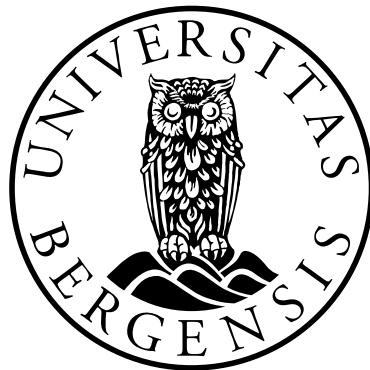


Infected Hip and Knee Arthroplasties in Rheumatoid Arthritis

A register-based study with focus on risk factors

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Dissertation for the degree philosophiae doctor (PhD)
at the University of Bergen

05.09.2014

Scientific environment

As many as 17 candidates have accomplished their PhD degree at the Norwegian Arthroplasty Register (NAR) since its initiation in 1987. I have carried out my thesis in this environment, using the NAR database. Furthermore, I had access to the large dataset of the Nordic Arthroplasty Register Association (NARA), in which data from hip arthroplasty registers from Denmark, Finland, Norway and Sweden are merged.

This project was jointly financed by the Western Norway Regional Health Authority, the Department of Orthopaedic Surgery at Haukeland University Hospital and the Jan A Pahle Foundation.

The present thesis is included in the PhD programme at the Department of Clinical Science (K2), Faculty of Medicine and Dentistry, University of Bergen, Norway.



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Acknowledgements

I have been working on this PhD project since 2009.

Many people have been of great help and inspiration during this part of my life, so there are many I would like to thank.

Supervisors

First of all I wish to thank my main supervisor **Bjørg-Tilde Fevang**. Her positive attitude, enthusiasm, helpfulness, proficiency in the English language and great availability have been of invaluable help. Our discussions across disciplines have been constructive and inspiring. She has been an excellent supervisor. I owe her husband **Jonas Fevang** a great debt of gratitude for arousing my interest in scientific work and for recommending his wife as my main supervisor. I am also grateful to my co-supervisors **Geir Hallan** and **Prof. Lasse Engesæter**. Geir has given me invaluable and constructive feedback and support. I hope we will continue to have a Guinness or two together now and then. Lasse's energy and wealth of knowledge and experience in scientific work have been inspiring. I truly enjoyed working with this team.

Department of Orthopaedic Surgery, Haukeland University Hospital

The former head of the department **Prof. Ove Furnes** and his successor and current head **Kjell Matre** deserve great credit for accommodating my research and giving me the opportunity to combine research and clinical activity. I also would like to thank the Director of the Orthopaedic Clinic **Lars Oddvar Arnestad** for giving me good research conditions. The support of my kind colleagues of the Trauma section, **Knut Fjeldsgaard, Hege Framnes, Yngvar Krukhaug, Randi Hole, Trygve Metlie, Tarjei Vinje, Omar Arnasson** and **Pål Høvdning** is gratefully acknowledged. They have done all the clinical work during the entire research period.

Norwegian Arthroplasty Register (NAR)

I am also grateful to the current leader of the NAR and a co-author, **Prof. Leif Havelin** for his critical and constructive reviews of the manuscripts. A special thanks to the statisticians **Anne Marie Fenstad** and **Prof. Birgitte Espehaug**. They supported me in the complex world of statistics. The Register is a pleasant and interesting place to work. Many thanks are also due to a co-author and 'roommate' **Håvard Dale** for our constructive and productive discussions. I would like to thank the entire staff of the Register for their encouraging comments and inspirational discussions. I feel privileged to have been given the opportunity to use the data from the Register and from the other Nordic arthroplasty registers.

Co-authors

Many thanks are due to the other co-authors: **Olav Lutro**, **Prof. Håkon Sjørusen** and **Håkon Langvatn**.

Teachers

A special thanks to the late **Prof. Ludo Koekenberg** and **Tormod Bjerkeset**. I am privileged to have worked for and with these outstanding surgeons, who both had an appropriate attitude towards research.

Funding

I am grateful for the PhD grant from the **Western Norway Regional Health Authority** (Helse Vest) which has been essential for me to accomplish this study. I acknowledge my financial support through the **Jan A Pahle Foundation**.

Family and friends

I would like to thank my friends in supporting my efforts to complete this work. My relatives, **Tanny** (mother), **Cees** (brother), **Annemiek** and **Leo** give me relentless support and guidance in all sorts of choices in life.

Abbreviations

ASA	American Society of Anesthesiologists
BMI	Body Mass Index
CDC	Centers of Disease Control and Prevention (USA)
CI	Confidence Interval
DAIR	Debridement, Antibiotics and Implant Retention
DMARDs	Disease-Modifying Anti-Rheumatic Drugs
INR	International Normalized Ratio
NAR	Norwegian Arthroplasty Register
NARA	Nordic Arthroplasty Register Association
OA	Osteoarthritis
OR	Odds Ratio
p	Probability
PJI	Prosthetic Joint Infection
PJR	Primary Joint Replacement
RCT	Randomized Controlled Trial
RA	Rheumatoid Arthritis
RR	Relative Risk
<i>S. aureus</i>	<i>Staphylococcus aureus</i>
THR	Total Hip Replacement
TKR	Total Knee Replacement
TNF- α	Tumour Necrosis Factor alpha

List of publications

Paper I

Risk of revision for infection in primary total hip and knee arthroplasty in patients with rheumatoid arthritis compared to osteoarthritis. A prospective, population-based study on 108,786 hip and knee joint arthroplasties from the Norwegian Arthroplasty Register

Johannes C. Schrama, Birgitte Espehaug, Geir Hallan, Lars B. Engesæter, Ove Furnes, Leif I. Havelin, Bjørg-Tilde S. Fevang

Arthritis Care Res (Hoboken). 2010 April.

Paper II

Bacterial findings in infected hip joint replacements in patients with rheumatoid arthritis and osteoarthritis. A study of 318 revisions for infection reported to the Norwegian Arthroplasty Register

J.C. Schrama, O. Lutro, H. Langvatn, G. Hallan, B. Espehaug, H. Sjursen, L.B. Engesæter, B-T. Fevang

ISRN Orthopedics, Volume 2012, September

Paper III

Increased risk of revision for infection in rheumatoid arthritis patients with total hip replacements. A study of 390,671 primary arthroplasties from the Nordic Arthroplasty Register Association

Johannes Cornelis Schrama, Anne M Fenstad, Håvard Dale, Leif Havelin, Geir Hallan, Søren Overgaard, Alma B Pedersen, Johan Kärrholm, Göran Garellick, Pekka Pulkkinen, Antti Eskelinen, Keijo Mäkelä, Lars B Engesæter and Bjørg-Tilde Fevang

Submitted

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Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease which primarily affects and damages synovial joints. Patients with RA will therefore often undergo joint replacement surgery. Infections after such prosthetic joint replacements are rare but feared complications. RA patients are more susceptible to infections in general and the use of modern aggressive immunosuppressive treatment, such as TNF inhibition (from around the year 2000), may have increased this risk for infection. We have used data from the Norwegian Arthroplasty Register (NAR) from 1987 until 2008 (Paper I) and from the much larger database of the Nordic Arthroplasty Register Association (NARA) from 1995 to 2010 (Paper III) to compare the risk of revision for infection in and over time for RA and osteoarthritis (OA) patients.

The risk of revision for infection was 1.6 times increased in total knee replacements (TKRs) for RA patients compared to OA patients (Paper I). In total hip replacements (THRs) we found a 1.3 times higher risk of revision for infection in RA compared to OA (Paper III). We concluded that there was a higher risk of revision for infection in RA than in OA patients.

For TKRs there was no increase in the risk of revision for infection in RA or in OA patients after the year 2000. In the Norwegian study (Paper I) the incidence of revision for infection of THRs was higher in the period 2001-2008 than in the period 1987-2000. However the increase affected RA and OA patients to the same degree. In the Nordic study (Paper III) the relative risk for RA patients compared to OA patients was increased in the latter period (2002-2010). This coincides with the introduction of TNF inhibitors in the medical treatment of RA. Similarly conflicting results are also found in the literature.

From 5-6 years postoperatively, the risk of revision for infection was increased in RA compared to OA in TKRs and THRs (Paper I). Furthermore, we found a higher risk during the first three months and from around 8 years postoperatively in antibiotic-loaded cemented prostheses in RA-patients (Paper III), while no significant difference in the risk of infection for revision was found when comparing RA and OA patients with uncemented THRs. We conclude that the increased risk for late infections in RA is primarily seen for prostheses fixed with antibiotic-loaded cement.

