Infected Hip and Knee Arthroplasties in Rheumatoid Arthritis

A register-based study with focus on risk factors

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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.

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Acknowledgements

Abbrevations

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
S. aureus	*Staphylococcus aureus*
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

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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[R]), Etanercept (Enbrel[R]) and Adalimumab (Humira[R]). 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-born 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 Sjursen, 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.
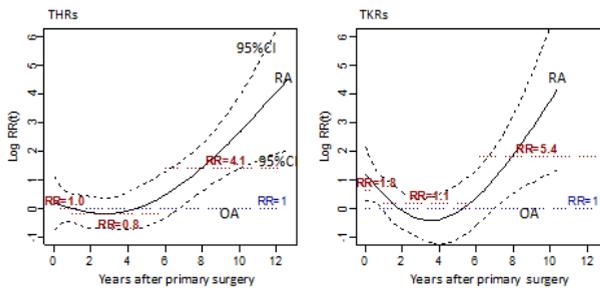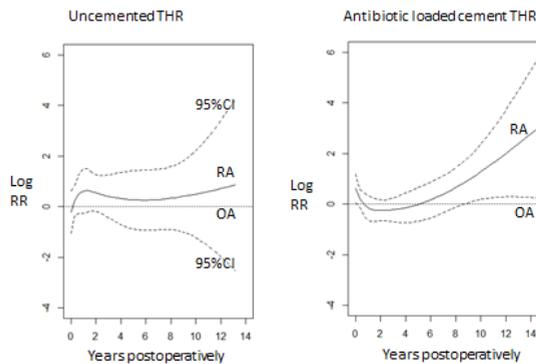
Early infections
The trend to an increased risk of revision for infection in the early postoperative period in TKRs (1 year in Paper I) and THRs with antibiotic-loaded cement (3 months in Paper III) in

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 PJIs 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-β). 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 (>38^0C), 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

XI Papers I-III

Risk of Revision for Infection in Primary Total Hip and Knee Arthroplasty in Patients With Rheumatoid Arthritis Compared With Osteoarthritis: A Prospective, Population-Based Study on 108,786 Hip and Knee Joint Arthroplasties From the Norwegian Arthroplasty Register

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Objective. To compare differences in the risk of revision for infection and changes in risk over time and in time from primary surgery to revision for infection after total hip replacement (THR) and total knee replacement (TKR) in rheumatoid arthritis (RA) and osteoarthritis (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 the end point were performed using Kaplan-Meier methods for constructing survival curves and multiple Cox regression to calculate relative risk (RR) estimates for diagnosis, age, sex, and year of primary surgery. An extended Cox model was used to estimate RR within different followup intervals.

Results. RA patients with TKR had a 1.6 times higher risk of revision for infection than OA patients, whereas there was no difference in the THRs. In the THRs, we found a higher risk of revision for infection from 2001 onward, 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 on 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 RR of revision for infection in RA compared with OA remained unchanged.

INTRODUCTION

Many patients with rheumatoid arthritis (RA) will undergo elective orthopedic surgery, especially prosthetic joint replacement surgery. The Scandinavian arthroplasty registers have shown that 3–15% of all prosthetic joint replace-

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ments in the hips and knees were done in RA patients (1–7). Replacements of other joints (e.g., elbows, wrists, fingers, and ankles) are predominantly performed in RA patients.

Patients with RA are generally considered to be more prone to infection, due to the nature of the disease and to the treatment with the traditional disease-modifying antirheumatic drugs (8–10). There are conflicting reports on whether this increased baseline risk of infections in RA patients might influence the risk of deep infection after primary total joint replacement surgery (1,5,11–18).

Prosthetic joint infection (PJI) is a devastating complication in elective orthopaedic surgery. The consequences for the patient will usually be removal or exchange of the implant associated with functional decline, prolonged hospital stay, and extended use of potentially toxic and antimicrobial resistance–encouraging antibiotics. In addition, the costs of the treatment of a PJI are substantial,

estimated to be more than \$50,000 per infection episode (19–22). This is approximately 3–7 times the costs of a primary knee joint replacement (21,23).

The major objectives of the present study were to investigate the risk of revision for infection after primary hip and knee joint replacements in patients with RA. We wished to compare RA patients with osteoarthritis (OA) patients in order to detect any differences in the risk of revision for infection and to compare changes in risk for the two groups over time. Furthermore, we investigated the time from primary surgery to revision for infection in these two patient groups and procedural groups. By comparing these diagnostic groups, a possible impact of changes in RA treatment might be revealed.

PATIENTS AND METHODS

Methods. The Norwegian Arthroplasty Register (NAR) was established in 1987, first as a hip replacement register, and from January 1994, it was extended to include knee joint replacements as well as replacement of other joints (24).

Individual reports of joint replacements were received from every hospital performing these procedures in Norway (population 4.8 million). Data concerning the identity of the patient, the diagnosis (indication), the date of surgery, whether the operation was primary or a revision, the cause of revision, the type of prosthesis, whether bone cement was used and the type of cement, the use of thrombosis prophylaxis, and antibiotics were registered in a form filled in by the operating surgeon (2,25). Using the unique identification number assigned to each resident of Norway, information from revision procedures involving exchange or removal of implants was linked to the corresponding primary operation.

