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COMPLICATIONS AFTER TOTAL HIP ARTHROPLASTY
– REGISTER-BASED STUDIES ON SURGICAL APPROACH AND INFECTIONS

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In association with
The Swedish Hip Arthroplasty Register

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To my family

Institutionen för molekylär medicin och kirurgi, enheten för ortopedi

Complications after total hip arthroplasty
- register-based studies on surgical approach and infections

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ABSTRACT

Background

The often excellent outcome of total hip arthroplasty (THA) is sometimes compromised by prosthesis related complications. There is an ongoing debate regarding the effect of surgical approach on prosthesis related complications and patient reported outcome. The incidence of periprosthetic joint infection (PJI) following THA in Sweden is unknown as well as the completeness of the Swedish Hip Arthroplasty Register (SHAR) to record reoperations due to infection.

Methods

Study 1 and 2 were solely based on data from the SHAR. In study 1, the risk of revision due to infection, dislocation and loosening of the prosthesis was compared between the posterior and the direct lateral approach for the most commonly used cemented THAs. Relative risks were calculated with a Cox regression analysis with respect to known confounders. In study 2, Patient Reported Outcome Measures (PROMs) were compared between patients that had received a THA for osteoarthritis by either the posterior or direct lateral approach. The postoperative pain, satisfaction and health related quality of life were compared by Chi^2-test, T-test and multivariate regression analysis.

In study 3 and 4 a large cohort of patients that had undergone primary THA were selected from the SHAR and their antibiotic consumption was extracted from the Swedish Prescribed Drugs Register (SPDR). For patients with ≥28 days of antibiotic treatment within 2 years after the surgery a medical records review was conducted. From this survey the cumulative incidence of early and delayed PJI was calculated. The number of reoperated THAs due to infection were compared with the SHAR reoperation database determining the completeness of the register. In Study 5, PJI-cases were compared to matched controls regarding known and suspected risk factors from the SHAR and the National Patient Register and analyzed by multivariate regression analysis.

Results

The posterior approach lead to superior PROM values for patients with OA and lead to less aseptic loosening but increased risk of dislocation in some of the investigated all cemented THAs. The cumulative incidence of early and delayed PJIs in Sweden for the study period was 0.9 % and the trend was slightly increasing. The registration completeness of reoperations due to infection in the SHAR was 67 %. Patient comorbidity had more influence than surgical or environmental factors on PJI risk.

Discussion

The discussion regarding the advantages of different surgical approaches in THA is not ended by these studies, but it seems that the surgical approach has influence on the outcome. The surgical approach should therefore perhaps be a part of the preoperative planning just as the method of fixation and implant and related to both patient factors and the reason for the THA.

In order to reduce the infection incidence it is important to define the magnitude of the incidence. This study presents a novel approach to incidence estimation and evaluates the SHAR reoperation database which has been the most commonly used measure of infections after THA in Sweden. As patient comorbidity seems to be the most important factor on a population level it will be difficult to further decrease the incidence.

LIST OF PUBLICATIONS

I. **The type of surgical approach influences the risk of revision in total hip arthroplasty**
A study from the Swedish Hip Arthroplasty Register of 90,662 total hip replacements with 3 different cemented prostheses

Lindgren V, Garellick G, Kärrholm J, Wretenberg P
Acta Orthop 2012 Dec;83(6):559-65. Epub 2012 Nov 1

II. **Patient reported outcome is influenced by surgical approach in total hip replacement**
A study of the Swedish Hip Arthroplasty Register including 42 233 patients

Lindgren J.V., Wretenberg P, Kärrholm J, Garellick G, Rolfson O
Bone Joint J 2014;96-B(5):590-6.

III. **Deep infection after primary total hip replacement – a method for national incidence surveillance**

Lindgren J.V., Gordon M, Wretenberg P, Kärrholm J, Garellick G,
Infect Control Hosp Epidemiol 2014;35(12): xx-xx

IV. **Validation of reoperations due to infection in the Swedish Hip Arthroplasty Register**

Lindgren J.V., Gordon M, Wretenberg P, Kärrholm J, Garellick G
Submitted

V. **Patient comorbidity is the most important factor contributing to increased risk of postoperative deep infection after primary total hip replacement**

Lindgren J.V., Nemes S, Kärrholm J, Garellick G, Wretenberg P
Manuscript

CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS

ASA-score	American Society of Anesthesiologists score
ATC-code	Anatomic Therapeutic Chemical classification system
CI	Confidence Interval
Completeness	The proportion of registered procedures per performed procedures at individual level
Coverage	The proportion of participating units per performing units
Cumulative incidence	Number of new cases in a defined population and time period
EQ-5D	The five dimension self-assessment tool from the EuroQol-group
ICD	International Classification of Diseases
Incidence density rate	The rate of new cases per population over a time period
IQR	Inter Quantile Range
NPR	National Patient Register
OA	Osteoarthritis
OR	Odds Ratio
PJI	Periprosthetic Joint Infection
PRISS	Prosthesis Related Infections Should be Stopped
PRO	Patient Reported Outcome
PROM	Patient Reported Outcome Measures
Reoperation	Any surgical procedure in close relation to an already implanted arthroplasty
Revision	Reoperation with exchange or extraction of all or parts of the implant
RR	Relative Risk
SD	Standard Deviation
SHAR	Swedish Hip Arthroplasty Register
SPDR	Swedish Prescribed Drug Register
THA	Total Hip Arthroplasty (equal to THR)
THR	Total Hip Replacement (equal to THA)
Validity	The extent to which a method of measurement provides a true assessment of that which it purposes to measure
VAS	Visual Analog Scale

1 BACKGROUND

1.1 THE HISTORY OF TOTAL HIP ARTHROPLASTY

The first attempts to surgically treat painful osteoarthritis were made in the beginning of the 19th century. The available method was interpositioning of various soft tissues in the joint but did not have long lasting effect (1). In 1938 Smith-Pedersen described interpositioning of a vitallium cup covering the femoral head which introduced the hip arthroplasty (2). The Judet brothers introduced the hip replacement arthroplasty by replacing the femoral head with an artificial head made by acrylic resin. It was however Wiles that introduced the first total hip arthroplasty (THA) (3). Although many doctors tried to refine the method and materials over the early period it was not until the 1960s that Sir John Charnley introduced the low friction arthroplasty that revolutionized the principles of hip replacement (4). The most important contributions were the principle of rigid fixation of the prosthesis to the bone, the replacement of both joint surfaces and the use of low friction polyethylene. The principles made by Charnley are still highly relevant today. Over the years many attempts have been made to refine the many aspects of hip replacement including prosthesis material, size and bearing surfaces, fixation methods, surgical approaches and more. Nowadays the result of a THA to increase function and reduce pain in different hip injuries and disorders is in general very good and the intervention has been called “the operation of the century” (1).

Some of the complications following a THA are not evident until after some years after the primary operation. Together with decreasing complication incidence, the evolution of arthroplasty design has been dependent on long term follow up in national joint replacement registries. By using the large populations of these registries statistic comparisons between implant designs, fixation methods etc. have been possible and this is an important factor that has contributed to today’s long survivorship of the modern THA (5).

Today more than 1 million procedures are undertaken each year worldwide (5). In an ageing population with higher demands on physical activity, treatment with THA for osteoarthritis will increase annually (6, 7). As a result of increasing implant survival, primary THA is a more attractive alternative in a younger age which also contributes to an increasing procedure incidence (8). Thus despite the good results today there is still an incentive to continuously improve the outcome of THA.

1.2 SURGICAL APPROACHES

There are many surgical approaches described for a THA. The most common approaches in Sweden 2012 were the posterior approach (52 %) followed by the direct lateral in side position (42 %) and direct lateral in supine position (5 %) (9).

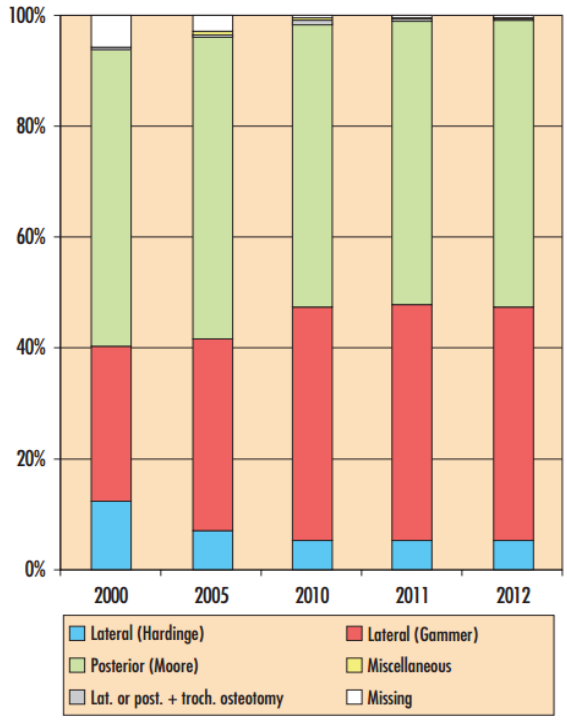

Figure 1.
Distribution of surgical approaches in primary THA in Sweden (from the Swedish Hip Arthroplasty Register - annual report 2012)

Recent years the use of the direct lateral approach without trochanteric osteotomy has increased on behalf of the posterior approach in Sweden. One reason may be reports of increasing dislocation rates following THA due to hip fracture operated in the posterior approach (10). Another reason may be that if the orthopedic surgeon operates without an assistant, which seems to become more frequent, the leg is easier to hold for the nurse when the direct lateral approach is used. The potential effect on the overall outcome in terms of risk of revision and Patient Reported Outcome (PRO) due to this development is however unclear.

A meta-analysis of clinical trials published 2006 found no convincing evidence supporting either the posterior or direct lateral approach as superior for THA for osteoarthritis (11), taking complications into account.

1.2.1 The posterior approach

The posterior approach was introduced by Moore in 1957 (12) and is performed with the patient in a side position. The incision runs slightly posterior to the greater trochanter and curves posterior in line with the fibers of the greater gluteus muscle. The fascia is incised and the fibers of the greater gluteus separated bluntly. This exposes the short external rotators (musculus gemellus sup & inf, musculus obturatorius and musculus piriformis) which are cut close to their insertion on the femur. The hip capsule is then incised and the hip joint is exposed and dislocated dorsally by flection and internal rotation of the hip, with the foot of the patient facing upwards. The collum femoris is cut and is along with the acetabulum prepared for the implant. When the implant is in position the external rotators are sometimes reattached and the fascia of the greater gluteus muscle, subcutaneous tissues and skin are closed separately.

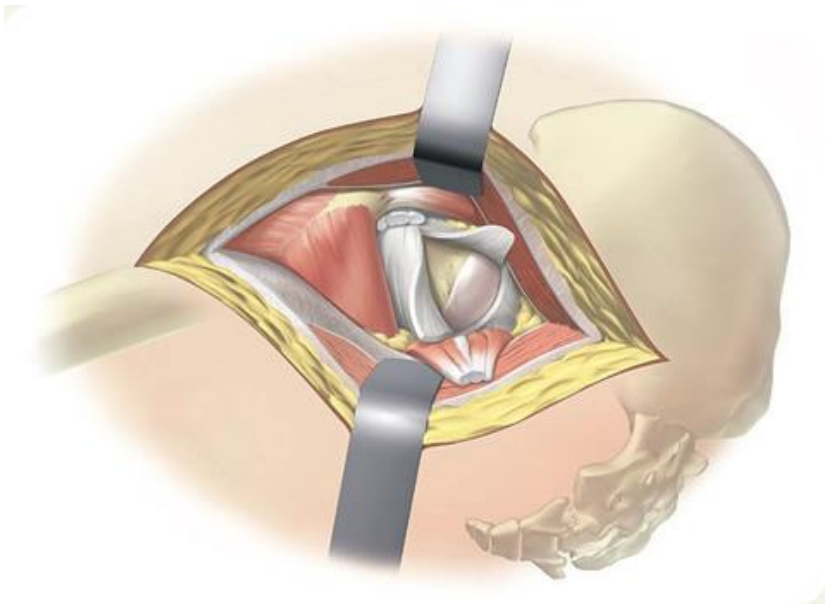

Figure 2. *The posterior approach, prior to THA (Published with permission from evertsmoth.com)*

The posterior approach give good access to the femur which may facilitate stem positioning. This may decrease the risk of malalignment and in turn a poor cement mantle, which could cause loosening (13). A hip joint is in its most extreme position by internal rotation and flection. As the posterior approach violates the posterior capsule and muscles this approach has been associated with postoperative instability and dislocation (14, 15).

1.2.2 The direct lateral approach

The direct lateral approach without trochanteric osteotomy can either be performed in supine position (as described by Hardinge (16)) or in a side position (as described by Gammer (17)). The skin and fascia are incised over and in line with the greater trochanter. The anterior part of the gluteus medius tendon is together with the anterior part of the vastus lateralis muscle (often along with its bony insertion) separated from the greater trochanter and reflected medially while the posterior parts of the muscles are left intact. The anterior part of the hip capsule is exposed and incised and the hip joint is dislocated anteriorly by external rotation, flection and adduction with the patient's foot pointing downwards (in case of operating in supine position – crossing the other leg). The collum femoris is cut and prepared along with the acetabulum. After the implant is in position the gluteus medius and vastus lateralis muscles are reattached to the trochanter and the fascia, subcutaneous tissues and skin are closed separately.

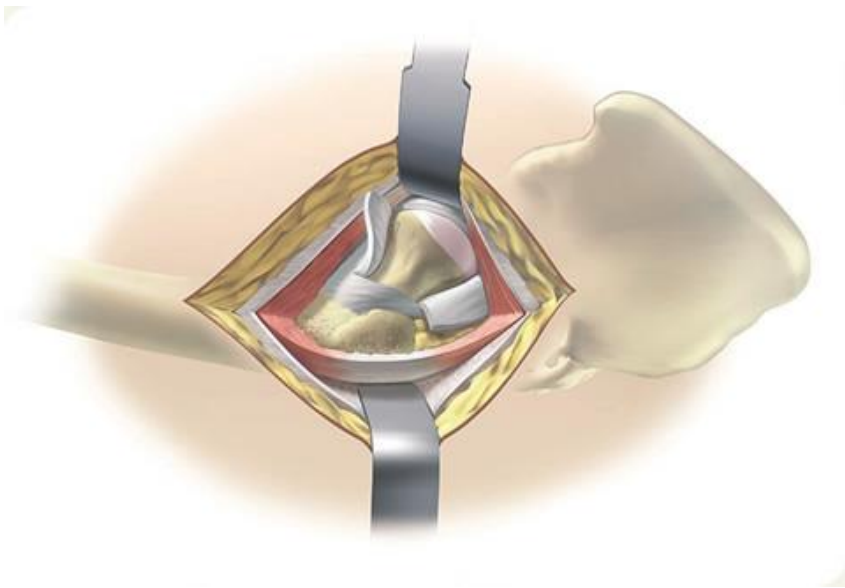

Figure 3. *The direct lateral approach prior to THA (Published with permission from evertsmith.com)*

The direct lateral approach spares the posterior stabilizing tissues but instead interferes with the abductor muscles which in case of non-healing or damage to its innervation can result in postoperative abductor weakness, limb and lateral hip pain. Patients operated with a THA by the direct lateral approach has been found to suffer higher risk of postoperative limp (18, 19). The direct lateral approach offers a good exposure of the acetabulum but can sometimes lead to an inferior access to the femur compared to the posterior approach.