Staphylococcus aureus (*S. aureus*) has been reported to be the most important causative bacteria in prosthetic joint infection (PJI) in RA. In addition, RA patients are by many authors considered to represent a high-risk group in terms of acquiring infections with bacteria of potentially oral or dental origin. In Paper II we compared the bacterial findings of infections leading to revision in THRs in RA patients with OA patients, based on data from the NAR. We identified 49 infection episodes in 37 RA patients and compared the bacterial findings with 269 infection cases in 255 OA patients. No difference in bacterial

findings between RA and OA was found and thus we could not confirm the higher incidence of *S. aureus* in RA reported previously. Bacteria of potentially odontogenic origin were not found in RA patients but were found in 4% of OA patients and based on our study we could not confirm that RA patients are high-risk patients for infection with bacteria of oral or dental origin.

I Introduction and background

1 Rheumatoid Arthritis

1.1 RA and total joint replacements

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease which particularly affects the joints. The synovial involvement ultimately leads to the destruction of cartilage and bone in these joints. Around 1-2% of RA patients needed at least one large joint replacement per year of follow up in the pre-biological agent era (before the year 2000) [1-4], and around 25% of all RA patients within 16-20 years of observation [5, 6].

The need for joint replacement surgery and also other types of disease-specific surgery such as synovectomies in RA seems to be declining [7, 8]. The more aggressive and meticulous use of conventional disease-modifying anti-rheumatic drugs (DMARDs) and the introduction of biologic medication may account for this [8].

The Nordic arthroplasty registers have shown, in different time periods, that between 15% and 3% of all primary total joint replacements in hips and knees were performed due to RA [9-15].

1.2 Infection in RA

RA patients are more prone to infections than the general population [16, 17] and this was already the case in the pre-steroid era [18]. The risk of developing infection in RA was estimated in one report to be twice the risk in non-RA subjects [16]. The higher susceptibility to infections might be explained by a primary disturbance of the immunological system in RA, an acquired impairment of the immune response, or a decrease in the resistance to infections which may occur in any chronic disease [18].

Among the sites with the highest infection risk were skin and soft tissue and bone and joints [16]. Infections in the bone and joints may also be attributed to local destruction of the normal anatomy leaving the joints more prone to infection. Glucocorticoids, which were introduced in 1949, have been shown to increase the risk of infection, for both infection-related hospitalizations and less serious infections [17, 19-22]. The risk is dependent on the duration of steroid use and the dose. The other non-biologic DMARDs have not with certainty been shown to increase the infection risk [22]. Age, comorbidities and disease activity are also regarded as risk factors for infection in RA [23, 24].

1.3 TNF- α inhibitors

Tumour necrosis factor alpha (TNF- α) is a central mediator in the normal inflammatory cascade. This pro-inflammatory cytokine is heavily involved in the immune system, and blocking TNF- α receptors not only reduces inflammation but is responsible for an immune suppressive effect.

TNF- α inhibitors were first licensed for clinical use in 1998. In Norway they were introduced in 1999. The first three agents approved for treatment of RA were Infliximab (Remicade[®]), Etanercept (Enbrel[®]) and Adalimumab (Humira[®]). At present, 5 different agents are frequently used in this patient group, and recently the first biosimilar version of Infliximab was taken into clinical use. TNF- α antagonists have been shown to slow the radiological progression of RA [25, 26]. Decreased disability and improved quality of life are other important effects of these drugs, and patients also described positive overall effects [27]. The use of TNF- α inhibitors has steadily increased since their introduction [28]. One study reported that in 2005 22% of RA and psoriatic arthritis patients were treated with TNF- α inhibitors in Norway [29].

1.4 TNF- α inhibitors and infection in RA

Because of the immune suppressive effect of the TNF- α inhibitors, the risk of serious infections has been a concern. A focused systematic review of the literature on the risk of infection due to TNF- α inhibitors was recently published [30]. Some observational studies have shown no increase in infection risk [31-37], while other such studies have revealed a clear increased risk of infection [38-42]. Conflicting results have also been reported in meta-analyses; some reported no increased risk of infection [43-45] whereas others showed an increased risk [46-48]. Relevant for orthopaedic surgery is the fact that some reports suggest a higher risk for skin and soft tissue infections [49] or septic arthritis in native joints [31] for patients using TNF- α inhibitors. Others have pointed out that the risk of infection is highest in the first period after initiation of the TNF- α antagonist use [32, 34, 39, 49]. Interestingly, the immune suppressive effect of anti-TNF- α agents is not limited to the possible increased occurrence of infection, but also to a potential deterioration of an already existing infection. The presence of any active infection is therefore a contraindication to start anti-TNF- α treatment [30].

2 Prosthesis-related infections

2.1 Prosthetic joint infections

A prosthetic joint infection (PJI) is a dreaded complication after joint replacement surgery. It occurs in 1-2% of all primary total hip and knee replacements [50-52]. The consequences of PJI for the patient are frequent repeat surgeries with the removal or exchange of part(s) or the total prosthesis. This is associated with a decline in joint function, prolonged hospital stay, and extended use of potentially toxic and antimicrobial resistance-encouraging antibiotics. In addition, the costs of the treatment to society are considerable. Earlier reports estimated the costs to be more than \$50,000 per infection episode [53-56]. Compared to an uneventful primary total knee replacement the costs were calculated to be 3-7 times as high [55, 57]. Cost-effective perioperative preventative strategies are therefore desirable [58].

2.2 Classification of PJI

Prosthetic joint infections are caused by bacteria which reach the prosthetic material by entering the surgical wound during or directly after surgery. Alternatively, bacteria from a distant source are transported by the bloodstream to the implant (haematogenous seeding or blood-borne infection). This may occur at any time after surgery. Classification of prosthesis-related infections may therefore be done according to the type of bacteria/virulence (e.g. low-grade) or according to the pathway of bacterial entry (postoperative versus haematogenous). Other systems classify according to the time from surgery or infection symptoms to diagnosis. These classifications are preferred by many clinicians because they aid in treatment decisions. A widely used system is named after Coventry [59] and divides the infections into early (0-3 months after surgery), delayed (3-24 months) and late (after 24 months) infections. More recently, possibly due to the increase in revision surgery and changes in treatment modalities (e.g. Debridement, Antibiotics and Implant Retention (DAIR)), Tsukayama's classification has become popular [60]. In this classification, an infection with the onset fewer than 4 weeks after surgery is called an 'early infection'. It seems that the eradication rate with different treatment modalities largely depends on the duration of the infection. Therefore, the duration of symptoms has become an important factor in some newer attempts to classify prosthetic joint infections [61, 62].

2.3 Definition of PJI, SSI and revision for infection

Prosthesis-related infections include all deep infections after prosthetic joint replacement and the definition is wider than the true PJI. Different definitions for PJI exist [50, 63, 64] (Appendix I). One definition of PJI is the deep incisional (or organ/space) surgical site infection (SSI) (Appendix II). An SSI is a surgical wound infection occurring within the first postoperative year after a joint replacement and one distinguishes between superficial (incisional), deep (incisional) and organ/space SSI [65, 66]. The concept of SSI is mainly used in hospital infection surveillance. A superficial SSI gives a 35-fold increased risk for a PJI [63]. In this thesis we used revision for infection as the endpoint in the survival analyses. Revision was defined as the surgical removal or change of parts or the whole implant. Deep infection as the reason for revision was determined by the surgeon and reported immediately after surgery to the NAR, based on pre- and peroperative evaluation. Infections that were treated with minor soft tissue surgery or not surgically revised were not included in the study. Therefore the true incidence of prosthetic joint infections would be higher than that reported in our studies.

2.4 Late infections

The majority (around two-thirds) of prosthetic joint infections occur in the first two years after the index joint replacement [58, 67, 68]. The literature on prosthetic joint infections is consequently mostly focused on this period. Late infections are generally defined as

infections which appear more than one to two years after the index operation [59-61]. Although low-virulent infections acquired at the index surgery may present many years after the operations, the majority of these late infections are probably caused by haematogenous seeding. Haematogenous infections seed from distant origins like the skin, teeth, urinary and respiratory tract [67]. RA has been shown to predispose for haematogenous infections [69-71], and the diagnosis of RA is a risk factor for late infection [72]. Little is known on the potential influence of RA medication on the occurrence of late, haematogenous prosthetic joint infections.

