Surgical Wound Infections after Lower Limb Vascular Surgery
Surgical Wound Infections after Lower Limb Vascular Surgery

To be presented by permission of the Faculty of Health Sciences, University of Eastern Finland for public examination in Carelia Auditorium C2, Joensuu, on Saturday, May 18th 2013, at 12 noon

Publications of the University of Eastern Finland
Dissertations in Health Sciences
Number 162

Department of Surgery, Institute of Clinical Medicine, School of Medicine, Faculty of Health Sciences, University of Eastern Finland
Kuopio
2013
Author’s address: Department of Surgery
North Karelia Central Hospital
Tikkamäentie 16
80210 Joensuu
FINLAND

Supervisors: Docent Tapio Hakala M.D., Ph.D.
Department of Surgery of North Karelia Central Hospital
University of Eastern Finland
KUOPIO
FINLAND

Docent Kimmo Mäkinen M.D., Ph.D.
Heart Center Kuopio University Hospital
University of Eastern Finland
KUOPIO
FINLAND

Reviewers: Professor Mauri Lepäntalo M.D., Ph.D.
Department of Vascular Surgery
University of Helsinki
HELSINKI
FINLAND

Docent Jukka Lumio, M.D., Ph.D.
Department of Internal Medicine
University of Tampere
TAMPERE
HELSINKI

Opponent: Docent Anders Albäck, M.D., Ph.D.
Department of Vascular Surgery
University of Helsinki
HELSINKI
FINLAND
The overall aim of this study was to evaluate the pathophysiology, risk factors, incidence and consequences of surgical wound infections (SWI) after lower limb vascular surgery, and to assess preventive measures in the SWI prophylaxis.

Study I was conducted to determine the incidence of SWI, to evaluate the risk factors and consequences of SWI, and to calculate the additional cost of services caused by SWI. The study cohort comprised of 184 consecutive adult patients undergoing lower limb vascular or infrarenal aorto-iliacal surgery. The incidence of SWI was 27% and the independent predictors for SWI were infrainguinal surgery, body mass index over 25 kg/m² and puncture site of arteriography on the operated area. The average costs attributable to SWI was €3,320.

Study II was conducted to examine quantitative and qualitative analysis of surgical wound bacterial colonization and its correlation with the development of SWI. Study cohort comprised 94 consecutive patients with 100 surgical wounds. Swabs for microbiological analyses were taken from surgical wounds at four different time intervals: just before surgical area had been scrubbed, at the end of surgery and, at the first and the second postoperative day. The incidence of SWI was 21%. Multivariate analysis revealed that high bacterial load at the second postoperative day and diabetes independently increased the risk of SWI.

Study III was a multicenter, double-blinded study designed to test whether triclosan-coated sutures are effective in the prevention of SWI after lower limb vascular surgery. The study cohort comprised of 276 consecutive adult patients who were randomised to either the study or the control group. In the study group the arterial exposure and vein harvest incisions were closed using triclosan-coated sutures for subcutaneous and intracutaneous closure. The overall incidence of SWI was 22%. There was no difference between the triclosan group and the control group in the incidence of SWI. Obesity and the use of corticosteroids were independent predictors of SWI in the multivariate analysis.

Study IV was aimed to test whether postoperative supplemental inspired oxygen is effective in the prevention of SWI. In this multicenter, investigator-blinded study, consecutive adult patients undergoing lower limb vascular surgery were randomised to either the study group (n=137) or the control group (n=137). The patients in the study group received 30% supplemental oxygen via mask in the recovery room after the operation and on the first postoperative day in the surgical ward. On the second postoperative day, patients inspired supplemental oxygen via a nasal cannula. The patients in the control group received usual postoperative care. There was a trend that the incidence of SWI was lower in the study group compared with the control group (18% and 25%, respectively, p=0.07). Asthma, coronary artery disease and infrainguinal incision were independent predictors of SWI in the multivariate analysis. In 103 patients with inguinal incision only, the use of supplemental oxygen significantly decreased the risk of SWI with odds ratio (OR) of 0.20.
In conclusion, surgical wound infection after lower limb vascular surgery is a remarkable problem with an incidence of 22-27%. Obesity, infrainguinal surgery, puncture site of arteriography on the operated area, asthma, coronary artery disease, use of corticosteroids, diabetes, and the high bacterial load of the surgical site at the second postoperative day increase the risk of the development of SWI after lower limb vascular surgery.

National Library of Medicine Classification:
Medical Subject Headings: peripheral vascular surgery, surgical wound infection, supplemental oxygen, triclosan-coated sutures, bacterial load
Alaraajavaltimoiden verisuonikirurgisia leikkausia tehdään joko parantamaan valtimoverenkkoa tai korjamaan vartimopullistumia. Lähtökohtana on potilaan alaraajan pelastaminen, liikuntakyvyn parantaminen tai vartimopullistumasta komplikaatioiden estäminen. Näiden toimenpiteiden jälkeinen leikkaushaavatulehdus on tavallinen ongelma, joka pahimmillaan voi johtaa alaraajan menettämiseen.


Toisessa osatyössä 95 verisuonikirurgisen potilaan 100 leikkaushaavalta otettiin bakteeriviljelyä laadullista ja määrällistä analyyysia varten. Näytteet otettiin leikkaushaavalta leikkaussalissa juuri ennen leikkausalueen pesua, leikkauksen lopussa sekä ensimmäisenä ja toisena leikkausenä päivänä. Leikkaushaavatulehdusten ilmaantuvuus oli 21% ja korkea bakteereiden määrä leikkausalueella toisena leikkausenä päivänä oli itsenäinen riskitekijä tulehdusten synnylle. Myös diabetes lisäsi infektioriskiä.

Kolmannessa osatyössä testasimme vähentääkö triklosaanilla päällystettyjen ommelaineiden käyttö leikkaushaavatulehdusten ilmaantumisen riskiä. Yhteensä 276 verisuonikirurgista potilaasta satunnaisesti toimii tutkimusryhmän ja kontrolliryhmän tavallisella ommelaineella. Leikkaushaavatulehdusten ilmaantuvuus tässä tutkimuksessa oli 22%, ryhmien välillä ei ollut eroa. Tulehdusten riskiä lisäsi ylipaino sekä kortikosteroidien käyttö.

Acknowledgements

The work of this thesis was carried out at the Department of Surgery of North Karelia Central Hospital in Joensuu, during years 2007-2012, in collaboration with Eastern Finland Laboratory Centre, Regional Laboratory of Joensuu, Departments of Vascular Surgery of Kuopio University Hospital, Helsinki University Hospital and Tampere University Hospital and, Departments of Surgery of South Karelia Central Hospital, Mikkeli Central Hospital, Central Finland Central Hospital and Lapland Central Hospital.

First and foremost I would like to express my respect and gratitude for my principal supervisor, Docent Tapio Hakala for his encouragement and personal guidance throughout the time of the study and for introducing me into the scientific research. His willingness to give advices whenever I needed and, valuable time we spent discussing the details of the thesis have inspired me to get this project done.

I wish to express my warm gratitude for my second supervisor Docent Kimmo Mäkinen, who has been my teacher in vascular surgery. I am most thankful for his professional and warm guidance during the first years of my career and, his contribution to the thesis project.

I thank Professor Mauri Lepäntalo and Docent Jukka Lumio, the official reviewers, for careful revision of the thesis. They provided numerous constructive comments that improved the final manuscript.

I am very grateful to Jari Karhukorpi M.D. Ph.D. for his valuable contribution in Study II and, his experience in the field of microbiology.

I owe my deep gratitude to my co-authors, Eija Saimanen M.D., Ph.D. for her most hard working and kind attitude towards this work and, Matti Reinikainen M.D., Ph.D. for his effort to Study IV and friendly support during my thesis project.

I wish to extend my warmest thanks to all other co-authors, Teemu Partio M.D., Antti Nykänen M.D., Ph.D, Docent Maarit Venermo, Jussi Kärkkäinen M.D., Jyrki Virkkunen M.D., Ph.D, Kari Vuorio M.D., Ilkka Uurto M.D., Ph.D. and, Timo Hakkasaiinen M.D. for data collection and, Vesa Kivinieni Ph.Lic for his expertise in statistics.

I owe my sincere thanks to vascular surgery ward nurses and operating theatre nurses in North Karelia Central Hospital for their positive attitude. Without their careful and accurate work in data collection this study would have been impossible to conduct. Furthermore, I want to thank all the nurses who have participated in data collection for this study in Central Hospital of Central Finland, Central Hospital of Shout Karelia, Helsinki University Hospital, Kuopio University Hospital, Lappland Central Hospital, Mikkeli Central Hospital and, Tampere University Hospital.

I thank Graham Lees Ph.D. for providing language review for this thesis.

I also want to thank staff at the Scientific Library of North Karelia Central hospital for providing effective and friendly services.

I wish to express my heartfelt thanks to all my dear colleagues at Department of Surgery of North Karelia Central Hospital for showing interest in my study and creating a positive working atmosphere. Furthermore, I want to thank all the patients who have participated into my study.

I dedicate my dearest thanks to my beloved parents Tuula and Olavi Laakkonen for their continuous love and support over the years and, for helping me whenever I needed. They have believed in me and let me choose my own path in life. I also want to thank all my rela-
tives and friends for their support and empathy. I feel very fortunate for having such wonder-
ful people in my life, especially my godmothers Mirja Varpula and Pirkko Koivisto who have
always showed interest in my life and warmly welcomed me in their homes.

I want to express my warmest and deepest thanks to my dear family; to my loving and
practical husband Tarmo for patience and support and, to our wonderful sons Janne, Ville and
Tommi for being just who they are; the sunshine of my life.

Finally, this dissertation is dedicated to my late father Väinö Jääskeläinen M.Phil who al-
ways encouraged me to increase my knowledge and understanding; his memory remains in
my heart.

This study was financially supported by grants from North Karelia Central Hospital.
List of the original publications

This dissertation is based on the following original publications:


The original publications are reprinted with kind permission of the copyright holders. In addition, some unpublished data are presented.
Contents

1 INTRODUCTION................................................................................................................................................. 1

2 REVIEW OF LITTERATURE ..................................................................................................................................... 3

2.1 SURGICAL WOUND ........................................................................................................................................... 3
   2.1.1 Classification of wounds .......................................................................................................................... 3
   2.1.2 Risk Index .................................................................................................................................................. 3
   2.1.3 Healing of surgical wound ........................................................................................................................ 4
   2.1.4 The role of oxygen in wound healing ...................................................................................................... 4

2.2 Surgical wound infection ................................................................................................................................... 5
   2.2.1 Definition and diagnosis ......................................................................................................................... 5
   2.2.2 Epidemiology and outcome .................................................................................................................... 6
   2.2.3 Pathogenesis .......................................................................................................................................... 6
   2.2.4 Microbiology of surgical wound infection ............................................................................................. 7
   2.2.5 Risk factors ........................................................................................................................................... 8
      2.2.5.1 Patients-related .......................................................................................................................... 8
      2.2.5.2 Procedure-related ....................................................................................................................... 11
   2.2.6 Prevention .......................................................................................................................................... 15
      2.2.6.1 Antibiotic prophylaxis ................................................................................................................. 15
      2.2.6.2 Triclosan-coated sutures ........................................................................................................... 18
      2.2.6.3 Supplemental oxygen in prevention of surgical wound infection ........................................... 20
      2.2.6.4 Other methods for preventing surgical wound infection ......................................................... 21

2.3 Surgical wound infection after vascular surgery ............................................................................................. 22
   2.3.1 Incidence .......................................................................................................................................... 22
   2.3.2 Risk factors for surgical wound infection after lower limb vascular surgery .................................. 24
   2.3.3 Causative agents .................................................................................................................................. 26
   2.3.4 Consequences of surgical wound infection after lower limb vascular surgery ................................ 26
      2.3.4.1 Impact on patient outcome .................................................................................................... 26
      2.3.4.2 Impact on resource utilisation ................................................................................................. 26
   2.3.5 Treatment of surgical wound infection after vascular surgery ......................................................... 26
   2.3.6 Prevention .......................................................................................................................................... 27

3 THE AIMS OF THE STUDY ................................................................................................................................. 29

4 PATIENTS AND METHODS .................................................................................................................................. 30

4.1 Patients .......................................................................................................................................................... 30
   4.1.1 Study I ................................................................................................................................................ 30
   4.1.2 Study II .............................................................................................................................................. 30
   4.1.3 Study III ............................................................................................................................................ 30
   4.1.4 Study IV ........................................................................................................................................... 32

4.2 Methods ........................................................................................................................................................ 34
   4.2.1 Data collection ................................................................................................................................... 34
   4.2.2 Antibiotic prophylaxis ......................................................................................................................... 35
   4.2.3 Sampling methods in study II ............................................................................................................. 35
   4.2.4 Outcomes .......................................................................................................................................... 36
   4.2.5 Additional costs related to postoperative surgical wound infection ............................................. 36
   4.2.6 Sample size calculation amd randomisation ...................................................................................... 36
   4.2.7 Statistics .......................................................................................................................................... 37
5 RESULTS ..................................................................................................................................... 38  
5.1 Study I ................................................................................................................................... 38  
5.2 Study II .................................................................................................................................. 40  
5.3 Study III ................................................................................................................................ 42  
5.4 Study IV ................................................................................................................................ 44  
5.4.1 Results of the main analyses ........................................................................................ 44  
5.4.2 Subgroup analysis for inguinal procedures .............................................................. 46  
6 DISCUSSION.............................................................................................................................. 47  
6.1 Limitations of the study ....................................................................................................... 47  
6.2 Patients ................................................................................................................................... 47  
6.3 Evaluation of methods ........................................................................................................... 47  
6.4 Incidence and risk factors for surgical wound infection  
    after lower limb vascular surgery (I) ................................................................................. 48  
6.5 Bacterial flora of surgical site in patients undergoing lower limb  
    vascular surgery (II) .............................................................................................................. 50  
6.6 Effect of triclosan-coated sutures in prevention of surgical wound  
    infection after lower limb vascular surgery (III) .............................................................. 51  
6.7 Effect of supplemental postoperative oxygen in prevention of surgical  
    wound infection after lower limb vascular surgery (IV) ................................................ 52  
7 SUMMARY AND CONCLUSIONS .......................................................................................... 54  
8. REFERENCES ............................................................................................................................ 55  
APPENDIX: ORIGINAL PUBLICATIONS (I, III AND IV)
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABI</td>
<td>Ankle brachial index</td>
<td>LD</td>
<td>Lethal dose</td>
</tr>
<tr>
<td>AGI</td>
<td>Aortic graft infection</td>
<td>LD50</td>
<td>Median lethal dose</td>
</tr>
<tr>
<td>ASA</td>
<td>American Society of Anesthesiologists</td>
<td>LOS</td>
<td>Length of stay</td>
</tr>
<tr>
<td>Asa</td>
<td>Acetyl salicylic acid</td>
<td>MRSA</td>
<td>Methicillin-resistant Staphylococcus aureus</td>
</tr>
<tr>
<td>bFGF</td>
<td>Basic fibroblast growth factor</td>
<td>NNIS</td>
<td>National Nosocomial Infections Surveillance</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
<td>NRI</td>
<td>Nutritional risk index</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary artery bypass graft surgery</td>
<td>OA</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary artery disease</td>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>CDC</td>
<td>The Centers for Disease Control and Prevention</td>
<td>PDGF</td>
<td>Platelet-derived growth factor</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
<td>%BF</td>
<td>Percent body fat</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
<td>PO2</td>
<td>Partial pressure of oxygen</td>
</tr>
<tr>
<td>CRP</td>
<td>C reactive protein</td>
<td>RA</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
<td>Redo</td>
<td>Repeated for a segment already surgically corrected</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
<td>RR</td>
<td>Risk ratio</td>
</tr>
<tr>
<td>EGF</td>
<td>Epidermal growth factor</td>
<td>SCCP</td>
<td>Scientific Committee of Consumer products</td>
</tr>
<tr>
<td>EPA</td>
<td>Enviromental Protection Agency</td>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>EnR</td>
<td>Enoyl reductase</td>
<td>ST</td>
<td>ST segment of ECG</td>
</tr>
<tr>
<td>ePTFE</td>
<td>expanded polytetrafluorethylene</td>
<td>SWI</td>
<td>Surgical wound infection</td>
</tr>
<tr>
<td>FabI</td>
<td>NADH-dependent enoyl reductase</td>
<td>VEGF</td>
<td>Vascular endothelial cell growth factor</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
<td>TGF-α</td>
<td>Transforming growth factor alpha</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
<td>TGF-β</td>
<td>Transforming growth factor beta</td>
</tr>
<tr>
<td>HIF</td>
<td>Hypoxia-inducible factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>Hazard Ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>Litre</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1 Introduction

Until the late 19th century, surgical patients commonly developed postoperative surgical wound infection often followed by sepsis and death. The mortality associated with ovariotomy and other types of major abdominal surgery, repair of open fractures, and limb amputation was 50% or higher owing to infection (Wangensteen and Wangensteen 1978). The first one who radically changed surgery from an activity associated with sepsis and high mortality to procedures that could prolong life was Joseph Lister, an English surgeon. In his landmark series of articles Lister systematically and scientifically described the effectiveness of new system of antisepsis with the use of carbolic acid (Lister 1867, Gawande 2012).

The father of the modern infection control is generally considered to be Professor Ignaz Semmelweis (1818-1865), who showed that puerperal sepsis was contagious and could be prevented with adequate hand hygiene. Semmelweis studied and worked in the Maternity Hospital in Vienna. He noticed that maternal mortality was 10% in Ward 1, where medical students came directly from post-mortem room, and 3% in Ward 2, where midwives devoted much attention to cleanliness. Semmelweis established a hand-washing program and the death rate in Ward 1 dropped to the same level as in Ward 2 (Rutkow 1993). These ideas, however, had been brought out for decades before Semmelweis’ work. Alexander Gordon had published his observations in 1795 and showed the contagiousness of puerperal fever and advised disinfection of the hands and clothes of doctors and midwives (Dunn 1998, Gould 2010).

Research of Louis Pasteur (1822-1895) and Robert Koch (1843-1910) improved the understanding of bacteria and antisepsis. By 1861 Pasteur demonstrated that putrefaction is caused by the presence of bacteria. Until that time, infection was believed to be owing to spontaneous generation. In 1875 Pasteur discovered the first anaerobic pathogen, Clostridium septicum. Robert Koch improved methods of fixing, staining and photographing bacteria. He also postulated that animal inoculation from the culture reproduces the disease and that the organism can be recovered from inoculated animals and again be grown in pure culture (Rutkow 1993).

Sir Alexander Fleming (1881-1955), a Scottish biologist and pharmacologist, while investigating the properties of staphylococci isolated penicillin in September 1928, and finally, there was an agent that could inhibit the bacterial growth, and even cure bacterial infections.

In Fleming’s laboratory one culture of staphylococci had been accidently contaminated with a fungus and he noticed that the colonies of staphylococci that had immediately surrounded fungus had been destroyed, whereas other colonies farther away were normal (Hare 1970).


Today the volume of surgical procedures is high – with at least 45 million inpatient procedures being performed annually in the United States (Hall et al 2012), which means, while the incidence of SWI is approximately 2.6% (Gaynes et al 2001), that there are 1.2 million SWIs each year in the US. Accordingly, the number of SWIs ranges between 450,000 and 6,000,000 per year in Europe (Leaper et al 2004). In Finland, the overall prevalence of SWI has reported to be 2.6% (Lyytikäinen et al 2008).

Prospective studies have revealed that independent predictors for SWI after peripheral vascular surgery are higher age, obesity, infrainguinal surgery, diabetes and redo vascular surgery (Richet et al 1991, Kent et al 1996). Furthermore, diabetes significantly prolongs the tissue healing time in patients operated due to critical ischaemia and tissue loss (Söderström et al 2008). Staphylococcus aureus, a microorganism of the skin’s normal flora, is the most frequently isolated pathogen occurring in 40-60% of SWIs after arterial reconstructions (Calligaro et al 1994, Lee et al 2000, Pounds et al 2005).

Since postoperative infections mainly occur at or around the suture lines, the role of suture material in the development of SWI may be important. In order to avoid microbial colonisation of suture material, triclosan-coated polyglactin 910 (Vicryl Plus; Ethicon, GmbH) and triclosan-coated poliglecaprone 25 (Monocryl Plus; Ethicon, GmbH) with antibacterial activity were developed. To date, nine prospective studies have been published in which the efficacy of triclosan-coated sutures for prevention of surgical site infection is assessed. However, there is no concordance between the results of these studies (Ford et al 2005, Rozelle et al 2008, Deliaert et al 2009, Mingmalairak et al 2009, Baracs et al 2011, Chen 2011, Galal et al 2011, Williams et al 2011, Zhang et al 2011).

Oxygen is vital for the healing of wounds and avoidance of infection. Supplemental inspired oxygen during surgery and postoperatively for 2-6 hours has been demonstrated to reduce the risk of SWI after colorectal resection (Grief et al 2000, Belda et al 2005, Bickel et al 2011). In contrast, there are studies with heterogeneous surgical patient populations that have not found supplemental perioperative oxygen to be protective against SWI (Pryor et al 2004, Mayzler et al 2005, Gardella et al 2008, Meyhoff et al 2009, Scifres et al 2011).

The overall aim of this study was to evaluate the risk factors, incidence and consequences of SWI after lower limb vascular surgery, and to assess preventive measures in SWI prophylaxis. Furthermore, in this study we try to define if there is a connection between bacterial contamination of operative wound and development of SWI in vascular surgery patients.
2 Review of literature

2.1 SURGICAL WOUND

2.1.1 Classification of wounds
Wounds are generally classified as acute or chronic. Acute wounds, either surgical or traumatic, are those that have been induced by external injury and that heal through an orderly and timely reparative process (Lazarus et al 1994, Bowler 2002). If wound-healing fails, wound is defined as being chronic. Chronic wounds are associated with pathophysiological abnormalities, for example venous leg ulcers or diabetic foot ulcers. To predict the risk of surgical wound infection (SWI), surgical sites are traditionally classified preoperatively into four categories (Stone et al 1976, Mangram et al 1999):

Class I/Clean: An uninfected operative wound which no inflammation is encountered and respiratory, alimentary, genital, or urinary tracts are not violated. Clean wounds are primarily closed and if necessary, drained with closed drainage. Operative incisional wounds that follow nonpenetrating (blunt) trauma should be included in this category if they meet the criteria.