All primary hip and knee replacements in patients with RA or OA in the period September 1987 to June 2008 were included in the present study. Therefore, we included 4,167 hips and 2,462 knees in the RA group, and 80,325 hips and 21,832 knees in the OA group. Patient characteristics are given in Table 1.

Survival analyses with revision for infection as the end point were performed separately for hips and knees. We compared joint replacements performed in patients with RA with those with OA. Thus, time-dependent changes possibly influencing the risk of infection were controlled for using the large group of OA patients as a control group.

Furthermore, revisions for infection were analyzed in 2 different time periods. Tumor necrosis factor α (TNFα)

antagonists used in the treatment of RA were introduced in Norway during the year 2000. However, very few patients used such treatment the first years, whereas these agents are now in widespread use in this patient group (more than 20% of the patients with RA) (26). In order to investigate any impact of these drugs on the rate of revision for infection, the time of primary replacement surgery was stratified into 2 time periods: from 1987 (1994 for knees) through 2000, and from 2001 onward. Revision for infection was evaluated for these time periods.

Statistical analysis. The end point in the survival analyses was revision for infection. Prosthesis survival times in patients who had died or emigrated and patients who were revised for other reasons than infection were censored at the time of death, emigration, or revision, respectively. The date of death or emigration was obtained from Statistics Norway (online at: www.ssb.no/English/). A revision of the implant was defined as the surgical removal or exchange of the whole or any part of the implant. Survival times were otherwise censored at end of the study: June 25, 2008. Survival curves and 1- and 5-year survival percentages were established using the Kaplan-Meier method. Separate survival curves were presented for OA and RA patients (Figure 1) and according to the year of the primary operation (through 2000 and from 2001 to June 25, 2008) (Figure 2) for total hip replacements (THRs) and total knee replacements (TKRs). Cox regression analyses were performed to estimate the relative risk (RR; incidence rate ratios) of revision for infection according to diagnosis (RA and OA), age (continuous), sex, and year of primary surgery (through 2000 and from 2001 to June 25, 2008). RRs were estimated separately for THRs and TKRs, and all were adjusted for the other variables. The RRs are an estimate of the relative difference in revision risk between the groups at any given time throughout the observation period.

Additional analyses were performed to detect any changes in revision risk with increasing time since the primary surgery, comparing RA and OA patients (indicating non-proportional hazards). We used tests and visual inspection of plotted scaled Schoenfeld residuals (Figure 3) (27). Adjusted RR estimates were further established within followup intervals using an extended Cox model including time-dependent covariates. These covariates were based on heavy side functions with cut points at 1 and 6 years after the primary operation.

Separate analyses were performed for the two time pe-

Table 1. Patient characteristics			
	Rheumatoid arthritis	Osteoarthritis	*P*
Total knee replacements, no.	2,462	21,832	
Total hip replacements, no.	4,167	80,325	
Age, mean $\pm$ SD years	64 $\pm$ 14	71 $\pm$ 9	< 0.001*
Women, %	73	69	< 0.001†
* Calculated by the Student's *t*-test. † Calculated by the chi-square test.			

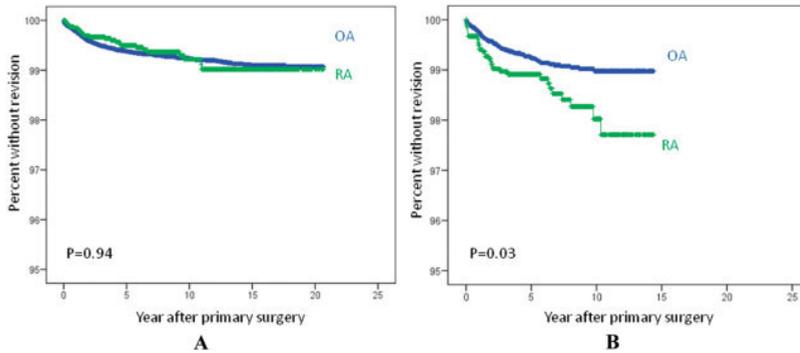**Figure 1.** **A**, Kaplan-Meier survival curves for total hip replacement (1987–2008), and **B**, Kaplan-Meier survival curves for total knee replacement (1994–2008), with revision for infection as the end point. *P* values were obtained from Cox regression analyses with adjustment for age, sex, and year of primary surgery. OA = osteoarthritis; RA = rheumatoid arthritis.

riods to see whether the difference in risk of infection between patients with RA and OA changed from the first to the second time period (data not shown).

P values less than 0.05 were considered statistically significant. All of the analyses were done with the statistical software programs SPSS, version 15.0 (SPSS, Chicago, IL), and R (28).

RESULTS

Of the 24,294 TKRs, 176 (0.7%) were revised for infection from 1994–2008, and among 84,492 THRs, 534 (0.6%) had a revision for infection from 1987–2008. Women had a significantly lower risk of revision for infection compared with men both in THRs (RR 0.41, 95% confidence interval [95% CI] 0.34–0.48) and in TKRs (RR 0.67, 95% CI 0.47–0.88) (Table 2).

