Negative pressure wound therapy in closed inguinal incisions after vascular surgery – randomised controlled trials

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Negative pressure wound therapy in closed inguinal incisions after vascular surgery – randomised controlled trials

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In the present thesis, incisional negative pressure wound therapy (postoperative wound dressings with a vacuum suction) is evaluated regarding prevention of incisional wound complications when applied on closed inguinal incision after vascular surgical procedures.

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Abstract

Background: Every surgical incision poses a risk for incisional wound complications, of which surgical site infections (SSI) dominate. The commonly used inguinal incision in vascular surgery is especially afflicted by SSIs which increase patient morbidity and use of limited healthcare resources. A proposed preventor of SSIs and other incisional wound complications is incisional negative pressure wound therapy (NPWT), postsurgical dressings applied on sutured incisions which deliver a negative pressure from a battery driven pump through a multi-layered pad. Incisional NPWT removes excess fluids, enhances lymphatic drainage, creates a sealed environment for the wound, reduces mechanical forces, and reduces postsurgical inflammatory response.

Aims: The aims of the present thesis were to compare incisional NPWT to standard dressings regarding:

- Incidence of SSIs and other incisional wound complications in inguinal incisions after endovascular aneurysm repair (EVAR) procedures with the primary intention of fascia closure (study I) and after any arterial surgical procedure (study III).
- Incisional scar formation after inguinal vascular surgical procedures (study II).
- Cost-effectiveness in inguinal incisions after open vascular surgical procedures (study IV).

Methods: A randomised controlled trial (RCT) was conducted between 2013 and 2020, including patients undergoing EVAR procedures with the primary intent of fascia closure. The incisions were randomised to either incisional NPWT or standard dressings and evaluated for SSIs and other incisional wound complications (study I). A subgroup of patients from the aforementioned RCT, those with bilateral inguinal incisions, was reinvited for scar evaluation (study II). A systematic review with meta-analysis of RCTs comparing incisional NPWT to standard dressings on inguinal incisions after any arterial surgical procedure was performed (study III). A cost-effectiveness analysis of incisional NPWT compared to standard dressings was conducted using data from patients operated inguinally with open vascular surgical procedures in a previously published RCT (study IV).

Results: The RCT of EVAR procedures showed a SSI incidence of 1.8% (n=3/168) with incisional NPWT and 4.8% (n=8/168) with standard dressings when operated with bilateral incisions (p=0.18), and 13.3% (n=2/15) and 11.5% (n=3/26), respectively, when operated with unilateral incisions (p=1.0) (study I). The visual grading of scars showed a median score of 4 (range 1-5) using Stony Brook Scar Evaluation scale in both the incisions treated with incisional NPWT and standard dressings, respectively, (p=0.86) (tudy II). The systematic review identified seven RCTs including 1,051 incisions, with meta-analysis showing an odds ratio of 0.35 (p<0.001) in favour of incisional NPWT (study III). The cost-effectiveness analysis showed a mean *vascular procedure-related cost* of €16,621 for patients treated with incisonal NPWT compared to €16,285 for patients treated with standard dressings (p=0.85). The SSI incidence were 11.9% (n=7/59) and 30.0% (n=18/60), respectively, (p=0.015) (study IV).

Conclusions: There was no difference in SSI incidence when comparing incisional NPWT to standard dressings after EVAR procedures with the primary intent of fascia closure (study I). Evaluation of incisional scars showed equally subtle visual appearance (study II). Meta-analysis demonstrated a significant reduction in SSI incidence in favour of incisional NPWT after any inguinal arterial surgical procedure (study III). Incisional NPWT was considered cost-effective in reducing SSI incidence when applied on inguinal incisions after open vascular surgical procedures (study IV).

Key words

Negative pressure wound therapy, closed incisons, surgical site infections, inguinal incisions, vascular surgery

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Cover photo: Apple with the Öresund sea in the background. The skin of the apple represents the thin protective barrier of the human skin and illustrates its fragility when disrupted by an incision, which relates to the incisional wound complications studied in the present thesis. Photo by Robert Svensson-Björk.

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1 Papers included in this thesis

This thesis is based on the following papers, referred to in the text by their Roman numerals. The papers are reprinted with permission from their respective publishers (study II and III) or copyright holders (study I and IV).

I. Svensson-Björk R, Hasselmann J, Svensson-Björk R, Asciutto G, Zarrouk M, Björk J, Bilos L, Pirouzram A, Acosta S. Randomised multi-centre trial comparing negative pressure wound therapy with standard dressings for the prevention of surgical site infections using fascia closure after EVAR. World J Surg. 2022;46(12):3111-3120.

II. Svensson-Björk R, Hasselmann J, Acosta S. Evaluation of inguinal vascular surgical scars treated with closed incisional negative pressure wound therapy using three-dimensional digital imaging—a randomized controlled trial on bilateral incisions. Wound Rep Reg. 2018;26:77-86.

III. Svensson-Björk R, Zarrouk M, Asciutto G, Hasselmann J, Acosta S. Meta-analysis of negative pressure wound therapy of closed groin incisions in arterial surgery. Br J Surg. 2019;106(4):310-318.

IV. Svensson-Björk R, Saha S, Acosta S, Gerdtham U-G, Hasselmann J, Asciutto G, Zarrouk M. Cost-effectiveness analysis of negative pressure wound therapy dressings after open inguinal vascular surgery – the randomised INVIPS-trial. J Tissue Viability. 2021;30(1):95-101.

2 Abbreviations

3D	Three-dimensional
ASA	American Society of Anesthesiologists
AUD	Australian Dollar
CDC	Centers for Disease Control and prevention
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
eGFR	Estimated Glomerular Filtration Rate
EVAR	Endovascular Aneurysm Repair
EQ-5D	European Quality of life Five Dimension
GBP	Great Britain Pound
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HUI-3	Health Utilities Index Three
INVIPS	Incisional NPWT on Vascular surgical Incisions in the Prevention of SSI
ICC	Intraclass Correlation Coefficient
ICER	Incremental Cost-Effectiveness Ratio
IQR	Interquartile Range
NICE	National Institute for Health and Care Excellence
NPWT	Negative Pressure Wound Therapy
NRS10	Ten-point graded Numeric Ranked Scale
OR	Odds Ratio
PICOS	Population, Intervention, Comparison, Outcome, and Study design
PCD	Percutaneous Closure Device

PRISMA	Preferred Reporting Items for Systematic review and Meta-analysis
PSAS	Patient Scar Assessment Scale
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomized Controlled Trial
SF-6D	Short Form Six Dimension
SSI	Surgical Site Infection
SBSES	Stony Brook Scar Evaluation Scale
TEA	Thromboendarterectomy
USD	United States Dollar

3 Thesis at a glance

Study	Aim	Methods	Main results
I. Randomised multi-centre trial comparing negative pressure wound therapy with standard dressings for the prevention of surgical site infections using fascia closure after EVAR.	To compare incisional NPWT with standard dressings regarding SSI and other incisional wound complication incidences in inguinal incisions after EVAR procedures closed with fascia closure.	A multi-centre RCT including patients with uni- or bilateral inguinal incisions after EVAR, randomised to either incisional NPWT or standard dressings.	No difference in SSI incidence but a trend towards fewer additional treatments due to any incisional wound complication with incisional NPWT in bilateral incisions.
II. Evaluation of inguinal vascular surgical scars treated with closed incisional negative pressure wound therapy using three-dimensional digital imaging – a randomized controlled trial on bilateral incisions.	To compare incisional NPWT with standard dressings regarding cutaneous scar quality in inguinal incisions after vascular surgery and to evaluate the use of 3D imaging in scar evaluation.	A post-hoc analysis of a single-centre RCT including patients with bilateral inguinal incisions after vascular surgery, receiving incisional NPWT and standard dressings on separate sides.	No difference in visual apperence or patient experience between scars from incisions treated with incisional NPWT or standard dressings. Scar visual evaluation with 3D imaging is possible.
III. Meta-analysis of negative pressure wound therapy of closed groin incisions in arterial surgery.	To compare incisional NPWT with standard wound treatment regarding incidence of SSIs after inguinal arterial surgery.	A systematic review with meta-analysis of RCTs comparing incisonal NPWT with standard treatment on closed inguinal incisions after arterial surgery.	Seven RCTs were identified and included. Meta-analysis showed a significantly reduced SSI incidence with incisional NPWT compared to standard dressings.
IV. Cost-effectiveness analysis of negative pressure wound therapy dressings after open inguinal vascular surgery – the randomised INVIPS-trial.	To evaluate the cost-effectiveness of incisional NPWT compared to standard dressings on inguinal incisions after open vascular surgical procedures	A cost-effectiveness analysis of a RCT comparing patients treated with incisional NPWT with standard dressings.	No difference in healthcare costs between incisional NPWT and standard dressings. A significantly lower SSI incidence in favour of incisional NPWT.

EVAR, endovascular aneurysm repair; NPWT, negative pressure wound therapy; SSI, surgical site infection; RCT, randomised controlled trial; 3D, three-dimensional; INVIPS, incisional NPWT on vascular surgical incisions in the prevention of SSIs.

4 Introduction

4.1 Inguinal vascular surgery

Surgical treatment of vascular diseases in the lower extremity, abdominal and thoracic aorta and its arterial branches frequently rely on vascular access to the femoral artery, thus imposing an inguinal incision. The characteristics of the inguinal incision vary between different surgical procedures. Vascular surgery is principally conducted with two different surgical techniques: open and endovascular.

In open vascular surgical procedures, an arterial segment is fully exposed by surgical incision and dissection. The most common open inguinal vascular surgical procedures are thromboendarterectomy (TEA) and bypass surgery. In a TEA, a short atherosclerotic occlusion or stenosis is removed with the intima-media layer of the artery, and the artery subsequently closed by primary suture or patch angioplasty (Figure 1C-D and 1E-F). It is conducted on the common femoral artery with or without extension to the profunda and/or superficial femoral artery. In bypass surgery, a long atherosclerotic occlusion is bypassed via a vein or prosthetic graft anastomosed proximally and distally to the occlusion or stenosis. In inguinal vascular surgical procedures, bypass surgery is mainly conducted between the common femoral artery and popliteal artery (above or below the knee joint).

In endovascular surgery, the artery is punctured, often percutaneously, and the operation conducted without vessel exposure. At the end, upon removal of the endovascular instruments, the arterial wall defect from the puncture must be handled to avoid extensive bleeding or postoperative development of an arterial stenosis. Small diameter punctures are managed by compression. In large diameter arterial access, local haemostasis is traditionally achieved via surgical incisions at the end of the procedure. The main arterial access site closure techniques are: fascia suture, where the adjacent fascia is sutured over the arterial wall defect (Figure 1A-B); and cut-down, where the artery is exposed further for primary suture (Figure 1C-D). In recent years, different percutaneous closure devices (PCD) have emerged as an alternative to surgical haemostasis. In PCDs, arterial closure is achieved by deploying either arterial sutures around or a haemostatic plug over the arterial wall defect upon removal of the PCD, thus enabling closure of large diameter access holes and performance of fully percutaneous endovascular procedures.[1] The most common endovascular procedure with large diameter arterial access is endovascular

aneurysm repair (EVAR), where an aortic and/or iliac aneurysm is treated with stent-grafts, covering the pathologically widened artery, to reduce the risk of rupture. EVAR is conducted mainly with arterial access via both common femoral arteries.

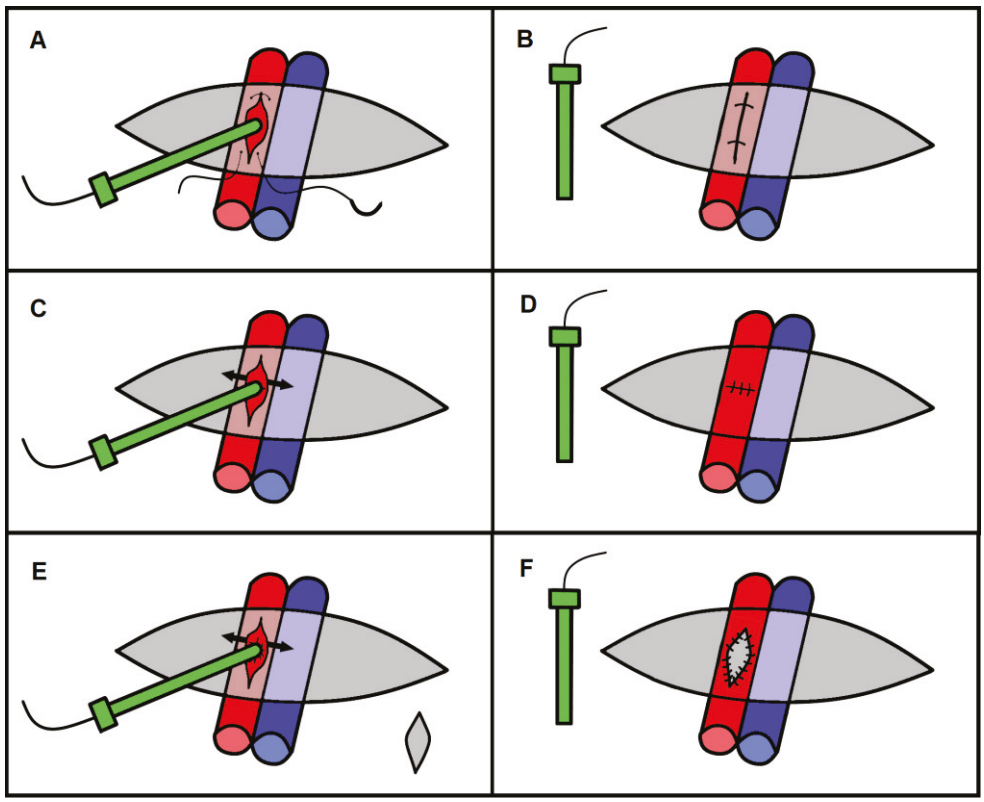

Figure 1 Open surgical arterial closure techniques in a inguinal incision on the right side
Fascia suture, where a suture in the adjacent fascia is tightened over the arterial wall defect as the endovascular instrument is removed (A-B). Cut-down, where the artery is disected further and the arterial punctuation is closed by primary suture (C-D). Patch angioplasty, where the artery is fully exposed wth dissection and a patch (autologous, xenogenous, or prosthetic) is sutured onto the arterial wall defect (E-F). Copyright held by the author.

4.2 Normal incisional wound healing

All surgical incisions impose a trauma to the skin and any underlaying structures affected by the incision, triggering a complex cellular and immunological response to restore the damaged tissue. The natural healing of an incisional wound is normally divided into four phases.[2]

The first and immediate phase is the haemostasis phase which starts with constriction of blood vessels, followed by aggregation of thrombocytes and finally activation of the coagulation cascade which results in deposits of fibrin threads around the thrombocytes and other blood cells to create a clot formation.[2]

The second phase is the inflammatory phase, a multicellular and biochemical response with the aim to protect the wound from exogen pathogens, remove damaged cells and excess proteins as well as promote wound healing. The inflammatory phase creates the classical clinical characteristics of swelling (tumor), redness (rubor), heat (calor) and pain (dolor). The inflammatory phase starts within an hour and lasts for days.[3]

The third phase is the proliferative phase. It involves the formulation of granular tissue which is rich in capillaries to provide oxygen and nutrition to the wound, fibroblasts which produce collagen fibres for structure and myofibroblasts which contracts the collagen fibres to close the wound. The proliferative phase also involves the re-epithelialization of the wound with new cells from the wound edges.[2]

The final phase is the remodelling phase when the wound tissue is transformed into scar tissue. It involves a shift from collagen fibres type III to I, aligning and crosslinking the collagen fibres for increased tensile strength and reduced volume, reducing myofibroblasts, fibroblasts and inflammatory cells through apoptosis, and reducing the vascularization of the tissue.[3] The remodelling phase starts approximately 21 days after the skin trauma and continues for years.[2]

4.3 Incisional wound complications

4.3.1 Surgical site infection

All surgical incisions disrupt the protective barrier of the skin, exposing underlaying structures to the skin's natural flora and other pathogens from the surrounding environment. This may result in a local infection – a surgical site infection (SSI). SSIs are defined as any infection affecting the adjacent tissue to the surgical incision. It is the most common nosocomial infection among surgical patients[4], with a previously reported incidence of 24.2% after inguinal vascular surgery.[5]

SSIs manifest clinically very differently depending on the tissue affected, the microbiological characteristics and the severity of the SSI. Superficial SSIs may clinically only delay wound healing and result in minor wound erythema and extra serous discharge, which can be handled with additional wound dressing changes and per oral antibiotics. Deep infections may manifest with a deep abscess or wound dehiscence with purulent discharge, requiring surgical debridement and intravenous antibiotics. A SSI may also affect the vascular prosthesis, causing pseudoaneurysm

development and/or acute arterial bleeding. Vascular prosthetic infections require long antibiotic treatments with or without surgical removal of the infected prosthetic material, with increased risk for amputation and death.[6] In rare occasions, a SSI may be the source of systemic spread and cause of sepsis – a life-threatening condition which may require critical care.

The diverse clinical manifestations and their similarity to normal postsurgical inflammation makes diagnosing and grading the severity of SSIs challenging. There are today several tools for SSI diagnosis and grading available.

The first SSI grading system published was the Szilagyi classification, first published in 1972 and aimed for reconstructive vascular surgery with arterial implants.[7] It grades the depth of the infection from 1-3: grade 1, affecting the dermis only; grade 2, involving subcutaneous tissue; and grade 3, involving the arterial implant. The Szilagyi classification relies on clinical diagnosis of SSIs and clinical assessment of affected tissues.

Later, the Centers for Disease Control and Prevention (CDC) provided a definition and grading of SSIs based on criteria, which has been updated several times over the decades. The CDC criteria also grades SSIs based on depth: superficial, involving the skin and subcutaneous tissue; deep, involving deep soft tissue; and organ/space, involving an organ or anatomical space not directly in contact with the incision (Table 1).[8]

In 1986, an objective scoring system was published for diagnosing and grading SSIs called the ASEPSIS-score (Additional treatment, Serous discharge, Erythema, Purulent exudate, Separation of the deep tissues, Isolation of bacteria and duration of inpatient Stay).[9] It converts presence of the forementioned clinical wound manifestations into points which are summarised into scores and interpreted as satisfactory healing, disturbance of healing, minor wound infection, moderate wound infection or severe wound infection (Table 2).[9]

Table 1 Definiton of surgical site infection according to the centers for disease control and prevention

The critera for the different grades of surgical site infections according to the centers for disease control and prevention from 1999.[8]

Superficial surgical site infection (SSI)
Infection occurs within 30 days after the operation
And
Infection involves only skin or subcutaneous tissue of the incision
And at least one of the following:
1. Purulent drainage, with or without laboratory confirmation, from the superficial incision.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
3. *At least one of the following signs or symptoms:*
3.1. Pain or tenderness.
3.2. Localised swelling
3.3. Redness
3.4. Heat
And
3.5. Superficial incision is deliberately opened by surgeon or attending physician.
Unless
3.6. Incision is culture-negative
4. Diagnosis of superficial incisional SSI by the surgeon or attending physician.
Deep SSI
Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operation
And
Infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision
And at least one of the following:
1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site.
2. *At least one of the following signs or symptoms:*
2.1. Fever (>38ºC)
2.2. Localised pain
2.3. Tenderness
And
2.4. A deep incision spontaneously dehisces or is deliberately opened by a surgeon.
Unless
2.5. Incision is culture-negative
3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of a deep incisional SSI by a surgeon or attending physician.
Organ/space SSI
Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operation
And
Infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation
And at least one of the following:
1. Purulent drainage from a drain that is placed through a stab wound into the organ/space.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of an organ/space SSI by a surgeon or attending physician.

