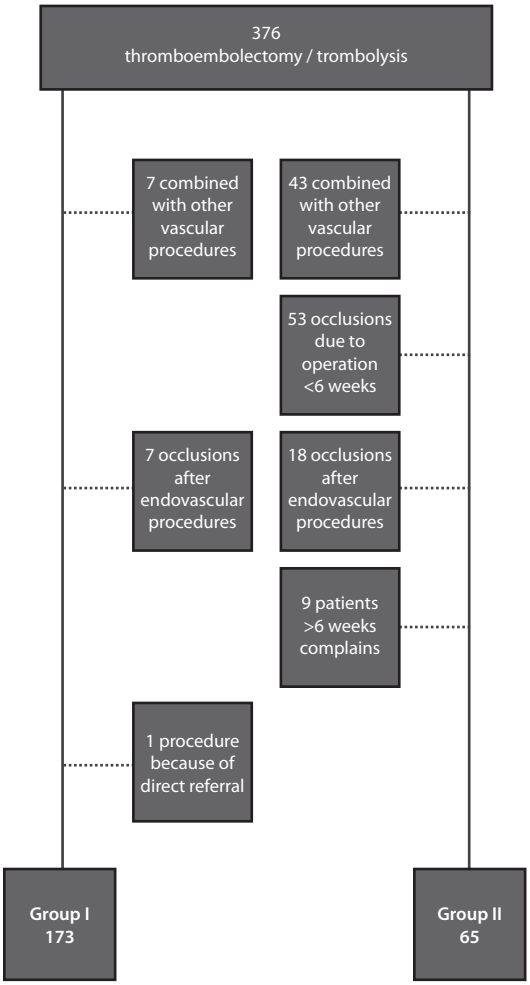

Figure 1. Flow-chart representing procedure selection of 376 codes for intra-arterial thrombolysis/ thromboembolectomy (January 2008 – December 2012); (Group I = intra-arterial thrombolysis; group II = thromboembolectomy).

Risk factors and comorbidities

Cardiovascular risk factors, comorbidity and clinical categories of ALI were registered according to the Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC) and the society of vascular surgery/North American Chapter of the International Society for Cardiovascular surgery (SVS/ISCVS) guidelines(13, 14). The American Society of Anaesthesiologists (ASA)-score and past-history of active malignancy and abdominal aneurysms were also collected.

Procedure

Procedural indications for intervention were based on the TASC and SVS/ISCVS guidelines(13, 14). Thromboembolectomies were performed according to standard vascular procedures. Thrombolysis was performed according to the hospitals standards (Appendix 1). Post-procedural success was defined as increased run-off after intervention. In general, all patients received acenocoumarol//Sintrom® until the target International Normalized Ratio (INR) was achieved (INR: 2.5 and 3.5) after all procedures. Thereafter heparin infusion was terminated.

Follow up and outcome

In general, anticoagulant therapy was terminated after 6 months of the initial procedure, unless other indications were present. To determine patency, patients underwent clinical examination, duplex ultrasound examination (DUE) and ankle brachial index (ABI) during routine examination. Patency -, limb salvage rates were determined according to TASC- and SVS/ISCVS guidelines (13, 14). Patency dates were recorded at the last visit at which the artery was proven to be open. The definition of limb salvage was freedom from having a major amputation after the procedure. Death was confirmed through the COMPET&T database from the company T&T Eindhoven, the Netherlands.

Adverse events

All adverse events (AEs) were registered during follow up from patient records. An AE was defined by the following general definition: "a condition or event, unfavorable to the patient's health or treatment causing unintentional damage or requiring a change in therapeutic policy or additional treatment, which occurred during admission or within 30 days after discharge or transferee to another department. The intended result of treatment, the likelihood of the adverse outcome occurring, and the presence or absence of a medical error causing it, is irrelevant in identifying an adverse outcome". This definition was confirmed by the Association of Surgeons of the Netherlands (ASN) and has been chosen with the explicit aim of excluding subjective judgment on cause and effect, and right or wrong (12, 15-18). Also the consequences of all AE were registered based on their severity. The potential consequences of the AEs were divided into: minor complication, no long-term consequence, additional medication or transfusion, surgical reoperation, prolonged hospital stay and irreversible damage (12, 19).

Registration and statistical analysis

Patient information was registered in an electronic patient file used for all patients during their admission intake. Statistical analyses were performed through a computerized software package, using IBM SPSS 20.0. Kaplan-Meier-survival methods were used to calculate the time curve of the cumulative patency -, limb salvage - and 1-year mortality rates determined at regular intervals

after the initial procedure. Log-rank tests were used to compare the results of both groups. Univariate analysis was performed using Chi-square, Fisher Exact- and unpaired Students t-test. For all statistical analyses, *P*-value <.05 was considered to be statistically significant.

RESULTS

Patients

A total of 238 procedures, performed on 191 patients, were included to this study: 173 intra-arterial thrombolytic procedures (70%: group I) and 65 thromboembolectomies (30%, group II) (Table 1). These procedures were performed on 145 men (61%) and 93 (39%) women with a mean age: 69±12.0 years.

Table 1. Basic characteristics.

Characteristics	Total (n = 238)	Group I (n = 173)	Group II (n = 65)	*P*-value
Gender				0.023*
Male	145	113 (65%)	32 (49 %)	
Female	93	60 (35 %)	33 (51 %)	
Age				0.19‡
Mean (±SD), years	69 (12.0)	68 (12.2)	70 (11.3)	
ASA-classification§				0.001*
Classification 1	24	16 (9.2 %)	8 (12 %)	0.49*
Classification 2	140	109 (63 %)	31 (48 %)	0.032*
Classification 3	58	43 (25%)	15 (23 %)	0.78*
Classification 4	16	5 (4 %)	11 (17 %)	0.000*
Comorbidity				
Malignancy	18	7 (4 %)	11 (17 %)	0.001*
Abdominal aneurysm	9	6 (4 %)	3 (5 %)	0.71†
Arterial hypertension	108	80 (46 %)	28 (43 %)	0.66*
Diabetes	50	43 (25 %)	7 (11 %)	0.017*
History of smoking	148	107 (62 %)	41 (63 %)	0.86*
Cardiac disease	84	62 (36 %)	22 (34 %)	0.77*
Pulmonary disease	39	27 (16 %)	12 (18 %)	0.60*
Renal disease	58	39 (23 %)	19 (29 %)	0.28*
Carotid disease	31	21 (12 %)	10 (15 %)	0.51*

* = χ^2-test; † Fisher's Exact test; ‡ independent student-t test; § = American Society of Anaesthesiologists; Group I= intra-arterial thrombolysis; group II = thromboembolectomy.

Risk factors and comorbidities

Most procedures were performed on ASA-2 patients (*n*=140; 59%). In group I, significantly more procedures were performed in male patients and patients with diabetes (*P*<.05). Thromboembolectomies were significantly more performed in patients with ASA-classification 4 or patients with active malignancies (*P*<.05). Age and all other comorbidities were not significantly different between both groups.

Table 2. Preoperative characteristics.

Characteristics	Total (n = 238)	Group I (n = 173)	Group II (n = 65)	*P*-value
ALI-classification§				
Class 1	2	2 (1.0%)	0 (0%)	1.00†
Class 2a	170	139 (80%)	31 (48%)	0.000*
Class 2b	64	31 (18%)	33 (51%)	0.000*
Class 3	2	1 (1 %)	1 (2 %)	0.47†
Days of complains				
Mean (±SD), years	5 (7.8)	6 (8.7)	3 (3.6)	0.001‡
Previous vascular surgery	118	97 (56%)	21 (32%)	0.001*
Location of occlusion				
Bypass	109	90 (52%)	19 (29%)	0.002*
Femorofemoral crossover	3	2	1	
Axillofemoral	6	1	5	
Supragenicular	30	26	4	
Infragenicular	35	30	5	
Femorocrural	23	20	3	
Aortobifemoral	8	7	1	
EVAR	4	4	0	
Aorto-iliac artery	29	19 (11%)	10 (15%)	0.36*
Common iliac artery	23	16	7	
External iliac artery	7	4	3	
Femoral arteries	52	26 (15%)	26 (40%)	0.000*
Common femoral artery	18	5	13	
Superficial femoral artery	33	25	8	
Femoral profunda artery	4	0	4	
Popliteal artery	33	27 (16%)	6 (9%)	0.21*
Crural arteries	12	8 (5%)	4 (6%)	0.74†

* = χ^2-test; † Fisher's Exact test; ‡ independent student-t test; § = ALI-class = acute limb ischemia classification; Group I= intra-arterial thrombolysis; group II = thromboembolectomy.

Procedure

Significantly more procedures were performed on patients with marginal threatened ALI in group I (group I: 80% vs group II: 48%; P<0.05). Significantly more procedures were performed on patients with immediate threatened ALI in group II (group I: 18% vs group II: 51%; P<0.05). There were no differences in procedures performed on patients with viable ALI and irreversible ALI. There was a significant difference between both groups concerning the mean days of complains before intervention (group I: 6±8.7 vs group II: 3±3.6 days; *P*<.05) (Table 2). In group I significantly more procedures were performed on patients with a past medical history of a vascular procedure (56% vs 32%; *P*<.05). Significantly more occluded bypass grafts were treated with thrombolysis compared to thromboembolectomies (52% vs 29%; *P*<.05) as listed in Table 2. A higher incidence of thromboembolectomies was registered in occluded femoral arteries. All other locations with occlusions were not significantly different between both groups.

Outcome

One year primary patency rates were not significantly different between group I and group II (Figure 2). Thirty days - and 1 year patency rates in group I and II were 78% and 49% vs 59% and 43% (*P*=.144) respectively.

There were also no differences in thirty days - and 1 year limb salvage rates (Figure 3). Limb salvage rates in group I and II were 91% and 71% vs 79% and 66% (*P*=.166) respectively.

After one year, significantly more patients were still alive after the procedure in group I (Figure 4). Thirty days – and 1 year survival analyses in group I and II were 94% and 82% vs 88% and 69% (*P*<.05) respectively.

Adverse events

A total of 195 AEs were registered in 131 procedures (55%). One-hundred and forty-nine (76%) of these AEs were procedure related. Haemorrhages were registered in 17 procedures (7%) and were equally divided between both groups. Surgical site infections were registered after 14 procedures (6%) and were also equally divided. Significantly more revascularisation failures occurred in group I (group I 28% vs group II 8%; *P*<.05). Significantly more arterial re-occlusions occurred in group II (group I 9% vs group II 23 %; *P*<.05). (Table 3).

Most AEs were procedure related (group I 77% vs group II 76%) and overall resulted in surgical reinterventions (group I 31% vs group II 49%). Overall irreversible physical damage were observed in 15% in group I and 25% in group II. Six percent of the total AEs resulted in death in group I and 12% of the AEs resulted in death in group II (Table 4).

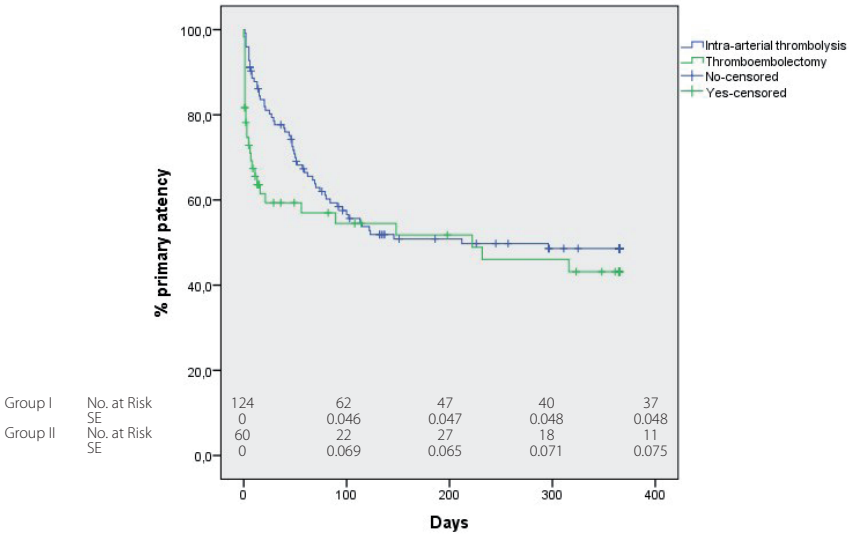

Figure 2. Kaplan-Meier curves representing primary patency rates of all successful intra-arterial thrombolysis (Group I) and thromboembolectomy (Group II) (log-rank, P = .144). SE, Standard error.

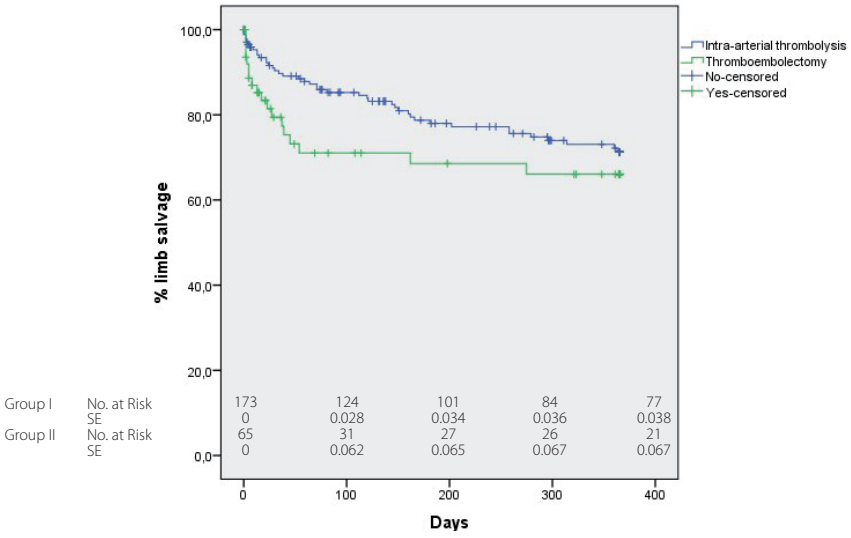

Figure 3. Kaplan-Me ier curves representing amputation-free survival of intra-arterial thrombolysis (Group I) and thromboembolectomy (Group II) (log-rank, P = .166). SE, Standard error.