RA versus OA. For THRs, the cumulative 5-year survival was 99.5% in RA patients and 99.4% in OA patients

(RR 0.98, 95% CI 0.65–1.48 for RA versus OA patients), with revision for infection as the end point. For TKRs, however, a statistically significant difference in survival was found: when comparing RA versus OA patients, the cumulative 5-year survival was 98.9% in RA patients and 99.3% in OA patients (RR 1.6, 95% CI 1.06–2.38). Kaplan-Meier survival curves comparing OA and RA patients illustrate this difference for TKRs (Figure 1B) and the lack of difference in THRs (Figure 1A). The separate analyses comparing RA and OA patients during the two time periods showed that, although not reaching statistical significance, the difference between RA and OA patients with TKR was seen both in early (1994–2000; RR 1.5, 95% CI 0.90–2.55) and late primary operations (2001–2008; RR 1.6, 95% CI 0.82–3.16). For THR, the lack of difference between OA and RA was present both during the first time period (1987–2000; RR 0.88, 95% CI 0.52–1.47) and during the second time period (2001–2008; RR 1.05, 95% CI 0.51–2.14).

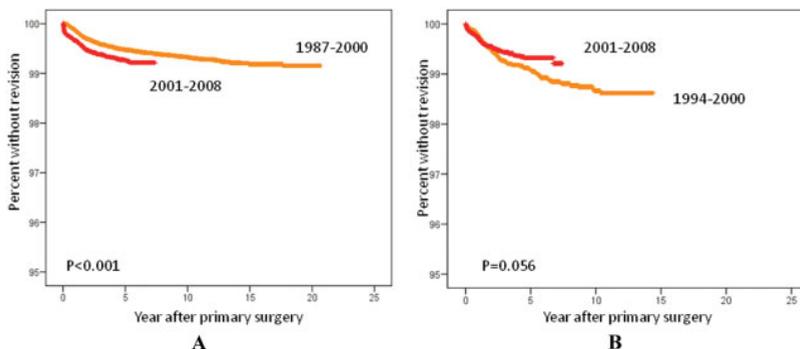**Figure 2.** **A**, Kaplan-Meier survival curves of all patients with total hip replacement in the period 2001–2008 versus 1987–2000, and **B**, Kaplan-Meier survival curves of all patients with total knee replacement in the period 2001–2008 versus 1994–2000, with revision for infection as the end point. *P* values were obtained from Cox regression analyses with adjustment for age, sex, and diagnosis.
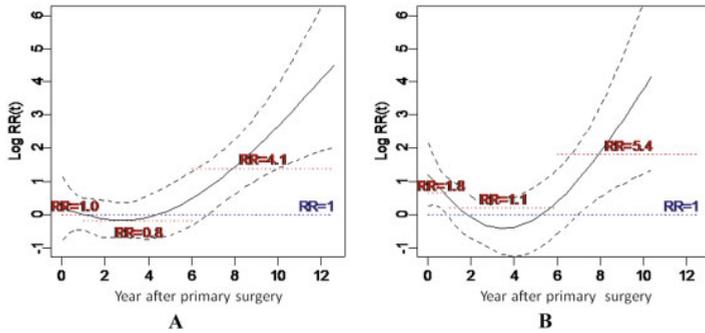
Figure 3. A, Total hip replacement (1994–2008), and **B**, total knee replacement (1994–2008). Log relative risk (RR) estimates of revision for infection for patients with rheumatoid arthritis versus osteoarthritis are shown by year after the primary surgery. Broken lines show the 95% confidence intervals. RR values, obtained from Cox regression analyses with time-dependent covariates, are given for the time intervals 0–1 year, 1–6 years, and beyond 6 years of followup. All RRs are adjusted for age, sex, and year of primary surgery.

Year of primary surgery. In THRs, we found a statistically significantly higher risk of revision for infection during the period from 2001–2008 compared with the period before 2001 (RR 1.48, 95% CI 1.23–1.77) (Table 2). A tendency toward the opposite was found when considering TKRs, with a lower risk of revision during the last time period (RR 0.74, 95% CI 0.54–1.00) (Table 2). The Kaplan-Meier survival curves illustrate these findings (Figures 2A and B).

Time of revision. In TKRs, an increased revision rate in RA patients as compared with OA patients was evident the first year after the primary operation, whereas no significant difference between the groups was present during the next 5 years. After this time, a higher risk was found in patients with RA (RR 5.4, 95% CI 1.9–16; $P = 0.002$) (Figure 3B). In THRs, no statistically significantly higher risk of revision for infection was seen during the first 6 postoperative years, whereas after 6 years, a statistically significantly higher risk of revision for infection was seen in patients with RA (RR 4.1, 95% CI 1.6–11; $P = 0.004$) (Figure 3A). No overall statistically significant difference in the risk of revision for infection after THR between the two diagnostic groups was present from 1994–2008 (RR 1.3, 95% CI 0.9–1.8). In Figure 3A, we excluded the hips from 1987–1993 in order to obtain comparable analyses.