1.3 COMPLICATIONS FOLLOWING TOTAL HIP ARTHROPLASTY

Complications after THA are rare. There are known medical complications such as deep vein thrombosis, pulmonary embolism, pneumonia, myocardial infarction and heart failure etc. (20, 21). The postoperative mortality is however low, less than 2 % within 3 months (22), especially in elective surgery. This thesis however only deals with complications related to the prosthesis. With modern implants >95 % of the implants remain unrevised at 15 years follow-up. As complications are rare and often occur late they are best determined by observational studies compared to randomized trials (23).

1.3.1 Aseptic loosening

The most common reason for revision of the total hip arthroplasty is loosening of the implant (24). Loosening is often discovered when a patient returns with complaints of a new pain from a previously replaced hip. It is a result of osteolysis (bone resorption) around the implant mediated by osteoclasts. Loosening is related to wear, inferior implant design and material and the patient's activity level (25). Malpositioning of the implant has been found to increase wear and thereby implant loosening (26). Loosening is often painful and can untreated lead to greater risk of periprosthetic fracture and dislocation. If the patient is healthy enough to withstand further surgery the prosthesis is therefore often revised.

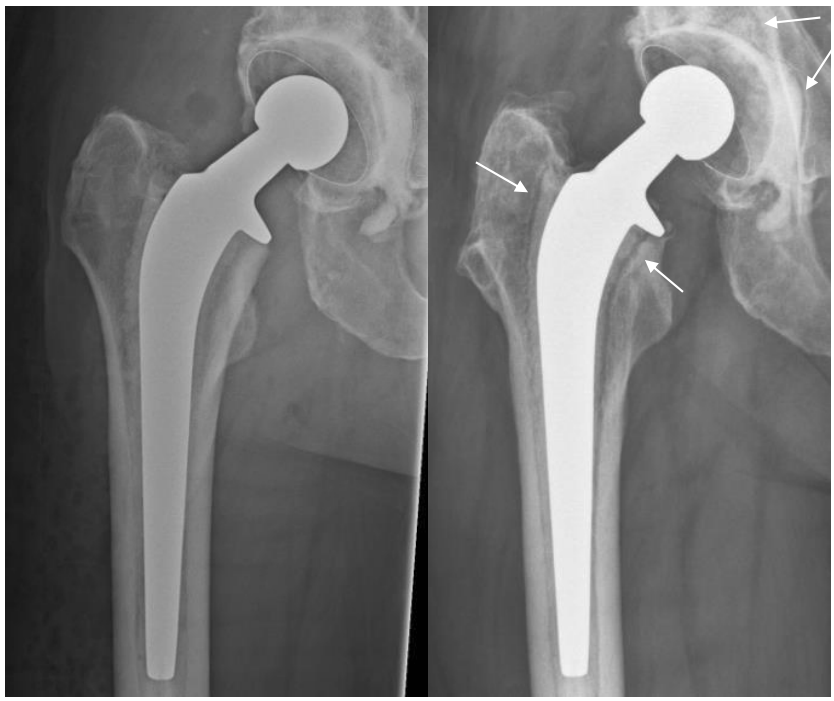

Figure 4. *Left: Direct postoperative radiograph of cemented total hip arthroplasty. Right: Radiograph of the same hip replacement, showing signs of loosening of femoral stem and acetabular cup (arrows).*

1.3.2 Dislocation

Dislocation of the prosthesis is an early (often within the first year) complication after THA, although it sometimes occurs several years after the primary operation secondary to trauma or wear of the acetabular cup that increase instability. The dislocation is most often posterior when the hip is in flexion and internal rotation, but can also be anterior by external rotation and extension of the hip. It is often very painful and is in its acute phase often treated with closed reduction with or without general anesthesia. If it is impossible to keep the prosthesis reduced, if the dislocation reoccurs or if the implant is loose open reduction with revision of the prosthesis is often inevitable if the patient is fit enough to undergo open surgery.
Most studies show an association between the posterior approach and an increasing risk of dislocation especially in combination with smaller head sizes (15, 27). The risk of dislocation however also depends on the reattachment of the posterior capsule and external rotators (28). Factors influencing risk of dislocation can be divided into groups referring to implant (1), operation (2), and patient characteristics (3). Important implant factors include head size, head to neck ratio (influencing impingement risk) and cup design (29). Operative factors include surgical experience, surgical approach, soft tissue treatment/reattachment and implant positioning (30). The most important patient characteristic is hip diagnosis (for example fracture compared to OA) (31), but alcohol abuse and/or postoperative confusion has also been described as risk factors (32).

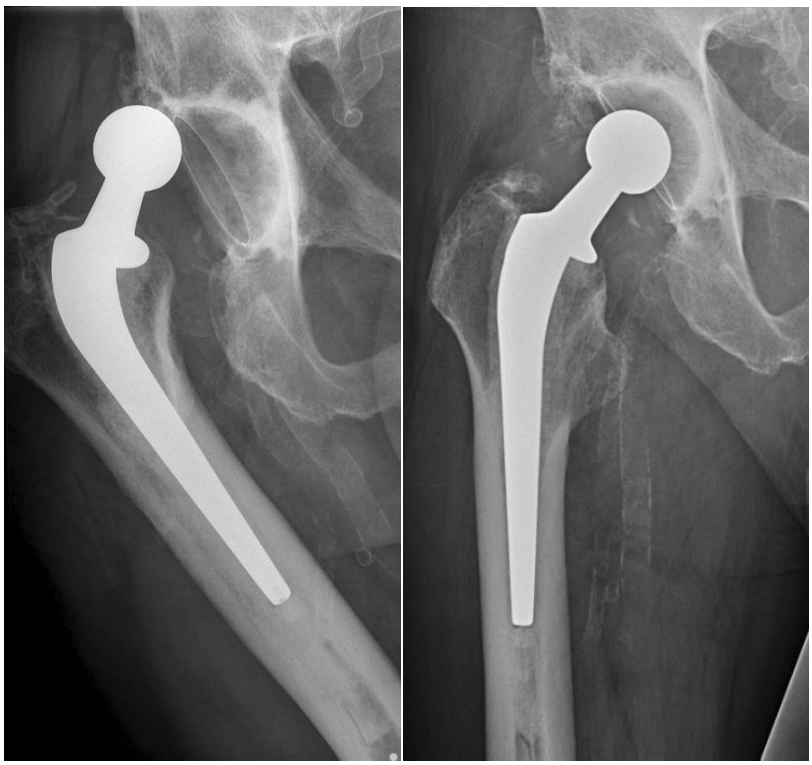

Figure 5. *Radiograph of dislocated total hip arthroplasty (left) and after reduction (right)*

1.3.3 Infection

The third most frequent complication following THA is periprosthetic joint infection (PJI) (24). Commonly it leads to a great suffering to the patient, requires large resources of the health care and is associated with high cost to society, especially if affecting patients of working age (33-36). Different treatment algorithms have been proposed based on experience. If diagnosed early and treated aggressively with debridement and irrigation it may be possible to retain the implant. If discovered late, one- or two-stage exchange or resection is often needed (37-39) due to biofilm formation on the prosthesis protecting the bacteria from antibiotic exposure. Regardless of the surgical intervention patients become dependent on antibiotics over a long period of time (40, 41). In the literature the incidence of deep infection following primary THA ranges from 0.2 up to 1.6 % depending on follow-up time and the methodology of the study (42, 43). Some studies have reported increasing risk of revision due to infection after THA (44, 45), but the reasons for this are unclear. This could very well reflect an increasing risk of infections, possibly due to that an older and medically more fragile population is subject for a primary THA. It could however just as well be the result of better diagnostics and more active revision policy or that the reporting to arthroplasty registries has improved. Concerns have been raised by Jämsen et al regarding the validity of recordings of revision due to infection in the Finnish Arthroplasty Register, and there is reason to believe that the same might apply to other registries as well (46).

The diagnosis of postoperative periprosthetic infection can be defined as early (diagnosed within 3 months), delayed (diagnosed between 3 months to 24 months) or late (diagnosed after more than 24 months after the primary procedure) (40). The early and delayed infections are often considered to be caused by peri- or intraoperative contamination. Whether the infection is diagnosed before or after 3 months may depend on the aggressiveness of the bacteria (40). Coagulase Negative Staphylococcus (CNS) and Staphylococcus Aureus (SA) are the most common isolated infecting microorganisms from perioperative cultures (47). There have been reports of increasing antibiotic resistant bacteria such as Methicillin-Resistant Staphylococcus Aureus (MRSA) and Methicillin-Resistant Staphylococcus Epidermidis (MRSE) which in the future will probably be an increasing clinical challenge (48).

Preventive measures should therefore perhaps be able to decrease the early and delayed infections but many factors, including both patient and surgical factors, contribute to the risk of developing a PJI which make this work difficult (49, 50). Obesity has in many studies been shown to increase the risk of infection (22, 51-53). Patient comorbidity described as an elevated Charlson index score (54) or ASA-score $\geq$3 (53, 55) are also known patient-related risk factors for the development of PJI. Surgical factors predisposing for infection includes fixation without antibiotic loaded cement (56), bilateral surgery (52, 53) and long duration of surgery (55). Other factors described in the literature possibly associated with increased risk of infection includes absence of laminar air flow in the operating theatre (57) and bleeding as well as blood transfusion (52). It has been found that the incidence differs between clinics and it has been stated that there might be other factors that can influence the risk of infection (55,

58). Historically many parallel interventions has been successful in decreasing the infection burden after THA, which in the early days were as large as 9 % (59).

In Sweden a multi professional initiative called PRISS (Prosthesis Related Infections Should be Stopped) was started in 2008 which objective was to reduce the incidence of infections by 50 %. The true incidence was however unknown. By 2013 the recommendations from this initiative were fully adopted by all orthopedic units in Sweden performing joint replacement surgery.

1.4 PATIENT REPORTED OUTCOME

Patient reported outcome is probably the most important parameter when evaluating the effect of a surgical procedure which indication is to restore function and relieve pain. It is therefore natural that studies evaluating PRO after orthopedic surgery has increased over the years. Patient reported outcome measures (PROMs) are often divided into generic instruments evaluating Health Related Quality of Life (HRQoL) and disease specific instruments. Commonly used generic PROM instruments in evaluation of THA include Short Form 36 (SF-36) and EuroQol 5 dimensions (EQ-5D). Disease specific instruments often used for evaluating the effect of THA are West Ontario and McMasters Universities Osteoarthritis index (WOMAC) and Oxford Hip Score (60).

Many factors influence the PRO after THA. First of all the preoperative function and pain are important parameters. Naturally the degree of change depends on the preoperative function – a low preoperative function can generate a lager increase than a good preoperative function. But even though the change is larger, a low function group might not reach as good postoperative scores as a group with better preoperative function. Thus both the degree of change and the final outcome, in other words – both the journey and the final destination - is important.

Previous studies have also shown that male gender, old age, Charnley category C (see chapter 1.5.2.3.2), preoperative anxiety/depression and low education level all influence the postoperative outcome negatively (61-67). Prosthesis related complications are also known to negatively affect the PROMs in terms of pain and function (68, 69). It is also possible that both the patient's and surgeon's expectation of the procedure affect the patient's postoperative satisfaction (70, 71).

A few studies have reported superior disease specific PROMs after the posterior approach compared to the direct lateral approach in a short follow up (68, 69), but according to one study this difference seems to disappear with time (72). It is however unclear if the surgical approach affects the generic HRQoL measurement EQ-5D, postoperative pain reduction and patient satisfaction and whether such an effect, if present, persist over time.

In clinical follow-up studies the reported dissatisfaction after a THA is around 10 % (65, 73, 74). There are many possible reasons to this. Patients suffering from a complication report worse outcome compared to the patients spared from a complication (68, 69) which could affect the postoperative satisfaction. The preoperative expectation of the procedure is also likely to play a role and it is therefore important that the doctor informs the patient of the expected result of the THA. Although failure to improve after the procedure cannot be equated with a complication the result can be equally important.

1.5 SWEDISH NATIONAL QUALITY AND HEALTH-CARE REGISTERS

1.5.1 The personal registration number

Epidemiologic research on populations by registry data has been very successful in Sweden. This is above all due to the introduction of the personal registration number in 1947 and to the liberal use of it in health registries. The personal registration number is a unique 10 digit long number. The first 6 digits contain the birth date (year, month and day). A hyphen separates this with the serial number of 3 digits where the third digit specifies the gender, an odd number indicates male gender and an even number indicates female gender. The last tenth digit is a control number. The use of the personal registration number introduces a possibility to match different registries that can complement each other in terms of data.

1.5.2 The Swedish Hip Arthroplasty Register

Quality registries in Sweden has a long history. The Swedish Hip Arthroplasty Register (SHAR) was the second national quality register started in 1979 in order to improve the results of THA by studying complications. Today all units performing total hip arthroplasty in Sweden voluntary participate (75), thus the coverage is 100 %.

1.5.2.1 Primary THA

About 16 000 primary THAs are recorded each year and the primary database is continuously automatically validated by matching with the National Patient Register (NPR). By the year 2012 the overall completeness of individual registration was 97.5 % (9). The register includes information about patient age, sex, diagnosis, side, surgical approach, type of fixation, implant design and type of hospital performing the operation etc. Until 1998 data on type of incision used was collected on hospital level, thereafter this information has been recorded on an individual basis.

1.5.2.2 Reoperation

The SHAR definition of reoperation is "any subsequent surgery in close relation to the already implanted prosthesis". Every reoperation is to be reported to the register. Revision of a prosthesis denotes a reoperation where parts, or the entire prosthesis is exchanged or extracted. In the reoperation database the reason for the surgery as well as surgical procedure, date, new implant (if applicable) is recorded. By combining the data with the primary database and the data in the Swedish Death Register the "survival-time" of the prosthesis can be calculated. To automatically evaluate the completeness of registration in the reoperation database is more difficult compared to the primary database as there are many more possible procedure codes and as the NPR is not side specific. The overall completeness has despite this been found to be high (76), which is a prerequisite to use the register as research material. That the data recorded in the register is correct is guaranteed as the medical records of the reoperation is sent to the SHAR for central register imputing.

Figure 6. *Swedish Hip Arthroplasty Register Annual Report 2012 (in Swedish)*

1.5.2.3 PROM programme in the SHAR

The SHAR gradually introduced pre- and postoperative Patient Reported Outcome Measures (PROMs) from 2002. By 2009 the PROM programme had been adopted by all operating units in Sweden. The response rate of the questionnaires in the PROM programme varies between 86 and 90 % (77). The high response rate is likely a result of a motivated group of patients, a short and easy questionnaire (both available as a paper-questionnaire and internet-based) and a well-established central and hospital register organization.

1.5.2.3.1 Generic PROM instruments in SHAR

The patients' general health is estimated by the generic health instrument EQ-5D developed by the EuroQol group (78). It is self-administered by the patient and divided into two parts.

