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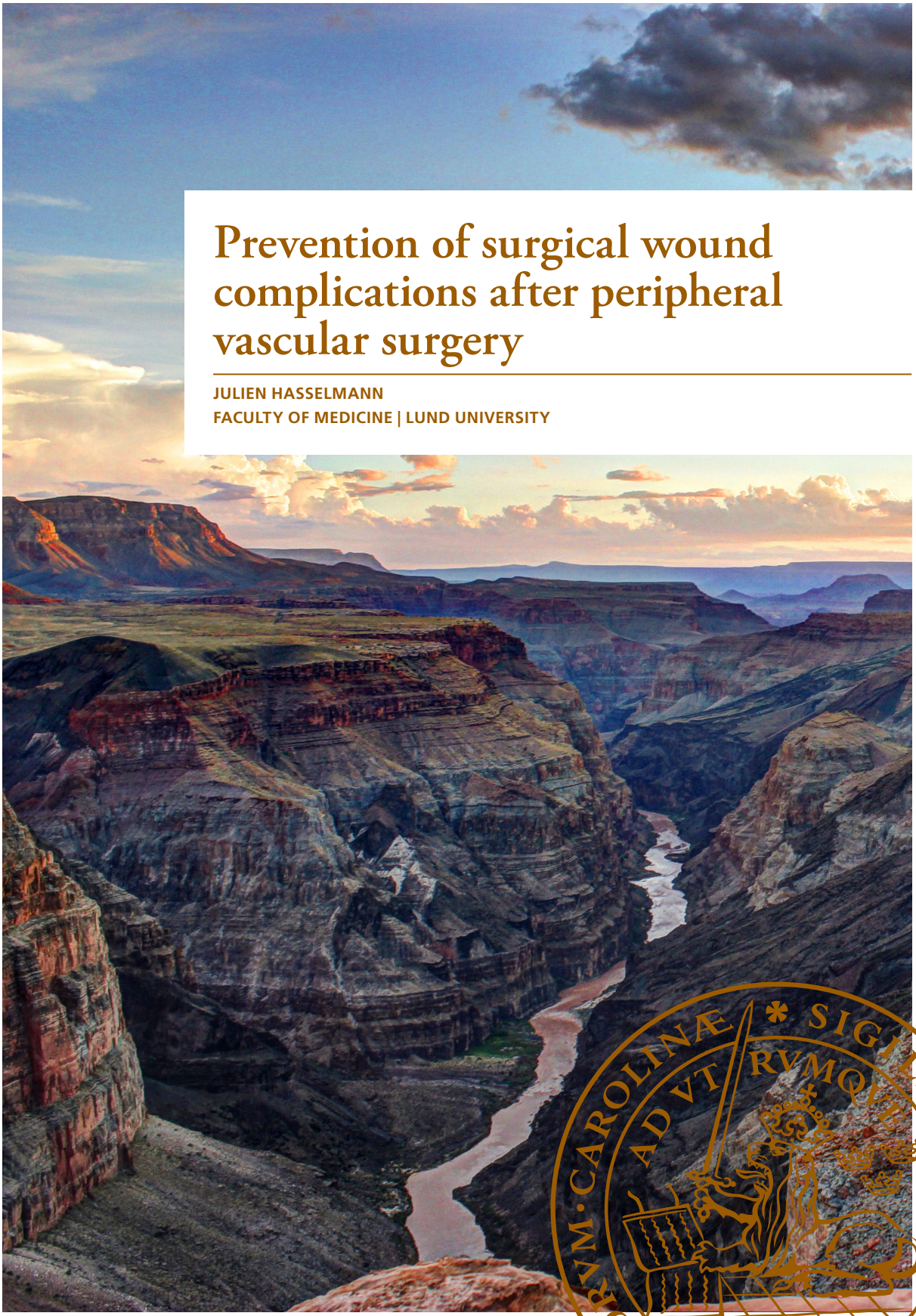

Prevention of surgical wound complications after peripheral vascular surgery

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Julien Hasselmann is a medical doctor specialized in Vascular Surgery. Born in Berlin, Germany in 1984, he received his medical degree from Semmelweis University in Budapest, Hungary before returning to Germany to begin his specialization. After his basic surgical training he completed his vascular surgical training at Vascular Center Malmö where the research projects for this PhD thesis were undertaken.

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Prevention of surgical wound complications after peripheral vascular surgery

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UNIVERSITY

DOCTORAL DISSERTATION

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Faculty opponent
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Donegal Clinical Research Academy

Organization LUND UNIVERSITY	**Document name** DOCTORAL DISSERTATION
	Date of issue September 13th 2019
Author Julien Hasselmann	Sponsoring organization

Title: Prevention of surgical wound complications after peripheral vascular surgery

Background:

Surgical wound complications (SWC) are a common complication of peripheral vascular surgery leading to patient suffering, surgeon frustration and high health care costs. One of the most feared SWC are surgical site infections (SSI) that can have devastating consequences when the vascular reconstruction is involved. One of the most critical anatomical areas in vascular surgery is the inguinal region where a relative mobility of the surgical site, an abundance of lymph vessels and proximity to the anogenital area pose significant risks for SSI and other SWC. One of the main preventive measures of SSI has been preoperative antibiotic prophylaxis. A more recent strategy is incisional negative pressure wound therapy (NPWT), promising a reduction of both SSI and other SWC. Comparing different methods aimed at preventing SWC is difficult because a comprehensive classification of SWC has not yet found broad acceptance.

Aims:

The aims were to study:

- The impact of changing the antibiotic prophylaxis regime from cloxacillin to trimethoprim/sulfamethoxazole before open vascular surgical procedures on the SSI rate of surgical wounds in the inguinal area.
- The effects of incisional negative pressure wound therapy on SSI rate and other SWC of vascular surgical inguinal incisions compared to conventional dressings.
- The clinical impact of SSI compared to other SWC by means of a new classification for SWC, focusing on therapy received and complication-related time spent as inpatients.

Material/methods:

In a retrospective cohort study of patients undergoing inguinal vascular surgical procedures within two time periods in 2012 and 2013, the frequency of SSI after changing the prophylactic antibiotic prophylaxis between the two time periods was compared. The publication of the design of a randomized controlled trial (RCT), including its power calculation, served to minimize its bias. This open-label single center RCT, evaluating the effects of incisional NPWT on vascular surgical inguinal incisions in regard to SSI and other SWC, included eligible patients between 2013 and 2018. Patients considered eligible for the trial, as well as some undergoing operations after trial completion, were included in another cohort study, exploring the impact of SWC on additional wound treatment and interventions received. This was done using a new classification for SWC.

Results:

Among the 219 patients included, no differences in inguinal SSI or types of isolated pathogens were observed after changing the antibiotic prophylaxis regime. The power calculation for the RCT showed that 147 inguinal incisions needed to be included to show the expected difference in SSI. The study included 139 patients or, as some patients received bilateral incisions, 159 inguinal incisions and showed reduced infection rates on wounds treated with NPWT compared to conventional dressings (11.9% versus 29.5% in the unilateral group [n=120], 5.3% versus 26.3% in the bilateral group [n=19] respectively; combined p=0.02). According to the proposed SWC classification in the second cohort study, there was a comparable clinical significance between SSI and other SWC after a follow-up time of four months.

Conclusions:

In addition to preoperative antibiotic prophylaxis, incisional NPWT could be a supplementary measure to decrease SSI rates. SWC other than SSI should not be disregarded as they seem to have a profound impact on patients and probably cost. The proposed SWC classification might help to make procedure and center-related SWC rates more comparable across surgical specialties.

Key words

Surgical wound complication, surgical site infection, negative pressure wound therapy, vascular surgery, antibiotic prophylaxis, classification

Classification system and/or index terms (if any)

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The Cover photo, taken by my friend Bill Hamilton, shows the Grand Canyon carved by the Colorado River in Arizona, USA. Its steep walls represent the wound edges of a vascular surgical site and the river on its bottom, a blood vessel.

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MADE IN SWEDEN

To my family

Table of Contents

1 Papers included in the thesis

This thesis is based on the following papers, referred to in the text by their Roman numerals and reprinted with permission from their respective publishers.

I. Hasselmann J, Kuhme T, Acosta S. Antibiotic Prophylaxis With Trimethoprim/Sulfamethoxazole Instead of Cloxacillin Fails to Improve Inguinal Surgical Site Infection Rate After Vascular Surgery. Vasc Endovascular Surg 2015;49:129-34.

II. Hasselmann J, Kühme T, Björk J, Acosta S. Incisional Negative Pressure Wound Therapy in the Prevention of Surgical Site Infection after Vascular Surgery with Inguinal Incisions: Rationale and Design of a Randomized Controlled Trial (INVIPS-TRIAL). Surgical Science 2015;6:562-71.

III. Hasselmann J, Björk J, Svensson-Björk R, Acosta S. Inguinal Vascular Surgical Wound Protection by Incisional Negative Pressure Wound Therapy, A Randomized Controlled Trial – INVIPS Trial. Ann Surg 2019;(In Press).

IV. Hasselmann J, Björk J, Svensson-Björk R, Butt T, Acosta S. Proposed Classification of Surgical Wound Complications – Analysis of a prospective study on elective open lower limb revascularization (manuscript)

2 Thesis at a glance

Paper	Aim	Method	Main results
I. Antibiotic prophylaxis with trimethoprim/sulfamethoxazole instead of cloxacillin fails to improve inguinal surgical site infection rate after vascular surgery.	To compare inguinal surgical site infection rate after changing the antibiotic prophylaxis	Retrospective cohort study of patients undergoing open inguinal vascular surgical procedures within two time periods in 2012 and 2013	No differences in terms of infection rate or types of isolated pathogens were noted between the two groups.
II. Incisional negative pressure wound therapy in the prevention of surgical site infection after vascular surgery with inguinal incisions: rationale and design of a randomized controlled trial (INVIPS-Trial).	To provide a detailed explanation of the study design of the randomized controlled trial (study III) as well as to publish its power calculation to reduce publication bias	Study protocol publication of a randomized controlled trial	The planned randomized trial (study III) needed to be divided into two separate arms. The required number of inguinal incisions in the open surgery arm of the study was 147.
III. Inguinal vascular surgical wound protection by incisional negative pressure wound therapy, A randomized controlled trial – INVIPS Trial.	To determine the effect of negative pressure wound therapy on closed incisions after inguinal vascular surgery regarding surgical site infections and other wound complications	Single-center open label randomized controlled trial	Incisional negative pressure wound therapy seems to decrease surgical site infection rate after vascular surgery with inguinal incisions.
IV. Proposed classification of surgical wound complications - analysis of a prospective study on elective open lower limb revascularization.	To propose a comprehensive classification of surgical wound complications and apply it to compare the clinical impact of surgical site infections to other wound complications	Retrospective analysis of a cohort of patient data prospectively collected in the randomized controlled trial (study III) including non-randomized patients	There seems to be a comparable clinical significance of surgical site infections with other wound complications.

3 Abbreviations

ASEPSIS	**A**dditional treatment, presence of **s**erous discharge, **e**rythema, **p**urulent exudate, **s**eparation of the deep tissues, **i**solation of bacteria, duration of inpatient **s**tay
CDC	Centers for Disease Control and Prevention
EVAR	Endovascular aortic repair
INVIPS-Trial	**I**ncisional **N**PWT on **v**ascular surgical **i**nguinal incisions in the **p**revention of **S**SI
ITT	Intention-To-Treat
MRSA	Methicillin-resistant Staphylococcus aureus
NPWT	Negative Pressure Wound Therapy
PP	Per-Protocol
RCT	Randomized Controlled Trial
SSI	Surgical site infections
SWC	Surgical wound complications
TMP-SMX	Trimethoprim-sulfamethoxazole
CMS	Centers for Medicare & Medicaid Services

4 Introduction

Surgical wound complications (SWC) are a dreaded downside to all surgical procedures. Although virtually all types of surgery involve some level of risk for SWC, there is a wide range in terms of their appearance, frequency and severity among different surgical specialties and procedures.

4.1 Normal wound healing

Wound healing is a complex process that is typically divided into overlapping stages. After hemostasis, involving platelet aggregation and fibrin production, the inflammatory phase lasts about six days. Here, inflammatory cells adhere to the fibrin scaffold of which neutrophils clear cellular debris and bacteria by phagocytosis. In the proliferative phase, fibroblasts lay down collagen and glycosaminoglycans and form a core that helps stabilize the wound. Reepithelialization occurs with migration of cells from the wound edges, as well as neovascularization. Once the collagen fibers have been laid down on the fibrin scaffold, the maturation or remodelling phase begins and last up to a year.

4.2 Common surgical wound complications

4.2.1 Lymphatic complications

Lymphatic damage is a well-known complication of surgeries in anatomical areas with traversing lymphatic vessels. One common site in this context is the inguinal area where lymphatics draining the lower limb cross towards the pelvis. Damage to lymph vessels can lead to postoperative leakage (lymphorrhea) or an accumulation of lymphatic fluid (lymphocele). Although often self-limiting, lymphatic leakage can persist for weeks and involve large volumes of fluid that can be difficult to manage on an outpatient basis. It can also disrupt normal wound healing and lead to SSI. If conservative measures fail, wound exploration with ligation of leaking lymph vessels and open wound negative pressure wound therapy become alternative

approaches. Although not always successful, intradermal injection of dyes, such as methylene blue, can be used to track lymph extravasation (Figure 1).

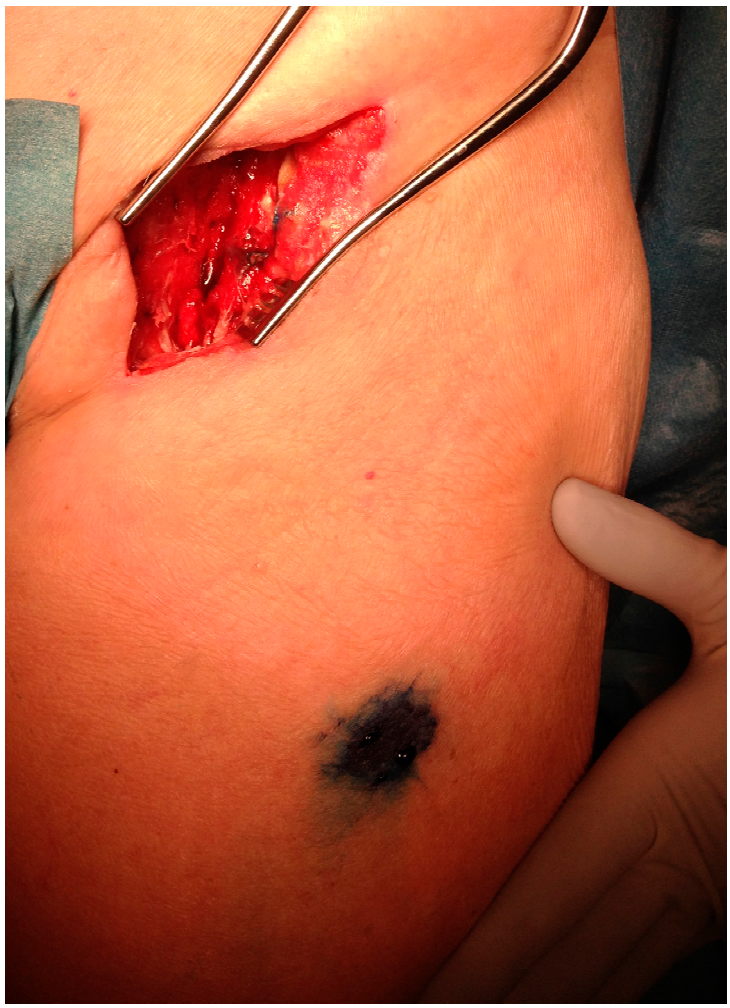

Figure 1. Intradermal methylene blue injection in the thigh to identify bluish discolored lymphatic leakage in inguinal wound

4.2.2 Seroma formation

A seroma is a collection of clear fluid occurring in a potential space (dead space) left after surgical procedures. Although the exact mechanism by which seromas occur is not completely understood, a combination of exudate accumulating in

unadapted tissue layers postoperatively in combination with tissue trauma-associated impaired lymphatic drainage has been postulated. Obliterating dead space with tension sutures upon surgical wound closure has been shown to decrease postoperative seroma formation[1].