2.5 Risk factors for PJI

Various patient-related risk factors for PJI after primary hip and knee joint replacement surgery have been found, such as systemic malignancy, rheumatologic disease, obesity (BMI>40), coagulopathy, preoperative anaemia, comorbidity (ASA>2), immunosuppression, cardiovascular disease, excessive anticoagulation (INR>1.5) and diabetes mellitus [68, 73-75]. Most of them refer to the risk of acquiring postoperative infections. Rheumatoid arthritis is generally accepted as a patient-related risk factor for PJI. In TKRs the evidence for this is solid [14, 75-77] with a reported infection rate in RA 2-4 fold that of OA patients [78]. For THRs, however, the literature is conflicting [9, 79]. There are also conflicting reports regarding populations which included a combination of TKRs and THRs [63, 72, 80, 81].

2.5.1 Nasal carriage of *S. aureus* as a risk factor for SSI

Carriage of *S. aureus* has been shown to be a risk factor for SSIs in general [82, 83]. In the majority of cases, the infecting *S. aureus* in SSIs is transmitted endogenously [66, 84]. Elimination of *S. aureus* organisms from the nares in nasal carriers with a 5 day preoperative course of intranasal mupirocin and a chlorhexidine total body wash to decolonize the skin was, in a well-designed trial, found to reduce the frequency of SSIs [85]. A positive effect was also shown in a smaller study of total joint arthroplasty surgery [86, 87], while other earlier reports have been conflicting [88-90]. The routine use of screening for nasal carriage and a mupirocin (and chlorhexidine soap) course in nasal carriers ahead of total joint replacement surgery, is therefore still not recommended. The number of carriers of *S. aureus*, oral and nasal, has been shown to be higher in people with RA than in healthy adults [91-93] and one report revealed that as much as 37% of the PJIs in RA were caused by *S. aureus* [54]. Consequently, RA patients could be a subgroup that would benefit from preoperative screening and treatment.

2.5.2 Dental intervention as a risk factor for late PJI

It has been suggested that dental procedures may be a risk factor for late PJI. Transient bacteraemia during dental work and consequent haematogenous seeding to the artificial joint is thought to be the pathogenesis [67]. The potential association between dental intervention and PJI was proposed in 25 cases reported in the literature until 1995, which

suggests that it is a rather rare event [94]. It has been estimated that only 0.04-0.07% of PJIs are caused by oral bacteria [67, 95], but a more recent report suggested a much higher risk [96]. Importantly, there is a discrepancy between the bacterial findings in PJI and the bacteria supposed to cause bacteraemia during dental procedures. While staphylococci are predominantly (>50%) cultured in PJI, they are of no importance in bacteraemia during dental procedures [97]. Furthermore, in less than 10% of PJIs the cultured bacteria are of odontogenic origin [98] contrasting with more than 40% in infective endocarditis, where antibiotic prophylaxis against these odontogenic bacteria is well-established [94].

Over three decades the prophylactic use of antibiotics before dental intervention has been a subject of discussion in the literature for dentists, orthopaedic surgeons and infectious disease specialists. A review of all English, German and French language literature evaluated 144 publications on this topic [99] and the authors concluded that PJIs due to haematogenous spread following dental work are very rare and that the scientific rationale for antibiotic prophylaxis at best is very weak. Furthermore, they stated that the use of perioperative antibiotic prophylaxis in selected, high-risk patients is based 'more on fear than on science'. A recent study by Berbari [100] found no increased risk of PJI after dental interventions and no statistically significant reduction of PJI after using antibiotic prophylaxis targeting odontogenic microbes. Analyses of the high-risk subgroups (e.g. RA) showed that dental procedures were not a risk factor for PJI in any of the subgroups. A review from 2010 focused on the potential role of staphylococci originating from the mouth as cause of PJI after dental interventions [101]. The conclusion was to follow the preceding AAOS/ADA 2003 recommendations [102]. Here RA patients are considered high-risk patients who should receive antibiotic prophylaxis in high-risk dental procedures. Somewhat surprisingly, they recommend some non-staphylococcal agents (e.g. amoxicillin) in cases of prophylaxis.

Various national guidelines and different recommendations exist [99, 103-112]. Whether all RA patients with artificial joint replacements should receive antibiotic prophylaxis before dental interventions is still unclear. Our study in Paper II may contribute to this discussion in Norway.

2.5.3 RA medication as a risk factor for SSI

2.5.3.1 Corticosteroids and synthetic DMARDs

Corticosteroids have a negative influence on normal wound healing. They cause disturbance of the angiogenesis, collagen production and reepithelialisation of dermal wounds [113]. There is also a reduction of the neutrophil chemotaxis. The clinical consequences of these effects include delayed wound healing, dehiscence of the incision site and wound infection [114]. The magnitude of the problem seems to depend on the duration of use and the doses of the corticosteroids [17, 20]. It is not known at which dose (daily or cumulative) these anti-proliferative effects have clinical relevance [115]. There is scant knowledge of perioperative complication rates and corticosteroid usage in

orthopaedic surgery. Of four different studies, only one reported an increase in postoperative wound infection rate [116-119]. The other three studies were small, the corticosteroid dosage was generally low, there were different indications for corticosteroid use as well as different patient populations, and various surgical procedures were included [120]. The authors of a recent review of perioperative care for RA patients, stated that “prednisone is associated with one of the highest overall infection rates, far exceeding the risk associated with most conventional DMARDs and biologics” [121]. It is uncertain whether this may be extrapolated to the setting of orthopaedic surgery and joint replacement surgery.

Of the synthetic disease modifying anti-rheumatic drugs (DMARDs), Methotrexate is the most commonly used in RA. Methotrexate inhibits leukocyte chemotaxis [113] and also seems to influence various immune mechanisms without completely eliminating them [115]. A wound infection may arise as a postoperative complication in patients taking Methotrexate [113], but most available studies have shown little to no effect of Methotrexate on postoperative complication rate after orthopaedic surgery. In a large prospective randomized trial including 388 patients, no increased infection or wound complication rate was found after orthopaedic surgery in patients continuing Methotrexate compared to those who withheld Methotrexate perioperatively [122]. Of the numerous retrospective and prospective studies evaluating the impact of Methotrexate on surgical complications [121], only two small studies (including 13 and 19 patients) came to a different result [123, 124]. Based on these findings, more recent literature advocates the continuation of Methotrexate perioperatively [120, 121]. However, modern RA treatment using the “treat to target” and tight control principle involves increasingly high doses of Methotrexate, often in combination with corticosteroids and/or other DMARDs [8, 120]. Future research will possibly show the influence on the infection risk.

With regard to other commonly used DMARDs including sulfasalazine (Salazopyrin^R), hydroxychloroquine (Plaquenil^R), leflunomide (Arava^R), and azathioprine (Imurel^R), research addressing adverse surgical events in association with these drugs is insufficient but in general, continuation perioperatively seems reasonable [121].

2.5.3.2 TNF- α inhibitors as a risk factor

As described in Section 1.4, the risk of infection is of particular concern as a side effect of TNF- α inhibitors. The literature addressing anti-TNF- α treatment as a risk factor for infection after joint replacement surgery in RA is conflicting [125-134] (Appendix III). Some of these studies are clearly underpowered to detect a difference in a rare complication such as PJI. The other studies are difficult to compare since a variety of orthopaedic procedures with different baseline infection risks are included and the outcome measures are not uniform. In addition, SSI, which is a commonly used outcome in some of these studies, is not validated for joint replacement surgery [135]. Consequently, these studies are unable to conclude as to whether anti-TNF treatment is a risk factor for infection after

total joint replacement surgery in RA patients. Because of the persistent concerns regarding the safety of anti-TNF treatment, most guidelines recommend the discontinuation of anti-TNF treatment perioperatively [136-138].

2.5.4 Antibiotic-loaded cement as a risk factor for late PJI in RA

Antibiotic-loaded cement in combination with antibiotics systemically has been shown to provide the best survival of the implant in primary THR surgery [139-141]. Furthermore, the risk of revision for infection was higher in THRs fixed with cement without antibiotics than in uncemented THRs and THRs fixed with antibiotic-loaded cement [139, 141]. In Scandinavia almost all cemented primary THRs are performed with antibiotic-loaded cement (The Danish Arthroplasty Register, The Norwegian Arthroplasty Register and The Swedish Arthroplasty Register).