Class II/Clean-Contaminated: An operative wound in which the respiratory, alimentary, or urinary tract is being operated on under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx included in this category, provided no evidence of infection or major aberration in technique is encountered.

Class III/Contaminated: Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g., open cardiac massage) or gross spillage from the gastrointestinal tract, and incisions in which acute, nonpurulent inflammation is encountered are included in this category.

Class IV/Dirty/Infected: Old traumatic wounds with retained devitalised tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation.

2.1.2 Risk Index
The surgical wound classification has been widely used to predict SWI risk. However, incidence of SWI varies largely within categories, for example 1-16% in the clean wound category (Haley et al 1985). Therefore, reporting SWI rates stratified by wound class alone is not recommended (Mangram et al 1999). The US-based NNSI risk index system was created in order to have improved predictor of risk for patient to develop SWI.

The NNSI SWI risk index system includes the conventional wound classification system, the American Society of Anesthesiologists (ASA) score, and duration of an operation. The patient’s fitness before surgery is assessed with the ASA score. Patients are given scores from 1 to 5: 1 indicates a healthy patient; 2 is a patient with mild systemic disease; 3, a patient with severe systemic disease; 4, a patient with severe systemic disease that is a constant threat to life; and 5, a patient not expected to survive (Am S Anesthes 1963).

The simplified risk index has range of 0 to 3 points. Each operation is scored by counting
the number of following factors: 1 point if an operation is classified as contaminated or dirty-infected; 1 point if a patient has an ASA preoperative assessment score of 3, 4 or 5, and 1 point if the operation has a duration of over 'T' hours, where 'T' depends on the operative procedure being performed (Culver et al 1991). The NNSI risk index is found to be significantly better predictor for SWI than the traditional wound classification system alone. The surgical wound infection rates range from 0.5-1.5% with none of the risk factors, to 5-13% for patients with all three of the risk assessment points (Culver et al 1991, Gaynes et al 2001).

2.1.3 Healing of surgical wound
Acute wounds normally heal in order of four distinct, but overlapping phases: haemostasis, inflammation, proliferation and remodelling. The healing process begins at the moment tissue is injured.

In the haemostasis phase, the platelets, after they come into contact with collagen and other components of extracellular matrix, release clotting factors, growth factors and cytokines such as platelet-derived growth factor (PDGF) and transforming growth factor beta (TGF-β). Then neutrophils enter the wound site and begin phagocytosis to remove foreign materials, bacteria and damaged tissue. During this inflammatory phase, macrophages continue the phagocytosis as well as releasing PDGF and TGF-β. Once the wound is cleaned out the proliferative phase begins: fibroblasts migrate to the site to deposit new extracellular matrix (Diegelmann and Evans 2004). Epithelisation is stimulated by presence of epidermal growth factor (EGF) and transforming growth factor alpha (TGF-α) that are synthesised by activated macrophages, platelets and keratinocytes (Schultz et al 1991). A new blood supply is provided during the process of angiogenesis which is stimulated by vascular endothelial cell growth factor (VEGF), basic fibroblast growth factor (bFGF) and TGF-β (Tonnesen et al 2000). The new collagen matrix then becomes cross-linked and organized during the remodelling phase.

Collagen accounts for 30 % of human body protein (Prockop and Kivirikko 1995). In normal tissues collagen provides strength, integrity and structure. When tissues are disrupted, collagen is needed to repair the defect and restore anatomic structure and function (Diegelmann and Evans 2004).

2.1.4 The role of oxygen in wound healing
The vital parameter for the healing of wounds is oxygen that is required in almost every step of the healing process (Schreml et al 2010). The oxygenation level of tissue, including wound tissue, is most often assessed by partial oxygen pressure (PO₂) and described in millimetres of mercury (mmHg). The oxygenation of wound tissue is based on three following factors: (1) delivery of oxygen from lungs to the tissue, (2) transport of oxygen from blood to tissue, and (3) oxygen consumption in tissue (Gotttrup 1994).

Collagen production and deposition, which provides the strength of the wound, is directly correlated with PO₂ (Jonsson et al 1991). Molecular oxygen is required for the hydroxylation of proline and lysine during collagen synthesis and without it only functionally deficient pro-collagen is produced (Hunt et al 1969).

During the epithelisation a layer of epithelium covers the wound surface. The process, based on the differentiation, proliferation and migration of epidermal keratinocytes, is stimulated by EGF and TGF-α. The epithelisation is highly metabolic and oxygen dependent (Diegelmann and Evans 2004).

Low oxygen tension stimulates the expression of hypoxia-inducible factor (HIF) that regulates the expression of VEGF and thus stimulates angiogenesis (Gerber et al 1997). However,
it has been shown that also increased oxygenation increases the amount of angiogenesis-stimulating VEGF in wound fluid (Sheikh et al 2000).

Oxidative killing is a critical defence against wound pathogens. Bacteria in wounds are destroyed inside a leukocyte, and molecular oxygen is necessary for the production of bactericidal oxygen radicals (Babior 1978). Bacterial killing capacity of leucocytes is reduced at low oxygen tension (Jönsson et al 1988, Allen et al 1997). On the other hand, hyperoxia increases the production of reactive oxygen species which destroy pathogens (Qadan et al 2010).

2.2 SURGICAL WOUND INFECTION

2.2.1 Definition and diagnosis
The US National Nosocomial Infections Surveillance (NNIS) of The Centers for Disease Control and Prevention (CDC) has developed standardised and commonly used criteria for defining postoperative SWI (Horan et al 1992). These criteria are presented in Table 1. SWIs are classified as superficial or deep infections, or infections involving organs or body spaces. Infection is classified to be SWI if it occurs within 30 days of the operation if no implant is placed in the surgical site or within one year if implant is in place and the infection appears to be related to the operation (Horan et al 1992).

A surgical wound can be considered uninfected if it heals primarily without discharge. The diagnosis of SWI is based on clinical and laboratory findings. However, SWI can occur without any haematologic or serologic laboratory abnormalities.

Table 1. CDC Criteria for Defining a Surgical Wound Infection (SWI)

<table>
<thead>
<tr>
<th>SUPERFICIAL INCISIONAL SWI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection occurs within 30 of the operative procedure and involves only skin or subcutaneous tissue of the incision, and at least one of the following is present</td>
</tr>
<tr>
<td>1. Purulent drainage from superficial incision</td>
</tr>
<tr>
<td>2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.</td>
</tr>
<tr>
<td>3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat- and superficial incision is deliberately opened by surgeon, unless culture of incision is negative.</td>
</tr>
<tr>
<td>4. Diagnosis of superficial incisional SWI by the surgeon or attending physician</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DEEP INCISIONAL SWI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection occurs within 30 days of the operative procedure 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 operative procedure and the infection involves deep soft tissues (e.g. fascial and muscular layers) of the incision, and at least one of the following is present</td>
</tr>
<tr>
<td>1. Purulent drainage from the deep incision but not from the organ/space component of surgical site.</td>
</tr>
<tr>
<td>2. A deep incision spontaneously dehisces or is deliberately opened by surgeon when the patient has at least one of the following signs or symptoms: fever (≥38°C), localized pain, or tenderness, unless culture of incision is negative.</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>4. Diagnosis of deep incisional SWI by a surgeon or attending physician.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ORGAN/SPACE SWI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection occurs within 30 days of the operative procedure if no implant in in place, or within 1 year if implant is in place and the infection appears to be related to the operative procedure and if infection involves any part of anatomy (e.g., organs or spaces) other than the incision opened or manipulated during the operative procedure, and at least one of the following is present</td>
</tr>
<tr>
<td>1. Purulent drainage from a drain that is placed through a stab wound into the organ/space.</td>
</tr>
<tr>
<td>2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.</td>
</tr>
<tr>
<td>3. An abscess or other evidence of infection involving the organ/space on direct examination, during reoperation, or by histopathologic or radiologic examination.</td>
</tr>
<tr>
<td>4. Diagnosis of an organ/space SWI by a surgeon or attending physician.</td>
</tr>
</tbody>
</table>

Adapted from Horan et al 1992
2.2.2 Epidemiology and outcome

In the United States SWI is the second most common type nosocomial infection, also known hospital acquired infection or health care-associated infection. Approximately 5-10% of patients admitted to US acute care hospitals develop nosocomial infection and 25% of these infections are SWIs (Wenzel 2007). Comparatively, in Finnish acute care hospitals nosocomial infection occurs in 8.5% of patients and SWI comprises 29% of all nosocomial infections. (Lyytikäinen et al 2008).

Nosocomial infections cause extra costs because of prolonged hospitalisation, additional diagnostic tests, therapeutic use of antibiotics and sometimes additional surgery (Urban 2006, Broex et al 2009). SWI increases the hospital costs of surgical procedures by approximately 115%. In other words, a treatment of one surgical patient with SWI costs as much as a treatment of two surgical patients without SWI (Broex et al 2009).

A review with 48 European studies reported 1.5-20% postoperative SWI, and the rate depends on the type of surgery and wound classification. The authors considered that there are an estimated 30 million surgical procedures conducted in Europe each year, which leads to number of SWI to range between 450,000 and 6,000,000. An average cost per day in hospital is €325 and an average extended hospital stay is 10 days, this means that SWI could be costing European health care systems between €1.47 billion and €19.1 billion (Leaper et al 2004). A study with 140 English hospitals participating found the extra postoperative length of stay (LOS) because of SWI ranging from 3.3 days for abdominal hysterectomy to 21 days for lower limb amputation. The additional costs attributable to SWI ranged from £959 to €6,103 (€1,154-7,342). Patients with SWI following hip prosthesis replacement, vascular surgery or large bowel surgery have a mortality rate significantly higher than those without SWI (Coello et al 2005). In US hospitals 1,737,125 nosocomial infections and 290,485 SWIs were reported in 2007. And mortality related to nosocomial infection and SWI was 5.7% and 2.8%, respectively (Umscheid et al 2011). Furthermore, a long-term study conducted in France reported that 38% of the deaths that occurred in patients with SWI were directly attributable to the infection, and SWI increases mortality with an odds ratio (OR) of 1.6 [95% confidence interval (CI) 1.3-2.2] (Astagneau et al 2001). A case-control study estimated that median cost of a single coronary artery bypass surgery (CABG) followed by sternal infection is $49,500 (€36,300) compared to $18,200 (€13,400) in patients with no infection (Graf et al 2011).

A cross-sectional and retrospective study that covers all surgical wound infection injury claims made in Finland during 1988-1990 was conducted by using the records of the Patients Injury Act. The study revealed that 0.23% of all surgical procedures led to a compensation claim and about 70% of them led to a grant of compensation. The mean extra hospital stay per infection was 33.2 days (Hyrylä et Sintonen 1994).

2.2.3 Pathogenesis

The likelihood that SWI occurs is a relationship among (1) microbial characteristics and contamination, (2) patients characteristics and (3) surgical characteristics (Anderson 2011). Contamination of the surgical site with bacteria and other microorganisms occurs during surgery. In a prospective study with 201 cardiac surgery procedures 98% of patients showed bacterial growth on the skin surrounding the surgical wound at the end of the operation (Kühme et al 2007). Although nearly all surgical wounds become contaminated (Robson 1979, Saleh et al 2011), only a small number of patients develop a clinical infection (Olson et al 1984, Santos et al 2010).
Intraoperatively microbial contamination of the surgical wound remains one of the most accepted risk factors for SWI. The greater the degree of bacterial load in the surgical wound, the higher is the risk of postoperative SWI (Anderson 2011, Saleh et al 2011). The risk of SWI is markedly increased when the contamination level of tissue exceeds $10^5$ microorganisms per gram of tissue (Bendy et al 1964). However, a lower dose of contaminating microorganisms may be sufficient when foreign material is present at the surgical wound (Mangram et al 1999).

For most SWIs, the source of pathogens is the patient’s endogenous flora on skin, mucous membranes or in hollow viscera (Altemeier et al 1968). Endogenous organisms are usually aerobic gram-positive cocci, but may include anaerobic bacteria and gram-negative aerobes when incisions are made near perineum or groin. The microbes that most commonly contaminate the surgical wound by the end of the operation include the following bacteria of skin normal flora: coagulase-negative staphylococci, propionibacterium acnes and staphylococcus aureus (Saleh et al 2011, Kühme et al 2007). If the gastrointestinal organ is opened during surgical procedure, the organisms isolated from SWI are typically gram-negative bacilli, gram-positive organisms and anaerobes (Mangram et al 1999). Wound contamination occurs primarily near to the surgical site. However, patients with an infection somewhere in the body remote from the wound are in risk of endogenous bacterial contamination via bloodstream or lymphatic system (Robson 1997).

Exogenous sources of wound contamination include surgical personnel, the operating room environment and surgical instruments (Mangram et al 1999). SWIs owing to exogenous sources most commonly occur sporadically (Anderson 2011).

2.2.4 Microbiology of surgical wound infection

Pathogens responsible for SWIs vary with the type and anatomic location of the procedure. Staphylococcus aureus, microorganism of the skin normal flora, is the most frequently isolated pathogen occurring in 8-36% of SWIs (Table 2). Other endogenous bacteria responsible for SWI are coagulase-negative staphylococci, Enterococcus species and Escherichia coli. Typical SWI isolates after gastrointestinal procedures are gram-negative bacilli (e.g., Escherichia coli), gram-positive organisms (e.g. enterococci), and sometimes anaerobes (e.g. Bacteroides fragilis) (Mangram et al 1999).

Methicillin-resistant Staphylococcus aureus (MRSA) as a causative agent of SWI is an increasing problem in several countries. The proportions of MRSA of staphylococcus aureus isolated from SWI have reported as follows: The United States 47% (Kassavin et al 2011), Great Britain and Ireland 40% (Naylor et al 2001), Serbia 64% (Suljagic et al 2010), Greece 56% (Roumbelaki et al 2008), Switzerland 11% (Sax et al 2011) and Italy 11% (Di Leo et al 2009). At the present, MRSA is not a remarkable causative agent for SWI in Finland.

Exogenous flora responsible for SWI are predominantly aerobes, especially gram-positive organisms such as staphylococci and streptococci (Mangram et al 1999). Unusual bacterial isolates from the hospital environment as well as fungi are occasionally found to be agents of SWI (Mangram et al 1999, Barie and Eachempati 2005, Anderson 2011).
Table 2. Pathogens isolated from surgical wound infections after various types of surgical procedures. Results of 12 prospective or prevalence studies that have been aimed to determine the etiology of SWI.

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>PRECENTAGE OF ISOLATES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>7-36</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>12-29</td>
</tr>
<tr>
<td>Enterococcus sp.</td>
<td>3-16</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>2-21</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>1-21</td>
</tr>
<tr>
<td>Enterobacter sp.</td>
<td>2-11</td>
</tr>
<tr>
<td>Proteus spp</td>
<td>1-14</td>
</tr>
<tr>
<td>Klebsiella sp.</td>
<td>3-13</td>
</tr>
<tr>
<td>Acinetobacter spp</td>
<td>2-6</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>6</td>
</tr>
<tr>
<td>Streptococcus sp.</td>
<td>2</td>
</tr>
<tr>
<td>Bacteroides sp.</td>
<td>6</td>
</tr>
<tr>
<td>Clostridium</td>
<td>8-30</td>
</tr>
<tr>
<td>Culture negative</td>
<td></td>
</tr>
</tbody>
</table>


According to the review of Rasnake and Dooley (2006), published studies of microbiology of SWIs suggest that 10-30% of all cultures do not exhibit bacterial growth, even when clinical signs of infection are present. Reasons for culture-negative SWI are speculated to be antibiotic therapy prior to culture and lack of growth on routine culture. Some atypical pathogens do not grow on standard culture media or they grow so slowly that growth is not apparent at the time plates are discarded. Microbial pathogens that do not grow using routine culture methods include: rapidly growing mycobacteria, Mycoplasma, Ureaplasma, Legionella, “Small-colony variant” Staphylococcus aureus and anaerobic pathogens (Rasnake and Dooley 2006).

2.2.5 Risk factors

2.2.5.1 Patients-related

2.2.5.1.1 Co-morbidities

It has been well established that diabetes mellitus (DM) is an independent risk factor for postoperative SWI (Nagachinta et al 1987, Harrington et al 2004, Drapeau et al 2007, Di Leo et al 2009, Ata et al 2010, Ahmed et al 2011, Mannien et al 2011). The increased infection risk in patients with DM is supposed to be associated with hyperglycaemia or with features in the DM state such as microvascular and immunologic changes. Some studies have revealed that perioperative hyperglycaemia increases the risk for SWI (Ambiru et al 2008, Olsen et al 2008, Ramos et al 2008, Serra-Aracil et al 2011), even in non-diabetic patients (Swenne et al 2005).

Body mass index (BMI), defined as weight in kilograms divided by height in meters squared (kg/m²), is the commonly used measure for obesity. According to the definition of the World Health Organisation (WHO) underweight, normal weight, overweight and obese people are those with a BMI under 20 kg/m², 20-25 kg/m², 25-30 kg/m² and over 30 kg/m², respectively. Obesity is a common medical condition in the Western world; 25-30% of adults in the US and the UK are obese (Baskin et al 2005, Rennie and Jebb 2005). In Finland the prevalence of obesity is 22% among adults (Lahti-Koski et al 2010).
Obesity, defined as an increased BMI, has been found to be an independent risk factor for SWI after various surgical procedures. A study with prospectively collected data of 4,476 coronary artery bypass procedures (CABG) showed that obesity is an independent risk factor of sternal wound infection (OR 1.8, 95% CI 1.4-2.3) (Harrington et al 2004). Another prospective study with 4,066 patients undergoing cardiothoracic procedures including CABG and valve surgery revealed that obesity increases the risk of SWI with an OR of 2.0 (Mannien et al 2011). Retrospective studies have also confirmed obesity to be an independent risk factor for SWI after cardiac surgery (Olsen et al 2002, Dietz et al 2007).

Obese patients are at significantly increased risk for SWI after colorectal surgery. Retrospective analysis with 7,020 colectomy patients revealed that obesity increases the risk of SWI with an OR of 1.59 (Wick et al 2011). Another study with 176 elective colorectal resection showed, that BMI 25-29 kg/m\(^2\) increases the risk of SWI with an OR of 2.9, and a BMI over 30 kg/m\(^2\) with an OR of 3.0 (Smith et al 2004).

Obesity is also an independent risk factor for SWI after spinal surgery with an OR varying between 2.2 and 2.4 (Olsen et al 2008b, Pull ter Gunne and Cohen 2009, Koutsoumbelis et al 2011). An Italian prospective multicenter study included 2,262 patients undergoing clean general surgery revealed that obesity increased the risk of SWI with an OR of 4.01 (Moro et al 1996).

While obesity is commonly defined as a BMI ≥ 30 kg/m\(^2\), percent body fat (%BF) might be an even more sensitive predictor for SWI risk. Obesity is then defined as a %BF of over 25 in men and over 31 in women. A study with 591 elective surgical patients revealed that obesity defined by %BF increased significantly the risk of SWI (OR 5.3, 95% CI 1.2-23.1) whereas a BMI of over 30 kg/m\(^2\) was not a risk factor for SWI even in univariate analysis (Waisbren et al 2010).

Chronic obstructive pulmonary disease (COPD) also increases the risk of SWI, especially in patients undergoing cardiovascular surgical procedures (Dietz et al 2007, Haridas and Malangoni 2008, Greenblatt et al 2011).

A study using data from the Norwegian Arthroplasty Register with 108,786 primary total joint replacement revealed that after total knee replacement patients with rheumatoid arthritis (RA) have a 1.6 times higher risk of revision for infection than patients with osteoarthritis (OA). There was no difference in incidence of SWI after total hip replacement (Schrama et al 2010). A case control study at Mayo Clinic showed that RA compared with OA increases the risk prosthetic joint infections (HR 4.08, 95% CI 1.35-12.33) (Bongartz et al 2008).

A prospective observational study conducted in Italy revealed that the incidence of SWI in patients infected with human immunodeficiency virus (HIV) is 9.5% after various surgical procedures. The surgical wound infection rate was two-fold higher than rates reported earlier in Italian and European studies with general population (Drapeau et al 2009). Furthermore, a prospective cross-sectional study in Tanzania found HIV to be an independent risk factor for SWI with an OR of 11.0 (95% CI 2.6-64.2) (Mawalla et al 2011). The risk of SWI is higher in symptomatic HIV patients compared to asymptomatic (Abalo et al 2010).

### 2.2.5.1.2 Malnutrition

Malnutrition is often defined as hypoalbuminemia (serum albumin under 30g/l) or weight loss more than 10%. A nutrition risk index (NRI) is calculated as follows (Buzby et al 1988):

\[
\text{NRI} = 1.519 \times \text{serum albumin (g/l)} + 41.7 \times (\text{current/usual bodyweight}).
\]

Patients with an NRI of more than 97.5 are considered to be non-malnourished, those with an NRI of 83.5-97.5 moderately malnourished and those with an NRI of under 83.5 severely malnourished (Schneider et al 2004).
A French prospective study with 1,637 patients showed that malnutrition defined as NRI under 83.5 increases the risk of nosocomial infection among surgical patients with an OR of 4.98 (95% CI 4.6-6.4) (Schneider et al 2004).

Hypoalbuminemia has been found to be risk factor for SWI in two retrospective analyses; a study of 524 gastrointestinal surgery patients revealed that hypoalbuminemia increases the risk of SWI development with RR of 5.68 (Hennessey et al 2010). In addition, a study of 10,253 general surgery patients found hypoalbuminemia to be an independent risk factor for SWI with an OR of 1.8 (Haridas and Malangoni 2008).

In an analysis of prospectively collected data from 5,031 noncardiac surgical procedures, the incidence of SWI was 12.3% in patients with more than 10% weight loss 6 months prior to surgery and 7.1% in patients without weight loss, p=0.01. However, weight loss was not found to be an independent risk factor for SWI by logistic regression analysis (Malone et al 2002).