4.2.3 Hematoma formation

Hematomas are a common complication after surgical procedures and range from mild discolorations to palpable masses that can exert pressure on surrounding structures causing wound dehiscence and manifest themselves in severe ischemic changes such as skin necrosis. Postoperative hematomas can develop into SSI. Apart from meticulous hemostasis and careful dissection, accurate tissue adaption and dead space obliteration play important roles in its prevention. Although imperfect hemostasis can be seen as the most likely cause in most cases, the increased use of anticoagulation and antiplatelet therapy has led to an increased incidence of wound hematomas (Figure 2)[2].

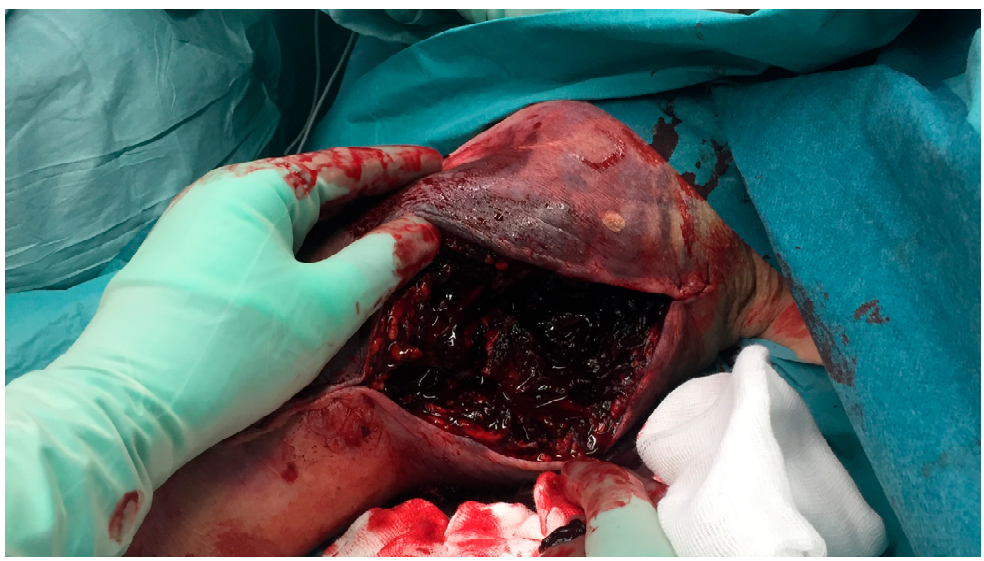

Figure 2. Large hematoma after arteriovenous fistula surgery in the right arm

4.2.4 Wound dehiscence

Surgical wound dehiscence describes the separation of the margins of a closed surgical incision. Wound dehiscence (Figure 3) always involves the skin but can

extend to deeper tissues and affect parts of, or the entire wound length. Several causes for surgical wound dehiscence have been identified and belong to one of three categories: technical issues, such as unravelling of suture knots, mechanical stress, as occurs in wounds overlying joints, and disrupted healing which can occur due to comorbidities or secondary to other wound complications.

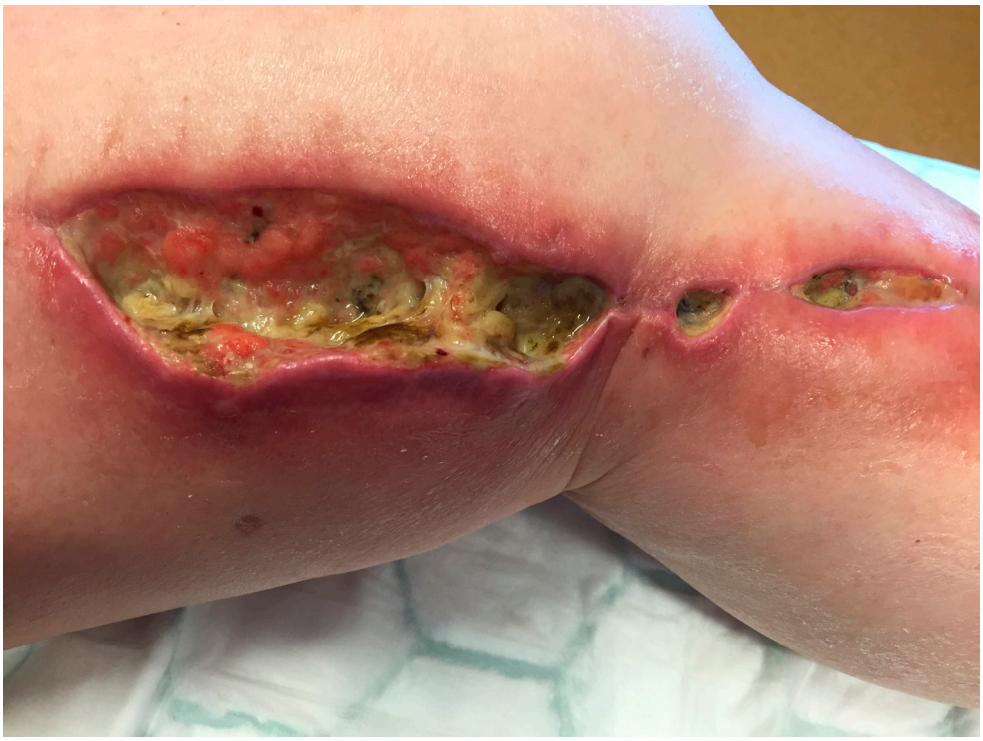

Figure 3. Surgical wound dehiscence after femoropopliteal bypass surgery in the left leg

4.2.5 Surgical site infections

Surgical site infections (SSI) are infections that occur after surgery in the part of the body where the surgery took place (Figure 4).

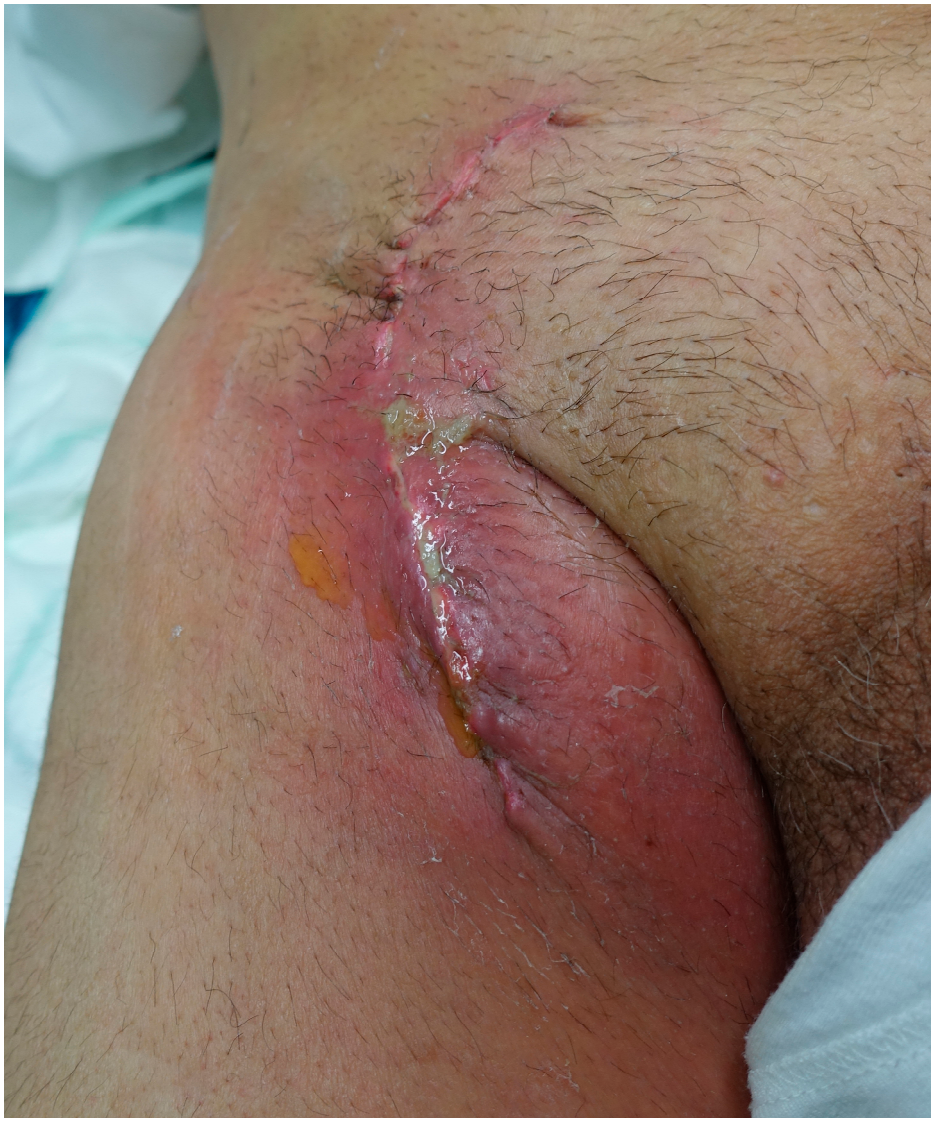

Figure 4. Surgical site infection after right femoral thrombendarterectomy

4.2.5.1 Definitions

One of the most commonly used definitions for SSI, is the one published by the Centers for Disease Control and Prevention (CDC)[3]. According to this definition, SSI are divided into superficial, deep and organ/space (Table 1).

Table 1. Adapted from the CDC classification of surgical site infections

Extent of infection	Mandatory criteria
Superficial	Date of event occurs within 30 days after operative procedure (where day 1 = procedure date) **AND** Involves only skin and subcutanous tissue of the incision **AND** Patient has at least one of the following: a. Purulent drainage from the superficial incision b. Organism identified from an aseptically obtained specimen by culture or non-culture based microbiologic testing c. Superficial incision that is deliberately opened by a surgeon, attending physician* or other designee **AND** patient has at least ***one*** of the following signs or symptoms: localized pain or tenderness; localized swelling; erythema; or heat. d. Diagnosis made by the surgeon, attending physician* or a designee.
Deep	The date of event occurs within 30 or 90 days** after operative procedure **AND** Involves deep soft tissue of the incision (for example fascial and muscle layers) **AND** Patient has at least one of the following: a. Purulent drainage form the deep incision b. A deep incision that spontanously dehisces, or is deliberately opened or aspirated by a surgeon, attending physician* or other designee **AND** Organisms identified by culture or non-culture based microbiologic testing method **AND** patient has at least ***one*** of the following signs or symptoms: fever (>38°C); localized pain or tenderness. c. An abscess or other evidence of infection involving the deep incision on gross anatomical, histopathological exam or imaging test
Organ/Space	Date of event occurs within 30 or 90 days** after operative procedure **AND** Involves any part of the body deeper than the fascial/muscle layers that is opened or manipulated during the operative procedure **AND** patient has at least ***one*** of the following: a. Purulent drainage from a drain placed into the organ/space b. Organisms identified from fluid or tissue in the organ/space c. An abscess or other evidence of infection involving the organ/space that is detected on gross anatomical, histopathological exam or imaging test
* surgeon, infectious disease or other specialist on the case or physician's designee; ** 90 days for peripheral vascular surgery	

An attempt was made by Wilson and colleagues in 1986 to establish an objective and reproducible method of postoperative wound assessment, resulting in the ASEPSIS score, where points are given for the need of **a**dditional treatment, the presence of **s**erous discharge, **e**rythema, **p**urulent exudate, and **s**eparation of the deep

tissues, the **i**solation of bacteria, and the duration of inpatient **s**tay) (Table 2)[4], which today is regarded as one of the most objective means to characterize postoperative wound healing.

Table 2. ASEPSIS score - point scale for daily wound inspection and scoring

Wound characteristic	**Proportion of wound affected (%)**					
	0	<20	20-39	40-59	60-79	>80
Serous exudate	0	1	2	3	4	5
Erythema	0	1	2	3	4	5
Purulent exudate	0	2	4	6	8	10
Separation of deep tissues	0	0	4	6	8	10

ASEPSIS score – Overall scoring

Criterion	**Points**
Additional treatment:	
Antibiotics	10
Drainage of pus under local anesthesia	5
Debridement of wound (general anesthesia)	10
Serous discharge*	Daily 0-5
Erythema*	Daily 0-5
Purulent discharge*	Daily 0-10
Separation of deep tissues*	Daily 0-10
Isolation of bacteria	10
Stay as inpatient prolonged over 14 days	5
* Given score only on 5 of first 7 postoperative days.	

Category of infection: total score 0-10 = satisfactory healing; 11-20 = disturbance of healing; 21-30 = minor wound infection; 31-40 = moderate wound infection; >40 = severe wound infection

A different approach was chosen in a publication by Clavien et al in 1992[5]. Noticing differences in the reporting of surgical complications after cholecystectomy, they stated: “It is our opinion that the lack of standardized reporting of complications and other negative outcomes in the surgical literature greatly hinders interpretation of results.”

A grading system of surgical complications was established that was based on the invasiveness of procedures to treat the respective complication and on its outcome. Table 3 presents its revised version published in 2004 by Dindo and colleagues[6].

Table 3. The Clavien-Dindo classification

Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs such as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIA	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of patient
Suffix “d”	If the patient suffers from a complication at the time of discharge, the suffix “d” (for “disability”) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

* Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks. CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

A well-established classification of vascular surgical SSI with vascular implants is the Szilagyi classification (Table 4), first published in 1972[7]. The authors classified SSI similarly to today’s CDC classification by the depth of the tissues involved.

The consequence of a Szilagyi grade III infection can be the formation of pseudoaneurysms (Figure 4a and b) and severe bleeding.

