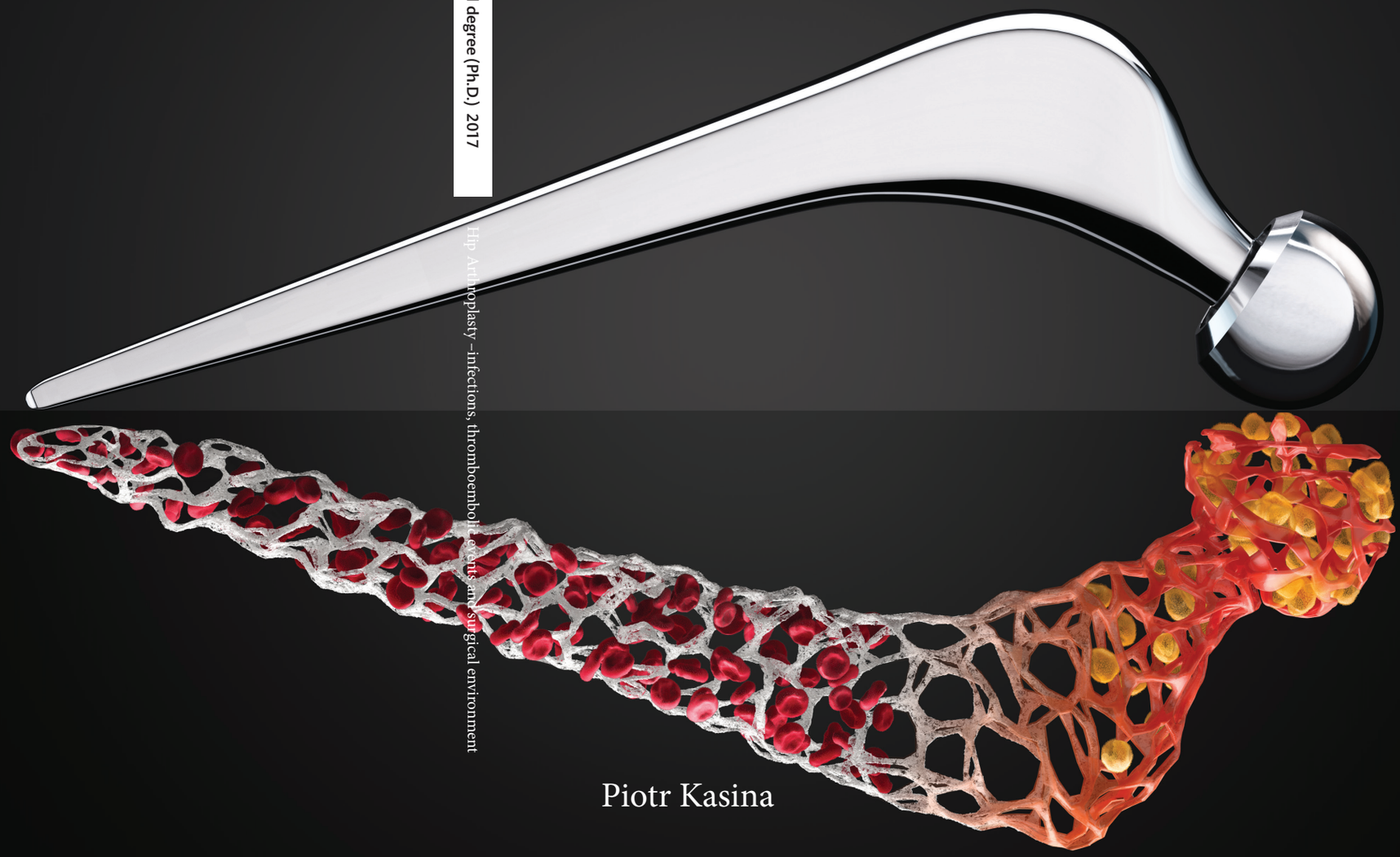
Thesis for doctoral degree (Ph.D.)
2017

Hip Arthroplasty

-infections, thromboembolic events and surgical environment



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Hip Arthroplasty –infections, thromboembolic events and surgical environment

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Hip Arthroplasty

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To my beloved family

ABSTRACT

Background

Each year hip arthroplasties increase the quality of life for over 1 million patients worldwide. Although the complication rates are low, the absolute numbers are rising as the numbers of procedures increase. Prosthetic joint infections resulting from intraoperative contamination are regarded as compensable by the Swedish patient insurance. Healthcare personnel are obliged to inform patients about their injury and the possibility to claim it. In this thesis aspects of two complications after hip arthroplasty are discussed. Both have gone from being relatively frequent complications of uncommon procedures in the early days of hip arthroplasty, to infrequent complications of common procedures, resulting in many suffering patients. Prosthetic joint infection (*Study I – III*) is the most feared complication and venous thromboembolism is the most common medical complication, (*Study IV*).

Methods

Studies I and II are based on outcomes of operations performed at the Department of Orthopaedics, Stockholm South General Hospital (Södersjukhuset). Studies III and IV cover the nationwide population of Sweden and are based on data from national quality and healthcare registers.

Study I: 3 884 patients operated between 1996 and 2005, due to degenerative hip disorder or hip fracture (primary and secondary fracture prostheses) were analysed for the incidence, microbiology and outcome of prosthetic joint infection after hip arthroplasty.

Study II: Air quality in the operating room was evaluated through comparison of three clothing systems through 244 measurements of colony forming units per square meter, during 37 operations.

Study III: A national cohort of prosthetic infections after total hip arthroplasties in patients operated between 2005 and 2008 has previously established. We analysed the number of filed patient claims in 441 infections and examined the incidence and outcome (accepted, rejected, approved disability).

Study IV: Low molecular weight heparins and new oral anticoagulants were compared as thromboprophylaxis after 32 663 elective hip arthroplasties, through determination of effectiveness as incidence of venous thromboembolic events and assessment of safety by analysis of bleedings, reoperations and mortality.

Results

Study I: The infection rates for degenerative hip disorder and primary and secondary fracture prostheses were 0.4%, 2.1% and 2.5% respectively. The patient factors associated with a significantly increased risk for developing a surgical-site infection were both fracture indication for surgery and male gender. Staphylococcus Aureus and Coagulase-Negative Staphylococci dominated as microbiological agents. Treatment of 27 (44%) patients resulted in permanent resection arthroplasty, of which 22 (81%) were fracture patients.

Study II: Compared with the two other reusable suits, the significantly lowest values of colony forming units were observed with the single-use polypropylene BARRIER® Clean Air Suit.

Study III: 329 (75%) of patients did not file a claim of injury to LÖF and of those 112 that did, 108 (96%) were accepted as eligible for compensation. Patients' age above 72 years and fracture diagnosis were the only significant factors associated with not filing a claim of injury.

Study IV: Compared to low molecular weight heparins, new oral anticoagulants reduced the risk of venous thromboembolic events with more than 50% with simultaneously remained safety profile. In the subset of patients treated with low molecular weight heparins no significant difference with regards to the studied outcomes was observed.

Conclusion

Patients with fractures of the neck of femur, treated with primary or secondary fracture prostheses, have a greater risk of infection and display worse outcomes compared with patients operated due to degenerative hip disorders. Additionally, among the overall low rate of patient claims, fracture patients stand out with an even greater share of non-claimants (87%). Healthcare personnel should increase their knowledge about LÖF. Improving air quality is difficult in existing facilities. Evaluation of clothing in real-life surgical environments can, by decreased counts of airborne bacteria, result in better prevention of infections. Compared to low molecular weight heparins, thromboprophylaxis with new oral anticoagulants extending for a minimum of 28 days is a superior regimen for the majority of patients undergoing elective primary total hip arthroplasty.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following studies, which can be found at the end of this work and are referred to in the text by their roman numerals (Studies I-IV):

I. **Prosthetic joint infection following hip fracture and degenerative hip disorder: a cohort study of three thousand, eight hundred and seven consecutive hip arthroplasties with a minimum follow-up of five years.**
Richard Blomfeldt, Piotr Kasina, Carin Ottosson, Anders Enocson, Lasse J Lapidus
Int Orthop. 2015 Nov;39(11):2091-6. doi: 10.1007/s00264-015-2989-y.

II. **Comparison of three distinct clean air suits to decrease the bacterial load in the operating room: an observational study.**
Piotr Kasina, Ann Tammelin, Anne-Marie Blomfeldt, Bengt Ljungqvist, Berit Reinmüller, Carin Ottosson
Patient Saf Surg. 2016 Jan 7;10:1. doi: 10.1186/s13037-015-0091-4.

III. **Patient claims in prosthetic hip infections -a comparison of nationwide incidence and patient insurance data.**
Piotr Kasina, Anders Enocson, Viktor Lindgren, Lasse J Lapidus
Submitted

IV. **Thromboprophylaxis in total hip arthroplasty; nationwide prescription pattern and outcome.**
Piotr Kasina, Alexander Wall, Lasse J Lapidus, Ola Rolfson, Johan Kärrholm, Szilard Nemes, Bengt I Eriksson, Maziar Mohaddes
Manuscript

CONTENTS

LIST OF ABBREVIATIONS

ATC-code	Anatomical Therapeutic Chemical code
ASA	Acetylsalicylic acid
ASA-score	American Society of Anaesthesiologists score
BMI	Body mass index
CAS	Clean Air Suit
CFU	Colony forming units
CI	Confidence interval
DVT	Deep vein thrombosis
HS	Haematogenous spread
IC	Intraoperative contamination
ICD	International Classification of Diseases, 10th version
HA	Hemiarthroplasty
HR	Hazard ratio
LAF	Laminar airflow
LISA	Statistics Sweden's longitudinal integration database for health insurance and labour market studies
LMWH	Low molecular weight heparin
LÖF	Landstingens Ömsesidiga Försäkringsbolag
NOAC	New oral anticoagulants
OR	Odds ratio
PE	Pulmonary embolism
PIN	Personal identity number
PJI	Prosthetic joint infection
SHAR	Swedish Hip Arthroplasty Register
SNPR	Swedish National Patient Register
SPDR	Swedish Prescribed Drug Register
SSI	Surgical-site infection
THA	Total hip arthroplasty
TP	Thromboprophylaxis
VTE	Venous thromboembolism

1 INTRODUCTION

1.1 HISTORICAL REVIEW

1.1.1 Thromboembolism

The history of complications and concepts of this thesis begins with Abu Ali al-Husayn ibn Abd Allah ibn Sina (980 - 1037), known as Avicenna in Europe, a Persian physician, philosopher and scientist, who completed his book The Canon of Medicine in 1035[1]. It set the standards for medicine and was used as a textbook for over 700 years. Avicenna described numerous and various conditions and treatments, therein also a partial description of the clinical picture of deep vein thrombosis (DVT) and recommended open surgical thrombectomy[2]. He also cautioned that *"care should be taken while cleaning the veins from the obstructing material or the particles might migrate to the upper organs*".

In 1271 Guillaume de Saint Pathus reported what is believed to be the first description and treatment of DVT in "La vie et les miracles de Saint Louis"[3]. A young cobbler, Raoul of Normandy, suffered unilateral pain and swelling of his right calf that progressed proximally to the thigh. He was initially advised to wait but developed an ulcer and was exposed to several unsuccessful treatment attempts. Eventually advice was given to visit the tomb of King Saint Louis, where Raoul spent several days praying to the saint. During his stay, he collected the dust from the stone covering the tomb and applied it directly on the ulcer. This cured Raoul´s condition and he lived for another 11 years.

During the Renaissance, pregnancy was the only reported cause of DVT and was considered as a consequence of retention of "evil humors" or menstrual blood[4]. Discharge of these humors was performed by bloodletting, a popular treatment method of that time[5]. On the contrary, the cause of postpartum DVT was believed to be retention of unconsumed milk ("milk leg") and breast-feeding was encouraged as prophylaxis against DVT[3]. In 1676, Richard Wiseman hypothesized why blood might clot by describing two of the three factors that later came to constitute Virchow's triad, stasis and hypercoagulability: *"Blood, which being transmitted into the veins, either by reason of the depending of the part, or from some other pressure upon the vessel, or else by its own grossness, proves unapt for circulation. Then instead of continuing its current to the other parts, it stops in the place and coagulates"*[6]. In 1784 James Hunter performed the first venous ligations above thromboses, to prevent extension of clots[7]. However traditional treatments as bloodletting via application of leeches were generally considered as more effective to relieve congestion and inflammation[8]. Generally before the discovery of heparin, treatment for DVT mainly relied on bed rest with limbs in iron splints to prevent the thromb from migration, elevation of the involved leg to favour venous return and application of heat to reduce vasospasm and increase collateral circulation[7].

In 1856 Rudolf Ludwig Virchow described the famous triad of factors contributing to development of venous thrombosis: hypercoagulability, stasis and vascular injury. It is doubtful however if the triad was originally described as presented today, in contemporary medical literature. Virchow focused his research on pulmonary embolism (PE) and coined the terms "embolism" and "thrombosis" but it took almost one hundred years before he was credited for the triad explaining the formation of thrombi[6].

In 1872, Trendelenburg, founder of the German Surgical Society, developed the left parasternal thoracotomy for acute treatment of PE, accessing the pulmonary artery for removal of the embolus. His pupil, professor Kirschner, could later report a successful procedure in 1924, yielding widespread enthusiasm. During the following decade 300 acute pulmonary embolectomies were performed in Germany with only 10 survivors[9].

The path of non-surgical treatment and prophylaxis of thromboembolism is complex. Already Hippocrates, in ancient Greece, recommended chewing salicylate-containing willow leaves for analgesia in childbirth. Description of salicylates can also be found throughout the Middle Ages and their use is likewise reported by Europeans in the New World, on the advice of Native Americans[10]. Charles Gerhardt in France was the first to synthesize acetylsalicylic acid (ASA) in 1853, but the agent was initially ignored. Eventually the salicylate trail led to the Bayer Company in Germany that introduced the analgesic and antipyretic drug commercially in 1899, under the name aspirin[10]. In 1967 Weiss discovered the inhibition of platelet activation[11]. Following, in 1971, Vane published his findings of aspirin´s inhibition of prostaglandin synthetase[12] and was later awarded the Nobel Prize in Medicine. Simultaneously clinical reports proved the drugs efficacy in prevention cerebral transient ischemic attacks[13]. The following trials in the 70s and 80s confirmed ASA prophylactic properties against venous thromboembolism (VTE)[14,15].

Heparin was discovered in 1916 by a medical student, McLean, and his supervisor, Howell, continued the work of purification[16]. Finally three teams from Toronto, Stockholm and Copenhagen were working independently to further isolate, purify and achieve a reliable and stable substance[10]. In 1935 Erik Jorpes purified and solved the chemical structure in Stockholm[17]. Later the same year Hedenius and Wilander tested heparin on human volunteers and Clarence Crafoord started treatment of general surgery patients at Sabbatsberg Hospital in Stockholm[18]. This led to fast spread of this effective thromboprophylaxis (TP), which later also played a significant roll in the broader introduction of hip arthroplasties. After the discovery of heparin fractions' higher ratio of anti-factor Xa activity, synthetic preparation of low molecular weight heparin (LMWH) begun in the 70s. LMWHs were introduced in Europe in the 80s and were granted approval in the United States in 1993[10].

As heparin was introduced, coumarin was also discovered in 1940s. It started in 1921 with a mysterious haemorrhagic disease of cattle after ingestion of spoiled sweet clover in North Dakota and Alberta. Karl Paul Link linked the disease to coumarin and described its properties. In 1940, he continued with developing his well-known rodenticide. After an unsuccessful suicide attempt of a navy inductee, Link realized that this drug was not as toxic as initially believed[19]. The complementary mechanism of fast acting heparin and the slower coumarin allowed for sequential use in DVT treatment, already described in the late 1940s[20].

The introduction of new oral anticoagulants (NOAC) represents the most recent advancement in TP. The first approvals for drugs in this group, dabigatran and rivaroxaban, were granted in 2008 in Europe and two years later in the United States.

1.1.2 Hip arthroplasty

Generally hip arthroplasties are classified based on two aspects. The first classification is based on the implanted components; total hip arthroplasty (THA) replaces both the head of femur and the pelvic acetabulum with separate components, whereas in hemiarthroplasty (HA) only the head of femur is replaced. The second classification is based on the method of fixation. In cemented fixation bone cement made of polymethyl methacrylate is used as a mantle interface between the bone and the implant. Uncemented implants are instead covered with special surface coatings, which facilitates the bone to remodel and bond to the implant. Both cemented and uncemented arthroplasties have proven their excellent results and long-term survival[21,22] and the choice of fixation depends on both patient factors and the preference of individual surgeons.

However, the era of surgical treatment of painful osteoarthritis started in the late 19th century with an interpositional arthroplasty. Various tissues, including fascia lata, skin, and even submucosa of pig´s urinary bladders, were placed between the articulating surfaces of the hip joint in attempt to relief pain[23]. Marius Nygaard Smith-Petersen was a Norwegian born surgeon that heralded the era of hip arthroplasty. He emigrated to the USA at age 16, where he studied medicine and received his surgical training. In 1923 he introduced his original arthroplasty design, a hollow hemisphere of glass that could fit over the femoral head. The intension was to stimulate cartilage regeneration on both sides and remove the glass mould after the cartilage had been restored. The glass could not withstand the weight bearing stresses and experimentation with various materials followed in the 1930s. After suggestion from his dentist, Smith-Petersen developed the Vitallium cup in 1938 and perfected the operation through design of instruments and techniques[24].

The French brothers, Jean and Robert Judet, introduced the first HA in 1940s. They removed the femoral head and replaced it with one made of acrylic resin. Early results were brilliant but the resin was also too weak and the fit was not perfect, which resulted in subsequent failure[25].

Philip Wiles overcame some of these difficulties with the first THA. The stainless-steel acetabular cup and femoral head fitted each other and the head was anchored in a lateral plate through a sliding stem. Due to reduced movement and bone absorption, Wiles could only report satisfactory results in 2 out of 8 patients[25].

In the 50s many surgeons experimented with different designs and materials. The most famous is the Austin Moore HA prosthesis[26], which through modifications, is still used today in fracture surgery of the neck of femur.

Sir John Charnley is considered to be the father of modern hip arthroplasty. In 1961 he opened the well-known hip centre in Wrightington and his revolutionary principles of the low friction arthroplasty concept were published the same year[27]. Charnley's three major contributions to the evolution of THA were the idea of low friction torque between the components, rigid fixation of component to bone through acrylic cement and the use of high-density polyethylene as bearing material[23]. His structured follow-up of patients and meticulously collected data enabled further development in surgical technique, implant design and postoperative care[28].

Due to the considerable amount of surgical-site infections (SSI), Charnley was also devoted to prevention of infections and improving air quality of the operating room[29]. However not everyone accepted Charnley's concepts and early failures of cemented stems were frequent. The observed osteolysis led to the assumption that premature loosening was related to the so-called cement disease[30]. In retrospective, it is believed that this frequent phenomenon was due to the initially deficient cementation technique. This led to further development of uncemented components[23]. Nevertheless Charnley's work is still highly relevant today and constitutes the basis of modern hip arthroplasty design and surgery.

Many years of development and improvement made the long survival of today's hip arthroplasties possible. Each year the procedure brings an increased quality of life to over 1 million patients worldwide[31]. The main indication for surgery is still primary osteoarthritis but many other conditions are also threated with arthroplasties. Therefore THA can be considered "the operation of the century"[23] and the number of annually implanted arthroplasties continues to grow[32,33]. Today´s choice of implants is almost infinite. However not every implant is used in every country and the preferences are based on traditions, experience, price and methods of assessment of their survival and outcomes.