Table 2. Cox regression analysis of revision for infection according to diagnosis, sex, and year of primary surgery*						
	No. of patients	No. of revisions	1-year survival, %†	5-year survival, %†	RR (95% CI)‡	*P*
THR						
Diagnosis						
OA	80,325	509	99.8	99.4	1	
RA	4,167	25	99.9	99.5	0.98 (0.65–1.48)	0.94
Sex						
Men	26,252	273	99.6	99.0	1	
Women	58,240	261	99.9	99.6	0.41 (0.34–0.48)	< 0.001
Year of surgery						
1987–2000	48,327	314	99.9	99.5	1	
2001–2008	36,165	220	99.7	99.3	1.48 (1.23–1.77)	< 0.001
TKR						
Diagnosis						
OA	21,832	144	99.8	99.3	1	
RA	2,462	32	99.5	98.9	1.6 (1.06–2.38)	0.027
Sex						
Men	6,905	63	99.6	99.0	1	
Women	17,389	113	99.8	99.3	0.67 (0.47–0.88)	0.006
Year of surgery						
1987–2000	7,687	89	99.8	99.1	1	
2001–2008	16,607	87	99.7	99.3	0.74 (0.54–1.00)	0.056

* RR = relative risk; 95% CI = 95% confidence interval; THR = total hip replacement; OA = osteoarthritis; RA = rheumatoid arthritis; TKR = total knee replacement.
† Estimated using the Kaplan-Meier method (unadjusted).
‡ Derived from the Cox model, which also included the variable age.

Table 3. Rheumatoid arthritis (RA) as a risk factor for revision for infection of a primary joint replacement (PJR)				
Author, year (ref.)	**Study period**	**No. of replacements**	**Site of replacement**	**RA is a risk factor for prosthetic joint infection**
Wilson et al, 1990 (17)	1973–1987	4,171	Knee	Yes
Bengtson and Knutson, 1991 (11)	1975–1985	12,118	Knee	Yes
Robertsson et al, 2001 (5)	1988–1997	41,223	Knee	Yes
Jämsen et al, 2009 (15)	1994–2007	40,135 (PJR)	Knee	Yes
Fitzgerald et al, 1977 (14)	1969–1972	3,215	Hip	Yes
Furnes et al, 2001 (1)	1987–1999	53,698	Hip	No
Wymenga et al, 1992 (18)	1986–1988	3,013	Hip and knee	No and yes
Berbari et al, 1998 (12)	1969–1991	26,505	Hip and knee	No
Bongartz et al, 2008 (13)	1996–2004	657	Hip and knee	Yes
Poss et al, 1984 (16)	1970–1979	3,936 (PJR)	Hip and knee	Yes

DISCUSSION

A major finding in the present study was that in TKRs, an increased risk of infection leading to revision was seen in patients with RA compared with those with OA, whereas this was not seen in THRs. A possible explanation might be that the vulnerable soft tissue envelope around the knee joint could make the TKR in RA patients more susceptible to infection, since the connective tissue disease RA and its potentially immunomodulating medication are risk factors for skin and soft tissue infections (29,30).

Our findings of an increased risk of deep infection confirm findings in several previous reports on TKRs (5,11,15,17,18,25). For THRs, the literature is conflicting (1,14,18). We did not confirm the findings of some study groups who reported an increased risk of deep infection in RA patients both in TKR and THR (13,16). Nor did we agree with Berbari et al (12), who reported no increased risk in TKR as well as THR (Table 3).

An increasing number of revisions due to infection in the latest study period was found in patients with THR. This has recently been shown by Dale et al (31). Possible explanations are discussed in the study by Dale et al, and include that patients undergoing THR in the later time period probably have more comorbidity, a possible increase in virulent or antimicrobial resistant microbes causing PJI, an improvement in diagnostic tools leading to an easier detection of infection, and an increased surgeon awareness combined with potential changes in reporting and revision policy. There has been a reduction in the use of monoblock prostheses and an increased use of modular hip prostheses (32). Only revisions that involve the removal or exchange of at least one component are reported to our register. During soft tissue debridement, which is a current recommended treatment of early PJI (33), the femoral head and the acetabular liner are often exchanged in modular hip prostheses. This may have contributed to the increase in the number of (early) revisions reported.

In contrast to the development for THR, the rate of failures due to infection in TKR had a tendency to decrease in the later time period. Compared with PJI in the hip, a PJI in the knee is considered to be more easily clinically diagnosed. Consequently, one reason why the increase in revision for PJI in THR was not found in TKR might be that the improvement in diagnostic tools that could have contributed to our findings in the THR did not have the same impact on the diagnosis of PJI in the knee. An increased

use of bicompartmental TKRs, which are less prone to revision due to infection than tricompartmental TKRs (25,32), and a possibly improved preventive surgical technique along with awareness in patients with tricompartmental TKR in the later time period, could be other causes.

In a Norwegian study from 2005, more than 20% of patients with RA and psoriatic arthritis were treated with a TNFα inhibitor (26). There have been conflicting reports concerning the risk of serious infections associated with the use of these drugs in patients with RA.

Some authors like Bongartz et al (34), Curtis et al (35), and Listing et al (36) reported an increased risk of serious infection in RA treated with TNFα antagonists. On the other hand, Wolfe et al (37) and Schneeweiss et al (38) found no increase in serious infections, and den Broeder et al (39) did not find any significant association between the use of TNFα antagonists and surgical site infections. Pappas and Giles (40), in a recent review of 5 additional studies, describe 4 of which concluded that TNF inhibition perioperatively does not increase the risk of postoperative infections in orthopaedic surgery. Furthermore, Dixon et al (29) found no overall increased risk of serious infections, but there were more skin and soft tissue infections with the use of TNFα inhibitors, which could have a potentially negative influence on the healing of surgical wounds and thus facilitate development of a PJI.