Table 4. Szilagyi classification of SSI after vascular reconstructions with arterial implant

Classification	**Depth of involvement**
Grade I	Dermis only
Grade II	Subcutaneous
Grade III	Arterial implant

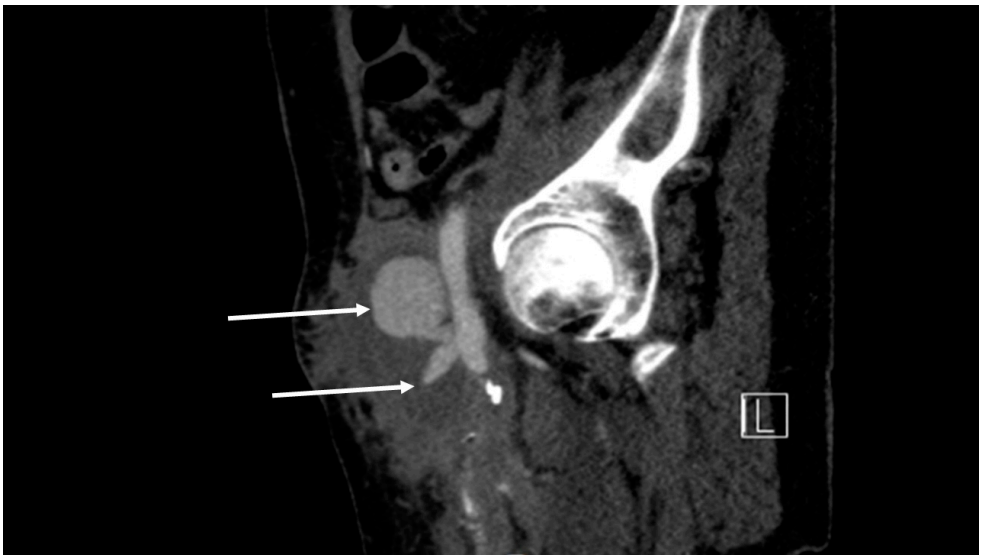

Figure 4a. Pseudoaneurysm formation characterized by contrast extravasation (arrows) after thrombendarterectomy

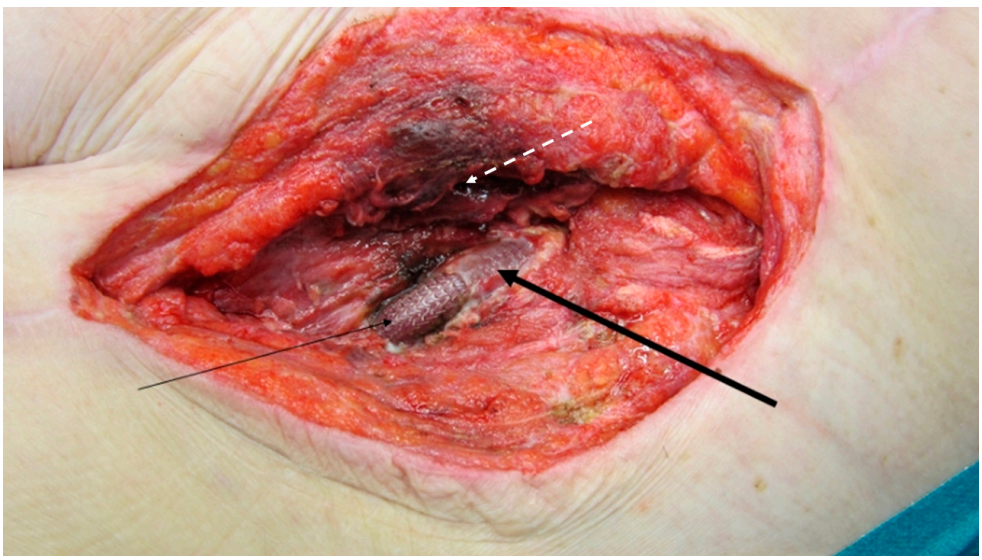

Figure 4b. Szilagyi grade III SSI after left-sided thrombendarterectomy of the common and deep femoral arteries with bovine patch plasty. The patient presented three months postoperatively with fever, shivering and pain in the left inguinal region. C-reactive protein concentration was 130 mg/L, blood cultures showed growth of Staphyococcus lugdunensis and antibiotic therapy was initiated with cloxacillin. Computed tomography angiography (CTA) (Figure 4a) revealed a large femoral pseudoaneurysm. The patient underwent an EndoVac procedure where a large part of the artery, including the disrupted patch and patch anastomosis area, was lined with stentgrafts followed by surgical debridement of the wound and open NPWT. The distal part of the patch was completely dissolved at the first dressing change exposing the stentgraft (thin arrow), leaving a part of the patch visible in its proximal aspect (thick arrow). Signs of hematoma remain visible (interrupted arrow) on the medial side of the wound.

4.2.5.2 Perioperative measures for SSI prevention

The World Health Organization (WHO) released recommendations for perioperative measures to prevent SSI[8,9] and categorized them as strong or conditional, as well as characterizing their scientific foundation as high, moderate, low or very low.

Strong recommendations (quality of evidence) were, among others, decolonization of nasal carriers of Staphylococcus aureus undergoing cardiothoracic and orthopedic surgery (moderate), preoperative hair removal only in necessary cases and only with clippers (moderate), administration of antibiotic prophylaxis within 120 minutes before incision (moderate), surgical hand preparation by scrubbing with antimicrobial soap or alcohol-based hand rub before donning sterile gloves (moderate), usage of chlorhexidine gluconate solutions for surgical skin preparation (low to moderate), usage of high fraction of inspired oxygen (moderate) and to refrain from prolonged antibiotic prophylaxis postoperatively (moderate). Although bundle of care approaches to reduce SSI have shown promising results[10], compliance with these guidelines has been found to be poor[11].

4.2.6 Abnormal scar formation

Although mechanical stress is required for normal wound healing and accelerates the gain in tensile strength, it can also have a negative impact on scar formation.[12] This is especially true for areas overlying joints, such as the scapular and inguinal regions[13]. Hypertrophic scars can cause significant distress due to poor cosmetic appearance, pruritus, pain and contractures.

4.3 Risk factors for surgical site complications

In their consensus document, the World Union of Wound Healing Societies (WUWHS) summarized general risk factors for SWC and identified major risk factors that individually pose a high risk for SWC (Table 5)[14].

Table 5. General risk factors for surgical site complications

Category	Patient-related risk factors	Procedure-related risk factors
Major risk factors	BMI ≥ 40 kg/m^2 or ≤18 kg/m^2	Extended duration of surgery*
Presence of 1 = high risk of surgical site complication	Uncontrolled insulin-dependent diabetes mellitus	Emergency surgery
	Renal dialysis	Hypothermia
Moderate risk factors	ASA Physical Status > II	Anemia/blood transfusion
Presence of ≥ 2 = high risk of surgical site complication	Age <1 year or >75 years	High wound tension after closure
	BMI 30-39.9 kg/m^2	Dual antiplatelet treatment
	Diabetes Mellitus	Suboptimal timing or omission of prophylactic antibiotics
	Chronic obstructive pulmonary disease ≥ GOLD class 2	Tissue trauma/large area of dissection/large area of undermining
	Renal insufficiency/chronic kidney disease	
	Immunosuppression	
	Steroids for a chronic condition	
	Chemotherapy	
	Pre-existing infection at a body site remote from operative site	
	Serum albumin <2.5 g/dl	
	Smoking (current)	
Minor risk factors	African or African-American race	Failure to obliterate dead space
Presence of any = increased risk of surgical site complications	BMI 25-29.9 kg/m^2	Location of incision
	Extended pre-operative hospitalization or residency in a nursing home	Previous surgery
	Peripheral vascular disease	Surgical drains
	Congestive heart failure with left ventricular ejection fraction <30%	

*Defined as >T (hours) which is dependent of the type of surgical procedure, and is the 75th percentile of duration of surgery for a particular procedure, eg coronary bypass graft has a T of 5 hours and cesarian section has a T of 1 hour

Table shown with permission from the World Union of Wound Healing Societies

4.4 Negative Pressure Wound Therapy

Negative Pressure wound therapy (NPWT) is a technique by which wounds are subjected to a suction device removing fluid and cellular debris. Although variants of this technique have, among others, been described in 1952 after radical mastectomies[15] and in 1993 after open fractures[16], it wasn't until the collaboration of plastic and reconstructive surgeon Louis C. Argenta MD and biomedical engineer Michael J. Morykwas, PhD, that Vacuum Assisted Closure (VAC)[17,18] or NPWT developed and became commercially available in 1995. Since then, the technique has been used for various indications, spanning from acute to chronic wounds.

4.4.1 Mechanism of action

Most of the research related to NPWT has at this point been done on open wounds, where the technique facilitates wound healing by secondary intention (Figure 5a-c). Although the exact mechanisms of NPWT on wound healing remain an active area of research, some basic concepts have been elucidated.[19]

Macrodeformation – As the polyurethane foam in the wound is subjected to 125 mmHg of suction, the foam volume is reduced creating an approximation of the wound edges in all three dimensions, thereby causing the wound to contract.

Microdeformation – Mechanical forces induce cellular proliferation and angiogenesis[20]

Stabilization of the wound environment – The semiocclusive polyurethane drape covering creates a barrier with limited permeability to gases and water vapor and impermeability to proteins and microorganisms, while maintaining a moist wound environment. A moist wound environment is an important prerequisite for normal wound healing as it promotes epithelialization of the wound surface.

Decreasing edema – Evacuating excess fluid from the wound tissues decreases edema, clears out cellular and microbial debris and aids wound healing.

Formation of granulation tissue – The formation of the highly vascularized granulation tissue is part of the proliferative phase of wound healing and is expedited by NPWT.

Microvascular blood flow – Decreased microvascular blood flow 0.5cm from the wound edges and increased microvascular blood flow 2.5 cm from the wound edges have been observed[21] and could aid in wound healing.

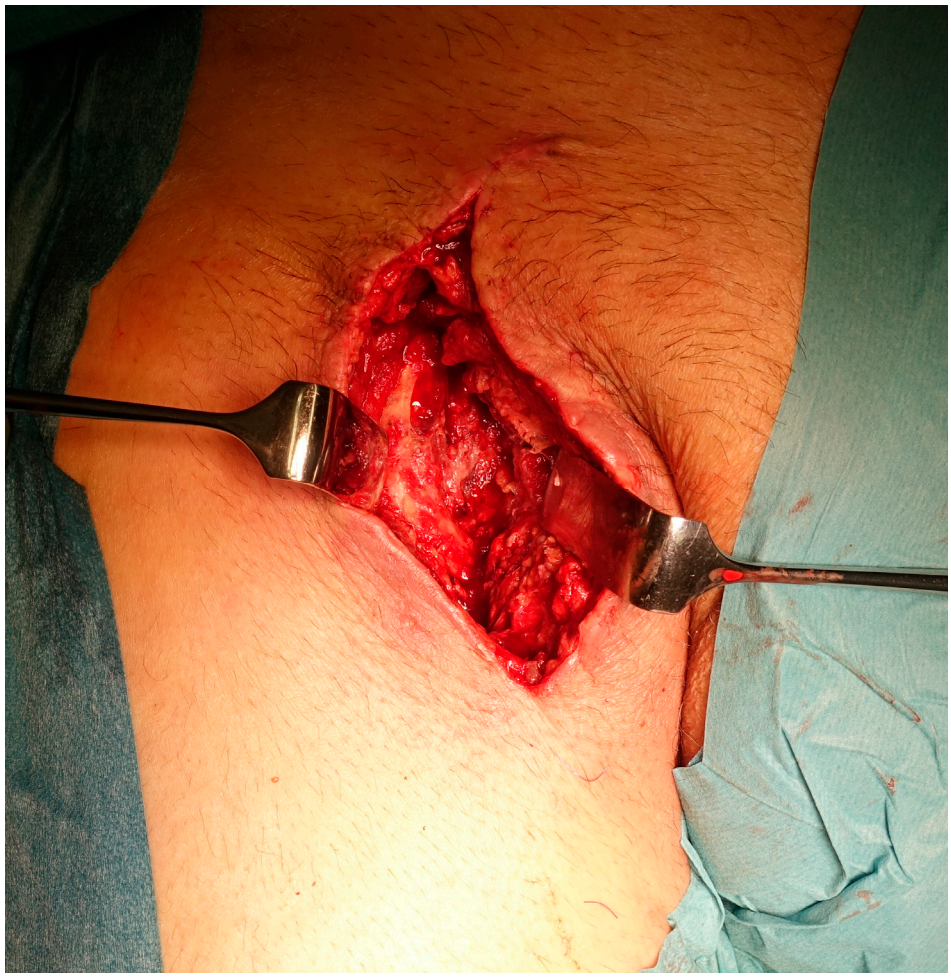

Figure 5a. An infected inguinal wound after removing skin and subcutanous suture material and wound debridement.

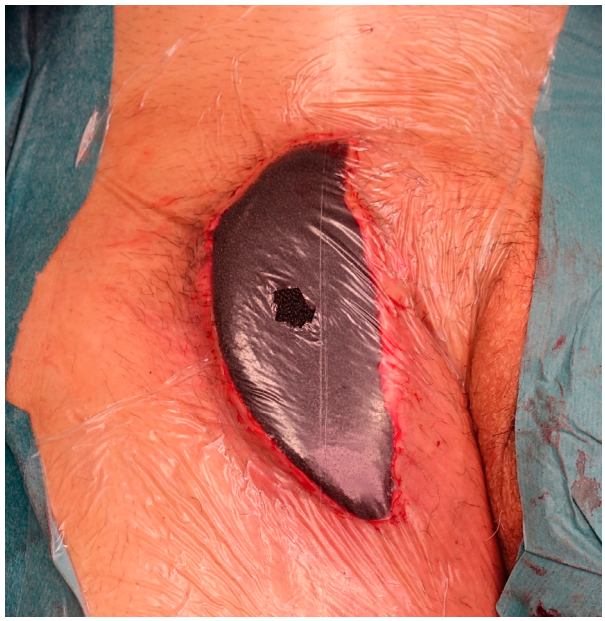

Figure 5b. After wound debridement, size-adjusted foam is placed in the wound, the wound area covered with adhesive plastic drape that is incised to enable communication with the vacuum pump.

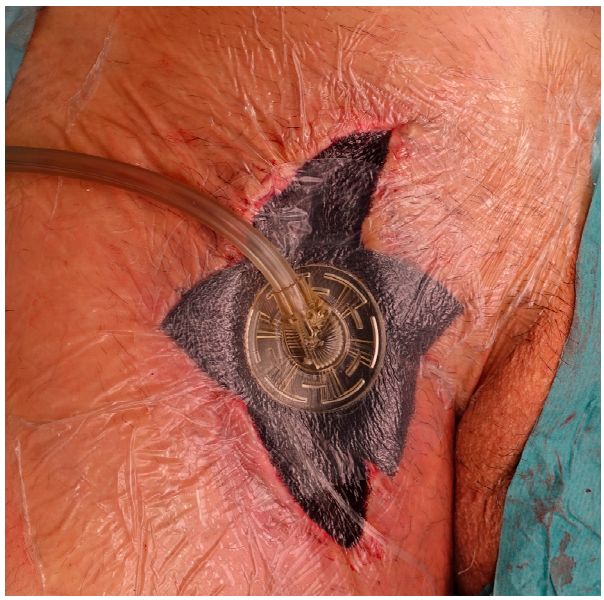

Figure 5c. An optional piece of foam is placed over the plastic drape gap to prevent the suction pad from damaging the wound edges. After adding another layer of plastic drape and creating another incision, the suction pad and tubing connect the system to the vacuum pump.

4.5 Incisional Negative Pressure Wound Therapy

A newer development within NPWT is its application on closed surgical incisions to aid wound healing by primary intention.

The so called incisional NPWT entails placing a multi-layered dressing on conventionally sutured surgical incisions. Active suction, generated by a battery-powered pump, is then applied to the dressing through flexible tubing.

As some of the effects elucidated for open wound NPWT, such as increased granulation tissue formation and macrodeformation, seem less relevant in wounds with approximated wound edges, other effects have been explored. Fluid removal across the wound edges, an enhanced draining capacity of the lymphatic system[22], as well as decreased biomechanical stress on the suture lines[23] and microvascular perfusion changes[24], have been described.

Two of the most common commercially available incisional NPWT systems are the PICO (Smith & Nephew, London, UK; Figure 6a and b), utilized in paper III, and the Prevena (Acelity/KCI, San Antonio, Texas; Figure 7) systems.

Both systems utilize a continuous negative pressure regime that is pre-set to last seven days. The main difference between these devices is that the PICO system uses a canister-free approach and is disposable. Its pump is connected to a four-layer absorbent dressing with an in vitro estimated[25] fluid management capacity of up to 200 mL per week, eliminating fluid predominantly by evaporative loss. The Prevena system, on the other hand, can, if required, collect large amounts of fluid by either replacing the 45-mL canister or attaching the device to a pump with a larger canister. In addition, the Prevena system uses a two-layer dressing that consists of an inner silver-impregnated polyurethane-coated layer and an outer polyurethane foam layer with large pore-sizes, designed to drain fluid. Whereas the PICO system has a pre-set unadjustable negative pressure effect of -80 mmHg, the Prevena system is set to -125 mmHg[26].