Table 2 The ASEPSIS-score
The scoring system and interpretation of the ASEPSIS-score.[9]

Criterion	Points					
	Proportion of wound affected (%)					
	<20	20-39	40-59	60-79	>80	If present
Additional treatment						
Antibiotics						10
Drainage of pus under local anesthetics						5
Debridement of wound (general anesthetics)						10
Serous discharge*	1	2	3	4	5	
Erythema*	1	2	3	4	5	
Purulent exudates*	2	4	6	8	10	
Separation of deep tissues*	2	4	6	8	10	
Isolation of bacteria						10
Stay in hospital prolonged over 14 days						5
Interpretation						**Total**
Satisfactory healing						0-10
Disturbance of healing						11-20
Minor wound infection						21-30
Moderate wound infection						31-40
Severe wound infection						>40

* Given only on 5 of first 7 postoperative days

4.3.2 Lymphatic complications and seroma

The lymphatic vessels of the lower limb, perigenital and perianal area mainly drain to lymphatic nodes located in the inguinal area. Surgical injury to the inguinal lymphatic system is therefore a potential complication of inguinal vascular surgery. The acute complications are lymphatic leakage (lymphorrhea) or accumulation of lymphatic fluid between tissue layers (lymphocele). If not treated, severe lymphorrhea may develop into a lymphatic fistula. Another potential long-term complication is chronic lymphoedema, needing life-long compression treatment.

The surgical incision also results in increased serous exudate from the damaged small vessels and the inflammatory response. When produced in high volumes, into closed spaces caused by the surgical procedure which are not adapted to absorb exudate (dead spaces), and potentially combined with decreased lymphatic drainage, it can accumulate into a seroma – a pocket of serous exudate.

Due to the clinical similarities between lymphatic complications and seroma, they are presented together. A previous systematic review demonstrated a lymphatic complication or seroma incidence of 10.0% after inguinal vascular surgery.[10]

4.3.3 Hematoma

Development of hematoma after inguinal vascular surgical procedures is common, both after open and endovascular procedures, with a previously reported incidence of 5,5%.[10] The high use of intraoperative unfractionated heparin as well as pre- and postoperative anticoagulation and antiplatelet therapy contributes to the high risk of hematoma in vascular surgery. The condition is often self-limiting with natural resorption from the surrounding tissue. Occasionally, the volume of extravasated blood in the tissue is so high that it causes pressure to the surrounding structures, which may lead to skin necrosis and wound dehiscence.

4.3.4 Wound dehiscence

Wound dehiscence is a total or partial, in length or depth, rupture of the sutured incision. Wound dehiscence can occur primary, either due to excess mechanical forces or due to failure of the sutures. Mostly it occurs secondary to other incisional wound complications, which exert internal mechanical pressure upon the wound sutures and hindering the incisional wound edges to heal. Wound dehiscence has previously been reported in 4,8% of incisions after inguinal vascular surgery.[10]

4.3.5 Abnormal scarring

Abnormal scarring is generally divided into hypertrophic and keloid scars. Hypertrophic scars are elevated, broad, and hard, caused by excess collagen deposition and prolonged inflammation. They do not infiltrate the adjacent skin and generally improve in time. Keloid scars are also broad and elevated, but with a shiny surface and softer consistency. In keloid scarring the inflammatory response with collagen deposition is stronger and even further prolonged, which is why keloid scars often spread beyond the original wound and progress over time.[11]

There are several risk factors for development of hypertrophic and keloid scars. For hypertrophic scars young age, allergy, bacterial colonisation, and mechanical stretch are risk factors while chemotherapy, smoking, and statins are protective factors.[12] Keloid scars are highly associated with coloured skin, the location of skin trauma (high risk areas: ear lobe, cheeks shoulders, upper arms and sternum), age (10-30 years old) and elevated hormone levels (i.e. puberty or pregnancy).[13]

Despite not being hypertrophic nor keloid scars, incisional scars may carry several disadvantageous characteristics such as pain[14], itch[15], and psychological discomfort.[16] Incisional scars may therefore affect patients' life without any visual impact.

4.4 Interaction, management, and consequences of incisional wound complications

In clinical practice, distinguishing between different incisional wound complications is often challenging due to their similarities in characteristics. For instance, there are few clinical differences between a lymphorrhea, serous discharge from a SSI and incisional discharge from a seroma. Furthermore, the incisional wound complications often coexist and develop from each other. In Figure 2, an initial hematoma developed into a SSI, resulting in wound dehiscence over a period of six days.

The management of incisional wound complications also bares many similarities between the different complications. One exception is the antibiotic treatment only reserved for SSIs, which is why correct identification of SSIs are important in order to avoid under- and overuse of antibiotics. The non-antibiotic treatment of incisional wound complications is either conservative (no additional treatment or extra wound dressing changes) or invasive (surgical debridement, negative pressure wound therapy [NPWT] [described in section 4.7][17-20], or surgical flap reconstruction[21, 22]). The severity of the incisional wound complication dictates the treatment strategy.

The consequences of an incisional wound complication vary by its severity and treatment strategy. Incisional wound complications increase the risk of failure of the vascular intervention[23, 24], with subsequent increased risk of amputation or mortality. Incisional wound complications and their treatment strategies also pose a strain on healthcare resources and patient morbidity with prolonged hospital stay, extra outpatient visits, re-admission, and re-operations.[25-27]

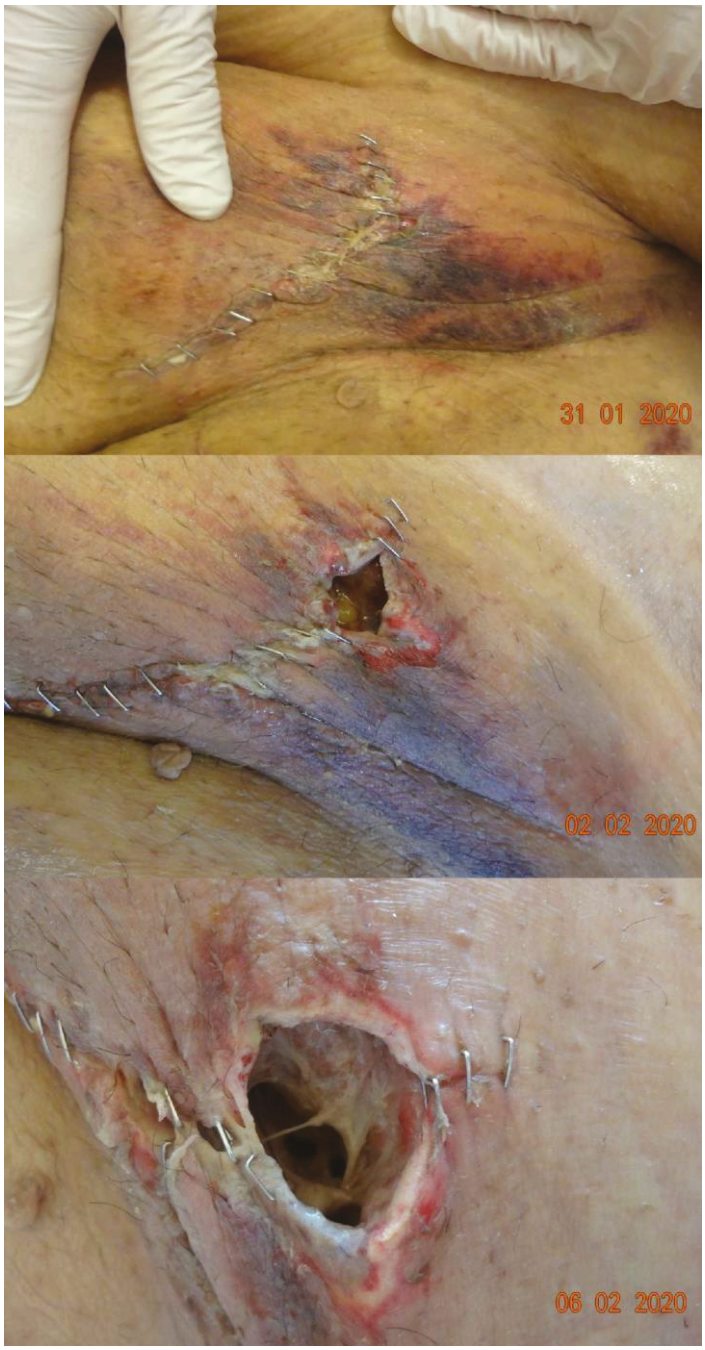

Figure 2 Hematoma, surgical site infection and wound dehiscence
An initial hematoma in the left groin after endovascular aneurysm repair, where the skin over the arterial access site was closed with staples, developed into a surgical site infection with a wound dehiscence within six days, illustrating the dynamics and coexistence of incisional wound complications. Copyright held by the author.

4.5 Risk factors for incisional wound complications

The exact cause of a SSI, the dominating incisional wound complication, cannot be exactly determined on an individual level. There are however risk factors, which are generally divided into patient or procedure related. Wiseman *et al*[28] identified both patient and procedure related risk factors for SSIs after major vascular surgery for aneurysm or lower extremity occlusive disease (Table 3). The authors also developed a model demonstrating that risk factors had an additive effect, leading to exponential risk increases.

Table 3 Patient and procedure related risk factors for surgical site infections
Patient and procedure related risk faktors for surgical site infection development identified by Wiseman *et al*[28]. The risk factors are presented according to their individual risk increase, with the highest risk factor stated first in their respective columns.

Patient related risk factor	Procedure related risk factor
Obesity, body mass index (BMI) ≥30 kg/m^2	Lower extremity revascularisation
Overweigth, BMI 25-29.9 kg/m^2	Aortoiliac procedure
Insulin dependent diabetes mellitus	Operation time >6 hours
Non-insulin dependent diabetes mellitus	Operation time 4-6 hours
Smoking	Groin anastomosis
Hypertension	
Critical limb ischemia	
Dyspnea with moderate exertion	
ASA classification[1] ≥4	
Chronic obstructive pulmonary disease	
Coronary arery disease[2]	
Neurologic disease[3]	

[1] American Society of Anesthesiologists classification: 1, A normal healthy patient; 2, A patient with mild systemic disease; 3, A patient with severe systemic disease; 4, A patient with severe systemic disease that is constant threat to life; 5, A moribund patient who is not expected to survive without operation; 6, A decleared brain-dead patient whose organs are being removed for donor purposes.
[2] Angina, myocardial infarction, percutaneous coronary intervention, or caronary arterial surgery.
[3] Cerebrovascular accident or stroke with or without neurologic deficit; transient ischemic attack; hemi-, para or quadriplegia; central nervous system tumor; or impaired sensorium.

Different inguinal vascular surgical procedures are associated with different risks for development of incisional wound complications. In particular, a large difference in SSI incidence between open (13-33%)[5] and EVAR procedures (2.4-3.5%)[29, 30] has been reported. Further subgrouping of the open vascular surgical procedures has shown a SSI incidence of 22.2% after femoral TEA and 41.1% after lower limb bypass surgery.[31]

4.6 Prevention of incisional wound complications

4.6.1 Surgical site infections

The dominating incisional wound complication is SSIs, and it is estimated that approximately 55% of the SSIs are preventable.[32] Decreasing SSI incidence is therefore the main focus in reducing incisional wound complications. The CDC published an updated guideline for SSI prevention in 2017[33], highlighting the following evidence based pre-, peri- and postoperative prophylactic measures:

- *Antibiotic prophylaxis* – administered preoperatively to obtain an effective serum concentration at the point of the surgical incision.
- *Perioperative glycaemic control* – maintaining a normal level of blood glucose with the target level of <200mg/dl in both patients with and without diabetes mellitus.
- *Normothermia* – maintaining normal body temperature.
- *Increased oxygenation peri- and postoperatively* – increasing the fraction of inspired oxygen in patients with normal pulmonary function undergoing general anaesthesia with endotracheal intubation.
- *Antiseptic preparation* – a full body shower/bath using a soap or antiseptic agent and intraoperative skin preparation with an alcohol-based antiseptic.

In addition, the CDC identified the recommendation from the 1999 guideline to use laminar air flow in operating rooms as accepted practice.[33] Laminar air flow is a ventilation and filtrating system which imposes a homogenous flow of air away from the patient to reduce airborne contamination. It has been used in arthroplasty procedures for decades following the pioneering work of Lidwell *et al*[34] in 1982. Its effect on SSI incidences after vascular surgery is sparsely investigated. Bosanquet *et al*[35] demonstrated in a retrospective cohort study a trend towards fewer SSIs with laminar air flow. Multivariate analysis identified non-laminar air flow as a significant predictor for SSIs in patients receiving arterial grafts.

4.6.2 Non-infectious incisional wound complications

Different surgical approaches have been proposed to minimise the risk of lymphatic complications in inguinal vascular surgery. The use of a transverse incision instead of a vertical has demonstrated a decreased incidence of lymphatic complications[36], while the use of a lateral incision compared to a direct incision over the common femoral artery has not.[37] Careful dissection towards the artery to avoid damaging the fragile and adjacent lymphatic vessels is paramount.[38]

Regarding the risk of postoperative seroma formation, a systemic review with meta-analysis showed a significantly reduced incidence when using quilting and tension sutures for dead space obliteration, however with no studies on inguinal vascular surgical incision included. It also highlighted that usage of drains and adequate time of removal of drains reduced the risk of seromas significantly.[39] This is however not applicable in inguinal vascular surgery, with a RCT demonstrating low volumes of fluids drained and no significant reduction in seroma or hematoma formation.[40]

Regarding abnormal scarring, there are several approaches available to prevent hypertrophic and keloid scar development from surgical incisions. The use of corticosteroid injections has demonstrated significant results in both the prevention and treatment of existing hypertrophic or keloid scars.[13] Non-invasive treatment with silicone gel sheeting[41], union extract[42], and tension-reduction tape[43] have also demonstrated significantly protective effects.

4.7 Negative pressure wound therapy

4.7.1 Introduction and mechanism of action

NPWT was initially developed for the treatment of open wounds by secondary intention. It consists of a semi-permeable polyurethane foam placed within the wound cavity and the application of a sub-atmospheric (i.e. negative) pressure through the foam. The technique was first described in 1997, demonstrating wound healing in 98.7% (n=296/300) of the mainly chronic wounds.[44] Later, several mechanisms of action have been identified as contributors to the favourable results of NPWT[45]:

- *Macrodeformation* – wound shrinkage from the negative pressure distributed through the polyurethane foam.
- *Microdeformation* – the mechanical forces upon the cells in the interface between foam and tissue caused by the suction.
- *Fluid removal* – the removal of excess fluids reduces microbial and toxin load as well as reduces oedema which in turn decreases tissue pressure thereby increasing wound perfusion.
- *Optimising of wound environment* – the semipermeable polyurethane foam maintains wound temperature, moisture and protects the wound from further contamination.

These principal mechanisms of NPWT have secondary effects upon the wound. The mechanical tensions of the macro- och microdeformation increase cellular proliferation and migration of epithelial, endothelial and fibroblast cells. It also

initially decreases the wound edge perfusion, thereby stimulating angiogenesis towards the wound surface. In combination with macrocyte migration and deposition of extracellular matrix, a granulation tissue is formed.[46]

NPWT for open wounds are still in clinical use today, with indication for acute and chronic wounds of traumatic, surgical, burn, diabetic, or pressure origin.[47] It is an established treatment for inguinal SSIs and lymphatic complications after vascular surgery[17-20], and used as well after surgical debridement of seroma or hematoma.

4.7.2 Incisional negative pressure wound therapy

A development from the original NPWT for open wounds are the NPWT dressings for closed incisions – incisional NPWT. These are applied directly on the sutured incision for the purpose to facilitate primary wound healing and to prevent SSIs and other incisional wound complications.

All mechanisms of action of the NPWT for open wounds are not directly applicable for incisional NPWT. Incisional NPWT removes excess fluids[48], enhances lymphatic drainage[49], creates a sealed environment thus preventing direct contamination from the adjacent perianal flora when applied in the groin, reduces mechanical forces on the sutures[50], and reduces the postsurgical inflammatory response[51].

There are several variants of incisional NPWT from different brands available, but the principal constitution is a semi-permeable, multilayer pad through which a negative pressure is applied.[52] The most studied incisional NPWT dressings are the Prevena™ incisional management system (KCI, San Antonio Texas, USA) (Figure 3A) and PICO™ (Smith & Nephew, Watford, UK) (Figure 3B).[5] The Prevena™ incisional management system consists of a two layered dressing with an inner silver-coating, using a continuous pressure of -125 mmHg to drain wound fluids to a 45 ml cannister. The PICO™ dressing consists of four layers, using a continuous pressure of -80 mmHg and handles excess fluids by evaporation. The recommended length of use is 7 days for both dressings.

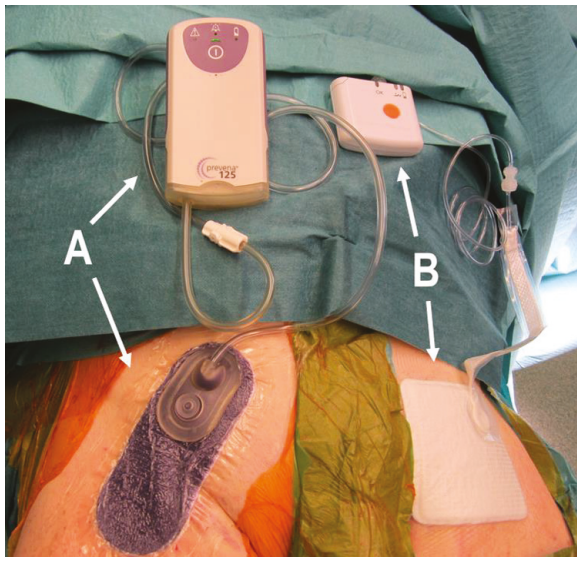

Figure 3 Incisional negative pressure wound therapy dressings
Patient with bilateral inguinal incisions treated with incisional NPWT dressings, right side Prevena™ incisional management system (KCl) (A) and left side PICO™ (Smith & Nephew) (B). Copyright held by Stefan Acosta.

4.8 Cost-effectiveness analysis

4.8.1 Definition

A cost-effectiveness analysis is a type of health economic evaluation which compares an interventional and controlled treatment regarding cost in relation to an effect, for instance cost in relation to survival. This should not be confused with cost-minimisation analyses where the effect of the evaluated treatments is considered equal and evaluated regarding cost only, nor with cost-benefit analyses where the effect of the evaluated treatments is valued in monetary units.[53] The purpose of cost-effectiveness analyses is to guide decisionmakers into where to allocate limited healthcare resources.

To aid comparison of cost data throughout the thesis, costs were, in addition to the originally published currency, also reported as corresponding values in euros at 2019 price year. This mean adjusted for consumer price index of each currency to the year of 2019 and converted according to the mean exchange rate of year 2019.[54]

4.8.2 Interpretation

The result of a cost-effectiveness analysis can be illustrated in a cost-effectiveness plane (figure 4), with cost on the Y-axis (north-south direction) and effect on the X-axis (east-west direction). It constitutes of four quadrants, representing the four principal outcomes. In the southeast quadrant (Figure 4H) the intervention has a lower cost and more beneficial effect. The intervention is then considered dominant to the control treatment and thereby also cost-effective. In the opposite quadrant, the northwest (Figure 4A), the interventional treatment has a higher cost and less beneficial effect. Then the intervention is considered dominated by the control treatment and not cost-effective. In the northeast (Figure 4C) and southwest (Figure 4F) quadrants, the intervention has a higher cost but a more beneficial effect, or a lower cost but a less beneficial effect, respectively. In those quadrants, the determination on whether the intervention is cost-effective or not is decided by the society's willingness to pay for a more beneficial effect or its willingness to accept a less beneficial effect, respectively.[55]

Cost-effectiveness can also be determined when the result is located on the intersections between the quadrants of the cost-effectiveness plane. The intervention is considered cost-effective if it has an equal cost and more beneficial effect (Figure 4E) or a lower cost and equal effect (Figure 4G). The intervention is not considered cost-effective if it has an equal cost and lower effect (Figure 4D) or a higher cost and equal effect (Figure 4B).