The release dynamics of antibiotics from the cement is not clear, but it is probably a combination of a surface and bulk phenomenon [142]. Little is known about the duration of the prophylactic antimicrobial effect of the antibiotics in cement. It varies in the literature from days to several years [143, 144]. Cement in itself, due to its surface properties, has shown increased bacterial adherence and colonization compared to polyethylene and metal [144, 145].

In RA there is a higher susceptibility to (late) haematogenous prosthetic joint infections than in non-RA [69, 71]. Inactive cement, after cessation of the elution of antibiotics, may reinforce this susceptibility to (late) prosthetic joint infection in RA.

II Aims of the projects

Paper I

To compare the risk of revision for infection after THRs and TKRs between RA patients and OA patients based on data in NAR

To detect changes in the relative risk of revision for infection in THRs and TKRs over time for RA and OA patients

To investigate the time from primary surgery to revision for infection in THRs and TKRs in RA patients and OA patients

Paper II

To compare the bacterial findings in infections leading to revision of THR in RA patients and OA patients

To assess the incidence of *S. aureus* infections and compare this in RA and OA patients

To compare the incidence of infections leading to revision of THR caused by microorganisms potentially of oral or dental origin in RA patients and OA patients

Paper III

To compare the risk of revision for infection after THRs in RA patients and OA patients in a large Nordic study population

To evaluate any changes with time in the relative risk of revision for infection in THRs in RA and OA patients

To investigate the time from primary surgery to revision for infection in THRs, and evaluate the revision risk of RA and OA patients with uncemented and antibiotic-loaded cemented THRs specifically

III Patients and methods

1. Health registers

The Nordic countries have long-standing traditions of high-quality national health registries. The use of personal identification numbers enables the merging of data between different registries and surveys. These health registers offer an unique opportunity to study diseases and treatment modalities in large unselected populations and over a long period of time. Results from registry research thus, in general, provide results which are generalizable to all patients (excellent external validity). The large number of patients included allow for the evaluation of rare events in uncommon diseases (such as PJIs in RA patients) which may be difficult to study in other research settings. Furthermore, the longitudinal design with unlimited follow-up time offers the possibility to study complications, adverse events of treatment or death occurring late in the disease course, when other studies have usually been terminated. In addition, register-based studies are comparatively inexpensive and most often clinically solid endpoints may be studied. However, some limitations should be mentioned. Due to the nature of these registries with continuous registration by a number of doctors/nurses involved in the treatment of patients, the number of variables must be limited and for research purposes, important variables may be lacking. Thus, one may have to investigate proxy variables which reflect the outcome of interest (such as arthroplasty surgery which reflects joint destruction in RA). Also, possible confounding factors are controlled for by the randomization in an RCT, while such factors must be adjusted for using statistical analyses in register-based studies. Only a limited number of potentially confounding factors are registered, and several factors that can skew the results may be unknown. In addition, some authorities are concerned about the privacy aspect of using these health register data for medical research.

2. The Norwegian Arthroplasty Register (NAR)

The Norwegian Arthroplasty Register (NAR) was initiated in 1987 as a national hip arthroplasty register. From 1994 knee arthroplasties and prosthetic replacements of other joints were also registered [10]. The NAR is a national quality register approved by the Norwegian Data Protection Authority. Furthermore, it represents the cornerstone of the National Centre of Competence for Joint Replacements approved by the Norwegian Ministry of Health in 2002. The NAR is owned by the Norwegian Orthopaedic Association and is an integrated part of the Department of Orthopaedic Surgery, Haukeland University Hospital. The main objective of the register has been to detect inferior implants, bone cements and procedures, rapidly or as early as possible after introduction. Data on the primary implantation and any subsequent revision surgeries of the same joint is collected

and linked for each individual patient. Revision is defined as a reoperation where a part, various parts or the whole implant are exchanged or removed. In the study periods in Papers I and II, minor soft-tissue procedures were not reported to the NAR.

The following information is, amongst other variables, reported to the register: any previous surgeries to the joint, the date and laterality of the operation, whether the operation is a primary or revision operation, which joint was operated, the indication for surgery (diagnosis), all data on the prosthetic components and bone cement used, reason(s) for revision (e.g. deep infection), type(s) of revision, data on systemic antibiotic prophylaxis and prophylaxis against thrombo-embolism, the type of operating theatre, operation time, perioperative complications etc. The operating surgeon fills in the register form immediately after the operation and sends it to the NAR. The registration is not compulsory, but the completeness for primary total joint arthroplasties of the hip and knee, as well as revisions, was more than 90% [146, 147]. The completeness of registration for removal procedures (e.g. Girdlestone) was somewhat (20%) lower [147]. In Paper I we identified 108,786 primary total hip and knee joint replacements in patients with RA and OA operated from 1987 (1994 for knees) until June 2008 in the NAR database. For Paper II, the NAR was used to identify patients revised due to infected hip prostheses from 1987 until October 2007. 318 revisions for infection in 292 patients with RA and OA were included in the study.

3. The Nordic Arthroplasty Register Association (NARA)

Acknowledging the importance of surveillance of joint replacement surgery, arthroplasty registers were established in a number of countries. The Danish, Finnish and Swedish hip arthroplasty registers were instigated in 1995, 1980 and 1979, respectively. The similar health care systems and the use of personal identity numbers in Norway, Finland, Denmark and Sweden make it possible, logical and desirable to combine and compare the data in these national arthroplasty registers. In 2007 a collaboration of the registers, the Nordic Arthroplasty Register Association (NARA), was established [148, 149]. For our study in Paper III we defined a set of parameters where all the national registers were able to provide data: age, gender, laterality, diagnosis (e.g. RA), date of primary THR, type of fixation, type of bone cement cup/stem, date and reason of revision (e.g. deep infection) and date of death. In all registers, the definition of revision was surgical removal or exchange of part(s) of or the whole prosthesis. The completeness of data in the individual registers is high [15, 147, 150]. In Paper III we identified in the NARA 390,671 primary total hip replacements in RA and OA patients from 1995 to 2010.

4. Bacterial findings in revised hip prosthesis

We identified 1443 revisions for infection in the NAR from 1987 until October 2007. The 10 hospitals performing most revisions for infection, with a total of 730 revisions, were visited. The medical records of these patients were systematically reviewed. Incomplete or missing data were found in 228 revisions. Of the remaining 502, only 287 revisions were

performed in OA (269) and RA (18) patients. To increase the number of revisions in RA patients, we obtained the medical data of another 31 revisions for infection in RA patients from several other hospitals than those originally visited and we extended the period for RA patients from 2007 until 2009. Thus we included 269 revisions (in 255 OA patients) in the OA group and 49 revisions (in 37 RA patients) in the RA group.

5. Methods

A major focus of this study was to understand distinct features of patients with RA in the setting of arthroplasty surgery and risk for infection of the implant. We compared patients with RA and OA in all three studies (Papers I-III). The larger group of patients with OA served as a control group as general changes such as changes in operating theatres, treatment policy, antibiotic and thrombosis prophylaxis, would presumably be similar for both groups. Using a control group gave us the opportunity to put our findings and conclusions concerning RA patients in a certain perspective.

In the NAR, patients who are dead or lost to follow-up due to emigration are registered and the follow-up period is terminated at the date of death or emigration. For missing data, staff of the registry contact the relevant staff at each hospital to complete the forms. Thus, all patients registered have complete data on the basic variables such as demography, date and cause of surgery, implant type, and revision. However, patients may be re-operated abroad without having emigrated, and such surgeries would not be registered. Furthermore, erroneous registration must be expected to occur occasionally, and the completeness of registration to the NAR, although very high, is not 100% and thus some operations may not be registered. Even so, we have no reason to suspect a systematic mis-registration or loss of patients or revisions.

In Paper I we included 2,642 knees and 4,167 hips in the RA group, and 21,832 knees and 80,325 hips in the OA group, all of which were primary procedures. Statistical analyses were performed separately for knees and hips. In Paper III 13,384 RA THRs and 377,287 OA THRs were included. In Studies I and III we compared the total risk of revision for infection in RA patients to OA patients. Furthermore, we evaluated the risk of revision for infection in two time periods (1987(1994)-2000 and 2001-2008 in Paper I, 1995-2001 and 2002-2010 in Paper III), and we studied the timing of the revision procedure (early or late infections). The use of the much more extensive NARA database in Paper III meant that the group of RA patients revised due to infection was much larger (710 in Paper I and 2315 in Paper III). We were thus able to perform sub-analyses, mainly concerning the influence of the type of implant fixation on the risk of revision for infection. In addition, using a larger database and including patients from several countries improves the external validity of our findings.