In Sweden above 20 000 arthroplasties are performed each year, out of which 16 500 are THAs, and 4 000 are HAs[21]. The most predominant indication for THA is osteoarthritis which results in 13 700 operations per year, where as approximately 1 400 patents are operated due to an acute fracture. The remaining 1 400 are patients with femoral head necrosis, complications to previous fracture treatment, paediatric diseases, malignancies and inflammatory diseases. The HAs are mainly operated for fractures in fragile or older patients. Additionally, patients with unsuccessful outcomes of previous fracture treatments as well as fragile patients suffering from malignancies may receive a HA.

1.1.3 Airborne contamination

Florence Nightingale, an English nurse named after her city of birth, started to practice her ideas during the Crimean War in 1854. She was also a statistician and manager that realised the importance of good ventilation, hygiene, nutrition as well as organization of supplies. Nightingale observed that far more soldiers died from infections than from the wounds suffered on the battlefield. She introduced bathing of wounds with clean individual cloths and cross-contamination was reduced by separate beds. Her managing skills and efforts on hygiene resulted in a drop of mortality from 33% to 2%[34].

Around the same time Ignaz Philipp Semmelweis was gathering sanitary observations at the Allgemeine Krankenhaus in Vienna. There were two maternity clinics at this hospital. Medical students performed deliveries in the first clinic and midwifes in the second. Although the same patient population was treated and the same corridors and linen were used, the mortality rates at the first clinic exceeded the second 10-fold. The admitted street-births also had lower mortality rates, independently of the clinic of admission. The explanation of this difference in survival rates was the educational encouragement of medical students to learn from the mortuary. After the handling of corpses they would return to clinic and examine the patients. Introduction of hand disinfection before vaginal examination reduced mortality to the levels of the second clinic. Semmelweis also observed similar contamination in surgical wounds. His conclusion that doctors' hands were the carriers of diseases was not easy to accept and it took 13 years before his observations were published in 1861[35].

The discoveries of the French biologist Louis Pasteur in 1850s and 60s provided direct support for the germ theory[36] and inspired the British surgeon Joseph Lister. At that time most of the operations were followed by hospital gangrene and death was believed to be inevitable or coincidental. As in Vienna, surgeons rarely washed their hands and instruments were only wiped clean. Lister observed that infections were more prevalent in in-hospital patients and noted that more then half of patients with their bones exposed to air died. In 1867 he published his first paper on antiseptic treatment of open fractures with carbolic acid. Consequently Lister begun to sterilize instruments and hands. He developed a sterilized catgut ligature and a steam-operated carbolic acid spray for purification of contaminated air in the operating room[37].

The first observation on airborne bacteria and their influence on infection was published in 1946, based on observations during changing of dressings in a burns unit[38]. In 1960 Blower and Crew defined principles for design of ventilation: filtration of input air and adjusted air pressure gradients to force airflow from cleaner to dirtier zones[39]. In the same decade Charnley contributed with his work on clean air enclosures of glass and drapes, keeping the anaesthetist out of the clean area. He improved ventilation and introduced body suits. In the beginning of the 70s Charnley had achieved infection rates of well below 1%[40]. In 1975 Noble found that during walking 40 000 skin scales/min are released and about 10% of these carry bacteria[41]. Both aerobes and anaerobes can survive long enough to make an airborne route of infection possible[42]. The first recommendations for operating rooms were published in 1983 in UK, based to a large extend on Lidwell's studies on air quality and bacteria carrying particles. He found an association between airborne bacteria and incidence of PJI in hip and knee arthroplasties[43] and concluded that ultra clean air with less then 10 colony forming units per square meter (CFU)/m^3 together with prophylactic antibiotics prevents almost all prosthetic joint infections (PJI) in THA surgery.

1.2 BACKGROUND

1.2.1 Prosthetic joint infections after hip arthroplasty

Following aseptic loosening and dislocation of prostheses PJI is the third most frequent complication in THA surgery[21,44]. Moreover, PJIs possibly result in the highest economic burden for the healthcare systems[45,46] and cause the greatest suffering for patients[47,48]. The literature presents a great variation of incidence of PJI, ranging from 0.2% up to 9.0%[49-56]. This difference can be explained by different populations, follow up time and indications for surgery. The risk of PJI does not show a further decrease and some studies have even reported an increase[57,58]. It is difficult to explain this finding but most probably it is a multifactorial phenomenon. More fragile patients receive a hip arthroplasty today than before, which increases the risk of PJI. We have also become more aware of the serious consequences of PJI and have access to better diagnostic tools resulting in more successful diagnostics. The treatment has also become more aggressive, with consequently higher reoperation rates. Finally the increased reporting and catchment of registers in healthcare may play a role.

PJI can be classified into 3 groups, depending on the time of diagnosis. The first group, early infections, are diagnosed during the first 3 postoperative months. The second group are delayed infections occurring between 3 and 24 months after the primary operation and consequently the third group, late infections, occur beyond 24 months[59]. The early and delayed infections are most often regarded as SSIs, resulting from intra- or perioperative contamination. Similarly, late infections are often a result of haematogenous spread (HS). The type and aggressiveness of bacteria is related to the emergence of symptoms. Coagulase negative staphylococcus and staphylococcus aureus are the most common bacteria in PJI[59,60] and do not generally cause aggressive infections. This yields a diagnostic challenge. Additionally, the formation of biofilm is also an important aspect endangering curative outcome[61,62].

The treatment of PJI often includes long hospital stays with possibly several reoperations and long lasting antibiotic treatments. There is no consensus regarding preferred treatment strategies but the time of diagnosis, type of bacteria and patient factors must be taken into account. Some patients may even need removal of their implant, a resection arthroplasty[63], in order to enable resolution of the infection. Although this procedure is often followed by insertion of a new prosthesis in the so-called two-staged treatment, the patients' general condition does not always allow for the second stage, resulting in a permanent resection arthroplasty. Previous studies have reported an incidence of this outcome of up to 32%[56]. Although permanent resection arthroplasty often results in effective resolution of PJI, it is not a successful outcome for the affected patients.

The true numbers of incidence and final outcomes of PJI treatment are difficult to establish and represent a difficult challenge. A structured follow-up of patients and registers with both good coverage as well as completeness are needed[64,65].

1.2.2 Air quality in surgical environment

Orthopaedic joint implant surgery is regarded as one of the most infection sensitive procedures. Modern ventilation systems are needed to achieve good air quality through dilution and dispersion of bacteria carrying particles in the operating room[66]. Improvement of existing ventilation systems, through reconstruction or installation of new or additional components is often a significant investment. It can often be impossible to implement in older buildings, even without the economic limitations. Additional mobile laminar airflow (LAF) units can help to improvement of current ventilation systems[67]. However, in our department, their use was perceived to have a negative influence on the surgical working environment.

Better clothing systems may also help to increase the air quality. There are requirements for clothing systems as the European Standard EN 13795 of the so-called Clean Air Suit (CAS)[68] and manufacturers test their systems in standardised settings for certification purposes. This assessment is not always possible to confirm in real life settings and therefor we have to rely on certifications. Measurements carried out during movements in closed dispersal chambers[69] can assess the source strength of CASs (individually emitted CFU/s). The high physical activity in these chambers produces higher values of CFU/s than observed in the surgical environment. There is no precise knowledge of an established association between the differences of measurements of garments with different density in the dispersal chambers and the differences in the real operative conditions[70]. Thus, standardised settings do not reflect the true CFU levels in surgical environments and the desired air quality is not always met[71,72]. Different numbers of operating personnel with diverse activities and special constellations (not infrequent at multidisciplinary centres) creates inevitably highly diverse and variable surgical environments. Moreover, heat generated by both staff and medical equipment generates powerful vortex patterns even in assumed predictable settings. Different reversed airflows can create inlet jets into the operating field, between the patient and personnel[73].

Counting of particles in the air can assess air quality but the correlation to microbiological load is poor. An established method to assess the quality of air is to measure the formation of living bacteria colonies per cubic meter of air by counting CFU values[74]. This is done by a set amount of suction of air from the operating field through a filter, which is changed according to set time intervals. These filters are subsequently incubated in laboratory settings and the developed colonies of bacteria are counted to calculate CFU/m^3 values.

Current requirements of air quality in infection prone surgery are <5 CFU/m^3 with simultaneous use of CAS[75,76]. As there is yet no scientific evidence for any safe maximal values, we have to aim for even lower counts. The currently most common CASs in Sweden are reusable CASs made out of a mix of cotton and polyester fibres. Single-use suits made of polypropylene may generate lower CFU/m^3 counts[72] but create more waste and are therefor controversial in the aspect of the healthcare's policy to reduce the negative impact it produces on our environment.

1.2.3 The patient insurance scheme in Sweden

Patient insurance schemes can be grouped into two different systems, based on their legal background. The first scheme is negligence-based malpractice tort law and has three purposes: to discourage and prevent healthcare and individual physicians from practicing beyond their expertise, to punish the providers of low quality care and to compensate injured patients[77]. This scheme is internationally widespread and used in e.g. the United States and the United Kingdom. However malpractice tort law does not deliver to its expectations. Injuries are seldom persuaded and patients may need to file suits to learn whether negligence occurred[78]. Also it forces physicians to practice expensive defensive medicine[79]. The second scheme is non-tort and based on "avoidability" and preventability of patient injuries. This scheme has been practiced in Scandinavian countries for over 4 decades and Sweden pioneered the approach[80].

Everyone treated in the Swedish publicly financed healthcare system is insured against injury resulting from avoidable patient injuries. Public healthcare makes up approximately 96% of all provided healthcare in Sweden. In some areas, e.g. hip arthroplasties, this number reaches well above 99%. Infection-related injuries are compensable if the infectious agent was transmitted from an external source during the delivery of care and if the infection's rarity and severity were unexpected as assessed from the patients' past and current medical status. PJIs after hip arthroplasty surgery, resulting from intraoperative contamination (IC) and not from HS, are therefor considered as compensable injuries in Sweden.

Patients´ claims are handled by the national patient insurance company Landstingens Ömsesidiga Försäkringsbolag[81], founded in 1975 and co-owned by the Swedish 21 county councils (public healthcare). According to the Patient Injury Act all medical professions are covered by LÖF[82], with increasing number of claims annually. LÖF handled 16000 claims in 2016 and almost one third of reimbursed claims were injuries related to orthopaedic procedures[81]. Moreover cemented THA is the procedure associated with highest numbers of claims[83]. According to conditions of insurance, six types of injuries are covered, resulting from: treatment injury, technical damage, inferior diagnostics, infection, patient accidents in care and injury related to incorrect application of medications. Patients report their injuries free of charge and this must be done within ten years. LÖF then obtains full medical records before review of claims by specialists with expertise within the concerned medical field. In case the event was not avoidable and no causative relation or inferiority between given treatment and outcome is observed, LÖF can reject a claim. If the opposite is observed, LÖF subtracts a lesser deductible and compensates for the prolonged recovery time or awards pay-outs for sustained permanent disability, in accordance with Insurance Sweden consensus tables[84].

The economic compensation is non-tort, reimbursing income loss, unreimbursed medical costs and a limited compensation for pain and suffering caused by the injury. It is also blame-free for practitioners and no records are shared with regulatory authorities. Therefore it is neither punitive damage compensation nor a sanctioning tool of healthcare providers but more precisely it supplements the extensive coverage offered by Swedish social and medical care systems. This can partly explain the lower compensations then in Anglo-American tort systems but simultaneously results in a simpler procedure for the claimants and with higher overall appeal success rates of 47% to 49.5% vs. 30% in the United States[83,85].

1.2.4 Thromboembolic events and prophylaxis

The most severe consequence of an acute VTE is sudden death, resulting from acute massive PE. Fortunately, postoperative fatal PE is a rare complication and often occurs in patients with other risk factors[86]. The long-term complications of VTE include recurrent VTE, postthrombotic syndrome and chronic thromboembolic pulmonary hypertension. The incidence of recurrence of VTE after first-episode of DVT has been reported to be 24% within 5 years, with 20% of the recurrent VTE episodes being PEs[87]. The postthrombotic syndrome is a chronic condition characterised by oedema, pain, venous ectasis and severe cases painful leg ulcers[88]. The incidence rate is shown to be 4% to 6% within 7 years after a DVT following arthroplasty surgery of the hip or knee[89]. Finally, chronic thromboembolic pulmonary hypertension may occur after a single episode of PE and, if untreated, cause right heart failure[90]. The incidence within 2 years after an event of PE is 1% to 5%[91].

Elective primary hip and knee arthroplasties are common, standardised and widespread operations. Both of these major orthopaedic procedures carry a considerable risk of thrombosis and the most frequent medical complication of THA is VTE[92]. These operations have therefore become popular models for assessing TP treatments. Apart from studying outcomes of two different operations, the abundant studies describing the incidence of VTE focus mainly on two end-points, which results in a difficult comparison between studies. The first end-point is subclinical DVT assessed by routine venography or ultrasound examination regardless of symptoms. This method detects more events and may be regarded as a better measure of efficacy of treatment. However screening in trials may detect subclinical DVTs, raising the reported incidence and simultaneously preventing some from becoming symptomatic and detectable in clinical practice. The second end-point is the incidence of symptomatic DVTs, where the events are detected after a clinical suspicion. This approach resembles real clinical settings and focuses on the efficiency of TP drugs.

Older randomised controlled trials show a symptomatic rate of VTE of 15% to 30% without prophylaxis[93]. Current studies report an incidence of symptomatic VTE within 90 days of surgery as 0.7% to 1.8% in patients with postoperative TP[94-98], including both DVT and PE. The use of TP is well established and recommended by several guidelines worldwide[93,99,100] but without consensus regarding both length of treatment and the preferred therapeutic agent.

The most commonly used TP medications after THA worldwide include ASA, fondaparinux, warfarin, LMWH and the recently introduced NOAC. NOACs have proved their efficiency as TP after THA in several clinical trials[101-105]. Besides their efficacy and efficiency, compared to LMWH, they offer reduced over-all costs due to oral administration[106] and are often preferred by patients[107]. However concerns are raised regarding prolonged wound drainage[108,109] and higher risk of bleeding[110-112], but this is likewise contradicted by other studies[113,114].

1.2.5 Swedish national quality and healthcare registers

The unique Swedish personal identity number (PIN) facilitates linkage-studies between population and health data registers. It was introduced in 1947 and constitutes the basis of almost all aspects of everyday life, from direct assignment to new-borns, through schools, banks and employments, to all aspects of healthcare use. The consistency of its use is the reason behind the success of Swedish epidemiologic and socioeconomic research.

Swedish National Patient Register (SNPR) was established in 1964 and is administrated by the governmental National Board of Health and Welfare. The register covers all (private and public) inpatient care since 1987 and outpatient care since 2001. The primary care is not covered. SNPR contains data in 4 different categories: patient related data (PIN, sex and place of residence –county, municipality, parish), caregivers' data (assigned hospital and department number), administrative data (date and mode of admission and discharge, acute or elective care) and medical data (primary and secondary diagnosis, cause of injury or poisoning and procedures). The diagnoses and injuries are registered according to the 10th version of International Classification of Diseases (ICD) and SNPR does not register laterality. Currently over 99% of all hospital discharges and hospital based outpatient visits are registered and the PIN is found missing in only 2.9% of all discharges[115].

Swedish Prescribed Drug Register (SPDR) was initiated in 1999 and is also under the administration of National Board of Health and Welfare. In 2005 PIN was included in the register, which enabled matching of data with other registers. SPDR includes information on all prescribed outpatient drugs in Sweden, through automatic reporting by the pharmacies[116]. The following is reported for every individual prescription: PIN, date of prescription and expedition, name of the drug and its Anatomical Therapeutic Chemical (ATC) code, dose, prescribed quantity, instructions from the prescriber and prescriber details (profession and clinic).

Swedish Hip Arthroplasty Register (SHAR) started in 1979[117] as the second national quality register in Sweden. All orthopaedic units performing hip arthroplasties report to SHAR. The completeness of the register is reported as above 98%[21]. All primary operations and reoperations are to be reported to SHAR. It defines reoperation as any subsequent surgery in close relation to the already implanted prosthesis. Revisions are defined as a reoperation where parts or the entire prosthesis is exchanged or extracted. Registered data includes: PIN, age, sex, ICD-coded diagnosis, side, surgical approach, type of fixation, type of implant and cement, hospital, surgeon. Prosthesis survival is calculated by matching with the Swedish Death register. Finally, pre- and postoperative patient reported outcome measures are also registered.

Statistics Sweden is a governmental agency responsible for producing national statistics through assignments from the government and other government agencies. The beginning of Statistics Sweden can be traced back to the church registration, imposed by the Church Law of 1686. The field of Statistics Sweden is diverse and extensive but in the content of this thesis, they supplied information from LISA (Longitudinal integration database for health insurance and labour market studies).

2 AIMS OF THE THESIS

The aims of this thesis were to investigate the following aspects of hip arthroplasty:

- Analyse and compare the incidence, microbiology and outcome of PJI after hip arthroplasty due to degenerative disorder and fracture, including both primary and secondary fracture surgery. **- Study I**

- Evaluate the air quality with two new CAS systems through comparison with an existing and widely used CAS system, which was additionally complemented by two mobile LAF-units. **- Study II**

- Determine the proportion and outcome of patient claims which were filed to LÖF after PJIs and analyse any presence of socioeconomic, age and sex-linked differences among claimants. **- Study III**

- Compare LMWH and NOAC as TP after elective THA, through determination of effectiveness as incidence of VTE and assessment of safety by analysis of bleedings, reoperations and mortality.
  - Study IV

3 PATIENTS AND METHODS

Studies I and II are based on outcomes of operations performed at the Department of Orthopaedics, Stockholm South General Hospital (Södersjukhuset). The hospital is owned by The Stockholm County Council but works in close collaboration with the medical university Karolinska Institutet. It offers healthcare to more than 2 million inhabitants of the County Council but is far from the only provider. Every year the hospital receives more than 160 000 emergency visits, holds over 600 beds, employs 4 600 co-workers and 6 000 operations are performed in the orthopaedic department.

Studies III and IV cover the nationwide population of Sweden, a country of 10 millions inhabitants. These studies are mainly based on national quality and healthcare registers.

3.1 STUDY I

All patients operated between 1996 and 2005 were prospectively registered in a clinical audit database, where all complications (both early and late) were registered. During the study period a consecutive series of 1 155 HAs (406 uncemented unipolar HAs, 353 cemented unipolar HAs and 396 cemented bipolar HAs) and 2 728 THAs (2 442 cemented THAs, 215 uncemented THAs and 71 hybrids/reversed hybrids THAs) were identified in the registry and included in the study, in total 3 883 hips. The indication for surgery was a degenerative or inflammatory hip disorder in 1 687 cases and hip fracture in 2 127 hips. Primary fracture prosthesis was performed in an acute displaced femoral neck fracture (Garden III and IV)[118] and secondary fracture prosthesis due to fracture healing complications after internal fixation. After exclusion of patients operated due to malignancy, acetabular fractures and patients living abroad (therefore lost to follow-up), 3 807 arthroplasties remained and were included in the study.

All patients received preoperative full body wash and prophylactic intravenous antibiotics and additional one or two doses of antibiotics postoperatively, according to guidelines at the time. For patients with either a registered PJI or a registered reoperation, individual patient records were searched until May 31, 2011, or death, in order to find information about all details regarding the PJI. Late PJIs and reoperations from our own department were crosschecked against SHAR (no additional cases were found) and SNPR (two additional cases), to find patients who had been reoperated or treated elsewhere in Sweden for a PJI up to December 31, 2010.

Microbiology

Microbiological records were requested from the laboratories involved and data about the type of sampling material and culture results were registered. Independent reviewers analysed the culture results and decided the final causative bacterial agent(s). An etiological agent was defined according to following criteria:

1. Superficial or deep wound culture with staphylococcus aureus.
2. Superficial or deep wound culture with monoculture of beta-haemolytic streptococci.
3. Periprosthetic biopsies with the same bacterial finding in at least 50 % of the samples, minimum three biopsies.
4. Three independent cultures of either perioperative deep swab or perioperative tissue samples, with the same bacterial agent.
5. Positive blood culture in combination with skeletal changes, evident on X-ray or at surgery, and symptoms from this region.