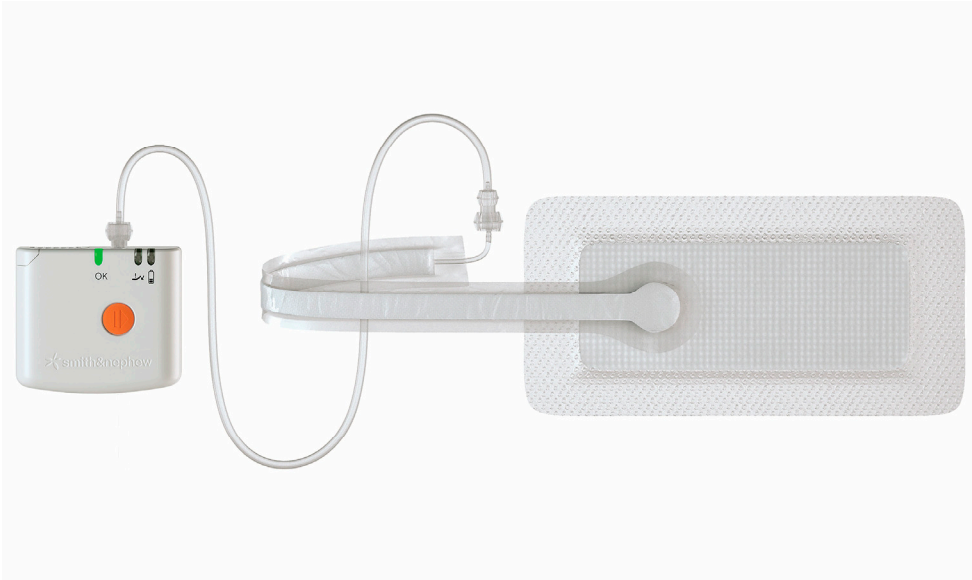

Figure 6a. PICO Incisional Negative Pressure Wound Therapy system (Smith & Nephew, London, UK)

Figure 6b. Layers of the PICO-system from down to up: wound contact layer with perforated flexible adhesive silicone, air lock layer, fluid absorption layer and high vapor transmission rate film layer

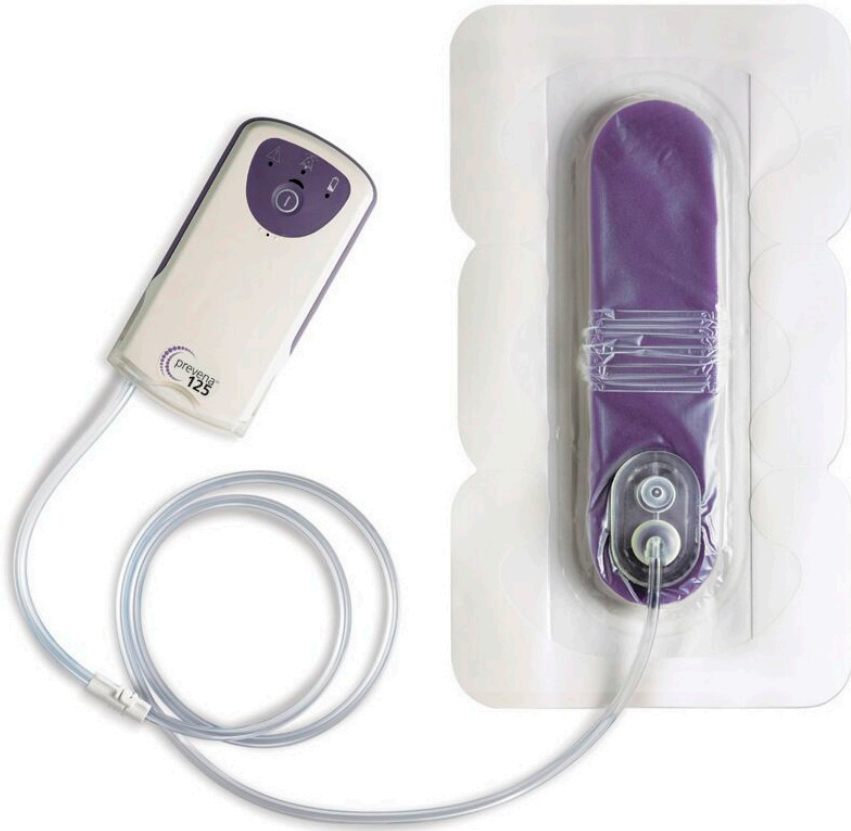

Figure 7. Prevena incisional management system consisting of an inner silver-impregnated polyurethane-coated layer and an outer polyurethane foam layer (Acelity/KCI, San Antonio, Texas)

5 Aims of the thesis

Surgical site complications are a potential risk for all surgical procedures. Peripheral vascular surgery, which often is performed on individuals with significant comorbidity, is no exception. The overall purpose of this thesis was to explore ways to decrease the frequency of surgical wound complications and to classify them in a meaningful, simple and comprehensive way.

Specific aims:

1. To compare the infection rates of vascular surgical inguinal incisions after changing the prophylactic antibiotic regime from Cloxacillin to Trimethoprim-Sulfamethoxazole.
2. To evaluate the effects of incisional negative pressure wound therapy on surgical wound complications after vascular surgical procedures with inguinal incisions.
3. To propose a classification of surgical wound complications that reflects meaningful clinical information.
4. To evaluate if surgical site infections carry a more profound morbidity than other surgical wound complications and therefore deserve the focus they have enjoyed thus far.

6 Patients and methods

6.1 Ethics and clinical trial registration

Paper I was considered a clinical quality follow-up study and therefore exempted from ethical research board approval. The randomized controlled trial (RCT) (papers II and III) was approved by the research ethics board of Lund University and registered at the US National Institutes of Health at ClinicalTrials.gov (registration number NCT01913132). Paper IV analyzed data derived partially from the RCT but also from non-randomized patients, where data collection fell under the ethical conditions of clinical quality follow-up studies.

6.2 Setting

Patients of all four papers were treated at Vascular Center, Malmö, Skåne University Hospital, a tertiary referral center in Scania, the southernmost province of Sweden, with a primary catchment population of 800,000 inhabitants. The center carries out around 300 open and 1100 endovascular procedures annually.

6.3 Overview of the studies

Table 6. Overview of study designs and patients

Paper	Design	n patients	Procedure timing	Timeframe
I	Retrospective cohort study	219	Acute/elective	2012-2013
II	Clinical Trial Design paper	Not applicable	Elective	Since 2013
III	Randomized controlled trial	139	Elective	2013-2018
IV	Cohort study	223	Elective	2013-2019

6.4 Data Collection

Data collection was comparable across the different studies. Baseline data concerning previous medical and surgical history, medication and perioperative data

were extracted from the hospital´s electronic data systems. Transfusion data was made available upon request by the central transfusion registry.

6.5 Definitions

SSI were defined by the Centers for Disease Control and Prevention in papers I-III. In paper III the ASEPSIS score criteria were added and used exclusively in paper IV.

Conventional or standard wound dressings referred to wound dressings other than NPWT dressings.

6.6 Perioperative routines

All studies shared the same standard routines for perioperative care in elective patients.

6.6.1 Patient and surgical site preparation

Patients were instructed to carry out two double showers separated by a four-hour interval with an antiseptic agent containing chlorhexidine gluconate two days and one day preoperatively according to the manufacturer's instructions. Patients were admitted one day preoperatively where they received fresh hospital gowns and a bed with clean drapes.

In the operating room, the surgical site was prepared by trimming hair with an electrical surgical clipper, washing the operating field with a 4% chlorhexidine gluconate solution followed by disinfection with chlorhexidine gluconate 5mg/ml. Surgical draping was applied after the disinfected had been permitted to dry completely. All patients undergoing open vascular surgical procedures involving the lower limb received antibiotic prophylaxis. Following wound closure, a final disinfection with chlorhexidine solution 2mg/ml was carried out before application of the wound dressing.

6.6.2 Surgical wound care

Conventional wound dressings were left in place for at least 48 hours postoperatively. Had they to be removed prior to that, this was done using sterile

technique. New routines were introduced in the fall of 2018 by which the wound dressings were left in place for at least one week as is the case with NPWT dressings.

6.7 Wound surveillance

The already well-established outpatient routines, guided by the Swedish Vascular Registry's (Swedvasc) requirements, were used in all studies to monitor wound healing. Hospital visits in the entire province and wound cultures requested by all the province's health care institutions were viewed in the patient's electronic journal.

6.8 Statistics

In case of two ordered groups, differences in proportion were analyzed using Chi-squared or Fisher's exact test, continuous variables expressed in median and interquartile range, and group differences with the Mann-Whitney U test. In case of more than two ordered groups (paper IV), differences in proportion were analysed using linear-by-linear association and Jonckheere-Terpstra test for analyzing group differences of continuous variables. Bilateral incisions were treated as dependent entities and analyzed using McNemar's test for paired data (papers II/III). The obtained p-values from the uni- and bilateral incisions were subsequently combined using Fisher's method for combining p-values. P-values <0.05 were considered significant.

In paper IV, rank correlation between ordinal variables were analyzed using Spearman's rank correlation coefficient. Wilcoxon signed-rank test was used to compare repeated measurements of ordinal data. Inter-rater and test-retest reliability were assessed using Cohen's Kappa coefficient. As a rule of thumb, Kappa coefficients were interpreted as follows: values ≤ 0 indicating no agreement, 0.01-0.2 as none to slight, 0.21-0.4 as fair, 0.41-0.6 as moderate, 0.61-0.8 as substantial and 0.81-1 as almost perfect agreement.

Floor or ceiling effects in paper IV were assessed by calculating the percentage of patients receiving the lowest or highest grades possible. The presence of a floor or ceiling effect was defined as >15% receiving the lowest or highest grades possible, respectively.

6.9 Methods – Study I

All patients undergoing vascular surgery with inguinal incisions between March 1 and June 30 in 2012 (group A) and 2013 (group B) were included. Between these time periods, a change in antibiotic prophylaxis from cloxacillin to trimethoprim/sulfamethoxazole (TMP-SMX) was carried out (Figure 8). Patients in group A were routinely given three doses of cloxacillin 2g intravenously, where the first dose was administered at the induction of anesthesia, the second after three and the third after seven hours. Patients in group B were given TMP-SMX 800/160 mg once orally in the morning of the procedure in elective and 800/160 mg intravenously 30-60 min preoperatively in acute procedures (Table 7). Patients with known allergy to sulfa-containing drugs, received cefotaxime 1g intravenously 30 minutes prior to the operation.

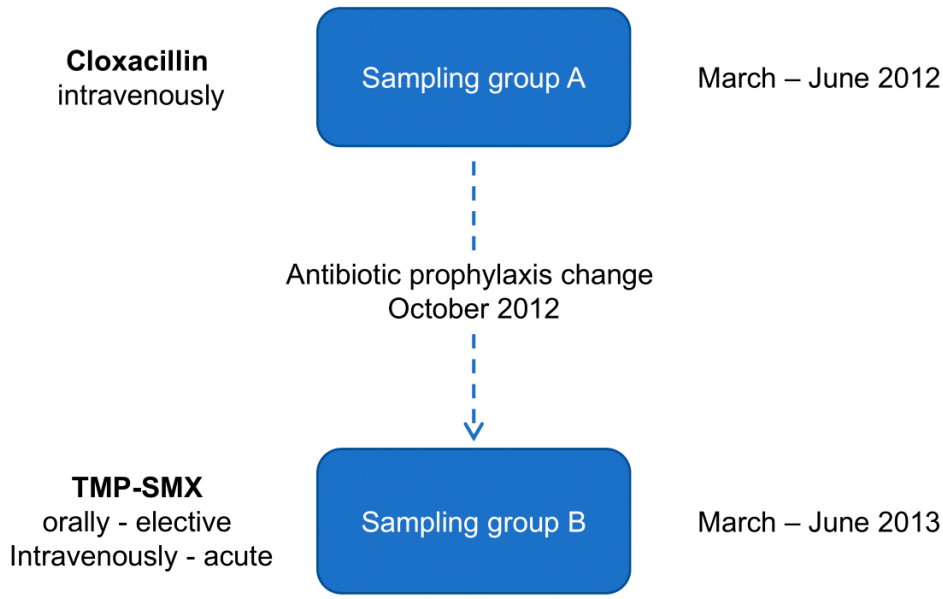

Figure 8. Overview of study design

Table 7. Comparison of antibiotics used

	Cloxacillin	**Trimethoprim/Sulfamethoxazole**
Antibiotic class	Penicillinase-resistant penicillin	Sulfonamide/dihydrofolate reductase inhibitor
Mode of action	Disrupts bacterial cell wall synthesis	Inhibits folate synthesis
Half-life ($t^{1/2}$)	30 minutes	10-12 hours
Antimicrobial spectrum	Gram postive Cocci except Enterococcus faecalis; Staphylococci except MRSA; gram positive anaerobes.	Streptococci, Staphylococci including MRSA, intestinal flora bacteria
Price ($) per dose	18.46 (intravenous)	0.86 (tablets)

6.10 Methods – Study II and III

All adult patients undergoing elective vascular surgical procedures with inguinal incision were eligible to participate. Randomization took place at the outpatient clinic and the randomization result was effectuated by the scrub nurses at the end of the procedure. In unilateral cases, patients could either receive NPWT or the standard dressing. In bilateral cases (Figure 9), the randomization result (NPWT or standard dressing) was always applied to the right inguinal incision and the left incision received the opposite dressing.

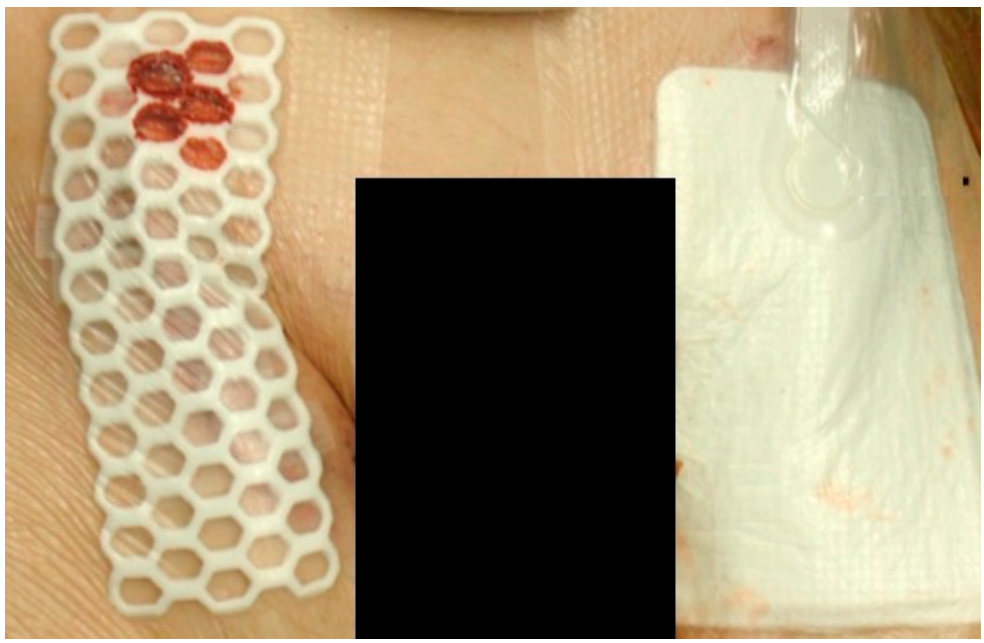

Figure 9. Open vascular procedure with bilateral incisions, randomized to standard dressing (OPSITE postop visible in this case) which was applied to the right incision wheras the left incision received the opposite dressing type, NPWT.

Exclusion criteria were inability to comprehend the study or give written consent as well as ongoing inguinal infections. Data for the power calculation stemmed from a reanalysis of patients in group B, paper I, focusing on elective procedure outcomes only. Due to their vastly different risk profiles for wound complications, two vascular surgical procedure groups were defined (Table 8). The OPEN-group consists of open vascular surgical procedures such as femoral thrombendarterectomy, aortofemoral and peripheral bypass operations, and the EVAR-group of patients undergoing endovascular aortic repair (EVAR) with open access-closure technique such as fascial or direct arterial suturing. Paper III reports the outcome of patients in the OPEN arm of the INVIPS-Trial.