In our study, the difference in infection risk in TKR between the RA patients and the OA patients remained the same in both time periods. Furthermore, the lack of difference in infection risk for THR remained unchanged during the two time periods. Consequently, in our study that includes data from an entire country (4.8 million inhabitants) with a long observation period, no increase in the risk of infection leading to revision was seen in RA patients compared with OA patients. The use of OA patients as the control group was useful in that time-dependent factors possibly influencing the risk of infection in general were controlled for. Therefore, there is no reason to believe that the risk of revision due to infection has increased in RA patients, as might be suspected due to the new use of biologic agents. However, since the difference between OA and RA was greatest for late infections, patients who were operated on during the last time period have had a shorter followup, and an increase in late infections might be revealed after a longer followup time.

PJIs occurring more than 2 years after implantation are

often referred to as late infections and can be attributed to hematogenous seeding, in contrast to the early infections that are generally related to contamination during surgery (41). RA patients are considered to be susceptible to late and (potentially) blood-borne infections of their implant, and it has been reported that late infections account for more than 50% of the prosthetic knee joint infections in RA patients (42). In agreement with Poss et al (16), our analyses showed an increased risk of revision for late infection in both THR and TKR in RA patients from approximately 6 years postoperatively on, comparing RA with OA (Figures 3A and B). This finding supports the view that RA patients have a higher susceptibility for late and (potentially) blood-borne PJIs (43,44). We found that this was statistically significant and more evident in the TKRs, which was also described by Deacon et al (45).

Within the first postoperative year, there was a tendency toward more revisions for infections in RA patients with TKRs (RR 1.8, 95% CI 0.9−3.4; P = 0.07) compared with the OA group (Figure 3B). No such finding was seen after THR surgery (Figure 3A). Furthermore, from the first to approximately the fifth postoperative year, no difference, or rather the opposite tendency, was seen.

This finding might be due to a potential difficulty to differentiate between an RA disease flare and a PJI, which could give an underestimation of infections and a possible delay in revision surgery. Furthermore, a reluctance to revise a newly placed prosthetic joint in RA patients caused by potentially more surgical difficulties such as bone stock and soft tissue problems could represent another cause of delay.

Although 108,786 THRs and TKRs were included in our study, a drawback of this study is the low numbers of the infected and revised cases. The incidence of PJIs after total hip and knee arthroplasty has been reported to be approximately 1−2% and 2−4%, respectively (46). In our material, less than 0.7% of included primary operations were revised because of a PJI. This low revision rate was due to the fact that PJIs treated with only debridement and retention of the total arthroplasty were not registered in the NAR, and thus were not included.

Furthermore, we do not have information on the medical treatment of our RA patients. This represents a limitation when evaluating the influence of antirheumatic drugs, such as the TNFα inhibitors, on the risk of infection leading to revision of the primary joint replacement. In addition, the positive effects of these new drugs might potentially have diminished the need for joint replacement surgery. Therefore, we cannot from the present study come to a conclusion on the impact of patient medication. We did not, however, find any evidence to suggest an increase in infection in RA compared with OA patients during the study period.

The completeness of data in the NAR is a strength of this study. In a published study from our register, the completeness of primary THR was 97%, whereas 99% of the primary TKRs had been registered. The completeness of the registration of revisions was more than 97% for revisions for all reasons of THRs and TKRs. Registration completeness regarding revisions involving only removal of prosthetic parts, performed predominantly in patients with a PJI, was lower than for exchange revisions. For hip replacements, up to 20% of the total removal revisions (Girdlestone procedures) were not reported (47,48). It is unlikely that this would have affected our survival curves, since there is no reason to believe the missing patients represent a different group of patients than those reported.

Furthermore, this is one of the largest population-based studies with a long followup. The use of OA patients as the control group was useful because time-dependent factors possibly influencing the risk of infection in general were controlled for. Variables like prosthetic design, surgical technique, revision policy, and measures to prevent, diagnose, and treat infection would be equally changing over time in the two study groups. An influence of RA-specific factors, on the other hand, such as antirheumatic drugs, would influence the results in the RA group only.

In conclusion, the overall risk of revision due to infection of primary TKR was 1.6 times higher in RA patients than in OA patients. No such difference was found for THR. In THR, only an increase in the RR in RA patients compared with OA patients was demonstrated from approximately 6 years onward after the primary surgery. From the year 2001 onward, the risk of revision for infection increased in THRs, whereas a tendency to decrease in the risk of TKRs was seen in this period. The RR of revision for infection in RA patients compared with OA patients did not change during the study period. Late infections leading to revision of the primary total hip and knee joint replacement were more frequent in RA compared with OA patients.

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II

Research Article

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

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High rates of *Staphylococcus aureus* are reported in prosthetic joint infection (PJI) in rheumatoid arthritis (RA). RA patients are considered to have a high risk of infection with bacteria of potentially oral or dental origin. One thousand four hundred forty-three revisions for infection were reported to the Norwegian Arthroplasty Register (NAR) from 1987 to 2007. For this study 269 infection episodes in 255 OA patients served as control group. In the NAR we identified 49 infection episodes in 37 RA patients from 1987 to 2009. The RA patients were, on average, 10 years younger than the OA patients and there were more females (70% versus 54%). We found no differences in the bacterial findings in RA and OA. A tendency towards a higher frequency of *Staphylococcus aureus* (18% versus 11%) causing PJI was found in the RA patients compared to OA. There were no bacteria of potential odontogenic origin found in the RA patients, while we found 4% in OA. The bacteria identified in revisions for infection in THRs in patients with RA did not significantly differ from those in OA. Bacteria of oral or dental origin were not found in infected hip joint replacements in RA.