For each of the following five dimensions the patient classifies their health into 3 levels of severity (1 through 3: no problems, some problems or severe problems):

- Mobility,
- Self-care,
- Usual activities,
- Pain / Discomfort and
- Anxiety / Depression.

A total of 243 combinations of answers are possible. The different dimensions are weighted separately depending on country of residence into an index ($EQ\text{-}5D_{INDEX}$) spanning from -0,594 through 1. Answers below 0 describes a health condition worse than death and 1 describes full health. The instrument used in the SHAR is translated into Swedish, but is weighted by the British tariff (79) as no Swedish tariff has been developed.

The preoperative $EQ\text{-}5D_{INDEX}$ show a bimodal distribution with a few top values. After THA the distribution show a trimodal distribution with a large group reporting top values (63).

Apart from the index the instrument includes a self-reported estimation of the general health on a visual analogue scale (VAS), 0 (=worse possible health state) to 100 (=best possible health state) (EQ_{VAS}).

The patient is asked to complete the EQ-5D questionnaire prior to the planned primary THA and again 1, 6 and 10 years after the primary THA to evaluate the perceived HRQoL.

1.5.2.3.2 Disease specific PROM instruments in SHAR

The preoperative questionnaire includes a VAS of pain ($Pain_{VAS}$) in the hip planned for a THA. The VAS ranges from 0 (no pain) to 100 (worst imaginable pain). The patient is asked to "Put a cross on the line that you think corresponds to your average pain perception from the hip in question during the last month". Below the scale there are 5 subcategories of pain: 0-20 no or slight pain, 21-40 mild pain, 41-60 moderate pain, 61-80 severe pain and 81-100 unbearable pain. Postoperatively the patient is asked to report the pain from the current hip at 1, 6 and 10 years after the THA and the same VAS as preoperatively is used.

The patient is also asked for their satisfaction with the procedure at 1, 6 and 10 years after the operation. Satisfaction is measured on a VAS where the patient is asked to "Put a cross on the line that you think corresponds to how satisfied you are with the result of the surgery". The scale ranges from 0 to 100 and divided into 5 subcategories: 0-20 very satisfied, 21-40 satisfied, 41-60 moderately satisfied, 61-80 doubtfully satisfied and 81-100 dissatisfied.

Compared to an ordinary VAS the scales used in the SHAR is thus adapted for two reasons. To be easier for an older population to understand and to be able to use both on a computer screen and in a pen and paper form.

Both preoperatively and in the postoperative follow-ups the patients are also asked to report their hip function according to the Charnley functional categories developed by Sir John Charnley (80). Category A denotes a patient who has unilateral hip disease, Category B denotes a patient with bilateral hip disease and Category C denotes a patient with multiple joint disease or other medical condition resulting in difficulties to walk normally. The registered category is determined by the questions "Do you have any symptoms from the other hip?" and "Do you have problems walking because of other reasons? (E.g. pain from other joints, back pain, angina, or any other medical condition impairing your walking capacity)".

1.5.3 The National Patient Register

The NPR was started in the 1960s by the Swedish National Board of Health and Welfare in order to collect inpatient data from the public hospitals in Sweden. It contains information about the care episode and is divided into 4 different categories, patient data (including personal registration number, sex and age), administrative data (date of admission and discharge, acute or elective care), geographical data (hospital and department), medical data (main and secondary diagnosis, cause of injury and procedures). The diagnosis and causes of injury are set according to the International Classification of Diagnosis version 10 (ICD-10) since 1997. The NPR covers all inpatient care provided by private and public hospitals in Sweden since 1987 and all outpatient care since 2001. Primary care is not included. The NPR is updated once a year and the quality and validity of the data has been found to be high (81).

1.5.4 The Swedish Prescribed Drug Register

The Swedish Prescribed Drug Register (SPDR) is a national health care register started by Swedish National Board of Health and Welfare in 1999. The objective was to increase patient safety. Since the July 1, 2005 the personal registration number was included in the register and thereafter it is possible to match the data with other health care and quality registries. Every dispensed outpatient prescription in Sweden is automatically recorded in the register and the data collected contains aside from the personal registration number, name of the drug, the Anatomic Therapeutic Chemical classification (ATC-code), size of container, dose and the date of prescription and expedition of the drug. It also contains the instructions from the prescriber, profession of the prescriber, the type of clinic and region. Both oral and intravenous drugs are included. The register is updated each month and each year about 100 million new prescriptions are included.(82)

2 AIMS OF THE THESIS

The aims of this thesis were to:

- Compare the risks of revision between the posterior and direct lateral approach in side position in all cemented THAs in Sweden.
- Compare the patient reported outcome measures between the posterior and direct lateral approach in Sweden in THAs for osteoarthritis.
- Determine the incidence of early and delayed deep periprosthetic joint infections following primary THA in Sweden.
- Determine the completeness of the Swedish Hip Arthroplasty Register in recording reoperations due to infection after primary THA.
- Explore possible risk factors to develop a deep periprosthetic joint infection after primary THA.

3 PATIENTS AND METHODS

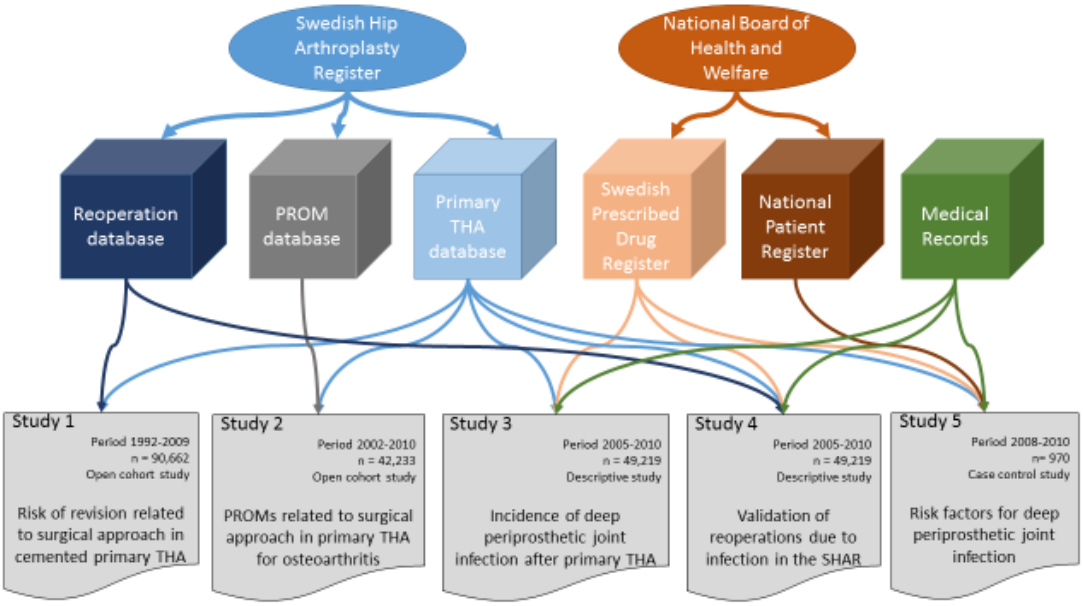

Figure 7. *Sources of data in the included studies*

3.1 STUDY I

Data between 1992 and 2009 was extracted from the SHAR for the 3 most used stems still in use 2009; Lubinus SPII, Exeter Polished and Spectron EF Primary. In order to reduce a potential influence of variations of the design of the cup only combinations of these stems with their most frequently used cemented acetabular components were studied. Accordingly, the Lubinus SPII stem and FAL or Lubinus All-Poly cup (n=66,405), the Exeter Polished with Contemporary Hooded Duration, Exeter Duration or Exeter All-Poly cup (n=18,711) and Spectron EF Primary stem in combination with the Reflection cup (n=5,546), were included. All diagnoses, except insertion of THA due to tumour, were included. In the analysis, diagnoses were classified as osteoarthritis, fracture (including both fresh fracture and sequelae after fracture) or other (inflammatory arthritis, sequelae after childhood hip disease, osteonecrosis or other) (Table 1). Bilateral operations were included. Patients operated with any other incision than the posterior (12) or the direct lateral with the patient in side position (17) were excluded.

More patients had been operated with the Lubinus SPII stem, than with the 2 other designs (Table 1). The Spectron EF Primary had been inserted through a direct lateral incisions in 75 % of the hips, whereas this approach only had been used in 18 % of the cases operated with an Exeter and 25 % of those operated with a Lubinus stem. Female sex was more common in the Spectron group (65 %) than in the Lubinus (60 %) and Exeter (60 %) groups. Osteoarthritis was slightly more common in the Exeter group (83 %) than in the Lubinus (81 %) and Spectron group (77 %).

		Lubinus SPII		Exeter Polished		Spectron EF Primary	
			66,405		18,711		5,546
			n (%)		n (%)		n (%)
Age (years)		<50	922 (1)	<50	468 (2)		
		50-59	5,903 (9)	50-59	2,099 (11)	<60	393 (7)
		60-75	36,935 (56)	60-75	10,040 (54)	60-75	2,895 (52)
		>75	22,645 (34)	>75	6,104 (33)	>75	2,258 (41)
	Mean		71		70		73
Sex	Male		26,568 (40)		7,449 (40)		1,916 (35)
	Female		39,837 (60)		11,262 (60)		3,630 (66)
Side	Left		30,237 (46)		8,432 (45)		2,532 (46)
	Right		36,168 (55)		10,279 (55)		3,014 (54)
Diagnosis	Osteoarthritis		53,993 (81)		15,431 (83)		4,284 (77)
	Fracture		8,126 (12)		1,689 (9)		857 (16)
	Other		4,286 (7)		1,591 (8)		405 (7)
Head		Co-Cr	58,673 (88)	Metal	18,711 (100)	Metal	5,546 (100)
		Ceramics	7,732 (12)				
Cup		FAL	5,142 (8)	Cont HD	3,956 (21)	Reflection	5,546 (100)
		All-Poly	61,263 (92)	Duration	10,325 (55)		
				All-Poly	4,430 (24)		
Approach	Direct Lateral		16,493 (25)		3,291 (18)		4,174 (75)
	Posterior		49,912 (75)		15,420 (82)		1,372 (25)
Order	1st hip		54,710 (82)		15,457 (83)		4,581 (83)
	2nd hip		11,695 (18)		3,254 (17)		965 (17)
Follow-up (years) mean (SD)							
	All		5.7 (3.8)		6.0 (3.7)		5.3 (2.5)
Revision due	to **Dislocation**		2.1 (3.0)		2.6 (3.4)		2.4 (2.3)
	to **Infection**		1.8 (2.1)		2.5 (3.0)		1.6 (1.4)
	to **Loosening**		7.2 (3.7)		7.0 (3.8)		5.3 (2.3)

Table 1. *Study demographics, variables presented in numbers (%), except for follow-up time presented in mean (SD).*

3.2 STUDY II

From the SHAR all patients operated with a THA due to osteoarthritis between 2002 and 2010 with complete pre- and 1 year postoperative PROM data registered were extracted. Only patients operated by the posterior approach (12) or the direct lateral transgluteal approach without trochanter osteotomy on either side (17) or supine (16) position (called direct lateral approach) were selected. If the patient had bilateral hip replacements only the first hip arthroplasty was included as an earlier experience might affect the outcome of the second procedure. Patients operated with a resurfacing prosthesis were excluded as these patients differ from the general population in age, gender and physical activity and are mainly operated by the posterior approach.

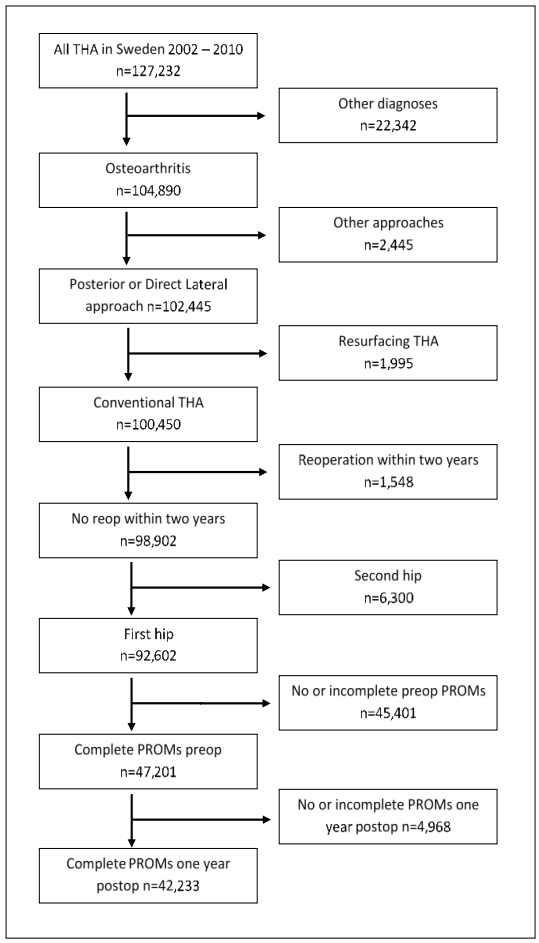

Figure 8. *Study II Flowchart*

A total of 42,233 patients met the selection criteria and of these the majority 58 % (n=24,358) were operated by the posterior approach. 4,962 patients in the cohort had complete 6 year postoperative data registered and the majority 67 % (n=3,310) of these were operated by the posterior approach. The reason for a difference in proportions in the 1 and 6 year cohort is the gradual introduction of the PROM-program and the fact that surgical approach is often related to the operating clinic. The majority of the patients were women (58 %) and the proportion of reported Charnley category was similar in the two groups with the majority of the patients in group A and C.

3.3 STUDY III & IV

All operations between July 1, 2005 and December 31, 2008 reported to the Swedish Hip Arthroplasty Register for a primary THA were included in the study (n=49,219). All diagnoses, bilateral arthroplasties and all types of implants regardless of the method of fixation were included. By using the patients' personal registration number, the cohort was then matched with the Swedish Prescribed Drugs Register for all dispensed antibiotic prescriptions between July 1, 2005 and December 31, 2010.
As current recommendations in Sweden for treatment of PJIs all include long term antibiotic treatment (83) and as uncomplicated wound infections were excluded the search was limited to include only the dispensed amount of antibiotics suggesting a continuous medication for ≥28 days (Table 15). The observation time was limited to 2 years after the primary THA for each patient as the object of interest was early and delayed PJIs. The dispensed antibiotics where the instruction from the prescribing doctor specifically indicated treatment for other infection (e.g. urinary tract infection, pneumonia) than a PJI were excluded.
1,989 patients with 2,217 THAs had been prescribed and dispensed >4 weeks of antibiotic treatment within the first 2 years after the primary THA. A questionnaire for each of the 2,217 THAs, including a list of dispensed antibiotics, was sent to a doctor at the primary operating unit (76 different units) to complete and return.