Statistical analysis was performed on an intention-to-treat (ITT) basis, requiring the surgical wound to be covered with the correct type of wound dressing at the end of the procedure, in order for the incision to qualify to be included in the analysis.

Table 8. Characteristics of the two arms of the INVIPS trial

		EVAR		OPEN	
		Unilateral	Bilateral	Unilateral	Bilateral
		20%	80%	76%	24%
Procedural characteristics[1]	**SSI rate**	4.4%		30%	
	Orientation of incision	Mostly horizontal		Mostly vertical	
	Median operating time (Range)	214 (536)		178 (321)	
	Surgical wound exposure	At end of the procedure		During entire procedure	
	1-year mortality	6.7%		0%	
Power calculation[2]	**n assuming only bi/unilaterality**	750	340	138	120
	n as weighted average based on laterality proportion	422		134	
	n including estimated loss to follow-up due to mortality	452		134	
	n + 10% for other loss to follow-up	497		147	

[1] based on earlier data collection, [2] n= required number of groin incisions, EVAR indicated endovascular aortic repair, SSI, surgical site infections

6.10.1 Wound dressings

Although the study was planned as a comparison between one NPWT (PICO) and one conventional dressing (VitriPad), one other conventional dressing was used during the study period (OPSITE Post-Op Visible) (Table 9).

Table 9. Comparison of the wound dressings used

	NPWT	Conventional	
	PICO	Vitri Pad	OPSITE Post-Op Visible
Material	4-layer, non-transparent, semipermeable, water-resistant	2-layer, non-transparent semipermeable, waterproof	3-layer, transparent, semipermeable, waterproof
Fluid absorbance	high	low	high
Wound visibility	None	None	Partially visible
Manufacturer	Smith and Nephew	ViTri Medical	Smith and Nephew

Specifications according to the manufacturer's product information

6.11 Methods – Study IV

Adult patients who had undergone elective peripheral vascular surgery were extracted from the OPEN arm of the INVIPS Trial, including non-randomized cases, and included in the study. The study was comprised of patients undergoing surgery between November 2013 and February 2019, and thereby also included patients operated after the completion of the INVIPS Trial inclusion period. All unilateral cases with lower extremity vascular wounds were evaluated. SWC were graded by three different physicians at one and four months postoperatively. The result of the grading of the principle investigator was presented in this study whereas the grading of all three raters served to establish data on test-retest and inter-rater reliability.

6.11.1 Definitions

An ASEPSIS score >10 was used to define disturbed wound healing, >20 to characterize SSI. Surgical wound morbidity was defined as length of wound complication-related in-hospital stay. Prolonged inpatient treatment was defined as being more than twice the median time for the same type of procedure. In the current study, this applied to inpatient times of more than ten days for TEA and more than 16 days for bypass procedures.

6.11.2 Proposed classification of surgical wound complications

Grade 0	Normal surgical wound healing without unplanned visits to health care institutions
Grade 1	SWC requiring at least one additional visit to any outpatient treatment facility without additional inpatient treatment
Grade 2	Prolonged inpatient treatment at least partially due to wound complications, defined as more than twice the median time for the same type of procedure
Grade 3	Readmission due to SWC after discharge from the index procedure, without invasive wound treatment, except initiation of open wound NPWT or other dresings without wound revision or intensive care
Grade 4	Readmission due to SWC after index procedure with surgical wound revision
Grade 5	SWC requiring intensive care or leading to severe complications such as major amputation due to SWC
Grade 6	Fatal outcome due to SWC

6.11.3 Wound grading

Wound grading was conducted at one and four months postoperatively.

6.11.4 Inter-rater and test-retest reliability

Three raters consisting of one vascular surgical specialist, one vascular surgical resident and one medical intern each received a data file containing patient identification number, procedure date and type of procedure. In addition, they received instructions for use outlining the SWC grading system (Figure 10). After completed grading of the surgical wounds at one and four months, the files were merged and the data evaluated.

Surgical Wound Complication Classification - INSTRUCTIONS FOR USE		
Grade	Description	
0	No complication	
1	Complication requiring outpatient treatment	Surgical wound complication that requires at least one extra visit at any outpatient clinic due to wound issues without the need for inpatient treatment. Included in this category is open wound NPWT started in outpatient setting. Open NPWT started in the operating room is classified as grade 4.
2	Complication requiring prolonged inpatient treatment	Inpatient stay prolonged to more than twice the median time* for the same type of procedure due to a surgical wound complication.
3	Readmission with conservative treatment	Readmission due to surgical wound complication after discharge from primary operation **without** invasive treatment of the wound, active opening of the wound edges, open wound NPWT treatment initiated in OR and intensive care. Open NPWT treatment initiated in the ward falls under this category.
4	Readmission with invasive treatment	Readmission due to surgical wound complication after primary operation with wound revision including open NPWT treatment initiated in OR.
5	Major wound-related complication	Major amputation due to a surgical wound complication, surgical wound complication requiring intensive care.
6	Death	Mortality secondary to surgical wound complication.

Assessment entails the time period at one and four months postoperatively. In case the patient dies before four months postoperatively, the worst grade reached to the point of death is registered. *Median inpatient stay in days: thrombendarterectomy (TEA) = 5, femoropopliteal bypass 8; NPWT indicates negative pressure wound therapy

Figure 10. Surgical wound complication classification - Instructions for use

7 Results

7.1 Results - Study I

7.1.1 Brief summary of main findings

I. No difference in SSI rate was observed between patients receiving TMP-SMX compared to cloxacillin as their antibiotic prophylaxis (Table 10).

II. Despite coverage of intestinal flora bacteria, TMP-SMX did not lead to isolation of fewer intestinal flora bacteria from cultured wounds (Table 11).

Table 10. Patients, procedures and outcomes

	2012, n (%)	2013, n (%)	p
Primary antibiotic prophylaxis	Cloxacillin	Trimethoprim/Sulfamethoxazole	
n (patients)	105	114	
Median age (IQR) in years	71 (66-76)	72 (66-78)	.41
Female sex	35 (33)	31 (27)	.32
Median body mass index (IQR)	26.5 (23.5-30.2) (n=100)	25.8 (23.5-28.4) (n=108)	.41
Acute/elective surgical procedure	31:74	34:80	.96
EVAR/TEVAR	67 (64)	71 (62)	.82
Femoral thrombendarterectomy	25 (24)	28 (25)	.90
Femoral bypass	16 (15)	13 (11)	.40
Length of procedure (IQR) in minutes	200 (120-270)	178 (124-263)	.47
Length of procedure >220 minutes	44 (42)	38 (33)	.19
Concomitant foot ulcer	11 (10)	12 (11)	.99
Diabetes mellitus	25 (24)	24 (21)	.63
>2 units pRBC perioperatively until 7 days postoperatively	46 (44)	40 (35)	.19
Prolonged antibiotic prophylaxis	8 (8)	12 (11)	.46
Patients with resistent isolates in regards to antibiotic prophylaxis	12/18 (67)	6/14 (43)	.18
Groin infections	20 (19)	20 (18)	.77
Acute/elective surgical procedure	4/16	2/18	.38
Superficial/deep infection	14/6	16:4	.47
Sythetic graft infection	0	1	-
Concomitant foot ulcer	4 (20)	5 (25)	.70
Intestinal flora	12/18 (67)	13/16 (81)	.34
Staphylococcus aureus	7/18 (39)	4/16 (25)	.39

Abbreviations: IQR, interquartile range; EVAR, endovascular aortic repair; TEVAR, thoracic endovascular aortic repair; pRBC, packed red blood cells.

Table11. Microbiological isolates

Antibiotic prophylaxis	2012, N Cloxacillin	2013, N Trimethoprim/Sulfamethoxazole
Skin flora		
Staphylococcus aureus	12	10
MRSA	0	0
Staphylococcus epidermidis	1	
Staphylococcus species	1	
Streptococcus	2	2
Skin flora total	**16**	**12**
Intestinal flora		
Enterococcus faecalis	8	5
Enterococcus faecium	2	3
Enterococcus species	1	3
VRE	0	0
Pseudomonas aeruginosa	2	3
Proteus mirabilis	3	2
Escherichia coli	2	3
Enterobacter cloacae	1	3
Enterobacteroaceae	4	
Klebsiella pneumoniae	1	2
Enterobacter aerogenes	1	
Serratio marcescens	1	
Intestinal flora total	**26**	**24**
Anaerobic bacteria		
Bacteroides fragilis		2
Enterococcus species	1	3
Faecal flora	1	
Mixture of flora	1	
Anaerobic bacteria total	**3**	**5**
Fungi		
Candida		2
Total number of isolates	**44**	**40**

MRSA indicates Methicillin-resistant Staphylococcus aureus; VRE = Vancomycin-resistant Enterococcus

7.2 Results - Study II-III

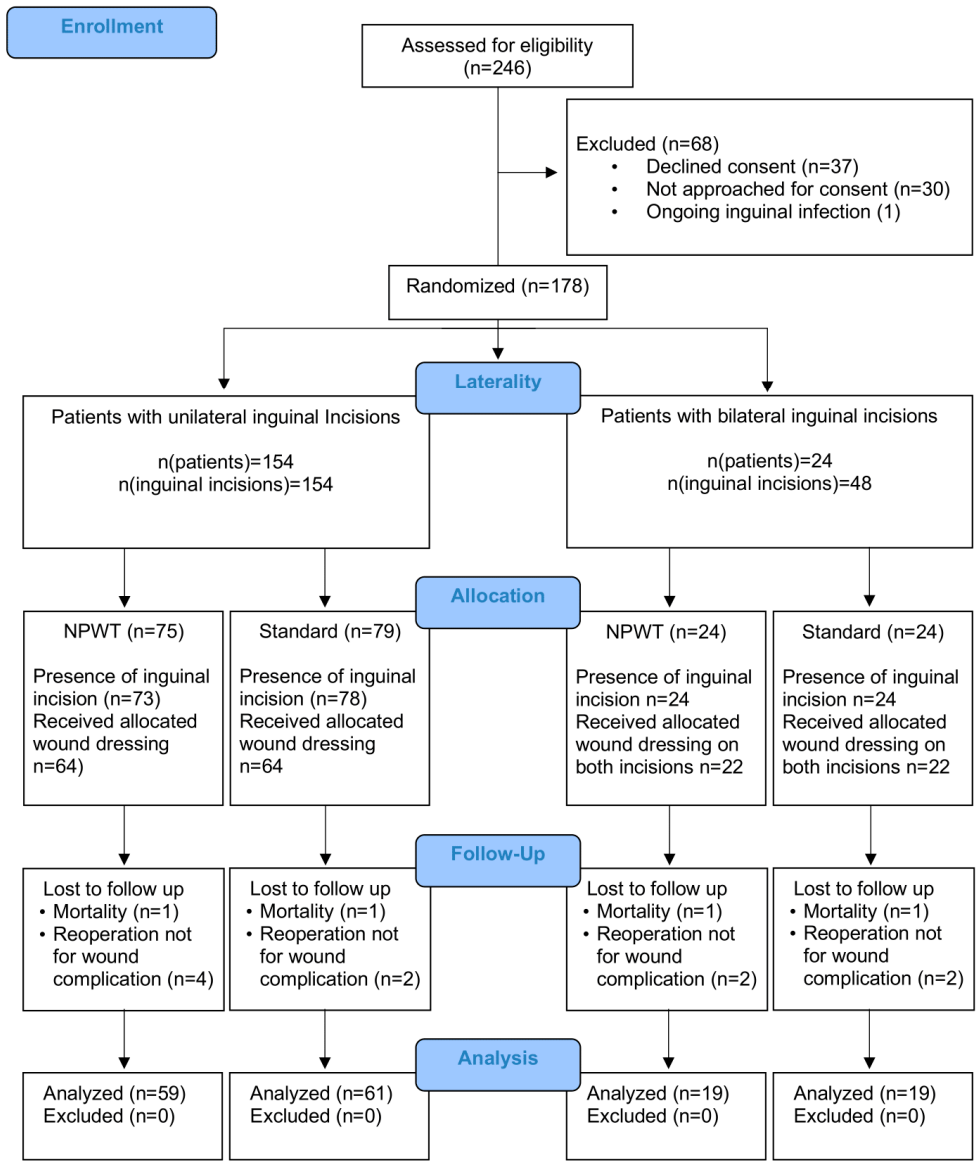

Figure 11. OPEN arm of INVIPS Trial - Consort diagram

7.2.1 Brief summary of main findings

I. A lower rate of SSI was observed in patients in the NPWT group compared to the control group.

II. No difference in the rate of other surgical wound complications was detected between the NPWT and the control group.

7.2.2 Patient characteristics

Of 246 patients screened for eligibility, 178 patients were randomized between November 2013 and October 2018 with the 90-day follow-up completed by December 2018. One hundred twenty patients with unilateral and 19 with bilateral incisions were included in the analysis (Figure 11, Table 12, Table 13).

7.2.3 Outcomes

At 90 days follow-up, SSI among patients with unilateral incisions was observed in seven (11.9%) patients in the NPWT group according to both ASEPSIS score and CDC criteria, whereas it was diagnosed in 18 patients using the ASEPSIS score (29.5%, $p = 0.024$) and in 17 patients according to CDC criteria (27.9%, $p = 0.039$) in the control group. In the bilateral group, SSI was recognized in both incisions in one patient and on the standard dressing side only, in four cases (5.3% vs 26.3%, $p = 0.125$), (Table 14). After combining p-values from the analysis of the uni- and bilateral groups, a SSI rate reduction was observed in the NPWT group compared with the control group using both ASEPSIS score ($p = 0.02$) and CDC criteria ($p = 0.03$). Among patients not participating in or excluded from the trial, SSI as per CDC criteria was observed in 28 of 88 (31.8%) incisions at follow up.