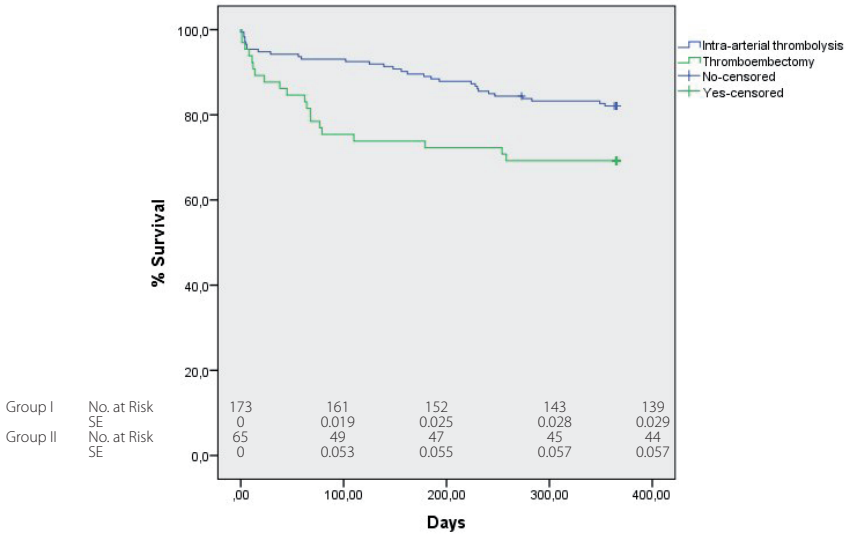

Figure 4. Kaplan-Meier curves representing 1 year survival of intra-arterial thrombolysis (Group I) and thromboembolectomy (Group II) (log-rank, P = .020). SE, Standard error.

Group I: thrombolysis

One hundred and forty-four AEs were registered after 93 procedures (Table 4). Most AEs were procedure related and reflected 77% of all AEs in group I. Thirty-nine per cent resulted in minor complications, 4% in additional medication or transfusion, 39% in reinterventions, 17% in irreversible physical damage and 1 % in early death. Infection related AE's were registered in 8 % of all AEs in group I. Seventy-five per cent resulted in additional medication or transfusion, 17% resulted in early death and 8% in early death. Fifteen percent of all AEs in group I were organ related. Thirty-two per cent resulted in additional medication or transfusion, 27% in prolonged hospital stay, 5% in irreversible physical damage and 36% in early death.

Group II: Thromboembolectomies

Fifty-one AEs occurred after 38 thromboembolectomies. Procedure related AEs reflected 76% of all AEs in group II. Ten per cent resulted in minor complications, 51% reinterventions, 31% in irreversible physical damage and 8% resulted in early death. Twenty per cent of all AEs in group II were infection related. Ten per cent resulted in additional medication or transfusion, 50% in reinterventions, 10% in prolonged hospital stay, 10% in irreversible physical damage and 20% in early death. Four per cent of all AEs in group II were organ related. Fifty per cent resulted in additional medication or transfusion and 50% in early death (Table 4).

Table 3. Adverse Events registered after 131 procedures during admission or within 30 days after discharge.

Characteristics	Total (n = 238)	Group I (n = 173)	Group II (n = 65)	*P*-value
Procedure related				
Revascularization failure	54 (23%)	49 (28%)	5 (8%)	0.001*
Re-occlusion	38 (16%)	15 (9%)	23 (35%)	0.000*
Compartment syndrome	12 (5%)	7 (4%)	5 (8%)	0.32†
Hemorrhages	17 (7%)	15 (9%)	2 (3%)	0.14*
Hematoma	24 (10%)	20 (12%)	4 (6%)	0.22*
Pseudo aneurysm	3 (1%)	3 (2%)	-	0.56*
Seroma	1 (0%)	1 (1%)	-	1.000†
Infection related				
SSI	14 (6%)	6 (3%)	8 (12%)	0.47†
Pneumonia	6 (3%)	5 (3%)	1 (2%)	1.000†
Urinary tract infection	2 (1%)	1 (1%)	1 (2%)	0.47†
Organ related				
Urinary retention	1 (0%)	1 (1%)	-	1.000†
Acute renal failure	4 (2%)	4 (2%)	-	0.58†
Myocardial infarction	2 (1%)	2 (1%)	-	1.000†
Congestive heart failure	5 (2%)	4 (2%)	1 (2%)	1.000†
Arrhythmia	2 (1%)	2 (1%)	-	1.000†
Ileus	1 (0%)	1 (1%)	-	1.000†
Bowel ischemia	1 (0%)	1 (1%)	-	1.000†
Anaphylaxis	2 (1%)	2 (1%)	-	1.000†
Stroke	2 (1%)	2 (1%)	-	1.000†
Delirium	4 (2%)	3 (2%)	1 (2%)	1.000†

* = χ^2-test; † Fisher's Exact test; ‡ independent student-t test; Group I= intra-arterial thrombolysis; group II = thromboembolectomy.

Table 4. Adverse events (causes and consequences) after treatment for ALI of the total sample (n = 195).

	Adverse events	Total	Consequences					
			1A	1B	2A	2B	3	4
Group I	Procedure related	110 (77)	43 (39)	4 (4)	43 (39)	0 (0)	19 (17)	1 (1)
	Infection related	12 (8)	0 (0)	9 (75)	2 (17)	0 (0)	1 (8)	0 (0)
	Organ related	22 (15)	0 (0)	7 (32)	0 (0)	6 (27)	1 (5)	8 (36)
	Total AE's	144 (100)	43 (30)	20 (14)	45 (31)	6 (4)	21 (15)	9 (6)
Group II	Procedure related	39 (76)	4 (10)	0 (0)	20 (51)	0 (0)	12 (31)	3 (8)
	Infection related	10 (20)	0 (0)	1 (10)	5 (50)	1 (10)	1 (10)	2 (20)
	Organ related	2 (4)	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)	1 (50)
	Total EA's	51 (100)	4 (8)	2 (4)	25 (49)	1 (2)	13 (25)	6 (12)

Data are presented as n and (%); *ALI* = acute limb ischemia; *AE* = adverse event; 1A = minor complications, no long-term consequence; 1B = additional medication or transfusion; 2A = surgical reoperation; 2B = prolonged hospital stay; 3 = irreversible physical damage; 4 = death; Group I= intra-arterial thrombolysis; group II = thromboembolectomy.

DISCUSSION

Results from this present study demonstrates no superiority of intra-arterial thrombolysis on patency or amputation rates after 1 year follow-up. There was a considerable amount of adverse events registered which mostly were procedure related. Surgical reinterventions were the most frequently observed consequence of both treatments (group 1: 31% and group II: 49%). Irreversible physical damage was observed in 15% in group I and 25% in group II. Six percent of the AEs resulted in death in group I and 12% of the AEs resulted in death in group II.

Procedures

Patency - and limb salvage rates were not significantly different between both procedures after 1 year, which was comparable to prospective randomised controlled trial in literature(5-9). We did observe a significantly higher mortality rate in the thromboembolectomy group. This observation could be explained by a potential selection bias in choosing the initial treatment for certain patients. In our clinic, we preferably use intra-arterial thrombolysis in patients with ALI and reserve thromboembolectomy for situations in which rapid invention is indicated or intra-arterial thrombolysis is contra-indicated because of a patient clinical condition(13, 14).

Adverse events

We registered more re-occlusions after thromboembolectomies. A possible explanation for this is that the passage of an inflated thromboembolectomy catheter through a vessel lumen can cause serious endothelial damage(20). The loss of endothelial cells can potentially lead to clod-formation in the acute phase as well (21). Long-term effects of this injury are not known. Although, endothelial damage could theoretically also occur after thrombolytic therapy by the inserted catheter, it is more likely that this will occur more often after thromboembolectomies (21).

Major haemorrhages are frequently mentioned AEs after thrombolysis (11, 20, 22) and are also frequently registered in our study. Although the incidence of haemorrhages were slightly higher after thrombolysis, we did not observe a significant difference in this AE between both procedures. Also more post procedural strokes were registered after intra-arterial thrombolysis with no significant difference between both groups. The non-significant difference is probably a result of the small numbers in our study since two meta-analyses demonstrated a significant higher risk of haemorrhages and stroke after intra-arterial thrombolysis (8, 9).

Although thrombolysis is a minimal invasive endovascular intervention, more systemic AEs (organ related AE's) were registered in this group. These AEs result in extensive morbidity and mortality (12).

Reducing AEs is a major topic in contemporary medicine since this is largely related to patient

quality of life and health care cost (12, 18). We observed a large percentage of surgical/procedural AEs (77% of all AEs after intra-arterial thrombolysis and 76% after thromboembolectomies) suggesting possibilities for improvement. This could be achieved by structured changes in perioperative management and surgical protocols, eventually resulting in reduced AEs(23).
Additionally, many isolated pharmaco-mechanical thrombolysis systems have been developed to minimize severe systemic adverse events or major haemorrhages after intra-arterial thrombolysis(24-34). Although these results are promising most reports about these new techniques are based on case reports or small clinical studies. Future large clinical studies should be performed to demonstrate the value of these techniques in reducing AEs.

Limitations

Our study has limitations because of its retrospective design, which should be considered when interpreting the results. Patients with more than 6 weeks of complaints or patients with combined procedures were excluded in this study to reduce the effect of other procedures on adverse events. Results could therefore not be interpreted on these patients samples. We acknowledge that our data is collected from one single hospital and although it is a large referral hospital with 5 vascular surgeons AE rates might differ in other centres. We also acknowledge the fact that all AE registration systems will have some sort of underestimation. Future prospective studies have to be performed to replicate our findings about AEs after contemporary treatment of ALI. Finally, it should be appreciated that our result were obtained in one, high volume hospital based on a large patient population with ALI.

CONCLUSION

Acute limb ischemia is a serious clinical condition with high change of morbidity and mortality. Both, intra-arterial thrombolysis and thromboembolectomies are adequate therapies but result in a wide variety of adverse events resulting in serious morbidity and even death.

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APPENDIX 1

Thrombolysis protocol Amphia Hospital, (the Netherlands, Breda).

Procedural information:

- Pre-procedural measures were Angiography or Magnetic Resonance Angiography (MRA).
- Most procedures were approached from the contralateral femoral artery using a 6 F 45 cm Terumo® sheath.
- The entire occluded segment was passed using a Terumo® glidewire.
- A 4 F McNamara® catheter was introduced into the occluded segment.
- Angiographic control every 8 or 12 hours; depending on the extensiveness of the lesion .
- Depending of the underlying vascular lesion an endovascular procedure was performed after thrombolysis.
- Thrombolysis was stopped in case of hemorrhage or no technical success after 24-48 hours or fibrinogen <2g/l.
- Post-procedural hemostasis was derived using 6Fr AngioSeal (St Jude Medical) or manual compression of the puncture site.

Thrombolysis

- A bolus of Urokinase® (250.000 IU) was administered into the occluded segment, followed by infusion of 100.000 IU/h.
- Heparin was also administered at the start of the procedure (5000 IU), followed by infusion of 800-900 IU/h.
- APTT and fibrinogen were checked every 4 hours and APTT-time was set to 60 sec.

PART II

Prevention and treatment of SSI

CHAPTER *5*

Implementation of a bundle of care to reduce surgical site infections in patients undergoing vascular surgery

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ABSTRACT

Background: Surgical site infections (SSI's) are associated with severe morbidity, mortality and increased health care costs in vascular surgery.

Objective: To implement a bundle of care in vascular surgery and measure the effects on the overall and deep-SSI's rates.

Design: Prospective, quasi-experimental, cohort study.

Methods: A prospective surveillance for SSI's after vascular surgery was performed in the Amphia hospital in Breda, from 2009 through 2011. A bundle developed by the Dutch hospital patient safety program (DHPSP) was introduced in 2009. The elements of the bundle were (1) perioperative normothermia, (2) hair removal before surgery, (3) the use of perioperative antibiotic prophylaxis and (4) discipline in the operating room. Bundle compliance was measured every 3 months in a random sample of surgical procedures and this was used for feedback.

Results: Bundle compliance improved significantly from an average of 10% in 2009 to 60% in 2011. In total, 720 vascular procedures were performed during the study period and 75 (10.4%) SSI were observed. Deep SSI occurred in 25 (3.5%) patients. Patients with SSI's (28,5±29.3 vs 10.8±11.3, $p<0.001$) and deep-SSI's (48.3±39.4 vs 11.4±11.8, $p<0.001$) had a significantly longer length of hospital stay after surgery than patients without an infection. A significantly higher mortality was observed in patients who developed a deep SSI (Adjusted OR: 2.96, 95% confidence interval 1.32-6.63). Multivariate analysis showed a significant and independent decrease of the SSI-rate over time that paralleled the introduction of the bundle. The SSI-rate was 51% lower in 2011 compared to 2009.

Conclusion: The implementation of the bundle was associated with improved compliance over time and a 51% reduction of the SSI-rate in vascular procedures. The bundle did not require expensive or potentially harmful interventions and is therefore an important tool to improve patient safety and reduce SSI's in patients undergoing vascular surgery.

INTRODUCTION

The occurrence of surgical site infections (SSI's) in surgery results in reduced quality of life, increased hospital length of stay, increased likelihood of mortality, higher change of readmissions and re-interventions (1). In vascular surgery deep infections lead to re-operations with a high morbidity and even mortality, especially in patients who received a prosthetic graft resulting in higher health care costs (2, 3). Therefore in 2007 a study was performed in the Netherlands to determine the amount of preventable mortality in Dutch hospitals (4). SSI's were amount the leading causes and based on these findings the Dutch hospital patient safety program (DHPSP) was developed. The DHPSP disseminates knowledge to the Dutch hospitals, especially in preventive programs and networking opportunities. Since the start in 2009, they set up a goal to reduce these highly preventable complications by 50% at the end of 2012. The program included a bundle to prevent the development of SSI (http://www.vmszorg.nl/10-Themas/POWI) and consisted of four process measures which should be implemented with a total compliance of at least 90%. To quantify the effect of the interventions on the outcome the SSI-rate was measured using validated methods in a national registry (http://prezies.nl). The bundle elements were: (1) perioperative normothermia, (2) appropriate hair removal before surgery, (3) the use of perioperative antibiotic prophylaxis and (4) discipline in the operation room. The first three measurements are evidence-based and are included in the current national guidelines for the prevention of SSI (http://www.wip.nl/free_content/Richtlijnen/100720powi%20def.pdf). The effect of improved discipline is generally recognized as an important aspect but few studies have addressed it. This is mainly caused by the lack of reliable methods to measure discipline. The expert team for SSI-prevention of the DHPSP decided to use the number of door openings during surgical procedures as a surrogate marker for discipline.

The objective of this study was to implement the bundle of care in vascular surgery and evaluate the effects on the overall SSI-rate as well as the deep SSI-rate while adjusting for confounders.

METHODS

A prospective surveillance study for SSI's based on the criteria of the Centers for Disease Control (5) was performed in the Amphia hospital in Breda. This is a large teaching hospital located in the south of the Netherlands with 45.000 clinical admissions in 2011 and five consultant vascular surgeons. The hospital's infection control committee and the board of directors as part of the patient safety program approved this study. Also the medical ethical committee of the Amphia Hospital in Breda, the Netherlands, permitted this project and waived informed consent.