The criteria were set according to the present recommendations from the Infectious Diseases Society of Sweden. If more than one pathogen matched the criteria, we made no judgement as to which pathogen being more virulent and therefore likely to have caused the infection. The material from which the microbiological diagnosis was made was also registered. In the case that the bacterium was present in more than one type of culture, the culture material considered to have the trustworthiest significance was registered. Biopsy findings were considered more significant than synovial fluid, which was considered more reliable than blood culture findings, which was considered more significant than wound cultures. If more than one bacterium matched the criteria the infection was defined as polymicrobial and these are presented separately.

All infections were classified into 3 types depending on the time to first symptoms of an infection. We used the criteria set up by the Swedish Association of Infectious Diseases[119] and by Zimmerli and Ochsner[59]; Infections with symptom onset within 3 months were defined as early, infections with symptom onset between 3 months and 2 years were defined as delayed and infections with symptom onset at 2 years or more were defined late.

3.2 STUDY II

All operations in this study were performed in 2013. The surgical procedures included in the study (elective total arthroplasties of hips and knees) were all performed in standardised setting, in the same OR, equipped with turbulent ventilation, HEPA-filter and air-intake of 620L/s. The procedures included cemented, uncemented and hybrid implants, all performed by experienced orthopaedic surgeons with one junior assistant. In total there were between 6 to 9 staff present at each operation, including both the operating personnel, as well as the passive observers responsible for data collection. We had strict door control with only one opening throughout all of the operations.

Three clothing systems were studied prospectively, all supplied as brand-new. There were 13 operations performed in, at that time currently used, reusable mixed material Mertex P-3477, Textilia AB (69% cotton, 30% polyester and 1% carbon fibre) accompanied by two mobile LAF units (TOUL, Meditech AB, Västerås, Sweden) with a joint airflow of 220 L/min. In 13 operations reusable Olefin, Textilia AB (woven polypropylene/polyethene material) was used, without any TOUL-device. The third clothing system, single-use BARRIER® Clean Air Suit, Mölnlycke Health Care (non-woven, spunbonded polypropylene), was used to perform 11 procedures, also without any TOUL-device. Both the Mertex P-3477 dress and the BARRIER® Clean Air Suit, have cuffs at the bottom of the long legged pants and the short-sleeved shirts (at the arms, bottom and neckline). Olefin dresses had no cuffs at the bottom of the shirts and were therefore worn inside the pants. The clothing systems were evenly distributed between morning and afternoon operations. During each operation, all staff present in the OR wore the same kind of clothing system and changed garments before next procedure.

Air quality measurements

Measurements were all performed by the same, experienced OR nurse, not involved in the surgical procedure. Air sampling was done with Sartorius Air Sampler MD8® (Sartorius AG, Goettingen, Germany). There are no international standards of air sampling but the Sartorious device is a long-established method[120] and recommended by the Swedish Standards Institute[75]. Air was sucked through a sterile tube with standardised airflow of 100L/min over a gelatine filter, placed 35 - 50 cm from the operating field. Special care was taken to avoid any splashes of fluids from the operating area[71]. It was changed every 10 minutes, with six or seven measurements per operation. The 10-minute interval is the recommended time, as longer sampling times may decrease the bacterial counts through dehydration[75]. Each filter was placed, immediately after removal, on a sterile blood agar plate and sent (on the same day) to the laboratory of Clinical Microbiology at the Karolinska University Hospital in Huddinge. The plates were incubated for two days at $35^{O}C$ and the amount of colonies were then counted and expressed as CFU/m^3. Samples with condensate on the lid of the agar plate, macroscopic fluid or touch contamination, and damaged filters were excluded from analysis. Operations with over 50% excluded samples were subsequently dropped from the analysis.

3.3 STUDY III

This study is based on a previously described population[55] with regard to the national incidence of PJI after primary THA in Sweden. All patients who had undergone a primary THA, between 1st of July 2005 and 31st of December 2008, were initially retrieved from SHAR and matched with the SPDR for continuous outpatient antibiotic medication for at least four weeks after surgery. The observation time was set to two years postoperatively, to include only early and delayed PJIs[59]. This protocol allowed for inclusion of the compensable PJIs, since IC occurs within the first 2 years. Simultaneously the late appearing PJIs caused by HS were excluded. No additional selection was made to exclude any possible HS infections within the first two postoperative years. Antibiotic treatments with indications other then PJI were excluded. A questionnaire for each of the identified patients was sent to the operating units. This verified treatment for PJI and the case-specific diagnostic criteria of PJI, according to the definition by the Workgroup of the Musculoskeletal Infection Society[121]. 99% of all questionnaires were returned, resulting in a final number of 443 treated PJIs.

We identified 441 patients with PJIs in the LISA database. This enabled matching on highest achieved level of education as a socioeconomic factor, which was combined into four levels; elementary school, high school, post graduate and unknown. For each patient, we also recorded gender, performing hospital, age at primary THA operation and the indication for surgery. Primary osteoarthritis and hip fracture are the two most common indications, with apparent different patient characteristics. Consequently we wanted to present these two groups separately in our analysis. All other indications were merged together into a third group, called other. To examine any national differences, each operating unit was classified according to its location by provision of care (the 21 Swedish counties) and separately by order: university hospital, referral county hospital, local hospital and private.

Patient claims

Finally we compared all PJIs with LÖF's database in November 2016 for patient claims and outcome of claims review. The timeframe was regarded as sufficient for both patients to file claims after delayed infections in case of complicated and prolonged PJI treatment and also for LÖF to review and conclude their decision. Filed patient claims were recorded and their decisions were grouped into six outcomes: rejected claims, approved prolonged recovery (grouped as prolonged by less or more than 3 months) and approved acquired permanent disability (classified as levels of 1% to 15%, 16% to 30% and above 30%).

3.4 STUDY IV

This study is based on a previously cross-linked register database, initiated by SHAR[122] and 78 066 primary THAs, operated between years 2008 and 2012, were extracted. In bilaterally patients operated (n= 7 105) only the first hip was included. This allowed for better tracing of prescriptions and complications, as well as exclusion of possible additive effect of a second operation. Patients with other diagnoses than primary osteoarthritis (n= 12 186) were excluded. Using ICD-coding from SNPR, we additionally excluded subjects with VTE, up to five years before operation (n= 1 121), to limit any effect of previous conditions on outcome. To reduce bias from on-going or recent potent antithrombotic agents at time of surgery, we excluded patients who had been prescribed Warfarin, LMWH and NOAC, up to six months prior to the THA (n= 4 971). This was done using data recorded in SPDR. From SPDR we also collected data on postoperative prescribed and purchased TP medication. Patients with no data on purchase of postoperative TP treatment (n= 16 899) were excluded. A subanalysis revealed that most patients purchased the prescribed TP medications on the third to fifth day after the index operation. We decided that setting a cut-off of purchase within 10 postoperative days, will limit the inclusion of high-risk patients by exclusion of those who, possibly due to comorbidities, required longer hospital care (n= 3 151). 32 663 patients operated with a THA were included in this study (Figure 1).

We recorded sex, age at operation, body mass index (BMI), American Society of Anaesthesiologists score (ASA-score), Elixhauser score, purchase of platelet aggregation inhibitor (within 6 months before operation) and type of implant fixation for each patient. Duration of TP was calculated as the sum of postoperative hospital days and the amount of prescribed daily doses. TP was defined as short, if the patients had received treatment for less than 28 days. Consequently TP of 28 days or longer was classified as extended. The data from LISA provided both the patients´ highest achieved level of education and their civil state at the time of operation.

We divided the TP medications into two groups, LMWH and NOAC. In the LMWH group we included three medications by their corresponding Anatomical Therapeutic Chemical (ATC) codes: dalteparin, enoxaparin and tinzaparin. The regimen was one daily subcutaneous dose of 5000, 4000 and 4500 IU respectively. The NOAC group consisted of dabigatran (twice-daily oral dose of 110mg) and rivaroxaban (one daily oral dose of 10mg oral dose). A list of all antithrombotic agents and their categorization is presented in Table 1.

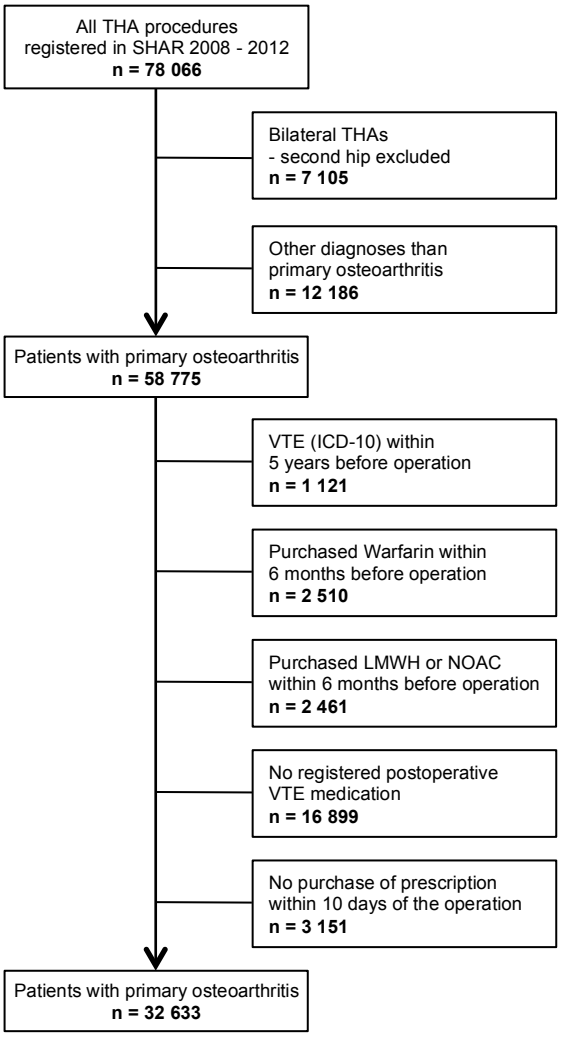

Figure 1
Study flowchart of patient selection

The occurrence of all events was studied up to 90 days postoperatively. This timeline was based on previous findings of time course of thromboembolic events after joint replacement surgery[95,96,123]. Our primary effectiveness outcomes of VTE, DVT and PE, were analysed through SNPR by the corresponding ICD-codes. The secondary safety outcomes of bleedings were also extracted from SNPR. Due to absence of recognized standards of reporting bleeding complications in register studies, a deliberately wide-ranging, catchall definition was chosen. No distinction was made between major and minor bleedings and every code resulting in inclusion of possible bleeding complication was included. Both reoperations (any open surgical intervention following THA) and mortality within 90 days of the index operation were collected from SHAR. A complete list of the ICD-codes for diagnostic outcomes is presented in Table 2.

Table 1
List of antithrombotic agents, grouped and categorized by study's variable type

GROUP	NAME	ATC-CODE*	VARIABLE		
			excluding**	studied	confounding
Vitamin K antagonists	Warfarin	B01AA03	X		
Heparin group	Dalteparin	B01AB04	X	X	
	Enoxaparin	B01AB05	X	X	
	Tinzaparin	B01AB10	X	X	
Platelet aggregation	Clopidogrel	B01AC04			X
inhibitors	Acetylsalicylic acid	B01AC06			X
excluding heparin	Dipyridamole	B01AC07			X
	Epoprostenol	B01AC09			X
	Iloprost	B01AC11			X
	Abciximab	B01AC13			X
	Eptifibatide	B01AC16			X
	Tirofiban	B01AC17			X
	Treprostinil	B01AC21			X
	Prasugrel	B01AC22			X
	Ticagrelor	B01AC24			X
	Combination agents	B01AC30			X
Direct trombin inhibitors	Dabigatran etexilate	B01AE07	X	X	
Direct factor Xa inhibitors	Rivaroxaban	B01AF01	X	X	

* = Anatomical Therapeutic Chemical Code
** = Excluded patients from the final cohort if prescribed within 6 months preoperatively

Table 2
ICD-10 codes of studied outcomes, grouped by the study's endpoints:
primary (effectiveness) and secondary (safety).

EFFECTIVENESS			SAFETY*										
VTE	DVT	PE	Identified bleedings				No identified bleedings						
I82.8	I81.9	I26.0	D62.9	K22.6	M25.4G	S06.5	H35.6A	I60.7	K25.2	L60.8J	N42.1	N95.0X	T79.6
I82.2	I82.9	I26.9	H11.3	K25.0	M25.4H	S06.50	H35.6B	I61.0	K25.6	M25.4	N50.1A	R04.1	T81.1
I82.3	I82.8		H35.6	K25.4	N02.4	S06.6	H35.6C	I61.1	K26.4	M25.4B	N50.1B	R04.8	T84.8X
I26.0	I82.2		H43.1	K26.0	N02.9	T140A	H35.6W	I61.2	K26.6	M25.4C	N89.7	R19.8A	T85.6
I26.9	I82.3		I60.0	K26.2	N92.4	T81.0	H35.6X	I61.3	K27.0	M25.4D	N83.6	R23.3	
I81.9			I60.8	K29.0	N95.0	T84.8	H45.0	I61.5	K27.2	M62.2	N83.7	R23.3A	
I82.9			I60.9	K55.0	N95.0A	T84.8F	H92.2	I61.6	K27.4	N02.0	N85.7	R23.3B	
			I61.4	K62.5	N95.0B	T84.9	I31.2	I62.1	K27.6	N02.1	N89.7	R23.3C	
			I61.8	K62.6	R04.0	T85.8	I60.1	I62.9	K28.0	N02.2	N92.2	R23.3W	
			I61.9	K92.0	R04.2	T85.9	I60.2	I69.2	K28.2	N02.3	N92.3	S06.40	
			I62.0	K92.1	R04.9	T88.7	I60.3	I85.0	K28.4	N02.5	N93.0	S06.41	
			I64.9	K92.2	R31.9	T88.7X	I60.4	I98.3	K28.6	N02.6	N93.8	S06.51	
			I69.0	M25.0	R58.9	T88.8	I60.5	J38.3J	K66.1	N02.7	N93.9	S06.60	
			I69.1	M25.4F	S06.4	T88.9	I60.6	K05.0	K76.2	N02.8	N95.0W	S06.61	

* = Presented with distinction between codes that did and did not confirm bleedings

3.5 STATISTICAL ANALYSES

Study I

The Mann-Whitney U-test was used for scale variables in independent groups. Nominal variables were tested with the Fisher's exact test. Cox regression analysis was used to evaluate factors associated with a PJI. Age, sex, indication for surgery, microbiological finding and type of prosthesis was tested as independent variables in the model. First, crude associations for each factor were studied in univariable models. Secondly, a multivariable model with all independent factors was used to study the adjusted associations. The associations are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). All tests were two-sided and the level of significance was set to $p < 0.05$. We used IBM SPSS Statistics software (ver. 21).

Study II

We calculated the median and mean values of CFU for each operation as well as each clothing system. The Olefin clothing and the BARRIER® Clean Air Suit were then independently compared to our existing TOUL-assisted Mertex P-3477 garment. As outliers and non-standard distribution was observed in all three clean air suits, the comparison was based on median values, using the Mann-Whitney U-test. We used IBM SPSS Statistics software (ver. 21).

Study III

The Mann–Whitney U test was used for scale variables in independent groups and the Pearson Chi-Square test was used for nominal variables. Subsequently logistic regression analysis was performed on patients' characteristics to evaluate factors associated with insurance claim. We analysed both a univariate and multivariate model. Associations are presented as odds ratios (ORs) with 95% confidence intervals (CIs). We used IBM SPSS Statistics software (ver. 23).

Study IV

The statistical analysis was performed using R, version 3.4.2. The data was analysed in a binary logistic regression model to determine the odds ratio (OR) with a 95% confidence interval (CI). A p-value below 0.05 was considered statistically significant. Each of the observed outcomes was used as the dependent variable in the regression analysis. We calculated the OR both in a univariate (unadjusted) and a multivariate analysis, adjusted for length of TP, sex, age and previous treatment with platelet aggregation inhibitors as confounders.

3.6 ETHICS

All studies were conducted according to the World Medical Association's Declaration of Helsinki and approved before initiation by the regional ethical review boards:

Study I

The Regional Ethical Review Board at the Karolinska Institutet, Stockholm
(ref no 2013/1190-31/1)

Study II

The Regional Ethical Review Board at the Karolinska Institutet, Stockholm
(ref no 2013/246-31/4)

Study III

The Regional Ethical Review Board at the University of Gothenburg
(ref no 622-16)

Study IV

The Regional Ethical Review Board at the University of Gothenburg
(ref no 271-14)

4 RESULTS

4.1 STUDY I

We identified 62 of 3 807 (1.6%) hips reoperated due to a PJI. There were seven (0.4%) SSIs in patients operated for degenerative hip disorder; 47 (2.2%) were found in patients operated with fracture prosthesis: 22 from the primary (2.0%) and 25 from the secondary (2.5%) fracture prosthesis group, respectively. HS infections dominated with six hips in the degenerative hip disorder group compared with two in the primary fracture prosthesis group.

Microbiological cultures showed a dominance of staphylococcus aureus and coagulase-negative staphylococci in the fracture group, whereas there was a trend to more polybacterial infections in patients with degenerative hip disorder. Baseline and infection data for all patients is presented in Table 3.

Finally a multivariate Cox regression analysis was performed to analyse factors associated with a significantly increased risk for developing a surgical-site PJI. We adjusted for age, gender, surgeon experience, prosthesis type and indication for prosthesis as independent factors in. The only factors with significant association were both fracture indication for surgery, primary (HR 4.3) and secondary (HR 6.1) fracture prosthesis, and male gender (HR 2.0). The analysis is presented in Table 4.

When examining the treatment outcome of PJIs, we found that 25 (10%) patients were treated with open debridement and had the prosthesis preserved, 10 (16%) patients underwent a two-stage revision with exchange of prosthesis components and the treatment of 27 (44%) patients resulted in permanent resection arthroplasty. In 11 patients this was performed as part of the primary treatment plan and 16 resections were the result of treatment failure. 22 (81%) of resection arthroplasties were performed in fracture patients.

Life-long antibiotic therapy was required for 10 patients; in four after their resection procedure and in six patients in the prosthesis-preserving group. None in the two-stage revision group needed life-long antibiotic treatment. Finally 6 patients (10%) died during the treatment for infection, 5 of which were in the hip-fracture group.