TNF- α inhibitors were introduced in 1999/2000. From 2000 on, the use increased steadily [28], also among patients undergoing joint replacements [8]. Using 2000 (Paper I) and 2001 (Paper III) as cut-off points, we divided the patients into one group (operated during the

later time period) in which a considerable proportion of the RA patients were treated with TNF- α inhibitors and another group (operated during the earlier time period) in which none or very few received such treatment. RA and OA patients were compared within the two time periods (particularly in Paper III, Table 3) and the relation between the diagnostic groups was compared in order to evaluate a possible influence of the TNF- α inhibitors on infection risk. By using the OA joint replacements as a control group, we controlled for most time-dependent changes, such as treatment policy, operating theatres and awareness, which may have influenced infection risk. Factors such as increased comorbidity (particularly diabetes and obesity) or an increased focus on prosthesis infection and thus possibly improved reporting of such revisions to the NAR, may have contributed to the overall increase in revisions for infections seen during the study period. However, since there is no reason for such factors to have influenced RA patients differently than OA patients, studying the difference in infection risk between RA and OA patients enables the detection of particular features or changes in the RA group. Of course, unknown factors may still have influenced one of the groups differently. This is an inherent problem with observational studies.

Furthermore, we evaluated the time span from primary implantation until revision for infection and compared this between the two diagnostic groups (for knees and hips separately, Paper I). In Paper III, in which the very large number of THRs from the NARA was studied, we compared this time span in RA and OA patients with uncemented THRs and with antibiotic-loaded cemented THRs. This was done to determine whether the fixation mode had an influence on the time from index operation until infection leading to revision. Every THR where antibiotic-loaded cement was used (both components cemented or hybrid/reverse hybrid) was included in the antibiotic-loaded cement group.

In Paper II we collected the bacterial findings of revisions for infection in RA and OA patients by visiting and reviewing the medical reports initially in a selection of 10 hospitals in which the highest number of revisions for infections had been performed. In patients having had more than one revision for infection in the same joint, data from all revisions were included. Since we were most interested in the occurrence of *S. aureus* (highly-virulent bacteria), only one (or more) positive bacterial culture was considered sufficient to define it as causative for the infection. Usually, more than one positive culture is needed for the diagnosis of PJI [50, 62-64, 151]. The following bacteria were considered as potentially odontogenic bacteria (as defined by Berbari [100]): Viridans group streptococci, beta-haemolytic streptococci, *Peptostreptococcus* species, and streptococcus-like bacteria not further identified.

6. Statistics

We used the Student's t-test to detect any group differences in normally distributed continuous variables (e.g. age, mean follow-up time). The Pearson chi-square test (and Fisher's exact test in cases of low numbers) was used to test for group differences in categorical variables (e.g. gender, bacterial findings in RA/OA). Similar statistical methods were used in Papers I and III. In the survival analyses the start point was the primary arthroplasty. The follow-up time was estimated until the first revision for infection of the arthroplasty or until the patient was censored at death or emigration, at the end of the respective studies, or if the arthroplasty was revised for other causes than infection. The NAR is continually updated using Statistics Norway on patients who die or emigrate. Unadjusted survival analyses were performed using the Kaplan-Meier method [152]. To estimate the relative risk (RR) with 95% CI, Cox regression analyses with adjustment for age, gender, diagnosis, year of primary surgery (and fixation mode in Paper III) were performed [153]. We used an extended Cox model to estimate the (log) RR within different follow-up intervals. P-values lower than (or equal to, Paper III) 0.05 were considered statistically significant. The statistical analyses were performed using the statistical software programmes SPSS (SPSS, Chicago, IL), versions 15.0 (Paper I) and 20.0 (Paper III), and the statistical software package R [154].

IV Summary of Papers I-III

Paper I

Risk of revision for infection in primary total hip and knee arthroplasty in patients with rheumatoid arthritis compared to osteoarthritis. A prospective, population-based study on 108,786 hip and knee joint arthroplasties from the Norwegian Arthroplasty Register Johannes C. Schrama, Birgitte Espehaug, Geir Hallan, Lars B. Engesæter, Ove Furnes, Leif I. Havelin, Bjørg-Tilde S. Fevang

Objectives: We compared the differences in risk of revision for infection, changes in risk over time and in time from primary surgery to revision for infection after THRs and TKRs, in RA patients and OA patients.

Methods: In the Norwegian Arthroplasty Register, 6,629 and 102,157 primary total joint replacements in patients with RA and OA, respectively, were identified from 1987 (1994 for knees) until 2008. Survival analyses with revision due to infection as endpoint were performed using the Kaplan-Meier method for constructing survival curves and multiple Cox regression to calculate relative risk (RR) estimates for diagnosis, adjusted for age, gender and year of primary surgery. An extended Cox model was used to estimate RR within different follow-up intervals.

Results: RA patients with TKR had 1.6 times higher risk of revision for infection than OA patients, while there was no difference in the THRs. In the THRs we found a higher risk of revision for infection from 2001 onwards, whereas the development for TKRs was the opposite. These time effects affected the RA and OA groups equally. The risk of revision for infection from 6 years postoperatively onwards was higher in RA patients.

Conclusion: The overall risk of revision for infection after TKR was higher in RA patients. The risk of late infection leading to revision of the TKR and THR was higher in RA patients than in OA patients. After the year 2000, the relative risk of revision for infection in RA, compared to OA, remained unchanged.

Paper II

Bacterial findings in infected hip joint replacements in patients with rheumatoid arthritis and osteoarthritis. A study of 318 revisions for infection reported to the Norwegian Arthroplasty Register

Johannes Cornelis Schrama, Olav Lutro, Håkon Langvatn, Geir Hallan, Birgitte Espehaug, Håkon Sjørnsen, Lars B. Engesæter, Bjørg-Tilde Fevang

Objectives: To detect the bacterial cause of infected THRs in patients with RA compared to patients with OA.

Methods: 1443 revisions for infection were reported to the NAR from 1987-2007. The 10 hospitals with the highest number of revisions for infections were visited and a total of 730 revision records were systematically reviewed. For this study 269 infection episodes in 255 OA patients served as control group. We identified 49 infection episodes in 37 RA patients from 1987-2009. The bacterial findings were obtained from the microbiological reports in the patients' medical records.

Results: The RA patients were, on average, 10 years younger than the OA patients and there were more females (70% vs. 54%). We found no difference in the bacterial findings in patients with RA and OA. A tendency towards a higher frequency of *Staphylococcus aureus* (18% vs. 11%) causing PJI was found in the RA patients compared to the OA patients. There were no bacteria of potentially oral or dental origin found in the RA patients, while we found these in 4% of the OA patients.

Conclusion: The type of bacteria that were identified in patients with RA did not significantly differ from those in OA patients. Bacteria of potentially odontogenic origin were not found in infected THR in RA patients.

Paper III

Increased risk of revision for infection in rheumatoid arthritis patients with total hip replacements. A study of 390,671 primary arthroplasties from the Nordic Arthroplasty Register Association

Johannes Cornelis Schrama, Anne M Fenstad, Håvard Dale, Leif Havelin, Geir Hallan, Søren Overgaard, Alma B Pedersen, Johan Kärrholm, Göran Garellick, Pekka Pulkkinen, Antti Eskelinen, Keijo Mäkelä, Lars B Engesæter and Bjørg-Tilde Fevang

Objectives: We studied the risk of revision due to infection and changes over time after primary THRs in patients with RA and OA during a 16-year period. Time from primary implantation to revision was compared between the two diagnostic groups. Uncemented THRs and those fixed with antibiotic-loaded cement were studied separately.

Methods: We identified 13,384 THRs in RA patients and 377,287 THRs in OA patients from 1995 to the end of 2010 in a dataset of the NARA. Kaplan-Meier survival curves, with revision for infection as the endpoint, were constructed. Cox regression analyses were performed to calculate the RR of revision for infection adjusted for age, gender, fixation technique and year of primary surgery. An extended Cox model was used to estimate RR within various follow-up intervals in patients with uncemented THRs and THRs fixed with antibiotic-loaded bone cement.

Results: RA patients had a 1.3 times (CI 1.0-1.6) higher risk of revision for infection than OA patients. After 2001 the risk of revision for infection after THR increased more for RA patients than for OA patients. During the first 3 months and from 8 years postoperatively the risk of revision for infection was higher in RA patients with THRs fixed with antibiotic-loaded cement than in OA patients with THRs similarly fixed.