Patients with a peripheral or central vascular reconstruction between March 2009 and January 2012 were included for analysis. The following characteristics were recorded: age, gender, ASA-score, length, weight, body mass index, wound class, type of procedure, central versus peripheral procedure, elective versus urgent, temperature at the end of surgery, duration of surgery, surgeon, number of vascular procedures per surgeon during the study period, admission date, date of surgery, discharge date, readmission within the post-discharge period, development of a SSI, development of a deep SSI and mortality within 6 months after the initial procedure.

Registration of SSI`s was performed by dedicated and specifically trained infection control personnel routinely performed the surveillance. Post-discharge surveillance was performed on all patients until 6 months after the date of the procedure.

The definition for SSI's and deep-SSI's, as described elsewhere, was based on the criteria of the Centers for Disease Control (5).

In 2009 the bundle to reduce SSI's as defined by the DHPSP was implemented in our hospital. Starting in June 2009 bundle adherence was measured every three months using a random sample of 10 procedures. Normothermia was defined as a core temperature between 36.0ºC and 38.0ºC at the end of the surgical procedure. Perioperative prophylaxis was considered correct when the indicated antibiotic (according to the hospital formulary) was given between 15 and 60 minutes before the incision. Hair removal was preferably not performed and when it was done a clipper had to be used. Use of a razor blade was not allowed. Finally, the number of door-openings was measured from opening of the sterile equipment until the surgical wound was closed. This was done by visual inspection performed by infection control personnel. The target for door-openings was <10 per hour. Besides the amount of door-openings the reason for entering the operation room was also recorded. Eventually these data were used for feedback and development of strategies for improvement.

The development of the introduction of the bundle was evaluated after each measurement in a multidisciplinary team consisting of surgeons, anesthetists, the head of the operating room, operating room personnel and infection control personnel. Every three months the

results of the adherence to the bundle was communicated to all personnel involved in the surgical process. They received a newsletter that informed them about the results of the bundle compliance and recommendations for improvement. The management of the hospital supported the program (which included more surgical specialties than vascular surgery) by the allocation of one full time equivalent infection control nurse to the program for surveillance of SSI, bundle measurements and feedback.

The following interventions for improvement were performed:

1. Hair removal was performed by a clipper instead of a razorblade
2. Timing and the use of pre-operative antibiotics were agreed upon by all participants and written in a protocol that could be handled by anesthesia personnel without consulting the surgeon. Before the operation started a time-out procedure was in place, which included the administration of antibiotic prophylaxis.
3. Temperature of the patient was measured during the entire process from the ward to the operating theatre and back to the ward. Based on the findings an isolation blanket was administered to patients on the ward before they were transported to the operating room. Previously this blanket had been administered in the operating theatre.
4. Door openings were subjected to a root-cause analysis. The multidisciplinary team critically assessed the determinants of openings and recommendations for improvement were made. The management of the OR was responsible for implementation of these recommendations. The main interventions were: reducing changes of the team for coffee breaks, making sure all equipment was present before the surgical procedure started and not entering the operating room for social talks during the surgical procedure.
5. For the implementation of the bundle a safety culture was promoted, in which personal feedback was done when the bundle adherence was at risk.
6. After each bundle measurement a newsletter as described before was provided as feedback about the progress of the introduction of the bundle.

Statistical analysis

All variables were univariate tested as appropriate by Fishers exact test or Students T-test. Variables with $P < 0.2$ in univariate analysis were included in a multivariable logistic regression model. $P < 0.05$ was considered statistically significant. Mortality was compared using Kaplan Meier survival analysis. A Cox-regression analysis was performed to adjust for confounders.

RESULTS

Figure 1 shows that the compliance of the bundle per annual quarter started at 10% and improved to 80% by the end of 2011. At the start, the individual bundle elements had a variable compliance. Correct prophylactic antibiotic use was already high from the start of the program. Door movements were the most resilient topic for improvement (Figure 2). The annual compliance with the bundle elements increased gradually and statistically significant from 10% in 2009 to 60% in 2011 (Fig 2, $p<0.05$).

Table 1. Categorical variables in relation to the occurrence of surgical site infections (SSI) after vascular surgery.

Determinant		Deep SSI/N	%	RR	95% CI	*p*-value
Gender	Male	54/538	10.0			
	Female	21/182	11.5	1.17	0.69-2.00	0.576
Procedure	Central	23/368	6.2			
	Peripheral	52/352	14.8	2.36	1.48-3.78	<0.001
Number of procedures per surgeon during study	1-100	27/229	11.8			
	>100	48/491	9.8	0.83	0.53-1.30	0.433
ASA class	1 or 2*	18/179	10.1			
	3,4 of 5	57/532	10.7	1.07	0.61-1.88	0.889
Wound score	1	73/700	10.4			
	≥2	2/20	10.0	0.95	0.22-4.20	1.000
Urgency of procedure	Elective	71/642	11.1			
	Non-elective	4/77	5.2	0.44	0.16-1.24	0.164
Death within 6 months	Yes	11/69	15.9			
	No	64/651	9.8	0.62	0.342-1.11	0.143
Year	2009	27/181	14.9			
	2010	27/290	9.3	0.62	0.35-1.10	0.074
	2011	21/249	8.4	0.57	0.31-1.03	0.043

ASA class: American Society of Anesthesiologists classification; Wound class: Classification based on the intrinsic contamination of the incision site; * ASA 1: 3 pts, ASA 2: 176 pts.

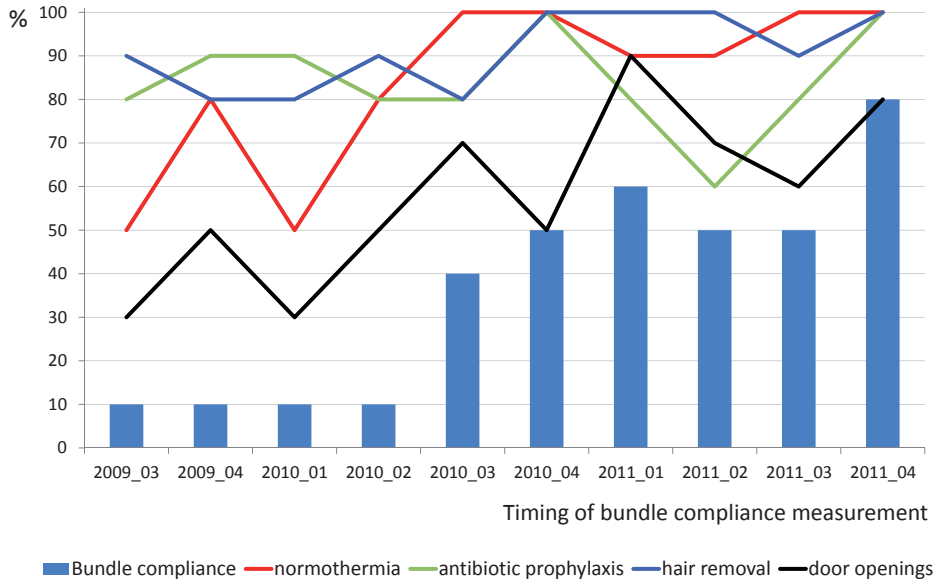

Figure 1. Compliance with the bundle and its individual components in repeated measurements from June 2009 through October 2011.

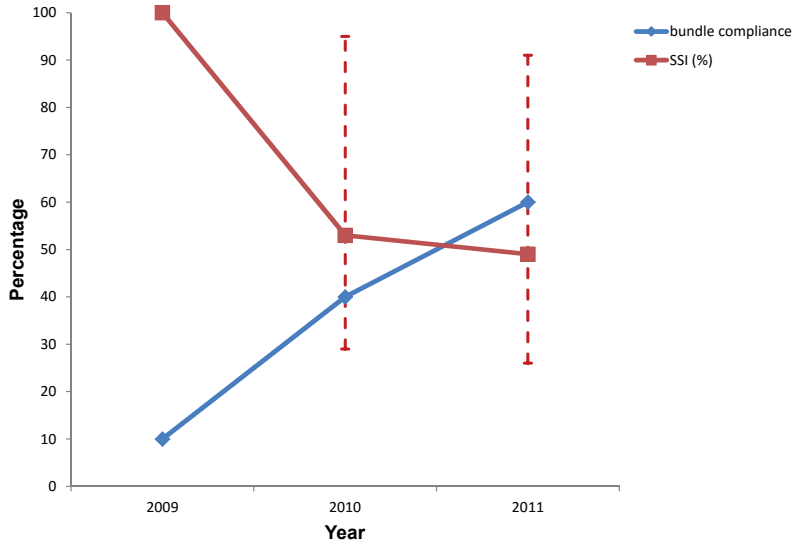

Figure 2. Annual changes in the surgical site infection (SSI) rate and bundle compliance and the 95% confidence interval.

Surgical site infections

In a total of 720 vascular procedures 75 (10.4%) SSI's were documented. The SSI-rate was significantly higher in peripheral versus central procedures (table 1). The SSI-rate declined significantly over time. Compared with 2009, the SSI-rate was 44% lower in 2011. Continuous variables in relation to the occurrence of SSI demonstrated that patients who developed a SSI had a significantly longer duration of the surgical procedure (Table 2).

Table 2. Continuous variables in relation to the occurrence of surgical site infections (SSI) after vascular surgery.

	With SSI		Without SSI		
	Mean	SD	Mean	SD	*p*-value
Age in years	68.9	11.5	70.8	9.8	0.129
Duration of surgery in minutes	168.0	74.5	146.4	65.6	0.008
Body mass index in kg/m^2	26.1	5.0	25.6	4.0	0.367
Length of hospital stay after surgery	28.5	29.3	10.8	11.3	<0.001

A significant reduction of the SSI rate was observed in 2010 and 2011, with a 51% reduction in the last year of the study, compared to 2009. The increased compliance with the bundle was therefore associated with a decrease of the SSI-rate (Fig. 2).

Deep surgical site infections

In a total of 720 vascular procedures 25 (3.5%) deep-SSI's were documented. This occurred significantly more in peripheral versus central procedures and the incidence in 2011 compared to the start of the study in 2009 was 44% lower (table 3 and 4).

To adjust for confounding a logistic regression analysis was performed as shown in table 5. With the exception of gender, age and elective versus non-elective procedures most variables that were identified in the univariate analysis retained their statistical significance.

Table 3. Categorical variables in relation to the occurrence of deep surgical site infections (deep SSI) after vascular surgery.

Determinant		Deep SSI/N	%	RR	95% CI	*p*-value
Gender	Male	17/538	3.2			
	Female	8/182	4.4	1.41	0.60-3.32	0.482
	Peripheral	5/368	1.4			
Procedure	Central	20/352	5.7	4.18	1.59-11.02	<0.001
Number of procedures per surgeon during study	1-100	12/229	5.2			
	>100	13/491	2.6	0.51	0.23-1.09	0.084
ASA class	1 or 2*	7/179	3.9			
	3,4 of 5	18/532	3.4	0.86	0.35-2.10	0.815
Wound score	1	23/700	3.3			
	≥2	2/20	10.0	3.27	0.72-14.94	0.150
Urgency of procedure	Elective	23/642	3.6			
	Non-elective	2/77	2.6	0.72	0.17-3.11	1.000
Death within 6 months	Yes	7/69	10.1			
	No	18/651	2.8	0.27	0.12-0.63	0.006
Year	2009	9/181	5.0			
	2010	9/290	3.1	0.62	0.24-1.60	0.33
	2011	7/249	2.8	0.57	0.21-1.55	0.27

ASA class: American Society of Anesthesiologists classification; Wound class: Classification based on the intrinsic contamination of the incision site; * ASA 1: 3 pts, ASA 2: 176 pts.

Table 4. Continuous variables in relation to the occurrence of deep surgical site infections (deep SSI) after vascular surgery.

	With SSI		Without SSI		
	Mean	SD	Mean	SD	*p*-value
Age in years	72.0	10.9	70.5	9.9	0.472
Duration of surgery in minutes	150.9	53.1	148.6	67.3	0.861
Body mass index in kg/m^2	25.5	4.9	25.7	4.1	0.764
Length of hospital stay after surgery	48.3	39.4	11.4	11.8	<0.001

Outcome in patients after surgical site infections

Patients who developed a SSI had a longer post-operative length of stay in the hospital (mean additional length of stay: 18 days (Table 2). In patients who developed deep SSI the post-operative length of stay was even longer (mean additional length of stay: 37 days (Table 4).
No statistical significant difference was seen in the Kaplan Meier curve for 6 months mortality of patients with and without a SSI (P:0.126 using the Log rank test). However, there was a significant difference in 6 months mortality of patients with and without deep SSI (P<0.001 (fig 3)). Cox-regression analysis demonstrated a statistical significant difference for mortality between patients with and without deep SSI's adjusted for ASA score and age (adjusted OR: 2.96, 95% confidence interval 1.32-6.6).

Table 5. Multivariate analysis of variables in relation to the occurrence of surgical site infections (SSI) after vascular surgery with adjusted Odds ratio's (AOR) and the 95% confidence interval (CI).