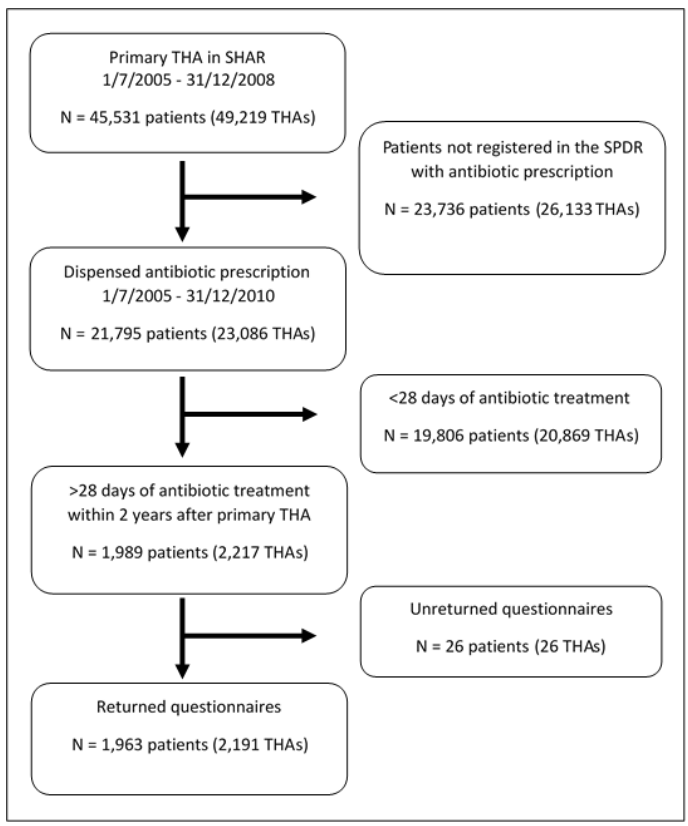

Figure 9. *Study III & IV Flowchart*

Of the 2,217 questionnaires sent out, 2,191 (99 %) were returned and all orthopedic clinics contributed. 4 of the patients had incorrectly been registered in the SHAR as primary THA when in fact they had a revision THA. These cases were excluded reducing the final study group to 2,187 THAs in 1,959 patients.

In the questionnaire the receiving physician verified if the patient had been treated for a deep PJI after the primary THA. If so, supplementary information on date of diagnosis and how the diagnosis was set including clinic presentation, laboratory markers and number of positive cultures.

In Study 3, the diagnosis of deep PJI was established when a patient met one or more of the following objective criteria (adapted from the definition established by the Workgroup of the Musculoskeletal Infection Society) (84):

1. Open sinus tract to the joint.
2. 2 or more positive perioperative cultures of the same pathogen.
3. When the patient met 2 or more of the following criteria:
   a) Systematic infection and pus in the artificial joint
   b) C-reactive Protein (CRP) >10 or
      Eurythrocyte Sedimentation Rate (ESR) >30
   c) One positive culture from joint fluid aspirate.

We excluded superficial infections, PJI after revision surgery and infections prior to THA (most often THA after failed infected osteosynthesis).

Information regarding if the patient was reoperated and in that case when and which kind of reoperation was to be filled in. Finally the established infecting microorganism, if known, was to be specified.

For Study 4 the reoperation database in the SHAR were searched for all reoperations due to infection within 2 years after the primary THA for all 49,219 THAs, to calculate the completeness of the data in the SHAR.

3.4 STUDY V

The study was designed as a case control study. Cases were extracted from the previous infection incidence study and all patients with PJI after the primary THA from 2008 were selected as cases. To each case four controls were selected matched by age group (<50, 50-59, 60-75, >75) gender and hospital type (n=776). The controls were extracted from the SHAR and registered with a primary THA in 2008 (n=14 010 patients) with preoperative complete BMI, Charnley category, patient reported EQ-5D, EQ-VAS and pain (n=8 687 patients).

The following factors were assessed:

Patient related factors

Data on comorbidities were extracted partly from the SHAR-database: Hip diagnosis (divided into groups: osteoarthritis, inflammatory joint disease, dysplasia, osteonecrosis, acute cervical hip fracture, tumour (including pathological fracture), other fracture, sequelae after fracture or sequelae after infection), BMI (underweight

(<18.5), normal (18.5-24.99), overweight (25-29.99),obese (>30)), ASA-score (85) (1-2, 3 or 4-5), preoperative Charnley category (86) (A, B or C). Patient reported preoperative Pain-VAS (0-no pain; 100-worse possible pain), EQ-5D index (-0.59-1) and EQ VAS (0-100) (continuous variables) (78, 87). Elixhauser comorbidity score (88) was calculated based on the ICD-10 codes from the National Patient Register (NPR) including all hospital in and outpatient visits for each patient 2 years prior to the THA (0, ≥1).

Surgical factors

From the SHAR data regarding cement fixation of the prosthesis (uncemented or fixation with antibiotic loaded cement), surgical approach (posterior, lateral in side, lateral in supine position or other) and bilateral operations on the same day (yes or no) were extracted.

Environmental factors

From the previous study of PJI infection incidence the PJI incidence for 2007 (continuous scale) as well as the volume of THAs 2007 (continuous scale) for each of the operating units was calculated.

3.5 ETHICS

Ethical permissions for all studies were obtained from the Regional Ethics Committee in Gothenburg, Sweden. For Study I and II on January 23, 2012 (ref no 1136-11) and for study III - V on October 11, 2010 (ref no 553-10).

4 STATISTICAL METHODS

4.1 STUDY I

Follow-up started on the day of the primary THA operation and ended on the day of revision, death, emigration or by December 31, 2009. Separate Cox proportional hazard models were used to analyse the 3 designs of implants. For each implant 3 endpoints were used, revision because of infection, dislocation or aseptic loosening. Adjustment for age, sex, diagnosis, side, design of the acetabular cup, and number of operation (first or second in the same patient) was done. In the groups operated with Lubinus SP II and Exeter stems age was divided into 4 groups (<50, 50-59, 60-75, >75 years). In the Spectron EF Primary group the classification was condensed into 3 groups because small number of cases (n<100) in the youngest group. The adjusted relative risk ratio (RR) of revision with 95 % confidence interval (CI) for the different surgical approach is presented. To investigate the assumption of proportionality, hazard function plots and log-minus-log plots of all covariates were visually inspected. For each of the analyses there was no sign of insufficient proportionality, and log-minus-log plots ran parallel for all covariates.

4.2 STUDY II

All PROMs were calculated in means with standard deviation (SD) and medians with interquantile range (IQR). Differences in proportions were calculated by the chi^2 test, differences in means were calculated by the 2 sample independent T-test or analysis of variance (ANOVA) as appropriate. Group ranks and differences in medians were calculated by Mann-Whitney U test. Probability values < 0.01 were considered significant and 99 % Confidence Intervals (CI) were chosen. Linear regression was used with 1 year postoperative $EQ\text{-}5D_{INDEX}$ and $Pain_{VAS}$ as dependent values and surgical approach, age, gender, preoperative value of the index of interest, method of fixation (cemented, uncemented, hybrid or reverse hybrid) and preoperative Charnley category (A, B or C) (86) as independent values.

4.3 STUDY III

Incidence of PJI was described both as the 2-year cumulative incidence and incidence density rate. Each individual primary THA was studied separately (thereby including patients with bilateral THA). The cumulative incidence was calculated by dividing the total number of identified cases within 2 years after the primary THA by the total number of THAs in patients still alive and unrevised (except for infection) at 2 years after the primary operation. The incidence density rate was described by the number of diagnosed infections divided by the number of THAs at risk within two periods of time, before 3 months and 3-24 months. Incidence density rates were expressed per 10,000 THA-weeks, where a THA-week is a unit of follow-up equal to one THA followed for one week. THAs in patients that died within each time period were censored and once a THA was infected it was excluded for further follow-up time. Confidence intervals were calculated based on the binomial distribution with the Wilson score interval. Cumulative incidence was also calculated by each half year within the study period and trends were tested with the Binomial Proportion Trend test. Time to diagnosis was described as a

median. If the date of diagnosis was missing, the first reoperation date was chosen as date of diagnosis.

4.4 STUDY IV

The cumulative incidence of reoperation due to infection was calculated by dividing the number of reoperated THAs (in both questionnaire and SHAR reoperation data) by the total number of primary THAs in Sweden between July 1, 2005 and December 31, 2008 excluding the THAs in patients that died without reoperation within 2 years after the primary THA (n= 47,358). Each THA was studied separately as one patient could have more than one THA. Each reoperated THA was only counted once even though it might have been reoperated several times. Completeness of reoperation registration in the SHAR was calculated by dividing the number of THAs that were registered with a reoperation due to infection registered in the SHAR with the total number THAs with a known reoperation due to infection based on the information from the questionnaire and SHAR.

4.5 STUDY V

We used generalized linear mixed model with binary outcome (infection yes or no) to explore the effect of patient related, surgical and environmental factors on postoperative PJI. Every clinic was assumed to have a different baseline infection risk (different intercept in the model). Both Univariate and Multivariate regression analysis were used to explore the Odds ratio for each variable in the model. 95 % Confidence Intervals were chosen and p-values <0.05 were considered significant. Missing PROM data for the cases (n=23) were imputed using Multivariate Imputations by Chained Equations.

4.6 SOFTWARE

All statistical analyses were carried out in the IBM SPSS Statistics software (versions 19-22) for Windows.

5 RESULTS

5.1 STUDY I

Lubinus SPII
Use of the direct lateral approach decreased the risk with 34 % of subsequent revision due to dislocation (RR 0.7 CI: 0.5-0.8) compared to the posterior approach. Increased risk was observed for males, patients with diagnosis other than osteoarthritis and use of the FAL cup (Table 9). Most commonly the cup was exchanged (51 %) with or without stem exchange (Table 10).

The choice of surgical approach had no influence on revision rate due to infection. Male sex and patients with fracture or sequelae after fracture had an increased risk of revision because of infection.

Hips operated through a direct lateral approach showed a slightly higher probability for revision due to aseptic loosening (RR 1.3 CI: 1.0-1.6). Young age and male sex also had a negative influence, whereas the FAL cup and the ceramics head proved to be associated with decreased risk to undergo revision due to loosening. Most frequently both components were revised (48 %) followed by a cup revision only (30 %) (Table 10).

Exeter Polished
With the Exeter prosthesis the surgical approach did not influence the risk of revision for either dislocation, infection or aseptic loosening. Male sex and other diagnoses than osteoarthritis had a negative effect on implant survival with regard to revision due to infection and dislocation (Table 11).

Young age and use of the All-Poly cup were associated with increased risk of revision due to loosening. Most commonly the cup (59 %) or the cup and stem (32 %) were exchanged during revision due to loosening (Table 12).

Spectron EF Primary
Use of the direct lateral approach decreased the risk of revision due to dislocation (RR 0.3 CI: 0.1-0.4), whereas fracture diagnosis increased this risk (Table 13). Most commonly the cup, with or without stem exchange, were revised when this complication occurred (32 of 44 cases, 73 %)

The choice of approach had no influence on the risk of revision due to infection. The only obvious risk factor for this complication was male sex (Table 13).

The direct lateral approach implied a higher risk of revision due to aseptic loosening (RR 1.6 CI: 1.0-2.5) as did low age (Table 13). Most frequently the cup (49 %) or both components (33 %) were revised for this diagnosis (Table 14).

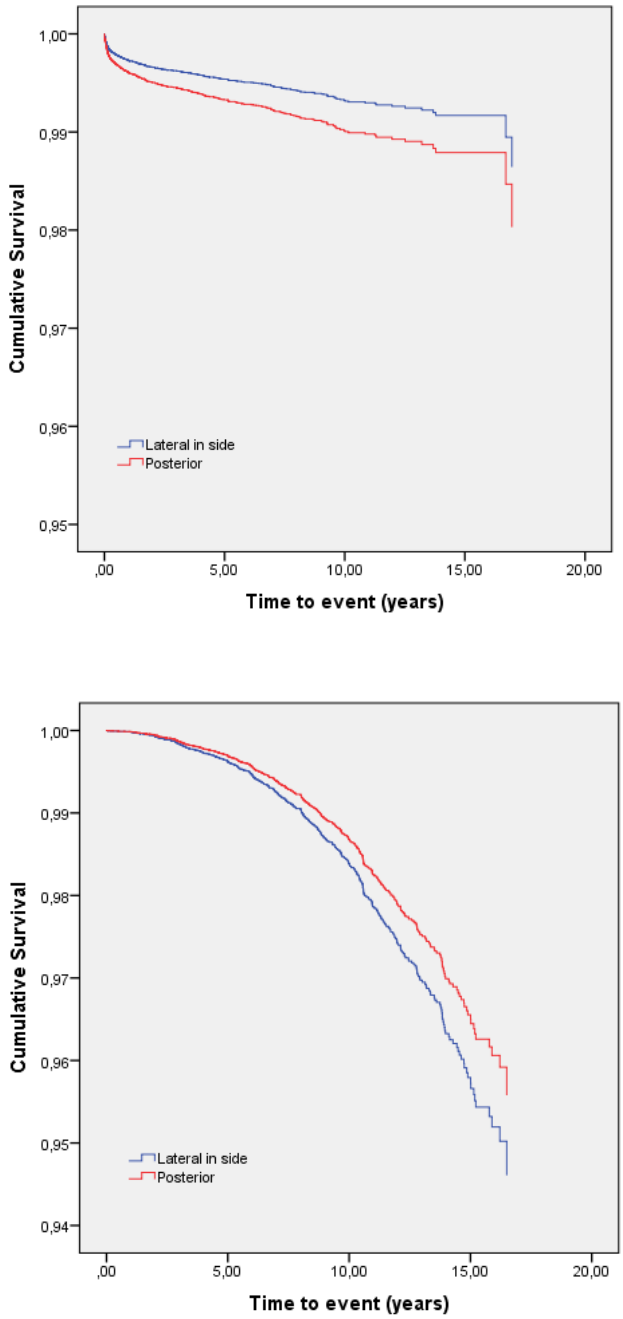

Figure 10. *Cumulative survival for the Lubinus SPII prosthesis by either Posterior or Direct lateral approach in side position calculated by Cox Regression analysis with revision due to dislocation (top) and due to aseptic loosening (bottom).*

5.2 STUDY II

Overall, favorable statistical significant mean differences were seen postoperative in all aspect of the PROMs investigated.