Table 12. OPEN arm of INVIPS Trial – Baseline characteristics

	Unilateral			
	NPWT	**Standard**	**Bilateral**	
Patients	n = 59	n = 61	n = 19	
Median age in years (IQR)	72 (9.5)	70 (11.6)	73.2 (10.1)	
Male sex (%)	44 (74.6)	44 (72.1)	13 (68.4)	
Cerebrovascular disease (%)	11 (18.6)	12 (19.7)	3 (15.8)	
Arterial hypertension (%)	46 (78.0)	51 (83.6)	16 (84.2)	
Ischemic heart disease (%)	26 (44.1)	25 (41)	6 (31.6)	
Median BMI in kg/m^2 (IQR)	26 (6.8)	26.4 (5.2)	25.2 (8.5)	
Smoker current/previous (%)	16 (27)/36 (61)	19 (31)/37 (61)	6 (32)/13 (68)	
Previous vascular surgery (%)	18 (30.5)	27 (44.3)	6 (31.6)	
Atrial fibrillation (%)	12 (20.3)	7 (11.5)	2 (10.5)	
Diabetes mellitus (%)	19 (32.2)	22 (36.1)	3 (15.8)	
Medication (%)				
Anticoagulation	10 (16.9)	8 (13.1)	3 (15.8)	
Aspirin	41 (69.5)	49 (80.3)	16 (84.2)	
Steroids	6 (10.2)	4 (6.6)	0 (0)	
			NPWT	**Standard**
Ipsilateral inguinal surgery (%)	18 (30.5)	16 (26.2)	8 (42.1)	6 (31.6)
Ipsilateral foot wound	20 (33.9)	12 (19.7)	2 (10.5)	3 (15.8)
Indication (%)				
Lower leg ischemia				
Claudication	32 (54.2)	31 (50.8)	13 (68.4)	
Critical limb ischemia	22 (37.3)	19 (31.1)	6 (31.6)	
Rutherford class				
0	0 (0)	2 (3.6)	0 (0)	
1	1 (1.8)	3 (5.4)	0 (0)	
2	9 (15.8)	12 (21.4)	4 (21.1)	
3	13 (22.8)	8 (14.3)	7 (36.8)	
4	15 (26.3)	19 (33.9)	5 (26.3)	
5	16 (28.1)	12 (21.4)	3 (15.8)	
6	3 (5.3)	0 (0)	0 (0)	
Aneurysmal disease (%)				
Popliteal aneurysm (%)	1 (1.7)	4 (6.6)	0 (0)	
Femoral pseudoaneurysm	1 (1.7)	1 (1.6)	0 (0)	

BMI indicates body mass index; IQR, interquartile range

Tabel 13. OPEN arm of INVIPS Trial – Perioperative data

	Incisions			
	Unilateral		Bilateral	
	NPWT	Standard		
	n = 59	n = 61	n=19	
Preoperative				
Antibiotic treatment (%)	2 (3.4)	3 (4.9)	2 (10.5)	
Anemia	23 (39)	27 (44.3)	8 (42.1)	
Median BAC in g/L (IQR)	39 (3.8)	38 (5.0)	37 (8.5)	
Median GFR in mL/min/1.73m2 (IQR)	67.5 (29)	74 (28.0)	70 (26.0)	
Median BGC in mg/dL (IQR)	51.8 (18.6)	53.8 (23.9)	46.5 (10.0)	
ASA score 1/2/3/4	0/0/58/1	0/0/60/1	0/0/19/0	
Intraoperative				
Antibiotic prophylaxis received (%)	57 (96.6)	57 (93.4)	17 (89.5)	
Type of anesthesia (gen/reg/local)	55/2/2	58/3/0	19/0/0	
Procedure (%)				
Femoral TEA	24 (40.7)	29 (47.5)	8 (42.1)	
Femoropopliteal bypass	18 (30.5)	14 (23)	-	
Femoral TEA and iliac artery stent	16 (27.1)	16 (26.2)	9 (47.1)	
Aortobifemoral bypass	0 (0)	0 (0)	2 (10.5)	
Pseudoaneurysm repair	1 (1.7)	1 (1.6)	0 (0)	
Axillounifemoral bypass	0 (0)	1 (1.6)	0 (0)	
Inguinal incision (%)			**NPWT**	**Standard**
Longitudinal	55 (93.2)	60 (98.4)	17(89.5)	18 (94.7)
Transverse	4 (6.8)	1 (1.6)	2 (10.5)	1 (5.3)
Vascular grafts/patches (%)				
Autologous graft	27 (45.8)	31 (50.8)	7 (36.8)	8 (42.1)
Xenograft	20 (33.9)	20 (32.8)	7 (36.8)	7 (36.8)
Synthetic graft	7 (11.9)	7 (11.5)	1 (5.3)	2 (10.5)
Permanent foreign material	27 (45.8)	27 (44.3)	8 (42.1)	9 (47.4)
Local antibiotic material (%)	6 (10.2)	2 (3.3)	2 (10.5)	
Antimicrobial incision drapes (%)	12 (20.3)	14 (23)	6 (31.6)	
Hemostatic agents left in wound (%)	48 (81.4)	50 (82)	15 (78.9)	
Type of standard dressing (%)				
Vitri Pad	-	43 (70.5)	-	10 (52.6)
OPSITE PostOp Visible	-	16 (26.2)	-	9 (47.4)
Missing data	-	2 (3.3)	-	0 (0)
Wound closure (%)				
Resorbable intracutanous	37 (62.7)	42 (68.9)	16 (84.2)	
Non-resorbable mattress	20 (33.9)	16 (26.2)	2 (10.5)	
Staples	2 (3.4)	3 (4.9)	1 (5.3)	
Median procedure time (IQR)	193 (73)	187 (114)	254 (91)	
Postoperative				
Intensive care (%)	1 (1.7)	0 (0)	1 (5.3)	
Median in-hospital stay in days (IQR)	7 (5)	7 (3)	9 (6)	
Antibiotic treatment (%)	7 (11.9)	10 (16.4)	2 (10.5)	
Hyperglycemia* (%)	15 (25.4)	18 (29.5)	4 (21.1)	
>2 units PRBC transfused **	6 (10.2)	5 (8.2)	5 (26.3)	

*Postoperative glucose concentration >200 mg/dL first 48 h postoperatively. **Intraoperatively until first week postoperatively. ASA indicates American Society of Anesthesiologists; BAC, blood albumin concentration; BGC, blood glucose concentration; gen, general; GFR, glomerularfiltration rate; IQR, interquartile range; loc, local; PRBC, pack red blood cells; TEA, thrombendarterectomy.

Table 14. OPEN arm of INVIPS Trial – Outcome at 3-month Follow-up per Inguinal Incision

Outcome	Unilateral Group		p	Bilateral Group		p
	NPWT n = 59	Standard n = 61		NPWT n = 19	Standard n = 19	
Surgical site infection						
ASEPSIS criteria (%)	7 (11.9	18 (29.5)	0.024	1 (5.3)	5 (26.3)	0.125
Satisfactory wound healing	46 (78)	41 (67.2)		17 (89.5)	14 (73.7)	
Disturbed wound healing	6 (10.2)	2 (3.3)		1 (5.3)	1 (5.3)	
Minor wound infection	6 (10.2)	12 (19.7)		1 (5.3)	4 (21.1)	
Moderate wound infection	1 (1.7)	4 (6.6)		0 (0)	0 (0)	
Severe wound infection	0 (0)	2 (3.3)		0 (0)	0 (0)	
CDC criteria (%)	7 (11.9)	17 (27.9)	0.039	1 (5.3)	5 (26.3)	0.125
Superficial	6	13		1	5	
Deep	1	2		0	0	
Organ/Space	0	2		0	0	
Per type of Standard dressing (%)						
Vitri	-	9/43 (20.9)		-	2/10 /20)	
OPSITE PostOp Visible	-	7/16 (43.8)		-	3/9 (33.3)	
Unknown	-	1/2 (50)		-	0/0 (0)	
Median time to SSI (IQR) in d	15.4 (9)	17 (7.0)		14	13.6 (5)	
Surgical wound revision (%)	2 (3.4)	4 (6.6)		1 (5.3)	1 (5.3)	
Hematoma (%)	1 (1.7)	4 (6.6)		0 (0)	0 (0)	
Seroma/lymphocele (%)	13 (22.0)	14 (23.0)		3 (15.8)	4 (21.1)	
Wound dehiscence	12 (20.3)	7 (11.5)		2 (10.5)	2 (10.5)	
Readmission any cause 30 d postoperatively (%)	10 (16.9)	5 (8.2)		3 (15.8)	2 10.5)	

IQR indicates interquartile range; SSI, surgical site infection

7.3 Results – Study IV

7.3.1 Brief summary of main findings

I. One in five patients not diagnosed with SSI were treated for wound complications.

II. Patients with foreign material vascular grafts had a lower rate of SSI after four months of follow-up than patients with autologous material.

III. The burden of SWC according to the proposed classification was similar between patients operated with foreign and those operated with autologous material.

IV. Although lower SSI rates were observed in patients treated with NPWT as opposed to conventional dressings, no difference in proportion of high grade SWC was observed.

V. Patients suffering from higher grades of SWC more frequently had a history of vascular surgical procedures, preoperative anemia and longer inpatient stay after the primary operation.

7.3.2 Surgical Wound complications

Of 223 patients, 63 (28.3%) suffered from SSI at the four-month follow-up mark (Table 15). Among the 160 patients not diagnosed with SSI (ASEPSIS score <21), 35 (21.8%) were treated for SWC; 26 (16.3%) as outpatients (grade 1) and 9 (5.6%) as in-patients (grade 3-4), of which three (1.9%) patients underwent SWC-related reoperations in the course of their treatment (grade 4).

Sixteen of 223 patients had suffered from disturbed wound healing (ASEPSIS score 11-20) but were not diagnosed with SSI. These 16 patients had a similar accumulated median wound-related length of inpatient stay as patients with SSI (n=63), 13 days (IQR 5.5-21) versus 13 days (IQR 8-26), respectively (p=0.53) (Table 15).

Among those 144 of 223 (64.1%) patients that had satisfactory wound healing (ASEPSIS score <11) at the four-month follow-up mark, 25 (17.4%) received treatment for wound complications, seven (4.9%) patients had to be readmitted (grade 3) of which three (2.1%) underwent re-operations (grade 4).

There was a high correlation between the proposed classification of SWC and SSI outcome defined by both ASEPSIS score ($r=0.77$; $p<0.001$) and CDC criteria ($r=0.76$; $p<0.001$).

Table 15. Surgical wound Complication grading and ASEPSIS score

SWC	Total number of patients (n = 223))		
	Surgical wound complication (ASEPSIS score >10)		
	Yes n = 79 (35.4)		No n = 144 (64.6)
	SSI n = 63 (79.7)	No SSI n = 16 (20.3)	
Grade 0	2 (3.2)	6 (37.5)	119 (82.9)
Grade 1	19 (30.2)	7 (43.8)	19 (13.2)
Grade 2	8 (12.7)	0 (0)	1 (0.7)
Grade 3	11 (17.5)	2 (12.5)	3 (2.1)
Grade 4	21 (33.3)	1 (6.3)	2 (1.4)
Grade 5	2 (3.2)	0 (0)	0 (0)
Grade 6	0 (0)	0 (0)	0 (0)
Median (IQR) inpatient stay during index procedure in days	8 (6-17)	11.5 (5-21)	6 (5-8)
Median inpatient total stay* in days (IQR)	13 (8-26)	13 (5.5-21)	6 (5-8)

SWC indicates surgical wound complication severity; IQR, interquartile range, SSI, surgical site infection as defined by ASPEPSIS score >20; *of index procedure and additional inpatient treatment related to wound complcations within four months postoperatively

7.3.3 Surgical site infections and foreign material vascular grafts

Of 223 procedures, 94 (42.6%) were performed using foreign material vascular grafts. Among patients with foreign material vascular grafts, 19/94 (20.2%) were diagnosed with SSI as opposed to 44/129 (34.1%) without implanted foreign material (p=0.025). Median procedure times (IQR) for synthetic and autologous vascular reconstructions were 180 (142-226) minutes and 196 (156-254) minutes, respectively (p=0.08). The burden of SWC according to the proposed classification in patients with foreign material vascular grafts (SWC grade 0, n=59, grade 1, n=18, grade 2, n=2, grade 3, n=9, grade 4, n=6), was not different from patients with autologous vascular reconstructions (SWC grade 0, n=68, grade 1, n=27, grade 2, n=7, grade 3, n=7, grade 4, n=18, grade 5, n=2), p=0.08.

Among the 63/223 (28.3%) patients diagnosed with SSI, five had perivascular infection, of which four received grade 4 and one grade 5 in the SWC classification. Nineteen out of 63 (30.2%) patients with SSI had newly inserted foreign material vascular implants (bovine pericardial patch 12/19 (63.2%), polytetrafluoroethylene [PTFE] 5/19 (26.3%) and polyethylene terephthalate [Dacron] 2/19 (10.5%). In these 19 patients with SSI and foreign material vascular grafts, 11/19 (57.9%) were classified as superficial (SWC grade 0, n=1, grade 1, n=5, grade 2, n=1, grade 3, n=4), 7/19 (36.8%) as deep (SWC grade 2, n=1, grade 3, n=1, grade 4, n=5) and 1/19 (5.3%) as perivascular (SWC grade 4, n=1) according to the Szilagyi classification.

7.3.4 NPWT compared to conventional wound dressings

Wounds primarily treated with NPWT had significantly lower SSI rates compared to conventional wound dressings, both according to ASEPSIS score (18/93 [19.4%] versus 45/130 [34.6%], p=0.016) and CDC criteria (19/93 [20.4%] versus 48/130 [36.9%], p=0.011). No difference in proportions of high grade SWC were observed between these two groups (Grade 2-6, NPWT n=18/93 [19.4%] versus conventional 33/130 [25.4%], p=0.33).

7.3.5 Surgical wound complication grading and baseline data

Baseline characteristics of the different SWC grades are described in Table 16. A history of previous vascular surgery was found more often in patients with high grade SWC (SWC grade 2-6, p=0.033). There was a tendency to more frequent steroid use in high grade SWC (p=0.087).

Table 16. Surgical wound complication grading in relation to baseline characteristics

	Grade 0	Grade 1	Grade 2-6	p-value
N patients	127	45	51	
Median age in years (IQR)	72 (66-77)	70 (65-75)	71 (66-77)	0.48
Male gender (%)	87 (68.5)	33 (73.3)	38 (74.5)	0.39
Cerebrovascular disease (%)	22 (17.3)	7 (15.6)	11 (21.6)	0.58
Arterial hypertension (%)	101 (79.5)	37 (82.2)	42 (82.4)	0.63
Ischemic heart disease (%)	57 (44.9)	15 (33.3)	23 (45.1)	0.79
Median BMI in kg/m^2 (IQR)	25 (22-28)	25 (23-29)	26 (23-31)	0.13
Current smoker (%)	34 (26.8)	18 (40)	10 (19.6)	0.60
Atrial fibrillation (%)	19 (15)	5 (11.1)	5 (9.8)	0.32
Diabetes mellitus (%)	46 (36.2)	20 (44.4)	20 (39.2)	0.58
Ipsilateral inguinal surgery (%)	40 (31.5)	8 (17.8)	14 (27.5)	0.38
Vascular surgery (%)	49 (38.6)	19 (42.2)	29 (56.9)	0.033
Medication (%)				
Anticoagulation	19 (15)	5 (11.1)	8 (15.7)	0.98
Aspirin	98 (77.2)	36 (80)	44 (86.3)	0.18
Steroids	7 (5.5)	2 (4.4)	7 (13.7)	0.087
Indication (%)				
Lower leg ischemia				
Claudication	55 (43.3)	19 (42.2)	18 (35.3)	0.35
Critical limb ischemia	65 (51.2)	22 (48.9)	31 (60.8)	0.31
Rutherford class				0.61
0	7 (5.5)	4 (8.9)	2 (3.9)	
1	4 (3.1)	0 (0)	8 (3.6)	
2	24 (18.9)	10 (22.2)	39 (17.5)	
3	27 (21.3)	9 (20)	45 (20.2)	
4	30 (23.6)	12 (26.7)	57 (25.6)	
5	33 (26)	9 (20)	58 (26)	
6	2 (1.6)	1 (2.2)	3 (1.3)	
Aneurysmal disease (%)				
Popliteal aneurysm	5 (3.9)	3 (6.7)	2 (3.9)	0.87
Femoral aneurysm	2 (1.6)	1 (2.2)	0 (0)	0.49

IQR indicates interquartile range; BMI, body mass index

7.3.6 Surgical wound complication grading and perioperative data

Compared to SWC grades 0 and 1, patients suffering from SWC grades 2-6 more often had preoperative anemia (p=0.025) and their initial inpatient stay was longer (p=0.026). More complex index procedures tended to be seen in groups with higher SWC grades; Femoral TEA procedures were more commonly found in SWC grade 0 patients (p=0.035), whereas femoropopliteal bypass operations tended to be more common in grades 2-6 (p=0.083) (Table 17).