Variable	AOR	95% CI	*p*-value
Gender	1.09	0.63-1.91	0.753
Central versus peripheral procedure	0.40	0.23-0.68	0.001
Elective versus acute procedures	0.45	0.23-1.92	0.447
Duration of surgery (10 minutes)	1.04	1.00-1.00	0,022
age (years)	0.98	0.96-1.00	0.106
year (2010 versus 2009)	0.53	0.29-0.95	0.032
year (2011 versus 2009)	0.49	0.26-0.91	0.024

DISCUSSION

Our results confirm that SSI's are relatively frequent (10.4%) and severe complications among patients who undergo vascular surgery. In this study, patients who developed a SSI had a prolonged hospital stay (18 days), which was even more pronounced when deep SSI occurred: mean length of hospital stay (37 days) and in these patients there was also a significantly higher mortality rate. This stresses the importance in preventing surgical site infections. The introduction of the bundle as defined by the DHPSP was associated with a strong and significant reduction of the SSI-rate in patients after vascular surgery. Due to the design of the study we cannot entirely be sure that there have been other unknown factors that

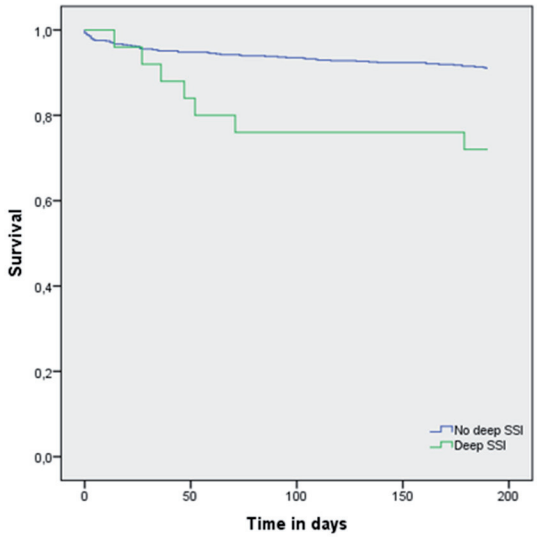

Figure 3. Kaplan-meier curve of 6 months survival in patients with and without a deep surgical site infection (deep SSI).

contributed to the reduction of the SSI-rate. As we adjusted for confounders we consider it very likely that the reduction of the SSI-rate was largely due to the introduction of the bundle. The bundle exists of four components, which are scientifically proven and do not require expensive or complicated interventions. For vascular surgery, a 50% reduction would mean that approximately 18 SSI are prevented per year in our institute. Based on the additional length of stay of 18 days this would potentially save over 300 days of hospital stay per year. The mean costs a day in our hospital are estimated to be approximately €500, meaning that the total savings would be close to €150,000. Since the bundle elements are cheap it is likely that this is a highly cost-effective intervention. Our maximum bundle compliance per measurement was 80%. This is less than the 90% that was defined as a target at the onset of the program. Therefore, additional improvements are possible and may even further reduce the SSI-rate. We have continued the program and by the end of 2012 the compliance was 90%. As the SSI-rate can only be determined after a follow up of half a year the effects on the SSI-rate cannot be determined at this moment.

The importance of a bundle of care to reduce hospital infections have become clear since a large multicenter study was performed in the United States of America to reduce catheter-related-infections and in a later study the reduction of ventilator-associated pneumonia in

the ICU (6, 7). A few studies have described the effects of a bundle of measurements on the prevention of SSI's after colorectal surgery. One study in colorectal surgery demonstrated a positive trend but had a small sample size so no definite conclusions could be drawn (8). Another randomized study had a disappointing result, as the SSI-rate in the group with the bundle was increased (9). The main criticism on this study is that the bundle used, was mainly based on technical adjustments and did not encourage a structural improvement in the overall surgical process to create a safety culture.

The bundle that we used has already been described before (10). It was studied in the same time period in our hospital for the prevention of SSI's after colorectal surgery (11). Also after colorectal surgery a substantial (36%) and significant reduction of the SSI-rate was observed after implementation of the bundle. We observed an even stronger effect of the implementation of the bundle on the reduction of SSI's in vascular surgery. Another study published in august 2012 also described a reduction of SSI's in patients having colorectal surgery after the implementation of a comparable bundle of care. The following bundle of six measurements was introduced: standardization of skin preparation; administration of preoperative chlorhexidine showers; selective elimination of mechanical bowel preparation; warming of patients in the preanesthesia area; adoption of enhanced sterile techniques for skin and fascial closure; addressing previously unrecognized lapses in antibiotic prophylaxis (12). After implementation, they observed a 33.3% reduction of SSI's, which was comparable to the results with colorectal surgery in our institute. Due to their SSI's reduction they also concluded that the implementation of the bundle resulted in major annual cost savings in their institution. This assumption is not entirely valid since it cannot be assumed that patients with SSI's or deep SSI's will not be suffering from other underlying reasons that cause their longer length of hospital stay. However it is likely that reducing SSI's is associated with lower annual cost.

In our study, the wound care and compliance with hand hygiene during the postoperative phase could also contribute to the development of SSI's and this was not included in the intervention. However, since we adhered to the national guidelines on wound care (www.wip.nl) and only included primary closed wounds which are less prone to post-operative contamination and did not require special postoperative wound care we assume no important contributory effect of wound care on the development of SSI's. The effects of hand hygiene compliance on the wards could have had a negative effect on the development of SSI's and should not be underestimated. In this study, we did not analyze the hand hygiene compliance. A contributory effect can therefore not be excluded.

The longer length of hospital stay in patients with SSI's is, as mentioned before, not necessarily caused by the SSI's but may in part be due to other underlying factors. This study cannot define the contribution of SSI's to the observed increase in the length of hospital stay.

However, others have shown that SSI's cause a substantial length of hospital stay and a double blind randomized study using a preventive intervention showed that prevention of SSI's is associated with substantial cost savings (13). Therefore, we conclude that SSI's will have an important effect on the length of hospital stay but the exact amount cannot be determined in this study.

There are some other limitations to be mentioned to this study. First we could not demonstrate a direct causal relationship between the implementation of the bundle and the reduction of SSI since we did not use a randomized controlled study design. This study design is not feasible, when a change in behavior is part of the intervention. Health care workers cannot change their behavior based on individual randomization. Second, the year before the introduction of the bundle, our hospital was participating in the SURPASS study (14) that introduced the time-out procedure and the preoperative checklist. Since this study finished one year before we started this study, we cannot exclude a residual effect of this study on our results. Third, we did not perform an interrupted time series analysis since the interventions were implemented over a longer period of time (1 year and through the entire study period). Finally, we cannot exclude the positive effects of the routine feedback moments and discussions causing unknown behaviour effects on SSI reduction. They may have contributed to the reduction of SSI-rate as well.

In vascular surgery SSI's have been reported to occur in 5-10% of patients (central and peripheral procedures) and could become life-threatening especially when prosthetic grafts are involved. This makes SSI-reduction an important topic for improvement. Mostly technical preventative measurements have been described to reduce vascular SSI's. There are also studies suggesting the importance of maintaining peri-operative physiological parameters (oxygen, temperature, blood sugar and intravascular volumes) (2, 3). To our knowledge none of these evidence based inventions has been bundled and structurally implemented to reduce surgical site infections in vascular surgery. To reduce these SSI's, we implemented a bundle of measurements introduced by the DHPSP. Others and we demonstrated that the strict implementation of the bundle results in a substantial and significant reduction of the infection rate and therefore improves the safety for surgical patients having vascular procedures. As the bundle did not involve expensive or potentially harmful elements we recommend the implementation of this bundle on a large scale.

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CHAPTER 6

Surgical Site Infection after multiple groin incisions in peripheral vascular surgery

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ABSTRACT

Background: Patients with peripheral arterial disease (PAD) are at risk for revision surgery in the groin and therefore at potential risk for surgical site infections (SSIs). In an observational study, a cohort of patients with peripheral arterial disease was followed to examine the effect of different incision intervals on SSI-free survival.

Methods: Patients, needing peripheral vascular surgery because of PAD, were retrieved from a prospectively collected database on SSIs after vascular surgery between March 2009 and January 2012, the group consisting of 720 patients. Of these, 255 patients were selected (age 71.9 – 10.4 y). Cox proportional hazards models were used for event-history analyses. The effect of incision interval was estimated with adjustment for a number of potential confounders. Effects were quantified by means of hazard ratios (HRs) with 95% confidence intervals (CIs).

Results: No significant effect on the incision interval on SSI-free survival was observed. After separating incisional SSIs into superficial- and deep-seated, a significant linear trend effect of the groin incision interval on deep-incisional SSI development was observed: the shorter the interval, the higher the event rate (HR 1.5 per category, 95% CI 1.1–2.1, $p = 0.22$). Besides the incision interval, the Rutherford classification was a significant risk factor for SSI development (HR 3.0; 95% CI 2.1–4.2; $p < 0.0005$).

Conclusion: Revision surgery in the groin puts patients at risk for deep-incisional SSI. No effect on superficial incisional SSI development was observed. Besides the incision interval, the Rutherford classification was a significant risk factor for both superficial- and deep-incisional SSI. Quality improvement and better risk stratification schemes are suggested.

INTRODUCTION

Severe peripheral arterial disease (PAD) is associated with major complications after vascular surgery, as well as higher cardiovascular event rate, comorbidities, and death (1, 2) Given this information, better outcome predictions for this particular group are needed to improve treatment strategies.

A common complication after vascular surgery is a surgical site infection (SSI) (3), which is associated with increased hospital length of stay (LOS), morbidity, readmissions, re-interventions, and death (4). Deep-incisional SSI could, with the use of prosthetic grafts, lead to high morbidity and mortality rates. Reduction of the incidence of these SSIs therefore is necessary.

A groin incision for femoral artery access is a risk factor for these SSIs (5, 6). Additionally, in an aging population wherein risk factors for the development of severe PAD increase, a higher demand for peripheral surgical revascularization and re-intervention is expected (4, 7, 8). Multiple groin incisions could lead to a high incidence of complications; e.g., SSI.

To our knowledge, there is little information on the effect of different groin incision intervals on patient outcomes such as SSI. This lack of knowledge could have serious clinical consequences. The present study was performed to evaluate the effect of different groin incision intervals after elective vascular procedures on patients with moderate to severe PAD with regard to SSI development. Previously, groin incisions, performed at different times, were analyzed for their influence on SSI-free survival.

METHODS

Data collection and study population

A prospectively collected database on surgical site infections (SSI) after 720 central and peripheral vascular procedures performed between March 2009 and January 2012 (3) was studied to retrieve all patients with PAD seen in the Amphia Hospital. For this database, the hospital's infection control committee and the board of directors as part of the patient safety program and the medical ethical committee approved this study and waived informed consent.

All patients were selected on the basis of operation codes corresponding to endarterectomy of the femoral artery and peripheral bypass surgery. Patients undergoing popliteal aneurysm repair, endovascular procedures of the lower and upper extremities, central vascular procedures, or endarterectomy of the carotid artery were excluded from this study.

Procedures were performed in an institution with five vascular surgeons. All patients were

worked up via duplex ultrasound examination and magnetic resonance angiography. Endartectomies were performed according to standard vascular procedures. Whenever possible, autologous grafting was performed in peripheral bypass surgery. Alternatively, an expanded polytetrafluoroethylene (ePTFE) pre-cuffed Dynaflo® graft (Bard Peripheral Vascular Inc., Tempe, AZ USA) was used for supragenicular femoropopliteal bypass reconstructions and the Distaflo® (Bard Peripheral Vascular) for infragenicular femoropopliteal and femoralcrural bypass reconstructions (9).

Surgical site infections (SSI), defined according to the criteria of the Centers of Disease Control(10), were monitored prospectively. A distinction was made between superficial and deep-incisional SSI's. Registration of SSIs was performed by dedicated and trained infection control personnel. The presence of a SSI was ascertained by a microbiologist and a vascular surgeon (3).

Previous procedures were recorded (before and at inclusion) and procedures during the follow-up period in which the groin was involved. A previous groin procedure was defined as a procedure at the groin to improve vascular circulation (patch, bypass, or thrombectomy) or to stop major bleeding, there being no indication of an infection. Drainage from abscesses, seromas, hematomas, or wound debridement was not included in the analyses as a previous groin incision. Also, percutaneous transluminal angioplasty (PTA) and thrombolysis were not included in the groin procedures.

Other data, aside from SSI's and procedures, collected from patient records were age, gender, the American Society of Anaesthesiologists (ASA)-score, height, weight, and body mass index (BMI); presence of diabetes mellitus, chronic obstructive pulmonary disease (COPD), or chronic kidney disease; Rutherford classification; the use of synthetic grafts (bovine patches or ePTFE bypasses); amputation; and death.

Outcome measures:

The outcome variable to be analyzed was SSI-free survival time. The endpoint was either an SSI or death while SSI-free. Also, a distinction was made between superficial and deep-SSI. Censoring of the follow-up was at the predetermined 90th day after the inclusion operation and could therefore properly assumed to be non-informative for the incidence time of the endpoint as defined.

Follow-up:

Surveillance was performed in a time period in which the patient was considered most prone to infections. All patients were followed until 90 days after the date of the initial procedure (during admission and on the outpatient clinic) or till the day of death when earlier than 90 days.

Statistical analysis:

The purpose of the statistical analyses was to estimate the effects of a number of independent variables on SSI-free survival time using event-history analysis. Primary interest was in the effect of previous groin procedures on SSI-free survival time. Of interest was the interval between two consecutive incisions. This interval was defined as the time between the two last incisions prior to the occurrence of an event and so was accounted for in the analysis as a time-dependent covariable. The following categorization for the groin incision-interval between the last-but-one incision and the last incision was used: less than 2 weeks, between 2 weeks and 6 months and more than 6 months, versus no previous groin operation.

The Cox proportional hazards model was used for the event-history analyses. Firstly an unadjusted effect of the incision-interval as defined above was estimated. In more elaborate analyses the effect of the incision-interval was estimated with adjustment for a number of potentially confounding variables. Along with incision-interval, age (in years) was entered in the model being an important risk factor in elderly patients. Occurrence of an amputation during follow-up was considered a confounding covariable to be adjusted for when considering the effect of incision-interval on SSI-free survival time. So, amputation (y/n) was entered in the model as a time-dependent covariable. Entry of other explanatory variables in the model was based on a backward elimination procedure so as to delete variables from the model with a p-value above 0.20 in a stepwise manner. Those candidate other variables were mentioned above. The synthetic graft variable was based on the last operation before the occurrence of an event and thus was entered in the model as a time-dependent covariable. Effects of the independent variables on the various survival times were quantified by means of hazard ratios (HR) with 95% confidence intervals (CI) and p-values. Logistic regression analysis was performed among the patients with an SSI in order to investigate which variables were able to discriminate between deep seated and superficial SSI's. Those discriminating variables should have an effect on the occurrence rate of a deep SSI that differs from that on the occurrence rate of a superficial SSI.

Statistical analyses were done using the SPSS® software program version 20 (IBM, Armonk, New York, USA). *P*-values below 0·05 were considered to denote statistical significance.

RESULTS

This study included 255 consecutive patients who had a surgical revascularization because of PAD (Rutherford class 3-6) in our hospital. The mean age for all patients was 71.9±10.4 years, 173 (68%) were male. At the time of inclusion, 184 (72.2%) underwent a primary procedure and were not involved in a previous groin incision, none had a groin incision less than 2 weeks ago, 8 (3.1%) had an incision between 2 weeks and 6 months ago and 63 (24.7%) had an incision more than 6 months ago. These numbers were updated during follow-up after each operation. After 90 days of follow-up 236 patients were still alive, 160 (67.8%) did not undergo another operation, 15 (6.4%) had a groin incision less than 2 weeks ago, 12 (5.1%) had an incision between 2 weeks and 6 months ago and 49 (20.8%) had an groin incision more than 6

Table 1. Baseline characteristics of study population (n= 255).