Conclusion: Overall, we found a slightly higher risk of revision for infection in RA patients than in OA patients, but this difference was only present after 2001. In antibiotic-loaded cement THRs the risk of early and late infections leading to revision was increased in RA compared to OA patients. In the uncemented THRs no statistically significant difference in risk of revision for infection between RA patients and OA patients was revealed.

V General discussion

1. Overall risk of revision for infection in RA versus OA

Paper I showed that the risk of revision for infection in TKRs was 1.6 times higher in RA than in OA patients (RR 1.6 (1.1-2.4)), while there was no difference in THRs when comparing RA and OA (RR 0.98 (0.7-1.5)). In Paper III we found a 1.3 times higher risk of revision for infection in THRs in RA compared to OA (RR 1.3 (1.0-1.6)). The discrepancy in the result in THRs between Papers I and III is difficult to explain. One explanation may be that the number of patients in Paper III is much greater which may enable the detection of smaller differences, and render them statistically significant. Alternatively, the results may indeed be different, possibly due to the inclusion of patients from four countries and/or by a slight difference in study periods (1987(1994) to June 2008 in Paper I and 1995-2010 in Paper III). For TKRs our findings confirm the findings of other authors [14, 75-77] describing an increased risk of revision for infection in RA patients. For THRs, however, the literature is conflicting [9, 79], which to some extent is illustrated by the difference in results in our Studies I and III. Thus, based on our studies as well as other previous studies, there is a higher general risk of revision for infection in RA patients compared to OA patients, but for THR, if present at all, this increased risk seems to be small and of uncertain clinical importance.

2. Risk of revision for infection in two time periods

The cut-off for the two time periods was quite similar in Paper I (2001) and Paper III (2002). In Paper I, the relationship between RA and OA patients in the risk of revision for infection in TKRs and THRs did not change over the whole study period. In Paper III we found no difference in revision for infections between RA and OA patients in the first period, but a difference became evident in the last period (RR 1.4 (1.0-1.8)). As mentioned above, and maybe to a larger extent in this case, the greater numbers included in Study III may explain the discrepancy in results between Papers I and III, as may the inclusion of an additional two and a half years of inclusion and follow-up with more RA patients potentially on aggressive immune-modulating therapy.

In the following, I will focus on the findings in Paper III.

Post aut propter (after this or on account of this)

In the last period (2002-2010) the risk of revision for infection was higher in RA patients than in OA patients. This was not the case in the earlier time period (1995-2001). There are a few possible explanations for this finding. First, the relative increase in risk of revision for infection coincides with a change in the general treatment of RA. Over the last 5-10 years the 'treat to target' principle has been developed and implemented in the management of RA. This means a more aggressive medical treatment with initially frequent and regular follow-up and appropriate therapeutic adaptation aiming at rapid remission with low

disease activity [155]. Generally, higher doses of Methotrexate, corticosteroids and more often combination regimes have been used. This may have contributed to a greater susceptibility to infection in the last period.

Second, the immune-modulating TNF- α inhibitors were introduced in the treatment of RA around 1999/2000. The use has increased steadily [28], also in patients undergoing total joint replacements [8]. Later, other biologic drugs have been introduced including rituximab (MabThera^R), abatacept (Orencia^R) and tocilizumab (RoActemra^R). If a major negative impact of biologic treatment on infection risk had been present, there is reason to expect that it would have influenced the results markedly. A small increase in risk of infection leading to revision was indeed found during the last time period, in Paper III, which may indicate such an effect; however, the magnitude of the difference was small. Moreover, we did not have data on the use of biologics or other drugs and thus could not tell whether the patients with infected implants used biologics or not. Thus, our findings may have been due to other time-dependent factors that we were not able to identify from our registry dataset.

Other possible factors that may have influenced the infection risk in RA patients during the last 10-year period could be that RA patients were treated differently from OA patients by the surgeons in the last period, for instance in the choice of antibiotic prophylaxis or fixation mode. However, one would rather expect such measures, if taken, to have the opposite effect on the results. Furthermore, there is no literature to support a general increase in disease severity in RA patients which could explain an increase in infection risk. On the contrary, some authors believe that the disease severity has become milder during recent years, although it is difficult to know whether such a change is due to improved treatment or to changes in disease features [156]. Increasing overweight in the population during recent years is well known, but there is no literature to support such a development to be greater in RA patients than OA patients. On the contrary, obesity is an important risk factor for developing OA.

Thus, we believe changes in the medical treatment for RA to have been a major cause of this increase in risk of revision for infection in RA THRs during recent years. However, the magnitude of the increase was small and of limited clinical importance and based on our findings, we recommend continued close surveillance and additional studies to further illuminate this issue.

3. Risk of early and late revision for infection

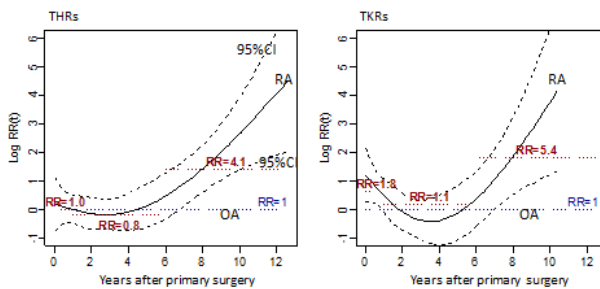
In Paper I we evaluated the time from the primary TKR and THR until revision for infection. In the first postoperative year there was a trend towards a higher risk of revision for infection in RA compared to OA patients in the TKRs (RR 1.8 (0.9-3.4)). From 5-6 years postoperatively onward we found an increased risk of revision for infection in RA compared to OA in both the TKRs and THRs, with RR 5.4 (1.9-16) and RR 4.1 (1.6-11), respectively. This was statistically significant from about 7 years postoperatively, but the

gap between the risks in RA and OA patients started to appear at 5-6 years postoperatively.

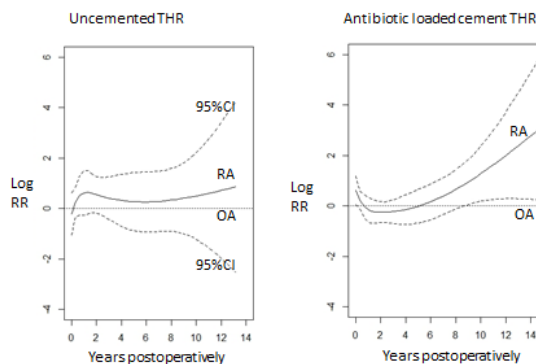
In Paper III we wished to study this observation more closely and we therefore analysed the time from primary THR until revision for infection in uncemented and antibiotic-loaded cemented prostheses separately. In the uncemented THRs we found a trend towards a higher risk in RA compared to OA throughout the follow-up period (the RR from 3 months to 2 years was 1.1 (0.6-2.2, $p=0.72$), from 2 years to 8 years 1.4 (0.6-2.9, $p=0.44$) and longer than 8 years postoperatively 1.5 (0.3-6.8 $p=0.62$). In antibiotic-loaded cemented THRs a significantly higher risk in RA was revealed during the first three months postoperatively (RR 1.8 (1.1-3.0)) and from 8 years onward (RR 2.7 (1.2-6.3), Figure 1).

Figure 1. Time from primary operation to revision for infection comparing RA to OA patients in Paper I, THRs and TKRs, and in Paper III, THRs inserted uncemented or with antibiotic-loaded cement.

Paper I



Paper III



Early infections

The trend to an increased risk of revision for infection in the early postoperative period in TKRs (1 year in Paper I) and THRs with antibiotic-loaded cement (3 months in Paper III) in

RA compared to OA can be explained by higher rates of wound infection in RA [157]. The lack of this finding in THRs in Paper I and in uncemented THRs in Paper III may be explained by a combination of a general higher risk of infection leading to revision in replacements of knees than in replacements of hips when comparing RA to OA (Paper I) and by the lower numbers in Paper I than in Paper III and therefore greater uncertainty of the results. There was no significant difference in risk of revision for infection between RA and OA in uncemented THRs in the first 3 months (RR 0.4 (0.1-1.8)), whereas there was a significantly higher risk in RA than in OA in antibiotic-loaded cemented THRs (RR 1.8 (1.1-3.0)). This difference in findings between uncemented and antibiotic-loaded cemented prostheses found in Paper III may be explained by a possible selection of low risk (less comorbidities, younger, etc.) RA patients for the uncemented THRs.