Table 3

Baseline and infection data for all patients included in relation to the indication for surgery

	All (n= 3807)	**Degenerative hip prosthesis** (n= 1682)	**Primary fracture prosthesis** (n= 1122)	**Secondary fracture prosthesis** (n= 1003)	**p-value**
BASELINE					
Age mean (SD)	75.7 (12.1)	69.3 (12.1)	82.1 (8.1)	81.3 (10.7)	<0.001
Gender –n (%)					
Female	2755 (72)	1098 (65)	873 (78)	784 (78)	
Male	1052 (28)	584 (35)	249 (22)	219 (22)	<0.001
Type of prosthesis –n (%)					
THA	2656 (70)	1681 (100)	348 (31)	627 (63)	
Cemented HA	745 (20)	0 (0)	583 (52)	162 (16)	
Uncemented HA	406 (11)	1 (0)	191 (17)	214 (21)	<0.001
Surgeon's experience –n (%)					
Registrar	751 (20)	390 (23)	208 (19)	153 (15)	
Postregistrar	3056 (80)	1292 (77)	914 (81)	850 (85)	<0.001
INFECTIONS –n (%)	**62 (1.6)**	**13 (0.8)**	**24 (2.1)**	**25 (2.5)**	
Symptom onset –n (%)					
Early	47 (76)	7 (54)	19 (79)	21 (84)	
Delayed	6 (10)	1 (8)	2 (8)	3 (12)	
Late	9 (14)	5 (38)	3 (13)	1 (4)	0.08
Type of infection –n (%)					
Surgical site	54 (87)	7 (54)	22 (92)	25 (100)	
Haematogenic	8 (13)	6 (46)	2 (8)	0 (0)	<0.001
Bacterial specimen* –n (%)					
Staph. aureus	30 (56)	5 (38)	12 (67)	13 (56)	
CoNS	7 (13)	1 (8)	1 (6)	5 (22)	
G- + Poly	13 (24)	6 (46)	5 (28)	2 (9)	
Others	4 (7)	1 (8)	0 (0)	3 (13)	0.09

THA= total hip arthroplasty, HA= hemiarthroplasty, CoNS: coagulas-negative staphylococci,

G- + Poly= Gram negative infections and polymicrobial infections, Others= streptococci, peptostreptococci

*8 cases without defined bacterial specimen, all fracture prosthesis, primary (6 cases) and secondary (2 cases)

Table 4

Reoperation rate for patients with surgical site infections and multivariable Cox regression adjusting for: age, gender, surgeon's experience, type of prosthesis and indication for surgery

	Reoperation rate n (%) (total n= 54)	**Multivariable Cox regression** HR (95% CI)	p-value
Age group			
< 75 years (n=1504)	16 (1.1)	1 (reference)	
≥75 years (n=2303)	38 (1.7)	0.9 (0.5-1.7)	0.7
Gender			
Female (n=2755)	34 (1.2)	1 (reference)	
Male (n=1052)	20 (1.9)	2.0 (1.2-3.6)	0.01
Surgeon's experience			
Registrar (n=751)	7 (0.9)	1 (reference)	
Post registrar (n=3056)	47 (1.5)	1.5 (0.7-3.3)	0.3
Type of prosthesis			
THA (n=2656)	26 (1.0)	1 (reference)	
Cemented HA (n=745)	18 (2.4)	1.7 (0.8-3.5)	0.2
Uncemented HA (n=406)	10 (2.5)	1.8 (0.8-3.9)	0.2
Indication			
Degenerative hip disorder (n=1682)	7 (0.4)	1 (reference)	
Primary fracture prosthesis (n=1122)	22 (2.0)	4.3 (1.6-11.7)	0.004
Secondary fracture prosthesis (n=1003)	25 (2.5)	6.1 (2.5-15.1)	<0.001

THA= total hip arthroplasty, HR= hazard ratio, HA= hemiarthroplasty, CI= confidence interval

4.2 STUDY II

Out of the total 244 measurements, we had to exclude 37 (15%). This was done due to the condensate on the lids of the agar plates (25 measurements), macroscopic fluid splash contaminations (7 measurements), damaged filters (4 measurements) and one tactile contamination. In three operations with the Olefin clothing, more than half of the measurements were excluded. Therefore, these three procedures were not regarded as representable and were consequently eliminated from the analysis. Conclusively we analysed 201 measurement, 78 of which with the TOUL-assisted Mertex system, 52 with the Olefin clothing and 65 measurements with the BARRIER® Clean Air Suit.

We had one door opening, with BARRIER® Clean Air Suit, which did not show any evident rise in measured CFU-values.

Our main finding was the significantly lowest median CFU/m^3 of the BARRIER® Clean Air Suit. The median values of the studied clothing systems were 20.0 CFU/m^3 for the TOUL-assisted Mertex system, 22.5 CFU/m^3 for the Olefin system and 12 CFU/m^3 for the BARRIER® Clean Air Suit. The results are summarised in Table 5. We observed a wide spread of measurements between the different clothing systems, as well as between individual operations within the same clothing systems. The noticeably higher mean values (27.9 CFU/m^3 of the TOUL-assisted Mertex system, 38.8 CFU/m^3 of the Olefin clothing and 22.8 CFU/m^3 of the BARRIER® Clean Air Suit) reflect the impact of the outliers, present in every clothing system. The reason of the high outlying values could not be traced back or explained by a specific date of surgery, temporary failure of ventilation or sterile processing department, malfunctioning Clean Air Suit items, nor by the surgical teams or specific individuals.

Table 5
Comparison of all included operations and measurements of the three clothing systems

Clothing system	Operations total n= 37	Measurements total n= 207	CFU/m^3 Median	Mean	Min - Max	p-value
Mertex P-3477 + two TOUL devices	13	78	20.0	27.9	1-148	1 (reference)
Olefin clothing	10	52	22.5	38.8	0-228	0.622
BARRIER® Clean Air Suit	11	65	12.0	22.8	0-280	0.009

CFU/m^3 = Colony Forming Units per cubic meter

4.3 STUDY III

We identified that 329 (75%) of the total 441 patients with PJIs did not file a claim of injury to LÖF. Of those 112 that did, 108 (96%) were accepted as eligible for compensation. Table 6 summarizes patients' baseline data and claim rates. Patients' age above the median of 72 years (OR= 0.4, CI 0,3 - 0.7, p= 0.001) and fracture diagnosis (OR= 0.4, CI 0.2 - 0.9, p= 0.02) were the only significant factors associated with not filing a claim of injury in a univariate logistic regression model. When adjusted for age, gender, diagnosis and level of education in the later multivariate model, they remained significant, with identical OR, CI and p-values. The analysis is presented in Table 7.

The variation in claims between counties ranged between 50% (1 of 2 PJIs) and none (of 3 PJIs). Both were identified in smaller counties. Only two counties, Västra Götaland (Gothenburg) and Stockholm, had more then 10 claimants (26 with 38% claim rate and 23 with 30% claim rate respectively). We could not observe any national differences in claims above the county level. Patients from smaller hospitals filed claims more often, with the highest rates from the private hospitals (34%) and lowest from university hospitals (16%) (p= 0.059). We could not observe any correlating trends to higher or lower age of patients between claim rates and types of hospitals; university ($\overline{x}$= 68.2, SD 14.7), county ($\overline{x}$= 71.5, SD 10.7), local ($\overline{x}$= 70.1, SD 9.6) and private ($\overline{x}$= 69.7, SD 11.5). Private hospitals operated only patients with osteoarthritis, with only one patient with other diagnosis (femoral head necrosis).

Analysis of LÖFs claim decisions, as visualized in Figure 2, reveals that 44 (39%) claimants were compensated for prolonged recovery time and 64 (57%) for permanent disability, due to PJI. There was an equal distribution of age groups within the three largest decision groups; recovery <3 months ($\overline{x}$= 66.2, SD 12.0) recovery >3 months ($\overline{x}$= 68.3 SD 8.7) and disability 1-15% ($\overline{x}$= 67.0, SD 11.1).

Table 6
Baseline data for all patients included in relation to claim of injury at LÖF.

	All (n= 441)	**No claim** (n= 329, 75%)	**Claim** (n= 112, 25%)	**p-value**
Age (%)				
Mean (SD*)	70,7 (11)	71,8 (11)	67,4 (10)	<0,001
Distribution (%)				
<50	15 (3)	10 (67)	5 (33)	
51-60	66 (15)	45 (68)	21 (32)	
61-70	116 (26)	78 (67)	38 (33)	
71-80	167 (38)	126 (76)	41 (25)	
>80	77 (18)	70 (91)	7 (9)	0,003
Gender (%)				
Female	222 (50)	158 (71)	64 (29)	
Male	219 (49)	171 (78)	48 (22)	0,096
Diagnosis (%)				
Primary osteoarthritis	328 (74)	236 (72)	92 (28)	
Hip fracture	67 (15)	58 (87)	9 (13)	
Other	46 (10)	35 (76)	11 (24)	0,042
Education (%)				
Elementary school	205 (47)	161 (79)	44 (22)	
High school	167 (38)	119 (71)	48 (29)	
Post graduate	66 (15)	46 (79)	20 (30)	0,176
Unknown	3 (1)	3 (100)	0 (0)	
Hospitals (%)				
University	55 (13)	46 (84)	9 (16)	
County	203 (46)	158 (78)	45 (22)	
Local	151 (34)	104 (69)	47 (31)	
Private	32 (7)	21 (66)	11 (34)	0,059

* SD =Standard deviation

Table 7
Logistic regression to evaluate factors associated with insurance claim.

	All	Claim made	Univariable		Multivariable	
	n	n (%)	OR* (95%CI)	p-value	OR* (95%CI)	p-value
Age						
<73 years	224	74 (33)	1 (reference)		1 (reference)	
≥ 73 years	217	38 (18)	0.4 (0.3-0.7)	<0.001	0.4 (0.3-0.7)	<0.001
Gender						
Male	219	48 (22)	1 (reference)			
Female	222	64 (29)	1.4 (0.9-2.2)	0.1		
Diagnosis						
Primary osteoarthritis	336	92 (27)	1 (reference)		1 (reference)	
Hip fracture	67	9 (13)	0.4 (0.2-0.9)	0.02	0.4 (0.2-0.9)	0.02
Other	38	11 (29)	1.1 (0.5-2.3)	0.8	0.9 (0.4-2.0)	0.8
Level of education						
Elementary school	205	44 (22)	1 (reference)			
Secondary school	168	48 (29)	1.5 (0.9-2.3)	0.1		
University	65	20 (31)	1.6 (0.9-3.0)	0.1		

* OR= odds ratio

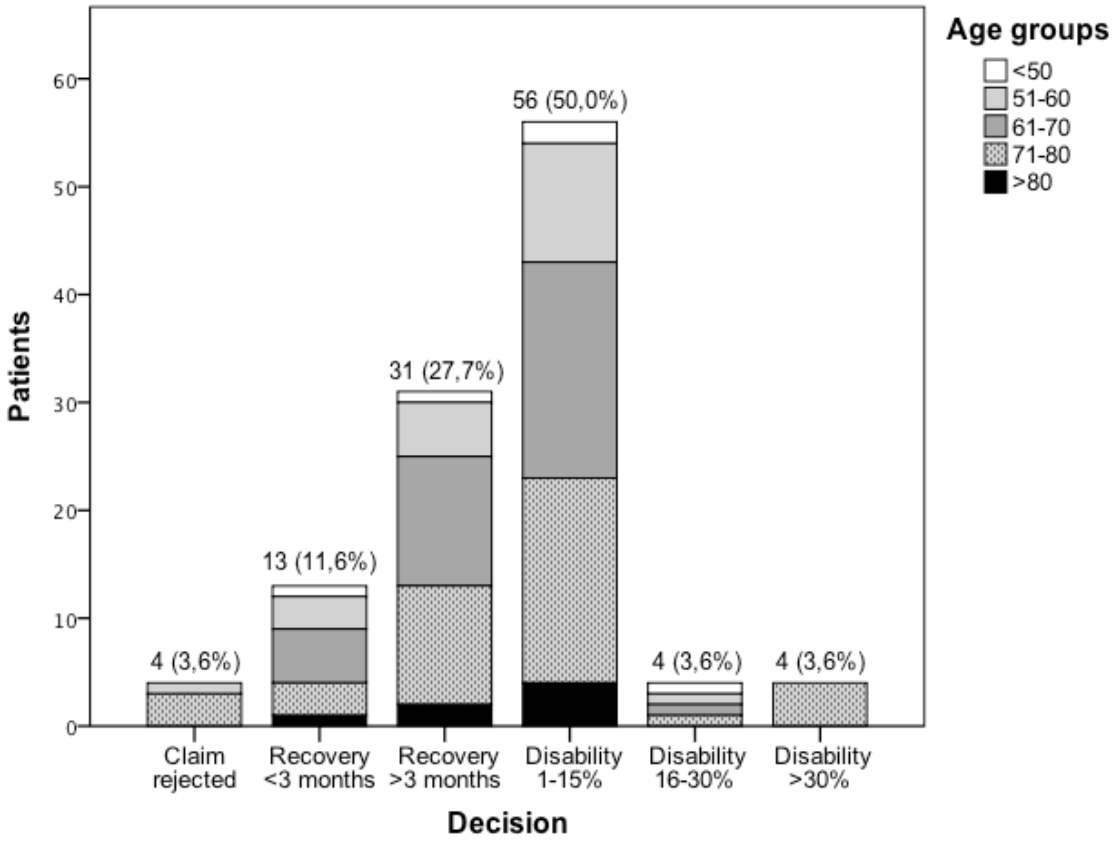

Figure 2
LÖF's claims grouped by decisions (n and % of total) with distribution of age groups within:
rejected claims, recoveries prolonged shorter and longer than 3 months and % of acquired permanent disability

4.4 STUDY IV

In the cohort of 32 663 THAs, we identified 5 752 (18%) patients with NOAC and 26 881 (82%) with LMWH TP treatment. Table 8 summarizes patients' characteristics and clinical properties of the two groups. The two depictions of comorbidities diverge as more NOAC patients belong to lower classes of ASA-score but reveal a 21% higher mean Elixhauser score. The achieved level of education was lower in individuals with NOAC treatment and they were also more frequently operated with cemented fixation. As dabigatran and rivaroxaban were approved for postoperative TP in 2008 in Europe, the NOACs prescription in the study's two initial years was low, but increased to a steady 25% share during the last three studied years.

Our primary finding was a significantly lower risk of VTE in the NOAC group (incidence 0.4%), compared to the LMWH group (incidence 1.0%), with adjusted OR= 0.42 (CI 0.26 - 0.67), as presented in Table 9. DVT was observed in 17 (0.3%) patients with NOAC treatment and 170 (0.6%) patients with LMWH, adjusted OR= 0.52 (CI 0.29 - 0.90). Consecutively 8 (0.1%) individuals in the NOAC group suffered PE vs. 108 (0.4%) in the LMWH group, adjusted OR= 0.32 (CI 0.14 - 0.67). In comparison with LMWH, NOAC did not present any significant difference in risk of the safety outcomes of bleedings, reoperations or mortality.

Majority (84%) of NOAC patients were prescribed extended TP, while LMWH was predominantly (83%) used as short TP. The distribution of TP duration is presented in Table 10 and visualized in Figure 3. The limited number of patients receiving short TP with NOAC did not allow for analysis of short versus extended prophylaxis in this group. However, adjusting for duration of TP in the subset of patients treated with LMWH did not show any significant difference with regards the incidence of VTE (OR= 0.95, CI 0.67 - 1.31).

Table 8
Baseline data for all included patients, grouped by thromboprophylactic regimen

	NOAC n=5752	**LMWH** n=26881	**p-value**
SEX= female -n (%)	3329 (57.9)	15339 (57.1)	0.264
AGE -mean (SD)	68.19 (9.97)	67.75 (9.95)	0.002
BMI (kg/m^2) -mean (SD*)	27.45 (4.45)	27.28 (5.29)	0.031
PROPHYLAXIS= extended duration -n (%)	4849 (84.3)	4461 (16.6)	<0.001
ASA -n (%)			
Healthy (I)	1605 (29.2)	6926 (26.5)	
Mild (II)	3280 (59.7)	15913 (60.9)	
Severe (III)	598 (10.9)	3228 (12.3)	
Life-threatening (IV)	7 (0.1)	70 (0.3)	
Moribund (V)	0 (0.0)	1 (0.0)	<0.001
ELIXHAUSER -mean (SD*)	0.76 (0.93)	0.63 (0.93)	<0.001
EDUCATION -n (%)			
Low	1929 (33.6)	8616 (32.1)	
Middle	2447 (42.6)	11113 (41.4)	
High	1372 (23.9)	7120 (26.5)	<0.001
CIVIL STATE -n (%)			
Couple	3260 (56.7)	15254 (56.8)	
Single	1622 (28.2)	7774 (29.0)	
Widow	866 (15.1)	3822 (14.2)	0.205
FIXATION -n (%)			
Cemented	4142 (72.1)	17123 (64.0)	
Uncemented	888 (15.5)	4371 (16.3)	
Hybrid	93 (1.6)	210 (0.8)	
Reversed hybrid	609 (10.6)	4607 (17.2)	
Resurfacing	13 (0.2)	463 (1.7)	<0.001

*SD= Standard deviation

Table 9
Thromboprophylactic regimen with outcome and logistic regression, both crude and adjusting for age, sex, length of thromboprophylaxis and previous treatment with platelet aggregation inhibitors

Outcome	Prophylaxis	Complication	Odds Ratio (95% CI)	
		n (%)	Unadjusted*	Adjusted*
VTE	LMWH	264 (1.0)	0.42 (0.27-0.63)	0.42 (0.26-0.67)
	NOAC	24 (0.4)		
DVT	LMWH	170 (0.6)	0.47 (0.27-0.74)	0.52 (0.29-0.90)
	NOAC	17 (0.3)		
PE	LMWH	108 (0.4)	0.35 (0.15-0.66)	0.32 (0.14-0.67)
	NOAC	8 (0.1)		
Bleeding	LMWH	468 (1.7)	1.00 (1.00-1.00)	0.99 (1.00-1.00)
	NOAC	102 (1.8)		
Reoperation	LMWH	162 (0.6)	1.13 (0.78-1.58)	0.99 (0.64-1.51)
	NOAC	39 (0.7)		
Mortality	LMWH	38 (0.1)	0.74 (0.28-1.62)	0.84 (0.28-2.25)
	NOAC	6 (0.1)		

* = with LMWH as 1 (reference)
CI -Confidence Interval, VTE -Venous Thromboembolism, DVT -Deep Venous Thrombosis, LE -Pulmonary Embolism

Table 10
Duration of prophylaxis with distribution of therapeutic agents within groups

Agent		Duration of prophylaxis		Total
		Short	Extended	
LMWH (%)		22420 (83)	4461 (17)	26881
	Dalteparin (%)	13979 (76)	4458 (24)	18437
	Enoxaparin (%)	3128 (100)	0 (0)	3128
	Tinzaparin (%)	5313 (100)	3 (0)	5316
NOAC (%)		903 (16)	4849 (84)	5752
	Dabigatran (%)	726 (19)	3189 (81)	3915
	Rivaroxaban (%)	177 (10)	1660 (90)	1837
Total (%)		23320 (71)	9310 (29)	32633

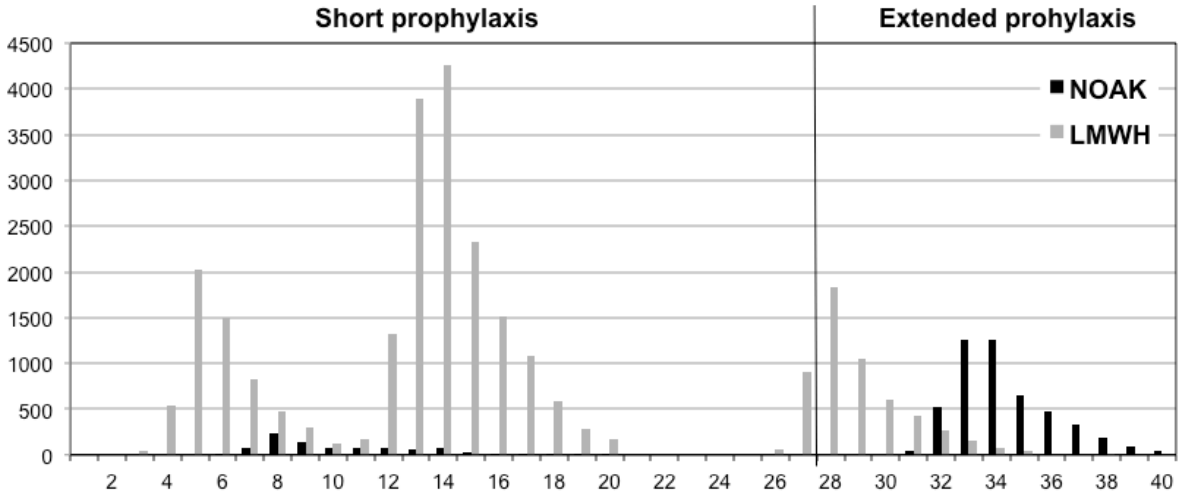

Figure 3
Distribution of NOAK and LMWH according to duration of thromboprophylaxis in days

5 DISCUSSION

The success of hip arthroplasties is reflected in the great and increasing numbers of operations performed each year. The improving implant survival offers surgical treatment to younger patients[124], simultaneously as the increasing safety of operative techniques and perioperative care enables older patients and those with increased comorbidities to benefit from arthroplasties. Even though the complication rates are low, the absolute numbers of patients with complications are rising as the numbers of procedures increase. This represents both a great challenge and a call for continuous improvement.