Characteristic	
Mean age in years (± SD)	71.9 ± 10.4
Male/Female	173 (68)/82(32)
ASA-classification*	
I or II	54 (21.2)
III, IV orV	200 (78.4)
Mean BMI (± SD)	25.3 ±3.6
Comorbidity	
COPD	50 (19.6)
Chronic kidney disease	30 (11.8)
Diabetes	86 (33.7)
Rutherford classification	
3	97 (38)
4	70 (27.5)
5/6	88 (34.5)
Total procedures performed	292
Primary procedure at inclusion	184 (72.2)
Procedures at inclusion	
Endarterectomy, CFA	97 (38)
Supragenicular bypass (%)	61 (23.9)
Infragenicular bypass (%)	48 (18.8)
Femorocrural bypass (%)	49 (19.2)

Data are presented as n and (%), unless otherwise specified, *ASA* American Society of Anesthesiologists score, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *CFA* common femoral artery.

months ago. The 255 patients contributed 292 operations, of which in 173 operations (59.2%) synthetic grafts were used. Other basic patient characteristics are listed in table 1.
The 255 operated patients contributed in total 21,863 person-days alive after operation. During follow-up 19 patients (7.5%) died and 38 patients (14.9%) developed an SSI (*s. aureus* cultured in 45%). Of these 38 patients, 15 patients (5.9%) turned out to have a deep-SSI.

SSI-free survival

During follow-up, the following events were registered in 51 patients: 38 patients developed an SSI and 13 patients died while SSI-free. The unadjusted overall effect of the incision-interval on event-free survival was not significant (p = 0.38). In the subgroup with an incision-interval less than two weeks a non-significantly higher event rate was seen compared to the subgroup with no former incision (HR = 2.09; 95% CI: 0.87-5.02; p = 0.10).
After adjusting for potential confounders, no significant effect of the groin incision-interval on SSI-free survival was observed either (p = 0.97); see Table 2. An incision-interval less than 2 weeks resulted in a 1.2 times higher event rate than in case of no previous groin incision, although this was also not significant. The Rutherford classification (HR = 3.0 per 1 point higher) had a significant effect on SSI-free survival. During follow-up 14 patients underwent a major amputation while SSI-free. After an amputation the event rate was not significantly higher (HR = 1.4; p = 0.56) than that of patients who had no amputation at that time. Also the effect of age (a 2 % event increase per year) was not significant (p = 0.36). Each of the variables that were backwards eliminated from the model (gender, diabetes, synthetic graft, COPD, renal impairment, ASA-score or BMI) did not have a significant effect on SSI-free survival when added to the final model presented in Table 2 (p-values ranging from 0.5 to 0.9; data not shown).

Table 2. Results of Cox proportional hazards regression analysis on SSI-free survival based on 51 events in 255 patients.

Explanatory variable	Coefficient	Hazard ratio (95 % CI)	P-value
Interval between two last groin incisions			0.97
None	0	1	
< 2 weeks	0.192	1.21 (0.42-3.48)	
2 weeks - 6 months	-0.255	0.78 (0.18-3.29)	
> 6 months	-0.015	0.99 (0.51-1.92)	
Rutherford-classification (+ 1 point)	1.101	3.01 (2.15-4.20)	< 0.0005
Age (+ 1 year)	0.015	1.02 (0.98-1.05)	0.36
Amputation (time-dependent)	0.307	1.36 (0.48-3.84)	0.56

Model test: $\chi^{2} = 68.860$ (df = 6); p < 0.0005.

Deep-SSI

In 15 of the 38 patients with an SSI the SSI turned out to be a deep seated SSI. The variables that significantly differed between patients with a deep-SSI and those with a superficial SSI were: last incision-interval before the SSI (the shorter the interval, the larger the probability that the SSI was deep), Rutherford classification (effect in favor of a deep seated SSI) and BMI (effect in favor of a superficial SSI). In these analyses incision-interval as linear trend variable (with no previous incision defined as the highest category) gave a better fit than incision interval as categorical nominal variable. After having entered these three variables simultaneously in a logistic regression model, the Rutherford classification lost its significance ($p = 0.41$). The variables incision-interval and BMI kept their effects in the directions as just mentioned (both p-values 0.003). In order to further investigate the effects of these variables on SSI-free survival while distinguishing between deep and superficial SSI's we entered these variables simultaneously in two Cox proportional hazards regression analyses: one for deep-SSI with 29 events (15 SSI's and 14 deaths) and the other one for superficial SSI with 41 events (23 SSI's and 18 deaths). Incision-interval appeared to have a significant linear trend effect on deep-SSI-free survival: one category shorter incision-interval was associated with an HR of 1.5 (95% CI: 1.1-2.1; $p = 0.022$). A non-significant reverse linear trend effect of incision-interval was seen on superficial SSI-free survival: HR = 0.75 per category shorter incision-interval ($p = 0.19$). The Rutherford classification had large positive significant effects on the event rates concerning deep- as well as superficial SSI-free survival with respective HR's of 6.7 and 3.0 per point higher on the scale (p-values < 0.0005). BMI appeared to have a significant reverse effect on the event rate concerning deep-SSI-free survival: HR = 0.89 per 1 unit kg/m^2 (95% CI: 0.81-0.99; $p = 0.025$). A non-significant positive effect of BMI was found on the event rate concerning superficial SSI-free survival: HR = 1.06 per 1 unit kg/m^2 (95% CI: 0.98-1.14; $p = 0.15$). The extent to which these results on SSI-free survival differed between deep and superficial SSI-free survival was in line with the above mentioned results of the logistic regression analysis on the 36 SSI's, as it should.

DISCUSSION

The results from the present study demonstrate that the frequency of repeated vascular revision surgery at the groin is not a risk factor for SSI development. Only after separating SSIs into superficial and deep-seated, a significant linear trend effect of the groin incision interval on deep-SSI development was observed: the shorter the interval, the higher the event rate. This suggests early revision surgery in the groin to be a risk factor for deep-SSI development. The incision interval had no significant effect on superficialincisional SSI development. Besides

the incision interval, the Rutherford classification is a significant risk factor for superficial as well as deep-seated incisional SSI development. This effect did not differ significantly between superficial and deep-seated-incisional SSIs.

Each shorter incision interval was associated with an increased risk of deep-incisional SSI development (1.5 per category). Kolakowski et al. reported early revision of lower extremity bypass grafts (within one month), compared with late revision (after one month) to be a risk factor for graft infection (11) and stated reintervention should be delayed until one month after initial surgery. Unfortunately, in most cases, revision surgery cannot be delayed because of severe, even critical, limb ischemia (12). Alternative procedures for vascular revision could therefore be considered. For example, extra-anatomic surgical approaches and percutaneous transluminal interventions might be performed to resolve stenosis or occlusions (13), but current literature on these interventions performed in this situation is lacking.

The Rutherford classification turned out to be a strong risk factor for SSI development. We could not demonstrate that the effect of the Rutherford classification on deep-incisional SSI development differed from that on superficial-incisional SSI development ($p = 0.41$ adjusted for incision interval). The poor peripheral and subcutaneous vascularization status in which wound healing might be impaired and micro-organisms have a better chance of growth could be an explanation.

The BMI was a non-significant risk factor for superficialincisional SSI development in this study and had a significant protective effect on deep-incisional SSI development. This effect of BMI differed significantly between superficial and deep-seated incisional SSIs. In the literature, BMI is associated with SSI development (14, 15), but no distinction was made between superficial and deep-incisional SSIs in these studies. A potential explanation is that in the case of a high BMI, prosthetic grafts are better embedded in subcutaneous tissue.

A synthetic graft infection is a well-known risk factor for amputation (15). A logical explanation for this could be the fact that, at the time of presentation, no reconstructive options are available if a limb is not salvageable because of critical limb ischemia. Besides this, SSIs are also is associated with higher morbidity and mortality rates (4). The reduction of SSI is therefore highly desirable. In our hospital, several interventions have been undertaken to reduce SSIs, namely the introduction of the Surgical Patient Safety System (SURPASS) checklist (16) and of a bundle of care consisting of ensuring compliance with four evidence-based measures: perioperative normothermia, hair removal, perioperative antibiotic prophylaxis, and discipline in the operating room (3). In this study, we found a significant association between early revision surgery (within two weeks) and deep-seated SSI development. Future trials should be performed on alternative interventions or strategies to reduce SSI after peripheral vascular surgery.

There were some limitations to this retrospective study that should be considered when interpreting the results. First, data were based on patients with peripheral arterial obstructive disease having peripheral reconstructive surgery. Patients with central reconstructive surgery were excluded from the analyses. Results therefore could not be applied to these patients. Second, the data were collected from one single center with five vascular surgeons; the SSI prevalence could differ from that at other centers. Finally, it should be appreciated that this single-center study nonetheless is based on a relatively large sample. There was a good collaboration between the medical microbiology department and the surgery department, so the presence of a surgical site infection was checked from both sides, limiting the possibility of detection bias.

The presence of an SSI is a risk factor for morbidity and death after peripheral vascular surgery. Reduction of SSI therefore is an important area for improvement. Early revision surgery in the groin, especially that performed within two weeks, is a risk factor for deep-incisional SSI. Besides this, the Rutherford class is a risk factor for both superficial and incisional-seated SSI. Further research has to be performed on risk stratification models to improve the outcomes of patients with peripheral arterial disease.

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CHAPTER 7

Treatment of surgical site infections (SSI) in patients with peripheral arterial disease: an observational study

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ABSTRACT

Introduction: The management of surgical site infections (SSI's) in vascular surgery has been challenging over the years. To assess the outcomes associated with the various strategies, we performed a review of all SSI's after elective vascular procedures in patients with moderate to severe peripheral arterial disease in a single centre hospital.

Methods: All patients with a SSI after peripheral vascular surgery were retrieved from a database on Surgical site infections (SSI)-surveillance after vascular surgery between March 2009 and January 2012. At admission, all patients were approached by microbiological wound sampling and empirical start of antibiotics. Further wound management was based on personal experience and preference of the attending vascular surgeon. Endpoints were treatment success (complete wound healing while staying alive and without major amputation), survival and major amputation during one year follow up.

Results: A total of 40 patients with a SSI were identified (60% superficial SSI and 40% deep SSI). In 92% of the patients with a superficial SSI's were successfully treated with adjusted antibiotics and incisional drainages. In the contrast, 25% of the patients with deep-SSI's were successfully treated. No particular treatment was more successful than the others.

Conclusion: Adjusted antibiotic use and adequate wound drainage are sufficient strategies for superficial SSI management. The management of deep-SSI's is a challenging undertaking and future research on indications and timing of these wide arrays of treatment options is suggested.

INTRODUCTION

Surgical site infections (SSI's) are rare but serious complications after vascular surgery resulting in an increased risk for morbidity and mortality(1). The consequences are worse when a prosthetic graft is involved, e.g. anastomotic-bleeding, reinfection which eventually leads to high amputation rates, sepsis and mortality. Besides prevention, also proper management of these SSI's are important for better patient outcomes.

The management of SSI's in vascular surgery has been challenging. Many treatment strategies of infected grafts have been suggested in the literature. Complete removal of the graft with extra-anatomic reconstruction with in situ or antimicrobial-impregnated replacement were traditionally considered as the 'golden standard' (2-4). More recently, the focus has shifted towards graft preservation and the previously mentioned strategies are considered to be associated with increased morbidity and mortality(5). Several successful graft preservation-strategies are mentioned like, muscle flaps and negative pressure wound therapies with or without muscle flaps (6-9).

To assess the outcomes associated with the various strategies, we performed a review of all SSI's after elective vascular procedures in patients with moderate to severe peripheral arterial disease in our clinic.

PATIENTS AND METHODS

All patients with peripheral arterial disease (PAD) who developed a SSI after a peripheral vascular surgery were retrieved from a prospectively collected database on SSI-surveillance after vascular surgery between March 2009 and January 2012 in the Amphia Hospital, Breda, the Netherlands(1). Patients were selected based on operation codes corresponding with endarterectomy of the femoral artery and peripheral bypass surgery (Figure 1).

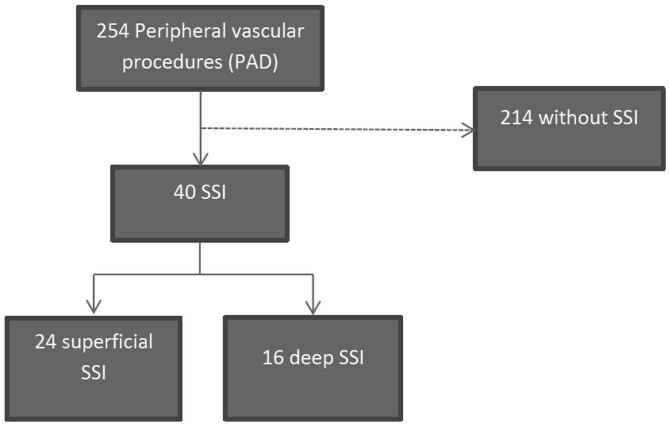

Figure 1. Flowchart of the patient population.

Procedures were performed in an institution with five vascular surgeons. All patients received duplex ultrasound or magnetic resonance angiography (MRA) to determine peripheral arterial disease. All patients received Cefazolin intravenously as preoperative antibiotic prophylaxis (10). Whenever possible, autologous grafting was performed. Alternatively an expanded polytetrafluoroethylene (ePTFE) pre-cuffed Dynaflo® or Distaflo® was used (11). Alternative patches for endarterectomies were bovine patches (vascu-Guard®).

Postoperative follow-up examinations include ankle-brachial pressure index, duplex ultrasound and surgical wound examination, routinely.

Registration of SSI`s was performed by dedicated and specifically trained infection control personnel routinely performed the surveillance (12). Post-discharge surveillance was performed on all patients until 6 months after the date of the procedure. The presence of an SSI was ascertained by a microbiologist and a vascular surgeon. Surgical site infections (SSI), defined according to the criteria of the Centers of Disease Control (13).

Although no standard protocol for treatment of vascular SSI's is present in our hospital, the general approach for SSI treatment includes; microbiological wound sampling and empirical start of antibiotics (amoxicillin/clavulanic acid or other antibiotics based on earlier microbiological cultures). Antibiotic use was adjusted based on the microorganism cultured and its antibiogram. Further wound management was based on personal experience and preference of the attending vascular surgeon.

Patient characteristics included age, gender, the American Society of Anaesthesiologists (ASA)-score, body mass index (BMI), diabetes mellitus, chronic obstructive pulmonary disease (COPD), chronic kidney disease, history of smoking, Rutherford classification, cerebrovascular

disease, surgical procedures, opening of wounds for drainage, graft removal, use of antibiotics, duration of antibiotic usage, the use of synthetic grafts (bovine patches (vascu-guard®) or ePTFE bypasses), amputation and death within 6 months after initial procedure were collected from the patient records.