Table 17. Surgical wound complication grading and perioperative data

	Grade 0	Grade 1	Grade 2-6	p-value
N patients	127	45	51	
Preoperative				
Anemia	51 (40.2)	21 (46.7)	30 (58.8)	0.025
Median BAC in g/L (IQR)	38 (35-41)	38 (36-41)	37 (34-39)	0.055
Median GFR in mL/min/1.73m^2 (IQR)	67 (52-83.4)	73 (61-84)	64 (42-84)	0.34
Median BGC in mg/dl (IQR)	8 (6.3-9.7)	7.6 (6.2-84)	8.3 (7.1-10.4)	0.26
ASA score 1/2/3/4	0/2/122/4	0/0/45/0	0/0/51/0	
Intraoperative				
Type of anesthesia (gen/reg/loc)	120/4/3	43/2/0	51/0/0	
Procedure (%)				
Femoral TEA	63 (49.6)	17 /37.8)	17 (33.3)	0.035
Femoral TEA and iliac artery stent	27 (21.3)	14 (31.1)	12 (23.5)	0.056
Femoropopliteal bypass	34 (26.8)	12 (26.7)	21 (41.2)	0.083
Axillounifemoral bypass	0 (0)	0 (0)	1 (2)	-
Popliteopopliteal bypass	0 (0)	1 (2.2)	0 (0)	-
Revision of aortobifemoral reconstruction	1 (0.8)	0 (0)	0 (0)	-
Femoral artery aneurysm plasty	2 (1.6)	1 (2.2)	0 (0)	-
Longitudinal incision (%)	122 (96.1)	43 (95.1)	49 (96.1)	0.98
Vascular reconstruction with foreign material (%)	59 (46.5)	19 (42.2)	17 (33.3)	0.1
Hemostatic agent left in wound (%)	96 (75.6)	34 (75.6)	43 (84.3)	0.25
Type of wound dressing (%)				
Conventional	70 (55.1)	27 (60)	33 (64.7)	0.23
Incisional NPWT	57 (44.9)	18 (40)	18 (35.3)	0.23
Median procedure time in minutes (IQR)	191 (143-246)	173 (148-227)	193 (158-257))	0.63
Postoperative				
Intensive care	2 (1.6)	0 (0)	3 (5.9)	0.14
Median in-patient stay after index procedure in days (IQR)	7 (5-9)	6 (5-8)	9 (6-18)	0.026

BAC indicates blood albumin concentration; IQR, interquartile range; GFR, glomerular filtration rate; BGC, blood glucose concentration; ASA, American Society of Anesthesiologists; TEA, thrombendarterectomy

7.3.7 Surgical wound complication grading in relation to outcomes

In 13/223 cases (5.8%), the severity grade worsened after the one-month follow-up mark. The median total inpatient stay within four months postoperatively related to surgical wound complications was associated with the highest SWC grades (grade 2-6) (p<0.001) (Table 18). There were no significant differences between groups in terms of major amputation, mortality or amputation-free survival, although both mortality and major amputation within one year postoperatively were higher in

grades 2-6. There was a trend (p=0.087) towards an increased proportion of major amputations within one year postoperatively in SWC grades 2-6.

Table 18. Surgical wound complication classification in relation to patient outcomes

	Grade 0	Grade 1	Grade 2-6	p-value
N patients	127	45	51	
Median long term follow-up time in months (IQR)	38 (26-53)	40 (25-44)	37 (23-44)	0.41
Median inpatient stay* in days (IQR)	7 (5-9)	6 (5-8)	17 (12-29)	<0.001
Mortality one year postop (%)	5 (3.9)	1 (2.2)	3 (7.8)	0.35
Mortality within long-term follow-up period (%)	20 (15.7)	7 (15.6)	8 (15.7)	0.99
Major amputation one year postop (%)	4 (3.2)	1 (2.3)	5 (9.8)	0.087
Major amputation within long-term follow-up period** (%)	7 (5.5)	4 (8.9)	5 (9.8)	0.28
Amputation -free survival within long-term follow-up period** (%)	102 (80.3)	23 (75.6)	39 (78.5)	0.51

* Of index surgery and related to surgical wound complications within four months postoperatively; ** until May 2019; postop indicates postoperatively

7.3.8 Inter-rater and test-retest reliability

Comparison of grading scores between the evaluators showed substantial to almost perfect agreement (rater 1 versus 2, k=0.81, 87.9% agreement; rater 1 versus 3, k=0.71, 82.1% agreement; rater 2 versus 3, k=0.7, 80.7% agreement).

Test-retest reliability showed almost perfect agreement among all three raters (rater 1, k=0.91, 94.6% agreement); rater 2, k=0.87, 85.2% agreement; rater 3, k=0.91, 94% agreement).

7.3.9 Floor and ceiling effects

A floor effect was observed in 127 (57%) patients receiving grade 0 as the most severe grade observed throughout the four-month follow-up period. Two (0.9%) patients obtained grade 5 indicating the absence of a ceiling effect.

8 Discussion

8.1 Surgical Site infections

Two approaches, aimed at reducing the frequency of surgical site infections after vascular surgical procedures with inguinal incisions, were explored. The study described in paper I evaluated SSI-related parameters after changing the preoperative antibiotic prophylaxis, studies II and III the effect of incisional NPWT.

8.1.1 The role of antibiotic prophylaxis

Paper I found no changes in SSI frequency after changing the prophylactic antibiotic regime from cloxacillin to trimethoprim/sulfamethoxazole. Although antibiotic prophylaxis is one of the proven measures to decrease SSI rates after both vascular and other surgical procedures[27,28], this measure had no effect on the SSI rate at this center. Interestingly, another study even found an increased SSI rate after a similar change of antibiotic prophylaxis[29]. The authors of that study speculated, that the development of SSI might go beyond a simple drug-microbe interaction.

Additionally, using an antibiotic with a wider spectrum to include intestinal flora bacteria, did not influence the rate of occurrences where intestinal flora bacteria were isolated. This might be an indication of contamination or simple superficial colonization of the wounds, rather than deep-seeded infection with intestinal flora microbes.

8.1.2 Effects of incisional negative pressure wound therapy

In paper III, the SSI rate after elective open vascular surgical procedures with inguinal incisions was reduced in patients randomized to the NPWT dressing versus standard dressings. The lower SSI rate in the NPWT group was largely attributed to a reduction of superficial SSI, as opposed to deep or perivascular infections. This might be due to the fact that the NPWT effects only reach the superficial parts of the wound and provide an effective barrier to microbial inoculation through the suture lines. It can be speculated that deeper infections could more often result from surgical technical problems such as extensive tissue trauma or remaining dead

space, where tissues are not sufficiently adapted, subsequent seroma formation and eventually infection of the same. Dead space can occur at different depths of a surgical wound. Obliterating dead space has been shown to decrease seroma formation[30] resulting in fewer SWC. Although an experimental study of incisional NPWT in animal models, where dead space was created deliberately[31], found decreased fluid drainage volumes, larger tensile strength and increased skin perfusion, this might only apply to more superficial regions of the wound.

Another explanation for the reduced SSI rate in NPWT-treated inguinal wounds could be that a primary hematogenous dissemination of microbes from other locations such as urinary catheters or foot wounds to the inguinal area, might be prevented by NPWT effects such as better seroma clearance. Although seroma formation in addition to SSI was found to be decreased in a meta-analysis on orthopedic, breast and thoracic surgery patients[32], this has not been evaluated enough in vascular surgical inguinal incisions and a meta-analysis on the subject[33] found no differences between NPWT and standard dressings.

Lastly, superficial infections are generally more common than deep infections[34], and the lack of larger differences in the observed rate of deeper infections between the dressing types just might represent a statistical type II error, e.g. not large enough sample sizes.

8.1.3 Alternative methods to prevent surgical site infections

Apart from meticulous surgical technique, good perioperative patient and wound care, there are local techniques aimed at reducing the incidence and severity of SSI. The application of resorbable gentamycin-containing collagen implants[35] and antibiotic-impregnated biodegradable beads[36] are not novel methods, but a seemingly logical approach, as local delivery of antibiotics combines higher target-site concentrations with reduced risks of systemic effects[37]. Local antibiotic material was used in some patients in paper III but not routinely (Table 13).

In addition, triclosan-coated sutures have been shown to decrease SSI in abdominal surgery[38], but have not shown this effect in the only available RCT after lower limb revascularization[39].

Since cost associated with SSI after vascular surgery is considerable[40], cost-effectiveness analyses of the mentioned products should be conducted.

The timing of revascularization procedures is often dictated by the severity of ischemia. In less urgent cases, and especially if prosthetic vascular grafts have to be used, operating patients with active lower extremity skin and soft tissue infections should be avoided, as these have been shown to increase the risk for nosocomial infections, including SSI[41].

A different approach to decreasing SSI was explored by Tschan et al[42] where abdominal operations were observed by psychologists and the influence of surgical team communication related to the development of SSI. It was demonstrated that case-relevant communication during the entire procedure was associated with a decreased incidence of organ/space SSI, and more case-irrelevant communication during closure related to higher incidence of incisional SSI. This also supports the notion that surgical technique does indeed have an impact on SSI and should not be underestimated. Especially in light of a rising number of endovascular procedures, meticulous open surgical technique must continue to be practiced and taught.

One should also not forget the role patients themselves play in the prevention of SSI and the importance to encourage active participation in their care, both preoperatively to maximize prevention efforts and postoperatively to assist with surveillance and early identification[43].

8.1.4 Surgical site infections and the inguinal area

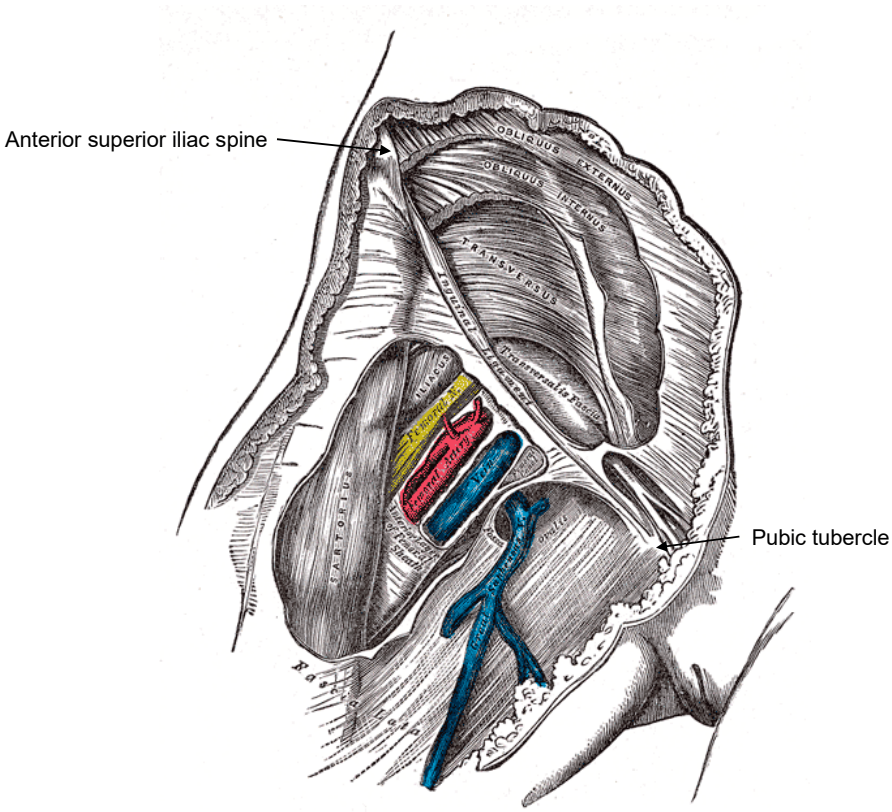

Figure 12. Inguinal region with important landmarks

One of the factors disturbing wound healing is tension on the surgical wound edges, as occurs when an incision is made over a joint. In case of the inguinal region, the anatomical area of interest not only overlies the hip joint, but other complicating factors such as the presence of traversing lymph vessels and the proximity to the anogenital area with its versatile bacterial flora play a role in making this a high-risk region for SSI and other wound complications (Figure 12).

A just comparison to inguinal vascular surgery might be open inguinal hernia repair. A post-discharge surveillance study[44], carried out at 32 Scottish hospitals, found a SSI rate of 5.3%, ranging from zero to 14.6% between the different centers. Although this SSI rate seems relatively low compared to the upwards of 30% observed for inguinal vascular surgery[45], some technical details make the comparison more difficult. A shorter duration of the procedure, incisions superior to the inguinal ligament and in a horizontal fashion, are some of the factors that might result in a lower SSI rate for hernia repair compared to vascular procedures in the inguinal area. The large difference in reported SSI rates, defined by the CDC criteria in the hernia study mentioned above, might indicate the unreliability of reporting SSI rates.

In an attempt to identify patients at high risk for SSI requiring operative intervention, Bennett et al developed a prediction model that established prior ipsilateral inguinal incision, female gender, high body mass, end-stage renal disease, malnutrition and urgent or emergency procedure status as independent risk factors[46]. Analyzing these risk factors might serve as a guide when deciding which patients would benefit from adjunctive therapies such as incisional NPWT.

8.1.5 Relevance of the diagnosis SSI

To accurately define a SWC as a SSI can be a difficult task. Different types of classifications and definitions of SSI are being used, and all of them entail an undeniable degree of subjectivity. The difficulty with classifying SWC as SSI was described in a paper by Wilson et al[47], where 5804 surgical wounds were classified according to CDC and National Nosocomial Infection Surveillance (NNIS) system definitions, ASEPSIS score, and the presence of pus alone. Major variation in estimated percentage of wound infection was noted which would prevent conclusive comparison between centers. A similar discordance in the determination of SSI has been reported by other authors[48].

If it is obviously so difficult, why is this definition so important?

In patients with synthetic graft material, SSI that involve the implant (Szilagyi grade III) can be very difficult to treat and involve significant morbidity and mortality. Targeted long-term antibiotic treatment can in those cases be an important treatment option, especially if not all the foreign material can be removed. Defining a surgical

wound as infected might warrant more aggressive efforts to isolate pathogens and implement treatment strategies.

Another reason for defining SWC as SSI is the tendency of health care systems to link reimbursement to surgical outcome. The US Centers for Medicare & Medicaid Services, for instance, used the Hospital-Acquired Condition Reduction Program and the Hospital Value-Based Purchasing Program to direct payment from hospitals providing lower-quality care to those providing high quality of care[49]. One of the major quality metrics used to establish quality of care are SSI rates. Although this is meant to improve health care, one can assume that this might also influence reporting behavior and might partially explain the large variation in reported SSI rates between different centers[45].

8.1.6 A word about wound cultures

In cases of clinical suspicion of infections, wound cultures can be obtained to help diagnosing infections and to guide antibiotic therapy, where this is deemed necessary. Specimens for culturing can be submitted in the form of tissue biopsies, aspirates and swabs. Although many consider tissue biopsies the most accurate specimen for culture, most centers use swabs as their main means of obtaining microbial cultures because they are easily and noninvasively obtainable. Swabs are often contaminated by normal skin flora and contaminants and might fail to identify microbes protruding to deeper tissues if adequate debridement and wound cleaning is not performed. A study on diabetic foot wounds did however show no differences in number of isolates per specimen between these two culturing methods[50].

Because of the fact that even normal healthy skin contains various microbes on its surface, and also because of potential technical difficulties with obtaining adequate wound cultures, microbiological testing should only be seen as an adjunct to clinical assessment of potentially infected wounds. Especially wound cultures showing growth of multiple microbes, might suggest contamination rather than infection.

8.1.7 Hospital facilities and SSI

Although studies evaluating the incidence of SSI and quality of surgical ward facilities do not exist and might be difficult to conduct, it seems probable that such a relationship does exist. The vascular surgical ward, where all patients involved in studies I-IV were treated, is situated in a building from the 1960s, that to a large extent seems to have retained the furnishing from that era. A disease control inspection carried out in January 2019[51], found that these facilities currently do not meet the established general hygiene standards and thus pose a risk to patient safety. Although it is difficult to identify individual factors that might be responsible for high SSI rates, it might be warranted to include the quality of patient treatment facilities when attempting to lower infection rates.

8.2 Other surgical wound complications

How much focus is placed on SSI, as opposed to other SWC, can easily be demonstrated by comparing the number of search results between different surgical wound complications on PubMed (Figure 13).