2.2.5.1.3 Smoking
Smoking impairs the process of wound healing by attenuating wound inflammation and fibroblast proliferation (Sørensen et al 2010a) and by affecting wound contraction and collagen metabolism (Sørensen et al 2010b), which may increase the risk for SWI. It has also been shown that smoking one cigarette decreases the tissue perfusion by more than 30% in more than 45 minutes in specific areas of the body (Jensen et al 1991). Furthermore, it has been shown that four weeks of abstinence from smoking reduces the incidence of wound infection (Sørensen et al 2003).

Smoking has found to increase the risk of SWI in patients undergoing cardiac surgery with an OR of 1.8 (Nagachinta et al 1987), orthopaedic surgery with an OR of 1.19-1.41 (Veeravagu et al 2009, Singh et al 2011), general surgery with an OR of 3.1 (Arabshahi and Koohpayezade 2006) and plastic surgery with an OR of 2.1 (Olsen et al 2008a).

2.2.5.1.4 Skin bacterial flora
Most of the SWIs are caused by the organisms of normal skin flora (see section 2.2.4). The relationship between bacterial load of surgical wound and development of SWI was studied in 18 patients undergoing dermatologic surgery. Quantitative and qualitative analysis of microbial composition were performed pre-, peri- and postoperatively. The study revealed that high postoperative bacterial load on surgical site was a significant risk factor for postoperative complications including SWI (Saleh et al 2011). Correspondently, a study with 125 cases of flap reconstruction found that surgical sites with intraoperative positive bacterial culture compared with negative bacterial culture wound had a 47% and 7.8% flap complication rate, respectively (P<0.001) (Lineaweaver et al 2011).

In contrast, a study with 609 neurosurgery patients did not find a relationship between prepreparation bacterial load and the incidence of SWI. There was, however, a light but not significant association between postpreparation bacterial load and the incidence of SWI (RR 1.79 95% CI 0.72-4.44) (Cronquist et al 2001).

2.2.5.1.5 Other patient-related risk factors
Age as a risk factor for SWI is not subject to modification. In a cohort study of 144,500 patients over 17 years of age, increasing age independently predicted an increased risk for SWI until age 65 years. At ages over 65 years, increasing age independently predicted a decreased risk of SWI (Kaye et al 2005).
Prolonged preoperative hospital stay has been associated with SWI (Nagachinta et al 1987, Mannien et al 2011). However, the length of preoperative stay depends on the severity of illness and co-morbid conditions requiring inpatient therapy before operation (Mangram et al 1999).

The data supporting the relationship between use of corticosteroid or other immunosuppressive medication is controversial: there are studies that have found that use of corticosteroids increases the risk of SWI (Gil-Egea et al 1987, Ismael et al 2011) and there are studies that do not support that finding (Eberhart et al 2011).

The leading causative agent of SWI is Staphylococcus aureus (Table 2). A prospective cohort study among patients undergoing heart surgery showed that the rate of SWI is significantly higher in patients who are nasal-carriers of Staphylococcus aureus compared with non-carriers (RR 3.1 95% CI 1.4-7.3) (Munoz et al 2008). Furthermore, a prospective observational study with 2400 orthopaedic patients showed that a patient with positive nasal MRSA culture is at an increased risk, with an OR of 11 to develop SWI compared with non-carriers (Yano et al 2009).

2.2.5.2 Procedure-related

2.2.5.2.1 Hair removal

Traditionally, patients undergoing surgical procedures have their hair removed from the intended surgical site preoperatively. Methods for hair removal are shaving, clipping and chemical depilation.

The Cochrane authors reviewed 14 trials to determine the influence of routine pre-operative hair removal (compared with no removal) and the timing or method of hair removal on SWI rate (Tanner et al 2011). In that analysis, there was no significant difference in incidence of SWI when comparing hair removal with clipping and no hair removal. Neither did the analysis show any difference in incidence of SWI between shaving and no hair removal. Furthermore, there were no difference in risk of SWI between patients who had hair removed and patients who did not. When shaving was compared with clipping, the analysis showed that more patients developed SWI when shaved rather than clipped prior surgery (RR 1.97, 95% CI 1.08-3.58). There was no difference in incidence of SWI if hair was shaved or clipped on the day before surgery compared with the day of surgery (Tanner et al 2011).

Body hair removal does not seem to be required before surgical procedures in order to reduce SWI rate. If hair removal is necessary, the clippers are associated with fewer SWIs than shaving with razors.

2.2.5.2.2 Surgical procedures

The risk of SWI varies by the type of surgical procedures, being highest after lower limb amputation. Table 3 shows the incidence of SWI after different surgical procedures. Ten prospective studies, with 868,194 surgical procedures, that have been conducted with the intention to describe the incidence and risk factors of SWI in certain areas and over certain time periods are included in the Table 3. It is not difficult to notice that the incidence of SWI has remained stable for the last 35 years.

A prospective study with almost 4,500 patients undergoing different surgical procedures revealed that the incidence of SWI was higher after emergency procedures than after elective surgery; 5.1% and 3.2%, respectively (Gil-Egea et al 1987). Furthermore, in a study with 5,031 noncardiac surgery patients emergency procedure compared with elective procedure increased the risk of SWI with an OR of 1.58 (Malone et al 2002).
Open surgery compared with laparoscopic surgery is associated with higher incidence of SWI in various surgical procedures. A retrospective analysis with 11,662 patients from 22 hospitals was performed to estimate nosocomial infection risks associated with laparoscopic as compared to open surgery in three procedures; cholecystectomy, appendectomy and hysterectomy. The analysis revealed that laparoscopic procedure decreased the risk of SWI after cholecystectomy and hysterectomy with an OR of 0.2 and 0.27, respectively (Brill et al 2008). In a study with almost 24,000 patients undergoing colorectal surgery the incidence of SWI was 9.4% after laparoscopy and 15.7% after laparotomy (p<0.0001) (Aimaq et al 2011). The risk of SWI is significantly reduced after laparoscopic versus open ventral or incisional hernia repair [risk ratio (RR) 0.26, 95% CI 0.15-0.46] according to a meta-analysis with 10 randomised prospective trials (Sauerland et al 2011). Another meta-analysis with 5,292 patients found that SWI rate is significantly lower after laparoscopic than after open appendectomy (OR 0.45, 95% CI 0.34-0.59) (Li et al 2010).

Reoperation, not executed because of infection, increases the risk of SWI after cardiothoracic surgery (OR 5.2, 95% CI 2.5-10.6) (Mannien et al 2011).

Excellent surgical technique including effective haemostasis, gently handling of tissues and removing devitalised tissue, is widely believed to reduce the risk of SWI (Mangram et al 1999), even though it has not been proved in randomised prospective trials. It is perhaps obvious that there is no need to conduct such studies.

Perioperative hypothermia, defined as a core body temperature below 36°C, is associated with increased SWI risk (Reynolds et al 2008). Hypothermia causes vasoconstriction that decreases the PO₂ and leads to lowered resistance to infection (Kurz et al 1996).
Table 3. Surgical wound infection rate by procedures during different periods of time reported by National nosocomial infection surveillance system based studies

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Limb amputation</td>
<td>12.4%</td>
<td>4.3-14.3%</td>
<td>16.7-25%</td>
</tr>
<tr>
<td>Small bowel surgery</td>
<td>10.4%</td>
<td>8.0-10%</td>
<td>4.8-24%</td>
</tr>
<tr>
<td>Colon surgery</td>
<td>8.9%</td>
<td>8.6-12.9%</td>
<td>10.2-17%</td>
</tr>
<tr>
<td>Prostatectomy</td>
<td>2.3%</td>
<td>1.4%</td>
<td>16%</td>
</tr>
<tr>
<td>Transplantation</td>
<td>5.3-12%</td>
<td>2.6-10.4%</td>
<td>3.6-11.1%</td>
</tr>
<tr>
<td>Vascular surgery</td>
<td>10.8%</td>
<td>6.6%</td>
<td>12%</td>
</tr>
<tr>
<td>Gastric surgery</td>
<td>1.5%</td>
<td>1.5-7.4%</td>
<td>3.0-11%</td>
</tr>
<tr>
<td>Thoracic surgery</td>
<td>1.0%</td>
<td>1.5%</td>
<td>1.8-11.1%</td>
</tr>
<tr>
<td>Craniotomy</td>
<td>6.4%</td>
<td>4.0%</td>
<td>1.9-7.7%</td>
</tr>
<tr>
<td>Breast surgery</td>
<td>3.4%</td>
<td>4.2-4.4%</td>
<td>3.6-5.3%</td>
</tr>
<tr>
<td>Appendicectomy</td>
<td>6.8%</td>
<td>4.2-4.4%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>2.2%</td>
<td>1.4-3.1%</td>
<td>2.3-4.3%</td>
</tr>
<tr>
<td>Open reduction of long bone fracture</td>
<td>3.1%</td>
<td>1.2-1.9%</td>
<td>0.9-4.1%</td>
</tr>
<tr>
<td>Hip prosthesis</td>
<td>5.6%</td>
<td>1.2%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Knee prosthesis</td>
<td>1.9%</td>
<td>1.2%</td>
<td>1.9-2.3%</td>
</tr>
<tr>
<td>Nephrectomy</td>
<td>1.4%</td>
<td>0.6-1%</td>
<td>0.9-2.1%</td>
</tr>
<tr>
<td>Laminectomy</td>
<td>3.1%</td>
<td>3.0-4.2%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Herniorrhaphy</td>
<td>Total</td>
<td>3.2-7%</td>
<td>2.6-12.3%</td>
</tr>
<tr>
<td>Coronary artery bypass graft</td>
<td>2001-2007</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


2.2.5.2.3 Operation time

There are some studies that have shown an association between prolonged operation time and the risk of SWI (Moro et al 1996, Pessaux et al 2003, Peersman et al 2006). Duration of operation might reflect other factors, such as blood loss, a patient’s hypothermia and decreased concentration of prophylactic antibiotics that increase the risk of SWI.

2.2.5.2.4 Foreign material in the surgical site

Infections associated with permanent implants including suture material, prosthesis, shunts, grafts, stents and meshes are likely to occur. Most implants have a non-shedding surface to which bacteria can adhere, form biofilms and potentiate SWI. Biofilms form whenever micro-organisms attach to a surface. Once attached, bacteria undergo a phenotypic change and, within minutes, deposit a matrix of extracellular polymeric substance or biofilm matrix. Biofilms are the dominant mode of microbial growth and at least 60% of all human infections are thought to involve biofilms. The biofilm bacteria are difficult to treat because, shielded within the matrix, they are less susceptible to antibiotics and antiseptics (Leaper et al 2010).

A prospectively collected data with 10,700 patients, found 0.5%-1% incidence of prosthetic joint infection after primary hip or knee replacement (Phillips et al 2006). The reported inci-
dence of mesh-related infection following hernia repair has been 1-8% in different series, and this incidence is influenced by underlying co-morbidities, the type of mesh, the surgical technique and the strategy used to prevent infections (Falakas and Kasiakow 2005).

A retrospective study including 12,300 patients who underwent sternotomy for cardiac surgery found the use of bone wax to be a risk factor for postoperative sternocutaneous fistulas (Steingrimsson et al 2009). Another retrospective study revealed that insertion of a breast implant or tissue expander is an independent risk factor after major breast operation (Olsen et al 2008a). Furthermore, foreign body implantation increases the risk of SWI after spinal surgery (Kanafani et al 2006).

2.2.5.2.5 Material for wound closure
Surgical wound closing devices can be divided into three main groups: absorbable and non-absorbable sutures and, staples. It has been documented that bacteria adhere with different affinity to various types of suture materials (Katz et al 1981). A study with a bioluminescent in vitro model evaluated bacterial adherence to commonly used sutures: polyglecaprone, a synthetic absorbable monofilament suture (Monocryl; Ethicon, Inc. Somerville, New Jersey); polypropylene, a synthetic nonabsorbable monofilament suture (Prolene; Ethicon, Inc.); silk, nonabsorbable suture composed of an organic protein (Ethicon, Inc.), polyglycolic, a synthetic absorbable braided suture (Vicryl; Ethicon, Inc.); and triclosan coated polyglycolic suture (Vicryl Plus; Ethicon, Inc). The study found that the Vicryl suture has the highest bacterial adherence compared with other examined sutures (Masini et al 2011).

The risk of developing SWI after orthopedic procedures are found to be over three times greater after staple closure than suture closure in a meta-analysis including 683 wounds (Smith et al 2010). Likewise, staple closure has been shown to be an independent risk factor for SWI after major lower limb amputation (OR 1.69, 95%CI 1.04-2.75) (Coulston et al 2012). However, there is no difference in incidence of SWI after infrainguinal bypass surgery (Wolterbeek et al 2002) or after vein harvesting for coronary artery bypass surgery (Biancari and Tiozzo 2010) when comparing staples with sutures for wound closure.

2.2.5.2.6 Blood transfusion
It has been reported that perioperative transfusion of leucocyte-containing allogenic blood increases the risk of SWI in comparison with transfusion of leucocyte-depleted red-cells (Jensen et al 1996). Furthermore, there seems to be a higher risk for SWI when transfusing homologous blood perioperatively compared with transfusing autologous blood (Heiss et al 1994). An observational study of cardiac surgery patients found that storage time of red blood cells over 14 days is positively associated with severe postoperative infection (Andreasen et al 2011).

In a study of 125,000 patients undergoing general surgery procedures, intraoperative transfusion of packed red blood cells was an independent risk factor of SWI (OR 1.25, p<0.05) (Bernard et al 2009). The findings are analogous to studies with smaller numbers of patients (Möhnle et al 2011, Karakida et al 2010). Blood transfusion for mildly anaemic surgical patients should be done after careful consideration because of the increased risk for SWI associated with transfusion.

2.2.5.2.7 Use of drainage
Drains are often required to remove excess fluid and blood from wound or body spaces. It has been clear for decades that to prevent infections drains should not exit through the working incision and that closed suction drainage is preferable to open drains (Alexander et al 2011).
Drain use after elective uncomplicated open or laparoscopic cholecystectomy and after lower limb major amputation increases wound infection rates (Gurusamy et al 2007, Gurusamy and Samraj 2007, Coulston et al 2012). However, the use of closed drainage is not shown to increase the risk of SWI after thyroid surgery (Gurusamy and Samraj 2007), orthopedic procedures (Parker et al 2007), or colorectal surgery with anastomosis (Karliczek et al 2006).

2.2.6 Prevention

2.2.6.1 Antibiotic prophylaxis

2.2.6.1.1 Systemic antibiotic prophylaxis
A meta-analysis of meta-analyses involving 250 clinical trials strongly supported the hypothesis that antibiotic prophylaxis is beneficial in preventing SWI in all 23 different types of surgery included in the study. The relative risk of developing SWI with antibiotic prophylaxis versus no prophylactic antibiotics varied from 0.19-0.82. Although the type of antibiotic and surgical procedure varied widely in this analysis, the use of prophylactic antibiotics as a whole decreased the incidence of SWI by one-half (Bowater et al 2009).

Some problematic issues arise in the use of antibiotic prophylaxis: there are significant costs involved with antibiotic administration; they can have serious adverse effects; and there is a risk of the development of antibiotic resistance pathogens or Clostridium difficile colitis (Alexander et al 2011). Antibiotic prophylaxis is indicated clearly for most clean-contaminated and contaminated procedures. In particular, for procedures where bone is incised (e.g., craniotomy, sternotomy), a prophylactic antibiotic is generally indicated (Barie and Eachempati 2005). Controversy exists in soft tissue clean surgery procedures. Randomised prospective trials or meta-analyses have shown a benefit from antibiotic prophylaxis in breast surgery (Terijian et al 2006), varicose vein surgery (Mekako et al 2007), and lower limb arterial revascularisation (Steward et al 2007). It has been found that antibiotic prophylaxis significantly reduces the rate of SWI after clean surgery in patients categorised as ASA 2 or ASA 3 risk groups, whereas ASA 1 patients undergoing clean surgery do not benefit from antibiotic prophylaxis (Iribarren and Araujo 2006). Table 4 lists meta-analyses of efficacy of antibiotic prophylaxis in different type of surgical procedures.

The antibiotics used for prophylaxis must be safe and effective against the expected bacteria. The major sources of infection are bacteria from patient’s own skin and, less frequently, the alimentary or female genital tract. The most common pathogens causing postoperative SWI are Staphylococcus aureus, followed by coagulase-negative Staphylococcus species and Enterococcus (Table 2). In clean and clean-contaminated cases the antibiotic chosen should be directed against staphylococci. Single-agent therapy is almost always effective except in colorectal operations, small-bowel procedures with stasis, emergency abdominal operations in the presence of polymicrobial flora, and penetrating trauma; in such cases, an antibiotic with anaerobic coverage is also required (Meakins and Masterson 2005). First-generation and second-generation cephalosporins are preferred agents for most patients in several recommendations (Barie and Eachempati 2005, Brazler and Houck 2005, Meaking and Masterson 2005). However, a meta-analysis of 90 studies confirmed that prophylactic ceftriaxone, a third generation cephalosporin, is more effective than most other prophylactic antibiotics to reduce the risk of postoperative SWI, urinary tract infection and pneumonia in procedures with increased risk of these infections (Woodfield et al 2009).
At the moment there is no intravenously administered first-generation cephalosporin in the market in Finland. Instead, the second-generation cephalosporin, cefuroxime, is the standard antibiotic used as prophylaxis in Finnish hospitals. Both ceftriaxone and cefuroxime are effective against Staphylococcus aureus, coagulase-negative Staphylococcus and Escherichia coli, the bacteria that are responsible for majority of the SWIs (Geroulanos et al 2001). In other words, ceftriaxone does not have any additional benefit compared with cefuroxime in preventing SWIs.

In case of β-lactam allergy the alternatives to cephalosporin are clindamycin and vancomycin. Vancomycin or clindamycin may be the preferred antimicrobial prophylaxis in institutions where SWIs caused by MRSA have been detected and for patients with MRSA colonisation (Mangram et al 1999, Muto et al 2003, Alexander et al 2011). Vancomycin has also been recommended for operative procedures in which prosthetic material is placed and for patients undergoing sternotomy or craniotomy. This is, however, a recommendation without strong evidence (Alexander et al 2011).

In patients undergoing procedures where Bacteroides fragilis and other anaerobes must be covered, metronidazole is recommended with addition of cephalosporin or, in the case of β-lactam allergy, gentamicin or a quinolone is recommended with the addition of clindamycin (Alexander et al 2011).

Effective use of prophylaxis in the prevention of SWI depends on correct timing of antibiotic administration. A study by Stone and colleagues demonstrated the importance of preoperative compared with postoperative antibiotic administration, in contrast to no antibiotic prophylaxis, in the prevention of SWI following gastric, biliary or colonic surgery (Stone et al 1976). The incidence of SWI was 3% among patients who received systemic cefazolin one hour before surgery and 14% among patients who received systemic cephazolin 1-4 hour after surgery (Stone et al 1976). Later study in patients undergoing elective clean or clean-contaminated surgical procedures confirmed the finding that administration of antibiotic prophylaxis within two hours before surgery reduces the risk of SWI (Classen et al 1992).

The chosen antibiotic should be given at a time that allows for maximum tissue concentration at the time of incision (Anderson 2011). When cefuroxime is used as a prophylactic antibiotic, administration 30-59 minutes before incision was found to be more effective than administration during the last half hour (Weber et al 2008). In general, antibiotic prophylaxis should be given 15-90 min before surgical incision and the timing of administration depends of the half-life of the drug (Esposito 1999).

According to a systematic review of 28 prospective randomised studies comparing single versus multiple doses of prophylactic antibiotic in major surgery procedures, there is no additional benefit of more than a single dose of antibiotic (McDonald et al 1998). Administration of a second dose of antibiotic prophylaxis is recommended only if the operation exceeds either 3 hours, or twice the half-life of the antibiotic, or if a massive haemorrhage occurred (Meakins and Masterson 2005). However, a meta-analysis of 12 studies with 7900 patients undergoing open heart surgery revealed that perioperative antibiotic prophylaxis of more than 24 hours may be more efficacious in preventing sternal wound infection compared to shorter regimens (Mertz et al 2011). Another meta-analysis with 59 trials concluded that antibiotic prophylaxis prolongation up to 48 hours after cardiac surgery might be beneficial (Lador et al 2012). In noncardiac thoracic surgery a single dose of antibiotic is recommended (Chang and Krupnick 2012).
Table 4. Efficacy of antibiotic prophylaxis against SWI. The most recent meta-analyses of different type surgical procedures.