In this thesis aspects of two complications after hip arthroplasty are discussed. Both have gone from being relatively frequent complications of an uncommon procedure in the early days of hip arthroplasty to infrequent complications of a common procedure, resulting in many more suffering patients. Prosthetic joint infection (*Study I - III*) is the most feared complication and venous thromboembolism is the most common medical complication, VTE (*Study IV*).

5.1 PROSTHETIC JOINT INFECTIONS

5.1.1 Incidence and outcome

PJI is a terrible complication and many parallels to other serious diseases, such as cancer, can be drawn[125]. The five-year mortality rate of patients with PJI is in some cases higher than of many cancers, up to 26% to 71%[48,56]. Also many patients do not survive treatment for PJI. In a cohort of patients operated between 1996 and 2009 a 7% mortality rate has been reported in two-stage regimen[126] when, after the removal of the original implant, an antibiotic loaded cement spacer is implanted for subsequent second stage reimplantation of a new permanent arthroplasty. The results of *Study I* show a 10% mortality rate during treatment, before resolution of infection.

Incidence rates of PJI after primary THA range between 0.2% and 1.6%[51,55,127,128]. The results from *Study I* with 0.4% SSIs after elective surgery for degenerative hip disorder corresponds to these previously reported findings. However the wide range of incidence reflects different follow-up times, populations, performing centres and diagnostic criteria for infection. The diagnosis is often set by multiple observations, such as the course and presentation of symptoms, x-ray studies, results of blood samples and joint aspirations. The most important findings are cultures, which also may be of multiple origins and thereby of varied clinical significance, e.g. wound swabs, blood or synovial fluid cultures, cultures of tissue samples and polymerase chain reaction (PCR) analyses for the 16S rRNA bacterial gen detection. Nevertheless, all of them may mislead clinicians due to false positive results (contamination) or false negative, occurring as a result of previous antibiotic treatment and poor sampling or management of samples. There are recommendations which may assist clinicians to establish the diagnosis[119,121] but they are not entirely comprehensive and have been debated[129].

The 2.2% incidence of PJI in primary fracture prostheses and 2.5% in secondary fracture prostheses (*Study I*) results in a significantly increased risk of PJI, compared with arthroplasty due to degenerative hip disorder (HR of 4.3 and 6.1 respectively). Several comorbidities are associated with increased risk of SSI after THA, such as obesity, diabetes ASA-score >3, bleeding, long surgery duration, pre-operative anaemia and rheumatologic disease[53,130-134]. While it was not possible to adjust for all these variables in our analysis, the higher mean age and the indication for surgery in both fracture populations indicates higher comorbidities and may be regarded as supportive of these previous findings. Conversely male gender was not previously described to be associated with increased risk of PJI after hip arthroplasty surgery. Also we have not found any analyses of risk of PJI after secondary hip prosthesis surgery. These patients' highest risk of PJI can be explained by increased surgical trauma, longer duration of surgery, increased risk of bleeding, higher comorbidities and decreased preoperative general condition.

The late occurring infections caused by HS predominantly occurred in the degenerative hip disorder population. An explanation of this finding is the overall shorter survival time of hip fracture patients[135].

The microbiology of infections in *Study I* showed a dominance of staphylococcus aureus and coagulase-negative staphylococci did not differ from previous findings[60,133]. Polybacterial infections were more common in degenerative hip disorder patients and some of these infections also included staphylococcus aureus and coagulase-negative staphylococci. We did not observe any infections caused by methicillin-resistant staphylococcus aureus and methicillin-resistant staphylococcus epidermidis. These antibiotic resistant bacteria are an increasing challenge in treatment of PJI[136].

The end results of PJI treatment in *Study I* showed that 27 patients (44%) had a resection arthroplasty as the final outcome (Table 11). Moreover, 22 patients (81%) of these patients were fracture patients. There are only few publications describing resection arthroplasty as outcome after PJI treatment. Westberg et al.[54] reported an incidence of 29% in a prospective consecutive series of 184 hip fracture patients treated with arthroplasty (3 THAs and 181 bipolar HAs) and followed for 18 months. From a retrospective registry study, Teterycz et al.[137] reported eight resection arthroplasties of 52 PJIs with a median follow-up of 2.3 years. Choi et al.[138] described 10 resection arthroplasties in 93 infected THAs (8 fracture patients) in a study with a mean follow-up of 4.9 years. Finally Guren et al.[56] reported a final result of 32% (12 cases of 37 PJIs) resection arthroplasties after PJI treatment of 519 HAs. In comparison, we found a higher incidence of performed resection arthroplasties. Differences in results could be explained by our longer follow-up time of minimum 5 years, the nation-wide coverage through SNPR and inclusion of secondary fracture prostheses. In our study, 56% of patients had a fracture diagnosis. Due to higher age and comorbidities in this population, compared with patients with a degenerative hip disorder, two-staged treatment is not always suitable for these frail patients.

Table 11
Final outcome of PJI in relation to indication for surgery

	All	PJIs	Final outcomes of treatment					
			Resection arthroplasty		Preserved prosthesis		2-stage revision	
	n=3807	n=62	n=27 (44%)**		n=25 (40%)		n=10 (16%)	
				Ab*		Ab*		Ab*
Degenerative disorder	n=1682	13	3	2	4	1	3	0
Primary fracture	n=1122	24	10	2	7	3	2	0
Secondary fracture	n=1003	25	10	0	8	2	5	0

* = Lifelong antibiotic therapy
**= 11 primary (performed as initial treatment) and 16 secondary (performed after failure of initial treatment strategy)

Furthermore, treatment of fracture patients with debridement, antibiotics and implant retention more often results in failure[56,139], which consequently worsen the outcome and may require a subsequent resection arthroplasty for resolution of the infection.

These reported outcomes are observations from cohort studies and can only partially reflect a true nationwide outcome. Some countries have introduced SSI surveillance systems to monitor postoperative infection rates, including hip arthroplasty surgery. These registries may be a reliable tool and include clinical established PJI diagnoses, regardless of the different diagnostic criteria. In practise it is however difficult to establish complete registrations from all operating units. Surveillance through nation registries has also shown underreporting[64,65]. Sweden lacks an infection specific register and a model of national incidence surveillance, through cross matching of registries, with a subsequent medical records review has been proposed[55]. This method may be the most all-embracing and therefor result in nearly optimal assessment of the true incidence of PJI on a national level. However, until better reporting systems are in place, the assessment of clinical outcome of treatment of PJI will remain within the scope of cohort studies.

Finally it is also important to mention the efforts to decrease rates of PJI. There are several guidelines that can potentially result in a significant decrease of PJI rate and, through earlier detection of infection, also improve outcome of treatment. Some of these recommendations are guidelines from: The World Health Organization (WHO), the Centre for Disease Control and Prevention (CDC)[140], the Society for Healthcare Epidemiology of America (SHEA)[141] and the National Institute for Health and Care Excellence (NICE) in the United Kingdom[142]. However a worldwide implementation of all suggested methods in each individual hip arthroplasty patient is challenging and possibly unachievable.

In Sweden all 72 (as of year 2015) orthopaedic departments performing hip and knee arthroplasties participate in the multi professional initiative PRISS (Prosthesis Related Infections Shall be Stopped). The project was initiated by LÖF in 2008 and fully adopted by all units in 2013. A study of patient insurance claims showed that prior to 2008, orthopaedics was the specialty that had the highest rate of compensated claims (33%), with postoperative infection as the most common reason[143]. The objective behind initiation of PRISS was to reduce the incidence of infections by 50%. PRISS consists of four sections of recommendations, each reviewed and summarized by an expert group:

1. Risk factors and preoperative optimization of patients
2. Prophylactic antibiotic treatment
3. Early detection and registration of infection
4. Optimal surgical environment in hip and knee arthroplasty surgery

The strength of this project was its wide approach and implementation through collaboration rather then imposing directives. This may have resulted in a broader implementation of recommended measures and an assessment of possible decrease of nationwide PJI rates is planned.

5.1.2 Air quality in surgical environment

As shown in *Study I*, the consequences of PJI can be devastating. As described earlier, improvement of surgical environment through better air quality control prevents PJIs. This is achieved through appropriate ventilation and CAS. The number of staff in operating rooms also influences CFU-values[144], as more individuals generate an increased amount of potentially bacteria carrying skin scales. Likewise, the behaviour and patterns of movement of operating room personnel also increases the amount of CFU in air[145,146]. Additionally, door openings contribute to contamination of air[144]. This equals out the pressure gradient between the operating room and surrounding spaces communicating with it, allowing contaminated air from outside to diffuse into the operating room.

In *Study II* we compared two new CASs with currently used arrangement of a CAS system combined with two mobile LAF units. This selection of current CAS followed previous measurements in our department[71]. The need for further improvement of air quality resulted in addition of LAF units. As they were perceived to influence the working environment negatively, new efforts were put in place to evaluate other CAS systems.

We did not achieve desired values of <5CFU/m^3. The BARRIER® Clean Air Suit was our best performer with median CFU/m^3 values of 12.0. Measurements of all three systems varied noticeably and this finding is consistent with previous studies[43,144,147]. Measurements with BARRIER® Clean Air Suit were later repeated and compared to another CAS system in our department with better and less variable values[148] then in our study. The reported mean value of 7 elective arthroplasties was 7.0 CFU/m^3; all performed in a different operating room with likewise turbulent mixing ventilation, but with a higher air intake (996L/s vs. 620L/s in *Study II*). Moreover, these measurements were assisted by a mobile air filtration unit (Dopair, ATA Medical, Nantes, France), which delivered 360L of purified air per second, vs. TOUL's combined 220L/s. The sizes of the operating room used in *Study II* and in this more recent assessment are comparable. Thus the results of the later study reflect the impact of ventilation, with improved CFU values achieved through more efficient dilution of air in the operating room.

Cederlund and Tell recently performed a well-conducted analysis of the impact of ventilation systems[70], which demonstrates the complexity of evaluation of the surgical environment. It started as an investigation ahead of the choice of a new ventilation system for the Karolinska Hospital in Huddinge, Stockholm. The challenge was approached in a comprehensive way: CFU measurements were conducted in multiple locations, air travel of micro particles was mapped, smoke was used to detect air-flow patterns and computer simulations, so called Computional Fluid Dynamics, were performed. Additionally the impact of heat generated by different equipment, on higher and previously not tested levels, was added to the analysis. This all-inclusive methodology resulted in new observations. The phenomenon of entrapment of air by shoulder-to-shoulder position of operating personnel resulted in slower dilutions of smoke and has not been described earlier. The positive and negative aspects of different ventilation systems were described and the investigation showed that sufficient LAF solutions increased the flexibility of choice of different CAS.

The observed outliers in both *Study II* and other studies[144,147], can not directly be explained by variations in number of staff in the operating room, the individuals within each operating team, the specific procedure performed, door openings or the ventilation. The lower airflow in the operating room used in *Study II* may also be too weak to compensate for the irregular air streams created through the required higher physical activity in joint replacement surgeries. This difficulty reflects the complex and multifactorial relationship of real conditions of the surgical environment of operating rooms, where industrial standards therefore fail to predict the real outcome[72]. Therefor, in procurements of ventilation systems, The Swedish Board of Health and Welfare suggests definition of CFU/m^3 level to be achieved during a standardised surgical procedure with a specified clothing system[149].

As mention earlier, different constellations, temperature gradients and diverse activities can create unforeseen air streams[73]. All these influencing factors and the consecutive variation of CFU values, indicates that we have to be cautious when comparing and discussing CFU values as a single outcome variable of air quality measurements in surgical environments. It can best be regarded as one of many tools of assessment of clinical settings.

As change of ventilation systems in already existing units is rarely an alternative. The assessment presented in *Study II*, together with previous measurements[71,72] and the subsequent study[148], represent our departments continuous efforts of improvement of air quality in our surgical environment.

5.1.3 Patient insurance

The Swedish Patient Safety Act, from 2011, obligates healthcare personnel to inform patients about the possibility of filing a malpractice claim[150]. According to the Swedish patient insurance scheme, claimants with SSI, resulting from IC, are entitled to compensation by LÖF.

Our main finding in *Study III* was the overall high incidence of non-claimants. However, an absolute majority of filed claims were accepted for compensation by LÖF. This relation indicates on the one hand that those few patients that are claiming an injury from PJI are well informed about individual circumstances and eligibility for compensation, but on the other hand it also strongly suggests insufficiency in information from healthcare personnel to a large number of patients who do not make a claim. Although *Study III* involved patients who were diagnosed with infection before the Patient Safety Act was applied (from 2005 to 2010), the knowledge about the act still varies among healthcare personnel[80]. It is tempting to explain this with deficient knowledge of the Patient Injury Act among the personnel and not nationwide neglect. On the contrary, LÖFs initiation of the PRISS project, between 2008 and 2013, may have increased the awareness of LÖF among healthcare personnel. Probably a combination of few faulty perceptions coincides. Except for a deficient awareness of legal obligations about patient information, other possible explanations may be incorrect impression of the system not being blame-free for practitioners, with a following unwillingness to report colleagues. Moreover, in cases of fast and relatively complication free recovery, healthcare personnel may not inform patients based on their own judgment, an assumption of certain cases not being severe enough to generate compensation. As shown in *Study I*, most PJIs are SSIs, resulting from IC. We believe that inclusion of infections caused by HS was limited by the postoperative observation time. Therefor HS infections cannot explain the high incidence of non-claimants.

Age above 73 years and fracture diagnosis were two significant factors associated with lower rates of filed claims. Higher rates of non-claimants in the elderly correspond to previous findings[78,151-154]. To our knowledge, specific claim rates of THAs operated as a result of fractures have not been studied previously. Their decreased claim rate suggests that healthcare personnel may be less prone to inform elderly patients, with possibly higher comorbidity, about the insurance. As described in *Study I*, increased age and fracture diagnosis, possibly due to associated comorbidities, are also associated with poorer outcome after treatment of PJI. Conversely in *Study III* age was not observed to affect LÖF's decisions of claims. Since the overall incidence of claims was low, it is not possible to draw any conclusions about outcome after PJI in the population of *Study III*. One possible explanation of our equal distribution of claims´ outcome is that the more frail patients never filed a claim. These results point towards several additive negative factors for elderly fracture patients.

Another trend is the higher rate of claimants among patients operated in private hospitals. Their population of elective patients, commonly healthier and more aware of their rights and entitlements, may explain this. The private units may also have a better dialogue with their patients, which also can be a contributive factor.

We chose the highest achieved educational level, as an indication of socioeconomic status, because of its accessibility in the population registers and conclusive definition. Income levels are difficult to match on lifetime earnings, family income or between monthly salaries and pensions. Higher rate of non-claimants in socioeconomic deprived areas has previously been described[151]. Classification of

these areas is controversial in their definition as well as the limited size of the studied population did not allow for such analysis. While we did not observe any significant association, a trend of higher education resulting in increased likelihood of filing a claim, was observed. Patients with higher education were younger, which could party explain our finding.

The 21 county councils are responsible for organization of healthcare in Sweden and each hospital has a natural geographic and organizational belonging. Populations vary between counties with consecutively lower absolute numbers of PJIs in smaller counties. This fact strongly influenced our analysis of national differences of claim incidence, since every claimant had a large impact in majority of counties. Consequently no national difference in claims rates was observed above the county level. The highest and lowest incidences were identified in smaller counties. Only two counties, Västra Götaland (Gothenburg) and Stockholm, had more then 10 claimants (26 with 38 % claim rate and 23 with 30 % claim rate respectively).

LÖF's compensations to individual patients vary considerably and are dependant on a many factors; e.g. disability, age, predicted loss of income and other reimbursements. However the total cost for the accepted claims was 8.8 million SEK until December 2016. Calculated for the non-claimants of the studied population, Swedish healthcare holds a potential reimbursement of 26.2 million SEK for these infections or above 80 000 SEK per patient, which is in line with LÖF's own estimation of costs of about 90 000 SEK per reimbursed infected patient[155].

The Insurance Sweden consensus tables set a permanent disability level of 40% after a resection arthroplasty[84]. The disability level, beyond permanent resection arthroplasty, was not possible to assess with our study design in *Study I*. However referring to these consensus tables, 44% (27 of 62) of patients with PJI in *Study I* reached a 40%-level of permanent disability. In *Study III*, only 3.6% of claimants where acknowledged a compensation of above 30% disability (Figure 2).

Through various patient safety projects, like PRISS, LÖF has taken on a roll as not only the insurer but also as an initiator of prevention of complications. This is facilitated by its reputation among healthcare personnel and patients, as well as its ownership by healthcare providers –the county councils. This unique constellation has a great potential for future improvements and evaluations of patient safety.

In summary, results of *Study III* suggest that the elderly fracture population is not informed and helped in filing claims by healthcare personnel. Additionally, these patients may refrain from filing claims due to perception of the process as difficult and long lasting. The fact of a free of charge, two page form and the relatively short time to decision (70% within 8 months)[85] is not obvious to the general population. It must be strongly suspected that most patients may not be aware that they have sustained an injury and thereby the system's recognition of it. It is therefore of major importance to actively inform patients suffering from PJI about their legal right of filing claims to LÖF and provide assistance when needed.

5.2 THROMBOEMBOLIC EVENTS AND PROPHYLAXIS

The most commonly used groups of TP drugs after elective THA in Sweden are LMWH and NOAC. In *Study IV* we examined unique nationwide cohort of 32 663 elective total hip arthroplasty patients. The study showed a significantly lower risk of VTE in the NOAC group, compared to the LMWH group. The efficiency of NOAC has been reported previously in several meta-analyses of symptomatic VTE, combining THA and total knee arthroplasty patients. They present adjusted results, favouring NOAC based on data of asymptomatic events[111,156]. Among recently published trials, only the large rivaroxaban phase IV XAMOS trial had symptomatic VTE as primary end point. A similar incidence of 0.3% was reported in THA patients with rivaroxaban TP, as compared to standard-of-care (OR 0.43, CI 0.24 - 0.80)[105] constituting of several different TP regimens as the comparator.

Clinical trials often fail to adhere to standardised definitions and reporting of bleeding complications[157]. Direct comparison is therefore difficult. However analysis of bleeding is important as safety assessment of TP. The selection of a TP regimen relies on the balance between the desire to minimise thromboembolic events and the attempt to reduce the risk of bleeding. The recommendations regarding assessment of bleedings usually include measures of blood loss, transfusions, fall in haemoglobin levels or bleeding leading to alternation or cessation of treatment[157,158]. These events can be assessed in clinical trials but are more difficult to evaluate in register studies. On the contrary, register studies offer an opportunity to include the larger populations needed to study infrequent adverse events. In *Study IV* there was no significant difference in risk of bleeding events between LMWH and NOAC. This is supported by the RE-NOVATE I and II dabigatran trials[102,103] and the rivaroxaban trials RECORD I and II[159], the XAMOS trial[105], as well as several meta-analyses[110,156]. Contrarily other meta-analyses found an increased incidence of bleedings[111,112]. Due to the high completeness of our registers, we consider the risk of a significant amount of missed bleedings to be negligible. Rather the opposite can exist, bleedings not related to TP may have been registered. Compared to other studies[92,108,114,159,160], the wide-ranging bleeding definition in *Study IV* results in a negative influence on our safety analysis but with equal distribution in both TP groups.