		Posterior mean *(SD)*	Lateral mean (*SD)*	Difference	99 % CI	p-value*
EQ-5D$_{INDEX}$	Pre-op	0.42 (0.31)	0.42 (0.31)	0	-0.01, 0.01	0.9
	1y postop	0.79 (0.23)	0.77 (0.24)	-0.03	-0.03, -0.02	<0.001
	6y postop	0.76 (0.26)	0.73 (0.28)	-0.03	-0.05, -0.01	<0.001
EQ$_{VAS}$	*Pre-op*	54 (22)	54 (22)	0.5	-0.7, 0.2	0.023
	1y postop	76 (20)	75 (20)	-1.5	-1.0, -2.0	<0.001
	6y postop	72 (21)	70 (22)	-1.8	-3.5, -0.1	0.005
Pain	*Pre-op*	62 (16)	62 (16)	0.2	-0.6, 0.2	0.278
	1y postop	13 (17)	15 (19)	1.5	1.0, 2.0	<0.001
	6y postop	15 (19)	17 (20)	2.3	0.8, 3.8	<0.001
Satisfaction	1y postop	15 (19)	18 (22)	2.9	2.3, 3.4	<0.001
	6y postop	15 (19)	19 (23)	3.2	1.5, 4.9	<0.001

Table 2. *Mean values for all PROMs for the posterior and direct lateral approach including differences. *by chi^2-test*

EQ-5D

The mean preoperative EQ-5D$_{INDEX}$ for the two groups was equal but the 1-year postoperatively mean EQ-5D$_{INDEX}$ value was significantly higher in the posterior group compared to the direct lateral group. This difference persisted after 6 years (Table 2). The preoperative impairment (i.e. reporting anything than "no problems") was greatest in the Pain/Discomfort and Mobility dimensions where almost all patients (93 vs. 99 % respectively) indicated impairment, followed by the Usual Activities dimension. There was no difference in preoperative impairment between the two groups except for the Anxiety/Depression dimension where there was a small but significant greater impairment in the direct lateral group. As a consequence the greatest postoperative improvement was seen for both groups in the Pain/Discomfort and Mobility aspects of the EQ-5D instrument. These two dimensions and the Usual Activities dimension also showed greatest difference between the two groups where a greater proportion of the posterior group reported improvement at both 1 and 6 years after surgery. Both groups improved as much in the Self-Care or Anxiety/Depression dimensions where no statistical significant differences were observed. (Table 3)

The mean preoperative EQ$_{VAS}$ were equal in the two groups but improved to a significantly higher postoperative mean for the posterior group in both the 1 and 6-year follow-up (Table 2).

Univariate regression analysis revealed that the posterior surgical approach increased 1-year post-operative EQ-5D$_{INDEX}$ with 0.025 (99 % CI: 0.019, 0.031). This change was persistent even after adjusting for pre-operative EQ-5D$_{INDEX}$, gender, age, Charnley category and method of fixation (0.027, 99 % CI: 0.021, 0.032).

EQ-5D dimension		Pre-operative impairment	1-year improvement	6-year improvement
Mobility				
	Posterior	93 %	58 %	52 %
	Lateral	93 %	49 %	48 %
	p-value*	0.051	< 0.001	0.001
Self-care				
	Posterior	23 %	19 %	20 %
	Lateral	23 %	19 %	19 %
	p-value*	0.179	0.434	0.374
Usual activities				
	Posterior	61 %	47 %	48 %
	Lateral	61 %	45 %	44 %
	p-value*	0.190	< 0.001	0.003
Pain/discomfort				
	Posterior	99 %	66 %	65 %
	Lateral	99 %	63 %	61 %
	p-value*	0.976	< 0.001	0.006
Anxiety/depression				
	Posterior	41 %	27 %	25 %
	Lateral	43 %	27 %	27 %
	p-value*	< 0.001	0.583	0.052

Table 3. *Differences in EQ-5D dimensions in the two groups *by chi^2-test*

Pain

A Box-plot reveals that the distribution of preoperative reported pain values were similar in the two groups. The postoperative values in the posterior group were however more condensed in the lower region of the scale compared to the direct lateral group both at 1 and 6 years. The postoperative median was lower in the posterior group compared with the direct lateral group at both 1 year 8(IQR:20) vs 9 (IQR:24) and 6 years 8 (IQR:20) vs 10(IQR:30). The difference was significant (p<0.001) and ranks were lower for the posterior group. (Figure 11)

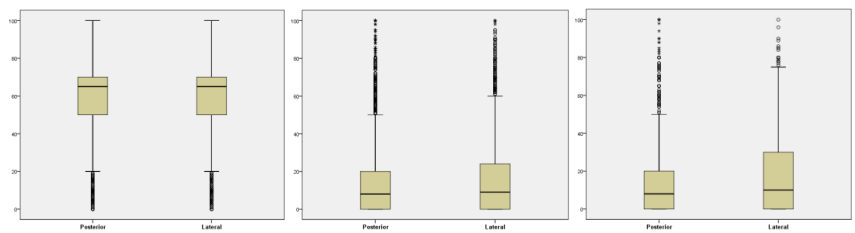

Figure 11. *Box-Plot of preoperative (left) and 1 year (middle) and 6 years (right) postoperative reported Pain (0-No pain, 100-Unbearable pain) for the two groups.*

The mean preoperative pain was severe and equal in the two groups but the posterior group reported less pain at one year compared to the direct lateral group. The reported pain slightly increased at 6 years but the difference between the two groups remained. The difference was significant with p<0.001 both at 1 and 6 years. (Table 2)
The proportion of patients reporting no or light pain was larger in the posterior group (78 %) compared to the direct lateral group (74 %) at 1 year (p<0,001, chi^2-test). This

proportion had decreased slightly at 6 years in both groups to 75 and 69 %, still with significant differences between them ($p<0.001$, chi^2-test).
Univariate regression analysis revealed that the posterior surgical approach decreased 1-year post-operative $Pain_{VAS}$ with -1.502 99 % CI: -1.956, -1.047). This change was persistent even after adjusting for pre-operative $Pain_{VAS}$, gender, age, Charnley category and method of fixation (-1.670, 99 %CI: -2.119, -1.220).

Satisfaction
A box-plot reveals that the satisfaction values reported by the group operated by the posterior approach were more condensed in the lower part of the scale and had fewer high values. The postoperative median was 10 for both groups at 1 and 6 years but the IQR was lower (24 vs 29) at 1 and 6 years as well as the ranks ($p<0.001$) for the posterior group. (Figure 12)

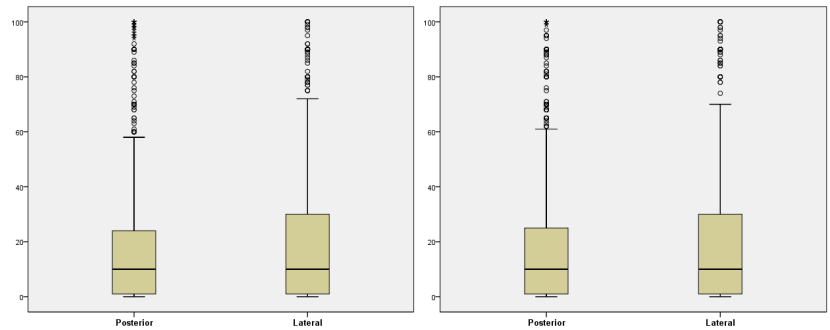

Figure 12. *Box-Plot of 1-year (left) and 6-year (right) postoperative reported Satisfaction (0- very satisfied, 100-dissatisfied) for the two groups.*

Patients operated through the posterior approach reported better mean satisfaction compared to the direct lateral approach and this difference was significant ($p<0,001$). The difference was unchanged after 6 years ($p<0.001$). (Table 2)
A larger proportion of the patients operated through the posterior approach reported that they were satisfied or very satisfied (90 % at 1 and 6 years) with the result of the surgery compared to the direct lateral (86 % at 1 year, 85 % at 6 years), a difference found to be statistically significant ($p<0.001$, chi^2-test).

5.3 STUDY III

443 THAs were treated for a deep PJI, representing an overall cumulative incidence of 0.9 % (95 % CI: 0.85-1.02). When dividing the 3.5 year study period into half-years an increasing incidence was found (Figure 13). 91 % of the deep PJIs were re-operated (n=405) as part of the treatment and 90 % (n=398) were diagnosed according to the specified objective criteria (Table 4).

Diagnosis criteria	n	%
1) Open sinus tract to the prosthesis	64	14.4
2) 2 or more positive perioperative cultivations	263	59.4
3a) + 3b) (Systemic infection and pus in joint + elevated CRP/ESR)	23	5.2
3a) + 3c) (Systemic infection and pus in joint + cultivation from joint aspirate)	19	4.3
3b) + 3c) (elevated CRP/ESR + cultivation from joint aspirate)	29	6.5
Clinical diagnosis / information lacking in questionnaire	45	10.2
Total	443	100

Table 4. *Distribution of diagnosis criteria*
(CRP=C-reactive Protein, ESR=erythrocyte sedimentation rate)

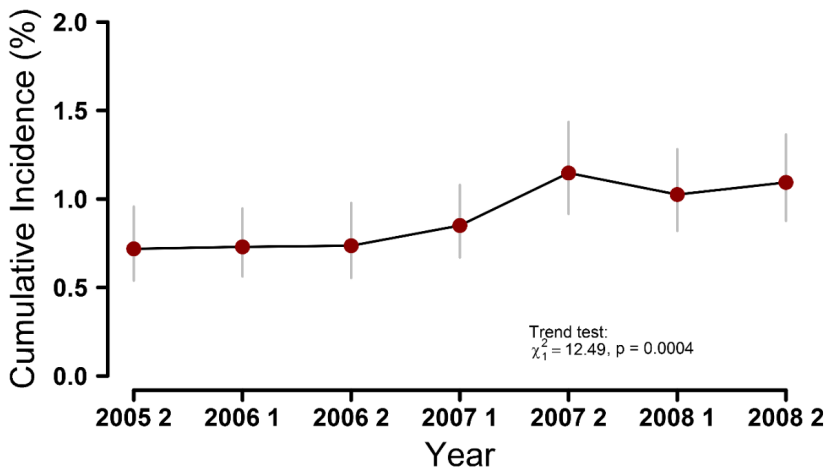

Figure 13. *The cumulative incidence (with 95 % Confidence Interval) of deep periprothetic joint infection after total hip replacement specified for each half-year of the study period.*

425 patients had a specified date of diagnosis or reoperation date and the median time to diagnosis was 24 days (Figure 14). The incidence density rate within the first three postoperative months was 5 cases per 10,000 THA-weeks (95 % CI: 4.70-5.83) and for the remaining 3-24 months it decreased to 0.3 cases per 10,000 THA-weeks (95 % CI: 0.21-0.31).

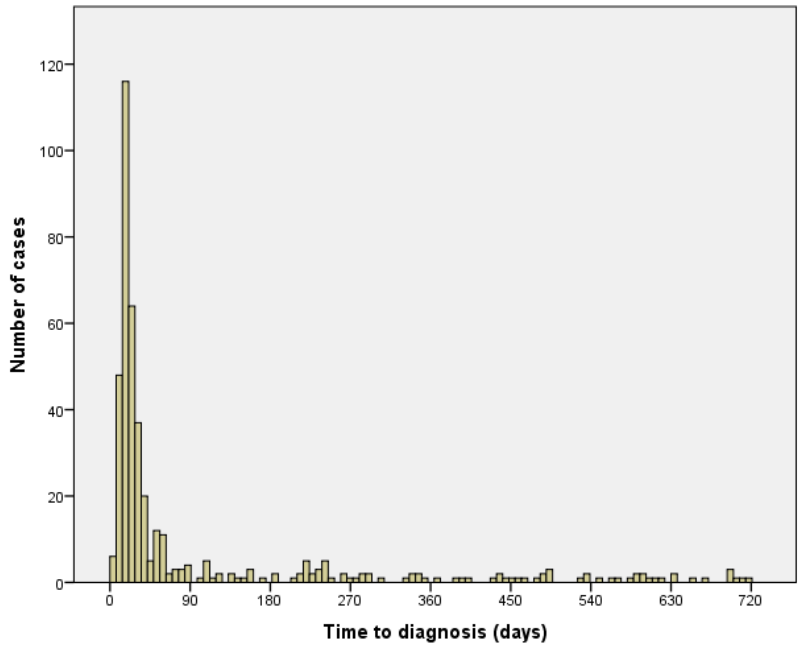

Figure 14. *Histogram illustrating time from primary total hip replacement to diagnosis of deep periprosthetic infection, each bar representing one week.*

The cumulative incidence of the individual clinics ranged from 0 to 4.2 % (median 0.8 %).

In 393 of the 443 deep PJIs a known pathogen was specified. Coagulase Negative Staphylococci (CNS) and Staphylococcus Aureus (SA) were alone or in combination with other microorganisms responsible in 70 % of the cases (Table 5).

Microorganism	n	%
Polymicrobial*	109	24.6
CNS	109	24.6
SA	89	20.1
Streptococci	32	7.2
Enterococcus feacalis	16	3.6
Miscellaneous	38	8.6
Unknown	50	11.3
Total	443	100

** all including either SA and/or CNS*

CNS = Coagulase Negative Staphylococcus

SA = Staphylococcus Aureus

Table 5. *Distribution of infecting microorganism*

5.4 STUDY IV

A total of 599 primary THAs were reoperated due to infection within 2 years after the primary operation making the cumulative incidence 1.3 %. Of these, 400 THAs were registered for a reoperation due to infection in the SHAR, resulting in an overall completeness of 67 %. The THAs with missing reoperation in the SHAR included all types of reoperations (Table 6).

Type of reoperation	total		Non-registered in SHAR	
	n	%	n	%
Reoperation without revision of prosthesis				
Wound revision	103	17.2	58	29.1
Irrigation of prosthesis	212	35.4	79	39.7
Total	315	52.6	137	68.8
Revision of prosthesis				
Exchange of parts or entire prosthesis	173	28.9	45	22.6
Extraction (with or without spacer)	111	18.5	17	8.5
Total	284	47.4	62	31.2
Total	599	100	199	100

Table 6. *Type of reoperation due to infection within 2 years after primary THA, total numbers and non-registered cases in the Swedish Hip Arthroplasty Register (SHAR)*

The number of non-registered reoperations for the individual primary operating units ranged between 0 to 100 % and was not associated to the total number of reoperated infections by each unit (Figure 15).

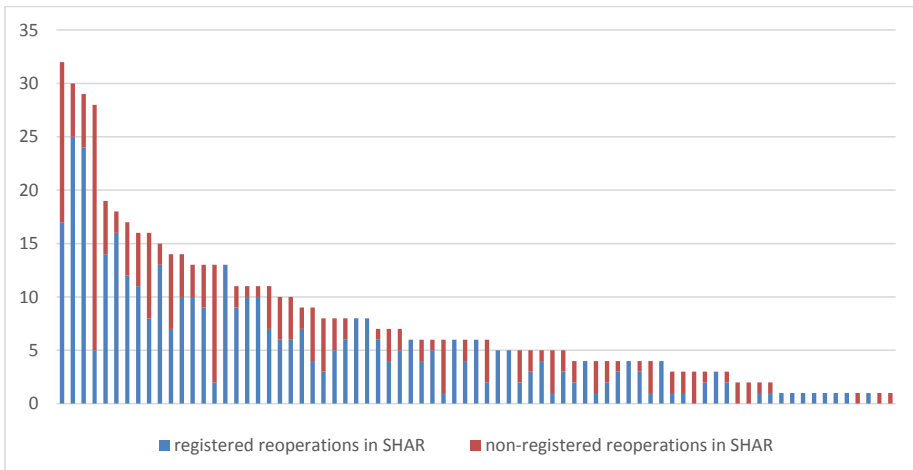

Figure 15. *The number of registered and non-registered reoperated primary THAs, within 2 years after index operation due to infection in the Swedish Hip Arthroplasty Register (SHAR), for each primary operating unit.*

5.5 STUDY V

Cases vs Controls
Compared to the controls the cases were less often of normal weight, were more often of ASA-score 3, had more often Elixhauser ≥1 and had less often osteoarthritis (all $p<0.001$). They were more often operated by the direct lateral approach in side position and were more often operated by a unit with greater PJI incidence ($p=0,031$ and $0,041$) (Table 7).