The primary endpoint was success of treatment. This was defined as complete wound healing objectified by a vascular surgeon without major amputation or death during follow up. Secondary endpoints were survival and major amputation. Follow up was performed until 1 year after the initial procedure. Continuous variables were expressed in means with standard deviations (SD). Whenever applicable differences between superficial and deep-SSI were analysed using chi-square, Fisher's exact or independent student-t tests. Statistical analyses were done using the SPSS® software program version 20 (IBM, Armonk, New York, USA). *P*-values below 0·05 were considered to denote statistical significance.

RESULTS

A total of 40 patients, mean age 72 ± 10.3 years, were identified with a SSI after vascular surgery because of PAD during the study period. Most patients were male (65%), smokers (60%) and classified with ASA-classification 3 or 4 (80%). Twenty patients (50%) suffered from diabetes mellitus and 12 patients (30%) from chronic renal disease (Table 1).

Table 1. Patient characteristics and comorbidities prior to revascularization.

Characteristics	Total (n = 40; (%))	Superficial SSI (n = 24)	Deep-SSI (n = 16)	*P*-value
Gender				0.34[a]
Male	26 (65)	17	9	
Female	14 (35)	7	7	
Age				0.68[b]
Mean	72	72	73	
(SD), years	(10.3)	(8.1)	(13.2)	
BMI				0.22[a]
<30 (non-obese)	31 (78)	17	14	
>30 (obese)	9 (22)	6	2	
ASA-classification				0.52[a]
Classification 2	8 (20)	4	4	
Classification 3-4	32 (80)	20	12	
Comorbidity				
Arterial hypertension	24 (60)	16	8	0.29[a]
Diabetes	20 (50)	13	7	0.52[a]
History of smoking	24 (60)	14	10	0.79[a]
Cardiac disease	21 53)	13	8	0.80[a]
COPD	9 (22)	5	4	1.00[c]
Chronic kidney disease	12 (30)	5	7	0.12[c]
Cerebrovascular disease	10 (25)	4	6	0.16[c]

ASA = American Society of Anesthesiologists; BMI = Body Mass Index; *a* = Pearson χ^2-test; *b* = Independent Student's T-test; *c* = Fisher's Exact Test.

Table 2. Procedure characteristics.

Characteristics	Total (n = 40)	Superficial SSI (n = 24)	Deep SSI (n = 16)	*P*-value
Rutherford classification				
Class 3	3	3	0	0.26[b]
Class 4	15	12	3	0.06[b]
Class 5/6	22	9	13	0.00[a]
Pre-procedural information				
Redo	16	7	9	0.09[a]
Presence synthetic graft	7	3	4	0.41[b]
Operation				
Endarterectomy	8	6	2	0.44[b]
Supragenicular bypass	13	7	6	0.73[a]
Infragenicular bypass	5	4	1	0.63[c]
Femorocrural bypass	14	7	7	0.50[a]
Synthetic grafts	23	10	13	0.01[a]
Patch	8	6	2	
ePTFE	15	4	11	
Vascular reintervention during follow up	4	0	4	0.02[b]

a = Pearson χ^2-test; *b* = Fisher exact-test.

The indication for surgery was in most cases critical limb ischemia (CLI; Rutherford classification 4-6). Pre-procedural information reported 16 patients (40%) with a previous vascular procedure and 7 patients (17.5%) with a previous implanted synthetic graft. Finally, 32 patients had peripheral bypass surgery (80%) (Table 2).

Superficial SSI

A total of 24 patients were identified with a superficial SSI (Supragenicular: 7 procedure; infragenicular 4 procedure; femorocrural: 7 procedures; endarterectomy: 6 procedures). No significant difference of patient characteristics were seen between superficial SSI and a deep SSI (Table 1). Most patients had surgery because of CLI. In 10 of the 24 patients with a superficial SSI, a synthetic graft was implanted (6 patch; 4 ePTFE) (Table 2).

The 24 superficial SSI's were identified after an average of 24±19.3 days (Table 3). Most of the isolated microorganisms were *Staphylococcus aureus* and the most chosen antibiotics were β – lactams (Table 4 and 5).

Table 3. Postoperative outcome.

	Total (n = 40)	Superficial SSI (n = 24)	Deep SSI (n = 16)	*P*-value
Time to SSI*	36 (55.7)	24 (19.3)	54 (83.3)	0.10[c]
Anastomotic bleeding	5	0	5	0.00[b]
LOS*	28 (26.7)	20 (18.7)	40 (32.4)	0.02[c]
Major amputation	9	1	8	0.00[b]
Mortality				
<30 days	1	0	1	0.22[b]
<6 months	6	1	5	0.02[b]
Success of treatment	26	22	4	0.00[a]

LOS = length of hospital stay; a = Pearson χ^2-test; *b* = Fisher exact-test; c = Independent student-t test, * mean in days ±SD.

Table 4. Antibiotics used for SSI treatment.

Choice of antibiotic	Total (n = 40)	Superficial SSI (n = 24)	Deep SSI (n = 16)
β – lactams	36	20	16
Aminoglycosides	1	0	1
Macrolides	6	4	2
Quinolones	10	4	6
Vancomycine	2	0	2
Sulfonamides	2	1	1

No other procedures were performed after the initial procedure to improve vascular status. In 23 out of 24 (96%) cases the wound was opened for drainage. Twenty one patients with a superficial SSI received antibiotics (oral and/or parental) for an average period of 16±13.9 days. Two patients were successfully treated with negative pressure wound therapy after drainage and debridement. No other surgical procedures were performed to improve wound healing (Table 6).

Table 5. Microbiology of SSI cultures.

Isolated microorganism	Total (n = 40)	Superficial SSI (n = 24)	Deep SSI (n = 16)
Staphylococcus aureus	18	12	6
Mixed flora	15	11	4
Enterococcus cloacea	4	1	3
Proteus mirabilis	4	3	1
Group G beta-hemolytic streptococcus	4	2	2
Pseudomonas aeruginosa	4	1	3
Corynebacterium species	2	1	1
Enterococcus faecalis	2	1	1
Escherichia coli	2	1	1
Streptococcus agalactiae	2	0	2
Citrobacter freundii	1	0	1
Enterococcus faecium	1	0	1
Proteus vulgaris	1	0	1
Bacillus cereus	1	0	1
Morganella morganii	1	1	0
Streptococcus pyogenes	1	1	0
Klebsiella pneumoniae	1	1	0

Twenty-two patients (92%) were successfully treated for superficial SSI's (complete wound healing while amputation free and alive). During 6 months follow up one patient died at the intensive care unit after an unsuccessful resuscitation because of congestive heart failure at the day of admission. One patients had undergone a major amputation because of end stage vascular disease. The average length of hospital stay was 20±18.7 days including potential re-admissions (Table 3).

Deep-SSI

For basic patient characteristics see table 1. Sixteen patients with a deep-SSI were identified and all had critical limb ischemia (Supragenicular: 6 procedure; infragenicular 1 procedure;

femorocrural: 7 procedures; endarterectomy: 2 procedures). Pre-procedural information reported 9 patients (56%) with a previous vascular procedure and 4 patients (25%) with a previous implanted synthetic graft. A synthetic graft was implanted in 13 of the 16 patients with a deep-SSI (2 patch; 11 ePTFE). Before deep-SSI development, 4 patients (25%) had another vascular procedure during follow up (Table 2).

All deep-SSI's were identified after an average of 54±83.3 days. All wounds were opened for drainage. Most of the isolated microorganisms were *Staphylococcus aureus* (n = 6; 38%), in three wounds *Pseudomonas aeruginosa* was cultured (table 5). All patients started with β – lactam antibiotics which were adjusted to the results of culture when appropriate (Table 4). The mean duration of antibiotic therapy (parental and/or oral agents) was 41±43.6 days and was significantly longer than in the superficial SSI group. One bovine patch was removed resulting in a successful treatment. One Sartorius muscle flap was used resulting in a treatment failure. Negative pressure wound therapy was used in 4 patients. Of these patients, one patient had a complete wound healing while staying alive and amputation free. During follow-up, 5 patients (31%) developed a septic bleeding because of infection after which the bypass was removed. In eight out of twelve patients the synthetic bypass was removed (5 (42%) totally; 3 (25%) partly). In one of these patients a successful treatment was accomplished (table 6).

Finally, four patients (25%) with a deep-SSI were successfully treated. Eight patients had a major amputation after deep-SSI development. After six months 5 patient died (31%). Three patients died because of sepsis. The other 3 patients died in the nursing home after they decided to stop all medical treatment because of high age and/or other comorbidities. The average length of hospital stay was 40±32.4 days including potential re-admissions (Table 3).

Table 6. Treatment strategies during follow-up.

Choice of treatment	Total (n = 40)	Superficial SSI (n = 24)	Deep SSI (n = 16)	*P*-value
Wound drainage	39	23	16	0.41[a]
Antibiotics used	37	21	16	0.14[a]
Total duration antibiotics*	26 (31.5)	16 (13.9)	41 (43.6)	0.014[c]
Negative pressure wound therapy	6	2	4	0.20[b]
Muscle flap	1	0	1	0.40[b]
Patch removal	1	0	1	0.40[b]
Bypass removal				
Partial	3	0	3	0.06[b]
Total	5	0	5	0.01[b]

a = Pearson χ^2-test; *b* = Fisher exact-test; c = Independent student-t test, * mean days ±SD.

DISCUSSION

The purpose of this article was to review the treatment of all SSI's in patients with PAD in our clinic. Wound drainage and the use of adjusted antibiotics were adequate therapies for treatment of superficial SSI's in this study. Clinical observation is suggested when prosthetic grafts are involved. Treatment of superficial SSI in the outpatient clinic is also applicable in carefully selected patients. Deep-SSI's were serious complications after vascular surgery with high mortality and amputation rates compared to superficial SSI's. No particular treatment was more successful than the others in this study. Considering the high rate of treatment failure with alternative approaches, complete graft removal could be the best choice for treatment.

The management of vascular SSI's demonstrates to be a challenging undertaking. Several successful graft preservation-strategies are mentioned like negative pressure wound therapies with or without muscle flaps (6-9). In this study, negative pressure wound therapy was only successful for superficial SSI treatment (2 patients). In patients with deep-SSI, one out of four patients treated with negative pressure wound therapy was treated successfully. Besides this, we also observed anastomotic-bleedings in 5 patients with a deep-SSI during follow up. This should be taken into account when considering negative pressure wound therapy in patients with deep-SSI especially when prosthetic grafts are used(14).

There was one patient who underwent Sartorius muscle flap coverage for graft infection treatment. Despite successful wound healing, failed patency resulted in a major amputation. Several articles have demonstrated the success of muscle flap coverage of infected grafts in the literature (8, 9, 15-17). One study demonstrated prophylactic muscle flaps in groin incisions to be effective in reducing wound-related complications(9). They suggested to use these muscle flaps in patients with certain high risk comorbidities to reduce SSI development. This could contribute to the reduction of SSI. However, because of its retrospective character, future prospective studies and the development of risk stratification models should be performed to evaluate the effect of prophylactic muscle flaps in these particular patient populations.

Treatment success also depends on the microorganism creating the infection. *Pseudomonas aeriginosa* is a well-known cause of graft failure in literature (18). Other articles demonstrated a success in treating this microorganism using negative pressure therapies and acetic acid(7). In our series we observed four patients with *Pseudomonas aeruginosa*. One patient was clinically treated with antibiotics and wound drainage but lost to follow up after discharge. Another patient was successfully treated with negative pressure therapy for 17 days. In another patient *P. aeruginosa* was cultured from a superficial SSI and initially treated on the outpatient clinic with wound drainage and antibiotics but was eventually admitted because of severe pain of the wound. After admission the wound was successfully treated. Finally the last patient with a deep-SSI had several anastomotic bleedings resulting in bypass removal and major amputation.

Complete graft removal with extra-anatomic reconstruction, in situ or antimicrobial-impregnated replacement have been considered as the 'golden standard' (2-4). In our series 8 (3 partly and 5 totally removed) from the 11 infected grafts (deep-SSI; ePTFE) were removed because of sepsis or anastomotic bleeding. Only one of these 8 patients achieved a full treatment success. All the other patients had either a major amputation or died. Complete graft removal could be the only solution for deep-SSI treatment but, because of the small numbers and study design, results should be carefully interpreted. On the other hand, a synthetic graft infection is a risk factors for undergoing major amputation because of the underlying PAD(19). Graft removal could therefore have serious consequences. Preventative measures and careful patient selection is of the essence to reduce these infections in the first place. Besides the retrospective character, the main limitation of this study is the wide variety of treatment strategies used for deep-SSI treatment. Therefore, no conclusions can be made about the superiority of a specific treatment above the other. On the other hand, the occurrence of a SSI after vascular surgery is relatively rare. A study population of 40 patients with PAD and a SSI is therefore relatively large. By reviewing these SSI treatment results, we tried to demonstrate that the treatment of deep-SSI in patients with PAD is still a challenge. Finally, the numbers of synthetic graft infections in this report seems to be relatively large. It should be taken into account that this observational study only includes patients with a SSI. In a previously published report we described an overall SSI rate of 10.4% and a deep-seated SSI rate of 3.5% which is comparable to the literature(1).

In conclusion, the management of SSI's in vascular surgery demonstrates to be challenging especially for deep-SSI management. Many effective treatment strategies of SSI's are suggested in literature but their precise indication remains unclear. Also in this cohort no clear treatment strategies were present for deep-SSI management and many treatment options were performed based on the surgeons experience. Future prospective studies have to be performed to evaluate the effect, indication and timing of specific treatment options for deep-SSI's in patients with PAD. Also better prediction models on patient outcome after deep-SSI development could attribute to better patient outcome.

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PART III

Summary, general discussion

CHAPTER 8

Summary, general discussion and future perspectives

SUMMARY, GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Epidemiologic data predict a significant increase in the number of patients with CLI within the next decades (1-3). Synchronous to this, an increase of vascular procedures is expected. In general, surgical interventions performed in this particular patient group is associated with potentially severe adverse events influencing the outcome. Providing insights of the outcome of specific procedures is an important topic in today's medicine. Results can be used to detect shortcomings, evaluate new and old treatment modalities and initiate new research projects. Moreover this will increase transparency for physicians, hospitals and patients. In this thesis, Peripheral vascular surgery: an appraisal of various clinical outcome measures, the outcome of a variety of daily-performed surgical procedures in the vascular clinic of the Amphia hospital (Breda, the Netherlands) was studied.