<table>
<thead>
<tr>
<th>Study</th>
<th>Procedure</th>
<th>Number of studies/patients</th>
<th>Incidence of SWI antibiotic/placebo</th>
<th>OR / RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barker 2002</td>
<td>Spinal surgery</td>
<td>6 / 843</td>
<td>2.2% / 5.9%</td>
<td>OR 0.37</td>
<td>0.17-0.78</td>
</tr>
<tr>
<td></td>
<td>Appendicectomy</td>
<td>47 / 8812</td>
<td>6.5% / 14.4%</td>
<td>OR 0.33</td>
<td>0.29-0.38</td>
</tr>
<tr>
<td>Andersen et al 2005</td>
<td>Blunt or penetrating chest trauma with chest tube</td>
<td>5 / 614</td>
<td>1.1% / 7.6% e</td>
<td>RR 0.19</td>
<td>0.07-0.5</td>
</tr>
<tr>
<td>Sanabria et al 2006</td>
<td>Breast surgery</td>
<td>5 / 1307</td>
<td>9.3% / 15.5%</td>
<td>RR 0.54</td>
<td>0.32-0.91</td>
</tr>
<tr>
<td>Terijian et al 2006</td>
<td>Craniotomy</td>
<td>6 / 1729</td>
<td>1.1% / 2.7%</td>
<td>OR 0.43</td>
<td>0.2-0.92</td>
</tr>
<tr>
<td>Sakra et al 2007</td>
<td>Gastrointestinal surgery</td>
<td>12 / 6705</td>
<td>2.9% / 3.9%</td>
<td>OR 0.64</td>
<td>0.48-0.85</td>
</tr>
<tr>
<td>Steward et al 2007</td>
<td>Peripheral arterial reconstruction</td>
<td>10 / 1297</td>
<td>4.1% / 15.7%</td>
<td>RR 0.25</td>
<td>0.17-0.38</td>
</tr>
<tr>
<td>AlBuhairan et al 2008</td>
<td>Total jointarthroplasty</td>
<td>7 / 3065</td>
<td>2.0% / 7.7%</td>
<td>RR 0.19</td>
<td>0.12-0.31</td>
</tr>
<tr>
<td>Nielson et al 2009</td>
<td>Colorectal surgery</td>
<td>10 / 813</td>
<td>10.2% / 38.6%</td>
<td>RR 0.30</td>
<td>0.22-0.41</td>
</tr>
<tr>
<td>Smaill and Gyte 2010</td>
<td>Cesarean section</td>
<td>77 / 11961</td>
<td>3.6% / 9.5%</td>
<td>RR 0.39</td>
<td>0.32-0.48</td>
</tr>
<tr>
<td>Gillespie 2010</td>
<td>Closed long bonefractures</td>
<td>7 / 3500</td>
<td>3.5% / 5.0% (sSWI)</td>
<td>RR 0.69</td>
<td>0.50-0.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.1% / 2.5% (dSWI)</td>
<td>RR 0.40</td>
<td>0.24-0.67</td>
</tr>
<tr>
<td>Yan et al 2011</td>
<td>Laparoscopic cholecystectomy</td>
<td>12 / 1990</td>
<td>3.5% / 3.3%</td>
<td>OR 1.11</td>
<td>0.68-1.82</td>
</tr>
</tbody>
</table>

OR= odds ratio, RR=risk ratio, SWI=surgical wound infection, sSWI=superficial SWI, dSWI=deep SWI, e=empyema, p=pneumonia

2.2.6.1.2 Topical antibiotics

The local delivery of antibiotic at the surgical site has received very limited approval in any surgical prophylaxis consensus guidelines. Compared with systemic antibiotics delivery, the use of topical delivery of antibiotics has some advantages as well as disadvantages (Lipsky and Hoey 2009, McHugh et al 2011). The benefits of local application include high concentration, the limited potential for toxicity, reduced use of antibiotics, and, possibly, decreased development of antibiotic resistance. The use of topical antibiotics may cause hypersensitivity, contact dermatitis or may disturb the wound healing (Lipsky and Hoey 2009).

In a randomised controlled trial with 972 minor dermatology surgery patients, the incidence of SWI was 6.6% in the group with a single topical dose of chloramphenicol and 11.0% in the control group, (p=0.01) (Heal et al 2009). The effectiveness of local antibiotics in prevention of SWI has also been studied in cardic surgery patients. A prospective study with 416 patients showed that local application of vancomycin to the cut sternal edge independently reduces the risk of sternal wound infection (Vander et al 1989). Another study with 2,741 patients undergoing cardiac surgery revealed that the use of local gentamicin reduces the risk of SWI with an RR of 0.47, 95% CI 0.33-0.69 (Friberg et al 2005). In contrast, a study with 1,502 cardiac surgical patients at high risk for sternal wound infection (diabetes, body mass index >30, or both) did not find the use of local gentamicin to be effective in prevention of SWI (Bennet-Guerrero et al 2010a).
A prospective study of 221 colorectal surgery patients tested whether the use of a local gentamicin-collagen sponge reduces the risk of SWI. In that study, the incidence of SWI was 5.6% in the gentamicin-collagen group and 18.4% in the control group (p<0.01) (Rutten and Nijhus 1997). However, a recent study with 602 colorectal surgery patients resulted in a higher incidence of SWI in the local gentamicin group compared with the control group (30% and 20.9% respectively, p=0.01) (Bennet-Guerrero et al 2010b). Two prospective studies were conducted to reveal the effect of local gentamicin use in wound healing after sinus pilonidal surgery. A study with 80 patients found local gentamicin to decrease the rates of infection and recurrence, and shortened the hospital stay (Yetim et al 2010). Whereas, a study with 161 patients showed no significant differences in the rates of wound infection, wound healing, and recurrences when local gentamicin-collagen sponge was used (Andersson et al 2010).

2.2.6.2 Triclosan-coated sutures

2.2.6.2.1 Triclosan
Triclosan (2,4,4'-trichloro-2’hydroxy-diphenylether) is a synthetic, lipid-soluble, broad spectrum antimicrobial agent used in humans for 40 years, mainly in soaps, toothpaste and cosmetics. The use of triclosan is controlled by the US Food and Drug Administration (FDA), the US Environmental Protection Agency (EPA) and the European Union’s Scientific Committee on Consumer Products (SCCP).

For many years, the mode of antibacterial action of triclosan was supposed to be through non-specific disruption of a cell membrane (Slater-Radosti et al 2001). Later studies, however, have revealed that triclosan targets fatty acid synthesis by inhibiting the enzyme enoyl reductase (enoyl-acyl carrier protein reductase [ENR], Fabl) (McMurry et al 1998). At low concentrations, triclosan is bacteriostatic by inhibiting the bacterial fatty acid synthesis. At higher concentrations triclosan is bactericidal by attacking different structures in the bacterial cytoplasm and cell membrane (Russell 2004, Escalada et al 2005, Yazdankhah et al 2006).

Triclosan is effective against numerous, but not all, types of gram-positive and gram-negative bacteria. It has also some antifungal, antiviral and anti-mycobacterial activity (Dellano et al 2009, Saleh et al 2010) and, it inhibits the growth of Plasmodium falciparum and Toxoplasma gondii (McLeod et al 2001).

2.2.6.2.2 Triclosan-coated sutures in prevention of surgical wound infection
All commonly used surgical sutures can become contaminated by various bacteria. It has been shown that braided sutures have greater inflammatory response than monofilament sutures (Masini et al 2011), and that the presence of contaminated suture materials increases the risk of SWI (Katz et al 1981).

To prevent microbial colonisation of suture material and surgical wound contamination, triclosan-coated polyglactin 910 (Vicryl Plus; Ethicon, GmbH) and triclosan-coated polyglecaprone 25 (Monocryl Plus; Ethicon, GmbH) with antibacterial activity were developed.

In studies based on in vitro models, triclosan-coated sutures have shown antibacterial efficacy against Staphylococcus aureus, Staphylococcus epidermidis, methicillin-resistant Staphylococcus aureus (MRSA), methicillin-resistant Staphylococcus epidermidis (MRSE), Escherichia coli, Klebsiella pneumoniae, Staphylococcus hominis, Staphylococcus haemolyticus, Staphylococcus auricularis, Enterococcus faecalis and Corynebacterium so (Rothenburger et al 2002, Edminston et al 2006, Gomez-Alonzo et al 2007, Ming et al 2008). The effect against Staphylococcus aureus, Staphylococcus epidermidis and E coli has also been demonstrated in

There is no evidence that long-term application of triclosan products to skin selects for triclosan-resistant populations. It is most unlikely that short-term exposure of triclosan within suture materials would cause development of resistance (Gilbert and McBain 2002). Animal model studies have not revealed triclosan to be carcinogenic, genotoxic or teratogenic. A lethal dose (LD) is an indication of the lethality of a given substance with the LD$_{50}$ being the median lethal dose of toxin required to kill half of the members of tested population. Dermal exposure of triclosan in rabbits resulted in an LD$_{50}$ value $>$9,300 mg/kg. It is considered that LD$_{50}$ values of 2,000-5,000 mg/kg indicate that a material offers relatively safety. The use of triclosan-coated sutures provides very low exposure levels of triclosan and does not result in any toxicity that would compromise safety (Barbolt 2002). One prospective randomised trial has shown an increased risk for surgical wound dehiscence related to use of triclosan-coated sutures (Deliaert et al 2009).

Although there is no clear evidence that antibacterial sutures would be effective in reducing the risk of postoperative SWI, triclosan-coated sutures are being used in many hospitals for that particular reason. The randomised prospective trials of triclosan-coated sutures in prevention of SWI are presented in Table 5. In six studies with adult patients undergoing gastrointestinal surgery, breast surgery, or head and neck surgery, and, in one study, with paediatric patients undergoing various surgical procedures, the use of triclosan-coated sutures did not have an effect on incidence of SWI (Ford et al 2005, Mingmalairak et al 2009, Zhang et al 2011, Chen et al 2011, Baracs et al 2011, Williams et al 2011). Furthermore, a meta-analysis of seven randomised prospective trials did not find triclosan-impregnated sutures to reduce the incidence of SWI (OR 0.77, 95% CI 0.21-5.43) (Chang et al 2012).

Wound closure with triclosan-coated polyglactin 910 sutures reduced significantly the risk of SWI after different surgical procedures in a trial involving 450 patients and conducted in Egypt at Cairo University Hospital. The results from a single hospital were reported although the trial was multicenter. The study included various surgical procedures from lipoma removal to vascular surgery (Galal and El-Hindwy 2011). Wound closure with triclosan-coated sutures was associated with a reduced risk of infection in cerebrospinal fluid surgery (Rozelle et al 2008).
Table 5. Triclosan-coated sutures in prevention of surgical wound infections (SWI). Prospective randomised studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Surgical procedures</th>
<th>Blinding</th>
<th>Follow-up period</th>
<th>SWI rate: study vs. control group</th>
<th>Univariate p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ford et al 2005</td>
<td>147</td>
<td>Various pediatric surgery procedures</td>
<td>No</td>
<td></td>
<td>3% vs. 0%</td>
<td>NS</td>
</tr>
<tr>
<td>Rozelle et al 2008</td>
<td>61</td>
<td>Implantation of cerebrospinal fluid shunting devices</td>
<td>Double blind</td>
<td>6 months</td>
<td>4.3% vs. 21%</td>
<td>0.038</td>
</tr>
<tr>
<td>Mingmalairak et al 2009</td>
<td>100</td>
<td>Appendicectomy</td>
<td>Double blind</td>
<td>1 year</td>
<td>10% vs. 8%</td>
<td>0.05</td>
</tr>
<tr>
<td>Galal and El-Hindawy 2011</td>
<td>450</td>
<td>Various different procedures</td>
<td>Double blind</td>
<td></td>
<td>7% vs. 15%</td>
<td>0.011</td>
</tr>
<tr>
<td>Zhang et al 2011</td>
<td>101</td>
<td>Mastectomy</td>
<td>No</td>
<td>90 days</td>
<td>4.3% vs. 11.1%</td>
<td>NS</td>
</tr>
<tr>
<td>Chen et al 2011</td>
<td>241</td>
<td>Head and neck cancer surgery</td>
<td>No</td>
<td></td>
<td>14.9% vs. 14.7%</td>
<td>NS</td>
</tr>
<tr>
<td>Baracs et al 2011</td>
<td>485</td>
<td>Colorectal surgery</td>
<td>No</td>
<td></td>
<td>12.2% vs. 12.2%</td>
<td>NS</td>
</tr>
<tr>
<td>Williams et al 2011</td>
<td>150</td>
<td>Breast cancer surgery</td>
<td>Double blind</td>
<td>6 weeks</td>
<td>15.2% vs 22.9%</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS=Non-significant SWI=surgical wound infection

2.2.6.3 Supplemental oxygen in prevention of surgical wound infection

As discussed earlier in section 2.1.3., oxygen is vital for wound healing. The association between supplemental perioperative oxygen and the risk of SWI has been studied for different types of surgical procedures. The prospective randomised studies that have investigated the effect of supplemental inspired oxygen on incidence of SWI are listed on Table 6. In one study the patients were randomly assigned to receive either 2 litres (L) of oxygen by nasal cannula (standard care) or 10 L of oxygen by nonrebreather mask (intervention group) (Scifres et al 2011). In the other 8 studies, patients were randomly assigned to receive either 80% oxygen or 30-35% oxygen during surgery. In one study supplemental oxygen delivery continued for 6 postoperative hours (Belda et al 2005), and in another study supplemental 80% oxygen was administered during the surgery only (Myles et al 2007). In the rest of the studies, the supplemental 80% oxygen delivery continued 2 hours postoperatively (Grief et al 2000, Pryor et al 2004, Mayzler et al 2005, Gardella et al 2008, Meyhoff et al 2009, Bickel et al 2011, Scifres et al 2011).

Four of the studies have shown that supplemental inspired oxygen reduces the risk of SWI. However, four studies did not find any difference in incidence of SWI between study and control groups, but another study found supplemental oxygen to be an independent risk factor for SWI. In a meta-analysis of 5 randomised controlled trials with 3001 patients the use of perioperative inspired supplemental oxygen was protective against SWI with risk ratio RR of 0.556 (95% CI, 0.383-0.808, p=0.002) (Qadan et al 2009). Another meta-analysis did not reveal any significant effects of supplemental perioperative oxygen on risk of SWI after colorectal surgery. However, supplemental oxygen appeared to confer a mortality benefit with OR of 0.18 (95% CI, 0.05-0.69, p=0.01) (Brar et al 2011).
Table 6. Supplemental oxygen in prevention of surgical wound infection

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Surgical procedures</th>
<th>Follow-up period</th>
<th>SWI rate: study vs. control group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grief et al 2000</td>
<td>500</td>
<td>Colorectal resection</td>
<td>15 days</td>
<td>5.2% vs. 11.2%</td>
<td>0.01</td>
</tr>
<tr>
<td>Pryor et al 2004</td>
<td>165</td>
<td>Major intra-abdominal procedure</td>
<td>14 days</td>
<td>25% vs. 11.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Belda et al 2005</td>
<td>291</td>
<td>Colorectal surgery</td>
<td>14 days</td>
<td>14.9% vs. 24.4%</td>
<td>0.04</td>
</tr>
<tr>
<td>Mayzler et al 2005</td>
<td>38</td>
<td>Colorectal surgery</td>
<td>30 days</td>
<td>12.5% vs. 17.6%</td>
<td>0.54</td>
</tr>
<tr>
<td>Myles et al 2007</td>
<td>2,050</td>
<td>Non-cardiothoracic surgery</td>
<td>30 days</td>
<td>7.7% vs. 10%</td>
<td>0.03</td>
</tr>
<tr>
<td>Gardella et al 2008</td>
<td>143</td>
<td>Cesarean delivery</td>
<td>14 days</td>
<td>25% vs. 10%</td>
<td>0.13</td>
</tr>
<tr>
<td>Meyhoff et al 2009</td>
<td>1,400</td>
<td>Abdominal surgery</td>
<td>14 days</td>
<td>19.1% vs. 20.1%</td>
<td>0.64</td>
</tr>
<tr>
<td>Bickel et al 2011</td>
<td>210</td>
<td>Open appendectomy</td>
<td>14 days</td>
<td>5.6% vs. 13.6%</td>
<td>0.04</td>
</tr>
<tr>
<td>Scifres et al 2011</td>
<td>585</td>
<td>Cesarean delivery</td>
<td>30 days</td>
<td>11.5% vs. 8.8%</td>
<td>0.28</td>
</tr>
</tbody>
</table>

SWI=surgical wound infection

Exposure to high-dose (100%) oxygen can cause pulmonary absorption atelectasis (Rothen et al 1995). In contrast, low-flow supplemental oxygen is regarded as quite safe (Benditt 2000) and a randomised prospective study showed that the incidence and severity of atelectasis were comparable in patients given 30% and 80% perioperative oxygen (Akca et al 1999). Furthermore, none of the studies listed in Table 6 have reported increased pulmonary complications associated with supplemental perioperative oxygen administration.

It seems plausible, that supplemental inspired oxygen is safe and it could be advantageous in preventing SWI. In addition, supplemental perioperative oxygen is a low-cost intervention.

2.2.6.4 Other methods for preventing surgical wound infection

Most SWIs are caused by skin organisms and, consequently, the number of bacteria colonising the skin should be decreased preoperatively. Preoperative bathing with chlorhexidine reduces pathogenic organisms on the skin but has a non-significant reduction in SWIs (Alexander et al 2011, Anderson 2011, Webster and Osborne 2011).

To decrease bacterial colonisation and prevent SWI, the surgical site is preoperatively scrubbed with antiseptic agents. There is clear evidence that preoperative cleansing with chlorhexidine-alcohol decreases the risk of SWI compared with preoperative cleansing with povidone-iodine (Darouiche et al 2010, Noorani et al 2010, Levin et al 2011).

It has been showed earlier that local intraoperative warming improves tissue oxygenation and presumably decreases the risk of SWI (Ikeda et al 1998). Furthermore, the systemic warming perioperatively reduces the blood loss and complications in surgical patients (Wong et al 2007). A meta-analysis of 25 studies with 3599 patients revealed that perioperative warming significantly reduces the risk of SWI and postoperative pain (Sajid et al 2009). There are several techniques for the warming of surgical patient perioperatively: simple cotton blankets, carbon-fibre sheets, circulating hot water mattresses, forced air warming, warm fluid infusion, and oesophageal heat exchange systems (Sajid et al 2009).
Handling tissue gently, minimising devitalised tissue and eradicating dead space at the surgical site are recommended to avoid SWI (Mangram et al 1999). However, there are relatively few large or rigorously well-conducted studies on surgical techniques and their impact on SWI (McHugh et al 2010).

There are studies that have compared the effect of intraoperative antiseptic lavage on the SWI rate, but their results are controversial (Angelini et al 1990, Bausz et al 2006). Therefore, a meta-analysis of 24 randomised controlled trials with 5,004 abdominal surgery, general surgery, gynaecological surgery and spinal surgery patients was conducted to assess effectiveness of intraoperative povidone-iodine (PVI) in the reduction of SWI. The meta-analysis revealed that intraoperative PVI application significantly reduces the rate of SWI (RR 0.58, 95% CI 0.4-0.83; p=0.003) (Fournel et al 2010).

Despite the fact that hyperglycaemia is associated with the development of SWI, it is not proven that tight glycaemic control would decrease the incidence of SWI (Kao et al 2009). Thus, current recommendations state that control of diabetes mellitus should be improved before surgery and postoperative serum glucose concentration should be maintained at less than 11 mmol/l (200mg/dl) for the first 48 hours after surgery (Anderson 2011).

Even though there is no clear evidence that malnutrition increases the risk of SWI, supplemental immunomodulating enteral diet reduces the risk of postoperative infections and wound complications in high-risk patients undergoing major surgery (Marik and Zaloga 2010).

Wound dressings, applied after wound closure, are widely used to provide physical support, protection from bacterial contamination and absorb exudate. The CDC guidelines recommend protecting incision with sterile dressing for 24 to 48 hours. However, a review of 16 randomised controlled trials did not find evidence that covering surgical wounds with dressing reduces the risk of SWI (Dumville et al 2011).

Staphylococcus aureus nasal carriage increases the risk of SWI (see section 2.2.5.1.5) and the eradication of those bacteria should be taken into consideration. Furthermore, a review of 4 studies with 686 patients showed that treatment with mupirocin significantly decreases the incidence of SWI among surgical patients with Staphylococcus aureus nasal carriage (RR 0.55, 95%CI 0.34-0.89) (van Rijen et al 2008).

### 2.3 Surgical Wound Infection After Vascular Surgery

#### 2.3.1 Incidence

The majority of arterial surgery procedures are classified as clean surgery by the National Research Council because the operative exposure and revascularisation is performed in uninfected tissues without inflammation and, the alimentary, respiratory or urinary tract is not entered (Bandyk 2008). Lower limb revascularisation surgery has been widely proven to be effective for the management of both claudication and critical limb ischaemia. According to the NNIS report with almost 85,000 surgical procedures the incidence of SWI after clean surgery is 2.1% (Culver et al). However, the incidence of surgical wound complication, either infection or failure to heal, after lower limb revascularisation surgery remains high compared with other clean surgery procedures.

Infection involving a vascular surgical wound may be superficial or deep or, the infection may involve vascular graft or operated native artery. For autogenous arterial revascularisations, only infections occurring within 30 days are classified as SWI, but when prosthetic graft is implanted the incidence of SWI is calculated for one year (Bandyk 2008).
There is an extensive variation in the reported incidence of SWI after lower limb vascular surgery. In prospective studies with the number of patients ranging from 69 to 561, the incidence of SWI was found to be between 3.5% and 32% (Richet et al. 1991, Chester et al. 1992, Josephs et al. 1993, Murphy et al. 1995, Kent et al. 1996, Ploeg et al. 2009, Virkkunen et al. 2009, Linni et al. 2012).