Patient related factors.
Both comorbidity measures (ASA- and Elixhauser score) had significant influence on the risk of PJI both in the uni- and multivariate analysis with increasing comorbidity (both $p=0.01$). Fracture diagnoses had increased odds for infection in the univariate but not in the multivariate analysis. Charnley category did not affect the risk of PJI and the preoperative PROMs had only limited effect on the univariate and multivariate analysis (Table 8).
Regarding BMI, both underweight and obesity had significant increased odds for PJI both in the uni- and multivariate analysis ($p=0.006$ and $p<0.0001$).

Surgical related factors.
The direct lateral surgical approach in side position showed increased risk of infection in the univariate analysis but none of the selected surgical related factors showed any increased risk of PJI in the multivariate analysis (Table 8).

Environmental related factors
The previous year infection incidence contributed to increased risk of PJI in the univariate model but none of the investigated environmental related factors showed increased risk of PJI in the multivariate analysis (Table 8).

Variable	Cases	Controls	P-value
Sample size	194	776	
Female gender (%)	95 (49.0)	380 (49.0)	1.000
Age group (%)			1.000
<50	5 (2.6)	20 (2.6)	
50-59	27 (13.9)	108 (13.9)	
60-75	97 (50.0)	388 (50.0)	
>75	65 (33.5)	260 (33.5)	
Hospital type (%)			1.000
University/Regional	31 (16.0)	124 (16.0)	
Central	84 (43.3)	336 (43.3)	
Rural	65 (33.5)	260 (33.5)	
Private	14 (7.2)	56 (7.2)	
BMI (%)			<0.001
Underweight	9 (4.6)	6 (0.8)	
Normal	43 (22.2)	260 (33.5)	
Overweight	74 (38.1)	344 (44.3)	
Obese	68 (35.1)	166 (21.4)	
Elixhauser ≥1 (%)	43 (22.2)	74 (9.5)	<0.001
ASA classification (%)			<0.001
1-2	128 (67.4)	640 (82.5)	
3	56 (29.5)	128 (16.5)	
4-5	6 (3.2)	8 (1.0)	
Charnley classification (%)			0.140
A	74 (39.8)	361 (46.5)	
B	16 (8.6)	77 (9.9)	
C	96 (51.6)	338 (43.6)	
Hip diagnosis (%)			<0.001
Osteoarthritis	139 (71.6)	708 (91.2)	
Other	2 (1.0)	1 (0.1)	
Acute cervical neck fracture	12 (6.2)	4 (0.5)	
Dysplasia	10 (5.2)	31 (4.0)	
Sequele after fracture	16 (8.2)	19 (2.4)	
Other fracture	3 (1.5)	0 (0.0)	
Inflammatory joint disease	3 (1.5)	9 (1.2)	
Osteonecrosis	5 (2.6)	4 (0.5)	
Post infection	1 (0.5)	0 (0.0)	
Tumour (incl path fracture)	3 (1.5)	0 (0.0)	
Preop Pain VAS (mean (SD))	64.15 (15.84)	61.27 (16.65)	0.067
Preop EQ-5D index (mean (SD))	0.35 (0.33)	0.41 (0.31)	0.062
Preop EQ VAS (mean (SD))	51.09 (20.46)	53.24 (21.35)	0.287
Surgical approach (%)			0.031
Posterior	76 (39.2)	390 (50.3)	
Lateral Side Position	108 (55.7)	351 (45.2)	
Lateral Supine Position	9 (4.6)	26 (3.4)	
Others	1 (0.5)	9 (1.2)	
Cemented fixation (%)	164 (85.9)	668 (86.1)	1.000
Bilateral THRs (%)	2 (2.0)	3 (0.4)	
Infection rate 2007 (mean (SD))	1.58 (1.17)	1.40 (1.09)	0.041
No of THRs 2007 (mean (SD))	270.89 (194.62)	275.82 (184.26)	0.742

Table 7. *Demographics of cases and controls. Categorical variables presented in numbers and percentages and continuous variables presented in means with standard deviation (SD). P-values calculated by t-test or Chi^2- test as appropriate.*

Variable		Univariate OR	Univariate 95 % CI	Univariate P-value	Multivariate OR	Multivariate 95 % CI	Multivariate P-value
Patient related factors							
BMI	Underweight	8.53	2.83; 25.68	<0.0001	5.39	1.63; 17.83	0.006
	Normal	ref			ref		
	Overweight	1.42	0.92; 2.17	0.106	1.36	0.88; 2.11	0.158
	Obese	3.14	1.98; 4.96	<0.0001	2.75	1.72; 4.39	<0.0001
Elixhauser score	0	ref			ref		
	≥1	2.13	1.4: 3.25	<0.0001	1.76	1.12; 2.52	0.01
ASA score	1-2	ref			ref		
	3	2.28	1.56; 3.32	<0.0001	1.68	1.12; 2.52	0.01
	4-5	-	-	-			
Charnley category	A	ref					
	B	0.99	0.53; 1.84	0.610			
	C	1.32	0.93; 1.88	0.634			
Hip Diagnosis	Osteoarthritis	ref					
	Infl. joint disease	0.91	0.25 3.23	0.880			
	Dysplasia	1.51	0.69; 3.30	0.296			
	Osteonecrosis	1.49	0.52; 4.25	0.455			
	Acute Cervical fracture	15.7	4.82; 51.29	<0.0001			
	Other fracture	-	-	-			
	Tumor (incl. path fx)	-	-	-			
	Sequelae after fracture	2.83	1.47; 5.47	0.002			
	Post infection	-	-	-			
	Other	-	-	-			
Pain VAS		1.01	1.002; 1.02	0.02	1.01	1.003; 1.025	0.014
EQ5D index		0.47	0.26; 0.87	0.014			
EQ VAS		0.99	0.98; 1.001	0.101			
Surgical related factors							
Surgical approach	Posterior	ref					
	Lateral in Side	1.82	1.24; 2.68	0.002			
	Lateral Supine	1.96	0.79; 4.84	0.142			
	Others	0.54	0.065; 4.48	0.569			
Prosthesis fixation	Uncemented	ref					
	Cemented	0.838	0.52; 1.35	0.47			
Bilateral surgery	No	ref					
	Yes	2.78	0.41; 19.09	0.29			
Environmental related factors							
Infection rate 2007		1.19	0.99;1.43	0.05			
No of THAs 2007		0.99	9.98; 1.01	0.25			

Table 8. *Uni- and multivariate analysis with Odds Ratio (OR) of risk factors including 95 % Confidence Intervals (CI) and p-values, non-significant values excluded in the multivariate analysis.*

6 DISCUSSION

6.1 SURGICAL APPROACH

The role of surgical approach in THA is an often debated issue and is not ended by this thesis. The change in distribution of surgical approaches in the SHAR over the years is probably a result of an attempt of orthopedic surgeons to improve the outcome of THAs. The most common early prosthesis related complication that has a relatively strong correlation to surgical approach is dislocation. This correlation seems even stronger considering that cervical femur fracture is an increasing indication for THA and in this group the surgical approach has great impact on dislocation risk (10). It can therefore be assumed that the increase in direct lateral approach seen in recent years is to reduce the risk of dislocation especially for training specialists finding their preferred approach. However, separation of reason for revision is important as the type of incision may reduce the risk of one complication but on the same time increase the risk of another complication. If these outcomes are compiled the overall risk may become neutralized and also more dependent on time to follow up since revisions due to loosening tend occur much later than those performed due to dislocation.

The findings in this study support the previous studies that the direct lateral approach decrease the risk of dislocation in THA (14, 15). An unexpected finding was that the Exeter prosthesis did not have a higher revision rate due to dislocation when inserted through a posterior approach. The reason for this is difficult to explain. It is possibly an effect of its head and neck design and/or the design of the cup rather than its straight tapered collarless stem. Stem revision after recurrent dislocation was more common for the Exeter prosthesis compared to Lubinus and Spectron, suggesting that correct stem placement is more difficult or perhaps that the Exeter stem is easier to revise.

Aseptic loosening of the implant is the most common reason for revision of a THA. There is only one previous study addressing the question of the impact of surgical approach on prosthetic loosening; Arthursson et al (2007) found that the Charnley prosthesis inserted through a direct lateral approach including trochanteric osteotomy was associated with lower revision rates both due to dislocation and aseptic loosening compared to those implanted using either a posterior or direct lateral approach without trochanteric osteotomy (89). They also found that use of the posterior or direct lateral approach without trochanteric osteotomy had no influence on the risk of revision of Exeter prosthesis.

Both approaches have their advantages and shortcomings of in terms of exposure and it is possible that the reason for the higher revision rate for the Lubinus and Spectron groups might have to do with malpositioning of the components. In both clinical and experimental studies inclination angle of the acetabular cup greater than 50 degrees have been found to correlate with increased acetabular wear (26, 90) which is often associated with loosening of the implant. Callanan et al (2011) found that the direct lateral approach lead to an increasing rate of malpostioned cups defined as an inclination angle lower than 30 degrees or greater than 45 degrees or anteversion lower than 5 degrees or greater than 25 degrees (91). If the direct lateral approach lead to a greater risk of malpositioning of the cup this could explain the increased risk of

revision due to loosening after this approach. The reason why only 2 of the stems had inferior results with the direct lateral approach is however more difficult to explain. Perhaps the cups used with the Lubinus and Spectron designs are more prone to be malpositioned than the cup used with the Exeter at least when inserted by the direct lateral approach.

Regarding the found differences for stems, it might be that the 2 non-polished stems are more sensitive to malpositioning. This can occur if the femoral canal is entered too anteriorly, which may be more frequent with use of a direct lateral approach. A direct lateral approach with a straight stem design often result in a thin cement mantle, or even stem-cortex contact, in the proximal anterior and distal posterior part of femur (92), but this might not result in an osteolysis with loosening of the polished straight stem (93, 94). The 2 non-polished stems are probably more sensitive to debonding and defects in the cement mantle resulting in higher production of cement and metallic debris (13). The relative distribution between cup and stem revisions with higher frequency of the latter procedure with the non-polished designs could support this theory. Poor access to the femoral canal can also lead to the use of a smaller stem size than appropriate. The smallest stem size of the Spectron and Lubinus design are associated with greater risk of loosening which also can contribute to the inferior result (95). The study confirmed the influence of young age and male sex as a risk factor for revision due to aseptic loosening.

The choice of incision is related to the surgeon's preference and experience, a factor that may render the interpretation of a clinical trial difficult. Further, large numbers are needed to gain statistical power and especially to study burden of infection, dislocation and aseptic loosening (11). When addressing these types of rare events large prospective observational studies are preferable especially when the time period between intervention and outcome (such as aseptic loosening) is long (23) and are proven useful even in orthopaedic surgery (96). The strength of this study is thus its large size, long observational time and external validity due to the nationwide study population and that both surgical approaches as well as the implants are still in use.

Neither Study 1 nor Study 5 show a correlation between surgical approach and risk of PJI or revision due to infection in the multivariate analysis.

The primary indication for THA is to relieve pain, restore hip function and increase quality of life although there is great variation in the assessment of indications (97). Patient reported outcome in THA has known problems with ceiling effects in the postoperative evaluation which is due to the often excellent outcome of the intervention for a patient with OA (98, 99). It is however well known that some patients respond poorly to the procedure and the reason for this is probably multifactorial (100, 101). Some patients might not be relieved of pain or suffer from a complication while others have other (perhaps unrealistic) expectations that are not met by the procedure. Although most patients have a great improvement on pain, HRQoL and hip function after a THA regardless of surgical approach, Study 2 indicate that the surgical approach does have an influence. It confirms the findings of superior PROMs after the posterior

approach in previous studies (68, 69), but contradicts the study that argue that the influence is transient (72).

The results do not mean that all patients are better off if operated by the posterior approach. The differences of the mean values for the investigated PROMs are small, but could still be clinically relevant. The less favorable means for the direct lateral group indicate that more patients report inferior values than in the posterior groups. This difference could reflect a general deterioration, where most patients report minor inferior values with variable clinical relevance or that a smaller subset of patients in the direct lateral group has more pronounced problems. The latter alternative seems more reasonable when considering the EQ-5D$_{INDEX}$. The difference in mean EQ-5D$_{INDEX}$ is a result of the difference in postoperative improvement in the different dimensions of EQ-5D. As the steps between the different answering options (such as no pain vs some or a lot of pain) are reasonably large, it is likely that this reflects a clinically relevant difference for some patients. The same goes for the postoperative VAS of pain and satisfaction shown by the box-plots diagrams and the statistically significant differences in percentiles (Figure 11 and 12).

The strength of this study is its prospective collection of data, the nationwide design and a large study group making the results statistically robust and highly generalizable to patients undergoing THA due to OA. It is also reasonable to believe that the outcomes are relevant in evaluating the effect of THA. For a large number of patients long-term data are evaluated and the differences between the two groups persist, indicating a permanent state.

A possible explanatory model for the difference in PROMs between the two groups could be the known complication of abductor weakness and Trendelenburg gait secondary to damage to the superior gluteal nerve or rupture/non-healing of the gluteus medius tendon. This condition is considered more common after insertion of a THA by the direct lateral approach compared to the posterior approach (15, 18, 69). This might be the reason why the largest difference between the two groups were detected in the mobility dimension of the EQ-5D instrument despite the lack of a specific information regarding postoperative limb. In some patients the damage to the superior gluteal nerve improves with time but several patients still suffer from Trendelenburg gait 1 year after THA (102, 103). The difference in mobility also decreases with time (1-year compared to 6-years postoperatively) but is still present 6 years after THA indicating a chronic impairment. A few patients in the direct lateral group also report less satisfaction and more hip related pain compared to the posterior group which could be a consequence of greater trochanteric pain, which might be another presentation of the same condition as abductor weakness.

There are many ways of determining the success or failure of a THA. These large prospective observational cohort studies indicate that the surgical approach has an impact on the outcome and that this should be taken into account when planning a THA. Even though the direct lateral approach decrease the risk of dislocation it may increase the risk of aseptic loosening and result in inferior patient reported outcome in the unrevised patients on a population level. Despite the seemingly small differences

between the groups, this observation has probably clinical relevance and especially against the background of the permanent nature of the differences observed and the large number of cases operated with these approaches. Prospective and randomized studies in this field would be of value to obtain more information about differences in clinical performance and PROs after use of these two approaches and to evaluate if these results can be generalized to other cemented implants and implants used with uncemented fixation especially regarding aseptic loosening.

6.2 PERIPROSTETHIC INFECTIONS

The most feared complication after THA is the deep periprosthetic joint infection. The problem with postoperative infections is likely to increase in the future as the number of performed THAs are estimated to increase as the indication for THA is expanding including both older and more fragile patients and younger patients with high demands of physical activity. There is also an increasing problem of antibiotic resistant bacteria leading to more difficult postoperative infections.

Study 3 presents a unique model to establish an incidence of deep PJI following primary THA by combining health registries with a medical records review. This is the first national incidence study by this method. As previously mentioned international studies have determined the PJI incidence after primary THA to between 0.2 and 1.6 % (42, 43). The different results in these studies suggests that the diagnosis criteria, the study population, and perhaps most importantly the length of follow-up have significant influence on the results.