OUTCOME AFTER PERIPHERAL VASCULAR SURGERY

Post-procedural success of a vascular procedure is among others determined by a manually measured ABI in our clinic (2). This measurement is concerned operator dependent and time-consuming (4). The use of an automated ABI device could resolve these disadvantages in postoperative care. The applicability of such a device has been demonstrated in the general population for PAD screening (5-9) but has not been used in postoperative ABI measurement. In **Chapter 2** the clinical applicability of an automated ABI device was compared to the manual method for determining the ABI after vascular surgery. This study demonstrated a high failure rate in ABI measures of the device with a structural higher ABI value compared to the manual method. Additionally, the odds of the automated method not producing a valid ABI-value was significantly influenced by gender (females to males OR 10.74 (95 % CI: 1.78-65.0; p = 0.010)) and the manual-measured ABI-value (OR 1.24 (95 % CI: 1.02-1.52; p = 0.035) per 0.1 point decrease in ABI-value). The use of an automated ABI device seems not clinically applicable in postoperative ABI-measurement.

Important outcome parameters in peripheral vascular surgery are patency- and limb salvage (2, 10). In **Chapter 3** the long-term results of pre-cuffed ePTFE and autologous vein bypass grafts were studied. Despite the advantage of a refined distal cuff of the pre-cuffed ePTFE grafts, the patency rates of the autologous vein grafts were significantly better. The use of a vein graft in peripheral vascular surgery remains the first choice conduit (2). With respect to limb salvage, the choice for a pre-cuffed ePTFE graft for peripheral bypass surgery seems to be reasonable in the absence of an adequate vein.

In an attempt to improve patency of synthetic bypasses the heparin bounded ePTFE (HePTFE) graft was developed. The results of these bypasses are conflicting in the literature, reporting excellent patency rates (11) but also comparable patency rates as ePTFE grafts (12, 13). The potential advantage of this bypass has therefore not yet been demonstrated.

Due to various reasons; e.g. previous lower extremity bypass procedures, coronary bypass grafting, trauma or poor vein quality, many patients do not have an adequate limb vein (14, 15) often forcing the surgeon to choose for synthetic conduits. The use of arm vein grafts could contribute to better alternatives in the absence of an adequate limb vein (16) and could be an acceptable intermediate step before choosing for synthetic conduits (17, 18). In our clinic the use of arm vein grafts for peripheral bypass surgery is not commonly used because of superficial veins of the upper arm are fragile and tedious to harvest, resulting in large wounds. Additionally those bypasses are known for stenosis leading to more re-interventions (17). Despite these disadvantages arm vein grafts could contribute to better patency- and limb salvage rates in particular for infragenicular or femorocrural bypass surgery.

Loss of patency can be caused by an acute occlusion of a bypass or native artery due to an embolism or thrombus resulting in acute limb ischemia (ALI) (19, 20). In **Chapter 4** the outcome of intra-arterial thrombolysis and thromboembolectomy were compared. Both one-year primary patency- and limb salvage rates were not significantly different. However, the one-year mortality rates were significantly higher in the thromboembolectomy group. A wide variety of adverse events were registered. Most were procedure related (77% thrombolysis vs 76% thromboembolectomy), resulting in surgical re-interventions. A considerable amount of adverse events resulted in irreversible damage and even death.

In the literature, no evidence in favor of any intervention as the preferred option in terms of patency, limb salvage or mortality is described (21). Also in our study, no difference was observed. Both interventions are effective in the treatment of patients with ALI. The high mortality rate after thromboembolectomy was explained by potential selection bias due to the retrospective study design.

To reduce the systemic effects of thrombolysis, many isolated pharmaco-mechanical thrombolysis systems have been developed (22-32). Although these systems are promising, most reports about these new techniques are based on case reports or small clinical studies.

PREVENTION AND TREATMENT OF SSI

An important topic in modern health care is the reduction of adverse events. A study, performed on adverse events among patients in Dutch hospitals, resulted in the conclusion that most adverse events were caused by healthcare management rather than by the patient's underlying disease (33). Surgical site infections (SSI's) were one of those potentially preventable adverse events. In **Chapter 5** the effect of the introduction of a bundle of care was studied to explore the effect on SSI-reduction after vascular surgery. The results demonstrated an overall SSI-rate of 10.4% in our clinic. Both superficial- and deep-seated SSI's occurred significantly more frequent after peripheral vascular procedures compared to central vascular procedures. If a superficial - or deep-seated SSI occurred, it resulted in a prolonged length of hospital stay of 18 days (superficial SSI) and 37 days (deep-seated SSI) demonstrating the importance of reducing these adverse events. After all, the implementation of the bundle resulted in a 51% reduction of SSI's in the last year, compared to the first year.

There are some contradictory results of a bundle of care on SSI reduction in the literature. A positive effect of using a bundle of care to reduce SSI was reported in studies on catheter- and ventilation related infections on the ICU (34, 35). In other studies after colorectal surgery, the effects of such a bundle could not be demonstrated (36, 37). The main criticism on those studies is that the bundle was mainly based on technical adjustments, which did not encourage a structural improvement in the overall surgical process to create a safety culture. A comparable study to our study was performed in our clinic after colorectal surgery which also demonstrated a reduction of SSI's after implementation of the bundle (38). We therefore recommend the implementation of this bundle on a large scale.

Redo-surgery is not an exception in the time-course of patients with PAD. In many of these procedures, a groin incision is involved. The interval between these procedures can also vary from no previous procedure, to procedures within days, months and even years. In the literature, a groin incision is a risk-factor for SSI development (39). In **Chapter 6** the occurrence of SSI after vascular surgery performed in different time-intervals was studied. The results demonstrated a significant linear trend effect of the groin incision interval on the development of deep-seated SSI's: the shorter the interval, the higher the event rate (HR 1.5 per category, 95% CI 1.1-2.1, $p = 0.022$). This suggests early revision surgery to be a risk factor for deep-SSI development. The incision interval had no significant effect on the development of superficial SSI's. Besides the incision interval, increased Rutherford-classification was a significant risk factor for superficial- as well as for deep-seated SSI development.

Misleading results could occur when vascular institutions are compared to each other based on SSI-rates, without taking the patient population into account. For example, the SSI-rate is expected to be much higher in a vascular population consisting of patients with deteriorated

stages of PAD. Also the amount of redo-procedures are assumed to be higher in this patient group compared to a vascular population consisting of patients with less deteriorated severe stages of PAD.

Alternative procedures to avoid dissection of a previously operated groin, like the use of endografts in creating an endoluminal bypass, are described in the literature (40). Results suggested this strategy to be a valid alternative although the level of evidence was low because of the small numbers of patients. This could also have a potential positive effect on SSI reduction and should be evaluated in future prospective studies performed on a larger population.

Both prevention and treatment of SSI's are important for improving patient outcome and quality of care. In the literature, a wide variety of treatment options have been described, all demonstrating good clinical results after treatment of SSI (41-47). Some studies suggest complete removal of prosthetic grafts, with replacement of new antimicrobial grafts or extra-anatomic reconstruction, others suggest graft preservation. Most of these studies are based on a selected patient populations and the indication for each different treatment strategy is often unclear. In **Chapter 7** the treatment of all our registered SSI after peripheral vascular surgery were studied. Wound debridement and the use of adjusted antibiotics seemed adequate treatment strategies in managing superficial SSI. The treatment strategies of deep-seated SSI were less successful which resulted in many comorbidities and even death. No particular treatment was more successful than the others in this study. Considering the high rate of treatment failure with alternative approaches, complete graft removal could be the best choice for treatment. Future prospective studies have to be performed to evaluate the effect, indication and timing of specific treatment options for deep-seated SSI's in patients with PAD. The use of prediction models could contribute to better patient outcomes.

FUTURE PERSPECTIVES

Patients with CLI are fragile, high-risk patients. Determining treatment strategies solely based on patency- and limb salvage rates may not be adequate in improving outcome after vascular surgery.

Due to technological developments and significant morbidity after infrainguinal bypass surgery, the use of endovascular interventions are more commonly performed for CLI compared to open procedures (48-50). Despite the rapid increase in new techniques and devices, results seem not to improve these outcome measures (51). Moreover, the interpretation of new techniques are increasingly complex because of the wide variety of treatment options in which the results are often overtaken by new developments or insights. Patient specific outcome measures are undervalued in clinical studies and mostly based on retrospective analyses providing insights into these endpoints (51). Considering the outcome of revascularization, limited life expectancy and the possible comorbidities that may arise after revascularization attempts, study results should be focused more on these outcome measures. In some cases, for example, conservative therapy or a major amputation could also be an important treatment strategy in the treatment of CLI (52, 53).

Risk stratification models on the outcome of patients with CLI could contribute to improve outcome by better decision-making (51). A few externally validated models already exist (54-57). Although these models are promising in predicting outcome of this specific patient population, they seem to be based on heterogeneous predictor variables resulting in modest predictive abilities (58).

Besides these risk stratification models, patient related outcome measures (PROMs) could also contribute to improving care in this patient population. The aim of PROMs is to capture the patient his perspectives of health, illness and the effects of health care interventions (59). An earlier report from our clinic demonstrated a significant increase in quality of life (QoL) 3 month after peripheral bypass surgery which was lost after midterm follow-up (60). They concluded no relation between quality of life (QoL) and traditional outcome measurements (patency-, limb salvage- and mortality rates). PROMs could add insights of provided care of specific procedures or specific patient groups we therefore decided to start a prospective study on QoL in the elderly vascular patient with CLI.

In conclusion, further refinement of risk stratification models and better insights in PROMs by prospective studies are important to improve patient outcome. Although, these models will never completely predict patient outcome, they can be used to improve patient and physician decision making and therefore improve patient outcome.

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chapter
8

CHAPTER 9

Samenvatting, algemene discussie en toekomstperspectieven

SAMENVATTING, ALGEMENE DISCUSSIE EN TOEKOMSTPERSPECTIEVEN

In de komende decennia zal naar verwachting het aantal patiënten met kritieke ischemie gaan toenemen (1-3). Met deze ontwikkeling zal er ook een toename van vasculaire procedures zijn. Het uitvoeren van chirurgische interventies in deze patiënten populatie is geassocieerd met potentieel ernstige complicaties. Inzicht verkrijgen in de uitkomsten van bepaalde procedures is dan ook een belangrijk onderdeel in de huidige geneeskunde. Resultaten kunnen worden gebruikt om tekortkomingen te ontdekken, oude en nieuwe behandelmethodes te evalueren en nieuwe onderzoeken te initiëren. Bovendien zorgt het voor transparantie bij zorgverleners, zorginstellingen en patiënten. In dit proefschrift, Perifere vaatchirurgie: een beoordeling van verschillende klinische uitkomsten, werden uitkomsten van verscheidene vaatchirurgische ingrepen, uitgevoerd in het Amphia ziekenhuis, bestudeerd.

UITKOMSTEN NA PERIFERE VAATCHIRURGIE

Het postoperatieve succes van een vaatoperatie wordt in onze kliniek onder andere bepaald door een handgemeten enkel/arm index (EAI) (2). Het meten van een handmatige EAI neemt veel tijd in beslag en vraagt enige expertise van de persoon die de metingen uitvoert (4). Een automatisch EAI apparaat zou hier uitkomst kunnen bieden. In de huisartsenpraktijk heeft een dergelijk apparaat al zijn meerwaarde getoond bij het diagnosticeren van perifeer arterieel vaatlijden (PAV) (5-9), echter nog niet in het meten van een postoperatieve EAI. Dit zou ook het geval kunnen zijn bij het bepalen van een postoperatieve EAI. In **Hoofdstuk 2** werd de klinische toepasbaarheid van een automatisch EAI apparaat vergeleken met de handmatige methode na vaatchirurgie. Deze studie liet zien dat het apparaat een hoge failure-rate had waarbij het een structureel hogere EAI produceerde vergeleken met de handmatige methode. De kans dat het apparaat niet instaat was een EAI te produceren werd significant beïnvloed door het geslacht (vrouwen vs mannen OR 10.74 (95 % CI: 1.78-65.0; p = 0.010)) en de handgemeten EAI-waarde (OR 1.24 (95 % CI: 1.02-1.52; p = 0.035) per 0.1 punt afname in EAI-waarde). Het lijkt dan ook dat een automatische EAI apparaat niet geschikt is om postoperatieve EAI metingen uit te voeren.

Belangrijke uitkomstmaten voor het weergeven van bepaalde vaatingrepen zijn patency en limb salvage (2, 10). In **Hoofdstuk 3** werden de lange termijn uitkomsten van pre-cuffed ePTFE- en autologe veneuze bypass grafts bestudeerd. Ondanks de aangepaste distale cuff van de pre-cuffed ePTFE bypass waren de patency-rates van de autologe bypass grafts significant beter. Het gebruik van een veneuze graft is daarom nog steeds de eerste keus in

perifere bypasschirurgie. Met het oog op limb salvage is de keuze voor een pre-cuffed ePTFE graft te verdedigen bij afwezigheid van een adequate autologe vene.
In een poging om patency-rates van synthetische bypasses te verbeteren zijn er heparine gecoate ePTFE (HePTFE) bypasses ontwikkeld. De literatuur toont echter tegenstrijdige resultaten met een studie met excellente patency-rates (11) en studies waarbij er geen verschil in patency-rates werd gevonden tussen HePTFE en ePTFE bypasses (12, 13). Een potentieel voordeel van deze bypasses is daarom nog niet geleverd.
Om verschillende redenen (eerdere perifere bypass procedures, coronaire bypass chirurgie, trauma of slechte kwaliteit van de vene) kan er bij een patiënt geen bruikbare vene meer aanwezig zijn (14, 15). Een arm vene zou een goede tussenstap kunnen zijn voordat er gekozen wordt voor een synthetische bypass (16-18). In onze kliniek maken wij sporadisch gebruik van arm vene. Doorgaans zijn deze oppervlakkige venen erg fragiel en lastig vrij te prepareren, leidend tot een grote wond. Daarnaast hebben deze bypasses meer kans op stenosering, resulterend in meer re-interventies (17).
Het verlies van patency kan worden veroorzaakt door een acute vaatocclusie van een natief vat maar ook door een embolus of trombus in een eerder aangelegde bypass wat uiteindelijk leidt tot acute ischemie (AI) (19, 20). AI kan worden verholpen middels trombolyse of een chirurgische embolectomie. In **Hoofdstuk 4** werden beide behandelingen met elkaar vergeleken met de daarbij opgetreden complicaties. Uit de studie bleek dat zowel de 1 jaar primaire patency- als de limb salvage-rates niet significant verschilden tussen beide behandelmethodes. We zagen wel een significant hogere mortaliteit na chirurgische embolectomie. Een grote verscheidenheid aan complicaties werden geregistreerd waarvan het leeuwendeel procedure gerelateerd waren (77% trombolyse vs 76% embolectomie), leidend tot chirurgische re-interventies. Er werd ook een aanzienlijk aantal complicaties geregistreerd die resulteerden in irreversibele schade en zelfs het overlijden van een patiënt.
In de literatuur wordt er geen bewijs geleverd over welke behandelmethode een betere uitkomst oplevert ten aanzien van 1-jaar patency, limb salvage of mortaliteit (21). Dit kwam ook uit onze studie naar voren. Beide behandelingen hadden een vergelijkbare uitkomst. De hogere sterfte na embolectomie werd verklaard door het retrospectieve design van de studie waarbij er mogelijk selectie bias heeft plaats gevonden.
Om het systemische effect van trombolyse te beperken zijn er de afgelopen jaren vele nieuwe methodes ontwikkeld die door hun lokale werking tot minder complicaties moet gaan leiden (22-32). Alhoewel dit veel belovende methodes lijken te zijn, is het bewijs vaak gebaseerd op case reports of kleine retrospectieve studies.