The rate of SWI varies among different types of vascular surgery procedures. The incidence of SWI, including patch infection after carotid surgery is 0.2-0.5% (Greenstein et al. 2007, Knight and Tait 2009). Open abdominal aortic surgery is associated with 2.4-6.3% risk of 30-day SWI (Giles et al. 2010), and 0.44-1.9% risk of graft infection (Vogel et al. 2008, Prager et al. 2001). In a retrospective analysis with 12,626 open abdominal aortic aneurysm reconstructions, the risk of developing graft infection was highest during first postoperative year: 32% of all graft infections developed during the first year after surgery (Vogel et al. 2008). For vascular access, created for haemodialysis, infection risk depends on the access material. Infection risks related to arteriovenous fistula and arteriovenous prosthesis are 0.9% and 9.1%, respectively (Schild et al. 2008). In prospective studies, the incidence of SWI after varicose vein surgery has been reported to vary between 5-14% (Defty et al. 2008, Mekako et al. 2010). It seems plausible to draw a conclusion that vascular surgery procedures including lower limbs are associated with a relatively high risk of SWI. SWI rates after vascular surgery procedures reported by various studies are presented in Table 7.
Table 7. Reported rates of surgical wound infection after different type vascular surgery procedures

<table>
<thead>
<tr>
<th>Study/ Year</th>
<th>Study/ Number of patients</th>
<th>Type of revascularisation procedure</th>
<th>Follow-up period</th>
<th>SSI rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenstein et al 2007</td>
<td>Retrospective / 9308</td>
<td>Carotid endarterectomy</td>
<td>30 days</td>
<td>0.2%</td>
</tr>
<tr>
<td>Vogel et al 2008</td>
<td>Retrospective / 12,626</td>
<td>Open abdominal aortic aneurysm repair</td>
<td>2 years</td>
<td>0.19% AGI: 0.5%</td>
</tr>
<tr>
<td>Murphy et al 1995</td>
<td>Prospective / 114</td>
<td>Proximal 25%</td>
<td>14 days</td>
<td>3%</td>
</tr>
<tr>
<td>Chester et al 1992</td>
<td>Prospective randomised / 149</td>
<td>Proximal 9% Extra-anatomical 5% Infrainguinal 71%</td>
<td>30 days</td>
<td>3.5%</td>
</tr>
<tr>
<td>Josephs et al 1993</td>
<td>Prospective / 69</td>
<td>Proximal 35% Extra-anatomical 17% Infrainguinal 52%</td>
<td></td>
<td>4%</td>
</tr>
<tr>
<td>Schild et al 2008</td>
<td>Retrospective / 1,700</td>
<td>Haemodialysis access</td>
<td>3 weeks</td>
<td>4.5%</td>
</tr>
<tr>
<td>Wolterbeek et al 2002</td>
<td>Prospective randomised / 170</td>
<td>Infrainguinal 100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giles et al 2010</td>
<td>Retrospective / 7,595</td>
<td>Proximal 21% Infrainguinal 79%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greenblatt et al 2011</td>
<td>Retrospective / 12,330</td>
<td>Extra-anatomical 11% Femoral endarterectomy 15% Infrainguinal 74%</td>
<td>30 days</td>
<td>11%</td>
</tr>
<tr>
<td>Kent et al 1996</td>
<td>Prospective / 119</td>
<td>Proximal 14% Extra-anatomical 10% Femoral endarterectomy 7% Infrainguinal 58%</td>
<td>6 weeks</td>
<td>15%</td>
</tr>
<tr>
<td>Virkkunen et al 2004</td>
<td>Retrospective / 5709</td>
<td>Proximal 10% Extra-anatomical 16% Femoral endarterectomy 9% Infrainguinal 61%</td>
<td>30 days</td>
<td>12.8%</td>
</tr>
<tr>
<td>Lee et al 2000</td>
<td>Retrospective / 978</td>
<td>Infrainguinal 100%</td>
<td></td>
<td>13%</td>
</tr>
<tr>
<td>Nguyen et al 2007</td>
<td>Retrospective / 1404</td>
<td>Infrainguinal 100%</td>
<td></td>
<td>20%</td>
</tr>
<tr>
<td>Vriesendorp et al 2004</td>
<td>Retrospective / 275</td>
<td>Femoral endarterectomy 8% Infrainguinal 78%</td>
<td></td>
<td>23%</td>
</tr>
<tr>
<td>Linni et al 2012</td>
<td>Prospective randomised / 103</td>
<td>Infrainguinal 100%</td>
<td>12 months</td>
<td>30%</td>
</tr>
<tr>
<td>Ploeg et al 2009</td>
<td>Prospective randomised / 171</td>
<td>Proximal 15% Extra-anatomical 15% Infrainguinal 70%</td>
<td>6 weeks</td>
<td>32%</td>
</tr>
</tbody>
</table>

Proximal: aorto-iliac, aorto-femoral or iliaco-femoral reconstruction; Extra-anatomical: femoro-femoral, axillo-femoral or iliaco-femoral bypass; SSI: surgical site infection; AGI: aortic graft infection

2.3.2 Risk factors for surgical wound infection after lower limb vascular surgery
The greater likelihood of SWI occurrence in the peripheral vascular-surgery patients compared with other clean-surgery patients is due to both procedure and patient-related factors. The risk of deep graft infection following vascular prosthesis implantation is 1-5% (Wilson 2001). However, the use of a vein graft has remained to be associated with increased risk of SWI compared with use of prosthetic graft or use of no graft (O’Brien et al 2011). That is most probably related to long exposures needed for vein harvesting. Furthermore, graft placed mainly in the subcutaneous location instead of subfascial location increases the risk of SWI, with RR of 11.6, in patients undergoing infrainguinal bypass surgery (Blankensteijn et al 1996). Prolonged operation time is associated with SWI (Chang et al 2003, Greenblatt et al 2011), which is speculated to be due to patient hypothermia, inadequate redosing of antibiotic,
retractor-related tissue trauma and breaks in sterile technique (Greenblatt et al 2011). Previous arterial surgery in the groin, earlier arteriographic procedure performed via operation site, and the use of wound drainage, have also shown to increase the risk of SWI (Landreneau and Raju 1981, Derksen et al 2009).

Incisions for vascular access at the groin may be either vertical crossing through the lymphatic tissue or oblique sparing all lymphatic tissue. Many surgeons prefer a vertical incision because it offers a direct approach and full exposure of femoral artery. However, the surgical technique used for vertical groin incision is associated with increased risk of wound complication and infection rate (Chester et al 1992, Beirne et al 2008, Swinnen et al 2012).

Infection of vascular prosthetics implanted for arterial occlusive disease occurs in approximately 1-5% of patients. The incidence of infection depends on the anatomical site, with the highest rate occurring in vascular access grafts placed for haemodialysis and in inguinal and lower extremity incisions in patients undergoing bypass procedures for femoral, popliteal or tibial occlusion (Wilson 2001). No difference has been found in the incidence of SWI when using either Polyester (Dacron) or polytetrafluoroethylene (ePTFE) vascular prostheses (Davidovic et al 2010).

Factors that increase the risk of aortic graft infection are graft contamination from skin flora during surgery, groin incision, graft revision, superficial SWI, emergency operation and postoperative bacteraemia (Perera et al 2006).

A study with 12,330 patients who underwent open surgery for lower limb peripheral vascular disease found obesity to be an independent risk factor for SWI development (OR 2.1, 95% CI 1.8-2.4) (Greenblatt et al 2011). Furthermore, obesity has increased the risk of SWI after peripheral artery surgery in other studies with smaller number of patients with an OR varying between 1.7 and 2.6 (Lee et al 2000, Giles et al 2010a, Patel et al 2007). In addition, morbid obesity (BMI≥40 kg/m²) has found to be an independent risk factor for SWI after open aortic aneurysm repair with an OR of 2.6 (Giles et al 2010b).

The reasons for higher risk of SWI in obese patients may be tissue hypoxia and low antibotic concentration. Wound and tissue oxygen tension has been found to be reduced during surgery among obese patients and this is associated with increased SWI risk (Kabon et al 2004). Pharmacokinetic analysis has revealed that Cephazolin, used as prophylactic antibiotic, has a reduced concentration within adipose tissue in obese patients compared to lean patients (Pevzner et al 2011).

Critical limb ischaemia manifests as chronic rest pain, nonhealing ulcers and gangrene and, patients with contaminated ulcers remote from surgical wound may be in the risk of endogenous bacterial contamination via bloodstream or lymphatic system. A retrospective study with 756 patients has shown that critical ishaemia with rest pain, ischaemic ulcer or gangrene (Fontaine III-IV), independently increase the risk of SWI after lower limb vascular surgery (OR 4.195%CI 1.88-8.88) (Ott et al 2012).

Other patient-specific risk factors for SWI in lower limb vascular surgery include diabetes mellitus, postoperative hyperglycaemia, COPD, female gender, and dialysis (Richet et al 1991, Josephs et al 1993, Lee et al 2000, Vriesendorp et al 2004, Patel et al 2007, Greenblatt et al 2011). COPD may be a risk factor to SWI owing a lowered oxygen delivery. An explanation of the association between female gender and inguinal SWI is thought to be gender-related differences in the amount and distribution of body fat and native skin flora (Greenblatt et al 2011). Patients with chronic renal failure and uraemia have impaired host defences and wound healing that can lead to increased risk of SWI (Chang and Wong 2001).
2.3.3 Causative agents
The most common causative agent associated with SWI after lower limb arterial surgery is Staphylococcus aureus which has been isolated from 33-60 % of infected wounds (Calligaro et al 1994, Pounds et al 2005). Methicillin-resistant Staphylococcus aureus has been reported to be responsible for 30-50% of Staphylococcus aureus wound infections in the United States (Calligaro et al 1994, Lee et al 2000, Pounds et al 2005). The other causative bacteria are as follows: Staphylococcus epidermidis 17-24%, Streptococcus 19%, Pseudomonas 12-20%, Enterococcus 6-12%, E coli 2-8% and Enterobacter 3- 9% (Himbeeck et al 1992, Calligaro et al 1994, Lee et al 2000, Pounds et al 2005).

Early prosthetic vascular graft infections are usually owing to Staphylococcus aureus or, in the case of aortoenteric fistulae, gram-negative species (Legout et al 2011). Late infections often involve more indolent species such as Staphylococcus epidermidis (Perera et al 2006).

2.3.4 Consequences of surgical wound infection after lower limb vascular surgery

2.3.4.1 Impact on patient outcome
Although most of the SWIs after vascular surgery procedures heal with treatment (Himbeeck et al 1992, Calligaro et al 1994), they may be a significant source of morbidity. Surgical wound infection increases the risk of graft failure requiring intervention (Giles et al 2010, Greenblatt et al 2011). Reported incidence of major amputation owing to SWI ranges from 2 to 25% being highest as a result of vascular graft infection (Pounds et al 2005, Nguyen et al 2007). Several studies have not found association between SWI and 30-day mortality (Himbeeck et al 1992, Stone et al 2010, Greenblatt et al 2011).

Especially problematic are epidemics of multiresistant bacteria; a matched case-control study revealed that an outbreak of multidrug-resistant Pseudomonas aeruginosa in vascular surgery ward was associated with decreased short-term amputation-free survival after infrainguinal bypass surgery in patients with critical limb ischaemia (Söderström et al 2009).

Mortality owing to prosthetic vascular graft infection has been variously reported to be 11-20% and 6.5-11% owing to lower limb prosthetic vascular graft infection (Calligaro et al 1994, Pounds et al 2005, O’Brien et al 2011, Legout et al 2011). Aortic graft infection increases the mortality with OR of 5.6 (95% CI 1.1-28.7) (Legout et al 2011).

2.3.4.2 Impact on resource utilisation
Surgical wound infection causes additional costs of vascular surgery procedures by delaying recovery, increasing the length of stay (LOS), and necessitating the need for additional treatment. Length of stay is increased by 2-14 days because of SWI (Giles et al 2010, O’Brien 2011), and it has been calculated, in 1996, that cost of one SWI is €405 per infected patient (Kent et al 1996). A database register study, conducted in the United States, with 870,000 elective vascular surgical procedures, including aortic, endovascular and lower limb revascularisation procedures, was performed to describe the infectious complications after elective vascular surgery. In that study, nosocomial infections increased the LOS from 4.2 to 13.8 days and the hospital costs from $12,000-38,000 (€9,000-29,000) (Vogel et al 2010).

2.3.5 Treatment of surgical wound infection after vascular surgery
The basic treatment of SWI is to open and drain the wound, and to remove the necrotic tissue. Culture should be performed to identify the source of infection and antimicrobial therapy should be adjusted. Superficial incisional infections can often be treated with oral antibiotics
only, without surgical debridement (Anderson 2011).

Treatment of vascular prosthetic graft infection remains a challenging problem. Traditional management of infected arterial grafts included total graft revision and complex extra-anatomical or venous revascularisation procedures. Since such management is associated with high mortality (26-34%) and limb loss rate (23-36%) (Liekweg and Greenfeld 1977, Lorentzen et al 1985), techniques for partial and total graft preservation have been developed. However, removal of the entire infected graft is still essential in patients who present systemic sepsis or with infected disrupted anastomoses or anastomotic bleeding (Calligaro et al 1994, Rutherford 2000).

In a study of 120 patients with infected extracavitary prosthetic arterial grafts (95 PTFE and 25 Dacron), complete or partial graft preservation was attempted in 94 (78%) patients. The hospital mortality rate was 12% and the hospital amputation rate among survivors was 13% (14/106). Patient treated by complete graft preservation, the long term complete graft preservation was successful in 71% (32/45) of cases. Partial graft preservation was successful in 85% (34/41) of surviving patients with occluded grafts (Calligaro et al 1994). Another study with 40 grafts (24 prosthesis, 3 vein and 13 biological) and 9 native arteries, reported 91% complete wound healing rate when, after radical debridement and graft preservation, negative pressure wound therapy was applied directly on the infected graft/wound. There was no difference in outcome between the various graft types involved (Mayer et al 2011). Coverage of exposed prosthetic material in the groin with a muscle flap may be an effective option for decrease morbidity, and to increase limb and graft salvage (Morasch et al 2004, Herrera et al 2009).

### 2.3.6 Prevention

There is a clear evidence of the benefit of prophylactic broad-spectrum antibiotics for vascular reconstruction (Steward et al 2007). A meta-analysis of 34 studies was conducted to evaluate the evidence for effectiveness of interventions to prevent wound and graft infection in peripheral vascular reconstructions. Of these trials, 22 were trials of systemic antibiotics. The meta-analysis demonstrated that prophylactic treatment with systemic antibiotics administered immediately preoperatively reduces the risk of wound infection and early graft infection between two thirds and three quarters (Steward et al 2007). Broad-spectrum cephalosporins, penicillin/β-lactamase inhibitors, or aminoglycosides would appear to confer similar benefits, and a 24-hour regimen of antibiotics appears to be an effective prophylaxis (Steward et al 2007).

Suction drains are commonly used to prevent postoperative haematoma formation. However, the use of drainage has shown to increase the risk of SWI (Landreneau and Raju 1981, Derksen et al 2009), and a meta-analysis of four trials revealed that the use of drainage confers no benefit following lower limb revascularisation (Karthikesalingam et al 2008). On the other hand, a postoperative incisional haematoma has been associated with SWI development (Lee et al 2000). Thus it seems plausible that both meticulous haemostasis and avoidance of surgical drainage would decrease the risk of SWI. In addition, efforts to reduce operation time, for example by using a “double-team”, would be beneficial since prolonged operation time is associated to SWI (Chang et al 2003, Greenblatt et al 2011).

Two retrospective studies (n=149, n=196) have revealed that oblique incision for vascular access at groin significantly decreases the incidence of SWI compared with vertical incision (Chester et al 1992, Beirne et al 2008). But, a later study using prospective collected data (n=171) showed no difference in incidences of SWI between direct and oblique groin incisions (Ploeg AJ et al 2009).

A study with dogs indicated that a gelatin-sealed graft pre-bonded with two antibiotics resists infection caused by S aureus graft contamination (Javerliat et al 2007). Thus, the risk of
SWI could be reduced by using rifampicin-bonded vascular graft when vein is not available. A prospective randomised study with 216 patients evaluated that postoperative silver-eluting dressing system decreases the wound complication rate (Childress et al 2007).

A meta-analysis of 21 studies with 2,799 patients undergoing coronary artery bypass surgery showed that open saphenous vein harvesting compared with minimally invasive vein harvesting increases the risk of SWI (OR 3.85 95%CI 2.53-5.86) (Markar et al 2010). Using the minimally invasive vein harvest technique for lower limb revascularisation surgery could also be beneficial in order to avoid SWI. A further study in the relationship between vein harvesting technique and SWI should be conducted.
3 The aims of the study

The overall aim of this study was to evaluate the pathophysiology, risk factors, incidence and consequences of SWI after lower limb vascular surgery, and to assess preventive measures in the SWI prophylaxis.

The specific aims were:

1. To determine the incidence of SWI, to evaluate the risk factors and consequences of SWI, and to calculate the additional cost of services caused by SWI.
2. To investigate whether bacterial flora on surgical site peri- and postoperatively has an effect on the development of surgical wound infection after lower limb vascular surgery.
3. To test whether triclosan-coated sutures are effective in the prevention of SWI after lower limb vascular surgery.
4. To test whether postoperative supplemental inspired oxygen is effective in the prevention of SWI after lower limb vascular surgery.
4 Patients and methods

4.1 Patients

The present study included adult 803 patients who underwent nonemergency lower limb arterial surgery and 25 patients who underwent nonemergency aortic surgery. The characteristics of the patients and procedures are presented in Table 8.

4.1.1 Study I

The multicentre prospective observational study included 184 adult patients who underwent non-emergency infrarenal aortic or lower limb arterial surgery. The exclusion criterion was patients’ refusal to participate.

The study took place in the following four hospitals: Kuopio University Hospital in Kuopio, North Karelia Central Hospital in Joensuu, South Karelia Central Hospital in Lappeenranta, and Mikkeli Central hospital in Mikkeli. Ethics Committees of all participating hospitals approved the study. The data were collected between June 2007 and January 2008. The collection period varied between three and five months in each hospital. Every patient provided a written informed-consent form.

4.1.2 Study II

The prospective descriptive study included consecutive adult patients undergoing non-emergency lower limb revascularization surgery. The exclusion criteria were patients’ refusal to participate, patients’ inability to give informed consent, antibiotic treatment two weeks prior the surgery, or patient’s cephalosporin allergy. Aorto-iliac procedures were not included in the study.

The study was conducted at the Department of Vascular Surgery, North Karelia Central Hospital. The data were collected between January 2012 and October 2012. Swabs for microbiological analysis were taken from all surgical wounds peri- and postoperatively. Qualitative and quantitative analyses of various bacterial species were performed at Eastern Finland Laboratory Centre, Regional Laboratory of Joensuu. Blinded microbiological analyses were performed by an investigator who remained unaware of the origins of the coded bacterial samples. The study was approved by Ethics Committee of Kuopio University Hospital. Every patient provided a written informed consent form.

One hundred and nineteen patients underwent lower limb revascularization surgery during the study period. Altogether 94 patients with 100 surgical procedures were included. Reasons for exclusion from the study were as follows; patient underwent surgery at night or during the weekend when it was not possible to analyze the bacterial samples (92%), patient was receiving an antibiotic treatment (4%), or patient was allergic to cephalosporin (4%).

4.1.3 Study III

Consecutive adult patients who underwent non-emergency lower limb arterial surgery were enrolled into this multicenter, prospective, double-blinded parallel-group study. Aortoiliac procedures were not included in the study. The exclusion criterion was patient’s refusal to participate. The study took place in three tertiary referral hospitals and two secondary referral hospitals in Finland: Helsinki University Hospital, Tampere University Hospital, Kuopio
University Hospital, North Karelia Central Hospital and South Karelia Central Hospital. The study was approved by Ethics Committees in all participating hospitals. Every patient provided a written informed consent form.

The data were collected between July 2010 and January 2011 but the collection period varied between 4 and 6 months among hospitals. There were 394 patients undergoing lower limb revascularisation during that time, and 276 of those patients were enrolled and randomised in the study. A total of 139 patients were assigned to the study group, and 137 patients were assigned to the control group. Ten patients died within 30 days following surgery. Nine of these patients had no SWI at the time of death, and we considered them to be uninfected in our analysis. The flow of participants is shown in Figure 1.

*Figure 1. Flow chart*
4.1.4 Study IV
The prospective, multicenter, investigator-blinded study included consecutive adult patients who underwent non-emergency lower limb arterial surgery. Patients with hypercapnic COPD or oxygen saturation of less than 90%-measured by pulse oximeter when the patient was breathing room air-were not included in the study. The patient was classified as having COPD if the COPD had been diagnosed earlier by a pulmonologist. Patient’s refusal to participate was the additional exclusion criterion.

The study took place in one tertiary referral hospital and five secondary referral hospitals in Finland: Kuopio University Hospital in Kuopio, North Karelia Central Hospital in Joensuu, South Karelia Central Hospital in Lappeenranta, Mikkeli Central Hospital in Mikkeli, Central Hospital of Central Finland in Jyväskylä and Lapland Central Hospital in Rovaniemi. Ethics Committees of all participating hospitals approved the study. Every patient provided a written informed-consent form.

The data collection took place between May 2009 and February 2010 but the collection period varied between three and six months amongst the hospitals. There were 343 patients undergoing lower limb revascularisation during that time, and 274 of those patients were enrolled and randomised in the study. A total of 137 patients were assigned to both the study and the control group. Four patients died within 30 days following surgery. Three of these patients had no SWI at the time of the deaths, and we considered them to be uninfected in our analysis. The flow of participants is shown in Figure 2.