The incidence of PJI is not always easy to determine in clinical practice since the predictive power of a single test is low. Many observations taken together such as clinical presentation, laboratory findings in blood and in joint aspiration, radiographic findings, histology and most importantly cultures are often used and needed to establish a diagnosis of PJI (104, 105). Cultures indisputably have a central role in the diagnosis but have considerable risks of being both false positive (contamination) and false negative due to preoperative antibiotic treatment, biofilm formation, poor managed samples and a lacking standard for cultivation (84, 106). Most studies have their own definition of a PJI and the historical absence of a standard makes comparisons difficult (107). The American Musculoskeletal Infection Society introduced a new standard in 2011 (84) , which practical usefulness has been subject to debate (108). The new standards accept the fact that a PJI can be present even though the criteria of diagnosis have not been fulfilled. Therefore all patients where the doctor reported a deep PJI even though the criteria were not fulfilled were included, as the opposite would definitely lead to an underreporting of PJI incidence. From a patient point of view it might not always be of importance how the diagnosis has been set but rather the clinical consequences of an infection and its treatment. Although 81 different doctors reviewed the medical records retrospectively, introducing a variability of data quality, most of the deep PJI cases included enough information in the questionnaire to establish the diagnosis consistent with the specified criteria adapted from the Workgroup of the Musculoskeletal Infection Society.

The incidence of infections increased during the period of observation, which has been suspected by an earlier study (45). Whether this is a result of deterioration of hygiene and prophylactic standards, increasing patient comorbidity or perhaps an increasing resistance and virulence of the microorganisms is however not answered by this study. Nevertheless it emphasizes the need for actions like the Swedish PRISS-initiative to reduce postoperative infection rates by improving all aspects of the pre-, per and postoperative care. Future studies are planned to determine the effect of this initiative in reducing the national infection burden.

The advantage of this study is both the nationwide coverage of all THA performing clinics, the large study population, the long follow-up and the possibility of an objective assessment of the clinical course after the surgical and medical treatment. The number of assessed medical records and returned questionnaires by the operating units is also a strength of the study. Study of medical records is also likely to give a more reliable validation compared to other methods such as questionnaires filled in by patients or procedure codes in administrative databases.

Compared to previous studies of national PJI incidence which are based solely on administrative data based on payment system (Medicare) (20, 43) the study identified infected patients by their treatment and not by coding of a diagnosis, a procedure which is probably more susceptible to different types of errors. Data based on International Classification of Diseases codes (ICD-codes) are easy to access and study but are imprecise in following specific PJIs as the codes indicating infection lack accuracy and are not side or joint specific. They can therefore result in an overestimation of infections or an underestimation depending on coding routines (20). Hopefully the method used in this study therefore result in a more specific and accurate estimation of the national incidence of deep PJIs in Sweden.

Many countries have introduced mandatory surgical site infection surveillance systems to monitor postoperative infections after specific surgical procedures, often including hip replacement surgery. Sweden lack such a register but instead have a possibility to combine and match information in different health-care and quality registers by the patient's personal registration number to find information that indicate a specific disease, for example infections. Therefore instead of inventing new registries a model for automated matching of registries in order to find possible postoperative infections is an attractive alternative (109). The SPDR introduces a possibility of an unbiased report of infection incidence as every dispensed prescription is recorded automatically. The SPDR seem to be sensitive in identifying patients with a possible postoperative infection but is not sufficient to monitor postoperative infections alone as the population observed have a risk of many other medical conditions requiring antibiotic treatment. Future studies are planned to investigate how to automatically combine register data in order to increase specificity and maintaining a high sensitivity without the need for review of medical records.

The microbial spectra with a majority of CNS- and SA-caused infections are consistent with previous studies (47, 52). The problem with increasing incidence of Methicillin-Resistant-Staphylococcus Aureus (MRSA) infections reported internationally does not

seem to have been a clinical problem in Sweden 2005-2008 as no MRSA infections were reported (110).

Study 4 presents an external validation of the SHAR reoperation database in terms of reoperation due to infection and shows that 67 % of the reoperated infections are reported to the register. The low completeness of registered reoperations due to infection in the SHAR varied greatly between the operating units, but seems to be a general problem of the Swedish orthopaedic community. The reason for the low completeness is probably multifactorial but one important reason might be that reoperations due to infection with no or minor implant exchange are performed in an acute setting and could therefore deviate from the standard routine reporting. Another reason might be that other orthopaedic quality registries (e.g. the Swedish Knee Arthroplasty Register) only record revisions (implant exchange or extraction) and not all reoperations introducing an uncertainty in the reporting routines to the SHAR. That 68.8 % of the reoperations not reported to the register were reoperations without implant exchange or extraction supports this (Table 6). There is also a possibility that units taking care of their own complications deliberately fail to report reoperations to the SHAR in order to improve their results in the SHAR annual report. However, the high compliance to the questionnaire, where all operating units participated speaks against this presumption.

The validity of a total joint replacement register is dependent on the coverage and completeness of the register. The coverage (i.e. the number of operating units that report to a register) is important, but the figures can be misleading if the completeness (i.e. the number of correct registrations on an individual level) is low at some or all operating units. This can lead to both an underestimation of the true total incidence of reoperations and to an incorrect relative incidence between the reporting units. It is therefore important to evaluate both coverage and completeness so that the results can be interpreted with justice.

Arthroplasty register data has been used to study the change of infection rates after total hip arthroplasty (44). An arthroplasty register only capture infections that are reoperated (and in some registries only the revised ones) and not the infections treated by antibiotics only (111). In Study 3 10 % of the deep infections during the study period were treated without surgical intervention. The change in infection rates can therefore reflect a change in reoperation policy or the change in arthroplasty modularity making it easier to revise the prosthesis by exchange of head or acetabular liner. The low completeness found in this study also imply that change in reporting routines could have a large impact on the change in infection rates in register data. That only 47.4 % of the reoperations due to infection in this study were revisions, implies that especially those arthroplasty registers that only record revisions seem less reliable when studying infection rates as revisions are dependent on the modularity of the prosthesis. In contrast to previous arthroplasty validation studies that have found extraction of prosthesis (i.e. Girdlestone procedure) due to infection to be the most common error in registration, this procedure was found to be the most reliable of the four categories in this study (112, 113). The conclusion is that national arthroplasty register data cannot with certainty be used as an estimation of the total infection burden after THA.

Study 5 confirmed the findings in previous studies that increasing ASA-score and obesity is associated with increased risk of PJI. It also found that underweight is a risk factor. The findings in the multivariate analysis suggest that the difference in incidence of PJIs observed in the different operating units substantially can be explained by the case-mix between clinics. The study indicate that further decreasing the incidence of PJIs after primary THA will be difficult.

7 LIMITATIONS

7.1 GENERAL CONSIDERATIONS ON STUDIES OF ARTHROPLASTY REGISTER DATA.

When studying complications there is always a risk of underestimation as 100 % follow-up is difficult to achieve especially if they occur long time after the intervention. Even in studies with data from national arthroplasty registers there is always a risk of underestimating the complication of interest as only re-operated or revised implants are recorded. Skewness in groups on e.g. age can lead to an under-representation of the number of patients in one group because of non-operative treatment due to old age or medical co-morbidity. The presence of the complication you are interested in can thus be influenced by the method of its treatment.

The validity of a register is above all dependent on the coverage and completeness of the register. The coverage of the SHAR is 100 % and the completeness of primary procedures are 97.5 % when compared with the NPR (9). In a study of the SHAR, Söderman et al have concluded that the completeness of the data was high although it differed depending on which parameter was measured (76). The results in study 4 highlight the problem with completeness of data.

Register data can be used to see correlations between exposure and outcome but does not allow the possibility to make causal connections. There are many possible confounders that might influence both the exposure and the outcome which are difficult to take into account. Therefore in general the results are often used in order to create hypotheses later proved by clinical trials that, in theory, would distribute these factors equally. Practically they are however often used to complement research where clinical trials are not conducted due to high costs, large number of patients and long observation time needed. In orthopaedic surgery such confounding factors might be surgical skills influencing for example bleeding, implant positioning, soft tissue management, and operating time that can influence the outcome both in terms of complications and PROs. Other factors that could influence the outcome but are difficult to include are smoking, daily activity, education and medical or psychiatric co-morbidity.

7.2 SPECIFIC CONSIDERATIONS REGARDING STUDY I

One concern with the study could be the skew distribution in the 3 implant groups between the 2 types of approaches studied. Nonetheless, the smallest group included more than 1 300 operations which should be sufficient for a reliable analysis. Another source of error could be that some cases classified as aseptic loosening were low grade infections. However, this would probably affect the different implant designs and surgical approaches evenly, especially when the study indicate that the revisions due to postoperative infection are equally dispersed among the different implants and surgical approaches.

From 1999 the SHAR has registered all information on an individual basis which is a guarantee for a reliable database. However, before this year some information was collected on a hospital basis meaning that variation in some variables in the same hospital not was considered. Instead the most commonly used variable was reported for all operations. Head size and surgical approach are examples of this kind of information. In Sweden each hospital had at that time a rather consistent use of a specific surgical approach and variations in head size of the prosthesis was rare. Nonetheless, this way of reporting means an increased risk of incorrect data collection during the early period of the study. This period was included to increase the observation time, which is of interest to obtain a better coverage of revisions due to loosening. Analysis of this problem based on the surgical approaches used and reported for individual operations performed during the year 2000 revealed that more than one type of approach was used on a regular basis in 12 of 55 departments, performing at least one of the implants in the study. If this finding is applicable to the period 1992-1998 this means that the relative share of misclassified cases would constitute 8.7 % of cases operated 1992-1998 and 2.2 % of the cases operated during the entire period of observation

7.3 SPECIFIC CONSIDERATIONS REGARDING STUDY II

Apart from the general considerations regarding register data studies the main limitation of studies on PROMs in THA is that the differences in PROMs between the two approaches are small although they are statistically significant. Are the differences truly clinically relevant? Small differences in mean values can derive from either small differences in many patients or large differences in a few patients or a mix of both. A small mean difference can however not automatically be dismissed as clinically irrelevant just because it is below a Minimally Clinically Important Difference (MCID) for an individual value. In this study the distribution in the box-plots and the cut-off values imply that the small and statistically significant mean difference derives from a large difference for a smaller group of patients. There is also risk of selection bias as only the patients that had completed and returned the pre- and postoperative PROM questionnaire were assessed.

7.4 SPECIFIC LIMITATIONS REGARDING STUDY III-V

As only outpatient antibiotic treatment is recorded in the SPDR the patients who died before discharge or those not receiving or complying with the antibiotic treatment would not be included in the questionnaire group. Also, patients never returning to the primary operating unit would not be recorded as a PJI or have had a reoperation even though they might have consumed large doses of antibiotics. This group of patients is not expected to be large as only long term antibiotic treatment was included and superficial infections were excluded in Study 3. Although the register data is collected prospectively, the diagnosis of PJI was set retrospectively which also is a possible weakness in this study. However the question if a patient had been reoperated due to infection is probably not affected by the retrospective analysis. With these concerns in mind it can be concluded that the incidence found in this study is probably a slight underestimation of the true incidence of PJIs and reoperations.

In Study 5, the nature of the data put extra strains on the statistical analyses. The patients were divided between 76 different clinics and the incidence rate of infections was generally low. As most potential predictors were categorical, some might contain very few observations. The direction and magnitude of the estimate odds are right, but due to the low incidence of the outcome their exact size might fluctuate by the addition or removal of a few patients in the model.

The NPR (used for comorbidity assessment in study 5) has proven to have high validity for a registered diagnosis but the absence of a diagnosis does not mean that it does not exist, i.e. the sensitivity of the register is likely low as a patient need hospital in- or outpatient care to be associated with a diagnosis. The calculated Elixhauser comorbidity score is probably lower than the true score, but likely so for both cases and controls. Factors that have been found influential in earlier studies were included in the multivariate analysis but it is possible that other factors that could have an impact were not included.

8 GENERAL CONCLUSIONS

Based on the findings in the studies of this thesis the following conclusions can be made:

1. The surgical approach is a factor worth taking into account when estimating the risk of revision in THA as it might influence the outcome differently depending on the implant at hand and the cause of revision.
2. The direct lateral approach is associated with inferior generic and hip specific PROMs compared to the posterior approach in THA due to osteoarthritis.
3. The national incidence of early and delayed deep PJIs after primary THA in Sweden 2005-2008 was 0.9 %.
4. The completeness of registered reoperations due to infection was 67 % in the Swedish Hip Arthroplasty Register during 2005-2008.
5. In Sweden, patient related factors seem to be more influential compared to environmental and surgical related factors on the risk of developing a PJI within the first two postoperative years following primary THA.

9 FUTURE PERSPECTIVES

9.1 IMPROVING THE RESULTS OF THA

To further improve the already very good results of THAs on a population basis some conclusions can be made from the presented studies. They highlight the importance of an individualized operation related to the various facts present in each case. Many doctors and clinics use only one surgical approach for all patients and diagnoses. The results of the presented studies however indicate that not only implant choice is an important factor for postoperative success but also the surgical approach.
Patients with increased risk of dislocation (such as patients with cervical hip fracture) motivate a THA through the direct lateral approach as this approach is in less extent associated with dislocation. The posterior approach should be advocated to allow for a greater chance of good PROMs and to decrease the future risk of aseptic loosening in patients with OA, especially those of young age.

Regarding the risk of early and delayed postoperative infections the findings indicate that patient comorbidity is the most important factor on a population base. Preoperative optimization of the patient is therefore of great importance although some of the risk factors are not possible to affect. Consequently a more active postoperative regimen (sterile wound dressings, early follow-up with wound control etc.) should be organized to minimize wound healing complications and if they occur to detect these as early as possible especially for patients with increased risk of infections.

9.2 FUTURE STUDIES

Monitoring systems are important when trying to minimize complications. Such systems need to be reliable with great sensitivity as well as specificity. Preferably they should not be expensive to allow for frequent evaluations. Surgical site infection surveillance systems have not been implemented in Sweden. This is perhaps because they are associated with high costs. Compared to other countries Sweden has the advantage of the many health care and quality registers that can be linked on a patient level via the personal identification number, enabling a possibility to follow specific complications. Instead of inventing new registries, automated cross-matching between existing registries together with an algorithm (defining for example infections) are possible methods for a continuous surveillance system that is likely very cost effective. Before implementing such a surveillance system it needs to be validated to ensure their sensitivity and specificity to be used for improvement work.

As the PRISS' pre-, per- and postoperative recommendations since 2013 are fully adopted by all clinics in Sweden performing THAs it is possible to evaluate the effect of this project on the nationwide incidence of PJIs. Hopefully the initiative has been effective. It is however possible that the initiative has led to an increasing interest of PJIs among doctors leading to better diagnostics and/or prolonged treatment of PJIs resulting in an increasing annual incidence.

The economic effect of PJIs and its burden on the healthcare system has been studied but the effect of a PJI on PROMs have not been fully investigated. This is probably dependent on the microbiology and number and type of surgical interventions performed on each individual. This is a possible future study of great interest especially for insurance providers.