PREVENTIE EN BEHANDELING VAN POSTOPERATIEVE WONDINFECTIES (POWI)

Een steeds belangrijker wordend onderwerp in de hedendaagse gezondheidzorg is het reduceren van postoperatieve complicaties. Uit een studie onder Nederlandse ziekenhuizen kwam naar voren dat de meeste postoperatieve complicaties werden veroorzaakt door zorg gerelateerde handelingen in plaats van patiënt gerelateerde co-morbiditeit (33). Postoperatieve wondinfecties (POWI) waren een van deze voorkombare complicaties. In **Hoofdstuk 5** werd het effect van de introductie van een bundel met zorgmaatregelen (veiligheidsmanagementsysteem (VMS)-bundel) op POWI-reductie na vaatchirurgie bestudeerd.

De resultaten van deze studie toonden dat in 10.4% van de geopereerde patiënten een POWI voorkwam. Zowel oppervlakkige- als diepe-POWI kwamen significant vaker voor na perifere vaatchirurgie dan na centrale vaatchirurgie. Als er zich een oppervlakkige- of diepe-POWI voordeed, resulteerde dit in een verlengde opnameduur van 18 dagen (oppervlakkige-POWI) en 37 dagen (diepe-POWI). Na het implementeren van de VMS-bundel werd er een 51% POWI reductie in het laatste jaar ten aanzien van het eerste jaar gezien.

Het gebruik van bundels voor het reduceren van POWI heeft tegenstrijdige resultaten opgeleverd in de literatuur. Een positief effect van een dergelijke bundel werd beschreven in studies naar de reductie van centrale lijn gerelateerde- en ventilatie gerelateerde infecties op de intensive care (34, 35). In andere studies kon dit effect niet worden aangetoond (36, 37). De gebruikte bundels waren met name toegespitst op technische veranderingen in het zorgproces waarbij er geen poging werd gedaan om een veiligheid cultuur te creëren. Een vergelijkbare studie als de onze werd verricht in ons ziekenhuis na colorectale chirurgie wat ook een significante POWI reductie liet zien na implementatie van de bundel (38). Op basis van onze bevindingen concludeerden we dat de bundel zoals gedefinieerd door VMS POWI een nuttig hulpmiddel is om een veiligheidscultuur te bewerkstelligen en daarmee de kwaliteit van de zorg en de patiëntveiligheid te verbeteren.

Redo-chirurgie is geen uitzondering in het ziektebeloop van patiënten met perifeer vaatlijden. Bij veel van deze ingrepen wordt er gebruik gemaakt van een liesincisie. Wanneer redo-chirurgie geïndiceerd is, kan het interval tussen de primaire operatie en de redo-operatie variëren van dagen tot maanden of zelfs jaren. In de literatuur worden liesincisies gezien als een riscofactor op het ontwikkelen van POWI (39). In **Hoofdstuk 6** werd het optreden van POWI na redo-chirurgie bestudeerd. De resultaten lieten zien dat een kort tijdsinterval leidde tot een hogere kans op het ontwikkelen van een diepe-POWI (HR 1.5 per categorie, 95% CI 1.1-2.1, p = 0.022). Het incisie interval had geen significant effect op het ontwikkelen van oppervlakkige-POWI.

Naast het incisie interval was de ernst van het perifeer vaatlijden een risicofactor voor het ontwikkelen van zowel oppervlakkige- als diepe-POWI.
De resultaten van deze studie laten niet alleen zien dat redo-chirurgie een risicofactor is voor het ontwikkelen van diepe-POWI maar het laat ook zien dat er verschillen bestaan tussen vaatpopulaties. Bijvoorbeeld bij het vergelijken van uitkomsten tussen verschillende vaatklinieken is het belangrijk om de samenstelling van de vaatpopulatie hierbij mee te nemen.
Redo-chirurgie is mogelijk te vermijden door alternatieve procedures te hanteren zoals endografts om endoluminale bypasses te creëren (40). Deze techniek is beschreven als alternatief voor redo-chirurgie zodat dissectie van eerder geopereerd gebied vermeden kan worden mogelijk leidend tot een reductie van POWI. De resultaten van deze studie waren veel belovend echter gebaseerd op kleine aantallen patiënten. Toekomstig prospectief gerandomiseerd onderzoek zou hier uitsluitsel over moeten geven.
Zowel preventie als de behandeling van POWI zijn belangrijk in het verbeteren van patiëntuitkomsten. In de literatuur wordt een uitgebreid palet aan behandelmogelijkheden beschreven die goede resultaten laten zien voor de behandeling van POWI (41-47). Enkele studies suggereren dat bij een POWI het synthetische materiaal in zijn geheel verwijderd dient te worden en vervangen dient te worden door of een in antibiotica gedrenkte graft of door extra-anatomische reconstructies. Andere studies suggereren weer tot het behoud van het materiaal. Het merendeel van deze studies zijn gebaseerd op geselecteerde patiëntengroepen waarbij de indicatie voor dergelijke behandelopties onduidelijk is. In **Hoofdstuk 7** wordt de behandeling van zowel oppervlakkige- als diepe-POWI in onze kliniek beschreven. Debridement van de wond en het starten van antibiotica was een adequate behandelstrategie voor de behandeling van oppervlakkige-POWI. De behandeling strategie van diepe-POWI bleek divers te zijn met weinig succesvolle behandelingen resulterend in complicaties en zelfs tot het overlijden van de patiënt. Geen van de behandel strategieën bleek succesvoller te zijn dan de ander. Gezien het hoge percentage gefaalde behandelstrategieën zou het volledig verwijderen van de graft de beste keuze voor behandeling kunnen zijn. Toekomstig prospectief gerandomiseerd onderzoek moet uitwijzen welke strategie het meest succesvol is bij de behandeling van diepe-POWI.

TOEKOMSTPERSPECTIEVEN

Patiënten met ernstig perifeer arterieel vaatlijden zijn doorgaans hoog-risico patiënten als ze geopereerd worden. Het bepalen van een behandeling alleen gebaseerd op patency- en limb-salvage rates lijkt niet afdoende in het verbeteren van de uitkomsten van vaatchirurgie.
Mede door de technologische ontwikkelingen en significante morbiditeit na perifere bypass chirurgie, worden er steeds vaker endovasculaire behandelingen verricht in de behandeling van PAD (48-50). Ondanks de toename van deze technologische ontwikkelingen lijken de resultaten van de behandeling van PAD niet significant te verbeteren (51). Daarnaast is het vaak lastig om nieuwe technieken goed in kaart te brengen vanwege de grote verscheidenheid aan behandelingen waarbij resultaten vaak al weer worden ingehaald door nieuwe inzichten en ontwikkelingen.
Patiënt specifieke uitkomstmaten zijn vaak ondergewaardeerd in klinische studies en vaak gebaseerd op retrospectieve studies (51). Resultaten van behandelingen, levensverwachting en mogelijke complicaties na een ingreep zouden meer meegenomen mogen worden in klinische studies. In sommige gevallen is bijvoorbeeld een conservatief beleid bij ernstig perifeer vaatlijden ook een goed te verdedigen (52, 53).
Risico predictiemodellen zouden kunnen bijdragen aan de verbetering van uitkomsten in patiënten met PAD door handvaten te bieden bij besluitvorming (51). In de literatuur zijn er al een aantal gevalideerde modellen beschreven (54-57), echter bleken deze modellen tot nu toe een matig voorspellend vermogen te hebben (58).
Naast deze risico predictiemodellen zouden PROMs (patient related outcome measures) ook kunnen bijdragen aan de verbetering van uitkomst in deze patiënten populatie. PROMs omvat resultaten die vanuit het perspectief van de patiënt inzicht geven tot zijn gezondheid, ziekte en effect van interventies (59). Een eerdere studie uit onze kliniek toonde al een verschil in QoL en traditionele uitkomstmaten (patency-, limb salvage- en mortaliteit) (60). Om dit soort inzichten te krijgen bij oudere patiënten zijn we gestart met een prospectieve studie na de kwaliteit van leven van de oudere patiënt met kritieke ischemie.
Tot slot, toekomstige prospectieve studies zullen moeten leiden tot verdere verbetering van risico predictiemodellen en een beter inzicht geven in PROMs om zo besluitvorming en patiënten uitkomsten te verbeteren.

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PART IV

Appendices

CHAPTER 10

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Acknowledgement - Dankwoord

ACKNOWLEDGEMENT - DANKWOORD

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List of publications

PUBLICATIONS

- **van der Slegt J**, Verbogt NP, Mulder PG, Steunenberg SL, Steunenberg BE, van der Laan L. The clinical applicability of an automated plethysmographic determination of the ankle-brachial index after vascular surgery. Vascular. 2016 Jan 19.
- **van der Slegt J**, Steunenberg SL, Donker JM, Veen EJ, Ho GH, de Groot HG, et al. The current position of precuffed expanded polytetrafluoroethylene bypass grafts in peripheral vascular surgery. Journal of vascular surgery. 2014 Jul;60(1):120-8.
- **van der Slegt J**, Flu HC, Veen EJ, Ho GH, de Groot HG, Vos LD, et al. Adverse events after treatment of patients with acute limb ischemia. Annals of vascular surgery. 2015 Feb;29(2):293-302.
- **van der Slegt J**, van der Laan L, Veen EJ, Hendriks Y, Romme J, Kluytmans J. Implementation of a bundle of care to reduce surgical site infections in patients undergoing vascular surgery. PloS one. 2013;8(8):e71566. PubMed PMID: 23967222.
- **van der Slegt J**, Kluytmans JA, Mulder PG, Veen EJ, Ho GH, van der Laan L. Surgical site infection after multiple groin incisions in peripheral vascular surgery. Surgical infections. 2014 Dec;15(6):752-6.
- **van der Slegt J**, Kluytmans JA, de Groot HG, van der Laan L. Treatment of surgical site infections (SSI) IN patients with peripheral arterial disease: an observational study. International journal of surgery. 2015 Feb;14:85-9.

PhD portfolio

PhD PORTFOLIO

Name PhD student: Jasper van der Slegt	PhD period: 2012-2015
Erasmus MC Department: Surgery	Promotor(s): Prof.dr. H.J.M. Verhagen, Prof.dr. J.A.J.W. Kluytmans
	Supervisors: dr. L. van der Laan

1. PhD training

	Year	Workload (Hours/ECTS)
General academic skills		
Monthly research meeting, Breda	2012-2015	2
Seminars		
Vascular rounds	2013-2015	0.5
Presentations poster		
National scientific poster presentations	2014-2015	1
Presentations oral		
National scientific presentations	2013	5
National scientific presentations	2014	3
International scientific presentations	2014	3
National scientific presentations	2015	1
(Inter)national conferences		
National conferences	2012	2
National conferences	2013	3
National conferences	2014	4
International conferences	2014	4
National	2015	3

2. Teaching activities

	Year	Workload (Hours/ECTS)
Supervising practicals and excursions, tutoring		
Supervising/teaching medical students	2012-2015	1.0
Supervising:		
S.L. Steunenberg	2013	2

Curriculum vitae

CURRICULUM VITAE

The author of this thesis, Jasper van der Slegt, was born on the 14th of December 1985 in Warnsveld, the Netherlands. During his childhood he lived in Zutphen where he graduated high school (Gymnasium) at the Baudartius college in 2004. After graduation, he continued to study Clinical Technology at the University of Twente. In 2005 he was admitted to the Erasmus University Rotterdam where he studied Medicine. During his studies and internships he developed an interest in surgery. After a surgical internship in South-Africa he completed his medical degree in January 2012 and started his career as an uncredited surgical resident (ANIOS) at the Amphia Hospital in Breda. In this period he started his research projects in vascular surgery which laid the foundation of this thesis. His work was conducted under the supervision of Prof. dr. J.A.J.W. Kluytmans and dr. L. van der Laan. Within this project he evaluated various clinical situations in the vascular clinic. The results are presented in this thesis. In 2014 he continued his residency at the Erasmus Medical Centre in Rotterdam and applied for the surgical training program. In January 2015 he was admitted to the surgical training program of the Erasmus Medical Centre in Rotterdam and started his training in the Amphia hospital in Breda under supervision of dr. L. van der Laan (Amphia ziekenhuis) and dr. B.P.L. Wijnhoven (Erasmus MC).

De auteur van dit proefschrift, Jasper van der Slegt, werd op 14 december 1985 geboren in Warnsveld, Nederland. Zijn jeugd en middelbare schoolperiode bracht hij door in Zutphen waar hij uiteindelijk in 2004 zijn gymnasium diploma behaalde aan het Baudartius college. Aansluitend ging hij Technische Geneeskunde studeren aan de Technische Universiteit Twente in Enschede. In 2005 werd hij aangenomen aan de Erasmus Universiteit in Rotterdam om geneeskunde te gaan studeren. Tijdens zijn studie en coschappen ontwikkelde hij een sterke interesse in de Heelkunde. Na een coschap in Zuid-Afrika behaalde hij zijn artsendiploma in januari 2012 en startte hij zijn carrière als arts assistent niet in opleiding tot specialist (ANIOS) in het Amphia ziekenhuis in Breda. In deze periode startte hij zijn onderzoek naar vaatchirurgie wat de basis legt van dit proefschrift. Zijn werk was verricht onder supervisie van Prof. dr. J.A.J.W. Kluytmans en dr. L. van der Laan. Binnen dit project evalueert hij verscheidene klinische situaties binnen de vaatkliniek. De resultaten hiervan worden gepresenteerd in dit proefschrift. In 2014 vervolgde hij zijn assistentschap in het Erasmus Medisch Centrum in Rotterdam waarna hij solliciteerde voor de opleiding tot chirurg. In januari 2015 werd hij aangenomen in het Eramus Medisch Centrum vanwaar hij zijn opleiding startte in het Amphia ziekenhuis in Breda onder begeleiding van dr. L. van der Laan (Amphia ziekenhuis) en dr. B.P.L. Wijnhoven (Erasmus MC).