An illustrative example of the queries handled in cost-effectiveness analyses is the evaluation of erlotinib (a monoclonal antibody for immunotherapy) in the treatment of advanced pancreatic cancer.[56] The clinical RCT demonstrated a significantly increased median survival time from 5.91 to 6.24 months ($p=0.023$), but also significantly increased incidence of the known side-effect diarrhoea ($p<0.001$).[57] The estimated cost increased from ¥60,493 (Corresponds to €7,562 at 2019 price year) to ¥99,595 (Corresponds to €12,452 in 2019 price year) with erlotinib as additional treatment. The minor increase in survival time was not estimated enough to motivate the substantially increased cost and the authors concluded that additional treatment with erlotinib was not considered cost-effective.[56]

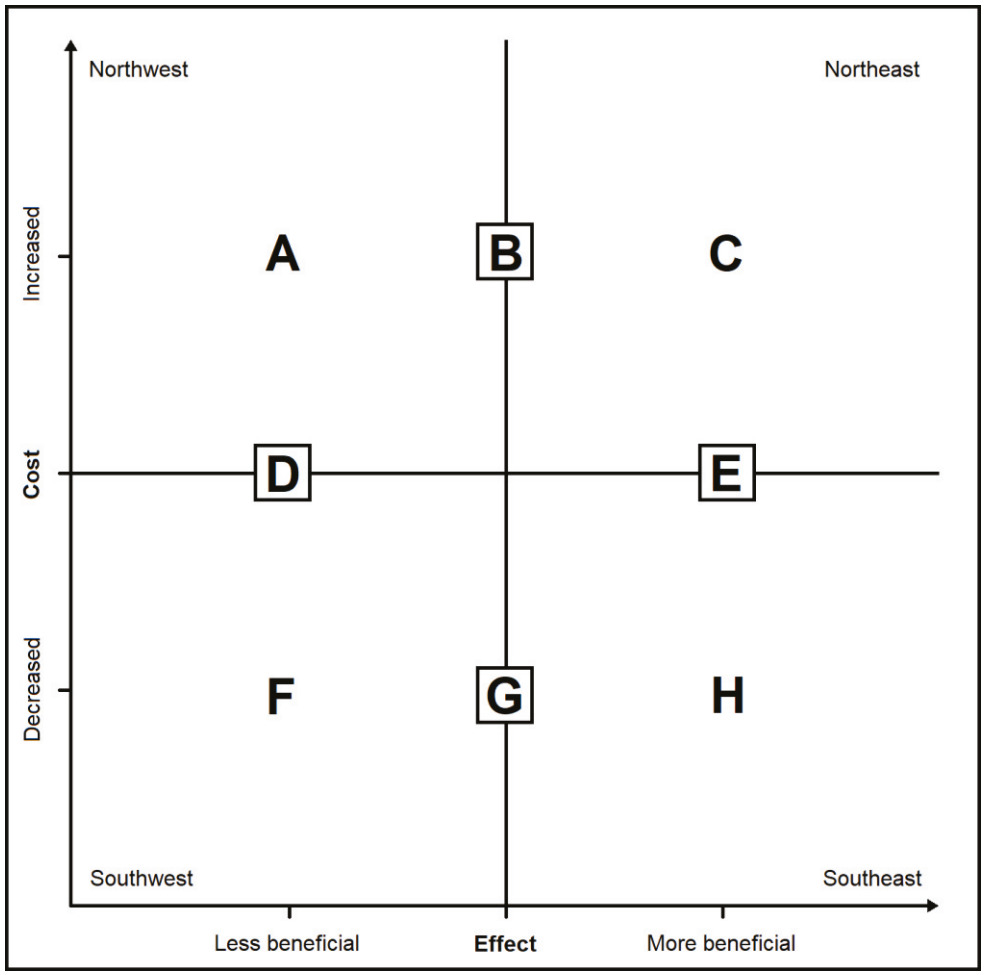

Figure 4 Cost-effectiveness plane
A cost-effectiveness plane illustrating the possible outcomes of a cost-effectiveness analysis, illustrating cost in relation to effect. The northwest quadrant (A), the intersection between the northwest and northeast quadrant (B), the northeast quadrant (C), the intersection between the northwest and southwest quadrant (D), the intersection between the northeast and southeast quadrant (E), the southwest quadrant (F), the intersection between the southwest and southeast quadrant (G), and the southeast quadrant (H). Copyright held by the author.

5 Aims of the thesis

The general aim of this thesis was to evaluate incisional NPWT applied prophylactically on sutured inguinal vascular surgical incisions regarding wound healing, incidence of SSIs and other incisional wound complications, and cost-effectiveness.

The specific aims of the projects were:

I. To compare incisional NPWT with standard dressings regarding incidences of SSIs and other incisional wound complications when applied on incisions after EVAR procedures with the primary intent of fascia closure.

II. To compare incisional NPWT with standard dressings regarding quality of cutaneous scars in bilateral inguinal incisions after vascular surgical procedures and to explore the possibility to evaluate scar visual appearance from three-dimensional (3D) images.

III. To compare incisional NPWT with standard dressings regarding SSI and other incisional complications incidences when applied on inguinal incisions after any arterial surgical procedure.

IV. To evaluate the cost-effectiveness of incisional NPWT compared to standard dressings when applied on inguinal incisions after open vascular surgical procedures.

6 Material and methods

6.1 Overview of studies

	Study I	Study II	Study III	Study IV
Design	Multi-centre RCT	Post-hoc analysis of a single-centre RCT	Systematic review with meta-analysis of RCTs	Cost-effectiveness analysis of a RCT
Study sample	INVIPS-trial's EVAR-arm. Included incisions, n=377.	Subgroup of the INVIPS-trial. Included bilateral incisions, n=66.	Included RCTs n=7. Included incisions, n=1,049.	INVIPS-trial's open-arm. Included unilateral incisions, n=119.
Enrolment	2013-2020	2013-2016	2018	2013-2018
Methods	Uni- or bilateral inguinal incisions after elective EVAR with the primary intent of fascia closure at Skåne University Hospital in Malmö or Örebro University hospital, randomised to incisional NPWT or standard dressings. Outcomes were SSIs and other incisional wound complications at 90 days and one year postoperatively, comparing incisional NPWT with standard dressings.	Bilateral inguinal incisions after elective vascular surgery at Skåne University Hospital in Malmö randomised to incisional NPWT and standard dressing on separate sides. Reinvited for scar evaluation by patient questionnaire and scar documentation with 3D photography. Outcomes were patient-reported satisfaction and visual gradings from 3D images.	Systematic search for RCTs comparing incisional NPWT with any alternative treatment on closed inguinal incisions after elective arterial surgery. Outcomes were incidence of SSIs and other incisional wound complications after all types of arterial surgery (main analysis) and after arterial procedures with open technique (sensitvity analysis).	Unilateral inguinal incisions after open, vascular surgical procedures at Skåne University Hospital in Malmö, randomised to incisional NPWT or standard dressings. Outcomes were *vascular procedure-related cost*, SSI incidence at 90 days postoperatively, and patient QoL.
Data analysis	Descriptive statistics. Fisher's exact test (unilateral). McNemar's test (bilateral). Fisher's method of combining p-values.	Descriptive statistics. Intraclass correlation coefficient. McNemar's test. Wilcoxon signed rank test.	Mantel-Haenszel test, random effect model (Main meta-anaysis) fixed effect model (Sensitivity analysis). I^2-test.	Descriptive statistics. Independent samples t-test. Chi^2-test. Fisher's exact test. Incremental cost-effectiveness ratio. Cost-effectiveness plane with bootstrapping

RCT, randomised controlled trial; NPWT, negative pressure wound therapy; INVIPS, incisional NPWT on vascular surgical incisions in the prevention of SSIs; EVAR, endovascular aneurysm repair; SSI, surgical site infection; 3D, three-dimensional; QoL, quality of life.

6.2 INVIPS-trial

The INVIPS-trial (Incisional NPWT on Vascular surgical Incisions in the Prevention of SSIs) was a RCT comparing incisional NPWT with standard dressings. It consisted of two arms: the open-arm (including open vascular surgical procedures only) and the EVAR-arm. All surgical procedures were elective and included both first time operations and reoperations. Both arms included procedures with both uni- and bilateral inguinal incisions. In bilateral incisions, the randomisation decided the dressing on the right side while the contralateral incision received the opposite type of dressing. Analysis was conducted on an incisional level, where uni- and bilateral incisions were handled separately.

The open-arm was a single-centre RCT including patients operated at Skåne University Hospital, while the EVAR-arm was a multi-centre RCT also including patients from Örebro University Hospital.

All wound dressings, both incisional NPWT and standard dressings, were applied directly onto the closed incision under sterile conditions while still in the operating theatre, to avoid contamination of the surgical incision. The incisional NPWT dressing used in the INVIPS-trial was the PICO™ (Smith & Nephew, Watford, UK). The type of standard dressing varied with surgical procedure, institution and timepoint of surgery (Table 4). All standard dressings included an absorbing pad with a semi-occlusive sheet.

Table 4 Standard dressings used
The stanard dressings used in the INVIPS-trial[1], with the type used varied with type of surgery, institution and timepoint of surgery. All dressings incorporated an absorbing pad with a semi-occlusive sheeting.

INVIPS-trial	Institution	Time period	Standard dressing
Open-arm[1]	Skåne University Hospital in Malmö	2013-2017	ViTri Pad (ViTri medical, Stockholm, Sweden)
		2017-2018	OPSITE Post-op visible™ (Smith & Nephew, Watford, UK
EVAR-arm[2]	Skåne University Hospital in Malmö	2013-2016	Tegaderm™ (3M, Maplewood, Minnesota, US)
		2014-2016	ViTri Pad (ViTri medical, Stockholm, Sweden)
		2014-2020	OPSITE Post-op™ (Smith & Nephew, Watford, UK
	Örebro University Hospital	2017-2020	Mepilex® border (Mölnlycke health care, Gothenburg, Sweden)

[1] Open technique study arm, including arterial procedures conducted with open technique.
[2] Endovascular aneurysm repair study arm, including EVAR-related procedures (EVAR, Thoracic-EVAR, Fenestrated EVAR, EVAR-extensions).

The primary outcome of the INVIPS-trial was SSI incidence, at 90 days (open-arm) or 90 days and one year (EVAR-arm) postoperatively. The secondary outcomes were incidence of other incisional wound complications (lymphatic complications, seroma, hematoma, and wound dehiscence) at the same time-intervals.

The definition and grading used for SSIs were the Szilagyi classification[7], CDC criteria from 1999[8] and a modified ASEPSIS-score[9] (where the original daily points [for a maximum of five days] based on the proportion of wound affected by serous discharge [0-5 points], erythema [0-5 points], purulent exudates [0-10 points] or separation of deep tissues [0-10 points], received a singular point of three [serous discharge or erythema)] or six points [purulent exudates or separation of deep tissues], if present irrespective of timepoint). There was no further modification of the ASEPSIS-score criteria or interpretation.

The study protocol was registered a priori at clinicaltrial.gov (NCT01913132), and has also been published.[58]

6.3 Ethics

Prior to the INVIPS-trial was started, it was approved by the regional ethics review board in Lund (Registration number 2013/322; date of approval 23 May 2013). In addition, a supplementing ethical permit was received from the regional ethics review board in Lund (Registration number 2016/886; date of approval 15 November 2016) for inclusion of patients from Örebro University hospital in study I, for reinvitation of patients from the INVIPS-trial for photographic documentation of scars in study II, and for the cost-effectiveness analysis in study IV. Written informed consent was retrieved for all study participants of the INVIPS-trial after written and oral information of the study. Additional oral informed consent was retrieved from participants of study II regarding their participation of photographic documentation and evaluation of incisional scars.

Study III is a systematic review with meta-analysis, thus not requiring any ethical permit.

6.4 Study I

Study I consists of the INVIPS-trial's EVAR-arm evaluating SSI incidence 90 days postoperatively, whose principal methodology has been described in paragraph 6.2.

Patients operated electively with any EVAR procedure (EVAR, thoracic-EVAR, fenestrated EVAR, EVAR-extensions) via inguinal incisions with the primary intent of fascia closure for femoral artery haemostasis were considered for inclusion. The RCT was conducted on an intention-to-treat basis, including incisions subsequently closed with other techniques as well. The alternative closure techniques were analysed in a per-protocol analysis, comparing SSI incidence with fascia closure compared to alternative arterial closure. EVAR-procedures operated percutaneously

using a percutaneous closure device for arterial closure were excluded due to the lack of a surgical incision. Recruitments were conducted at Skåne University Hospital in Malmö from 2013 to 2020 and Örebro University Hospital from 2017 to 2020.

The power calculation conducted in the study protocol stipulated a SSI incidence decrease from 4.4% with standard dressings to 1.0% with incisional NPWT, a 6.7% non-SSI related mortality rate, a 10% loss to follow-up of other reasons and a 20% proportion of unilateral incisions. This resulted in a calculated sample size of 497 incisions.[58]

6.5 Study II

Study II is a post-hoc analysis of a RCT evaluating postoperative scars from incisions treated with incisional NPWT compared to standard dressings. Study participants were patients of the INVIPS-trial operated with bilateral inguinal incisions at Skåne University Hospital in Malmö. The inclusion criteria were no additional surgical procedure in the inguinal area, no incisional wound complication, and a minimum of one year since surgery. Eligible patients were reinvited for scar evaluation regarding patient-reported satisfaction and visual appearance.

For patient-reported scar satisfaction, the Patient Scar Assessment Score (PSAS) was used as questionnaire. It consists of seven questions answered from one to ten (Table 5).[59]

Table 5 Patient Scar Assessment Scale
The patient scar assessment scale version 2, used as questionnaire for patient-reported satisfaction.

Question	Points	
	1 = No, not at all	**Yes, very much = 10**
1. Has the scar been painful the past few weeks?	1-10	
2. Has the scar been itching the past few weeks?	1-10	
	1 = No, as normal skin	**Yes, very different = 10**
3. Is the scar color different from the color of your normal skin at present?	1-10	
4. Is the stiffness of the scar different from normal skin at present?	1-10	
5. Is the thickness of the scar different from your normal skin at present?	1-10	
6. Is the scar more irregular than your normal skin at present?	1-10	
	1 = As normal skin	**Very different = 10**
7. What is your overall opinion of the scar compared to normal skin?	1-10	

The visual scar evaluation was conducted from 3D images of the inguinal area, taken by a medical photographer in a medical photography studio with predefined settings. A schematic illustration of the 3D camera system used in study II (3dMD trio system [3dMD LLC, Atlanta, Georgia, USA]) is provided (Figure 5).

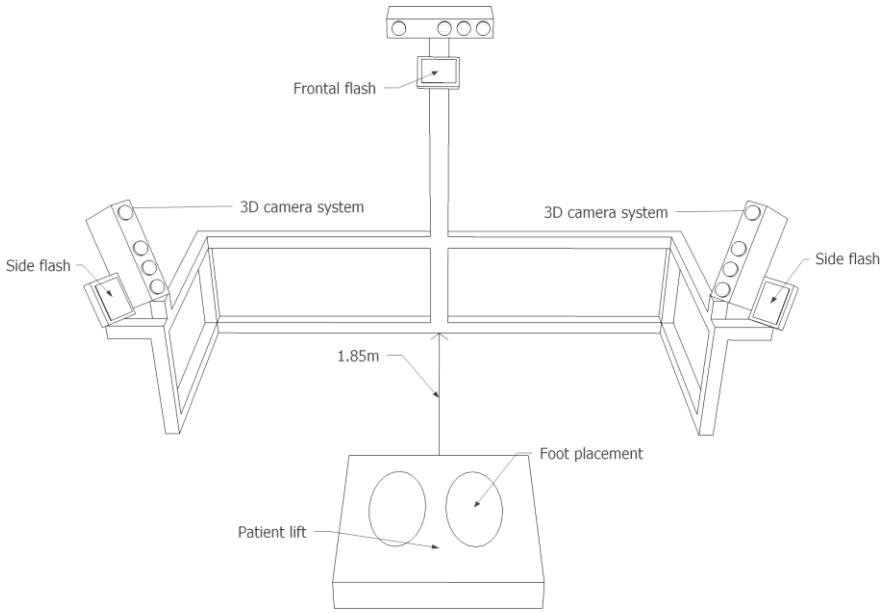

Figure 5 Three dimensional photographic documentation system
Schematic illustration of the three-dimensional camera system 3dMD trio system (3dMD LLC, Atlanta, Georgia, USA). Copyright held by the author.

Table 6 Stony Brook Scar Evaluation Scale and Numbered Ranked Scale
The scoring system of the Stony Brook Scar Evaluation Scale and Numbered Ranked Scale, respectively.

Stony Brook Scar Evaluation Scale	**Points**
Width	
>2 millimeters	0
≤2 millimeters	1
Height	
Elevated or depressed in relation to surrounding skin	0
Flat	1
Colour	
Darker than surrounding skin (red, purple, brown, or black)	0
Same colour or lighter than surrounding skin	1
Hatch marks or suture marks	
Present	0
Absent	1
Overall appearance	
Poor	0
Good	1
Numeric Ranking Scale	**Points**
Overall rating of skin appearance	1-10

The scars were graded for visual appearance according to the Stony Brook Scar Evaluation Scale (SBSES)[60] and a ten-point graded numeric ranking scale (NRS10), where one and ten represented worst and best visual appearance, respectively (Table 6). The grading was conducted by two senior plastic surgeons independently, each on two separate occasions. The assessors were blinded to the wound dressing allocation. Both SBSES and NRS10 were evaluated for intra- and inter-rater reliability.

6.6 Study III

Study III of the present thesis is a systematic review with meta-analysis of RCTs only. It was conducted in accordance with the Cochrane handbook for systematic reviews.[61] Prior to start, a study protocol including instructions for the systematic search, inclusion criteria, data extraction, data synthesis and data analysis, were published in Prospero (Registration number CRD42018090298).[62]

A search template for each included database were formulated. Both published and unpublished data were sought, with no restriction regarding publication language or date. The inclusion and exclusion criteria are summarised according to PICOS (Population, Intervention, Comparison, Outcome, and Study design) in Table 7.

Table 7 Inclusion and exclusion crieria
Summary of the inclusion and exclusion criteria for studies assessed for inclusion of the systematic review with meta-analysis (Study III) according to PICOS (Population, Intervention, Comparison, Outcome, and Study design).

Criterion	Inclusion	Exclusion
Population	Adults ≥18 years	Traumatic wounds
	Elective arterial surgery via groin incision	Acute surgical procedures
	Incisional NPWT[1] applied on closed incision for primary healing	
Intervention	PICO™ (Smith & Nephew, Watford, UK)	NPWT for open wounds
	Prevena™ incisional management system (KCI, San Antonio Texas, USA)	
Comparison	Any type of non-NPWT dressing	-
	No wound dressing	
Outcome	Surgical site infection	-
	Seroma formation	
	Wound dehiscense	
	Abnormal scarring	
	Adverse reaction to incisional NPWT dressing	
Study design	Randomised controlled trials	Cross-over trials
		Randomised trials with quasi-randomisation

1 Negative pressure wound therapy

The generated records from the systematic search were automatically screened for duplicates and manually assessed for inclusion, first through screening of titles and abstracts and then by full-text review of the selected RCTs. The screening and full-text reviews were conducted by two study administrators independently. Disagreements about eligibility were settled by consensus.

The included RCTs were graded for risk of bias using the Cochrane risk-of-bias tool.[61] The grading was undertaken by two of the study authors independently and disagreements solved by consensus. Any included RCT published by the study authors was graded by two adjudicators independent to the conducted systematic review and the study authors. The Cochrane risk-of-bias tool grades a RCT according to seven domains for risk of bias (low, unclear, or high risk) (Figure 6).