1. Introduction

Patients with rheumatoid arthritis (RA) often undergo joint surgery, especially prosthetic joint replacements. In the prebiological agent era (before 2000), 1-2% of patients with RA were estimated to need at least one major joint replacement per year followup [1–4], that is, 25% of the RA patients with 16–20 years of observation [5, 6].

Prosthetic joint infection (PJI) is a serious although infrequent complication to joint replacement surgery. In primary total hip replacements (THR) the risk of deep infection is around 1% [7, 8]. A recent study from the Norwegian Arthroplasty Register (NAR) showed that RA patients had

the same overall risk of PJI as patients with osteoarthritis in THR, while the risk of revision for infection more than 6 years postoperatively was higher in RA compared to OA patients [9].

In the present paper we seek to evaluate and compare bacterial findings in prosthetic hip joint infections in RA patients versus OA patients, for the following reasons. Firstly, PJIs in patients with RA have been reported to be caused by *Staphylococcus aureus* (*S. aureus*) in as much as 37% [10]. This could be a result of relatively high carriage rates of *S. aureus* in RA patients [11–13]. If this is the case, eradication of nasal *S. aureus* with intranasal mupirocin ointment perioperatively might offer an attractive

opportunity for prevention of postoperative prosthetic joint infections caused by *S. aureus* in RA patients undergoing total hip replacement surgery [14–16].

Secondly, RA patients with indwelling hip- or knee-joint prostheses are in some international guidelines considered as exceptional high-risk patients for infections caused by bacteria of potential dental or oral origin. These patients are recommended antibiotic prophylaxis to prevent PJI follow-ing bacteremia caused by dental procedures [17–23]. Other guidelines and more recent literature do not mention RA as a high-risk factor and thus do not recommend prophylaxis [24–29] (Table 1). The aims of this study were to evaluate the bacterial findings in PJI among RA patients and compare them to the findings in OA patients with PJI. We particularly focused on the frequency of *S. aureus*. Furthermore, we compared the incidence of PJI caused by microorganisms potentially of oral or dental origin between the groups. This information might contribute in the discussion as to the need for treating the RA patient group different from those with OA, concerning antibiotic prophylaxis.

2. Material and Methods

The Norwegian Arthroplasty Register includes information on patient identification, the operating hospital, the reason for and the type of primary and revision operations as well as details on the implant type, the fixation method, and the use of antibiotic prophylaxis in each individual case [30, 31]. Primarily included in the present study were all patients having had a PJI leading to a revision, (i.e., surgical exchange or removal of parts of or the whole prosthesis) in the period September 15, 1987 until October 2007. The diagnosis PJI was made by the operating surgeon(s) based on clinical judgement of the pre- and peroperative findings at time of revision surgery, since the registry forms are filled in immediately after surgery, and thus before the analysis of bacterial cultures are finished. During the study period 107,535 primary total hip replacements were registered. One thousand four hundred forty-three revision procedures for infection were reported to the NAR. The ten hospitals performing most revisions for infection, with a total of 730 revisions, were visited (during the year 2009) by one of the authors (H.L.). In 228 (mean age at revision: 70 years, 56% females) of the infection episodes the medical records ($n = 36$), bacterial tests ($n = 96$), or the surgical data were incomplete and/or missing ($n = 96$). Thus, bacterial test reports and the surgeons' description of the revision procedure for a total of 502 episodes were systematically reviewed (Figure 1). In 215 infection episodes the diagnosis, that is, indication for primary surgery, was other than OA or RA, and the major diagnostic groups included acute fracture, sequelae after dysplasia, sequelae after fractura colli femoris, M. Pertes/epiphysiolysis, caput necrosis, and unknown diagnosis. 269 infection episodes were seen in 255 patients with OA and in the present study these served as a control group.

In the above mentioned cohort 18 infection episodes (14 patients) were observed in patients with RA as the indication for primary surgery. In the complete NAR database another
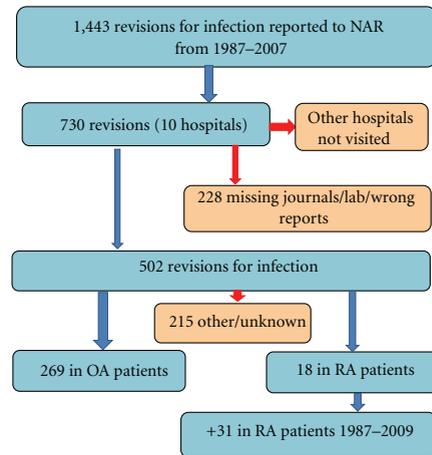

Figure 1: Flow chart showing the inclusion of patients for the study.

23 RA patients that had been revised at 10 hospitals not originally visited, were found and their records were obtained. The hospital with most patients was visited by one of the authors (J. C. Schrama) and the other hospitals were contacted by mail and asked to submit a copy of the medical records. A total of 49 infection episodes in 37 RA patients were thus finally included (Figure 1). Included in our analyses were 292 OA and RA patients (mean age at revision: 72 years, 56% females).