**Figure 2 Flow chart**

```
<table>
<thead>
<tr>
<th>Enrollement</th>
<th>Allocation</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underwent surgery for lower limb revascularization</td>
<td>Allocated to receive supplemental oxygen (n=137)</td>
<td>Analysed (n=137) Excluded from analysis (n=0)</td>
</tr>
<tr>
<td></td>
<td>Allocated to receive usual care (n=137)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lost to follow-up (n=0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lost to follow-up (n=0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Excluded (n=69)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Refused to participate (n=10)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unable to provide consent (n=14)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urgent surgery (n=18)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Was not asked (n=10)</td>
<td></td>
</tr>
</tbody>
</table>
```
Table 8. Demographics of the study groups (I-IV)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study I N (%)</th>
<th>Study II N (%)</th>
<th>Study III N (%)</th>
<th>Study IV N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (±SD)</td>
<td>Mean (±SD)</td>
<td>Mean (±SD)</td>
<td>Mean (±SD)</td>
</tr>
<tr>
<td></td>
<td>Study group</td>
<td>Control group</td>
<td>Study group</td>
<td>Control group</td>
</tr>
<tr>
<td>Age, years</td>
<td>71 (11)</td>
<td>72 (9)</td>
<td>72 (11)</td>
<td>72 (11)</td>
</tr>
<tr>
<td>Male gender</td>
<td>115 (63)</td>
<td>66 (66)</td>
<td>87 (62)</td>
<td>86 (63)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26 (5)</td>
<td>26 (4)</td>
<td>26 (4)</td>
<td>27 (5)</td>
</tr>
<tr>
<td>BMI&gt;25 kg/m²</td>
<td>99 (54)</td>
<td>65 (65)</td>
<td>92 (53)</td>
<td>65 (47)</td>
</tr>
<tr>
<td>CAD</td>
<td>87 (47)</td>
<td>47 (47)</td>
<td>43 (31)</td>
<td>44 (32)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>75 (41)</td>
<td>35 (35)</td>
<td>46 (35)</td>
<td>42 (31)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>116 (63)</td>
<td>58 (58)</td>
<td>86 (62)</td>
<td>93 (68)</td>
</tr>
<tr>
<td>COPD</td>
<td>15 (8)</td>
<td>4 (4)</td>
<td>16 (12)</td>
<td>23 (17)</td>
</tr>
<tr>
<td>Asthma</td>
<td>13 (7)</td>
<td>4 (4)</td>
<td>12 (9)</td>
<td>12 (9)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>7 (4)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Indication for surgery</td>
<td>68 (37)</td>
<td>47 (47)</td>
<td>44 (32)</td>
<td>27 (20)</td>
</tr>
<tr>
<td>Ischemic pain</td>
<td>33 (18)</td>
<td>25 (25)</td>
<td>48 (35)</td>
<td>42 (31)</td>
</tr>
<tr>
<td>Ischemic ulcer</td>
<td>51 (28)</td>
<td>22 (22)</td>
<td>34 (25)</td>
<td>39 (29)</td>
</tr>
<tr>
<td>Site of arteriography on operative field</td>
<td>72 (39)</td>
<td></td>
<td></td>
<td>46 (41)</td>
</tr>
<tr>
<td>Preop blood sample</td>
<td>132 (20)</td>
<td>133 (19)</td>
<td>128 (19)</td>
<td>131 (20)</td>
</tr>
<tr>
<td>White blood cells, E9/l</td>
<td>8.0 (2.3)</td>
<td>7.8 (2.2)</td>
<td>9.4 (10.3)</td>
<td>8.3 (2.7)</td>
</tr>
<tr>
<td>C-reactive protein, g/l</td>
<td>16 (31)</td>
<td>11 (18)</td>
<td>22 (40)</td>
<td>16 (39)</td>
</tr>
<tr>
<td>Creatinine value, µmol/l</td>
<td>108 (94)</td>
<td>82 (28)</td>
<td>95 (82)</td>
<td>103 (106)</td>
</tr>
<tr>
<td>Type of reconstruction</td>
<td>15 (8)</td>
<td>5 (5)</td>
<td>5 (4)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Fem-fem bypass</td>
<td>48 (26)</td>
<td>47 (47)</td>
<td>23 (17)</td>
<td>27 (20)</td>
</tr>
<tr>
<td>Femoral ea</td>
<td>47 (26)</td>
<td>20 (20)</td>
<td>52 (37)</td>
<td>38 (28)</td>
</tr>
<tr>
<td>Fem-popliteal bypass</td>
<td>34 (18)</td>
<td>13 (13)</td>
<td>25 (18)</td>
<td>25 (18)</td>
</tr>
<tr>
<td>Distal bypass</td>
<td>15 (8)</td>
<td>15 (15)</td>
<td>34 (24)</td>
<td>40 (29)</td>
</tr>
<tr>
<td>Other</td>
<td>64 (35)</td>
<td>18 (18)</td>
<td>39 (28)</td>
<td>25 (26)</td>
</tr>
<tr>
<td>Use of prosthetic material</td>
<td>88 (48)</td>
<td>47 (47)</td>
<td>92 (66)</td>
<td>79 (58)</td>
</tr>
<tr>
<td>Infrainguinal incision</td>
<td>32 (17)</td>
<td>29 (29)</td>
<td>32 (23)</td>
<td>36 (27)</td>
</tr>
<tr>
<td>Redo surgery</td>
<td>157 (88)</td>
<td>168 (90)</td>
<td>158 (71)</td>
<td>152 (80)</td>
</tr>
<tr>
<td>Operation time, min</td>
<td>729 (1232)</td>
<td>396 (474)</td>
<td>370 (350)</td>
<td>380 (460)</td>
</tr>
<tr>
<td>Blood transfusion peri-operatively</td>
<td>12 (12)</td>
<td>31 (22)</td>
<td>30 (22)</td>
<td>30 (22)</td>
</tr>
</tbody>
</table>

BMI: body mass index, CAD: coronary artery disease, COPD: chronic obstructive pulmonary disease, fem: femoral, ea: endarterectomy
4.2 METHODS

4.2.1 Data collection
Data including demographic characteristics and operative factors were collected prospectively. Magnetic resonance imaging or intra-arterial digital subtraction angiography (DSA) by experienced angiographers was used for peripheral arterial evaluation. Angiographer selected the puncture site. Body hair shaving around the intended surgical incision site was executed in the operating room just before surgery. Saphenous vein harvesting was performed under direct vision; *in-situ* saphenous vein bypass or minimal invasive vein harvesting techniques were not being used. The term “distal bypass” was used if the distal anastomosis was placed in the crural or pedal arteries. The term “inguinal incision” was used when the surgical incision was located on a groin area. The term “infrainguinal surgery” was used when there was an operative incision made below the groin.

In study I, a sample for bacterial culture was taken from the skin of the operation site after the patient had been scrubbed. In the case of critical ischaemia with ulcer or gangrene, a sample for bacterial culture was taken from the ischaemic area. The blood glucose level was measured twice daily, blood pressure, pulse and finger-tip oxygen saturation was measured three times a day, and the number of blood white cells, the C-reactive protein value, and the haemoglobin value was measured once a day for the first 3 postoperative days. In studies II, III and IV, the blood pressure, pulse, finger-tip oxygen saturation and blood glucose level were measured twice a day, and the number of blood white cells, the hemoglobin value and the C-reactive protein value once a day for 2 postoperative days. In study IV, the oxygen level of a toe on the operated lower limb was measured with a pulse oximeter six times a day for the first 2 postoperative days.

In study III, the arterial exposure and vein harvest incisions were closed using 2-0 Vicryl Plus for subcutaneous suture and 3-0 Monocryl Plus for continuous intracutaneous suture in the study group. In the control group incisions were closed with 2-0 Vicryl and 3-0 Monocryl sutures.

In study IV, the study group received supplemental oxygen postoperatively and the control group received usual postoperative care. The primary study design was to deliver supplemental oxygen via face mask for the first two postoperative days. However, patients in the study group found it uncomfortable to wear the face mask and thus the initial study design was changed 2 weeks after the data collection had started. The patients in the study group received 30% supplemental oxygen via a Venturi mask in the recovery room after the operation and on the first postoperative day in the surgical ward. On the second postoperative day, patients inspired supplemental oxygen via a nasal cannula. A constant oxygen flow rate of 5 l/min was used. Supplemental oxygen delivery continued from the end of the surgical operation until 10 pm on the second postoperative day. The patients in the control group breathed room air.

Any postoperative complications were recorded. Surgical wounds were examined at the 1 month follow-up visit by a vascular surgeon. In study I, the patients who developed any wound complication were followed up until the wound had healed. In studies II, III and IV, the patients who developed surgical wound infection were followed up until the wound had healed.
4.2.2 Antibiotic prophylaxis
In studies I, II and IV, a standardised antibiotic prophylaxis of 3 g of cefuroxime was administered within the hour before the incision. If the operation took more than 4h or if blood loss was over 1,500 ml a further dose of 1.5g of cefuroxime was administered.

In study III, antibiotic prophylaxis was standardised to 3g of cefuroxime being administered intravenously within the hour before the incision in three participating hospitals. In two participating hospitals antibiotic prophylaxis was standardised to 1.5g of cefuroxime being administered intravenously one hour prior to incision and in every 8 hours for the first 24 hours after operation. In one hospital patients also received intravenous vancomycin if a prosthetic graft was used.

4.2.3 Sampling methods in study II
A modified swabbing technique according to Levine was used in our study (Levine et al 1976). Here, the specimen for bacterial culture was collected with liquid-based Copan ESwab collection and transport system (Copan) by twirling the pre-wetted (0.9% sterile saline) nylon flocked swab applicator with a sufficient pressure on the surgical site area of 2-cm x 4-cm, for 30 seconds. The swabs were collected from groin in most of the cases. If the revascularisation surgery did not include the groin area, the swab was taken from the most proximal incision site. The applicator was placed on the ESwab transport tube containing 1 ml of modified liquid Amies according to instructions from the manufacturer.

Bacterial samples were collected at four different time intervals. Before surgery, the first sample was taken from the operative field just before surgical area had been scrubbed. At the end of surgery, the second sample was taken after suturing the wound and before dressing was applied. OpsiteTM -Post-Op dressing were used to cover the surgical wounds in all patients in the study. The third and fourth samples were taken directly from the wound on the first and the second postoperative days. The first two samples were taken in the operating room and last two in the surgical ward. An additional bacterial sample was taken from those surgical wounds that developed SWI.

Initially the ESwab tube containing the applicator was briefly vortexed to elute efficiently the bacteria from the nylon swab into the medium and to thoroughly mix the sample. To ensure more reliable counting of heavier bacterial loads a dilution series (1:10 and 1:100) was made as follows: One hundred microlitre of original sample was diluted with 0.9% sterile saline to create 1:10 dilution and this was further diluted to ten-fold to achieve 1:100 dilution. One hundred microlitre of original sample as well as 1:10 and 1:100 dilutions were plated onto duplicate blood agar plates. Additionally, the original sample and 1:10 dilution were plated onto chocolate agar, cysteine lactose electrolyte deficient (CLED) agar and anaerobic agar with 5-mcg metronidazole disc. All plates were incubated at deg 35 C for 48 hours. Blood agar and chocolate agar plates were incubated in 5% CO2, CLED agar plates in ambient air and anaerobic agar in anaerobic atmosphere. Bacterial growth was quantified by counting colony forming units (CFU). Bacterial identification was conducted according to standard methods and using automated bacterial identification system Vitek2 (bioMérieux, Marcy l’Etoile, France). Some isolates were identified with DNA sequencing. Antibiotic susceptibility testing was performed using EUCAST disk diffusion method (www.eucast.org) and Vitek2.
4.2.4 Outcomes
The primary outcome was the occurrence of surgical wound complication or infection in study I and occurrence of SWI in studies II, III and IV. The secondary outcomes were cardiac complications, renal complications, pneumonias, major amputations, strokes and graft thromboses.

Surgical wound complications were defined as follows: seroma: a pocket of clear serous fluid in the operated area; hematoma: a collection of blood outside the blood vessels in the operated area; wound necrosis: skin necrosis that does not reach the subcutaneous space; and wound dehiscence: spontaneous parting of the sutured layers of the surgical wound for more than 5mm from each other.

A surgical wound complication was considered to be an infection if it met the criteria set by the CDC (Horan et al 1992), i.e. if there are bacteria isolated from the wound or if there are areas of localised redness, heat, swelling and pain around the wound appearing within 30 days after the operative procedure. A superficial wound infection involves only skin and subcutaneous tissue, a deep wound infection involves both fascia and muscle layers, and finally a graft infection is defined as the involvement of an artery or a graft (vein or prosthetic) (Horan et al 1992).

- The general complications were determined as follows:
  - Cardiac complication: a new Q-wave in ECG or ischaemic ST changes in the ECG combined with a Troponin-T value over 0.5 µg/l or a clinical diagnosis of cardiac insufficiency and correlative changes in a chest x-ray.
  - Renal complication: Anuria or serum creatinin value elevation of more than 50 µmol/l/day.
  - Pneumonia: Clinical diagnosis and correlative changes in a chest x-ray.
  - Major amputation: Below or above knee amputation.
  - Stroke: Rapidly-developing loss of brain functions owing to ischaemia with correlative changes at computed tomography.
  - Graft thrombosis: Occlusion of graft or revascularised artery.

4.2.5 Additional costs related to postoperative surgical wound infection
In study I, the additional days of hospitalisation, surgical procedures, visits to the outpatients’ clinic and rehabilitation related to wound infection were recorded. The costs of these actions were estimated from each hospital’s cost-accounting system. These values were as follows: additional day of hospitalisation €397/day, operating department fees for re-exploration and revision €10/min, visits to outpatient clinic €127/visit, outpatient nursing €46/visit and rehabilitation €152/day. By summarizing the real expenses of these actions, the actual cost of each individual SWI was calculated. The cost of antibiotic treatment was not included in the calculation.

4.2.6 Sample size calculation and randomisation
Power analysis and sample size estimation were performed in Studies III and IV. Study I revealed the SWI rate of 27% after lower limb vascular surgery. Based on that expected incidence of SWI of 27% in one month, we calculated that 137 patients in both the study and the control group would be required to provide 80% power for detecting a 50% reduction in the SWI rate at α=0.05.

North Karelia Central Hospital served as the coordinating center and performed a block randomisation with block size of four. Pieces of paper containing the randomisation allocations were placed into sealed envelopes. Each randomisation envelope was opened by a
research secretary after the patient was enrolled to the study. The randomisation was performed before the surgery.

In Study III, only the nurses in the operating theatre knew to which group each patient had been randomised. The nurses took the suture out of the package and gave it to the operating vascular surgeon who was blinded because the triclosan-coated and non-coated sutures are indistinguishable. Neither the vascular surgeons, the nurses in the surgical ward nor the patients knew to which group each patient had been randomised. The randomisation code was kept separate from the trial data until the end of the study.

In Study IV, the nurses in the recovery room and in the surgical ward knew to which group each patient had been randomised. Nurses gave the face masks and nasal cannulas to the study group patients, and they also took care that the masks and cannulas were put out of sight of the surgeon during ward rounds and whenever the surgeon met the patient. Vascular surgeons remained blinded during the data collection.

4.2.7 Statistics
Descriptive and demographic data of the study population are presented using frequencies and percentages for categorical variables. Means and standard deviations are reported for continuous variables. Statistical analyses were made using the Statistical Package for the Social Sciences (SPSS) version 17.0 for Windows (SPSS, Chicago, IL). For categorical variables, we applied either Pearson’s χ²-test or Fisher’s exact test and for numerical variables we used either an independent samples t-test or Mann-Whitney U-test. The risk factors for infection were assessed with binary logistic regression analysis. We performed tests and analyses for all the patients entering the study. A priori criterion for variables entering the logistic regression analysis was a two-tailed P value of less than 0.10 in Study III and less than 0.20 in Study I, Study IV, and Study II in the single variable analysis. In addition, the variables that were suggested to have an effect on the infection probability in earlier studies were tested. The final model was evaluated with a backward-directed stepwise method (likelihood ratio), with the exception of the variables “supplemental oxygen” and “suture material” which were entered into all the models in Study III and Study IV, respectively. A P value of less than 0.05 was considered statistically significant. In study IV, a subgroup analysis of patients with only inguinal incision was performed.
5 Results

5.1 STUDY I

There were 184 patients included to the study. Sixty-three percent of the patients were men and the mean age was 71 years. Critical ischaemia was the indication for surgery in 46% of cases. Only 19 (10%) required urgent surgery. Femoropopliteal or femorodistal bypass was performed to 44% of the patients. In 64 (35%) patients the reconstruction was made using artificial graft or patch. All of the redo operations were lower limb not aortic procedures. Demographic and operative data of patients are presented in Table 8.

One hundred and sixty-four (89%) patients received the standardised antibiotic prophylaxis. The other 20 patients were receiving antibiotic treatment or some other antibiotic prophylaxis.

The incidence of surgical wound complication was 34%, and the incidence of SWI was 27%. Of those patients who did not receive the standardised antibiotic prophylaxis 20% developed SWL. The outcome of this group was not statistically different from the others. The wound infection was superficial in 37 (76%) of the 49 SWIs. Exposure of graft occurred in three cases, one was prosthetic and two were vein grafts. The infected femoropopliteal prosthesis was removed and replaced with saphenous vein graft. There were no signs of infection and the graft remained patent at two years follow-up.

The number of positive bacterial culture of infected wound was 35 (71%). Staphylococcus aureus was the most commonly identified species (40%) followed by coagulase-negative staphylococcal species (26%), and Escherichia coli (9%). There were 51 patients with ischaemic ulcer and nine (18%) of them developed SWI. The cultures from the ischaemic wound matched the cultures from the postoperative infected wound in four of these nine patients. In addition, there was a positive bacterial culture from the skin of the operative field in 18 patients. Four of them developed SWI and with two of these individuals the causative bacteria of SWI was the same that was found in the culture taken from the operative field prior to the incision.

Of the 49 patients who developed wound infection, 47 were healed with treatment with only two patients needing major amputation. In those two cases, SWI was the cause for one of the amputations and critical ischaemia for the other.

Graft occlusion was detected in eight (4%) patients at the end of the study. There were five (3%) major amputations in the whole study group. One month mortality was 6% and no deaths were attributed to SWI. The surgical wound complications and other complications are presented in Table 9.

The result of univariate analysis is presented in Table 10. Multivariate analysis identified four independent predictors for SWI. The factors which increased the risk of SWI were as follows: infrainguinal surgery, body mass index over 25 kg/m² and puncture site of arteriography on the operated area. Redo surgery was the only predictor which reduced the risk of postoperative wound infection. The result of multivariate analysis is presented in Table 11.

The average cost of SWI was €3,320. This sum does not include the costs of antibiotics or other extra medical treatment or sick leave.
Table 9. Wound and other postoperative complications in 184 operative patients

<table>
<thead>
<tr>
<th>Complication</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound complications all together</td>
<td>63 (34)</td>
</tr>
<tr>
<td>Seroma</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Wound necrosis</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Haematoma</td>
<td>12 (7)</td>
</tr>
<tr>
<td>Dehiscence</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Surgical wound infection</td>
<td>49 (27)</td>
</tr>
<tr>
<td>Postoperative complications</td>
<td></td>
</tr>
<tr>
<td>Graft thrombosis</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Cardiac complication</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11 (6)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Thirty-day mortality</td>
<td>11 (6)</td>
</tr>
<tr>
<td>Major amputation</td>
<td>5 (3)</td>
</tr>
</tbody>
</table>

a Only the most serious wound complication in each patient is included
b Forty-eight postoperative complications occurred in 28 (15%) patients

Table 10. Univariate analysis of 184 patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No Infection N=135</th>
<th>Infection N=49</th>
<th>Univariate p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender, N (%)</td>
<td>47 (35%)</td>
<td>22 (45%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Age, years</td>
<td>72.0 (10.5)</td>
<td>68.3 (10.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>Critical Ischemia</td>
<td>62 (46%)</td>
<td>22 (45%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Elective surgery</td>
<td>116 (86%)</td>
<td>49 (100%)</td>
<td>0.006</td>
</tr>
<tr>
<td>BMI over 25 kg/m²</td>
<td>63 (47%)</td>
<td>37 (75%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Preoperative angiographic access site in area of surgical wound</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>68 (50%)</td>
<td>19 (40%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Diabetes</td>
<td>49 (36%)</td>
<td>26 (53%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Hypertension</td>
<td>78 (58%)</td>
<td>38 (77%)</td>
<td>0.01</td>
</tr>
<tr>
<td>COPD</td>
<td>13 (10%)</td>
<td>2 (4%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Asthma</td>
<td>7 (5%)</td>
<td>6 (12%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Dialysis</td>
<td>5 (4%)</td>
<td>2 (4%)</td>
<td>0.91</td>
</tr>
<tr>
<td>Clopidogrel use</td>
<td>11 (8%)</td>
<td>3 (6%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>29 (22%)</td>
<td>10 (20%)</td>
<td>0.88</td>
</tr>
<tr>
<td>Corticosteroids use</td>
<td>8 (6%)</td>
<td>5 (10%)</td>
<td>0.32</td>
</tr>
<tr>
<td>Current smoking</td>
<td>40 (30%)</td>
<td>16 (33%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Prosthetic graft or patch</td>
<td>53 (39%)</td>
<td>11 (22%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Infragingual surgery</td>
<td>56 (42%)</td>
<td>33 (67%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Redo surgery</td>
<td>28 (21%)</td>
<td>4 (8%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Use of drainage</td>
<td>80 (59%)</td>
<td>34 (69%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>31 (39%)</td>
<td>8 (38%)</td>
<td>0.94</td>
</tr>
<tr>
<td>Skin colonisation by bacterium</td>
<td>13 (10%)</td>
<td>5 (12%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Preop. hemoglobin, g/l</td>
<td>132.3 (20.7)</td>
<td>133.0 (19.7)</td>
<td>0.84</td>
</tr>
<tr>
<td>Preop. white blood cells count, E9/l</td>
<td>7.9 (2.4)</td>
<td>8.2 (1.9)</td>
<td>0.40</td>
</tr>
<tr>
<td>Preop. CRP, mg/l</td>
<td>16.3 (30.7)</td>
<td>14.3 (33.3)</td>
<td>0.74</td>
</tr>
<tr>
<td>Preop. creatinine, μmol/l</td>
<td>110.3 (101.1)</td>
<td>102.3 (71.0)</td>
<td>0.62</td>
</tr>
<tr>
<td>Preop albumin, g/l</td>
<td>34.1 (6.4)</td>
<td>34.9 (5.2)</td>
<td>0.49</td>
</tr>
<tr>
<td>Operation time, min</td>
<td>159.6 (93.7)</td>
<td>147.8 (71.2)</td>
<td>0.43</td>
</tr>
<tr>
<td>Blood loss, ml</td>
<td>814.0 (1366.0)</td>
<td>485.7 (678.6)</td>
<td>0.12</td>
</tr>
<tr>
<td>Mean arterial pressure on 1st po. day, mmHg</td>
<td>88.1 (15.8)</td>
<td>92.0 (15.2)</td>
<td>0.72</td>
</tr>
<tr>
<td>Mean arterial pressure on 1st po. day, mmHg</td>
<td>94.9 (3.8)</td>
<td>95.1 (3.1)</td>
<td>0.87</td>
</tr>
<tr>
<td>CRP on 1st po day, mg/l</td>
<td>48.9 (36.8)</td>
<td>48.1 (38.0)</td>
<td>0.91</td>
</tr>
<tr>
<td>Hemoglobin on 1st po. day, g/l</td>
<td>111.1 (17.4)</td>
<td>111.8 (18.0)</td>
<td>0.62</td>
</tr>
<tr>
<td>White blood cells count on 1st po. day, E9/l</td>
<td>8.8 (2.5)</td>
<td>9.2 (2.7)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Categorical variables are presented as number of the patients and percentages. Continuous variables are presented as means and standard deviations. BMI = body mass index, CAD = coronary artery disease, COPD = Chronic obstructive pulmonary disease, CRP = C-reactive protein, po = postoperative, Preop. = Preoperative
Table 11. Independent predictors of surgical wound infections in multivariate analysis of 184 patients

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriograph puncture site on operation area</td>
<td>2.49</td>
<td>1.13-5.48</td>
<td>0.02</td>
</tr>
<tr>
<td>Infrainguinal surgery</td>
<td>7.18</td>
<td>2.92-17.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI over 25 kg/m²</td>
<td>6.08</td>
<td>2.44-15.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>REDO surgery</td>
<td>0.27</td>
<td>0.08-0.96</td>
<td>0.04</td>
</tr>
</tbody>
</table>

CI=Confidence interval, OR= Odds ratio, BMI= Body mass index

5.2 STUDY II

Sixty-six percent of the patients were men and the mean age was 72 years. Half of the patients had coronary artery disease and one-third had diabetes. The indication for surgery was critical ischemia in 47% of the cases. Thirty-three percent of the procedures were either femoropopliteal or femoro-distal bypasses. Vascular prosthesis or a prosthetic patch was used in 18 (18%) patients.