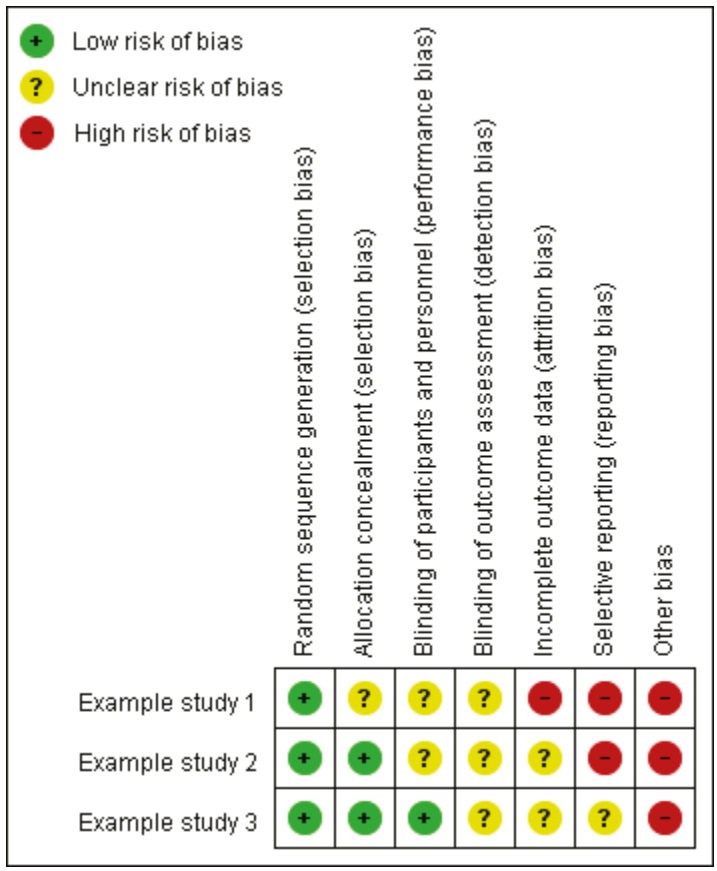

Figure 6 Cochrane risk of bias tool
An illustration demonstrating three studies graded for risk of bias according to Cochrane risk of bias tool. Copyright held by the author.

The data from the included RCTs were extracted and pooled for meta-analysis. The primary analysis included all inguinal incisions for any arterial surgical procedure. The sensitivity analysis included inguinal incisions for arterial revascularisation procedures with open technique only.

The quality of the outcomes of the meta-analyses were assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluation), which provide four levels of certainty of the evidence: high, moderate, low, or very low. A systematic review with meta-analysis of RCTs only starts with a high level of certainty and is thereafter assessed for: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Each domain could result in a downgrading of one or two levels if a shortage is identified.[63]

6.7 Study IV

Study IV is a cost-effectiveness analysis comparing incisional NPWT to standard dressings on inguinal incisions after open vascular surgical procedures. It is based on patients with unilateral incisions from the INVIPS-trial's open-arm (paragraph 6.2) which results were published prior to the cost-effectiveness analysis.[64]

The cost-effectiveness analysis was conducted from a healthcare perspective, including all direct costs to the in- and outpatient care at the hospital only. The cost data were based on the local county council's cost-per-patient system which contained the actual, individual cost data for each participating patient. Costs were reported as *all healthcare cost* and as *vascular procedure-related cost* only.

The effects included were SSI incidence and patient quality of life (QoL). SSIs were defined by ASEPSIS-score and patient QoL using Vascuqol-6. Vascuqol-6 is a peripheral vascular disease specific questionnaire for patient QoL, consisting of six items, graded from one (severe problems) to four (no problems) (Table 8).[65]

In the cost-effectiveness analysis, cost and effect data were reported as incremental cost-effectiveness ratios (ICER). ICERs are calculated by dividing the difference in mean cost by the difference in effect (Δcost/Δeffect) between the incisional NPWT and standard dressing group.

The ICERs of *vascular procedure-related cost* and difference in pre- and postoperative Vascuqol-6 score (point estimates) were plotted into cost-effectiveness planes. The uncertainty was measured using bootstrapping with 5,000 replications and plotted into the cost-effectiveness planes.[66] The distribution in each quadrant were calculated. An example of a cost-effectiveness plane with bootstrapping is shown in Figure 7.

Table 8 The Vascuqol-6 questionnaire

Vascuqol-6, the peripheral vascular disease specific questionnaire used to measure patient quality of life in study IV.

Question	Points
Because of the poor circulation in my legs, the range of activities that I would have liked to do in the past two weeks has been:	
Severly limited	1
Moderatly limited	2
Mildly limited	3
Not at all limited	4
During the past two weeks, my legs felt tired or weak:	
All of the time	1
Most of the time	2
Some of the time	3
None of the time	4
During the past two weeks, because of the poor circulation in my legs, my ability to walk has been:	
Extremly limited	1
Limitied to a large extent	2
Limitied to a small extent	3
Not at all limited	4
During the past two weeks, I have been concerned about having poor circulation in my legs:	
All of the time	1
Most of the time	2
Some of the time	3
None of the time	4
During the past two weeks, because of the poor circulation in my legs, my ability to participate in social activities has been:	
Totally limited	1
Very limited	2
Mildly limited	3
Not at all limited	4
During the past two weeks, when I have had pain in the leg (or foot) it has given me:	
A great deal of discomfort or distress	1
Moderate discomfort or distress	2
Some discomfort or distress	3
No discomfort or distress	4

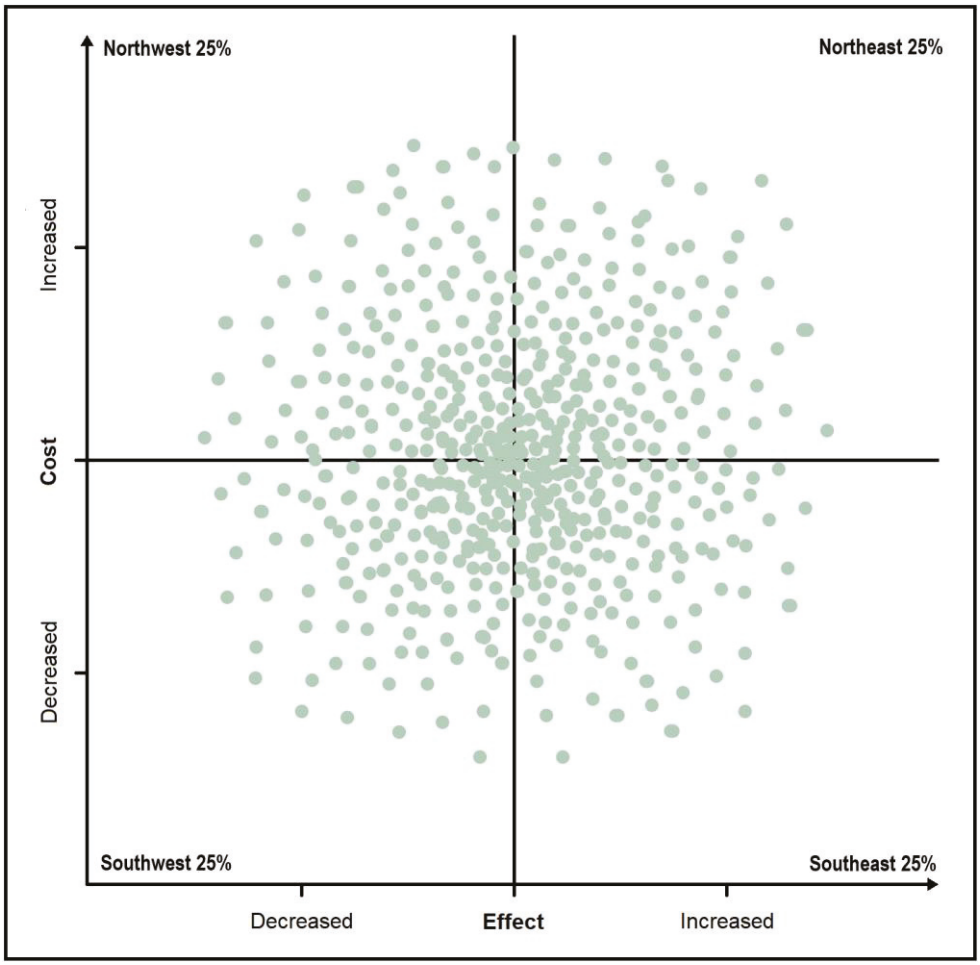

Figure 7 Example of cost-effectiveness plane with bootstrapping
A cost-effectiveness plane with bootstrapping illustrating the uncertainty of the cost and effect data. The allocation of bootstrapped data in the example cost-effectiveness plane is evenly distributed between the quadrants. Copyright held by the author.

6.8 Statistics

Incisions from uni- and bilaterally operated patients were handled separately. For comparison of frequencies between two groups, Chi^2 test or Fisher's exact test were used in unilateral incisions (study I, IV) while McNemar's test were used in bilateral incisions (study I, II). Continuous data were expressed as mean with standard deviation (study IV) or median with interquartile range (IQR) (study I, II). For comparison of continuous data, independent samples t-test were used in unilateral incisions (study IV) while Wilcoxon signed-rank test were used in bilateral incisions (study II). The obtained p-values from the separate analyses for uni- and bilateral incisions were combined using Fisher's method of combining p-values (study I). All p-values of <0.05 were considered significant.

Intra- and inter-rater reliability were assessed using intraclass correlation coefficients (study II), which were interpreted as: <0.20, poor; 0.21-0.40, fair; 0.41-0.60, moderate; 0.61-0.80, good; >0.81, very good.

In meta-analysis, Mantel-Haenszel test with random or fixed effect model was used. For assessment of meta-analysis heterogeneity, I^2 was used. The interpretation of I^2 was: <40%, might not be important; 30-60%: may represent moderate heterogeneity; 50-90%: may represent substantial heterogeneity; 75-100%, considerable heterogeneity.

Floor and ceiling effects were sought (study II) and defined as receiving >15% of the lowest or highest possible grade, respectively.

7 Results

7.1 Study I

7.1.1 Population

Between September 2013 and December 2020, 498 incisions (446 bi- and 52 unilateral) were randomised, of which 377 incisions (336 bi- and 41 unilateral) were included in the trial. For detailed information about patient enrolment, base-line characteristics, pre-, peri-, and postoperative data, see Figure 8 and Table 9-10.

Table 9 Base-line characteristics
Base-line characteristics of included patients, presented per incision.

Patient characteristis n, (%)	Bilateral		Unilateral	
	iNPWT[1] n=168	Std dres[2] n=168	iNPWT[1] n=15	Std dres[2] n=26
Median age, years (IQR[3])	73.3 (9.1)		75.2 (8.9)	74.3 (8.5)
Male sex	146 (86.9)		10 (66.7)	18 (69.2)
Median BMI[4], kg/m^2 (IQR[3])	27.0 (5.1)		28.7 (6.9)	26.0 (5.8)
Hypertension	130 (77.4)		15 (100.0)	21 (80.8)
Ischemic heart disease	69 (41.1)		7 (46.7)	12 (46.2)
Peripheral artery disease	9 (5.4)	9 (5.4)	0 (0.0)	6 (23.1)
Cerebrovascular disease	26 (15.5)		4 (26.7)	0 (0.0)
Diabetes mellitus	34 (20.2)		5 (33.3)	2 (7.7)
Lifestyle treatment	3 (1.8)		1 (6.7)	2 (7.7)
Non-insulin pharmacologic	21 (12.5)		0 (0.0)	0 (0.0)
Insulin treatment	10 (6.0)		4 (26.7)	0 (0.0)
Smoker				
Current	42 (25.0)		2 (13.3)	4 (15.4)
Previous	105 (62.5)		9 (60.0)	17 (65.4)
Previous vascular surgery	22 (13.1)		6 (40.0)	9 (34.6)
Previous groin incisions	27 (16.1)	23 (13.7)	6 (40.0)	9 (34.6)
Medication				
Anticoagulants	32 (19.0)		4 (26.7)	5 (19.2)
Platelet inhibitor				
Single	129 (76.8)		9 (60.0)	20 (76.9)
Dual	7 (4.2)		1 (6.7)	1 (3.8)
Steroid treatment	22 (13.1)		0 (0.0)	2 (7.7)
Ipsilateral foot wound	1 (0.6)	2 (1.2)	0 (0.0)	0 (0.0)

[1] Standard dressing
[2] Incisional Negative Pressure Wound Therapy
[3] Interquartile range
[4] Body mass index.

Table 10 Pre-, peri- and postoperative data

Pre-, peri- and postoperative data of included patients, presented per incision.

Patient characteristis n, (%)	Bilateral		Unilateral	
	iNPWT[1] n=168	Std dres[2] n=168	iNPWT n=15	Std dres n=26
Preoperative				
Anaemia[3] (%)	58 (34.5)		7 (46.7)	9 (34.6)
Antibiotic treatment (%)	2 (1.2)		0 (0.0)	0 (0.0)
Median albumin level, g/L (IQR[4])	38.0 (5.0), n=167		38.5 (7.5) n=14	38.0 (4.0)
Median glucose level, mmol/L (IQR)	7.1 (2.9)		6.8 (5.8)	7.0 (2.0)
Median eGFR[5], mL/min/1.73m^2 (IQR)	71.0 (27.8)		60.0 (36.0)	63.0 (34.5)
ASA[6] classification				
Grade 2 (%)	20 (11.9)		1 (6.7)	4 (15.4)
Grade 3 (%)	134 (79.8)		10 (66.7)	19 (73.1)
Grade 4 (%)	14 (8.3)		4 (26.7)	3 (11.5)
Perioperative				
Antibiotic prophylaxis (%)	168 (100.0)		15 (100.0)	26 (100.0)
Indication				
Abdominal aortic aneurysm (%)	141 (83.9)		7 (46.7)	11 (42.3)
Thoracic aortic aneurysm (%)	10 (6.0)		3 (20.0)	7 (26.9)
Iliac aneurysm (%)	8 (4.8)		1 (6.7)	0 (0.0)
Endoleak (%)	8 (4.8)		1 (6.7)	2 (7.7)
Pseudoaneurysm (%)	1 (0.6)		0 (0.0)	4 (15.4)
Aortic dissection (%)	0 (0.0)		1 (6.7)	2 (7.7)
Stent migration (%)	0 (0.0)		2 (13.3)	0 (0.0)
Type of surgery				
EVAR[7] (%)	115 (68.5)		6 (40.0)	8 (30.8)
Fenestrated/branched EVAR (%)	34 (20.2)		2 (13.3)	5 (19.2)
Thoracic EVAR (%)	10 (6.0)		4 (26.7)	11 (42.3)
Redo-surgery	9 (5.4)		3 (20.0)	2 (7.7)
Main device laterality (%)	85 (50.6)	11 (73.3)	11 (73.3)	18 (69.2)
Type of arterial closure				
Fascia closure (%)	117 (69.6)	120 (71.4)	8 (53.3)	18 (69.2)
Cut-down (%)	45 (26.8)	42 (25.0)	6 (40.0)	5 (19.2)
Patch angioplasty (%)	2 (1.2)	2 (1.2)	0 (0.0)	1 (3.8)
Patch angioplasty with TEA[8]	2 (1.2)	1 (0.6)	0 (0.0)	1 (3.8)
TEA[8] without patch (%)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
Interposition graft (%)	0 (0.0)	1 (0.6)	0 (0.0)	1 (3.8)
Femoro-femoro crossover (%)	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)
Unspecified (%)	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)
Skin closure				
Intracutaneous sutures (%)	157 (93.4)	158 (94.0)	14 (93.3)	25 (96.2)
Percutaneous matrass (%)	2 (1.2)	1 (0.6)	0 (0.0)	0 (0.0)
Staples (%)	9 (5.4)	9 (5.4)	1 (6.7)	1 (3.8)
Median operation time, min (IQR)	193.5 (121.8)		180.0 (223.0)	201.0 (178.8)
Postoperative				
Intensive care (%)	26 (15.5)		6 (40.0)	11 (42.3)
Prolonged antibiotic treatment (%)	10 (6.0)		1 (6.7)	3 (11.5)
Hyperglycemia[9] (%)	42 (25.8) n=163		4 (26.7)	11 (42.3)

[1] Standard dressing
[2] Incisional Negative Pressure Wound Therapy
[3] Haemoglobin concentration of <11.7 g/dL in females and <13.4 g/dL in males
[4] Interquartile range
[5] Estimated glomerular filtration rate
[6] American society of anaesthesiologists classification
[7] Endovascular aneurysm repair
[8] Femoral thromboendarterectomy
[9] Blood glucose concentration of >200 mg/dL.

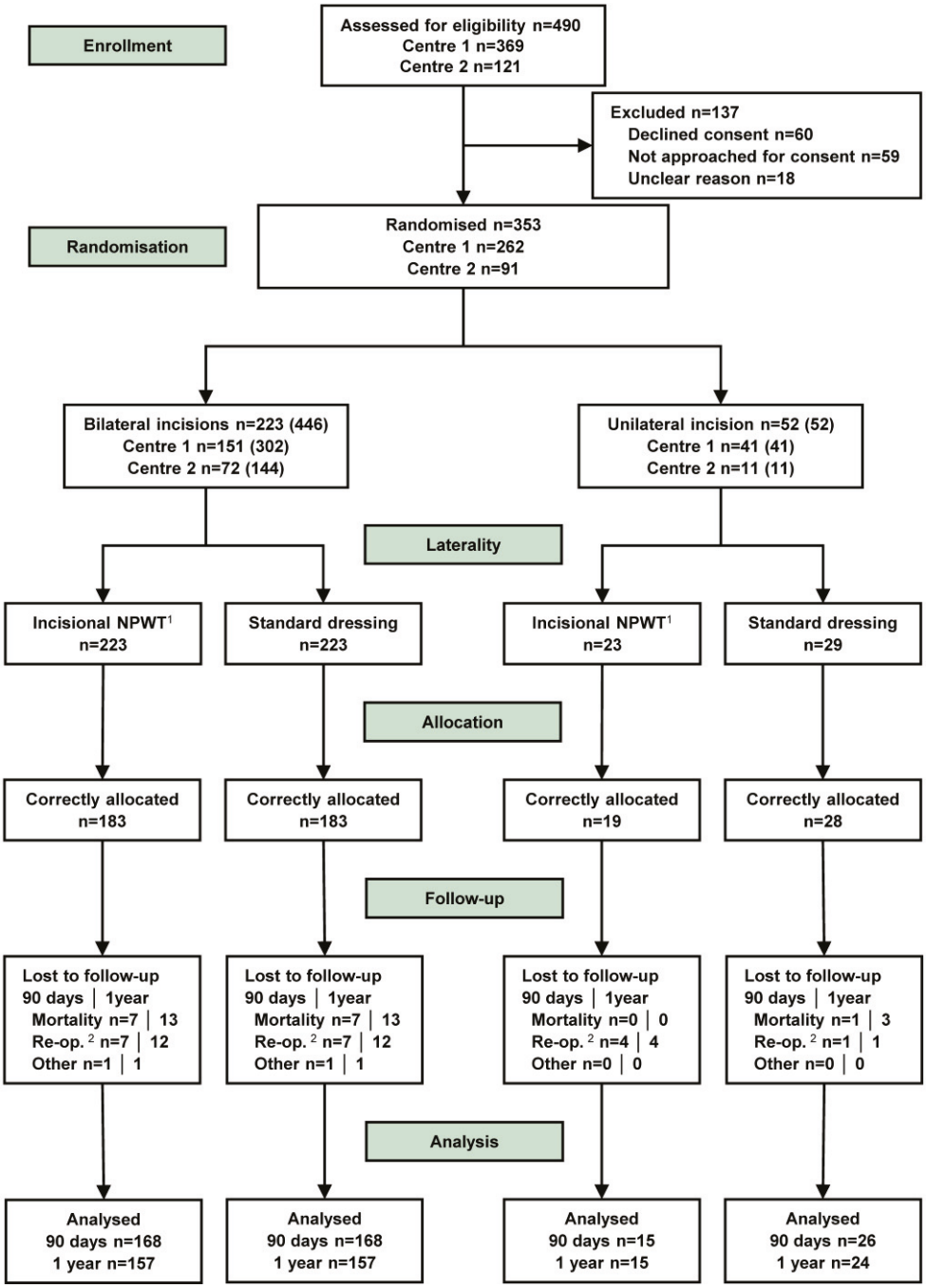

Figure 8 CONSORT flow chart
A CONSORT (Consolidated Standards of Reporting Trials) flow diagram illustrating the patient enrolment to the INVIPS-trial's Endovascular Aneurysm Repair-arm. [1] Negative Pressure Wound Therapy. [2] Re-operation.