The bacterial findings were obtained from the micro-biologic reports in the patient records. Negative cultures (deep and/or biopsy) taken during revision surgery were included and one or more positive cultures were considered as causative for the PJI. We also included bacterial cultures from joint aspiration or blood cultures on the day of revision or 1-2 days before revision surgery. Superficial cultures such as wound swab specimen or swabs from fistulae were excluded. An infection episode (i.e., revision for infection) was considered as a new episode if the patient was assumed clinically free of the former infection and showed unexpected new symptoms of a PJI. Polymicrobial infections, here considered as a separate entity, were defined as infec-tions in which at least two different microorganisms were found. We did not have access to the clinical presentation of the infections, thus no distinction between potentially causative organisms and organisms representing secondary colonisation, could be made. Viridans group streptococci, beta-haemolytic streptococci, *Peptostreptococcus* species and streptococcus-like organisms not further identified, were considered microbes of potential oral or dental origin, as previously described by Berbari et al. [24]. We defined late infections as infections (i.e., revisions for infection) occurring more than 3 months after implantation surgery according to the definition given by Little et al. [32] and Fitzgerald et al. [33].

TABLE 1: Overview of literature after year 2000 discussing whether rheumatoid arthritis patients are high risk patients for bacteremic prosthetic joint infection after dental treatment and therefore routinely needing antibiotic prophylaxis.

Authors	Year of publication	Country	RA high risk patients, thus antibiotics
ADA and AAOS [17]	2003	USA	Yes
Scott et al. [21]	2005	Australia	Yes
Tong and Theis [22]	2008	New Zealand	Yes
Kotze [18]	2008	South Africa	Yes
Rompen et al. [20]	2008	The Netherlands	Yes
AAOS [23]	2009	USA	Yes
Kuong et al. [19]	2009	Hong Kong	Yes
Seymour et al. [27]	2003	Great Britain	No
Uçkay et al. [29]	2008	Switzerland	No
Blomgren et al. [25, 26]	2009	Sweden	No
Berbari et al. [24]	2010	USA	No

3. Statistics

Patient characteristics in the RA and OA group were compared using the chi-square test for categorical variables and the student t-test for continuous variables. The proportion of a specific microbe in the RA and the OA group (versus the proportion of all other cases) were compared using the chi-square and the Fisher's exact test. Furthermore, multinomial logistic regression (results not shown in table) was used to investigate the relationship between primary diagnosis and bacterial findings. Results were calculated as odds ratios (OR) with 95% CI comparing the groups CoNS, gram negative bacteria, miscellaneous, mixed flora, and no growth to *S. aureus*. Since a total of 26 patients were registered with more than one revision in the same hip, analyses were also performed based on the first revision only.

Statistical significance was defined as a P value less than 0.05. Preceding power analysis showed that, based on Berbari's 10 findings of 37% frequency of *S. aureus* in RA patients our number of observations would achieve 82% power to reveal as statistically significant a 20% difference in group proportions.

4. Results

Seventy per cent of patients with RA were females versus 54% of OA patients ($P = 0.06$, Table 2). At the time of revision RA patients were on average 10 years younger than OA patients ($P < 0.001$, Table 2). The mean time interval from primary surgery until revision for infection was 3.8 years for RA patients and 3.1 years for OA patients ($P = 0.3$, Table 2). *Staphylococcus aureus* was cultured in 9 of the 49 infection episodes (18%) in RA patients and 30 of 269 episodes (11%) in OA patients ($P = 0.16$, Table 3). CoNS tended to be a more frequent finding in patients with OA than in those with RA, although the difference was not statistically significant (18% RA versus 29% OA, $P = 0.11$, Table 3). Using multinomial logistic regression, the odds for culturing CoNS compared to *S. aureus* in RA patients was lower than for OA patients (OR = 0.4, 95% CI: 0.1–1.0, $P = 0.06$) indicating that there were more *S. aureus* compared to CoNS in the RA group. Including only the first revision for infection,

TABLE 2: Patient characteristics.

	RA	OA	P
Mean age (years) (SD)*	64 (16)	74 (8)	<0.001
Sex (females%)**	70%	54%	0.06
Mean time to revision (years)*	3.79	3.13	0.3

*In 318 infection episodes, **in the 292 patients.

TABLE 3: Distribution of cultured bacteria at revision surgery in infected THR in RA patients versus OA patients.

	RA ($n = 49$)	OA ($n = 269$)	P*
Staphylococcus aureus	9 (18%)	30 (11%)	0.16
Coagulase negative staphylococci	9 (18%)	79 (29%)	0.11
Streptococci	1 (2%)	19 (7%)	0.33
Enterococci	1 (2%)	18 (7%)	0.33
Gram negative bacteria	3 (6%)	10 (3%)	0.43
Others	1 (2%)	10 (3%)	1.00
Polymicrobial flora	7 (14%)	20 (7%)	0.11
No growth	18 (37%)	83 (31%)	0.42
Bacteria potentially of oral or dental origin	0	12 (4%)	0.13

*Chi-square and Fisher's exact test.

the difference was statistically significant (OR = 0.3, 95% CI: 0.1–0.9, $P = 0.03$). Streptococci were cultured in 19 (7%) of the OA patients and in 1 (2%) RA patient ($P = 0.33$). We found no statistically significant difference between the two patient groups with respect to gram negatives ($P = 0.43$), enterococci ($P = 0.33$) and other bacteria ($P = 1.00$) (Table 3). There was however a tendency towards more polymicrobial cultures in the RA group (14 versus 7%, $P = 0.11$). Nor was there any statistically significant difference in the frequency of infections in which no bacteria were detected in the culture ($P = 0.42$). Causative microbes, potentially of oral or dental origin, were found in 12 (4%) of the OA and in none of the RA patients ($P = 0.13$, Table 3).