The incidence of SWI was 21%. Of the 21 SWIs, 76% were superficial and 19% were deep. In our material, there was one complication considered as graft infection; a patient with femoral endarterectomy developed a groin infection involving the femoral artery. The infection healed by wound radical revision and muscle flap covering. Four patients died during the study period, these patients had not developed SWI. Causes for death were myocardial infarction in three patients and cardiac insufficiency in one patient. Two patients needed a major amputation due to critical ischemia. In one patient with SWI due critical ischemia and graft thrombosis, SWI was the cause of major amputation. Postoperative complications are presented in Table 12. Of the 21 patients who developed SWI 20 were healed with treatment by end of study period.

Total microbial counts in the SWI group compared to the non-SWI group were statistically significantly higher only in samples taken on the second post-operative day (p=0.001). Thus this time-point was selected for further analysis. The dynamics of wound bacterial colonization at different time intervals is shown in Figure 3. There were five cases in which the second post-operative day sample was not taken or the sample was missing. For univariate and multivariate analysis, we divided the study material into two different groups: surgical wounds with bacterial counts greater than 400,000 CFU/ml (n=12) at second postoperative day and surgical wounds with bacterial counts less than 400 000 CFU/ml (n=88) at second postoperative day. In these groups, the SWI rate was 66.7% and 14.8% respectively (p<0.001).

Coagulase-negative staphylococci were the most common bacteria growing in 80% of the cultures. Other commonly isolated bacteria were Corynebacterium spp. (25%), Propionibacterium spp. (15%), Enterococcus faecalis (4%), Micrococcus spp. (3%) and Staphylococcus aureus (3%). Positive cultures of infected wounds were obtained in 20 (95%) of 21 patients. The most commonly identified species were Staphylococcus aureus (52%), Enterococcus faecalis (23%), Peptostreptococcus spp. (29%), Escherichia coli (24%) and Corynebacterium species (19%). No methicillin-resistant S. aureus (MRSA), vancomycin-resistant enterococci (VRE), extended-spectrum beta-lactamase producing (ESBL) E coli or Klebsiella species or multi-drug resistant (MDR) Pseudomonas aeruginosa or other MDR gram-negative rods were present in these samples. Polymicrobial flora were found in 71% of the infected wounds. In 13 (62%) of cases, same bacterial isolates were found from the perioperative study samples and from the infect-
ed wounds. S. aureus was the causative agent in 5 (71%) of the 7 SWI cases with non matching bacterial samples.

The univariate analysis found the following factors to increase the risk of SWI: male gender, body mass index (BMI) of over 25 kg/m², diabetes, and a high bacterial colonization of the surgical site on the second postoperative day when using the cutpoint of 400,000 CFU/ml. The result of the univariate analysis is presented in Table 13. Multivariate analysis identified the high bacterial colonization of the surgical site at the second postoperative day to be an independent risk factor for SWI with an odds ratio (OR) of 1.61. The other factor that increased the risk of SWI was diabetes. Redo surgery was the only predictor that decreased the risk of postoperative wound infection. The result of multivariate analysis is presented in Table 14.

Table 12. Postoperative complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical wound infection</td>
<td>21 (21)</td>
</tr>
<tr>
<td>Graft thrombisis</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Cardiac complication</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Major amputation</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Hemorrhage from surgical area</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Thirty-day mortality</td>
<td>4 (4)</td>
</tr>
</tbody>
</table>

Figure 3. Total bacterial counts (median) in patients with and without surgical wound infection before surgery, at the end of surgery, and at 1st and 2nd post-operative day. P-value refers to Mann-Whitney U-test.
Table 13. Univariate analysis of 100 surgical wounds

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No infection N=79</th>
<th>Infection N=21</th>
<th>Univariate p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, N (%)</td>
<td>48 (61%)</td>
<td>18 (86%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Age</td>
<td>71.8 (8.8)</td>
<td>70.9 (8.2)</td>
<td>0.66</td>
</tr>
<tr>
<td>Ischemic ulcer</td>
<td>16 (20%)</td>
<td>6 (29%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Claudication</td>
<td>36 (46%)</td>
<td>11 (52%)</td>
<td>0.59</td>
</tr>
<tr>
<td>BMI &gt; 25kg/m²</td>
<td>48 (61%)</td>
<td>17 (81%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Preop. haemoglobin, g/l</td>
<td>131.5 (18.8)</td>
<td>138.2 (19.8)</td>
<td>0.17</td>
</tr>
<tr>
<td>Preop. white blood cells count, E9/l</td>
<td>7.9 (2.3)</td>
<td>7.7 (1.6)</td>
<td>0.81</td>
</tr>
<tr>
<td>Preop. CRP g/l</td>
<td>11.8 (19.2)</td>
<td>8.2 (8.2)</td>
<td>0.21</td>
</tr>
<tr>
<td>Hypertension</td>
<td>43 (54%)</td>
<td>15 (71%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Diabetes</td>
<td>22 (28%)</td>
<td>13 (62%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Use of Asa</td>
<td>53 (67%)</td>
<td>15 (71%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Use of Warfarin</td>
<td>16 (20%)</td>
<td>4 (19%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Use of Clopidogrel</td>
<td>7 (9%)</td>
<td>3 (14%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Current smoking</td>
<td>30 (38%)</td>
<td>9 (43%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Infrainguinal incision</td>
<td>36 (46%)</td>
<td>11 (52%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Use of prosthetic material</td>
<td>18 (23%)</td>
<td>0 (0%)</td>
<td>0.016</td>
</tr>
<tr>
<td>Redo surgery</td>
<td>25 (32%)</td>
<td>4 (19%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>172.4 (91.3)</td>
<td>154.2 (85.0)</td>
<td>0.40</td>
</tr>
<tr>
<td>Blood loss during surgery (ml)</td>
<td>403.6 (453.5)</td>
<td>367.6 (554.3)</td>
<td>0.79</td>
</tr>
<tr>
<td>Use of drainage</td>
<td>66 (84%)</td>
<td>19 (91%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>11 (14%)</td>
<td>1 (4.8%)</td>
<td>0.25</td>
</tr>
<tr>
<td>CFU/Swab &gt; 400 000 at the second postoperative day</td>
<td>4 (5%)</td>
<td>8 (38%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Categorical variables are presented as number of the surgical wounds and percentages. Continuous variables are presented as means and standard deviations. Asa=acetylsalicylic acid, BMI=body mass index, CFU=colony forming unit, CRP=C-reactive protein, Preop=preoperative, Redo=reoperative

Table 14. Multivariate analysis of factors associated with surgical wound infection after lower limb vascular surgery

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redo surgery</td>
<td>0.81</td>
<td>0.67-0.98</td>
<td>0.040</td>
</tr>
<tr>
<td>CFU/Swab &gt; 400 000 at the 2. postoperative day</td>
<td>1.61</td>
<td>1.28-2.02</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.23</td>
<td>1.06-1.43</td>
<td>0.016</td>
</tr>
</tbody>
</table>

CFU=colony forming units, Postop= postoperative, Redo= reoperative, OR=odds ratio, CI=confidence interval

5.3 STUDY III

Clinical characteristics, the type of antibiotic prophylaxis, indications for surgery, and the duration of surgery were not statistically different between the groups. There were 152 bypass procedures and prosthetic graft was used in 67 (44%) cases.

The overall incidence of SWI was 22%. There was no difference between the triclosan group and the control group in the incidence of SWI. There were 24 (77%) versus 22 (73%) superficial wound infections and 5 (16%) versus 5 (17%) deep wound infections in the study and the control groups, respectively. The incidence of graft infection was similar in both groups; two (6%) patients in the study group and 3 (10%) patients in the control group developed vascular graft infection.
There were no difference in incidences of other postoperative complications, including graft thrombosis, cardiac complications, stroke, pneumonia, renal insufficiency, and major amputations between the triclosan group and the control group (Table 15). Ten (3.6%) patients died during the 1-month study period. Six of them belonged to the triclosan group and four to the control group. Two of the deaths were caused by pneumonia, three of the deaths were caused by a stroke and five of the deaths were the result of myocardial infarction. One patient who died during the 1-month postoperative period had SWI.

Obesity and the use of corticosteroids were independent predictors of SWI in the multivariate analysis. The results of the multivariate analysis are presented in Table 16. According to the multivariate logistic regression analysis, the odds ratio (OR) for SWI in the triclosan group was 1.10 [95% confidence interval (CI), 0.61-2.01; P=0.75].

A total of 245 patients (89%) received antibiotic prophylaxis according to the one out of three protocol standards: cefuroxime 3g intravenously (60%), cefuroxime 1.5g intravenously in every 8 hours for the first 24 hours (24%) or cefuroxime 1.5g and vancomycin intravenously in every 8 hours for the first 24 hours (5%). The other patients were treated as follows: 5 were allergic to cefuroxime and received other antibiotic prophylaxis, 1 patient didn’t get any antibiotic prophylaxis, 17 were treated for an infected ulcer, 1 was treated for urinary tract infection, 1 was treated for gastrointestinal infection and 1 was treated for pneumonia. Four patients received antibiotic prophylaxis for prevention of bacterial endocarditis. The most common antibiotics that were used to treat infections were meropenem, vancomycin, and ciprofloxacin. Whether the patient received any of the standardised antibiotic prophylaxis or received some other antibiotic prophylaxis or antibiotic treatment had no effect on the incidence of SWI.

Positive cultures of the infected wounds were obtained from 44 (72%) of the 61 patients with a clinically-diagnosed infection. A negative culture was obtained from 6 (10%) of the infected wounds, and 11 (18%) wounds were not cultured. The most common bacterial species found in these 61 infected surgical wounds were Staphylococcus aureus (29%), Enterococcus faecalis (21%), coagulase-negative staphylococcal species (25%) and Pseudomonas aeruginosa (3%). There was no difference in the type or prevalence of bacterial colonisation between the study and the control group.

Of the 61 patients who developed SWI, 57 (93%) were cured with treatment by the end of the study. Four (7%) patients died before their wound infections had healed, three of these four patients died after the 1-month postoperative period. One patient in the control group died from myocardial infarction on the 27th postoperative day and one from pneumonia on the 86th postoperative day. Two patients died as a result of complicated vascular graft infection; in study group one patient with vein graft infection died on the 65th postoperative day, and in control group one patient with prosthetic graft infection died on the 125th postoperative day. There were no major amputations because of SWI in this study.
**Table 15 Comparative outcomes between two study groups**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study group</th>
<th>Control group</th>
<th>Univariate P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical wound infection</td>
<td>31 (22.3)</td>
<td>30 (21.9)</td>
<td>0.94</td>
</tr>
<tr>
<td>Graft Thrombosis</td>
<td>7 (5.0)</td>
<td>6 (4.4)</td>
<td>0.80</td>
</tr>
<tr>
<td>Cardiac complication</td>
<td>3 (2.2)</td>
<td>6 (4.4)</td>
<td>0.30</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5 (3.6)</td>
<td>5 (3.6)</td>
<td>0.99</td>
</tr>
<tr>
<td>Stroke</td>
<td>4 (2.9)</td>
<td>1 (0.7)</td>
<td>0.18</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>2 (1.4)</td>
<td>1 (0.7)</td>
<td>0.57</td>
</tr>
<tr>
<td>Major amputation</td>
<td>4 (2.9)</td>
<td>5 (3.6)</td>
<td>0.72</td>
</tr>
<tr>
<td>Thirty-day mortality</td>
<td>6 (4.3)</td>
<td>4 (2.9)</td>
<td>0.55</td>
</tr>
<tr>
<td>Post-operative hospital stay, days</td>
<td>5.5 (6.5)</td>
<td>5.2 (4.3)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Data are expressed as means (SD) or percentages.

Cardiac complication: new Q-wave in ECG or ischaemic ST changes in ECG combined with a troponin value over 0.5 µg/l or clinical diagnosis of cardiac insufficiency and correlative changes on chest x-ray film.

Renal insufficiency: anuria or serum creatinine value elevation of more than 50 µmol/l/ day.

**Table 16 Factors associated with surgical wound infections in multivariate analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of triclosan coated sutures</td>
<td>1.10</td>
<td>0.61 - 2.01</td>
<td>0.75</td>
</tr>
<tr>
<td>BMI over 25 kg/m²</td>
<td>3.14</td>
<td>1.63 - 6.07</td>
<td>0.001</td>
</tr>
<tr>
<td>Current use of corticosteroids</td>
<td>3.13</td>
<td>1.35 - 7.22</td>
<td>0.008</td>
</tr>
</tbody>
</table>

**5.4 STUDY IV**

**5.4.1 Results of the main analyses**

The study and the control group were equal in terms of clinical characteristics, the type of antibiotic prophylaxis, indications for surgery and the duration of surgery. There were 173 bypass procedures and prosthesis grafts were used in 44 (25%) cases. Toe oxygen saturation levels were different between the groups at two time points: 24 hours after surgery the mean saturation was 94.4% in the oxygen group and 91.9% in the control group, p = 0.034, and 28 hours after surgery the mean saturation was 95.0% in the oxygen group and 92.4% in the control group, p = 0.025. However, the mean of all post-operative oxygen saturation measurements was not different between the study and the control groups [mean (SD), 95.0 (4.9) vs. 93.7 (3.5), respectively, p=0.082].

The overall incidence of SWI was 23% of which 75% was superficial. SWI occurred in 25 (18%) patients in the supplemental oxygen group and in 38 (28%) patients in the control group, p=0.06 (Table 17). According to the multivariate logistic regression analysis, the odds ratio (OR) for SWI in the supplemental oxygen group compared with the control group was 0.56 (95% confidence interval (CI), 0.30-1.04, p=0.07). There were 18 (13%) vs. 29 (21%) superficial wound infections and 7 (5%) vs. 7 (5%) deep wound infections in the study and the control groups, respectively. Two (3%) patients in the control group developed a vascular graft infection.

Asthma, coronary artery disease and infrainguinal incision were independent predictors of SWI in the multivariate analysis. In contrast, the use of prosthetic material reduced the risk of postoperative SWI. The results of the multivariate analysis are presented in Table 18.

The incidence of other postoperative complications including graft thrombosis, cardiac complication, stroke, pneumonia, renal insufficiency and major amputation were not differ-
ent in the supplemental oxygen and the control groups (Table 17). Three patients in the study group and one patient in the control group died during the one-month study period. One of the deaths was caused by aspiration pneumonia and three by myocardial infarctions.

Two hundred and forty-four (89%) patients received the antibiotic prophylaxis according to the protocol standard. The other patients were treated as follows: 10 received Cefuroxime 1.5 g as antibiotic prophylaxis, 4 patients didn’t receive any antibiotic prophylaxis, 11 were treated for an infected ulcer, 3 were treated for a urinary tract infection and 2 were treated for sepsis. The most common antibiotics that were used to treat different infections were meropenem, ciprofloxacin and clindamycin. Whether the patient received the standardised antibiotic prophylaxis or received some other antibiotic prophylaxis or antibiotic treatment or did not receive any antibiotic, had no effect on the incidence of SWI.

Positive cultures of the infected wounds were obtained from 41 (65%) of the 63 patients with a clinically-diagnosed infection. A negative culture was obtained from 11 (17%) of the infected wounds, and 11 wounds were not cultured. The most commonly identified species were Staphylococcus aureus (29%), Enterococcus faecalis (11%), coagulase-negative staphylococcal species (8%) and Pseudomonas aeruginosa (5%).

Of the 63 patients who developed SWI, 58 (92%) were cured with treatment by the end of the study. Three (5%) patients required major amputations. SWI was the cause of two amputations, and critical ischaemia because of graft thrombosis was the reason for one amputation. Of the two patients who required major amputation owing to SWI, one belonged to the study group and the other to the control group. Two (3%) patients died before their wound infections had healed. One belonged to the study group and died from myocardial infarction on the 30th postoperative day and the other belonged to the control group and died from renal failure on the 64th postoperative day.

### Table 17. Comparative outcomes between the two study groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Supplemental oxygen group N=137</th>
<th>Control group N=137</th>
<th>Univariate p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical wound infection</td>
<td>25 (18.2)</td>
<td>38 (27.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>Graft thrombosis</td>
<td>5 (3.6)</td>
<td>8 (5.8)</td>
<td>0.39</td>
</tr>
<tr>
<td>Cardiac complication</td>
<td>6 (4.4)</td>
<td>5 (3.6)</td>
<td>0.81</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (0.7)</td>
<td>4 (2.9)</td>
<td>0.18</td>
</tr>
<tr>
<td>Stroke</td>
<td>3 (2.2)</td>
<td>0 (0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>3 (2.2)</td>
<td>1 (0.7)</td>
<td>0.31</td>
</tr>
<tr>
<td>Major amputation</td>
<td>3 (2.2)</td>
<td>5 (3.6)</td>
<td>0.47</td>
</tr>
<tr>
<td>Thirty-day mortality</td>
<td>3 (2.2)</td>
<td>1 (0.7)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Data are expressed as means (SD) or numbers (%).
Cardiac complication: new Q-wave in ECG or ischaemic ST changes in ECG combined with a troponin value over 0.5 µg/l or clinical diagnosis of cardiac insufficiency and correlative changes in a chest x-ray.
### Table 18. Factors associated with surgical wound infections in multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of prosthetic material</td>
<td>0.20</td>
<td>0.08-0.50</td>
<td>0.001</td>
</tr>
<tr>
<td>Asthma</td>
<td>4.83</td>
<td>1.72-13.53</td>
<td>0.003</td>
</tr>
<tr>
<td>Infrainguinal incision</td>
<td>2.24</td>
<td>1.07-4.67</td>
<td>0.03</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.94</td>
<td>1.04-3.62</td>
<td>0.04</td>
</tr>
<tr>
<td>Supplemental oxygen</td>
<td>0.56</td>
<td>0.30-1.04</td>
<td>0.07</td>
</tr>
</tbody>
</table>

CI = Confidence interval, OR = Odds ratio

#### 5.4.2 Subgroup analysis for inguinal procedures

There were 103 (52 in the study group and 51 in the control group) patients who had an inguinal incision only. The incidence of SWI was 15% in this selected population. The following surgical procedures were performed: 84 femoral endarterectomies, 9 femoro-femoral bypasses, 2 embolectomies and 8 other procedures. Clinical characteristics, the type of antibiotic prophylaxis, indications for surgery and the duration of surgery were similar in these two groups. Surgical wound infection occurred in three (6%) patients of the study group and in 12 (24%) patients of the control group. That difference was statistically significant (p=0.01). There were no differences in secondary outcomes between these two groups (Table 19). In multivariate analysis a BMI over 25 kg/m\(^2\) was an independent risk factor for SWI in isolated inguinal incisions (OR 1.22, 95% CI, 1.03-1.45, p=0.02), whereas supplemental oxygen was associated with reduced risk of SWI (OR, 0.20, 95% CI, 0.04-0.95, p=0.04).

### Table 19. Postoperative data of 103 patients with inguinal incision only

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Supplemental oxygen group N=52</th>
<th>Control group N=51</th>
<th>Univariate p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical wound infection</td>
<td>3 (6)</td>
<td>12 (24)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cardiac complication</td>
<td>3 (6)</td>
<td>1 (2)</td>
<td>0.32</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>0.32</td>
</tr>
<tr>
<td>Major amputation</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>0.31</td>
</tr>
<tr>
<td>Post-operative hospital stay, days</td>
<td>5 (5)</td>
<td>5 (5)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Data are expressed as means (SD) or numbers (%). Cardiac complication: new Q-wave in ECG or ischaemic ST changes in ECG combined with a troponin value over 0.5 µg/l or clinical diagnosis of cardiac insufficiency and correlative changes in a chest x-ray.
6 Discussion

6.1 LIMITATIONS OF THE STUDY
The follow-up time was only one month meaning that we are not able to draw any conclusions about infections of vascular prosthesis. According to the CDC definition, wound complication is SWI if it appears within 30 days after operation or within one year if there is foreign material in place. Infections of prostheses generally occur a few months, sometimes years, after the initial surgery. Furthermore, the incidence of prosthesis infection in vascular surgery is 1-5% (Wilson 2001). There were 214 procedures with prosthetic material in the study, which means that not more than 2-11 infections of vascular prosthesis would have been expected to occur.

Study I included 25 (14%) aortic surgery patients although the aim of all studies was to evaluate the factors associated with wound infections after peripheral vascular surgery. Furthermore, the results apply only to patients undergoing peripheral vascular surgery. It is not clear if the result can be generalised to the other surgical procedures.

In Study I, we did not analyse whether the graft was placed in the subcutaneous or subfascial location. It has been found that the presence of a vascular conduit in the subcutaneous plane is associated with a higher risk for SWI as compared to the situation with deeply placed grafts (Chang et al 2003). In Studies I and IV, the type of suture material and technique were not recorded.

Because of relatively limited number of patients (184) in Study I, it is possible that there were some type 2 statistical errors with respect to some of the potential predictors of SWI. In study IV, the sample size calculation was based on the expectancy of a 50% risk reduction of SWI. It is probable that there is a type 2 error in our study owing to the small sample size (274), and with a bigger sample size the difference between the supplemental postoperative oxygen group and the control group might have been significant.

6.2 PATIENTS
Consecutive patients intended to undergo lower limb revascularisation surgery were enrolled to these four studies on which this thesis is based. Study I also included aortic surgery procedures. Only 20-30% of the patients were excluded from the study. The main reasons for exclusion were as follows: patient was undergoing urgent surgery or patient was not asked to participate to the study. We believe that the high participation rate of consecutive patients ensures that the results of this study can be generalised.

Patients undergoing aortic surgery procedures were not included to Studies II, III and IV. The rationale of excluding these patients was that the number of aortic surgery procedures was quite low in Study I and the incidence of SWI related to aortic surgery is lower than with lower limb revascularisation surgery.

6.3 EVALUATION OF METHODS
The surgical methods and procedures used in our studies are generally accepted and commonly used. Imaging technique changed during the study period; angiography was performed mainly by using the conventional digital subtraction technique during Study I and by using magnetic resonance imaging during Studies II, III and IV.

Studies I and II were prospective studies and Studies III and IV were randomised controlled trials. Studies I, III and IV were multicenter studies and Study II was single-center
study. Studies II and IV were investigator-blinded and Study III was double-blinded. The calculating of sample size was performed when designing Studies III and IV in order to achieve adequately powered sample size to allow clear conclusions.