7.1.2 Outcomes

In patients operated bilaterally, 1.8% (n=3/168) and 4.8% (n=8/168) of the incisions treated with incisional NPWT and standard dressings, respectively, developed a SSI at 90 days postoperatively (p=0.18). In unilateral incisions, 13.3% (n=2/15) and 11.5% (n=3/26) in the incisional NPWT and standard dressing group, respectively, developed a SSI at 90 days postoperatively (p=1.0). Combining the obtained p-values from bi- and unilateral incisions using Fisher's method yielded a combined p-value of 0.49. There was no difference in SSI incidence using the ASEPSIS-score or CDC criteria as SSI definition (Table 11). In all SSIs, bacteria were isolated in microbiological analysis of incisional wound cultures. No difference in SSI incidence were detected comparing the different standard dressings used within study I (p=0.40) (Table 12)

No SSI developed into a sepsis. One patient with bilateral incisions developed an aortic stent graft infection verified by PET-CT and microbiological analysis of aspirated fluid from the aneurysm sac. The source of the aortic stent graft infection was never determined, and the inguinal incisions had healed without complications.

The incidence of the non-infectious wound complications (seroma or lymphatic complications, hematoma, and wound dehiscence) showed no differences among incisions treated with incisional NPWT compared to standard dressings (Table 11).

Additional treatment due to any incisional wound complication was reported in 2.4% (4/168) and 6.5% (11/168) of bilateral incisions treated with incisional NPWT and standard dressings (p=0.065), respectively, and 13.3% (2/15) and 15.4% (4/26) of the unilateral incisions (p=1.0), respectively (Table 11).

7.1.3 Per-protocol analysis

A per-protocol analysis based on arterial closure technique used in both the bi- and unilaterally operated incisions showed a 90 days SSI incidence of 2.7% with fascia closure (n=7/263 [NPWT dressings: 2.4%, n=3/125; standard dressings: 2.9%, n=4/138]), 5.1% with cut-down (n=5/98 [NPWT dressings: 2.0%, n=1/51; standard dressings: 8.5%, n=4/47]), and 28.6% with patch angioplasty or interposition graft (n=4/14 [NPWT dressings: 16.7%, n=1/6; standard dressings: 37.5%, n=3/8]). Comparison of SSI incidence with fascia closure (2.7%, n=7/263) versus any of the bale-out techniques (8.0%, n=9/112), generated a combined p-value of 0.13.

Table 11 Outcomes of the INVIPS-trial's Endovascular Aneurysm Repair-arm

Outcomes of the INVIPS-trial's Endovascular Aneurysm Repair-arm with bi- and unilateral incisions presented separatly. P-values were caluculated with McNemar's test in bilateral incisions and Fisher's exact test in unilateral incisions.

Results n, (%)	Bilateral			Unilateral		
	iNPWT[1] n=168	Std dres[2] n=168	p-value	iNPWT[1] n=15	Std dres[2] n=26	p-value
Surgical site infecton (SSI)						
ASEPSIS score[3]	3 (1.8)	8 (4.8)	0.18	2 (13.3)	3 (11.5)	1.0
Satisfactory healing	160 (95.2)	155 (92.3)		13 (86.7)	23 (88.5)	
Disturbed healing	5 (3.0)	5 (3.0)		0 (0.0)	0 (0.0)	
Minor SSI	1 (0.6)	3 (1.8)		0 (0.0)	0 (0.0)	
Moderate SSI	0 (0.0)	1 (0.6)		0 (0.0)	0 (0.0)	
Severe SSI	2 (1.2)	4 (2.4)		2 (13.3)	3 (11.5)	
CDC criteria[4]	3 (1.8)	8 (4.8)	0.18	2 (13.3)	3 (11.5)	1.0
Superficial SSI	1 (0.6)	4 (2.4)		0 (0.0)	0 (0.0)	
Deep	2 (1.2)	4 (2.4)		2 (13.3)	3 (11.5)	
Organ/space	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Isolation of bacteria	5 (3.0)	9 (5.4)		2 (13.3)	3 (11.5)	
Median time to SSI, days (IQR[5])	14.0 (14.0)	8.0 (n/a)		7.0 (n/a)	18.0 (n/a)	
Other incisional wound complications						
Hematoma	16 (9.5)	15 (8.9)	1.0	3 (20.0)	5 (19.2)	1.0
Seroma/lymphatic complications	4 (2.4)	8 (4.8)	0.29	0 (0.0)	1 (3.8)	1.0
Wound dehiscence	4 (2.4)	6 (3.6)	0.73	2 (13.3)	3 (11.5)	1.0
Clinical implication scale						
Clinical implication scale ≥1	4 (2.4)	11 (6.5)	0.065	2 (13.3)	4 (15.4)	1.0
1. Prolonged in-hospital stay	1 (0.6)	0 (0.0)		0 (0.0)	0 (0.0)	
2. Extra outpatient visit	1 (0.6)	6 (3.6)		0 (0.0)	1 (3.8)	
3. Readmission without surgery	0 (0.0)	2 (1.2)		0 (0.0)	0 (0.0)	
4. Readmission with surgery	2 (1.2)	3 (1.8)		2 (13.3)	3 (11.5)	
5. Wound related amputation	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
6. Wound related death	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	

[1] Incisional Negative Pressure Wound Therapy
[2] Standard dressing
[3] Additional treatment, Serous discharge, Erythema, Purulent exudate, Separation of the deep tissues, Isolation of bacteria and duration of inpatient Stay
[4] Centers for Disease Control and Prevention
[5] Interquartile range

Table 12 Incidence of surgical site infections with different standard dressings

The incidences of surgical site infections with different types of standard dressings. Using Fisher's exact test, no significant difference between the different standard dressings was identified (p=0.40).

Standard dressing n (%)	Unilateral surgical site infection	Bilateral surgical site infection	Total surgical site infection
Tegaderm™ (3M, Maple-wood, Minnesota, US)	0/11 (0.0)	4/73 (5.5)	4/84 (4.8)
ViTri Pad (ViTri medical, Stockholm, Sweden)	0/3 (0.0)	1/28 (3.6)	1/31 (3.2)
OPSITE Post-op™ (Smith & Nephew, Watford, UK	2/8 (25.0)	1/2 (50.0)	3/10 (30.0)
Mepilex® border (Möln-lycke health care, Gothenburg, Sweden)	1/2 (50.0)	2/56 (3.6)	3/58 (5.2)
Unspecified	0/2 (0.0)	0/9 (0.0)	0/11 (0.0)

7.1.4 Main findings

I. No evidence of difference in SSI incidence when comparing incisional NPWT with standard dressings after EVAR with the primary intent of fascia closure.

II. A trend towards fewer incisions with additional treatment due to any incisional wound complication in incisions treated with incisional NPWT compared to standard dressings in patients operated bilaterally.

III. The SSI incidence after EVAR procedures with the primary intent of fascia closure was low and therefore must be analysed separately from incisions from other inguinal vascular surgical procedures.

7.2 Study II

7.2.1 Population

Of the 75 patients meeting the inclusion criteria, 53 were approached for inclusion and 33 patients were included in the post-hoc analysis of a RCT (Figure 9). The majority of base-line characteristics were patient-related and thereby identical for the bilateral incisions. There was no difference in incision-related characteristics between incisions treated with incisional NPWT compared to standard dressings (Table 13).

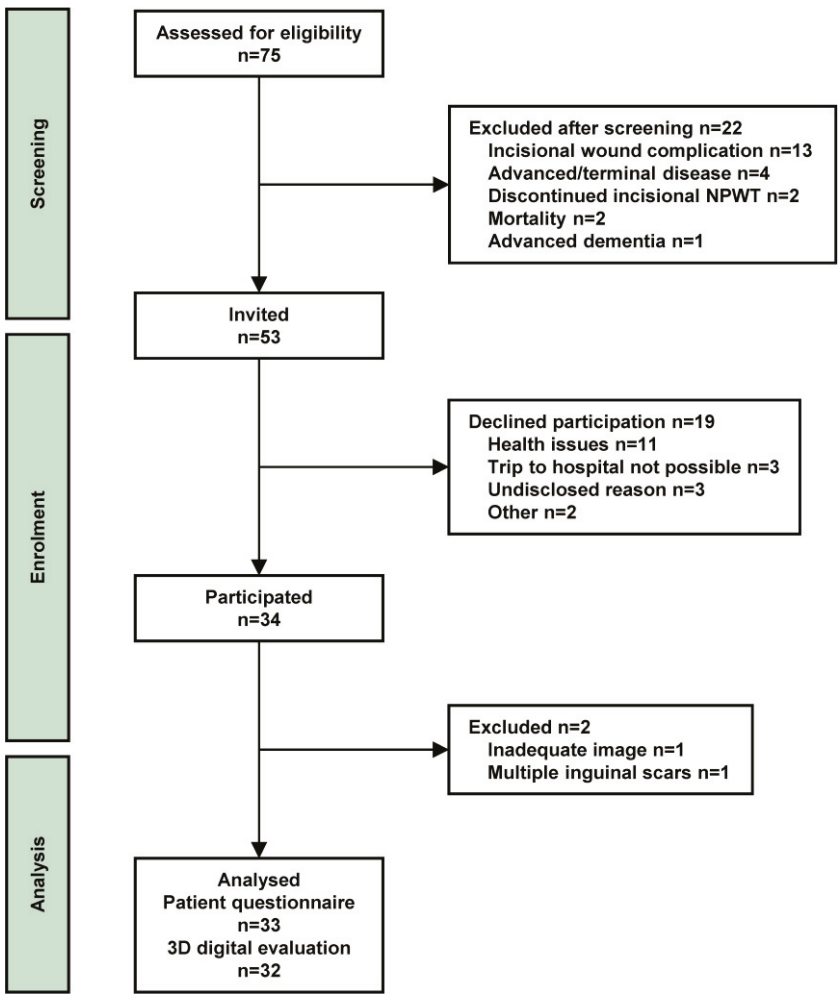

Figure 9 Flow chart of patient enrolment and inclusion
A flow chart of patient enrolment and inclusion.

Table 13 Base-line characteristics
Base-line characteristics of included patients, presented per incision.

Patient characteristis n, (%)	Incisional NPWT n=33	Standard dressing n=33
Median age, years (IQR[1])	71.3 (8.2)	
Male sex	27 (81.8)	
Median BMI[2], kg/m^2 (IQR[1])	27.1 (5.0)	
Hypertension	27 (81.8)	
Ischemic heart disease	11 (33.3)	
Cerebrovascular disease	4 (12.1)	
Diabetes mellitus	8 (24.2)	
Smoker, previous/current	16 (48.5)/11 (33.3)	
Preoperative anemia[3]	7 (21.2)	
Median preoperative albumin level, g/L (IQR[1])	38 (3), n=25	
Median preoperative glucose level, mmol/L (IQR[1])	8.6 (3.1)	
Median preoperative eGFR[4], ml/min/1,73m^2 (IQR[1])	75 (30.5)	
Surgical procedure		
EVAR[5]	32 (97.0)	
Femoral TEA[6]	1 (3)	
Incision		
Transversal	31 (93.9)	31 (93.9)
Longitudinal	2 (6.1)	2 (6.1)
Arterial closure		
Fascia suture	27 (81.8)	26 (78.8)
Cut-down	5 (15.2)	6 (18.2)
Patch angioplasty	1 (3.0)	1 (3.0)
Median operation time, minutes (IQR)	182 (98)	
Median hospital stay, days (IQR)	5 (2)	
Median time surgery to photography, days (IQR)	808 (273)	

[1] Interquartile range
[2] Body mass index
[3] Haemoglobin concentration of <11.7 g/dL in females and <13.4 g/dL in males
[4] Estmated glomerular filtration rate
[5] Endovascular aneurysm repair
[6] Thromboendarterectomy

7.2.1 Outcomes

The median total score of the PSAS questionnaire for patient-reported satisfaction was seven for scars from incisions treated with incisional NPWT (range 7-29 points) and standard dressings (range 7-51 points), p=0.13. The median total score of the SBSES visual grading was four (range 1-5) in both scars from incisions treated with incisional NPWT and standard dressings, p=0.86. The median NRS10 score of the visual grading was nine for scars from incisions treated with incisional NPWT (range 4-10 points) and standard dressings (range 3-10 points), p=0.80 (Table 14 and Figure 10).

Analysis of the distribution of scores for scars from incisions treated with incisional NPWT compared to standard dressings showed that 60.6% (n=20/33) and 57.6% (n=19/33) received the lowest possible PSAS total score, 18.8% (n=6/32) and 21.9% (n=7/32) received the highest possible SBSES total score, and 43.8% (n=14/32) and 37.5% (n=12/32) received the highest possible NRS10 score, respectively.

Table 14 Outcomes

Outcomes of the patient questionnaire (Patient Scar Evaluation Scale) and visual scar evaluation (Stony Brook Scar Evaluation Scale and Ten-point graded Numeric Ranking Scale), presented per incision.

Outcome Median score, (range)	Incisional NPWT	Standard dressing	P-value
Patient questionnaire	**n=33**	**n=33**	
PSAS[1] total	7 (7-29)	7 (7-51)	0.13
Pain	1 (1-3)	1 (1-5)	
Itching	1 (1-3)	1 (1-8)	
Colour	1 (1-5)	1 (1-7)	
Stiffness	1 (1-5)	1 (1-7)	
Thickness	1 (1-5)	1 (1-8)	
Irregularity	1 (1-5)	1 (1-9)	
Overall satisfaction	1 (1-7)	1 (1-7)	
Visual evaluation by three-dimensional images	**n=32**	**n=32**	
SBSES[2] total	4 (1-5)	4 (1-5)	0.86
Width >2 millimeters	0 (0-1)	0 (0-1)	
Elevated or depressed in relation to surrounding skin	1 (0-1)	1 (0-1)	
Darker than surrounding skin	1 (0-1)	1 (0-1)	
Hatch or suture marks	1 (1-1)	1 (1-1)	
Poor overall appearance	1 (0-1)	1 (0-1)	
NRS10[3]	9 (4-10)	9 (3-10)	0.80

[1] Patient Scar Assessment Scale
[2] Stony Brook Scar Assessment Scale
[3] Ten-point graded Numeric Ranking Scale

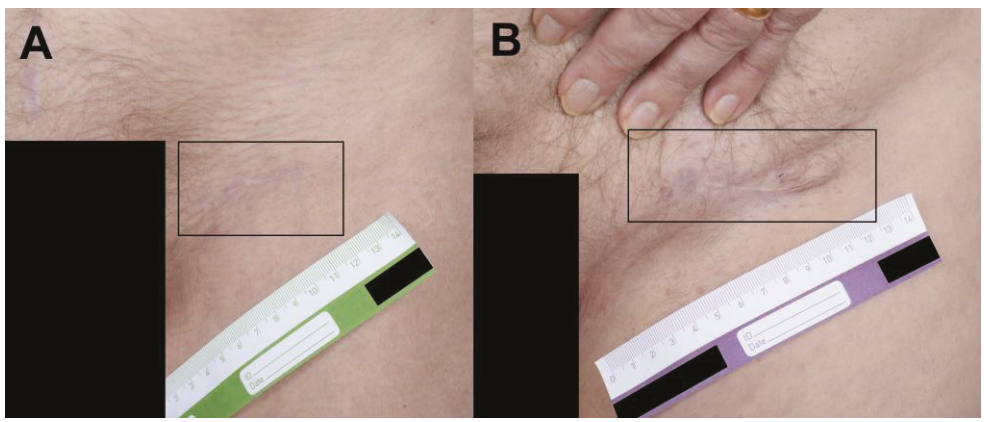

Figure 10 Examples of scars from inguinal incisions after endovascular aneurysm repair

Inguinal scars from incisions after endovascular aneurysm repair. Scar on left side (within black rectangle) receiving a mean Stony Brook Scar Assessment Scale (SBSES) score of five (A), and scar on left side (within black rectangle) receiving a mean SBSES score of two (B). Copyright held by the author.

The intra-rater reliability expressed as intraclass correlation coefficients (ICC) ranged from 0.77-0.88 for the SBSES total score and 0.66-0.85 for the NRS10 score, which are both interpreted as good to very good. The ICC for inter-rater reliability ranged from 0.56-0.78 for the SBSES total score and 0.37-0.77 for the NRS10 score, interpreted as moderate to good and fair to good, respectively (Table 15).

Table 15 Assessment of intra- and inter-rater reliability visual scar evalation

Intra- and inter-rater reliability for the Stony Brook Scar Evaluation Scale and Ten-point Numeric Ranking Scale expressed as intra-class coefficients with 95% confidence intervals.

Outcome	Incisional NPWT n=32		Standard dressing n=32	
	ICC[1]	95% CI[2]	ICC[1]	95% CI[2]
Intra-rater reliability, assessor no 1				
SBSES total score[3]	0.78	0.54-0.89	0.81	0.61-0.91
NRS10[4]	0.66	0.31-0.84	0.85	0.70-0.93
Intra-rater reliability, assessor no 2				
SBSES total score[3]	0.77	0.53-0.89	0.88	0.75-0.94
NRS10[4]	0.77	0.52-0.89	0.80	0.59-0.90
Inter-rater reliability, assessment no 1				
SBSES total score[3]	0.57	0.11-0.79	0.56	0.09-0.78
NRS10[4]	0.37	-0.30-0.69	0.59	0.15-0.80
Inter-rater reliability, assessment no 2				
SBSES total score[3]	0.78	0.54-0.89	0.70	0.38-0.85
NRS10[4]	0.68	0.34-0.84	0.77	0.54-0.89

[1] Intraclass Correlation Coefficient
[2] 95% Confidence Interval
[3] Stony Brook Scar Evaluation Scale
[4] Ten-point graded Numeric Ranking Scale

7.2.2 Main findings

I. Patient-reported and visual evaluation of scars from inguinal incisions treated with incisional NPWT compared to standard dressings after mainly EVAR procedures with bilateral incisions showed equally subtle visual appearance with few patient-reported symptoms.

II. Visual scar assessment from 3D images is possible and showed good to very good intra-rater reliability and fair to good inter-rater reliability.

7.3 Study III

7.3.1 Systematic search and included studies

The systematic search resulted in 1,567 records of which seven RCTs[67-73] were included after title and abstract screening and full-text review (Figure 11). The seven RCTs included 1,049 incisions from 872 patients. All RCTs included inguinal arterial procedures operated with open technique, four RCTs[67, 70, 72, 73] also included EVAR procedures and in one RCT[69] it was unclear if EVAR procedures were included. Six of the RCTs[68-73] used the Prevena™ incisional management system and one RCT[67] used the PICO™ dressing.