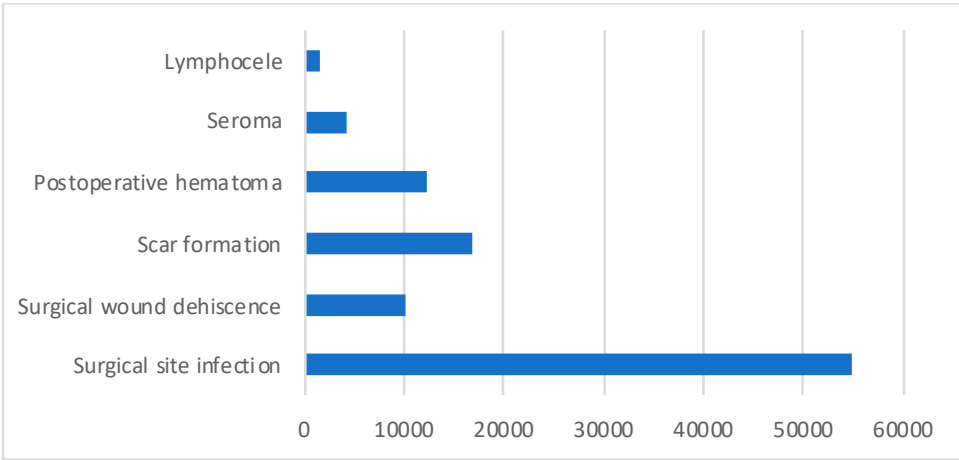

Figure 13. Number of PubMed database search results for different surgical site complications (July 15th 2019)

Study IV explored the consequences of SWC not classified as SSI and related them to SSI, defined by an ASEPSIS score >20 (Fig 14). It was shown that 21.9% of patients without SSI were treated for SWC, 5% were readmitted and 1.9% reoperated for SWC. This demonstrates that a relatively large portion of SWC would be overlooked, when only focusing on SSI. Reporting only SSI instead of all negative surgical wound outcomes, seems therefore unwarranted and should be reconsidered.

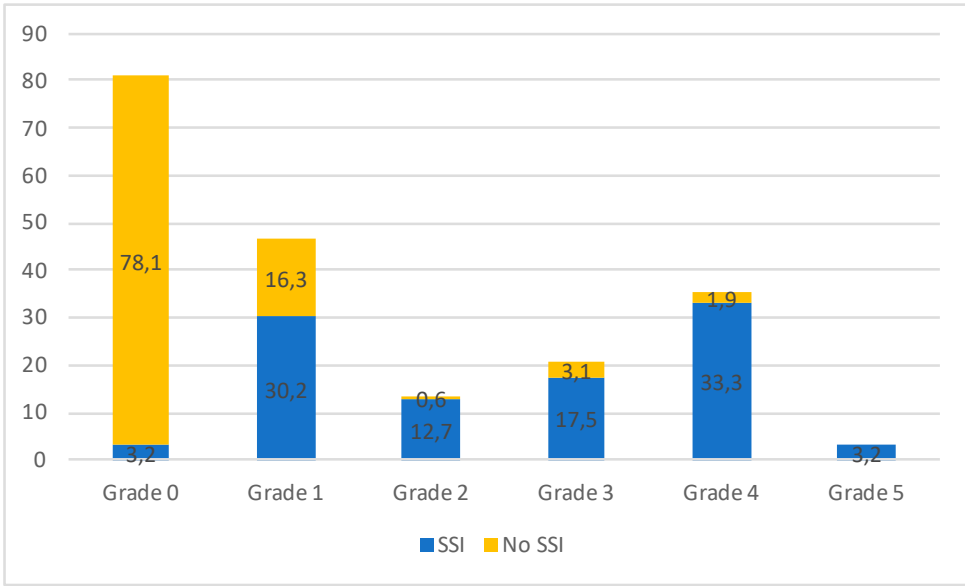

Figure 14. Percentage of SWC grading of patients with and without surgical site infection in paper IV.

This can be seen as relevant since different SWC of the same grade probably carry a comparable burden for the patient suffering from them. A patient who has to be reoperated and be burdened with an open wound NPWT treatment for weeks, including uncomfortable dressing changes, will probably be less impressed that his or her wound complication does or does not meet SSI criteria. The diagnosis SSI might entail consequences for patients with foreign material vascular grafts but might otherwise be less compelling. Furthermore, apart from reimbursement penalties directed at high SSI rates, other SWC most likely produce costs comparable to SSI.

8.3 Conducting randomized controlled trials

Evidence-based medicine relies on a hierarchical system of classifying evidence by its quality. Although there can be substantial variation in the quality of individual RCTs, they are considered to produce one of the highest levels of evidence, only surpassed by systematic reviews of RCTs. Key to high levels of evidence is the randomization of patients into two or more groups to combat selection bias. Apart from ethical and resource issues, there are other problems that make RCTs difficult to conduct.

In the RCT described in papers II and III, several stages were required for the patient to be included in the study. Informed consent was usually obtained by nurses in the outpatient clinic. Of those patients eligible for participating, 12.2% were not approached for consent and 15% declined participation. Communicating the key concepts of RCTs to eligible patients is an integral part of the process[52]. Another hurdle awaited in the operating room where the wrong wound dressing was applied to 13.6% of incisions. Both lack of clarity in the randomization instructions and a large scrub nurse staff turnover could serve as an explanation, but deliberate violation of the study protocol by some surgeons, who were convinced of the superiority of one dressing over the other, was a reoccurring issue. This could be seen as a sign that evidence-based medicine should not be taken for granted just yet.

The last obstacle that could prevent a patient from being included in the final data analysis, were reoperations due to indications other than local wound complications, and the patient's demise within 90 days postoperatively.

Overall, 139/246 (56.5%) patients eligible for randomization and 158/202 (78.2%) incisions randomized to either NPWT or standard dressing, were included in the study. These figures would not have been possible, if the study had not been supported by a dedicated research assistant who followed up all steps of the process.

8.3.1 Methodology

8.3.1.1 Intention-To-Treat vs Per-Protocol analysis

Two major means for analysis of RCTs exist: the intention-to-treat (ITT) and the per-protocol (PP) principles.

According to the ITT principle, every randomized patient has to be included in the analysis, even if the treatment is ended prematurely or the wrong study treatment was given. This typically results in a full analysis set with the randomization assignment unchanged and rules out potential bias due to patient exclusion. The ITT principle, which was used in the RCT described in this thesis, might also have the

advantage that it displays more real-life scenarios where a certain treatment might be given initially but then switched to another.

The PP principle on the other hand, aims to explore a treatment effect under optimal conditions assuming strict adherence to the treatment regime assigned. This results in the necessity to exclude certain patients.

Which method to choose depends on the nature of the study. Papers II and III represent a superiority study, exploring the potential benefits in using NPWT over standard wound dressings. It is generally considered more important to avoid making a statistical type I error, meaning showing a treatment effect when in reality there is none, than a type II error, occurring when one fails to prove an existing treatment effect. Since the ITT principle should ideally lead to a full analysis set, also non-compliant patients who, at least in medical trials, are generally more associated with negative outcomes[53], are included in the analysis. This leads to a diluted treatment effect. If, despite a diluted treatment effect, a difference in outcome between two treatments can still be proven, the risk for a statistical type I error has been minimized.

8.3.1.2 Hawthorne effect

One of the potential weaknesses of the RCT described in papers II and III is the fact that randomization was not conducted in the operating room. Randomizing patients preoperatively could have had an impact on the surgeon's decision-making in regard to operating or wound closure technique. Conducting studies can change the behavior of individuals in response to their awareness of being observed[54], known as the Hawthorne effect. Although one cannot be certain of the influence of the Hawthorne effect in the described RCT, the fact that similar outcome data were observed between the control group and reanalysis of previous data[34] might suggest that it had less of an impact.

9 Conclusions

- Changing the Center's prophylactic antibiotic regime from cloxacillin to trimethoprim/sulfamethoxazole after vascular surgical procedures did not improve surgical site infection rates in inguinal incisions.
- Prophylactic incisional negative pressure wound therapy on vascular surgical inguinal incisions did reduce surgical site infection rates within the three-month follow-up period, but had no influence on other surgical wound complications.
- A classification for surgical wound complications was proposed that focuses on their clinical consequences and therefore might reflect patient suffering, cost of treatment and their overall severity in a simple and comprehensive way.
- Surgical wound complications not classified as surgical site infections shared a similar burden as surgical site infections expressed by the proposed classification of surgical wound complications. To paint a clearer picture of the negative effects of surgical procedures, a broader view of surgical wound complications should be considered.

10 Future research

Incisional NPWT had a positive effect on the prevention of surgical site infections of vascular surgical inguinal wounds. To gather more evidence for this therapeutic approach, a multi-center study could be used to verify the findings with higher external validity. A larger data collection could also permit subgroup analysis to identify patients who will benefit the most from this method. As incisional NPWT dressings are currently much more expensive than conventional wound dressings, a cost-effectiveness analysis seems unavoidable.

It would also be interesting to find out how much of the positive effect of the NPWT dressings can be attributed to the negative pressure mechanism. A double-blinded RCT with conventionally operating NPWT dressings in one and manipulated dressings where the suction-effect is inhibited by a blocked tube, could elucidate this question.

Lastly, a direct comparison between the major types of NPWT dressings (the PICO and Prevena systems) could be intriguing. It is however likely that both will find their niche, the Prevena system, with its higher-capacity fluid-draining capability, in more fluid-producing wounds and the PICO system, with its superior portability, in more mobile patients.

The proposed classification of SWC needs to be validated. The assumed relationship between increasing SWC grade and treatment cost should be verified.

11 Populärvetenskaplig sammanfattning

Patienter med arteriella cirkulationsproblem i de nedre extremiteterna kräver ibland kärlkirurgiska åtgärder. Det är dock vanligt med sårläkningsbekymmer, framför allt i ljumsksnittet i form av infektion och andra sårkomplikationer som bristning av skikten i operationssåret, blodutgjutning, och/eller ansamling av sår- eller lymfvätska. Bidragande faktorer till uppkomsten av sårkomplikationerna är den rörliga och ojämna hudytan, den rikliga ansamlingen av lymfkärl och lymfkörtlar och den höga koncentrationen av bakterier på huden i ljumsken.

Som en del av denna avhandling vid Lunds Universitet har olika metoder för att minska sådana sårkomplikationer testats och förslag på ett nytt klassificeringssystem av kirurgiska sårkomplikationer utformats.

En viktig och beprövad metod för att förhindra kirurgiska sårinfektioner är administrering av antibiotika direkt före operationen. På grund av den höga infektionsfrekvensen av kärlkirurgiska operationssår i ljumsken och den höga förekomsten av tarmbakterier som påvisats efter sårodlingar, gjordes ett skifte av antibiotikaprofylax från cloxacillin till trimetoprim och sulfametoxazol. Denna regimförändring skulle leda till en lägre infektionsfrekvens, särskilt genom att minska infektioner orsakade av tarmbakterier. Detta kunde dock inte påvisas och både infektionsfrekvens och frekvensen av sårodlingar med växt utav tarmbakterier var oförändrade efter antibiotikaförändringen.

I den andra studien lottades patienter till att antingen erhålla ett speciellt undertrycksförband (PICO, Smith and Nephew) eller ett konventionellt sårförband ovanpå slutna operationssår i ljumsken efter kärlkirurgiska operationer. Studien pågick i fem år. Utvärdering visade att sår behandlade med undertrycksförband resulterade i färre sårinfektioner än konventionella förband. Det var ingen skillnad avseende andra sårkomplikationer mellan förbandstyperna.

Eftersom olika typer av kirurgiska sårkomplikationer ofta uppträder samtidigt och har en tendens att överlappa, utformades och utvärderades en pragmatisk klassificering av kirurgiska sårkomplikationer. Denna klassificering tar främst hänsyn till konsekvenserna av sårkomplikationerna så som ytterligare sjukhusinläggning, operationer och amputation/död till följd av sårkomplikationen.

Sår med läkningsstörningar men utan bevisad infektion genererade lika omfattande sjukhusinsatser för de drabbade patienterna som de patienter som hade sårinfektioner. Studien visade med denna klassificeringsmodell att alla patienter med sårkomplikationer efter kärlkirurgi i de nedre extremiteterna bör tas på allvar och redovisas för att kunna jämföra behandlingsresultat vid olika kärlkirurgiska centra. Klassificeringsmodellen torde kunna vara användbar efter andra kirurgiska ingrepp.

12 Populärwissenschaftliche Zusammenfassung

Arterielle Durchblutungsstörungen erfordern regelmäßig gefäßchirurgische Operationen an den Beinen. Es kommt jedoch besonders in der Leistenregion regelmäßig zu Wundheilungsstörungen, Infektionen und anderen Wundkomplikationen, wie Ansammlungen von Lymph- und Wundflüssigkeit oder Auseinanderweichen verschlossener Wundschichten. Zu Wundheilungsstörungen beitragende Faktoren sind empfindliche Lymphbahnen, die bei Eingriffen beschädigt werden können, eine vielfältige bakterielle Flora und bewegliche, unebene Hautverhältnisse.

Im Rahmen dieser PhD-Arbeit an der Universität Lund, wurden verschiedene Verfahren zur Bekämpfung solcher Wundkomplikationen getestet und eine neue Klassifikation für diese entworfen.

Eine wichtige und erprobte Methode, um Infektionen von Operationswunden vorzubeugen, ist die Gabe von Antibiotika direkt vor der Operation. Auf Grund der hohen Infektionsrate von gefäßchirurgischen Wunden und dem häufigen Nachweis von Darmbakterien in infizierten Wunden, wurde eine Änderung der Antibiotikaprophylaxe von Cloxacillin zu Trimethoprim und Sulfamethoxazol vollzogen. Von diesem Regimewechsel versprach man sich vor allem durch eine gezielte Bekämpfung von Darmbakterien eine niedrigere Infektionsrate. Dies bestätigte sich jedoch nicht. Sowohl die Infektionsrate als auch die Häufigkeit eines Darmbakterien-Nachweises waren nach dem Antibiotikawechsel unverändert.

In der zweiten Studie erhielten gefäßchirurgische Operationswunden in der Leiste nach dem Zufallsprinzip entweder einen herkömmlichen, oder einen speziellen Unterdruck-Verband (PICO, Firma Smith and Nephew). Nach fünf Jahren wurde die Studie planmäßig beendet und zeigte, dass bei Wunden, die mit Unterdruckverbänden behandelt wurden, Wundinfektionen deutlich seltener vorkamen, als mit herkömmlichen Verbänden. Andere Wundkomplikationen traten bei beiden Verbandsarten ungefähr gleich häufig auf.

Da unterschiedliche Arten von chirurgischen Wundkomplikationen oft gleichzeitig auftreten, und gerade Wundinfektionen zum Teil sehr unterschiedlich definiert werden, wurde eine übergreifende Klassifikation von chirurgischen

Wundkomplikationen geschaffen und ausgewertet. Diese stützt sich auf die Behandlungsweise der Wundprobleme, wobei solche die ohne zusätzlichen stationären Aufenthalt behandelt werden konnten, einen niedrigeren Grad zugewiesen bekamen als solche, die etwa durch erneute Operationen und lange stationäre Aufenthalte behandelt wurden. Hierbei fiel auf, dass Wundheilungsstörungen ohne nachgewiesene Infektionen eine genauso große Belastung für die betroffenen Patienten darstellten, wie Wunden mit nachgewiesenen Infektionen. Daraus wurde geschlussfolgert, dass nicht nur Wundinfektionen, sondern auch andere Arten von Wundheilungsstörungen und Wundkomplikationen ernst genommen werden müssen und diese bei dem Vergleich unterschiedlicher Zentren und Operationsmethoden berücksichtigt werden sollten.

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14 Humoristic quotes

Humor has been suggested to be associated with good physical and mental health, to serve as a buffer for negative effects of workplace stress and seems to promote effective functioning at work[55]. It is also believed to help achieve a sense of normality and perspective[56] in the professional context.

“ A good surgeon needs three things: a strong back, a short memory and the third, I don’t remember. “

Steinarr Björnsson

“ You can always get back surgery, but if you want to be strong, you have to train. “

Thorarinn Kristmundsson

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