10 SAMMANFATTNING PÅ SVENSKA

Den moderna höftprotesen introducerades på 1960-talet av Sir John Charnley och har sedan dess varit en framgångsrik metod att kirurgiskt behandla smärtsamma höftsjukdomar och skador. I Sverige genomförs årligen ca 16 000 höftprotesoperationer. Proteserna har genom åren utvecklats genom bland annat förbättrad fixation till skelettet och genom material med mindre slitage. Eftersom protesrelaterade komplikationer är ovanliga och ofta sker flera år efter operationen är det bästa sättet att studera dem genom observationella studier på stora patientgrupper under lång tid. Tack vare höftprotesregister har man tidigt kunnat identifiera dåliga protesmodeller och därigenom hitta de modeller som har bäst långtidsresultat. Utfallet av en höftprotesoperation kan bedömas utifrån patientens förbättrade livskvalitet och minskad smärta och utifrån förekomst av komplikation med eller utan behov av omoperation.

Denna avhandling innefattar 2 olika aspekter av komplikationer efter höftprotesoperation. De första två studierna behandlar det kirurgiska snittets inverkan på risken av att behöva byta ut protesen och på patientrapporterat utfall. De 3 sista arbetena studerar olika aspekter av djup infektion efter höftprotesoperation. Registerdata utgör grunden för samtliga studier.

Studie 1 är en kohortstudie med data från Svenska Höftprotesregistret (SHPR) av patienter som opererats med en primär cementerad total höftledsprotes av de 3 vanligast förekommande fabrikaten. Utfallet är risk för revision (byte av en eller flera protesdelar) och jämför de två mest använda kirurgiska snitten till höftleden. Studien inkluderar 90 662 patienter primärt opererade 1992-2009. Resultaten visar att ett bakre snitt associeras med ökad risk för revision av protesen på grund av luxation men med mindre risk för revision på grund av lossning jämfört med ett lateralt snitt, men att detta också skiljde sig åt mellan protesfabrikaten.

Studie 2 är en kohortstudie av patienter opererade med en total höftledsprotes på grund av artros och jämför snittets inverkan på patientrapporterat utfall såsom det registreras i SHPR. Den innefattar 42 233 patienter opererade mellan 2002-2010. Den visar att ett bakre snitt leder till ett något bättre utfall avseende smärta, nöjdhetsgrad och hälsorelaterad livskvalitet jämfört med ett lateralt snitt. Skillnaderna stod sig upp till 6 år efter primäroperationen.

Studie 3 och 4 är deskriptiva studier som studerar incidensen av djup protesinfektion inom 2 år efter primär höftledsprotesoperation. De innefattar 45 531 patienter med 49 419 höftledsproteser registrerade i SHPR. Dessa patienter matchades med läkemedelsregistret avseende förskriven antibiotika efter operationen. I en efterföljande journalstudie av de 2 219 patienter som haft minst 1 månads sammanhängande antibiotikabehandling inom 2 år efter operationen kunde incidensen av djup protesinfektion bestämmas till 0,9 % vilket presenteras i Studie 3. I Studie 4 jämfördes de identifierade omoperationerna i studien med SHPRs omoperationsdatabas och visade att en tredjedel av antalet omoperationer inte var registrerade.

Studie 5 är en fall-kontrollstudie som jämför olika faktorers inverkan på risken att drabbas av protesinfektion. Den innefattar de 194 patienter opererade under 2008 som postoperativt drabbats av infektion. Dessa jämförs med 4 matchade kontroller per fall och visar att patientens samsjuklighet spelar större roll för infektionsrisken än operations- och omgivningsfaktorer.

Sammanfattningsvis visar denna avhandling att det kirurgiska snittet påverkar utfallet efter en höftprotesoperation på olika sätt varför detta är en faktor att ta i beaktande vid planering av en operation. Avhandlingen beskriver en ny metod att bestämma incidensen av infektion efter höftprotesoperation och att SHPRs omoperationsdatabas inte med säkerhet kan användas för att följa incidensen av djup protesinfektion. Den visar att samsjuklighet spelar större roll än operations- och omgivningsfaktorer för risken att drabbas av en infektion, vilket försvårar förbättringsarbetet.

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13 APPENDIX

		Relative Risk	95 % CI	p-value
Dislocation				
Age (years)	<50	0.5	0.2-1.3	0.2
	50-59	0.9	0.6-1.3	0.5
	60-75	0.9	0.7-1.1	0.3
	>75	1		
Sex	Female	1		
	Male	1.2	1.0-1.5	0.03
Order	1st hip	1.0	0.8-1.3	0.9
	2nd hip	1		
Diagnosis	Osteoarthritis	1		
	Fracture	3.2	2.6-4.0	<0.001
	Other	1.5	1.0-2.1	0.03
Cup	FAL	1.7	1.3-2.4	<0.001
	Lubinus All-Poly	1		
Head	Ceramics	0.7	0.5-1.0	0.06
	Co-Cr	1		
Surgical approach	Lateral	0.7	0.5-0.8	0.001
	Posterior	1		
Side	Left	1		
	Right	1.0	0.8-1.2	0.8
Loosening				
Age (years)	<50	8.4	5.4-13.0	<0.001
	50-59	6.0	4.3-8.3	<0.001
	60-75	3.0	2.2-4.0	<0.001
	>75	1		
Sex	Female	1		
	Male	2.1	1.8-2.5	<0.001
Order	1st hip	1.0	0.8-1.3	1.0
	2nd hip	1		
Diagnosis	Osteoarthritis	1		
	Fracture	1.3	0.9-1.8	0.1
	Other	1.2	0.9-1.6	0.2
Cup	FAL	0.5	0.3-1.0	0.05
	Lubinus All-Poly	1		
Head	Ceramics	0.5	0.3-0.7	<0.001
	Co-Cr	1		
Surgical approach	Lateral	1.3	1.0-1.6	0.02
	Posterior	1		
Side	Left	1		
	Right	1.2	1.0-1.4	0.03
Infection				
Age (years)	<50	1.9	1.0-3.7	0.07
	50-59	1.1	0.7-1.7	0.7
	60-75	0.9	0.7-1.2	0.7
	>75	1		
Sex	Female	1		
	Male	2.2	1.7-2.7	<0.001
Order	1st hip	0.7	0.6-1.0	0.04
	2nd hip	1		
Diagnosis	Osteoarthritis	1		
	Fracture	1.8	1.3-2.6	<0.001
	Other	1.6	1.1-2.4	0.03
Cup	FAL	0.7	0.4-1.1	0.1
	Lubinus All-Poly	1		
Head	Ceramics	0.7	0.5-1.1	0.09
	Co-Cr	1		
Surgical approach	Lateral	0.9	0.70-1.2	0.6
	Posterior	1		
Side	Left	1		
	Right	1.2	0.9-1.5	0.2

Table 9. *Relative risks of revision for the Lubinus SPII (Cox regression). Parameters with value 1 are reference.*

	Dislocation				Loosening			
	Lateral		Posterior		Lateral		Posterior	
	n	%	n	%	n	%	N	%
Stem	2	3	13	4	28	24	93	20
Stem + Cup	11	14	20	5	50	43	231	49
Cup	37	47	137	37	34	29	139	30
Extraction	1	1	14	4	3	3	6	1
Other	28	35	186	50	1	1	1	0
Total	79	100	370	100	116	100	470	100

Table 10. *Components exchanged or removed due to dislocation or loosening of the Lubinus SPII*

		Relative Risk	95 % CI	p-value
Dislocation				
Age (years)	<50	0.7	0.3-2.0	0.5
	50-59	0.9	0.5-1.6	0.8
	60-75	1.1	0.8-1.5	0.7
	>75	1		
Sex	Female	1		
	Male	1.3	1.0-1.8	0.08
Order	1st hip	0.9	0.6-1.3	0.6
	2nd hip	1		
Diagnosis	Osteoarthritis	1		
	Fracture	3.4	2.2-5.1	<0.001
	Other	2.0	1.2-3.3	0.01
	Contemporary			
Cup	Hooded Duration	1		
	Exeter All-Poly	0.7	0.4-1.4	0.3
	Exeter Duration	0.9	0.5-1.5	0.6
Surgical approach	Lateral	0.6	0.3-1.1	0.1
	Posterior	1		
Side	Right	1.0	0.7-1.3	0.7
	Left	1		
Loosening				
Age (years)	<50	6.0	3.8-9.6	<0.001
	50-59	3.8	2.5-5.6	<0.001
	60-75	2.2	1.6-3.2	<0.001
	>75	1		
Sex	Female	1		
	Male	0.8	0.8-1.2	0.8
Order	1st hip	1.0	0.7-1.3	0.9
	2nd hip	1		
Diagnosis	Osteoarthritis	1		
	Fracture	0.6	0.4-1.1	0.09
	Other	1.2	0.9-1.7	0.2
	Contemporary			
Cup	HoodedDuration	1		
	Exeter All-Poly	2.5	1.3-5.7	0.01
	Exeter Duration	0.9	0.5-1.8	0.9
Surgical approach	Lateral	0.9	0.5-1.5	0.6
	Posterior	1		
Side	Right	1.1	0.9-1.3	0.6
	Left	1		
Infection				
Age (years)	<50	1.5	0.4-5.0	0.6
	50-59	1.1	0.7-2.9	0.3
	60-75	1.3	0.8-2.1	0.4
	>75	1		
Sex	Female	1		
	Male	2.2	1.4-3.4	<0.001
Order	1st hip	0.6	0.4-1.1	0.09
	2nd hip	1		
Diagnosis	Osteoarthritis	1		
	Fracture	4.3	2.5-7.5	<0.001
	Other	1.2	0.6-2.8	0.6
	Contemporary			
Cup	Hooded Duration	1		
	Exeter All-Poly	0.6	0.3-1.5	0.3
	Exeter Duration	1.3	0.6-2.6	0.5
Surgical approach	Lateral	1.1	0.6-2.3	0.7
	Posterior	1		
Side	Right	1.1	0.8-1.7	0.6
	Left	1		

Table 11. *Relative risks of revision for the Exeter prosthesis (Cox regression). Parameters with value 1 are reference*

	Dislocation				Loosening			
	Lateral		Posterior		Lateral		Posterior	
	n	%	n	%	n	%	N	%
Stem	5	31	32	22	0	0	26	8
Stem + Cup	0	0	27	18	9	45	102	32
Cup	8	50	56	38	11	55	190	59
Extraction	0	0	4	3	0	0	4	1
Other	3	19	28	19				
Total	16	100	147	100	20	100	322	100

Table 12. *Components exchanged or removed due to dislocation or loosening of the Exeter prosthesis*

		Relative Risk	95 % CI	p-value
Dislocation				
Age (years)	< 60	0.7	0.2-3.1	0.6
	60-75	1.2	0.6-2.1	0.7
	> 75	1		
Sex	Female	1		
	Male	1.0	0.5-1.9	1.0
Order	1st hip	1.6	0.6-4.5	0.4
	2nd hip	1		
Diagnosis	Osteoarthritis	1		
	Fracture	4.8	2.5-9.0	<0.001
	Other	1.4	0.4-4.9	0.6
Surgical approach	Lateral	0.2	0.1-0.4	<0.001
	Posterior	1		
Side	Right	1.0	0.5-1.8	1.0
	Left	1		
Loosening				
Age (years)	< 60	7.1	3.8-13.2	<0.001
	60-75	2.9	1.7-4.8	<0.001
	> 75	1		
Sex	Female	1		
	Male	1.3	0.9-1.8	0.2
Order	1st hip	0.7	0.5-1.1	0.2
	2nd hip	1		
Diagnosis	Osteoarthritis	1		
	Fracture	0.8	0.5-1.6	0.6
	Other	1.1	0.6-2.1	0.7
Surgical approach	Lateral	1.6	1.0-2.5	0.04
	Posterior	1		
Side	Right	1.1	0.8-1.5	0.7
	Left	1		
Infection				
Age (years)	< 60	1.9	0.7-5.1	0.2
	60-75	1.2	0.6-2.4	0.6
	> 75	1		
Sex	Female	1		
	Male	2.9	1.6-5.5	0.001
Order	1st hip	0.8	0.4-1.6	0.4
	2nd hip	1		
Diagnosis	Osteoarthritis	1		
	Fracture	1.5	0.6-3.6	0.4
	Other	2.5	1.1-6.0	0.04
Surgical approach	Lateral	0.9	0.5-1.8	0.8
	Posterior	1		
Side	Right	0.9	0.5-1.6	0.7
	Left	1		

Table 13. *Relative risks of revision for the Spectron prosthesis (Cox regression). Parameters with value 1 are reference.*

	Dislocation				Loosening			
	Lateral		Posterior		Lateral		Posterior	
	n	%	n	%	n	%	n	%
Stem	1	6	0	0	13	13	3	11
Stem + Cup	4	22	1	4	32	33	9	33
Cup	9	50	18	69	48	50	13	48
Extraction	2	11	1	4	4	4	2	7
Other	2	11	6	23				
Total	18	100	26	100	97	100	27	101

Table 14. *Components exchanged or removed due to dislocation or loosening of the Spectron EF Primary prosthesis*

Antibiotic	ATC-code	Daily dose	4 weeks treatment
Amoxicillin	J01CA04	750 mg 1x3	84
Amoxicillin and clavulanic acid	J01CR02	875/125 mg 1x2	56
Azitromycin	J01FA10	250 mg 1x1	28
Cefadroxil	J01DB05	1 g 1x2	56
Cefalexin	J01DB01	3 g 1x2	56
Ceftriaxon	J01DD04	2 g 1x1	28
Ceftributen	J01DD14	400 mg 1x1	28
Cefuroxim	J01DC02	250 mg 1x2	56
Ciprofloxacin	J01MA02	250 mg 1x2	56
		500 mg 1x2	56
		750 mg 1x2	56
Daptomycin	J01XX09	400 mg 1x1	28
Ertapenem	J01DH03	1 g 1x2	28
Erytromycin	J01FA01	250 mg 2x2	112
Fenoximetylpenicillin	J01CE02	1 g 2x3	168
Flukloxacillin	J01CF05	500 mg 2x3	168
		750 mg 2x3	168
Fusidic acid	J01XC01	250 mg 2x3	168
Klaritromycin	J01FA09	250 mg 1x2	56
Klindamycin	J01FF01	300 mg 1x2	56
Levofloxacin	J01MA12	500 mg 1x1	28
Linezolid	J01XX08	600 mg 1x2	56
Lorakarbef	J01DC08	200 mg 1x2	56
Metronidazole	P01AB01	400 mg 1x3	84
Moxifloxacin	J01MA14	400 mg 1x1	28
Norfloxacin	J01MA06	400 mg 1x2	56
Rifampicin	J04AB02	600 mg 1x1	28
Roxitromycin	J01FA06	150 mg 1x2	56
Sulfametoxazol and trimetoprim	J01EE01	160 mg/800 mg 1x2	56
Teikoplanin	J01XA02	400 mg 1x1	28
Telitromycin	J01FA15	400 mg 2x1	56
Vancomycin	J01XA01	1 g 1x2	56

Table 15. *Number of tablets/doses required for 4 weeks of continuous treatment. (ATC-code = Anatomic Therapeutic Chemical-code)*