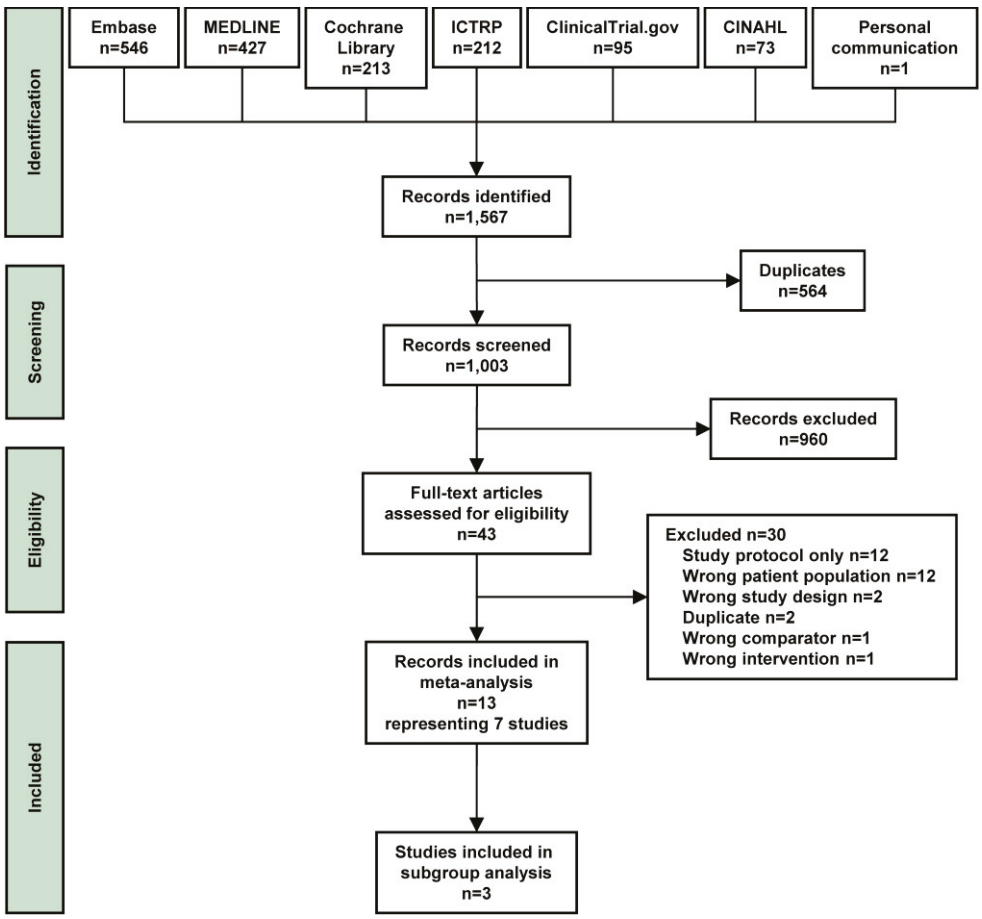

Figure 11 PRISMA flow chart
A PRISMA (Preferred Reporting Items for Systematic review and Meta-analysis) flow chart illustrating the systematic search, screening, full-text reviewing, and inclusion process.

The included RCTs were graded for risk of bias. Two RCTs were graded as high risk of bias in three or more domains, and two RCTs were graded as unclear risk of bias in five domains (Figure 12).

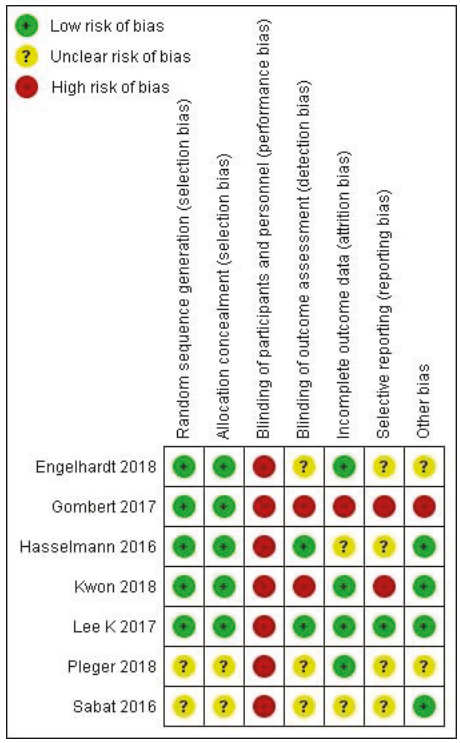

Figure 12 Risk of bias grading
Grading of the included randomised controlled trials for risk of bias according to the Cochrane risk of bias tool.

7.3.2 Outcomes

Meta-analysis of all included RCTs showed significantly decreased odds for SSI development with incisional NPWT compared to standard dressings, odds ratio (OR) 0.35 (95% confidence interval [CI] 0.24-0.50), $p<0.001$. All RCTs had results in favour of incisional NPWT and heterogeneity expressed as I^2 was 0% (Figure 13A). The certainty of the evidence received a GRADE score of moderate, downgraded for serious concerns about the risk of bias in the included RCTs.

A sensitivity analysis of inguinal incisions after arterial revascularisation procedures with open technique only showed significantly decreased odds for SSI development in favour of incisional NPWT, OR 0.37 (95% CI 0.22-0.63) $p<0.001$. I^2 was 0%

(Figure 13B). The certainty of the evidence received a GRADE score of low, downgraded for very serious concerns about the risk of bias in the included RCTs.

No meta-analyses were conducted on any of the secondary outcomes. Incidences of wound dehiscence and seroma or lymphatic complications were reported in three[68, 72, 73] and two[72, 73] RCTs, respectively. Sabat *et al*[68] reported two wound dehiscences, one in the incisional NPWT group (n=1/30) and one in the standard dressing group (n=1/33). Kwon *et al*[72] reported two wound dehiscences, one in the incisional NPWT group (n=1/59) and one in the standard dressing group (n=1/60), and two lymph leakages, both in the standard dressing group (n=2/60). Pleger *et al*[73] reported one seroma in the standard dressing group (n=1/71), and seven incisions with wound dehiscence, three in the incisional NPWT group (n=3/58) and four in the standard dressing group (n=4/71). No RCT included abnormal scar formation, and none reported any adverse event to the incisional NPWT dressing.

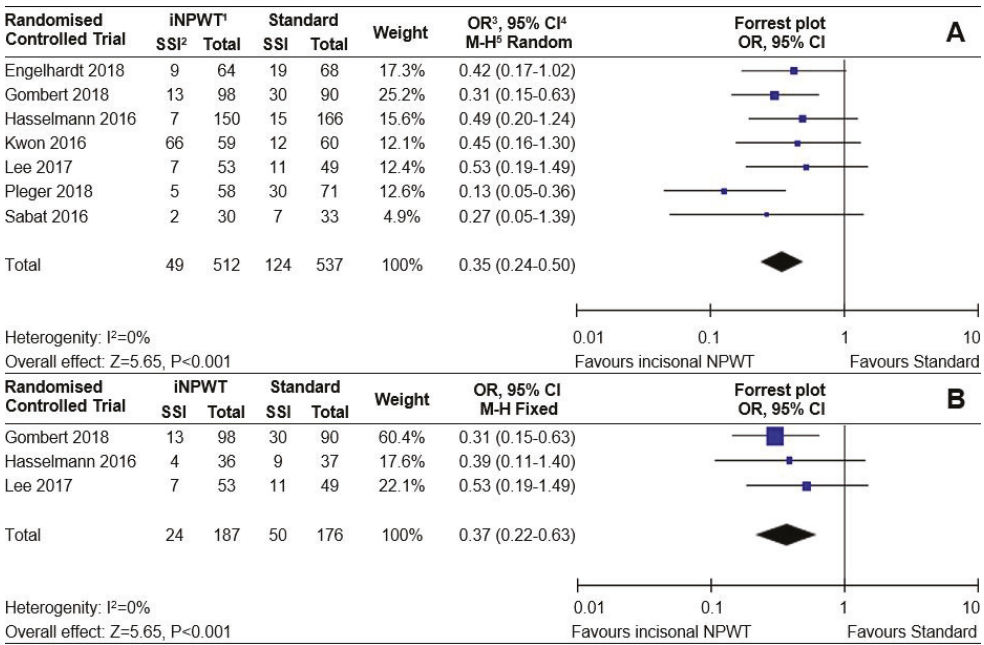

Figure 13 Meta-analyses and forest plots
Meta-analysis with forest plot of the analysis including all inguinal incisions from any arterial surgical procedure (A) and inguinal incisions from arterial procedures with open surgical technique only (B).

7.3.3 Main findings

I. A significant decrease in SSI incidence with incisional NPWT compared to standard dressings applied on inguinal incisions after elective arterial surgical procedures.

II. There was insufficient data to evaluate the effect of incisional NPWT on incidences of seroma and wound dehiscence with meta-analysis.

7.4 Study IV

7.4.1 Population

Of the original 139 patients of the INVIPS-trial's open-arm, 19 were excluded due to receiving bilateral incisions and one due to lack of cost data. Of the included 119 incisions, 59 received incisional NPWT and 60 standard dressings. The majority of patients received femoral TEA (incisional NPWT 67.8%, standard dressing 73.3%) or femoropopliteal bypass (incisional NPWT 30.5%, standard dressing 23.3%) and the indication was mainly chronic limb-threatening ischemia (incisional NPWT 57.6%, standard dressing 51.7%) or intermittent claudication (incisional NPWT 39.0%, standard dressing 40.0%). There was no difference in base-line characteristics. (Table 16).

Table 16 Base-line characteristics of included patients
Base-line characteristics of included patients from the INVIPS-trial's open-arm.

Base-line characterstics n, (%)	Incisional NPWT n=59	Standard dressing n=60
Patient characteristics		
Mean age, years (standard deviation)	70.9 (7.1)	71.5 (8.4)
Male sex	44 (74.6)	43 (71.7)
Diabetes mellitus	19 (32.2)	22 (36.7)
Smoker current/previous		
Current	16 (27.1)	19 (31.7)
Previous	36 (61.0)	36 (60.0)
Ipsilateral foot ulcer	20 (33.9)	12 (20.0)
Indication		
Intermittent claudication	23 (39.0)	24 (40.0)
Chronic limb-threatening ischemia	34 (57.6)	31 (51.7)
Popliteal aneurysm	1 (1.7)	4 (6.7)
Femoral pseudoaneurysm	1 (1.7)	1 (1.7)
Surgical procedure		
Femoral TEA[1] with or without iliac stenting	40 (67.8)	44 (73.3)
Femoropopliteal bypass	18 (30.5)	14 (23.3)
Axillounifemoral bypass	0 (0.0)	1 (1.7)
Pseudoaneurysm repair	1 (1.7)	1 (1.7)
Operation time, mean (standard deviation)	192.8 (64.6)	207.3 (78.7)

[1] Thromboendarterectomy

7.4.2 Outcomes

There was no difference in mean *all healthcare cost* or *vascular procedure-related cost* between incisions treated with incisional NPWT compared to standard dressings. The mean wound dressing cost of inpatient care was significantly higher in incisions treated with incisional NPWT. The cost of vascular procedure-related

outpatient care was significantly higher in incisions treated with incisional NPWT (Table 17).

The SSI incidence was significantly lower in incisions treated with incisional NPWT compared to standard dressings. There was no difference in incidences of other incisional wound complications (Table 17).

The patient-reported QoL by the Vascuqol-6 questionnaire showed a significantly lower preoperative mean score in the standard dressing group. There was no significant difference in postoperative or difference in pre- and postoperative mean score between the two groups. The number of patients fulfilling both the pre- and postoperative grading was 66.1% (n=39/59) and 70.0% (n=42/60) in the incisional NPWT and standard dressing group, respectively. Supplementing missing data with multiple imputation showed no significant differences in pre-, post- and difference in pre- and postoperative mean scores (Table 17).

Table 17 Outcomes included in the cost-effectiveness analysis
Summary of costs, incisional wound complication incidences, and patient-reported quality of life.

Outcomes	Incisional NPWT	Standard dressing	P-value
Cost **Mean in euros**	**n=59**	**n=60**	
All healthcare total cost	19,281	17,575	0.46[1]
Inpatient care	17,751	16,518	0.56[1]
Outpatient care	1,530	1,057	0.11[1]
Vascular procedure-related total cost	16,621	16,285	0.85[1]
Inpatient care	15,646	15,609	0.98[1]
Wound dressings	208	45	**<0.001**[1]
Outpatient care	975	675	**0.043**[1]
Incisional wound complication **n, (%)**			
Any incisional wound complication	18 /59 (30.5)	20/60 (33.3)	0.74[2]
Multiple incisional wound complications	9/59 (15.3)	15/60 (25.0)	0.19[2]
Type of incisional wound complication			
Surgical site infection	7/59 (11.9)	18/60 (30.0)	0.015[2]
Seroma/lymphatic complication	13/59 (22.0)	14/60 (23.3)	0.87[2]
Wound dehiscence	12/59 (20.3)	7/60 (11.7)	0.20[2]
Hematoma	1/59 (1.7)	4/60 (6.7)	0.36[3]
Quality of life **Mean score**			
Vascuqol-6			
Preoperative	9.1, n=41	10.6, n=43	**0.016**[1]
Postoperative 30 days	14.9, n=46	15.3, n=46	0.73[1]
Difference pre- and postoperative score	6.1, n=39	4.8, n=42	0.28[1]
Vascuqol-6, supplemented with multple imputation			
Preoperative	10.0	10.1	0.85[1]
Postoperative 30 days	15.7	14.4	0.15[1]
Difference pre- and postoperative score	5.7	4.3	0.15[1]

[1] Independent samples t-test
[2] Chi[2] test
[3] Fisher's exact test

7.4.3 Cost-effectiveness analysis

The ICER of *vascular procedure-related cost* and SSI incidence resulted in 19 euros of increased cost per decreased percent unit in SSI incidence. Sensitivity analyses relating mean *all healthcare cost* and *vascular procedure-related inpatient care cost* with SSI incidence showed an ICER of 94 and two euros in increased cost per decreased per cent unit in SSI incidence, respectively, (Table 18).

Relating *vascular procedure-related cost* with patient QoL according to difference in pre- and postoperative vascuqol-6 score showed a ICER of 719 euros in increased cost per gained point in Vascuqol-6 score. When supplementing the missing Vascuqol-6 data by multiple imputation, the ICER was reduced to 242 euros in increased cost per gained point in Vascuqol-6 score (Table 18).

Table 18 Cost-effectiveness analysis
Cost-effectiveness analysis reported as incremental cost-effectiveness ratios relating costs with surgical site infection incidence and patient-reported quality of life according to vascuqol-6, respectively.

Surgical site infection incidence	Cost difference Euros, €	Effect difference Per cent, %	ICER[1]
Vascular procedure-related cost	336		
Surgial site infection incidence		-18.1	19
All health care cost	1,706		
Surgial site infection incidence		-18.1	94
Vascular procedure-related cost, inpatient care only	37		
Surgial site infection incidence		-18.1	2
Patient quality of life	**Euros, €**	**Vascuqol-6 points**	
Vascular procedure-related cost	336		
Difference in pre- and postoperative vascuqol-6 score		1.3	719
Difference in pre- and postoperative vascuqol-6 score supplemented by multiple imputation		1.4	242

[1] Incremental cost-effectiveness ratio

A cost-effectiveness plane comparing *vascular procedure-related cost* (north-south direction) with difference in Vascuqol-6 score (east-west direction) resulted in 42% of the bootstrapped data located in the southeast quadrant where cost decreased and patient QoL increased with incisional NPWT (Figure 14A). A corresponding cost-effectiveness plane with *vascular procedure-related inpatient care cost* increased the proportion located in the southeast quadrant to 46%, also including the point estimate (Figure 14B).

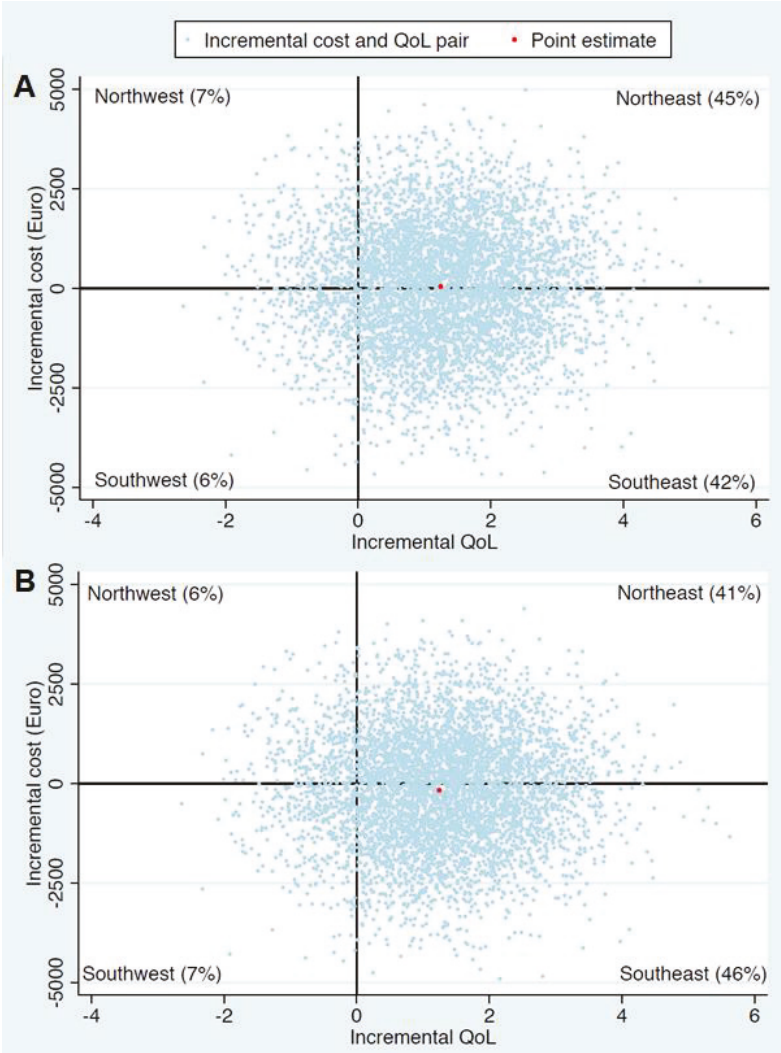

Figure 14 Cost-effectiveness planes comparing cost with patient quality of life
Cost-effectiveness plane of incremental *vascular procedure-related costs* (A) or *vascular procedure-related inpatient costs* (B) and difference in Vascuqol-6 score using bootstrapping with 5,000 replications. Copyright held by the author.

7.4.4 Main findings

I. No significant difference in cost was detected when evaluating inguinal incisions from open vascular surgical procedures treated with incisional NPWT compared to standard dressings.

II. Incisional NPWT was considered cost-effective in reducing SSIs, with no difference in cost and a significant decrease in SSI incidence.

8 Discussion

8.1 Aspects of different vascular procedures in relation to surgical site infections

8.1.1 Open vascular procedure versus endovascular aneurysm repair

The National Institute for Health and Care Excellence (NICE) identifies age, underlying illness (diabetes mellitus, increasing ASA [American Society of Anaesthesiologists] classification, malnutrition, steroid treatment, recent [<90 days] radiotherapy), obesity (BMI ≥35 kg/m^2), smoking, wound classification, and site and complexity of procedure (contamination level and length of procedure), as major factors to determine the risk of SSI development.[74]

Inguinal incisions from open vascular surgical procedures for lower limb revascularisation are associated with the highest risk for SSIs, with incidences of 13-33% previously reported.[5] The use of longitudinal incisions, extensive dissection around the artery, and long operation times, are procedure related risk factors associated with these incisions. Patients with peripheral arterial disease in the need of revascularisation generally have a risk factor profile encompassing high age, high abundance of smoking, and diabetes mellitus, further increasing the risk of SSI development.

The SSI incidence after EVAR procedures is lower compared to after open inguinal vascular surgical procedures, with previously reported incidences ranging between 2.4-3.5%.[29, 30] Surgical haemostasis in EVAR procedures requires a short transverse incision at the end of the procedure, exposing the artery only for a short period of time. The level of dissection needed is also lower compared to open inguinal vascular surgical procedures, both with fascia closure and cut-down technique – the primary and secondary surgical haemostasis technique used in study I. The main indication for EVAR is abdominal aortic aneurysm, a disease strongly related to high age and smoking habits[75], but not to diabetes mellitus.[76, 77]

The large difference in SSI incidence after open inguinal vascular surgical procedures compared to EVAR procedures has with this thesis been re-confirmed. The SSI incidences with standard incisional wound care of 30.0% and 4.4%, respectively, described in the pilot period leading up to the INVIPS-trial[58] were re-iterated in the INVIPS-trial's two study arms with incidences of 29.5% (unilateral incisions only) after open inguinal vascular surgical procedures[64] and 4.8% (bilateral incisions only) after EVAR procedures in study I. This highlights the importance of separating these procedures when evaluating inguinal vascular surgical incisions for SSIs. It also supports that inguinal incisions after open vascular surgical procedures should be considered high-risk incisions for SSIs, while incisions after EVAR-procedures with the primary intent of fascia closure should be considered low-risk incisions.