6.4 INCIDENCE AND RISK FACTORS FOR SURGICAL WOUND INFECTION AFTER LOWER LIMB VASCULAR SURGERY (I)

In our study, the incidence of SWI after abdominal aortic or lower limb vascular surgery was 27 % which was high compared with most previous reports. The incidence of SWI has ranged between 3.5 % and 32 % according to prospective studies (Richet et al 1991, Chester et al 1992, Josephs et al 1993, Murphy et al 1995, Kent et al 1996, Childress et al 2007, Ploeg et al 2009, Virkkunen et al 2009, Linni et al 2012) The high wound infection rate in our study is probably owing to our determination of SWI. Some studies (Himbeeck et al 1992, Josephs et al 1993) have defined a wound complication an infection only if there is a positive culture from the wound. We classified a wound complication as an infection if there were signs of infection even though the culture was negative. In fact, 29 % of infected surgical wounds in our study had a negative culture. On the other hand, an incidence of SWI as high as 43% after lower limb bypass surgery with graft placed subcutaneously has been reported (Blankensteijn et al 1996).

According with earlier studies (Richet et al 1991, Pounds et al 2005) we found infrainguinal surgery to be an independent predictor of SWI. The explanation for this might be reduced peripheral tissue perfusion and decreased tissue oxygenation.

Obesity was also the risk factor for SWI in our study. The predictive value of obesity has been demonstrated also in previous studies (Lee et al 2000, Patel et al 2007). It has been shown that surgical wound hypoxia and tissue hypoxia are both common in obese patients (Kabon et al 2004), and the presence of hypoxia could predispose the patient to SWI. Another reason for the high incidence of SWI in obese patients could be their richer bacterial skin flora.

The angiography puncture site within the operation area was the third independent predictor of SWI in our study. An elevated incidence of postoperative wound complications in the groin area has been demonstrated to be related to trans femoral arteriography in one previous study (Landrenau and Raju 1981), but this has not been confirmed in later studies (Himbeeck et al 1992, Josephs et al 1993).

Unexpectedly redo surgery was related to smaller number of SWI. One explanation for this surprising finding is that the upper arm vein or the opposite side lower extremity vein is used more often as a graft in the re-operation than in the primary operation. In this study, the ipsilateral saphenous vein was used as a graft in 34% of cases in redo surgery and in 92% of cases in the primary operation. In other words, there were no extensive surgical wounds in the ischaemic lower extremity if the vein graft had been taken from contralateral lower limb or upper arm.

The presence of an open extremity lesion has revealed to be a significant risk factor for developing of SWI (Josephs et al 1993, Ott et al 2012). In our study, neither the presence of ischaemic ulcer nor skin bacterial colonisation was found to be a risk factor to SWI.

Thirty-day mortality rate was 6%. Our finding is in concordance with a previous population-based study with 3.7 million surgical procedures which revealed that the mortality is highest (5.6%) after vascular surgery procedures compared to other surgical specialities (Noordzij et al 2010). The high mortality rate reflects the fact that most patients undergoing vascular surgery today are elderly and suffer from various co-morbidities and thus have many risk factors for major surgery.
Post-operative hyperglycaemia was reported to be a risk factor for post-operative infections in patients who underwent coronary artery bypass grafting (McAlister et al 2003). In our study, no association was found between postoperative hyperglycaemia and SWI.

In agreement with earlier studies, the leading pathogen was Staphylococcus aureus, found in 14 (29%) of infected wounds (Himbeeck et al 1992, Josephs et al 1993, Lee et al 2000, Pounds et al 2005). Methicillin-resistant Staphylococcus aureus (MRSA) was not isolated from any of the infected surgical wounds in our study. Other reports have shown MRSA to be leading causative agent for SWI (Pounds et al 2005, Lee et al 2000). At present, MRSA is not a major causative agent in any of the SWI encountered in eastern Finland where this study took place.

Overall, 96% of the surgical wound infections were healed. There was one major amputation but no deaths attributable to SWI. An earlier study with SWI rate of 11% found that 17% of SWI resulted to major amputation, and 7% of patients with SWI died as a consequence (Pounds et al 2005). In that study 66% of infections were graft infections whereas in our study only 6% of SWIs were graft infections.

SWI increased the cost of vascular surgery by €3,320 per infected patient. This amount does not include costs of the antibiotic treatment and, therefore, the final monetary value would be even greater. The postoperative use of antibiotics was very heterogeneous and thus difficult to estimate. One other study published around fifteen years ago calculated that the average cost for one surgical wound complication after vascular surgery procedure was €405 (Kent et al 1996).

According to Cochrane Collaboration, it is evident that antibiotic prophylaxis can reduce the risk of SWI after arterial reconstruction (Steward et al 2007). There is no evidence that continuing the antibiotic prophylaxis for longer than 24 hours confers any benefit (Steward et al 2007). In this study, a single dose of 3g of cefuroxime was administered before incision. If the operation took more than 4 hours or blood loss was over 1,500 ml, another dose of 1.5g of cefuroxime was provided. When considering peripheral vascular surgery procedures, there is no scientific evidence that a 24-hour regimen of antibiotic prophylaxis would be any more effective than the type of prophylaxis we used. There is also little guidance concerning the appropriate dose of antibiotic prophylaxis for obese patients (Edminston et al 2008).

There are some strategies to prevent SWI: meticulous surgical technique, basic skin cleanliness, and operating theater antisepsis procedures. Reduced operating time, placing the graft in the subfascial rather than subcutaneous position and applying silver-coated wound dressing may also confer some advantages (Blankensteijn et al 1996, Chang et al 2003, Childress et al 2007). Using MRI angiography and other non-invasive imaging techniques for an evaluation of peripheral artery disease might decrease the incidence of SWI. Landreneau and colleagues stated that the incidence of wound complication was lower if surgery was carried out within 24 hours after an arteriography or if there was a delay of 7 days or more. However, patients with critical ischaemia are not able to await surgery for over a week. Therefore a hybrid treatment involving an open surgery and an endovascular procedure for the patients with critical ischaemia might decrease the risk of SWI.

We conclude that surgical wound infection after vascular surgery is a frequent complication associated with increased morbidity and significant additional costs. The independent risk factors for SWI after an abdominal aortic and a lower limb vascular surgery seem to be infrainguinal surgery, obesity and an angiography injection site within the operating area. In this study redo surgery seemed to be protective against SWI. Further research will be required to identify if there are interventions that can reduce the risk of SWI.
6.5 BACTERIAL FLORA OF SURGICAL SITE IN PATIENTS UNDERGOING LOWER LIMB VASCULAR SURGERY (II)

The incidence of SWI after lower limb vascular surgery was 21% in our study. The main result of this study is that perioperative bacterial load is a significant risk factor for development of SWI. Similar results have been observed in two earlier studies, which found peri- and postoperative bacterial load to increase the risk of wound complications after dermatologic and plastic surgery (Lineaweaver et al. 2011, Saleh et al. 2011). The difference between those studies and ours is that instead of wound complication, we used wound infection as an outcome.

In contrast, a study with 609 neurosurgical patients did not find any correlation between intraoperative bacterial load and postoperative infection (Cronquist et al. 2001). In that study samples were taken only during surgery not postoperatively. However, we particularly found that the high bacterial load at the second postoperative day increases the risk of SWI. In addition, there was no significant relationship between high bacterial colonization perioperatively and the development of SWI.

Perioperative bacterial load independently increases the risk of SWI although only in 13 (62%) of cases, the same bacterial isolates were found from the perioperative or postoperative study samples and from the infected wounds. In the wound healing process, bacteria and debris are phagocytosed and removed by neutrophils during the inflammatory phase, which begins within 24 hours after injury (Diegelmann and Evans 2004). Proliferative phase follows and overlaps with the inflammatory phase, and is characterized by epithelial cells' migration across the new tissue to form a barrier between the wound and the environment (Diegelmann and Evans 2004). Until the complete epithelialisation has created the bacterial barrier, a wound may become colonized by bacteria. We suggest that if there is a large amount of any bacteria in surgical wound, the phagocytosis by neutrophils is not effective to prevent SWI during the period of wound healing when complete re-epithelialisation has not yet occurred. In other words, during the inflammatory and proliferative phase of wound healing the number of bacteria rather than bacterial species seems to be important in the development of SWI.

High bacterial growth of surgical wound predicts the development of SWI. Quantitative measurement of bacterial growth will not, however, be a screening method for infections, because by the time the bacterial samples analysis is performed the wound infection already exists. Instead in future, more prospective studies are warranted to test hypotheses about methods to decrease the bacterial load of the wound. One of such methods could be a wound washing with antiseptic agents postoperatively.

Diabetes and infrainguinal surgery were other independent risk factors for the development of SWI. The predictive values of diabetes and infrainguinal surgery have been demonstrated also in other studies (Richet et al. 1991, Josephs et al. 1993). Likewise in Study I, we found redo surgery to be protective against SWI. The explanation for this surprising result might be that vascular prosthesis was used more often as a graft at redo surgery, which means that there were no long vein harvesting incisions. In this study, prosthetic graft was used in 18 (62%) of 29 redo procedures.

In agreement with earlier studies coagulase-negative staphylococci were the predominant bacteria isolated from the study samples followed by Corynebacterium spp. and Propionibacterium spp. (Cronquist et al. 2001, Lineaweaver et al. 2011, Saleh et al. 2011). And, the leading causative agent for SWI was Staphylococcus aureus found in 52% of the infected wounds (Calligaro et al. 1994, Pounds et al. 2005).

We conclude that high bacterial load of surgical wound increases the risk of SWI after lower limb vascular surgery. Further research will be required to find methods to decrease the wound bacterial load postoperatively.
6.6 EFFECT OF TRICLOSAN-COATED SUTURES IN PREVENTION OF SURGICAL WOUND INFECTION AFTER LOWER LIMB VASCULAR SURGERY (III)

We report the result of a prospective, randomised, double-blinded, multicenter trial assessing the effect of triclosan-coated sutures on the incidence of SWI after lower limb vascular surgery. The surgical incisions were closed with the same technique in both groups. In the study group both subcutaneous and intracutaneous sutures were triclosan-coated. The main result of our trial is that wound closure with triclosan-coated sutures does not reduce the risk of SWI. *In vitro* preclinical studies have demonstrated that triclosan-coated polyglactin 910 antimicrobial sutures inhibit the growth of several bacteria including *Staphylococcus aureus*, *Staphylococcus epidermidis*, methicillin-resistant *Staphylococcus aureus*, *Enterococcus faecalis* and *Pseudomonas aeruginosa* (Rothenburger et al 2002, Edminston et al 2006). In our study the most common causative bacterial agents in the development of SWI were staphylococcal species, enterococcus and pseudomonas aeruginosa, with no difference between the study and control groups in the percentage of each causative bacteria. This demonstrates that in clinical use among vascular-surgery patients triclosan-coated sutures do not inhibit the growth of these bacteria.

Nine other prospective randomised trials have assessed the efficacy of triclosan-coated sutures in the prevention of SWI with divergent results. In accordance with our result, three studies with patients undergoing breast surgery found the use of triclosan coated sutures not to reduce the risk of SWI (Deliaert et al 2007, Williams et al 2011, Zhang et al 2011). Furthermore, studies that compared triclosan-coated and non-triclosan coated subcutaneous or fascial sutures in the closure of abdominal wounds after appendicectomy and colorectal surgery, and after neck cancer reconstruction did not find any difference in the incidence of SWI between groups (Mingmalairak et al 2009, Baracs et al 2011, Chen et al 2011). The feasibility of triclosan-coated sutures was tested in a study with pediatric patients undergoing various surgical procedures. The authors found the incidence of postoperative pain to be statistically reduced when triclosan-coated sutures were used compared to non-triclosan-coated suture use. However, the use of triclosan coated suture did not have an affect to the incidence of SWI (Ford et al 2005).

In contrast, there are two prospective studies that have indicated that triclosan-coated sutures reduce the risk of SWI. The effect of triclosan-coated sutures in the prevention of SWI after implantation of cerebrospinal fluid shunting devices was tested in 61 patients. The incidence of shunt infection was statistically lower in the triclosan group than in the control group (Rozelle et al 2008). However, the sample size in this study is far too small, and thus this study is underpowered to draw any conclusions on the effect of triclosan-coated sutures on the risk of SWI for this procedure.

Galal and colleagues reported a significant reduction of the incidence of SWI when surgical incisions were closed with triclosan-coated sutures. In contrast to our study, they had a heterogeneous study population of surgical patients: all patients undergoing different surgical procedures were included in the study. The surgical categories varied from vascular surgery, plastic surgery, gastrointestinal surgery and thyroidectomy to smaller lipoma extirpation. Neither the method of closing the surgical incision nor the antibiotic prophylaxis was standardised. Furthermore, they conducted a multicenter study but reported the results of a single center only (Galal et al 2010). In our study, only peripheral vascular surgery procedures were included and both antibiotic prophylaxis and method of closing surgical wound were standardised.

We conclude that wound closure with triclosan-coated sutures does not reduce the risk of SWI after lower limb vascular surgery.
6.7 EFFECT OF SUPPLEMENTAL POSTOPERATIVE OXYGEN IN PREVENTION OF SURGICAL WOUND INFECTION AFTER LOWER LIMB VASCULAR SURGERY (IV)

This randomised trial suggests that supplemental inspired oxygen after lower limb revascularisation surgery might reduce the incidence of SWI. Furthermore, we found that supplemental inspired oxygen significantly reduces the risk of SWI when only an inguinal incision is performed.

The amount of oxygen available to the tissues, called oxygen delivery, is determined by cardiac output and arterial blood oxygen content (Nichols and Nielsen 2010). The oxygen content of arterial blood is the sum of the oxygen carried by haemoglobin and the amount dissolved in the plasma. Under normal physiologic conditions, less than 2% of the arterial oxygen content is dissolved in the plasma (Harder and Boshkow 2010). Increasing the amount of oxygen in the inspiratory gas increases the partial pressure of oxygen in the blood ($P_O_2$). However, in normoxemic states this mainly increases the amount of oxygen dissolved into the plasma and leads only to a small increase in arterial oxygen content, because the haemoglobin oxygen saturation approaches 100% already at baseline. Thus it seems plausible that supplemental oxygen might be of no benefit for non-hypoxemic patients. On the other hand oxygen tension plays a major role in the transport of oxygen to the cells. The pressure gradient is responsible for the diffusion of oxygen from the capillary blood into the cells, from one cell to another, and within the cells into mitochondria (Loiacono and Shapiro 2010). Increasing $P_O_2$ with supplemental oxygen increases this pressure gradient. This might improve the diffusion of oxygen particularly when the diffusion distances are long or regional blood flow is suboptimal, which may be the case with patients suffering from severe arteriosclerosis.

Oxygen therapy can be associated with adverse effects. Long-term exposure to high-dose oxygen causes pulmonary oedema and interstitial fibrosis and may result in severe lung injury (Deneke and Fanburg 1980, Aoki et al 2008). On the other hand, low-flow supplemental oxygen is regarded as quite safe (Benditt 2000). In a recent study on guinea pigs, two-week exposure to 40% oxygen caused transient damage to some pulmonary epithelial functions and affected collagen metabolism, but these changes were successfully compensated for during the following weeks, despite continuous exposure to 40% oxygen, and no permanent injury was detected. On the other hand, exposure to 90% oxygen caused rapid and progressive destruction of the lungs (Aoki et al 2008). The amount of supplemental oxygen used in our study is well below the amounts that are regarded in the literature as potentially harmful to the lungs.

With patients suffering from COPD supplemental oxygen may depress ventilation and induce hypercapnia (Robinson et al 2000). This effect is generally small in magnitude when low-flow oxygen is used (Benditt 2000). Nevertheless, to avoid this potentially detrimental effect, we excluded patients with COPD and a known tendency for hypercapnia. It is still possible that patients with severe COPD would also benefit from supplemental oxygen after lower limb vascular surgery. This question is unanswered so far and we want to stress that whenever oxygen is administered to a COPD patient, he/she should be carefully monitored with the risk of hyperoxia-induced hypercapnia in mind.

The average toe tip oxygen saturation, which was measured every four hours after surgery for the first two postoperative days, did not differ between the study and the control groups. However, the oxygen saturation was higher in the study group at two time points: 24 and 28 hours after surgery. This confirms that supplemental postoperative oxygen is helpful in pre-
venting transient hypoxemia, which is in accord with our suggestion that improving tissue oxygenation with supplemental oxygen might reduce the incidence of SWI.

Several randomised controlled trials with other types of surgery have been conducted to study the association between supplemental oxygen and the risk of SWI. Four randomised controlled trials have shown that supplemental perioperative oxygen reduces the risk of SWI. In two of these studies elective colorectal surgery patients were included, one study included major non-cardio-thoracic surgery patients and, one included patients undergoing surgery for acute appendicitis. (Grief et al 2000, Belda et al 2005, Myles et al 2007, Bickel et al 2011). In contrast, one trial with major intra-abdominal surgical patients found that supplemental oxygen perioperatively increases the risk of SWI (Pryor et al 2004). The main difference between our study and the study by Pryor and colleagues was that in our study the patients in the supplemental oxygen group received 30% oxygen for the first 24 hours after an operation and then oxygen via nasal cannula for the next 24 hours. In the study by Pryor and colleagues the study group received 80% oxygen and the control group received 30% oxygen perioperatively and for the first two postoperative hours. The study by Pryor and colleagues has been criticised because the study groups were not standardised, which led to the following significant differences: patients receiving 80% inspired oxygen had higher BMI, lost more blood and required more fluid replacement than patients receiving 30% inspired oxygen.

Furthermore two studies with patients undergoing abdominal surgery and two studies with women undergoing caesarean delivery found no difference in the incidence of SWI in patients receiving supplemental oxygen during the perioperative time (Mayzler et al 2005, Gardella et al 2008, Meyhoff et al 2009, Scifres et al 2011).

A meta-analysis of five randomised controlled trials with 3,001 patients studied the effect of perioperative inspired supplemental oxygen on the development of SWI. That meta-analysis demonstrated that supplemental perioperative oxygen therapy resulted in a relative risk reduction of 25.3% (95% CI 8.1%-40.1%). The authors recommend the use of hyperoxia to reduce the rate of SWI (Qadan et al 2009). Another meta-analysis with five prospective randomised studies with colorectal surgery patients showed that supplemental oxygen did not significantly reduce the rate of SWI (OR=0.69, 95% CI 0.43,1.10). However, a significant mortality benefit was observed among patients receiving supplemental oxygen (OR 0.18, 95% CI 0.05, 0.69) (Brar et al 2011).

The incidence of SWI was 23%, which is in accordance with the result of Study I. Likewise in Study I, we classified a wound complication as an infection if there were signs of infection even though the culture was negative. In fact, 35% of infected surgical wounds in our study did not have a positive culture. The characteristics we used meet the criteria defined by the Centers for Disease Control and Prevention (CDC) (Horan et al 1992).

We conclude that supplemental inspired oxygen reduces the risk of SWI in groin incisions after lower limb vascular surgery. Further studies with larger sample sizes are warranted to find out whether supplemental oxygen reduces the risk of SWI after a lower limb vascular surgery in general, and not only after groin incisions.
7 Summary and conclusions

Based on these studies, the following conclusions can be drawn:

The incidence of SWI after lower limb vascular surgery is 22-27%. The independent risk factors of SWI are obesity, infrainguinal surgery, asthma, coronary artery disease, diabetes, current use of corticosteroids and, arteriography puncture site on the operation area. Moreover, high bacterial load of surgical wound on 2nd postoperative day independently predicts the increased risk of the development of SWI.

The average additional hospital cost of SWI is €3,320. The costs included are additional days of hospitalisation, operating department fees for re-exploration and revision, visits to outpatient clinic, outpatient nursing and rehabilitation.

The use of triclosan-coated sutures does not have an effect on incidence of SWI after lower limb vascular surgery.

The inspired supplemental postoperative oxygen does not significantly reduce the risk of SWI after lower limb vascular surgery. However, the subgroup analysis revealed that the postoperative inspired supplemental oxygen may decrease the risk of SWI after lower limb vascular surgery in patients with inguinal incision only.
8 References


Benditt JO. Adverse effects of low-flow oxygen therapy. *Respir Care* 2000;45:54-61.


Heal CF, Buettnner PG, Cruickshank R et al. Does single application of topical chloramphenicol to high risk sutured wounds reduce incidence of wound infection after minor surgery? Prospective randomized placebo controlled double blind trial. *BMJ* 2009;338:


Levine NS, Lindberg RB, Mason SD, Pruitt BA. The quantitative swab culture and smear: a quick, simple method for determining the number of viable aerobic bacteria on open wounds. *J trauma* 1976;16:89-94.


Meakins JL and Masterson BJ. Prevention of postoperative infection. 2005 WebMD.

Mekako AI, Chetter IC, Coughlin PA, Hatfield J, McCollum PT. Randomized clinical trial of co-amoxiclav versus no antibiotic prophylaxis in varicose vein surgery. *Br J Surg* 2010;97:29-36


Pharmacal Fennica 2010.


Sørensen LT, Toft BG, Rygaard J, Ladelund S, Teisner B, Gottrup F. Smoking attenuates wound inflammation and proliferation while smoking cessation restores inflammation but not proliferation. *Wound Repair Regen* 2010;18:186-92.a


Vascular surgery. W.B. Saunders company 2000. Edited by Rutherford RB


Webster J and Osborne S. Preoperative bathing or showering with skin antiseptics to prevent surgical site infection. *The Cochrane Library* 2011;1.


Peripheral vascular surgery procedures are usually performed in order to improve blood supply to extremities. Patients undergoing these procedures suffer from critical ischaemia or claudication. Surgical wound infection (SWI) is the most common complication after lower limb vascular surgery increasing the affected patient’s risk of major amputation as well as mortality. In this study, the incidence of SWI was 22-27% and, the average cost attributable to SWI was €3,320. Obesity, infrainguinal surgery, puncture site of arteriography on the operated area, asthma, coronary artery disease, use of corticosteroids, diabetes, and the high bacterial load of the surgical site at the second postoperative day increased the risk of the development of SWI after lower limb vascular surgery.