Late infections

After the early postoperative period (1 year in Paper I and 3 months in Paper III) the curves for RA patients show a similar course except in the uncemented THRs. In the majority of the total joint replacements in Paper I, antibiotic-loaded cement was used. In Norway only 15-20% of THRs and even fewer TKRs are uncemented [158]. This may explain why the curves of THRs and TKRs in Paper I are so similar to the cemented curve in Paper III. The course of these curves after the first postoperative year is characterized by a lack of difference between the two diagnostic groups the first 5-6 years followed by an increasing difference between the risks with time. This finding could be caused by an initial protective effect of the antibiotics in the cement lasting somewhat longer than 5 years but shorter than 10 years, which was also found by Josefsson [143]. After these 5-8 postoperative years the elution of the antibiotics and the protective effect cease. Not only the extra volume but also the surface properties (bacterial adherence/colonization) of the now inactive bone cement may reinforce the already higher susceptibility for haematogenous infections in RA patients possibly leading to late infections causing revision. This may also explain the lack of increase in late infections in RA patients operated with uncemented prostheses, since there is no (initial) protection of the antibiotics, and no late adverse effect of the cement. The 95% CI for the uncemented THR RA curve is quite wide, indicating some uncertainty of the results. This should be kept in mind when interpreting the findings. Due to the low number of patients having cemented prostheses without antibiotics, no sub-analyses were performed for the RA versus the OA patients and we may not conclude any potential impact of such fixation in RA patients.

4. Bacterial findings

In Paper II we found no statistically significant difference in bacterial findings in PJs in RA patients compared to OA patients. There was a trend towards a higher frequency of *S. aureus* in RA than in OA (18% vs. 11%) but we could not with certainty confirm the findings of Berbari who found 37% *S. aureus* in their study of THRs and TKRs in patients with RA

[54]. Bacteria of potential oral or dental origin (odontogenic) had an occurrence of 4% in OA, while in RA no such bacteria were found.

A substantial part of the material, 31-37%, was culture negative. This is much higher than other authors have reported (2-18%) [64]. The reason for this may be the use of antibiotics, inadequate taking, handling and/or culturing of the samples or an incorrect diagnosis of infection. In our study staphylococci were found in more than half of the positive cultures, which has also been reported by others [50, 159]. We performed a prior statistical power analysis based on the study by Berbari [54], which is the largest study performed in RA patients (see Chapter VII, *bacterial findings*). This showed a sufficient power with the numbers of infection episodes in RA patients which were actually included in our study. However, we expected a higher incidence and a greater difference in the frequency of *S. aureus* between the two diagnostic groups than were eventually found. The study was therefore underpowered and unable to detect (small) differences, if present. Our findings should therefore be interpreted with this in mind.

VI Conclusions

Paper I

The overall risk of revision for infection in TKRs was 1.6 times higher in RA than in OA patients. In THRs there was no difference in the risk of revision for infection between RA and OA patients.

The risk of infection for RA patients relative to OA patients did not change after the year 2000.

In both the TKRs and the THRs the risk of revision for infection was higher in RA patients than in OA patients from 5-6 years postoperatively.

Paper II

We found no difference in bacterial findings from infected THRs in RA patients and OA patients.

In RA patients we found a frequency of *S. aureus* of 18% and in OA patients 11%. This difference was not statistically significant.

Odontogenic bacteria causing infection leading to revision were found in 4% of OA patients, while no such bacteria were found in RA patients.

Paper III

The overall risk of revision for infection in THRs was 1.3 times higher in RA patients than in OA patients.

The difference in risk of revision for infection between RA and OA patients emerged after 2001. In the period 1995-2001 no difference was seen.

In patients having antibiotic-loaded cemented prostheses, the risk of revision for infection was higher in RA patients than in OA patients during the first 3 postoperative months and increasingly from 8 years postoperatively.

VII Methodological considerations

Quality of data

Studies I and III are register-based studies. These are prospective, observational (cohort) studies. The evidence level of such studies is inferior to randomized controlled trials (RCTs), which represent the gold standard in evidence-based medicine. A strength of our study is that we evaluate the occurrence of a rare event occurring in a relatively small diagnostic group of patients with THRs. Comparing the small RA group with a large control group (OA patients) over a long follow-up time was done to control for potential (time-dependent) confounders (e.g. changes in operating technique, operation theatres, pre-and postoperative procedures, threshold for operating older patients, awareness of prosthesis infections, diagnostics of infection, etc.). The studies thus offer a reasonably high internal validity.

The end point (i.e. revision for infection) of the studies was solid, but the designation of deep infection as the cause for revision depended on the judgment by the individual surgeon based on preoperative and perioperative findings. The results of cultures taken at revision surgery were not available when the register form was completed. The precision of the diagnosis is therefore uncertain.

The numbers and completeness of the data are high in both studies, making our results generalizable in terms of setting and population. The external validity is therefore also high, at least in a Caucasian population.

As mentioned above, the diagnoses registered in the NAR and NARA databases are made before the results of the tissue cultures from the surgery are ready. Therefore some patients will be erroneously diagnosed with infection and some infected cases will erroneously be diagnosed with aseptic loosening, pain alone or other diagnoses.

Studying the influence of medication and fixation mode on the risk of revision for infection

The optimal study design for the evaluation of the influence of certain medication regimes on infection rates would be an RCT. However, a very large number of RA patients would have to be included in order to have sufficient power to detect differences of the rare event of PJI. The follow-up period would also have to be quite long. Similarly, for studying mode of fixation, a vast number of RA patients would have to be randomized to cemented or uncemented fixation. Such studies have not been performed, presumably because they would be extremely difficult, time-demanding and expensive to undertake. In addition, the allocation of RA patients into specific treatment regimens for a very long period of time may represent an ethical dilemma. The medication of RA is highly individualized and appointing patients into predetermined treatment regimens could lead to suboptimal treatment of some patients.

Our register-based studies give information on the actual outcome in terms of revision for infection, in a large patient cohort followed for up to 21 (Paper I) and 16 years (Paper III).

To study the influence of medication in RA on the risk of revision for infection in joint replacements more accurately, a future study could be based on a linkage of the Norwegian Prescription Database and the NAR. The Prescription Database has person identifiable data from 2007, which was not sufficient for the present studies, but can be of great interest in the future.

It would have been of interest to study the impact of fixation mode more closely. We did not find a statistically significant difference in the risk of revision for infection in RA patients compared to OA patients with uncemented THRs. Even with the use of the large NARA database, the number of RA patients having uncemented THRs was rather low ($n = 3,034$). This caused our findings to be uncertain, as illustrated by the wide 95% confidence interval. However, in our study of around 3,000 RA patients and 83,000 OA patients with uncemented THRs, no difference in infection revisions was detected and we may conclude that, if present, a difference in risk between RA and OA patients must be small and probably clinically insignificant.

Bacterial findings

The study in Paper II is a retrospective study and consequently did not have an optimal quality of data. A large number of infection episodes had missing or erroneous data (228 of 730). Although not analysed, we had no reason to believe that these exclusions involved a selection bias. Furthermore, we performed a power analysis based on the findings of Berbari [54] who found 37% *S. aureus* in PJI in RA patients. Our number of infection episodes in RA and OA would achieve sufficient statistical power with a 20% difference in group proportions. In our present study we revealed only 18% *S. aureus* in RA versus 11% in OA. There thus were too few infection episodes in our RA patients to detect a statistically significant difference for *S. aureus*, if present. This represents a type II error. A type II error is the inability or failure to reject a false null hypothesis and is commonly caused by an insufficient number of observations. The probability of the type II error (β) is related to the power of the test ($1-\beta$). In other words, our finding of p-values in the non-significant range can either reflect a lack of difference between the patient groups or that there are too few infection episodes to show such a difference, if existent. In conclusion, a new study with additional collection of data from the last 6 years will probably give a better chance to detect any differences, if present.

VIII Clinical implications

In addition to the obvious burden to the patient caused by repeat surgery, long-term antibiotic treatment and hospital stays, and often reduced function, prosthesis-related infections are associated with substantial costs for the health care system (Chapter I 2.1). Of additional concern in RA patients is the need to pause important anti-rheumatic medical treatment during the infection episode, often resulting in flares of the rheumatologic background disease, thus adding to the burden of prosthesis infection in RA patients. These factors as well as the higher risk of revision for infection after joint replacements in RA patients compared to OA patients make specific preventive strategies desirable.