8.1.2 Percutaneous closure devices and surgical arterial closure

In EVAR procedures, PCDs has during the recent decade emerged as an alternative to surgical haemostasis with fascia closure or cut-down. PCD does not impose an inguinal incision and the entire procedure can be conducted percutaneously. The use of PCDs has increased in recent years. One systematic review with meta-analysis of RCTs and cohort studies has shown a significant decrease in SSI and seroma incidence but an increase in pseudoaneurysm incidence with PCD compared to cut-down[78], results which were not confirmed in two subsequent meta-analyses of RCTs only.[79, 80] PCDs is therefore considered an equivalent arterial closure technique to fascia closure and further comparisons between PCDs and surgical haemostasis is required to determine if any are superior to the other.

A practical aspect to PCDs versus surgical haemostasis is that PCD cannot be used if surgical haemostasis is unsuccessful, but both fascia closure and cut-down are possible rescue techniques when PCDs fail to achieve adequate haemostasis. A retrospective cohort study has however demonstrated significantly higher SSI incidences with incisions converted from PCD to cut-down compared to primary cut-down.[81] The results of study I also indicated increased SSI incidence when using cut-down as a rescue technique from failed fascia closure, however without achieving a significant difference which is why it should be interpreted with caution. Further studies are needed regarding SSI incidence in primary intent compared to rescue techniques for arterial closure.

8.2 Definition and grading of incisional wound complications

8.2.1 Different surgical site infection definitions

Identifying a SSI is challenging. One reason is that the clinical characteristics of SSIs are not specific. Every incision causes mechanical trauma, triggering an inflammatory response resulting in the classical characteristics of swelling, redness, heat, and pain[3], which are also listed as a criterion by the CDC definition of a superficial SSI[8] (Table 1). Increased body temperature and raised inflammatory biochemical markers such as C-reactive protein are common results of both postoperative inflammatory response and a SSI. Differentiating between a superficial SSI and normal postoperative inflammatory response is therefore often difficult. The difficulty in making an accurate diagnosis is a concern with the CDC criteria from 1999, where the fourth criterion of all grades of SSIs (diagnosis of superficial/deep/organ or space SSI by a surgeon or attending physician)[8] surpasses all other clinical, laboratorial, and microbiological criteria and makes diagnosis fully subjective and thereby susceptible for detection bias. This criterion has partially been removed following updates of the CDC criteria, but it remains in the definition of a superficial SSI in the present (January 2022) CDC criteria.[82]

In addition to sharing characteristics with normal wound healing, SSIs also share clinical characteristics with other incisional wound complications. For example, serous discharge and separation of deep tissues, criteria incorporated in the ASEPSIS-score[9], are also the hallmarks of a leaking seroma or a lymphorrhea.

Determining the presence of any invasive bacterium is also problematic due to the diagnostic limits with microbiological wound swabs. Firstly, wound infections are commonly caused by bacteria normally present on human skin, which is why contamination from surrounding skin is a recurring source of error. Secondly, colonisation of skin bacteria into an open wound is inevitable and generate positive microbiological wound cultures but does not confirm invasiveness of the bacteria. Thirdly, false negative microbiological swabs from the wound due to incorrect technique is a potential source of error. These aforementioned limits are especially a concern when defining a superficial SSI using the CDC criteria, where any presence of a positive culture from tissue or liquid from incisional wound, is enough for diagnosis of a superficial SSI – irrespective of other clinical characteristics.[8] In the ASEPSIS-score, the relatively high points (ten) awarded for isolation of bacteria[9] could result in missing superficial SSIs (total score 21-30 points) or underestimating the severity of SSIs when microbiological wound swabs are not secured, such as in superficial SSIs where wound swabs are not always performed.

Nevertheless, the positive predictive value of microbiological wound swabs in study I was high, 84.2% (n=16/19) where 19 of 377 incisions had an isolation of bacteria and of which 16 incisions were classified as SSIs.

8.2.2 Time of wound surveillance for surgical site infections

The length of wound surveillance for SSIs varies among the previously published RCTs reporting SSI incidence after inguinal vascular surgery. A systematic review by Norman *et al*[5] identified eight RCTs[64, 68, 70-73, 83, 84] evaluating incisional NPWT after inguinal vascular surgery. Of these, four reported SSI incidence after 30 days[71-73, 84], two after 90 days[64, 83], and two at other intervals (42 days[70] and four months[68]). The CDC guidelines from 1999 recommended wound surveillance for SSIs for 30 days or one year if any presence of an implant. Since the start of the INVIPS-trial (study I), the CDC guidelines have changed and the current guidelines recommend 90 days wound surveillance in all peripheral vascular surgical procedures.[82]

In study I, all SSIs were identified within the first 30 days of surveillance, indicating that the prolonged surveillance time with the new CDC guidelines had no or a minor impact upon SSI incidence as outcome. On the other hand, the previous guideline to monitor patients for 1 year if an implant was present, is considered insufficient to identify stent graft infections after EVAR procedures considering the previously reported mean time to stent graft infection of 22 months with a range of 0.2-158 months.[85] However, since SSIs are estimated to be the cause of stent graft infections in only a minority of cases[85], reducing SSIs will therefore have a minor impact upon stent graft infection incidence. Subsequently it is not considered a suitable endpoint to evaluate SSI incidence after EVAR procedures.

8.2.3 Grading of incisional wound complication by their implication

Incisional wound complications in inguinal incisions after vascular surgery often co-exist, develop dynamically, and share several clinical characteristics. As previously described, they also share many treatment strategies such as frequent wound dressing changes, debridement, NPWT for open wounds, and muscle flap coverage. To avoid the trouble of differentiating the different types of incisional wound complications, a proposed solution is to report incisional wound complications by their clinical implication rather than their entity.[86] In study I, there was no detected difference between incisional NPWT compared to standard dressings regarding incidences of the separate types of incisional wound complications, but a trend towards fewer additional treatment due to any incisional wound with incisional NPWT compared to standard dressings, highlighting the importance of including this aspect when reporting incisional wound complications.

8.3 Prevention of incisional wound complications

8.3.1 The role of incisional negative pressure wound therapy

NICE has evaluated the current evidence for the two most studied incisional NPWT dressings, the Prevena™ incisional management system[87] and PICO™ [88], regarding prevention of SSIs and seromas, as well as their cost-effectiveness, when applied on closed incisions after all types of surgery. They concluded that both incisional NPWT dressings are alternatives to standard wound care in high-risk incisions for SSI development, PICO™ also in high-risk incisions for seromas, and that the PICO™ is and the Prevena™ incisional management system probably is cost-effective.[87, 88]

The present thesis has provided support for the findings of the aforementioned guidelines. Study III confirmed the high SSI incidence and demonstrated a significant reduction in SSI incidence in favour of incisional NPWT compared to standard dressings in inguinal incisions after arterial surgery. Study IV demonstrated that incisional NPWT is cost-effective in preventing SSIs compared to standard dressings when applied on inguinal incisions after open vascular surgical procedures. Inguinal incisions after open vascular surgical procedures should therefore be considered high-risk incisions for SSIs. Any protective effect for seroma development was not seen in study III. In study I, the SSI incidence was low with no detected difference between incisions treated with incisional NPWT compared to standard dressings after EVAR procedures with the primary intent of fascia closure, which is why these incisions should be considered low-risk incisions for SSIs. Whether incisions after EVAR procedures with cut-down or patch angioplasty as rescue technique for surgical haemostasis should be considered high, intermediate, or low risk for SSI development remain undetermined.

8.3.2 Other measures in surgical site infection prevention

As described in section 4.6, approximately 55% of all SSIs are estimated to be preventable if the current guidelines were fully applied.[32] The CDC guidelines for SSI prevention lists antibiotic prophylaxis, antiseptic skin preparation, perioperative glycaemic control, perioperative normothermia, and increased peri- and postoperative oxygenation, as evidence based measures.[33] Fernández-Prada *et al*[89] showed in their observational study that implementation of the CDC guidelines (except increased peri- and postoperative oxygenation), reduced the SSI incidence after mixed open and endovascular procedures from 4.9% (n=3/61) to 0.0% (n=0/46), p=0.127, and after lower limb amputation from 33.3% (n=14/42) to 13.9% (n=6/43), p=0.035. Application of the aforementioned guidelines appears to be valid measures and are not in competition with use of incisional NPWT.

8.4 Cutaneous scars

8.4.1 Incisional negative pressure wound therapy and scars

Incisional scars are potential problems which in addition to cosmetic concerns may cause pain[14], itch[15], and psychological discomfort to the patient[16]. Incisional NPWT has been proposed to improve incisional scars by reducing inflammation[51, 90], mechanical tension[50, 91], and reducing incisional wound complications. Several RCTs have investigated the effect of incisional NPWT on incisional scars compared to standard dressings. Nagata *et al*[92] showed significantly thinner scar width at six months postoperatively with incisional NPWT after breast reconstruction with tissue expander. Tanaydin *et al*[93] demonstrated a significant improvement of observer estimated visual appearance and patient-reported satisfaction after breast reduction mammoplasty in favour of incisional NPWT at 90 days postoperatively, but no difference at one year postoperatively. Hyldig *et al*[94] reported no difference in observer estimated visual appearance and patient-reported satisfaction at 12 months after caesarean section in obese women, however in an intermediate analysis at 6 months reported significantly lower presence of hatch marks and higher portion of overall satisfied patients in favour of incisional NPWT. Timmermans *et al*[95] showed a significant improvement in patient-reported outcome but no difference in observer estimated visual appearance with incisional NPWT at 12 months after bilateral gender-affirming mastectomy.

The partially or fully beneficial effect of incisional NPWT on scar quality described in the aforementioned RCTs were not replicated in study II. One possible explanation were the generally fine scars, where 20.3% (n=13/64) and 40.6% (n=26/64) of the scars received the highest possible visual grading according to SBSES and NRS10, respectively, thereby making it hard to improve the visual appearance. There are several aspects considered contributing to the fine scars observed in study II. Firstly, the inguinal location of the incisions, an area rarely troubled with keloid scars.[13] Secondly, the high age of participating patients, considering that both hypertrophic and keloid scars are associated with young age.[12, 13] Thirdly, the high abundance of smoking, a factor associated with reduced risk for development of hypertrophic scars.[12] Fourthly, the lack of coloured skin among the included patients, considering that coloured skin is a risk factor for development of keloid scars.[13] Lastly, the long follow-up time of at least one year postoperatively, considering that scars may improve up to many years after surgery.[3] This final aspect was observed in the RCT of Tanaydin *et al*[93] which demonstrated an improvement of observer estimated visual appearance and patient-reported satisfaction after breast reduction mammoplasty in favour of incisional NPWT at 90 days postoperatively, but no difference at one year postoperatively as the scars improved substantially in both the incisional NPWT and standard dressing groups.

According to study II, inguinal incisions after mainly EVAR procedures do not seem to be an incision associated with hypertrophic or keloid scars. Future research evaluating the possible effect of incisional NPWT on scar formation should focus on high-risk incisions for the development of hypertrophic or keloid scars.

8.4.2 Difficulties with scar assessments

Assessing the quality of scars is challenging. There are several aspects to consider, such as: topography, colour, vascularity, itch, pain, pliability, aesthetic appearance, and psychological aspects. The many different aspects of scar quality have generated many different scales for scar assessment, illustrated in a systematic review where the included nine clinical studies reported observer estimated visual appearance using six different scales and patient-reported satisfaction using three different questionnaires. In addition, the timepoint for scar assessment varied from seven to 365 days.[96] The use of different scales and timepoints of scar assessment prohibited comparison between studies as well as conducting a meta-analysis, which could have been advantageous considering the low number of participants in the individual studies included in the systematic review (range 11-91 patients).[96] A consensus of which scales to use for each origin (i.e. surgical, burn or traumatic) of scars and which timepoint to evaluate, would be beneficial for future research on scars. It seems however important to evaluate both observer estimated visual appearance and patient-reported satisfaction, as patient and physician reported outcomes of scars often varies[97] and many patient-related aspects of scars (pain, itching, and psychological discomfort) cannot be estimated visually.

8.4.3 Scar assessment from three-dimensional photo documentation

The scar assessments in study II were conducted from 3D images, which was a novel method at the time. Scar assessments from two dimensional photos is possible[98] and is widely used, but fails in capturing the topography of scars – one of five aspects of the SBSES. The accuracy of the 3D camera system used in study II has later been described, with no difference in measurements when using 3D images.[99]

In study II, intra- and inter-rater reliability for scar assessments using SBSES was reported as good to very good and moderate to good, respectively, and using NRS10 moderate to good and fair to good, respectively. The variations in scar assessments are mainly considered due to the variance of the scar assessment scales which have previously been reported.[60] There was also a potential learning curve of the assessors as the ICC for inter-rater reliability increased for both SBSES and NRS10 from the first to the second assessment. A final possible source of error was incorrectly reported laterality of scar gradings, affecting intra- and inter-rater reliability negatively.

Studies validating the 3D camera system used in study II for scar assessment has yet not been conducted. However, there are several other 3D camera systems available and evaluated for 3D scar documentation: LifeViz® (Quantificare, Biot France)[100], MAVIS III Wound Camera (Perry Baromedical Corporation, Riviera Beach, Florida, USA)[101], and Antera 3D® (Miravex, Dublin, Ireland)[102]. In incisional scar assessments, two prospective trials, after mixed surgical interventions[103] and thyroidectomy[104], respectively, have used 3D camera systems with reported satisfaction. The use of 3D camera systems is considered a useful supplementing tool for scar measurements and assessments of visual characteristics.

8.5 Conducting a randomised controlled trial

8.5.1 Methodological strengths and limits

In 1989 Sackett[105] ranked RCTs as providing the highest level of evidence compared to other methodological approaches. He valued the level of evidence higher in sufficiently powered RCTs with correct identification of events, than in insufficiently powered RCTs with a high risk of false positive events (i.e. RCTs with risk for type II and I errors, respectively). The reason for the high level of evidence with RCTs is that when performed correctly, the only difference between groups is the intervention investigated, thus eliminating sources of confounders.

8.5.2 Risks of bias

The largest concern in RCTs is bias, which means introducing factors affecting the result. There are several pitfalls in conducting RCTs that risk imposing bias. The first pitfall regards patient enrolment. The population of the RCT should correspond to the population you aim to investigate. Therefore, it is important to approach and try to include all patients who meet the inclusion criteria and limit exclusion of patients, otherwise risking introducing selection bias to the study population which limits the applicability of the results. Transparency about patient enrolment and inclusion is achieved with a CONSORT (Consolidated Standards of Reporting Trials) flow chart. Another population-associated error which risks imposing selection bias is incorrect randomisation and allocation. This is limited by a blinded and truly random randomisation process which outcome cannot be foreseen. Both these factors were an issue in study I. Firstly, 137 of 490 patients assessed for randomisation were excluded (60 declined consent, 59 failed in approach for consent, 18 unclear reason). Secondly, 85 incisions from 45 patients were excluded due to incorrect allocation of wound dressings. These pose as limits to the result.

The second possible issue is insufficient blinding of patients and healthcare staff to allocated treatment. This is a risk for performance bias, that patients and healthcare staff, intentionally or not, change their behaviour which affects the measured outcome. All outcomes are however not susceptible to behaviour changes. The studied outcomes of the present thesis (incidence of SSIs and other incisional wound complications [study I and III], scar appearance [study II], cost [study IV], patient QoL [study IV]) is not considered susceptible to performance bias.

The third potential problem is insufficient blinding of assessors of outcome, a risk for detection bias – difference in outcome determination by knowledge of allocated treatment. All outcomes are not susceptible to detection bias, such as mortality in study I and cost in study IV. However, defining and grading a SSI (study I and IV), patient-reported satisfaction of scar appearance (study II) and patient-reported QoL (study IV), all involve elements of subjective evaluation which are considered susceptible to detection bias. Blinding of allocated wound treatment for healthcare staff and patients during ongoing wound treatment was not possible due to the principally different wound dressing characteristics. However, assessors of wound outcomes after index hospital stay were blinded to allocated wound treatment and 62.5% (n=10/16) of the SSIs in study I and 82.6% (n=19/23) of the SSIs in study IV, were diagnosed after hospital discharge.

A fourth potential pitfall is loss to follow-up. If a high proportion of randomised patients do not fulfil their participation or is lost to follow-up it may skew the result – attrition bias. This is not considered a problem in study I, as the proportion of loss to follow-up were lower than anticipated in the study protocol and all incisions lost to follow-up had reasons (mortality, re-operation, or withdrawn consent). Regarding study IV, one patient was lost to follow-up due to moving abroad and thereby prohibiting retrieval of cost data. This was neither considered a risk of attrition bias.

A fifth potential problem is selective reporting. Selective reporting is when parts of the conducted analyses of an RCT is not reported post hoc. To avoid this, study protocol should be published a priori to avoid selective reporting. The adherence to the study protocols of the papers included in the present thesis is considered good.

A final concern is industry sponsorship in research. Lundh *et al*[106] showed that industry sponsored studies more often reported favourable results of the intervention and more favourable conclusions of the results compared to non-industry sponsored studies. This applies to study I, II and IV since the INVIPS-trial did receive industry sponsorship from the manufacturer of the incisional NPWT dressing (Smith & Nephew). The research group received in 2013 an unconditional research grant of 15,500 USD (United States Dollar) (Corresponds to €14,702 in 2019 price year) and a donation of 100 PICO dressings. Smith & Nephew was not involved in study design, analysis and interpretation of data, or writing and submission of the manuscripts. This is still a possible bias which is important to be transparent about.

8.5.3 Different standard dressings

In the INVIPS-trial, the type of standard dressing used varied. This was since the control treatment was specified as the institutions' standard dressing and not a particular dressing. It was considered ethically important that the control treatment would be similar to the treatment received if not participating in the trial. This affected study I and IV. In study I, a sensitivity analysis of SSI incidence comparing the different standard dressings used did not show any difference. A corresponding sensitivity analysis in the INVIPS-trial's open-arm, which results are part of study IV, also did not show any difference.[64] The use of different standard dressings still poses a limit to the findings of study I and IV, though ideally the control treatment should be the same in different centres (study I) and over time (study I and IV).

8.5.4 Statistical aspects

One key statistical feature of the INVIPS-trial was the inclusion of bilateral incisions and their split person randomisation – that the same patient received both the incisional NPWT and standard dressing treatment, but on separate sides. This creates matching pairs of incisions which must be analysed separately from included unilateral incisions which are fully independent of each other. The obtained p-values from the separate analyses of bi- and unilateral incisions can be combined using Fisher's method of combing p-values. The use of paired (dependent) data increases statistical power, thus reducing the number of incisions needed. Failure to identify dependent data and analyse it as independent will increase type I errors.[107]

Incorrect statistical analysis of dependent data within the surgical field is however not uncommon. A systematic review investigated the frequency of included bilateral cases and how they were analysed in RCTs evaluating inguinal hernia repair. They concluded that it was unclear which statistical approach was used in 40% (n=20/50) of the RCTs, it was handled conservatively (and statistically correctly) by arranging randomisation by patient and only using one of the sides in bilateral hernias, if present, in 36% (n=18/50) of the RCTs, and the use of dependent (bilateral) data was not considered in the statistical analysis in 24% (n=12/50) of the RCTs.[107]

This was a concern in study III, with 1,049 incisions from 872 patients included. Among the seven RCTs[67-73], four[67, 68, 72, 73] included patients with bilateral incisions. Hasselmann *et al*[67] and Kwon *et al*[72] used split person randomisation, however only Hasselmann *et al*[67] presented uni- and bilateral incisions separately with correct statistical approach. Sabat *et al*[68] and Pleger *et al*[73] included bilateral incisions but it is unclear how the wound dressings were allocated and both RCTs failed to separate uni- and bilateral incisions statistically. The meta-analysis in study III was analysed on an incision level, thereby incorporating the statistical limitations in the aforementioned RCTs. This results in more type I errors and loss of power, which is a limit to the findings of study III.