During the last 3 years of the study 25% of patients were prescribed NOAC. A new, extended cross matching would be needed to assess today's distribution. However, with time NOACs have become a less novel choice and it is therefor probable their share as TP agents has increased. On the contrary National Joint Registry reports 24% of patients receiving NOAC as TP after primary THA in 2016[22].

The difference in duration of TP between the two groups reflects the absence of consensus and national guidelines. Our large study population allowed for a separate subanalysis of this occurrence in the larger LMWH group and showed that the treatment length did not influence the risk of VTE. In Figure 3 a pattern of treatment lengths can be observed, which follows regimens of TP duration of up to one, two and four weeks with LMWH and 5 weeks with NOAC. This can be interpreted as a reflexion of the various established regimens of TP and likewise tailored sizes of prescribed packages of medications, supplied by the pharmaceutical companies. Several earlier studies reported a prolonged risk of VTE and suggested a need for extended TP[104,161-164]. Out of the more internationally acknowledged guidelines, NICE[99] recommends extended TP of 28 to 35 days postoperatively, while it is only suggested by ACCP[93]. A recent Cochrane review concluded that there is moderate quality evidence suggesting extended duration of TP but it should be considered for patients undergoing

THA, although the benefit should also be weighed against the increased risk of minor bleeding[165]. On the contrary several studies report low rates of VTE with short duration TP and fast-track surgery[166-168]. Patients suitable for fast-track surgery are usually younger and healthier[168] and thereby able to take greater advantage of the VTE-preventing effect of faster mobilisation. A partial explanation to our finding of non-increased risk of VTE with short duration of TP in the LMWH group may lie in our exclusion criteria. The elimination of patients who did not purchase their TP medications within 10 days after operation, had a documented VTE five years prior to the operation and were prescribed LMWH, NOAC or warfarin 6 months preoperatively, most probably decreased comorbidity in our cohort. This could result in faster mobilisation and recovery in the studied population and conclusively a decreased overall risk of VTE in these patients.

The choice of TP after primary THA remains a subject of debate. Advances in anaesthetic techniques[92] and early mobilisation[166] are suggested to reduce the background risk for VTE[93] and thereby allow for use of less potent TP agents, such as ASA. This may decrease the risk of bleeding and wound complications[169-171], as well as being a more cost-effective alternative[172]. Although earlier usage of ASA as TP was debated, its popularity increased after the PEP trial[98]. This trial has been criticised as it allowed for parallel usage of other TP agents together with ASA. Nevertheless recent knowledge[173,174] and guidelines support the role of ASA in prevention of VTE. Various associations have changed their view on TP with ASA, which is now recommended by the American College of Chest Physicians (ACCP)[93], the American Academy of Orthopaedic Surgeons (AAOS)[175] and the British Hip Society[176]. However, the NICE guidelines do not recommend ASA as a sole agent with concern of limited literature comparing ASA with other TP agents[99,172]. The heterogeneity of patients undergoing THA surgery is difficult to cover by one optimal regimen and individualised therapies can be applied[177]. These are however difficult to establish. Among resent publication, one cohort study included 1 152 low-risk patients operated with a hip or knee arthroplasty and reported an incidence of symptomatic VTE of 1.1%, with combined aspirin and pneumatic compression treatment as a multimodal regimen of TP[178]. A large British register study of 108 584 patients found a significantly lower mortality with LMWH, compared to aspirin while the outcome of VTE (1.6% vs. 1.7% respectively) did show any significant differences[160]. A trial of elective THA patients with initial 10 days TP with dalteparin, followed by randomisation between continued TP with ASA or dalteparin for a total time of 28 days, reported a lower incidence of VTE in patients assigned to continued therapy with ASA then dalteparin (0.3% vs. 1.3%). The incidence of clinically significant bleeding was also lower in the ASA group (0.5% vs. 1.3%)[179]. However these results are based on only 778 subjects as the trial was stopped due to slow enrolment. In conclusion, there is evidence of ASA's effectiveness and safety[180] but limited by variations of comparison, quality of studies, administered doses and regimens with combinations of agents and multimodal approaches[178,179,181-184], incomplete follow-up[185], and risk of reversed causality[186]. The low incidence of VTE in *Study IV* can be compared to previous publications but, as the definitions of bleedings vary considerably between both cohort and register studies, safety outcomes should be compared with caution and attention to their definitions.

Study IV is a unique and large study, with nationwide coverage and analysis of effectiveness of TP, comparing NOAC and LMWH as postoperative TP after primary THA performed due to osteoarthritis. Moreover, the study was performed independently of any financing or affiliation with manufacturers or other interest groups. Our analyses showed a superiority of NOACs effectiveness in VTE prevention, reducing the risk of VTE by more than 50%, compared to LMWH, with remained safety profile. The quality of our registers and the large cohort reassures clinical generalizability of our results.

5.3 LIMITATIONS

Each of the studies of this thesis has its limitations. The main ones are presented below:

Study I

The long study period of 10 years spans over a period of many inconclusive regimens and is the main limitation of this study. No consensus or defined diagnostic criteria were used to ensure early detection of PJIs. Moreover surgeons decided on treatment regimen based on their own experience and opinion, which in many cases may have resulted in a deficient approaches, compared to current standards. This is supported by the comprehensive review of patients´ records. Inadequate and varied series of lavage and debridement were often used to salvage the implants. This may have resulted in higher frequencies of treatment failure and/or resection arthroplasties. On the contrary, nationwide register studies are limited by poor quality of data and deficient reporting from surgeons[64,65].

Study II

The Mertex CAS were supplied as brand new for this study, while in everyday practice these are used as washed (up to 50 times), reusable CAS. This can have a negative effect on their permeability of airborne particles. Consequently, the measurements of the daily used Mertex system may show even higher CFU values. Additionally, condensate on the lids of 25 measurements may have been avoided by allowing for longer time of adaptation to room temperature, after being taken out from their cold storage.

Comprehensive evaluation of surgical environments requires several different measuring methods and computing models. *Study II* presents a method for assessment and improvement of existing settings but its direct application on future projections and erections of operating rooms, ventilation systems or procurements of CASs should be done with caution.

Study III

As mentioned, the population of this study acquired their infections before both the Patient Safety Act of 2011 and the completion of introduction of PRISS. Despite the fact that the objective of PRISS is to decrease the incidence of PJI, and not to implement better obedience of the law, the implementation of PRISS may have resulted in higher awareness and knowledge of LÖF. Therefore these results do not directly reflect the current settings. However, we have reasons to believe that the knowledge of LÖF is deficient among healthcare personnel[80]. Additionally the overall annual increase of filed claims to LÖF of about 2%[81] suggests continued low rates of filed patient claims.

Study IV

The incidence of VTE and adverse events may have been decreased by our exclusion criteria, since patients with documented VTE five years prior to the operation and patients with prescribed LMWH, NOAC and warfarin 6 months preoperatively were excluded. Furthermore exclusion of patients, who didn't purchase their TP medications within 10 days after operation, may have excluded individuals with prolonged wound drainage[65,108,109] or higher comorbidity. Based on the high number of observations we think that there is a low probability for skewed distribution of possible confounders between the NOAC and the LMWH groups.

All patients where postoperative prescription data on TP was absent were excluded, consequently withdrawing 16 899 patients from this analysis. As this data is automatically transferred to SPDR, and after discussing the matter within the Swedish Hip and Knee Association (representing the majority of THR surgeons in Sweden) we are feeling certain that large proportion of these patients were provided a supply of TP medications on discharge, consequently bypassing the SPDR. No further analysis of these patients was performed and their impact on the true national incidence of VTE after THA is unknown.

There may be residual confounding in patients' demographic and clinical characteristics. For example patients with NOAC treatment had higher comorbidity according to the Elixhauser score. According to previous studies, this should have influenced results with higher incidence of VTE in the NOAC group[92,94]. The higher incidence of cemented fixation among the NOAC patients may also partly reflect the higher comorbidity in this group, as the preferred fixation for patients of higher age and comorbidities. However, the role of fixation on VTE, beyond the immediate postoperative period, is debated. Cemented fixation is reported as both associated with higher[187] and lower[188] incidence of VTE. Any association of cemented fixation and increased risk of VTE would consequently disadvantage NOAC.

6 CONCLUSIONS

- Patients with a displaced femoral neck fracture treated with primary or secondary fracture arthroplasties have a greater risk of PJIs and display worse outcomes compared with patients with a total hip replacement due to degenerative hip disorders.
  - Study I

- Single-use polypropylene clothing systems can replace mobile laminar airflow unit-assisted reusable mixed material-clothing systems. Measurements in standardized laboratory settings can only serve as guidelines as surgical environments in real settings present a much more difficult challenge.
  - Study II

- The incidence of patient claims of PJI is low but claims are usually accepted when filed. Healthcare personnel should increase their knowledge of LÖF and the Patient Injury Act to inform patients about possibilities of eligible compensation.
  - Study III

- Thromboprophylaxis with NOAC extending for a minimum of 28 days is a safe and more effective regimen than LMWH for the majority of patients undergoing elective primary THA surgery. It reduces the incidence of VTE by 50% with no difference in bleedings, reoperations and mortality.
  - Study IV

7 FUTURE PERSPECTIVES

When thinking of future perspectives, it is hard to not be inspired by the upcoming possibilities of artificial intelligence (AI). The first study on its possible implementation in orthopaedics has already been published[189]. Cross matching of registries for outcomes and their associations can potentially also be carried out by machine-learning algorithms, perhaps resulting in previously unidentified predictors. While further development and evaluation of implementation of these possibilities is needed, the suggested studies below may be undertaken much sooner.

Prosthetic hip infections and patient insurance

Arthroplasties included in *Study I* and *III* were performed prior to the Patient Safety Act and complete implementation of the PRISS project. An evaluation of the "post-PRISS" infection rate is planned. As PRISS mainly deals with prevention, it does not include recommendations regarding treatment. However it does recommend follow-up and early detection of infection, which in turn increases the likelihood of successful treatment. Therefore PRISS may not only have an impact on infection rates but also on outcome of treatment and consequently any acquired permanent disability. These are possible aspects of future studies of great interest to the suffering patients and insurance providers. In this context, the possibly increased awareness of LÖF, through PRISS, as well as the impact of the Patient Safety Act could also be assessed.

In a more distant future and stipulating higher rates of PJI claimed, feedback of patients' disability levels after treatment of PJI (as assessed by LÖF's expert reviews) could facilitate evaluation of different treatment regimens.

Thromboembolic events and prophylaxis

More studies are still needed to determine the best TP agent. Possibly there is not one but rather several treatments which should be distinguished for different groups of patients. Register studies capture large populations but fail to adjust for the variability of studied subjects. On the contrary, even large trials fail to include enough amount and diversity of patients. A large nationwide cluster-randomisation trial may have the potential to identify the right agents, were each hospital is a cluster treating patients with the allocated TP agent. A setting of different types and sizes of hospitals enables inclusion of satisfactory amount of subjects, through a catchall approach. Exclusion criteria could be, as far as possible, limited to obvious contraindications, e.g. advanced kidney failure. Randomisation of the different TP agents on hospital level facilitates adherence to the new local treatment regimens. Simultaneously it would enable standardised recording of patient factors and outcomes, particularly the bleeding and wound complications.

8 SAMMANFATTNING PÅ SVENSKA

De kliniska resultaten efter höftproteskirurgi är mycket goda idag. Livskvalitén kan höjas avsevärt för patienter med långdragna och invalidiserande smärttillstånd. Samtidigt är det även en mycket bra behandlingsmetod inom den akuta frakturkirurgin. Den låga komplikationsfrekvensen medför en ständig ökning av antalet operationer. Årligen behandlas över en miljon patienter världen över och ingreppet har utnämnts till århundradets operation. Denna utveckling, resulterar samtidigt i ett stigande antal komplikationer. Näst efter proteslossning och luxation är postoperativa, s.k. periprostetiska infektioner, den vanligaste och samtidigt den allvarligaste komplikationen för den drabbade individen. Behandlingen av infektioner är inte alltid framgångsrik och kan resultera i en livslång invaliditet. Venös tromboembolism, som utgörs av lungemboli och djup ventrombos, är den vanligaste medicinska komplikationen. Tre olika aspekter av infektioner (Studie I – III) och tromboskomplikationer (Studie IV) efter höftproteskirurgi diskuteras i denna avhandling.

Studier i avhandlingen

I studie I och II studerades patienter opererade på Södersjukhuset i Stockholm. Studie III och IV grundar sig på data ur nationella hälso- och kvalitetsregister.

Studie I: 3 884 patienter, opererade med höftprotes mellan 1996 och 2005, följdes i ett lokalt register. Patienter som erhöll höftprotes pga. degenerativ höftledssjukdom jämfördes med primära och sekundära (opererade pga. haveri av tidigare frakturbehandling) frakturproteser. Antalet periprostetiska infektioner och dess behandling samt utfall analyserades.

Studie II: Luftburna bakterier är en peroperativ smittokälla och god luftkvalité är därför ett krav för att erhålla en låg peroperativ infektionsfrekvens. Tre olika operationsdräkter jämfördes under 37 pågående ledprotesoperationer, genom 244 mätningar av mängden bakteriebärande luftburna partiklar.

Studie III: Alla patienter som behandlas inom svensk offentlig sjukvård är försäkrade i patientförsäkringen, LÖF. Tidiga och fördröjda periprostetiska infektioner klassificeras som regel som undvikbara vårdskador och patienterna har därmed möjlighet att få ersättning. Sjukvården är dessutom skyldig att informera patienterna vid uppkomst av vårdskada och möjligheten att anmäla denna till LÖF. En tidigare fastställd kohort av 441 periprostetiska infektioner jämfördes med LÖFs register över anmälda patientskador. Rapporteringsgraden till LÖF och utfall av anmälningarna studerades.

Studie IV: Genom trombosprofylax eftersträvas både en effektiv och säker behandling. Studien jämförde lågmolekulärt heparin och nya orala antikoagulantia, genom analys av effektivitet (utfall av lungemboli och djupa ventromboser) och säkerhet (utfall av blödningskomplikationer, reoperationer samt mortalitet) hos 32 663 patienter opererade med elektiva höftproteser.

Konklusion

Jämfört med patienter opererade pga. degenerativ höftledssjukdom, löper patienter med höftfraktur (opererade med primära eller sekundära höftproteser) en signifikant högre risk att drabbas av en periprostetisk infektion (0,4% vs 2,1% respektive 2,5%). Även utfallet av infektionsbehandlingen hos dessa patienter är sämre med en högre andel permanenta slinkleder, där höftprotesen avlägsnas för att behandla infektionen. Jämfört med artrospatienter, uppvisar frakturpatienterna därtill en signifikant lägre anmälningsfrekvens till LÖF (13% vs 28%). Den generella anmälningsgraden är låg (25%) men de flesta anmälningarna bifalles (96%). Detta antyder bristfällig kännedom om LÖF inom sjukvården.

Vi uppnådde inte de eftersträvade låga nivåerna av luftburna bakterier men engångsdräkter tillverkade av polypropylen var överlägsna de två andra undersökta flergångsdräkterna. Förbättring av luftkvalitén i befintliga operationssalar kan uppnås genom byte till engångskläder av polypropylen.

Behandlingsregim längre än 28 dagar med nya orala antikoagulantia halverar förekomsten av postoperativ venös tromboembolism hos patienter opererade med elektiv höftprotes. Den oförändrade säkerhetsprofilen antyder dessutom att en majoritet av höftprotespatienterna bör erbjudas förlängd profylax med nya orala antikoagulantia.

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10 REFERENCES

1. Nasser M, Tibi A, Savage-Smith E. Ibn Sina's Canon of Medicine: 11th century rules for assessing the effects of drugs. *J R Soc Med* 2009;102-2:78-80.

2. Bikdeli B, Sharif-Kashani B. Venous Thromboembolism: A Persian Perspective to Prevention, Diagnosis and Treatment. *North American Thrombosis Forum* 2010; Available at http://cl-natf-001.masstechnology.com/media/15133/persianvteperspectiveformat.pdf (accessed 1 Nov 2017).

3. Galanaud JP, Laroche JP, Righini M. The history and historical treatments of deep vein thrombosis. *J Thromb Haemost* 2013;11-3:402-11.

4. Mannucci PM. Venous thrombosis: the history of knowledge. *Pathophysiol Haemost Thromb* 2002;32-5-6:209-12.

5. Parapia LA. History of bloodletting by phlebotomy. *Br J Haematol* 2008;143-4:490-5.

6. Bagot CN, Arya R. Virchow and his triad: a question of attribution. *Br J Haematol* 2008;143-2:180-90.

7. Wright IS. Thrombophlebitis. *Bull N Y Acad Med* 1941;17-5:348-72.

8. Whitaker IS, Rao J, Izadi D, Butler PE. Historical Article: Hirudo medicinalis: ancient origins of, and trends in the use of medicinal leeches throughout history. *Br J Oral Maxillofac Surg* 2004;42-2:133-7.

9. McFadden PM, Ochsner JL. A history of the diagnosis and treatment of venous thrombosis and pulmonary embolism. *Ochsner J* 2002;4-1:9-13.

10. Mueller RL, Scheidt S. History of drugs for thrombotic disease. Discovery, development, and directions for the future. *Circulation* 1994;89-1:432-49.

11. Weiss HJ, Aledort LM, Kochwa S. The effect of salicylates on the hemostatic properties of platelets in man. *J Clin Invest* 1968;47-9:2169-80.

12. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nat New Biol* 1971;231-25:232-5.

13. Harrison MJ, Marshall J, Meadows JC, Russell RW. Effect of aspirin in amaurosis fugax. *Lancet* 1971;2-7727:743-4.

14. Harris WH, Salzman EW, Athanasoulis CA, Waltman AC, DeSanctis RW. Aspirin prophylaxis of venous thromboembolism after total hip replacement. *N Engl J Med* 1977;297-23:1246-9.

15. Alfaro MJ, Paramo JA, Rocha E. Prophylaxis of thromboembolic disease and platelet-related changes following total hip replacement: a comparative study of aspirin and heparin-dihydroergotamine. *Thromb Haemost* 1986;56-1:53-6.

16. McLean J. The discovery of heparin. *Circulation* 1959;19-1:75-8.

17. Jorpes E. The chemistry of heparin. *Biochem J* 1935;29-8:1817-30.

18. Crafoord C, Jorpes E. Heparin as a Prophylactic Against Thromboses. *JAMA* 1941;116-26:2831-5.

19. Link KP. The discovery of dicumarol and its sequels. *Circulation* 1959;19-1:97-107.

20. Holden WD. Treatment of deep venous thrombosis with reference to subcutaneous injection of heparin and use of dicumarol. *Arch Surg* 1947;54-2:183-7.

21. Karrholm J, Lindahl H, Malchau H, Mohaddes M, Rogmark C, Rolfson O. Swedish Hip Arthroplasty Register: Annual Report 2015. Gothenburg, Sweden. *Swedish Hip Arthroplasty Register,* 2016. Available at https://registercentrum.blob.core.windows.net/shpr/r/Annual-Report-2015-H19dFINOW.pdf (accessed 1 Nov 2017).

22. The NJR Editorial Board. 14th Annual Report 2017. *National Joint Registry for England, Wales, Northern Ireland and the Isle of Man.* Available at http://www.njrreports.org.uk/Portals/0/PDFdownloads/NJR%14th%Annual%Report%2017.pdf (accessed 1 Nov 2017).

23. Learmonth ID, Young C, Rorabeck C. The operation of the century: total hip replacement. *Lancet* 2007;370-9597:1508-19.