Preoperative considerations

The preoperative care of the RA patient undergoing joint replacement surgery should include a strict evaluation of the patient's medication, with particular focus on steroid therapy and biological agents. Most guidelines advocate the cessation of biologic drugs. A recent consensus group meeting (organized by orthopaedic surgeons) that dealt with periprosthetic infection proposed that all DMARDs including Methotrexate, biologic drugs and steroids should be discontinued prior to elective joint replacement surgery [151]. Furthermore, the disease activity of RA should be as low as possible when undergoing surgery.

Prevention of early postoperative infections

It has previously been shown that screening/selective decolonization will reduce the number of SSIs and that this procedure is cost-effective [160]. Furthermore, RA patients have a higher occurrence of nasal carriage of *S. aureus* than the non-RA population (Chapter I 2.5.1) and our study in Paper II showed a trend towards higher frequency of *S. aureus* in revisions for infection in RA than in OA patients. In addition, wound infection after joint replacement surgery appears more often in RA than in OA patients [157] and Berbari [63] showed that such SSIs represent a massive risk factor (RR=35) for PJI. Consequently, to prevent early infections, preoperative screening/selective decolonization of *S. aureus* could be considered introduced as a routine in RA patients. Preferably, this should be done in a clinical trial, although such a study might be difficult to accomplish due to the rareness of SSI.

Prevention of late haematogenous infections

RA patients with indwelling prosthetic joint replacements are especially susceptible to late, haematogenous infections leading to revision. Specific preventive measures include adequate (and prompt) treatment of all respiratory, urinary, odontogenic and skin and soft-tissue (especially of the same extremity) infections in such patients. However, in general the occurrence of haematogenous late infections after seeding from remote infections is probably low [161].

Based on our study in Paper II we are unable to conclude on whether to give routinely

prophylactic antibiotics before dental procedures in all RA patients with prosthetic joint replacements. Our Study II suggests that anti-staphylococcal antibiotics should be prescribed, if prophylactics are to be given. Individual evaluation of RA patients seems to be important [104] and is needed to determine the risk factors for infection. Immune-suppressed, high-risk RA patients (e.g. with high disease activity, lingering use/high steroid dose, leukopenia, use of biologics, etc.) should be considered for antibiotic prophylaxis before dental procedures.

Microorganisms

Based on our findings in Paper II, where a high percentage of negative cultures was revealed, a focus on detection of the bacteria in the setting of revision surgery (perioperatively) seems to be needed. An 'antibiotic holiday' before taking samples, an adequate number of samples, optimal handling of the samples and mode and duration of culturing should be evaluated more strictly.

Antibiotic-loaded cement

Paper III revealed a higher risk of revision for infection in THRs after 8 years postoperatively in RA compared to OA patients when antibiotic-loaded cement was used. However, no difference in the total risk of revision for infection was seen when comparing THRs with antibiotic-loaded cement to uncemented ones. In general, the use of antibiotic-loaded cement as the fixation mode in THRs is recommended in all high-risk patients to prevent PJIs [151]. Based on our findings, one should be aware that the risk of infection leading to revision increases slightly from 5-8 years onwards after implantation of a THR with antibiotic-loaded cement (or TKR (Paper I)) in RA patients compared to OA patients.

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X Appendices

Appendix I

Definition of PJI (Berbari 1998, Del Pozo 2009)

Presence of at least one of the following:

1. Acute periprosthetic inflammation on histopathological examination
2. Sinus tract communicating with the prosthesis
3. Gross purulence in the joint space
4. Isolation of significant amounts of the same microorganism from more than one cultures of joint aspirates

Another proposal to define a Periprosthetic Joint Infection (Parvizi 2011)

1. There is a sinus tract communicating with the prosthesis, or
2. A pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthetic joint, or
3. Four of the following six criteria exist:
 - a) Elevated serum erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) concentration
 - b) Elevated synovial leucocyte count
 - c) Elevated synovial neutrophil percentage (PMN%)
 - d) Presence of purulence in the affected joint
 - e) Isolation of a microorganism in one culture of periprosthetic tissue or fluid
 - f) More than five neutrophils per high-power field in five high-power fields observed from histologic analysis of periprosthetic tissue at 400 times magnification

PJI may be present if fewer than four of these criteria are met.

A third definition of Periprosthetic Joint Infection (Parvizi 2013)

1. Two positive periprosthetic cultures with phenotypically identical organisms, or
2. A sinus tract communicating with the joint, or

* Having 3 of the following minor criteria:

- a) Elevated serum C-reactive protein (CRP) AND erythrocyte sedimentation rate (ESR)
- b) Elevated synovial fluid white blood cell (WBC) count OR +change on leukocyte esterase test strip
- c) Elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%)
- d) Positive histological analysis of periprosthetic tissue
- e) A single positive culture

Appendix II

Surgical Site Infection (CDC Definition) (Horan 1992, Skramm 2013)

Superficial Incisional Surgical Site Infection

Infection within 30 days after the operation and only involves skin and subcutaneous tissue of the incision and at least one of the following:

1. Purulent drainage with or without laboratory confirmation, from the superficial incision
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision
3. At least one of the following signs or symptoms of infection: pain or tenderness, localised swelling, redness, or heat and the superficial incision is deliberately opened by the surgeon, unless the incision is culture-negative
4. The diagnosis of superficial incisional SSI is made by a surgeon or attending physician

Deep Incisional Surgical Site Infection

Infection occurs within one year if implant (e.g. joint replacement) is in place and the infection appears to be related to the operation and the infection involves deep soft tissue (e.g. fascia, muscle) of the incision and at least one of the following:

1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site
2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever ($>38^{\circ}\text{C}$), localised pain or tenderness, unless the incision is culture-negative
3. An abscess or other evidence of the infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination
4. Diagnosis of deep incisional SSI made by a surgeon or attending physician

Organ/Space Surgical Site Infection

Infection occurs within one year if implant (e.g. joint replacement) is in place and the infection appears to be related to the operation and the infection involves any part of the anatomy (e.g. organs and spaces) other than the incision which was opened or manipulated during an operation and at least one of the following:

1. Purulent drainage from a drain that is placed through a stab wound into the organ/space
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination
4. Diagnosis of organ/space SSI is made by a surgeon or attending physician

Appendix III

Publication		Surgery	Conclusions	Notes
Talwalkar (2005)	Anti-TNF treatment with or without perioperative continuation	Elective orthopaedic surgery	Anti-TNF treatment without cessation didn't increase the rate of infection	No serious wound infections in any of the patients. Underpowered
Wending (2005)	Anti-TNF treatment, with or without continuation	Mainly orthopaedic surgery	Uninterrupted use of anti-TNF treatment didn't increase the frequency of adverse events.	No pyogenic infections. Underpowered
Giles (2006)	Anti-TNF naïve vs. anti-TNF treatment	Elective orthopaedic surgery	Association between early serious postoperative infections and anti-TNF treatment	
Ruyssen-Witrand (2007)	Anti-TNF treatment with or without perioperative continuation	Elective and emergency orthopaedic procedures	A trend of more postoperative infections when continuation	Underpowered
Den Broeder (2007)	3 cohorts: anti-TNF naïve, anti-TNF treatment with and without continuation	Elective orthopaedic surgery	Continuation of anti-TNF treatment not an important risk factor for SSI	Not powered to detect small differences in infection rates
Gilson (2010)	Case control, Anti-TNF treatment and PJI vs. non-PJI	Total joint arthroplasty	Increased risk of PJI with anti-TNF treatment	Steroid use was a risk factor for PJI
Kawakami (2010)	Case-control, anti-TNF treatment vs. conventional DMARDs	Joint surgery	Increased risk of SSI for major orthopaedic surgery in anti-TNF treatment	Anti-TNF treatment was interrupted perioperatively. Flare ups in 17.2%
Suzuki (2011)	Anti-TNF treatment vs. non-biological DMARDs	Joint arthroplasty surgery and other orthopaedic surgery	Increased risk of SSI for joint replacements in anti-TNF treatment	Anti-TNF treatment was interrupted perioperatively
Momohara (2011)	Biological DMARDs vs. non-biologic DMARDs	TKR and THR	Increased risk of acute SSI for THR/TKR in anti-TNF treatment	
Berthold (2013)	Anti-TNF treatment with or without continuation	Elective orthopaedic and hand surgery	No increased risk of SSI with continuation of anti-TNF treatment	Historical control group

Studies on influence of anti-TNF treatment on risk of infection after orthopaedic surgery