8.6 Conducting a systematic review with meta-analysis

8.6.1 Methodological strengths and limits

In the traditional pyramid of evidence, systematic reviews with meta-analysis are placed at the top as the research methodology with the highest level of evidence – even higher than RCTs. The reason is the systematic approach of searching all available sources to identify all available data and the synthesis of included studies into a meta-analysis, which provide high statistical power by increasing the number of participants and events.

The quality of a systematic review with meta-analysis does not only rely on the quality of the conducted systematic review and its meta-analysis. The pooling of data also means the quality of the meta-analysis relies on the quality of the included studies. A primary distinction is the methodology used in the included studies. A systematic review with meta-analysis of RCTs compared to one of observational studies, generally provide a higher level of evidence.[63] A secondary distinction is based on the quality of the included studies. A systematic review by Robinson *et al*[108] discovered several quality deficiencies in published RCTs within the surgical field. Of the identified 388 RCTs, 242 (62.4%) trials had a study protocol registered a priori. Discrepancies between registered and finally published primary outcomes were seen in 81 (33.5%) of the trials. The overall risk of bias (Cochrane risk of bias tool 2) was graded as high risk of bias in 91 (23.5%) trials and as some concerns for bias in 211 (54.4%) trials. Industry sponsorship was found in 96 (33.3%) trials, of which 50 (50.1%) reported industry involvement in data analysis. Multiplicity (multiple treatment groups, outcomes and/or analyses) were identified in 175 (45.1%) trials, of which correct adjustments were performed in 35 (20.0%) trials.

8.6.2 Comparison with later systematic reviews with meta-analysis

Study III was the first systematic review with meta-analysis of RCTs to evaluate incisional NPWT after inguinal vascular surgery.[109] Since its publication, five other systematic reviews with meta-analysis of RCTs have been published.[5, 10, 110-112]

Four of the systematic reviews reported adherence to either the PRISMA (Preferred Reporting Items for Systematic review and Meta-analysis) statement[10, 112], Cochrane handbook of conducting systematic reviews[5], or both[110]. Three of the systematic reviews provided a study protocol published a priori[5, 10, 112] while one claimed an unpublished study protocol[111].

All of the systematic reviews provided a PRISMA-flow chart documenting the search and inclusion process. The results of the systematic searches ranged between 47-2,561 records and resulted in five[110], six[111], seven[112], eight[10] and nine[5] RCT's

included, respectively. Regarding Norman *et al*[5], one RCT included was a duplicate and one RCT had been published after the other systematic reviews were published. Gwilym *et al*[10] identified a RCT published only in German, not identified by any of the other systematic reviews including study III. There were some differences in inclusion criteria between the systematic reviews, Norman *et al*[5] included all surgical incisions, Gombert *et al*[111], included only RCTs using the Prevena™ incisional management system, and Gwilym *et al*[10] included both RCTs and observational studies (a separate meta-analysis of RCTs only was provided), explaining partially the diversity in search and inclusion results. In comparison, study III identified 1,003 records after duplicates were removed, and included seven RCT's, which is considered in line with the other systematic reviews.

All systematic reviews assessed the included RCT's for risk of bias, three using the original Cochrane risk of bias tool and two using the updated Cochrane risk of bias tool 2. There was large diversity in the grading for risk of bias among the systematic reviews, also in comparison with study III. In addition to study III, two of the systematic reviews were transparent about their grading for risk of bias.[5, 112] The diversity in assessments is partly considered due to the difficulty of finding all information about a trial, but also because the Cochrane risk of bias tool, despite providing a structured template, is mainly a subjective evaluation. Evaluation of the original and updated Cochrane risk of bias tool regarding inter-rater reliability have showed slight agreement[113] and no to fair agreement[114], respectively.

All the meta-analyses showed a significant result in favour of incisional NPWT. One meta-analysis[110] was conducted using Mantel-Haenszel test with fixed effect model while the remaining, as well as in study III, used the random effect model for the primary meta-analysis. The difference between the fixed and random effect models is that the random effect model also take heterogeneity between the included studies (Tau) into account. If there is no heterogeneity, the fixed and random effect models will generate similar results. Using the fixed effect model when there is heterogeneity between the included studies will incorrectly generate a narrower CI and lower p-value. The fixed effect model should therefore be used with caution.

Three systematic reviews included GRADE scores to assess the level of certainty of the outcome of the meta-analyses. One graded their finding as high[110] and two as moderate, however those GRADE scores were conducted on meta-analyses including observational studies[10] and non-vascular surgical procedures[5] as well. The GRADE score of moderate in study III is considered in line with the others.

Despite the systematic approach in search method, using same or similar guidelines, analysing mainly the same RCTs, and using similar assessment tools, the heterogeneity between the different systematic reviews (including study III of this thesis) is substantial. This highlights the need of following the guidelines available and being transparent about the inclusion and analysis process in order to ease comparison between different systematic reviews and their meta-analyses.

8.7 Conducting a cost-effectiveness analysis

8.7.1 Cost data in cost-effectiveness analyses

A central part of cost-effectiveness analyses is cost data. One principal difference in cost data is the perspective of which the cost-effectiveness analysis is conducted: healthcare or societal perspective. In the healthcare perspective, costs only related to the healthcare provider (costs for surgery, ward care, medication, outpatient visits, material usage) is considered, while in the societal perspective costs to society (society expenses and productivity loss) is added to the healthcare costs.[55] The cost-effectiveness analysis conducted in study IV was from a healthcare perspective, partly due to the difficulty in estimating societal costs and partly due to the high age of the population investigated, with the vast majority being retired from work thus limiting society's potential productivity loss.

Another factor about cost data is its validity and variance. Costs can be estimated using a simulation model incorporating cost data from previously published studies, or by using the exact data from the studied cohort.[55] When estimating costs by using a model, the challenge is external validity of the data used. Cost data vary between countries, healthcare systems, surgical procedures, surgical materials, and timepoint of intervention. This is not a concern when using exact data directly from a clinical trial, as in study IV, but then the variance in the cost data is a potential concern. There are many factors in addition to the intervention investigated that affect costs. For instance, haemodialysis is very expensive and not related to incisional wound complications, but it also affects total cost. This is particularly a problem in small cohorts as the 119 patients in study IV, where few non-incisional wound complication related factors in individual patients potentially had a large impact on total mean cost. To minimise the effect of potential drivers of cost unrelated to incisional wound complications in study IV, the cost data were also sub-grouped into *vascular procedure-related cost*. Nevertheless, variance in cost data and potential cost drivers unrelated to incisional wound complications is still a limitation in study IV.

8.7.2 Measurement of patient quality of life.

In cost-effectiveness analyses, costs are related to changes in effects of interest. The effects used in the cost-effectiveness analysis of the present thesis (study IV) were patient QoL and SSI incidence. Patient QoL is an established effect used in cost-effectiveness analyses, which can be measured in many ways. One validated method is Quality Adjusted Life Years (QALY), where patients' health related QoL is measured by patient questionnaires, mainly the EQ-5D (European quality of life five dimension)[115], SF-6D (short form six dimension)[116], or HUI-3 (Health Utilities

Index three)[117], to provide a utility score ranging between 0-1 (zero representing death and one representing perfect health), which is multiplied with the time that the patient remains within that health state.[118] QALY thereby captures both changes in patient morbidity and mortality. Another strength with QALY is that it is not specific to a particular intervention or disease, allowing comparisons of ICERs (cost per gained QALY) between different interventions and in different diseases. The cost-effectiveness of incisional NPWT after different surgical procedures using QALY are discussed in paragraph 8.7.3.

The use of QALY to measure the impact of SSIs on patients' health reported QoL is possible, but there are a few limitations to consider. Firstly, the low mortality rate of SSIs. Hasselmann *et al*[86] reported no SSI related mortality in a retrospective cohort with 63 SSIs, which indicates that SSI related mortality has a marginal impact on QALY. Secondly, the decrease in utility score with SSIs and incisional wound complications are minor and last only for a short period of time, as described by McGillicuddy *et al*[27], which also limits their impact on QALY. The combination of these factors results in a small difference in QALY between patients with and without SSI. The low numeric value of difference in QALY have in turn a large impact on the ICER, generating high ICERs even at marginal differences in cost.

QALY was not used in study IV to measure patient-reported QoL. Instead, a disease specific patient questionnaire was used – the Vascuqol-6. The Vascuqol-6 is a validated questionnaire to measure patient QoL in patients with peripheral artery disease.[65] The aim was to get a more sensitive measure of patient-reported QoL with a disease specific questionnaire. The disadvantage with the use of a disease specific questionnaire is that it hinders comparisons between cost-effectiveness analyses of other diseases, which QALY does not.

8.7.3 Cost-effectiveness of incisional negative pressure wound therapy

The cost-effectiveness analysis conducted in study IV detected no difference in mean *vascular procedure-related cost* between incisions treated with incisional NPWT compared to standard dressings, but a significant decrease in SSI incidence in favour of incisional NPWT, thereby concluding that incisional NPWT was cost-effective in reducing SSIs. Regarding patient-reported QoL, no difference in difference between pre- and postoperative Vascuqol-6 score was seen comparing incisions treated with incisional NPWT with standard dressings. The cost-effectiveness plane of *vascular procedure-related cost* (north-south direction) and difference in pre- and postoperative Vascuqol-6 score (east-west direction) showed that 42% of the bootstrapped data being in the southeast quadrant which corresponds to decreased *vascular procedure-related cost* and increased difference in pre- and postoperative Vascuqol-6 score.

After the cost-effectiveness analysis of the present thesis (study IV), another but simulation model-based cost-effectiveness analysis has been published. Bloom *et al*[119] showed decreased cost and increased QALY in favour of incisional NPWT.

In addition, incisional NPWT has been evaluated regarding cost-effectiveness in the prevention of SSIs within other surgical fields. Nherera *et al*[120] after hip or knee replacement, Nherera *et al*[121] again after coronary artery bypass grafting surgery, and Hyldig *et al*[122] on caesarean sections in obese women, all presented dominant results in favour of incisional NPWT (decreased cost and increased QALY). Heard *et al*[123] after caesarean sections in obese women and Costa *et al*[124] after lower limb trauma, both reported increased cost and increased QALY with ICERs of 42,340 AUD (Australian dollar) (Corresponds to €28,536 in 2019 price year) and 396,531 GBP (Great Britain Pound) (Corresponds to €460,343 in 2019 price year) per gained QALY, respectively, which were not considered cost-effective.

8.7.4 Society's willingness to pay

Cost-effectiveness analyses aim to guide decisionmakers into prioritising resources based on benefits related to costs.[125] If the result is not dominant, the definition of cost-effectiveness depends on society's willingness to pay for the measured outcome. Few countries provide limits on increased costs per gained unit of the measured outcome. NICE in the United Kingdom has set a threshold on 20,000-30,000 GBP (Corresponds to €22,810-34,215 in 2019 price year) per QALY gained, while the United States has the widely used threshold of 50,000 USD (Corresponds to €44,655 in 2019 price year) per QALY gained.[126, 127] In Sweden there is currently no threshold for willingness to pay per QALY. Instead, there are guidelines how to interpret different levels of cost per QALY gained. It considers a cost increase per QALY gained of less than 100,000 SEK (Swedish krona) (Corresponds to €9,450 in 2019 price year) as low, 100,000 to 499,999 SEK (Corresponds to €9,450-47,250 in 2019 price year) as moderate, 500,000 to 1,000,000 SEK (Corresponds to €47,250-94,500 in 2019 price year) as high, and more than 1,000,000 SEK (Corresponds to €94,500 in 2019 price year) as very high.[128]

There is however no defined threshold for willingness to pay for prevention of SSIs. In study IV, there was no difference in cost but a significant difference in SSI incidence in favour of incisional NPWT, thereby making incisional NPWT cost-effective without a willingness to pay threshold. The lack of guidelines for willingness to pay for non-QALY outcomes however remain a potential concern in cost-effectiveness analyses.

9 Conclusions

- Incisional NPWT on inguinal incisions after EVAR procedures with the primary intent of fascia closure did not show reduced incidence of SSIs but a trend towards fewer incisions receiving additional treatment due to any incisional wound complication when compared with standard dressings.
- Evaluation of scars from bilateral inguinal incisions after vascular surgical procedures treated with incisional NPWT compared to standard dressings demonstrated equally high patient-reported satisfaction and subtle visual appearance. Scar evaluation from 3D images is possible and showed good to very good intra-rater reliability and fair to good inter-rater reliability.
- Incisional NPWT on inguinal incisions after arterial surgical procedures significantly reduced SSI incidence compared to standard dressings when analysed with meta-analysis in a systematic review.
- There was no difference in cost comparing patients receiving incisional NPWT compared to standard dressings in inguinal incisions from open vascular surgical procedures, but a significant reduction in SSI incidence in favour of incisional NPWT, thereby making incisional NPWT cost-effective in reducing SSIs.

10 Future research

There is growing evidence for using incisional NPWT instead of standard dressings in the prevention of SSIs on high-risk incisions operated with open technique – vascular as non-vascular procedures.[5] Its role in incisions with low to intermediate risk for SSIs such as EVAR procedures with fascia suture remain unclear. The absence of difference in SSI incidence between the incisional NPWT and control dressings in study I needs to be verified in future RCTs to strengthen the external validity of the finding. Subgrouping of fascia closure, cut-down, and patch angioplasty as well as primary intent compared to rescue closure technique also remain as subjects of future research.

The effect of incisional NPWT compared to standard dressings on other incisional wound complications after inguinal vascular surgical procedures has yet not been demonstrated nor fully evaluated. This aspect should be included in future research, preferably RCTs.

With growing evidence for a beneficial effect on SSI incidence with incisional NPWT in high-risk incisions operated with open technique, comparison between different manufactures of incisional NPWT becomes the next area of investigation. In addition to incidence of SSI and other incisional wound complications, adverse effects, and patient experience should be included.

The possible effect of incisional NPWT on the quality of cutaneous scars should in future research be conducted on high-risk incisions for the development of hypertrophic or keloid scars, preferably using a RCT study design with a sufficient sample size. A consensus on how to report observer estimated visual appearance and patient-reported satisfaction of incisional scars is highly warranted.

The cost-effectiveness of incisional NPWT compared to standard dressings in inguinal vascular surgical incisions needs to be verified in future studies. A possible method could be a simulation model-based study, to reduce variance in cost and patient QoL data.

11 Populärvetenskaplig sammanfattning

Varje kirurgiskt ingrepp innebär en risk för sårkomplikationer i operationssnittet. Operationssnitt i ljumsken vid kärlkirurgiska operationer är extra utsatta för sårkomplikationer, framför allt sårinfektioner men även skador på lymfbanor, blödningar, sårruptur (bristning av ett eller flera hopsydda skikt i operationssnittet), ansamling av sårvätska mellan vävnadskikt i det opererade området och överdriven ärrbildning. Den höga andelen sårkomplikationer vid kärlkirurgiska operationer i ljumsken beror dels på ingreppets natur; närhet till lymfbanor, ljumskens och intilliggande hudområdens ogynnsamma bakterieflora, samt hög förekomst av kroppsfrämmande material, och dels på hög förekomst av patientbundna riskfaktorer; rökning, diabetes mellitus, hög ålder, samt nedsatt blodcirkulation i den opererade vävnaden.

En föreslagen åtgärd för att minska sårkomplikationer är undertrycksförband. Undertrycksförband är förband där ett undertryck (vakuumsug) från en batteridriven pump appliceras genom förbandets sårdyna vilken avleder överflödig sårvätska, stimulerar lymfflödet, minskar de mekaniska krafterna över det hopsydda operationssnittet, minskar inflammationen i sårkanterna, samt skyddar såret från bakterier från intilliggande hud.

Den här avhandlingen syftar till att studera effekten av undertrycksförband jämfört med konventionella standardförband efter kärlkirurgiska ingrepp i ljumsken avseende sårkomplikationer och kostnader.

Den första studien inkluderade patienter som opererats kärlkirurgiskt via ljumsken för åderbråck på stora kroppspulsådern och/eller dess förgreningar till ljumskartärerna med så kallad endovaskulär teknik. Denna operationsteknik innebär att man punkterar blodkärlet (artär) i ena eller båda ljumskarna och via dessa punktioner inför täckta metallstentar (nätformade metallcylindrar täckta med ett polyestermaterial) som man leder upp i stora kroppspulsådern där de utvidgas och infästes så att de täcker åderbråcket från insidan (endo) av kärlet (vaskulär). Efter ingreppet behöver punktionen av kärlet i ljumsken lagas, varvid man lägger ett operationssnitt över kärlet och syr ihop den överliggande hinnan över punktionen vilket förhindrar blödning. Patienter som opererats för åderbråck med endovaskulär teknik i Malmö och Örebro lottades till antingen undertrycksförband eller standard-

förband. Vid operationer via båda ljumskkärlen avgjorde lotten förbandstypen på höger sida medan vänster sida fick motsatt förband. Patienterna följdes därefter avseende sårkomplikationer i operationssnittet under ett år. Studien visade ingen minskning av sårinfektioner eller andra sårkomplikationer i operationssnittet i de ljumskar som lottades till undertrycksförband.

Den andra studien involverade patienter som opererats i båda ljumskarna samtidigt, i huvudsak åderbråck på stora kroppspulsådern med endovaskulär teknik avseende ärrbildning efter operationerna. Detta utvärderades med ett patientfrågeformulär och oberoende bedömning av ärrutseende av plastikkirurger från tredimensionella bilder av ljumskarna. Studien visade generellt diskret ärrbildning, få rapporterade biverkningar, samt ingen skillnad mellan ärr efter operationssnitt behandlande med undertrycksförband jämfört med standardförband.

Den tredje studien var en litteraturstudie där en systematisk sökning av databaser med publicerade vetenskapliga artiklar identifierade sju studier där man lottat patienter till undertrycksförband eller standardförband efter kärlkirurgiska ingrepp i ljumsken. Totalt inkluderades 1 051 operationssnitt. Summering av frekvenser av sårinfektioner i ljumskar behandlande med undertrycksförband jämfört med standardförband visade på en statistiskt säkerställd minskning av sårinfektioner i operationssnittet med undertrycksförband.

Den fjärde studien utvärderade undertrycksförbands kostnadseffektivitet i att minska sårinfektioner i operationssnittet vid användning efter kärlkirurgiska ingrepp med öppen teknik (operation direkt på ljumskens blodkärl via operationssnitt i stället för via punktioner) i ljumsken. Patienter hade lottats till antingen undertrycksförband eller standardförband. Studien visade ingen skillnad i kostnad men en statistiskt säkerställd minskning av antal sårinfektioner i operationssnitt behandlade med undertrycksförband jämfört med standardförband. Undertrycksförband bedömdes därför kostnadseffektiva i att minska sårinfektioner vid användning efter kärlkirurgiska ingrepp med öppen teknik i ljumsken.

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13 Other publications

The following publications has been made by the author but are not part of the present thesis:

- Svensson-Bjork R, Acosta S. Pitfalls in Conducting Studies on Wound Outcomes. Eur J Vasc Endovasc Surg. 2018;56(3): 449.
- Svensson-Bjork R, Acosta S. The Whole Nine Yards in Randomised Controlled Trials. Eur J Vasc Endovasc Surg. 2020;59(4): 642.
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