24. Hernigou P. Smith-Petersen and early development of hip arthroplasty. *Int Orthop* 2014;38-1:193-8.

25. Wiles P. The surgery of the osteo-arthritic hip. *British Journal of Surgery* 1958;45-193:488-97.

26. Moore AT. Metal hip joint; a new self-locking vitallium prosthesis. *South Med J* 1952;45-11:1015-19.

27. Charnley J. Arthroplasty of hip - a new operation. *Lancet* 1961;1-718:1129-&.

28. Gomez PF, Morcuende JA. A historical and economic perspective on Sir John Charnley, Chas F. Thackray Limited, and the early arthoplasty industry. *Iowa Orthop J* 2005;25:30-7.

29. Charnley J, Eftekhar N. Postoperative infection in total prosthetic replacement arthroplasty of the hip-joint. With special reference to the bacterial content of the air of the operating room. *Br J Surg* 1969;56-9:641-9.

30. Jones LC, Hungerford DS. Cement disease. *Clin Orthop Relat Res* 1987-225:192-206.

31. Pivec R, Johnson AJ, Mears SC, Mont MA. Hip arthroplasty. *Lancet* 2012;380-9855:1768-77.

32. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg Am* 2007;89-4:780-5.

33. Nemes S, Gordon M, Rogmark C, Rolfson O. Projections of total hip replacement in Sweden from 2013 to 2030. *Acta Orthopaedica* 2014;85-3:238-43.

34. Gill CJ, Gill GC. Nightingale in Scutari: her legacy reexamined. *Clin Infect Dis* 2005;40-12:1799-805.

35. Newsom SW. Pioneers in infection control. Ignaz Philipp Semmelweis. *J Hosp Infect* 1993;23-3:175-87.

36. Smith KA. Louis Pasteur he father of immunology? *Frontiers in Immunology* 2012;3:10.

37. Jessney B. Joseph Lister (1827-1912): a pioneer of antiseptic surgery remembered a century after his death. *Journal of Medical Biography* 2012;20-3:107-10.

38. Bourdillon RB, Colebrook L. Air hygiene in dressing-rooms for burns or major wounds. *Lancet* 1946;1-6400:601.

39. Blowers R, Crew B. Ventilation of operating-theatres. *J Hyg (Lond)* 1960;58-4:427-48.2.

40. Lidwell OM. Sir John Charnley, surgeon (1911-82): the control of infection after total joint replacement. *J Hosp Infect* 1993;23-1:5-15.

41. Noble WC. Dispersal of skin microorganisms. *British Journal of Dermatology* 1975;93-4:477-85.

42. Hambraeus A. Aerobiology in the operating-room - a review. *Journal of Hospital Infection* 1988;11:68-76.

43. Lidwell OM, Lowbury EJ, Whyte W, Blowers R, Stanley SJ, Lowe D. Airborne contamination of wounds in joint replacement operations: the relationship to sepsis rates. *J Hosp Infect* 1983;4-2:111-31.

44. Bozic KJ, Kurtz SM, Lau E, Ong K, Vail TP, Berry DJ. The epidemiology of revision total hip arthroplasty in the United States. *J Bone Joint Surg Am* 2009;91-1:128-33.

45. Bozic KJ, Ries MD. The impact of infection after total hip arthroplasty on hospital and surgeon resource utilization. *Journal of Bone and Joint Surgery-American Volume* 2005;87A-8:1746-51.

46. Kurtz SM, Lau E, Watson H, Schmier JK, Parvizi J. Economic Burden of Periprosthetic Joint Infection in the United States. *Journal of Arthroplasty* 2012;27-8:61-5.

47. Andersson AE, Bergh I, Karlsson J, Nilsson K. Patients' experiences of acquiring a deep surgical site infection: An interview study. *American Journal of Infection Control* 2010;38-9:711-7.

48. Zmistowski B, Karam JA, Durinka JB, Casper DS, Parvizi J. Periprosthetic Joint Infection Increases the Risk of One-Year Mortality. *Journal of Bone and Joint Surgery-American Volume* 2013;95A-24:2177-84.

49. Dale H, Skramm I, Lower HL, Eriksen HM, Espehaug B, Furnes O, Skjeldestad FE, Havelin LI, Engesaeter LB. Infection after primary hip arthroplasty A comparison of 3 Norwegian health registers. *Acta Orthopaedica* 2011;82-6:646-54.

50. Harrison T, Robinson P, Cook A, Parker MJ. Factors affecting the incidence of deep wound infection after hip fracture surgery. *Journal of Bone and Joint Surgery-British Volume* 2012;94B-2:237-40.

51. Ong KL, Kurtz SM, Lau E, Bozic KJ, Berry DJ, Parvizi J. Prosthetic Joint Infection Risk After Total Hip Arthroplasty in the Medicare Population. *Journal of Arthroplasty* 2009;24-6:105-9.

52. Phillips CB, Barrett JA, Losina E, Mahomed NN, Lingard EA, Guadagnoli E, Baron JA, Harris WH, Poss R, Katz JN. Incidence rates of dislocation, pulmonary embolism, and deep infection during the first six months after elective total hip replacement. *J Bone Joint Surg Am* 2003;85-a-1:20-6.

53. Ridgeway S, Wilson J, Charlet A, Kafatos G, Pearson A, Coello R. Infection of the surgical site after arthroplasty of the hip. *J Bone Joint Surg Br* 2005;87-6:844-50.

54. Westberg M, Snorrason F, Frihagen F. Preoperative waiting time increased the risk of periprosthetic infection in patients with femoral neck fracture. *Acta Orthop* 2013;84-2:124-9.

55. Lindgren V, Gordon M, Wretenberg P, Karrholm J, Garellick G. Deep infection after total hip replacement: a method for national incidence surveillance. *Infect Control Hosp Epidemiol* 2014;35-12:1491-6.

56. Guren E, Figved W, Frihagen F, Watne LO, Westberg M. Prosthetic joint infection-a devastating complication of hemiarthroplasty for hip fracture. *Acta Orthopaedica* 2017;88-4:383-9.

57. Dale H, Fenstad AM, Hallan G, Havelin LI, Furnes O, Overgaard S, Pedersen AB, Karrholm J, Garellick G, Pulkkinen P, Eskelinen A, Makela K, Engesaeter LB. Increasing risk of prosthetic joint infection after total hip arthroplasty. *Acta Orthop* 2012;83-5:449-58.

58. Kurtz SM, Lau E, Schmier J, Ong KL, Zhao K, Parvizi J. Infection burden for hip and knee arthroplasty in the United States. *Journal of Arthroplasty* 2008;23-7:984-91.

59. Zimmerli W, Ochsner PE. Management of infection associated with prosthetic joints. *Infection* 2003;31-2:99-108.

60. Phillips JE, Crane TP, Noy M, Elliott TS, Grimer RJ. The incidence of deep prosthetic infections in a specialist orthopaedic hospital: a 15-year prospective survey. *J Bone Joint Surg Br* 2006;88-7:943-8.

61. Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: A common cause of persistent infections. *Science* 1999;284-5418:1318-22.

62. McConoughey SJ, Howlin R, Granger JF, Manring MM, Calhoun JH, Shirtliff M, Kathju S, Stoodley P. Biofilms in periprosthetic orthopedic infections. *Future Microbiology* 2014;9-8:987-1007.

63. Girdlestone GR. Acute pyogenic arthritis of the hip: an operation giving free access and effective drainage. *The Lancet* 1943;241-6240:419-21.

64. Lindgren JV, Gordon M, Wretenberg P, Karrholm J, Garellick G. Validation of reoperations due to infection in the Swedish Hip Arthroplasty Register. *Bmc Musculoskeletal Disorders* 2014;15:6.

65. Jamsen E, Huotari K, Huhtala H, Nevalainen J, Konttinen YT. Low rate of infected knee replacements in a nationwide series--is it an underestimate? *Acta Orthop* 2009;80-2:205-12.

66. Hirsch T, Hubert H, Fischer S, Lahmer A, Lehnhardt M, Steinau HU, Steinstraesser L, Seipp HM. Bacterial burden in the operating room: Impact of airflow systems. *American Journal of Infection Control* 2012;40-7:E228-E32.

67. Pasquarella C, Sansebastiano GE, Ferretti S, Saccani E, Fanti M, Moscato U, Giannetti G, Fornia S, Cortellini P, Vitali P, Signorelli C. A mobile laminar airflow unit to reduce air bacterial contamination at surgical area in a conventionally ventilated operating theatre. *Journal of Hospital Infection* 2007;66-4:313-9.

68. European Committee for Standardization. The European Standard EN 13795:2011. *Swedish Standards Institute,* Stockholm 2011; Available at https://www.sis.se/api/document/preview/77550 (accessed 1 Nov 2017).

69. Reinmuller B, Ljungqvist B. Modern cleanroom clothing systems: people as a contamination source. *PDA J Pharm Sci Technol* 2003;57-2:114-25.

70. Cederlund B, Tell T. Tre nyanser av rent. *Ortopediskt magasin* 2016;4:20-5. (Article in Swedish)

71. Tammelin A, Ljungqvist B, Reinmuller B. Comparison of three distinct surgical clothing systems for protection from air-borne bacteria: A prospective observational study. *Patient Saf Surg* 2012;6-1:23.

72. Tammelin A, Ljungqvist B, Reinmuller B. Single-use surgical clothing system for reduction of airborne bacteria in the operating room. *Journal of Hospital Infection* 2013;84-3:245-7.

73. Sadrizadeh S, Tammelin A, Ekolind P, Holmberg S. Influence of staff number and internal constellation on surgical site infection in an operating room. *Particuology* 2014;13:42-51.

74. Cristina ML, Spagnolo AM, Sartini M, Panatto D, Gasparini R, Orlando P, Ottria G, Perdelli F. Can particulate air sampling predict microbial load in operating theatres for arthroplasty? *PLoS One* 2012;7-12:e52809.

75. Swedish Standard Institute (SIS). Teknisk specifikation SIS-TS 39:2012 -Mikrobiologisk renhet i operationsrum -Förebyggande av luftburen smitta - Vägledning och grundläggande krav. *Swedish Standards Institute.* Stockholm, Sweden: SIS Förlag AB, 2012. (Requirements in Swedish)

76. PRISS 4th expert group. Optimal operationsmiljö vid protesoperation i knä och höft (v. 2, rev 2015). PRISS, *Landstingens Ömsesidiga Försäkringsbolag*, 2015; Available at https://lof.se/wp-content/uploads/Optimal-operationsmilj%C3%B6.pdf (accessed 1 Nov 2017). (Recommendations in Swedish)

77. Sumner W. Health and life insurance as an alternative to malpractice tort law. *BMC Health Serv Res* 2010;10:150.

78. Studdert DM, Thomas EJ, Burstin HR, Zbar BI, Orav EJ, Brennan TA. Negligent care and malpractice claiming behavior in Utah and Colorado. *Med Care* 2000;38-3:250-60.

79. Studdert DM, Mello MM, Sage WM, DesRoches CM, Peugh J, Zapert K, Brennan TA. Defensive medicine among high-risk specialist physicians in a volatile malpractice environment. *Jama* 2005;293-21:2609-17.

80. Espersson C, Hellbacher U. *Patientskadelagen -en kommentar m. m.* Riga, Latvia: Vulkan, 2016.

81. LÖF. Anmälningar till LÖF 2016. Stockholm, Sweden: *Landstingens Ömsesidiga Försökringsbolag,* 2017; Available at http://lof.se/wp-content/uploads/Statistik-2016-Hela-Sverige.pdf (accessed 1 Nov 2017). (LÖF Injury report 2016 in Swedish)

82. Sveriges Riksdag. Svensk författningssamling, Patientskadelag (1996:799), 2017:43. Available at http://www.riksdagen.se /sv/dokument-lagar/dokument/svensk-forfattningssamling/ patientskadelag-1996799_sfs-1996-799 (accessed 1 Nov 2017). (The Swedish Parliament, Patient Injury Act)

83. Pukk-Harenstam K, Ask J, Brommels M, Thor J, Penaloza RV, Gaffney FA. Analysis of 23 364 patient-generated, physician-reviewed malpractice claims from a non-tort, blame-free, national patient insurance system: lessons learned from Sweden. *Qual Saf Health Care* 2008;17-4:259-63.

84. Insurance Sweden. Medicinsk Invaliditet –skador 2013. *Svensk Försäkring,* 2014. Available at http://www.svenskforsakring.se/globalassets/medicinska-tabellverk/medicinska-tabellverk/medicinsk_invaliditet_skador_rev_jan2014.pdf (accessed 1 Nov 2017). (Insurance tables in Swedish)

85. Kachalia AB, Mello MM, Brennan TA, Studdert DM. Beyond negligence: avoidability and medical injury compensation. *Soc Sci Med* 2008;66-2:387-402.

86. Bergqvist D, Lindblad B. A 30-year survey of pulmonary embolism verified at autopsy: an analysis of 1274 surgical patients. *Br J Surg* 1985;72-2:105-8.

87. Prandoni P, Villalta S, Bagatella P, Rossi L, Marchiori A, Piccioli A, Bernardi E, Girolami B, Simioni P, Girolami A. The clinical course of deep-vein thrombosis. Prospective long-term follow-up of 528 symptomatic patients. *Haematologica* 1997;82-4:423-8.

88. Sullivan SD, Kahn SR, Davidson BL, Borris L, Bossuyt P, Raskob G. Measuring the outcomes and pharmacoeconomic consequences of venous thromboembolism prophylaxis in major orthopaedic surgery. *Pharmacoeconomics* 2003;21-7:477-96.

89. Ginsberg JS, Turkstra F, Buller HR, MacKinnon B, Magier D, Hirsh J. Postthrombotic syndrome after hip or knee arthroplasty: a cross-sectional study. *Arch Intern Med* 2000;160-5:669-72.

90. Wittine LM, Auger WR. Chronic thromboembolic pulmonary hypertension. *Curr Treat Options Cardiovasc Med* 2010;12-2:131-41.

91. Lang IM, Klepetko W. Update on chronic thromboembolic pulmonary hypertension, a frequently undiagnosed condition. *Rev Esp Cardiol* 2009;62-2:120-5.

92. Pedersen AB, Mehnert F, Sorensen HT, Emmeluth C, Overgaard S, Johnsen SP. The risk of venous thromboembolism, myocardial infarction, stroke, major bleeding and death in patients undergoing total hip and knee replacement. *Bone & Joint Journal* 2014;96B-4:479-85.

93. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, Ortel TL, Pauker SG, Colwell CW, Jr. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141-2 Suppl:e278S-325S.

94. Pedersen AB, Sorensen HT, Mehnert F, Overgaard S, Johnsen SP. Risk Factors for Venous Thromboembolism in Patients Undergoing Total Hip Replacement and Receiving Routine Thromboprophylaxis. *Journal of Bone and Joint Surgery-American Volume* 2010;92A-12:2156-64.

95. Pedersen AB, Johnsen SP, Sorensen HT. Increased one-year risk of symptomatic venous thromboembolism following total hip replacement -a nationwide cohort study. *Journal of Bone and Joint Surgery-British Volume* 2012;94B-12:1598-603.

96. Warwick D, Friedman RJ, Agnelli G, Gil-Garay E, Johnson K, FitzGerald G, Turibio FM. Insufficient duration of venous thromboembolism prophylaxis after total hip or knee replacement when compared with the time course of thromboembolic events - Findings from the global orthopaedic registry. *Journal of Bone and Joint Surgery-British Volume* 2007;89B-6:799-807.

97. Jameson SS, Bottle A, Malviya A, Muller SD, Reed MR. The impact of national guidelines for the prophylaxis of venous thromboembolism on the complications of arthroplasty of the lower limb. *Journal of Bone and Joint Surgery-British Volume* 2010;92B-1:123-9.

98. The PEP Trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet* 2000;355-9212:1295-302.

99. NICE. National Clinical Guideline Centre – Acute and Chronic Conditions. Venus thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. 2010. *National Institute for Health and Care Excellence,* 2015. Available at https://www.nice.org.uk/guidance/cg92/evidence/full-guideline-pdf-243920125 (accessed 1 Nov 2017).

100. Socialstyrelsen. Socialstyrelsens riktlinjer för vård av blodpropp/venös tromboembolism. 2004. Available at https://www.alvsbyn.se/wp-content/uploads/2014/03/2004-102-3_20041023.pdf (accessed 1 Nov 2017). (Venous thromboembolism -recommendations by The National Board of Health and Welfare, in Swedish)

101. Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, Bandel TJ, Beckmann H, Muehlhofer E, Misselwitz F, Geerts W, Grp RS. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *New England Journal of Medicine* 2008;358-26:2765-75.

102. Eriksson BI, Dahl OE, Huo MH, Kurth AA, Hantel S, Hermansson K, Schnee JM, Friedman RJ. Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II*). A randomised, double-blind, non-inferiority trial. *Thromb Haemost* 2011;105-4:721-9.

103. Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Prins MH, Hettiarachchi R, Hantel S, Schnee J, Buller HR, Grp R-NS. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* 2007;370-9591:949-56.

104. Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, Soglian AG, Pap AF, Misselwitz F, Haas S, Investigators R. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet* 2008;372-9632:31-9.

105. Turpie AGG, Haas S, Kreutz R, Mantovani LG, Pattanayak CW, Holberg G, Jamal W, Schmidt A, van Eickels M, Lassen MR. A non-interventional comparison of rivaroxaban with standard of care for thromboprophylaxis after major orthopaedic surgery in 17,701 patients with propensity score adjustment. *Thrombosis and Haemostasis* 2014;111-1:94-102.

106. Hull RD. Treatment of pulmonary embolism: The use of low-molecular-weight heparin in the inpatient and outpatient settings. *Thrombosis and Haemostasis* 2008;99-3:502-10.

107. Wilke T. Patient Preferences for an Oral Anticoagulant after Major Orthopedic Surgery Results of a German Survey. *Patient-Patient Centered Outcomes Research* 2009;2-1:39-49.

108. Jameson SS, Rymaszewska M, James P, Serrano-Pedraza I, Muller SD, Hui ACW, Reed MR. Wound Complications Following Rivaroxaban Administration A Multicenter Comparison with Low-Molecular-Weight Heparins for Thromboprophylaxis in Lower Limb Arthroplasty. *Journal of Bone and Joint Surgery-American Volume* 2012;94A-17:1554-8.

109. Jensen CD, Steval A, Partington PF, Reed MR, Muller SD. Return to theatre following total hip and knee replacement, before and after the introduction of rivaroxaban -a retrospective cohort study. *Journal of Bone and Joint Surgery-British Volume* 2011;93B-1:91-5.

110. Loke YK, Kwok CS. Dabigatran and rivaroxaban for prevention of venous thromboembolism - systematic review and adjusted indirect comparison. *Journal of Clinical Pharmacy and Therapeutics* 2011;36-1:111-24.

111. Ning GZ, Kan SL, Chen LX, Lei SG, Feng SQ, Zhou Y. Rivaroxaban for thromboprophylaxis after total hip or knee arthroplasty: a meta-analysis with trial sequential analysis of randomized controlled trials. *Scientific Reports* 2016;6:12.

112. Venker BT, Ganti BR, Lin H, Lee ED, Nunley RM, Gage BF. Safety and Efficacy of New Anticoagulants for the Prevention of Venous Thromboembolism After Hip and Knee Arthroplasty: A Meta-Analysis. *J Arthroplasty* 2017;32-2:645-52.

113. Beyer-Westendorf J, Lutzner J, Donath L, Tittl L, Knoth H, Radke OC, Kuhlisch E, Stange T, Hartmann A, Gunther KP, Weiss N, Werth S. Efficacy and safety of thromboprophylaxis with low-molecular-weight heparin or rivaroxaban in hip and knee replacement surgery Findings from the ORTHO-TEP registry. *Thrombosis and Haemostasis* 2013;109-1:154-63.

114. Riva N, Dentali F, Permunian ET, Ageno W. Major Bleeding and Case Fatality Rate with the Direct Oral Anticoagulants in Orthopedic Surgery: A Systematic Review and Meta-Analysis. *Seminars in Thrombosis and Hemostasis* 2016;42-1:42-54.

115. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, Heurgren M, Olausson PO. External review and validation of the Swedish national inpatient register. *Bmc Public Health* 2011;11:16.

116. Wettermark B, Harnmar N, MichaelFored C, Leimanis A, Olausson PO, Bergman U, Persson I, Sundstrom A, Westerholm B, Rosen M. The new Swedish Prescribed Drug Register - Opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiology and Drug Safety* 2007;16-7:726-35.

117. Karrholm J. The Swedish Hip Arthroplasty Register (http://www.shpr.se). *Acta Orthopaedica* 2010;81-1:3-4.

118. Garden RS. Low-angle fixation in fractures of the femoral neck. *Journal of Bone and Joint Surgery-British Volume* 1961;43-4:647-63.

119. SILF. Vårdprogram för led- och skelettinfektioner, rev 2008. Svenska Infektionsläkarföreningen. Available at http://infektion.net/sites/default/files/pdf/Vardprogram_led_och_skelett_2008.pdf (accessed 1 Nov 2017). (Joint and skeletal infections, guidelines by the Swedish Association of Infectious Diseases, in Swedish)

120. Blomgren G, Hoborn J, Nystrom B. Reduction of contamination at total hip replacement by special working clothes. *J Bone Joint Surg Br* 1990;72-6:985-7.

121. Parvizi J, Zmistowski B, Berbari EF, Bauer TW, Springer BD, Della Valle CJ, Garvin KL, Mont MA, Wongworawat MD, Zalavras CG. New Definition for Periprosthetic Joint Infection: From the Workgroup of the Musculoskeletal Infection Society. *Clinical Orthopaedics and Related Research* 2011;469-11:2992-4.

122. Cnudde P, Rolfson O, Nemes S, Karrholm J, Rehnberg C, Rogmark C, Timperley J, Garellick G. Linking Swedish health data registers to establish a research database and a shared decision-making tool in hip replacement. *Bmc Musculoskeletal Disorders* 2016;17:10.

123. Bjornara BT, Gudmundsen TE, Dahl OE. Frequency and timing of clinical venous thromboembolism after major joint surgery. *Journal of Bone and Joint Surgery-British Volume* 2006;88B-3:386-91.

124. Kurtz SM, Lau E, Ong K, Zhao K, Kelly M, Bozic KJ. Future young patient demand for primary and revision joint replacement: national projections from 2010 to 2030. *Clin Orthop Relat Res* 2009;467-10:2606-12.

125. Hotchkiss RS, Moldawer LL. Parallels between Cancer and Infectious Disease. *New England Journal of Medicine* 2014;371-4:380-3.

126. Berend KR, Lombardi AV, Morris MJ, Bergeson AG, Adams JB, Sneller MA. Two-stage Treatment of Hip Periprosthetic Joint Infection Is Associated With a High Rate of Infection Control but High Mortality. *Clinical Orthopaedics and Related Research* 2013;471-2:510-8.

127. Urquhart DM, Hanna FS, Brennan SL, Wluka AE, Leder K, Cameron PA, Graves SE, Cicuttini FM. Incidence and risk factors for deep surgical site infection after primary total hip arthroplasty: a systematic review. *J Arthroplasty* 2010;25-8:1216-22 e1-3.

128. Lindeque B, Hartman Z, Noshchenko A, Cruse M. Infection After Primary Total Hip Arthroplasty. *Orthopedics* 2014;37-4:257-+.

129. Oussedik S, Gould K, Stockley I, Haddad FS. Defining peri-prosthetic infection do we have a workable gold standard? *Journal of Bone and Joint Surgery-British Volume* 2012;94B-11:1455-6.

130. Bozic KJ, Lau E, Kurtz S, Ong K, Rubash H, Vail TP, Berry DJ. Patient-Related Risk Factors for Periprosthetic Joint Infection and Postoperative Mortality Following Total Hip Arthroplasty in Medicare Patients. *Journal of Bone and Joint Surgery-American Volume* 2012;94A-9:794-800.

131. Malinzak RA, Ritter MA, Berend ME, Meding JB, Olberding EM, Davis KE. Morbidly Obese, Diabetic, Younger, and Unilateral Joint Arthroplasty Patients Have Elevated Total Joint Arthroplasty Infection Rates. *Journal of Arthroplasty* 2009;24-6:84-8.

132. Namba RS, Inacio MC, Paxton EW. Risk factors associated with surgical site infection in 30,491 primary total hip replacements. *J Bone Joint Surg Br* 2012;94-10:1330-8.

133. Pulido L, Ghanem E, Joshi A, Purtill JJ, Parvizi J. Periprosthetic joint infection: the incidence, timing, and predisposing factors. *Clin Orthop Relat Res* 2008;466-7:1710-5.

134. Bozic KJ, Ward DT, Lau EC, Chan V, Wetters NG, Naziri Q, Odum S, Fehring TK, Mont MA, Gioe TJ, Della Valle CJ. Risk Factors for Periprosthetic Joint Infection Following Primary Total Hip Arthroplasty: A Case Control Study. *Journal of Arthroplasty* 2014;29-1:154-6.

135. Wiles MD, Moran CG, Sahota O, Moppett IK. Nottingham Hip Fracture Score as a predictor of one year mortality in patients undergoing surgical repair of fractured neck of femur. *British Journal of Anaesthesia* 2011;106-4:501-4.

136. Parvizi J, Azzam K, Ghanem E, Austin MS, Rothman RH. Periprosthetic infection due to resistant staphylococci: serious problems on the horizon. *Clin Orthop Relat Res* 2009;467-7:1732-9.

137. Teterycz D, Ferry T, Lew D, Stern R, Assal M, Hoffmeyer P, Bernard L, Uckay I. Outcome of orthopedic implant infections due to different staphylococci. *International Journal of Infectious Diseases* 2010;14-10:E913-E8.

138. Choi HR, von Knoch F, Kandil AO, Zurakowski D, Moore S, Malchau H. Retention treatment after periprosthetic total hip arthroplasty infection. *International Orthopaedics* 2012;36-4:723-9.

139. Bergkvist M, Mukka SS, Johansson L, Ahl TE, Sayed-Noor AS, Skoldenberg OG, Eisler T. Debridement, antibiotics and implant retention in early periprosthetic joint infection. *Hip Int* 2016;26-2:138-43.

140. Parvizi J, Shohat N, Gehrke T. Prevention of periprosthetic joint infection -new guidelines. *Bone & Joint Journal* 2017;99B-4:3-10.

141. Anderson DJ, Podgorny K, Berrios-Torres SI, Bratzler DW, Dellinger EP, Greene L, Nyquist AC, Saiman L, Yokoe DS, Maragakis LL, Kaye KS. Strategies to Prevent Surgical Site Infections in Acute Care Hospitals: 2014 Update. *Infection Control and Hospital Epidemiology* 2014;35:605-27.

142. Leaper D, Burman-Roy S, Palanca A, Cullen K, Worster D, Gautam-Aitken E, Whittle M, Guideline Dev G. Guidelines -Prevention and treatment of surgical site infection: summary of NICE guidance. *British Medical Journal* 2008;337:3.

143. Gustafson P, Schultz T, Stefánsdóttir A. PRISS – Prosthesis-Related Infections Shall be Stopped. *Ljungbergs Tryckeri AB,* 2014. Available at https://lof.se/wp-content/uploads/2015/05/PRISS-final-report-oct2014.pdf (accessed 1 Nov 2017)

144. Andersson AE, Bergh I, Karlsson J, Eriksson BI, Nilsson K. Traffic flow in the operating room: An explorative and descriptive study on air quality during orthopedic trauma implant surgery. *American Journal of Infection Control* 2012;40-8:750-5.

145. Tammelin A, Domicel P, Hambraeus A, Stahle E. Dispersal of methicillin-resistant Staphylococcus epidermidis by staff in an operating suite for thoracic and cardiovascular surgery: relation to skin carriage and clothing. *Journal of Hospital Infection* 2000;44-2:119-26.

146. Whyte W, Hodgson R, Tinkler J. The importance of airborne bacterial contamination of wounds. *J Hosp Infect* 1982;3-2:123-35.

147. Scaltriti S, Cencetti S, Rovesti I, Marchesi I, Bargellini A, Borella P. Risk factors for particulate and microbial contamination of air in operating theatres. *Journal of Hospital Infection* 2007;66-4:320-6.

148. Tammelin A, Blomfeldt AM. Comparison of two single-use scrub suits in terms of effect on air-borne bacteria in the operating room. *Journal of Hospital Infection* 2017;95-3:324-6.

149. Socialstyrelsen. Att förebygga vårdrelaterade infektioner -Ett kunskapsunderlag. *Bergslagens Grafiska*, Lindesberg 2006. Available at https://www.folkhalsomyndigheten.se/contentassets/3692c757601b40eda5e49f890c2d11ca/att-forebygga-vardrelaterade-infektioner-ett-kunskapsunderlag-2006-123-12.pdf (accessed 1 Nov 2017). (Recommendations by The National Board of Health and Welfare, in Swedish)

150. Sveriges Riksdag. Svensk författningssamling, Patientsäkerhetslag (2010:659), 2017:786. Available at http://www. riksdagen.se/sv/dokument-lagar/dokument/svensk-forfattningssamling/patientsakerhetslag-2010659_sfs-2010-659. (accessed 1 Nov 2017). (The Swedish Parliament, Patient Safety Act)

151. Bismark MM, Brennan TA, Davis PB, Studdert DM. Claiming behaviour in a no-fault system of medical injury: a descriptive analysis of claimants and non-claimants. *Med J Aust* 2006;185-4:203-7.

152. Jarvelin J, Hakkinen U, Rosenqvist G, Remes V. Factors predisposing to claims and compensations for patient injuries following total hip and knee arthroplasty. *Acta Orthop* 2012;83-2:190-6.

153. Sager M, Voeks S, Drinka P, Langer E, Grimstad P. Do the elderly sue physicians? *Arch Intern Med* 1990;150-5:1091-3.

154. Zengerink I, Reijman M, Mathijssen NM, Eikens-Jansen MP, Bos PK. Hip Arthroplasty Malpractice Claims in the Netherlands: Closed Claim Study 2000-2012. *J Arthroplasty* 2016;31-9:1890-3.e4.

155. PRISS. Slutrapporten -PRISS symposium, Stockholm 21 november 2013. Available at http://docplayer.se/3427321-Slutrapporten-priss-symposium-stockholm-21-november-2013.html (accessed 1 Nov 2013) (PRISS Final report symposium lecture, in Swedish)

156. Neumann I, Rada G, Claro JC, Carrasco-Labra A, Thorlund K, Akl EA, Bates SM, Guyatt GH. Oral Direct Factor Xa Inhibitors Versus Low-Molecular-Weight Heparin to Prevent Venous Thromboembolism in Patients Undergoing Total Hip or Knee Replacement A Systematic Review and Meta-analysis. *Annals of Internal Medicine* 2012;156-10:710-U93.

157. Dahl OE, Quinlan DJ, Bergqvist D, Eikelboom JW. A critical appraisal of bleeding events reported in venous thromboembolism prevention trials of patients undergoing hip and knee arthroplasty. *Journal of Thrombosis and Haemostasis* 2010;8-9:1966-75.

158. EMA. Guideline on clinical investigation of medicinal products for prevention of venous thromboembolism (VTE) in patients undergoing high VTE-risk surgery (EMA/CHMP/325170/2012). *European Medicines Agency - Committee for Medicinal Products for Human Use (CHMP)*, 2013. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500143764.pdf (accessed 1 Nov 2017).

159. Lassen MR, Gent M, Kakkar AK, Eriksson BI, Homering M, Berkowitz SD, Turpie AGG. The effects of rivaroxaban on the complications of surgery after total hip or knee replacement -results from the record programme. *Journal of Bone and Joint Surgery-British Volume* 2012;94B-11:1573-8.

160. Jameson SS, Charman SC, Gregg PJ, Reed MR, van der Meulen JH. The effect of aspirin and low-molecular-weight heparin on venous thromboembolism after hip replacement: a non-randomised comparison from information in the national joint registry. *Journal of Bone and Joint Surgery-British Volume* 2011;93B-11:1465-70.

161. Comp PC, Spiro TE, Friedman RJ, Whitsett TL, Johnson GJ, Gardiner GA, Landon GC, Jove M, Enoxaparin Clinical Trial G. Prolonged enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement. *Journal of Bone and Joint Surgery-American Volume* 2001;83A-3:336-45.

162. Dahl OE, Gudmundsen TE, Haukeland L. Late occurring clinical deep vein thrombosis in joint-operated patients. *Acta Orthopaedica Scandinavica* 2000;71-1:47-50.

163. White RH, Romano PS, Zhou H, Rodrigo J, Bargar W. Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. *Arch Intern Med* 1998;158-14:1525-31.

164. Wilson D, Cooke EA, McNally MA, Wilson HK, Yeates A, Mollan RA. Changes in coagulability as measured by thrombelastography following surgery for proximal femoral fracture. *Injury* 2001;32-10:765-70.

165. Forster R, Stewart M. Anticoagulants (extended duration) for prevention of venous thromboembolism following total hip or knee replacement or hip fracture repair. *Cochrane Database of Systematic Reviews* 2016-3:130.

166. Husted H, Otte KS, Kristensen BB, Orsnes T, Wong C, Kehlet H. Low risk of thromboembolic complications after fast-track hip and knee arthroplasty. *Acta Orthopaedica* 2010;81-5:599-605.

167. Jorgensen CC, Kehlet H, Lundbeck Fdn Ctr Fast-track H. Early thromboembolic events <= 1 week after fast-track total hip and knee arthroplasty. *Thrombosis Research* 2016;138:37-42.

168. Jorgensen CC, Jacobsen MK, Soeballe K, Hansen TB, Husted H, Kjaersgaard-Andersen P, Hansen LT, Laursen MB, Kehlet H. Thromboprophylaxis only during hospitalisation in fast-track hip and knee arthroplasty, a prospective cohort study. *BMJ Open* 2013;3-12:e003965.

169. Huang R, Buckley PS, Scott B, Parvizi J, Purtill JJ. Administration of Aspirin as a Prophylaxis Agent Against Venous Thromboembolism Results in Lower Incidence of Periprosthetic Joint Infection. *J Arthroplasty* 2015;30-9 Suppl:39-41.

170. Parvizi J, Ghanem E, Joshi A, Sharkey PF, Hozack WJ, Rothman RH. Does "excessive" anticoagulation predispose to periprosthetic infection? *J Arthroplasty* 2007;22-6 Suppl 2:24-8.

171. Patel VP, Walsh M, Sehgal B, Preston C, DeWal H, Di Cesare PE. Factors associated with prolonged wound drainage after primary total hip and knee arthroplasty. *J Bone Joint Surg Am* 2007;89-1:33-8.

172. Parvizi J, Ceylan HH, Kucukdurmaz F, Merli G, Tuncay I, Beverland D. Venous Thromboembolism Following Hip and Knee Arthroplasty The Role of Aspirin. *Journal of Bone and Joint Surgery-American Volume* 2017;99-11:961-72.

173. Becattini C, Agnelli G. Aspirin for prevention and treatment of venous thromboembolism. *Blood Reviews* 2014;28-3:103-8.

174. Mackman N. Triggers, targets and treatments for thrombosis. *Nature* 2008;451-7181:914-8.

175. AAOS. Preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty - evidence-based guideline and evidence report. *American Academy of Orthopaedic Surgeons*, Rosemont IL, USA, 2011. Available at https://www.aaos.org/research/guidelines/VTE/VTE_full_guideline.pdf (accessed 1 Nov 2017)

176. BHS. Newsletter. *British Hip Society*, June 2011. London, United Kingdom. Available at https://www.britishhipsociety.com/uploaded/Newsletter%July 52011.pdf. (accessed 1 Nov 2017)

177. Parvizi J, Huang R, Rezapoor M, Bagheri B, Maltenfort MG. Individualized Risk Model for Venous Thromboembolism After Total Joint Arthroplasty. *J Arthroplasty* 2016;31-9 Suppl:180-6.

178. Vulcano E, Gesell M, Esposito A, Ma Y, Memtsoudis SG, Della Valle AG. Aspirin for elective hip and knee arthroplasty: a multimodal thromboprophylaxis protocol. *International Orthopaedics* 2012;36-10:1995-2002.

179. Anderson DR, Dunbar MJ, Bohm ER, Belzile E, Kahn SR, Zukor D, Fisher W, Gofton W, Gross P, Pelet S, Crowther M, MacDonald S, Kim P, Pleasance S, Davis N, Andreou P, Wells P, Kovacs M, Rodger MA, Ramsay T, Carrier M, Vendittoli PA. Aspirin Versus Low-Molecular-Weight Heparin for Extended Venous Thromboembolism Prophylaxis After Total Hip Arthroplasty A Randomized Trial. *Annals of Internal Medicine* 2013;158-11:800-+.

180. Azboy I, Barrack R, Thomas AM, Haddad FS, Parvizi J. Aspirin and the prevention of venous thromboembolism following total joint arthroplasty. *Bone & Joint Journal* 2017;99-B-11:1420-30.

181. An VVG, Phan K, Levy YD, Bruce WJM. Aspirin as Thromboprophylaxis in Hip and Knee Arthroplasty: A Systematic Review and Meta-Analysis. *Journal of Arthroplasty* 2016;31-11:2608-16.

182. Drescher FS, Sirovich BE, Lee A, Morrison DH, Chiang WH, Larson RJ. Aspirin Versus Anticoagulation for Prevention of Venous Thromboembolism Major Lower Extremity Orthopedic Surgery: A Systematic Review and Meta-Analysis. *Journal of Hospital Medicine* 2014;9-9:579-85.

183. Stewart DW, Freshour JE. Aspirin for the Prophylaxis of Venous Thromboembolic Events in Orthopedic Surgery Patients: A Comparison of the AAOS and ACCP Guidelines with Review of the Evidence. *Annals of Pharmacotherapy* 2013;47-1:63-74.

184. Wilson DGG, Poole WEC, Chauhan SK, Rogers BA. Systematic review of aspirin for thromboprophylaxis in modern elective total hip and knee arthroplasty. *Bone & Joint Journal* 2016;98B-8:1056-61.

185. Chu JN, Maselli J, Auerbach AD, Fang MC. The risk of venous thromboembolism with aspirin compared to anticoagulants after hip and knee arthroplasty. *Thrombosis Research* 2017;155:65-71.

186. Nielen JTH, Dagnelie PC, Emans PJ, Veldhorst-Janssen N, Lalmohamed A, van Staa TP, Boonen A, van den Bemt BJF, de Vries F. Safety and efficacy of new oral anticoagulants and low-molecular-weight heparins compared with aspirin in patients undergoing total knee and hip replacements. *Pharmacoepidemiology and Drug Safety* 2016;25-11:1245-52.

187. Schiff RL, Kahn SR, Shrier I, Strulovitch C, Hammouda W, Cohen E, Zukor D. Identifying orthopedic patients at high risk for venous thromboembolism despite thromboprophylaxis. *Chest* 2005;128-5:3364-71.

188. Kim YH, Oh SH, Kim JS. Incidence and natural history of deep-vein thrombosis after total hip arthroplasty - A prospective and randomised clinical study. *Journal of Bone and Joint Surgery-British Volume* 2003;85B-5:661-5.

189. Olczak J, Fahlberg N, Maki A, Razavian AS, Jilert A, Stark A, Skoldenberg O, Gordon M. Artificial intelligence for analyzing orthopedic trauma radiographs. *Acta Orthop* 2017:1-6.

11 SCIENTIFIC PAPERS

The scientific papers of this thesis (*Study I – IV*) can be found on the following pages.