5. Discussion

We found no statistically significant differences in the bacterial findings of infected THRs in RA compared to OA patients. Staphylococci were found in more than half (59.5%) of the positive cultures as reported by others [7, 34].

Mixed or polymicrobial infections had, however, a tendency to be more frequent in the RA group. This finding is in agreement with previous knowledge of wound infections in immune-altered hosts, in whom polymicrobial micro flora is more frequently seen, as for example, in patients with diabetes mellitus [35]. Furthermore, our finding of a high percentage of culture negative infections (31–37%) are caused by prior courses of antimicrobial therapy, inappropriate (handling of the) samples or wrong diagnosis.

Another finding in the present study was a tendency towards a higher frequency of *S. aureus* than, for example, CoNS in RA patients compared to OA patients, although the percentage of infections caused by *S. aureus* was not as high as 37%, reported by Berbari and coworkers, but in their study knee as well as hip replacements were included [10]. In the NAR we have no data on revisions for (early) infections in which no implant parts were exchanged or removed. Thus we may have missed some early infections which are frequently caused by virulent bacteria such as *S. aureus*.

Eight of the nine *S. aureus* infections (analyses not shown) found in the RA patients in the present study were late infections, that is, revised more than 3 months postoperatively. RA patients have previously been shown to be more prone to late infections [9, 36, 37]. These late, potentially blood-borne infections have, according to Maderazo et al. [38], skin and soft tissue as the most common remote sites of infection. *S. aureus* is generally considered unlikely to originate from the mouth and were consequently not included in the group of bacteria of potentially oral or dental origin, in our study. Several authors however advocate the possibility of *S. aureus* originating from the mouth [39, 40]. Particularly acute or chronic dental infections might increase the possibility of culturing Staphylococci species [39].

In the present study we found no significant difference in the occurrence of microbes potentially of oral or dental origin in RA patients compared with OA patients, and the numerical difference between the groups favoured patients with RA among whom no patient had such a microorganism cultured (as opposed to 12 OA patients). Consequently, our findings do not support guidelines that RA patients are high risk patients particularly vulnerable to PJIs caused by microorganisms after transient bacteremia during dental procedures. The findings are in agreement with the existing policy in Norway which has been that RA patients with THR are not given prophylactic antibiotics before dental treatment.

A strength of this study is that it includes data selected from a national registry comprising an entire country (4.8 million inhabitants) over a period of more than 20 years. Data completeness for hip replacements has been shown to be very good, even for revision operations [41]. Although a large RA cohort has been studied previously (200 infection episodes, Berbari et al. [10]), our material is unique in terms of the comparison of microbiology in one of the largest cohorts of RA and OA patients. A drawback is the insufficient statistical power of the study. A *P* value in the nonsignificant range can either reflect an actual lack of difference between the patient groups or that there are too few observations to demonstrate such a difference, if existent. Reported findings should be interpreted with this in mind. Our power calculation was based on the findings of Berbari et al. [10] In their material of 200 infection episodes from the prebiological agents era 37% *S. aureus* was seen in PJIs in patients with RA. We found only 18% *S. aureus* in our material and consequently, there were too few infection episodes in our RA patients to detect a statistically significant difference for *S. aureus* (if present). On the other hand our material is, to our knowledge, one of the largest microbiological materials including and comparing RA and OA patients. Another drawback is the large number of infection episodes with missing or wrong data (228 of 730). Although not analysed, we have no reason to believe that these exclusions represent any kind of selection bias.

Furthermore, patients with PJIs treated solely by conservative means or those treated with limited surgical procedures (not involving removal or exchange of prosthetic parts) were not reported to the registry, and thus were not evaluated in this study.

Finally, we had no information on the patients' medication, which might have had an influence on the microbiology. For instance, immune-modulating antirheumatic medication may increase the risk of infection caused by low-virulent microbes.

6. Conclusion

We found no differences in the microbiology of infected THRs in RA patients compared to OA patients. There tended to be an increased risk of PJIs caused by *S. aureus* in RA patients, but we did not confirm the high rates of *S. aureus* previously reported in RA. Whether or not there is reason to advise the use of intranasal mupirocine ointment perioperatively as prophylactic strategy against *S. aureus* in PJI's may still be a matter of discussion, but we found no reason to treat the RA group differently in this respect. Furthermore, RA patients seemed less, rather than more, prone to PJIs caused by potentially oral or dental microbes when compared to OA patients. Consequently we cannot, on the basis of our findings, recommend a different policy regarding antibiotic prophylaxis prior to dental treatment in RA patients. RA patients should be individually evaluated with particular emphasis on the patient's comorbidities and medication [25–27]. We advise to continue the common praxis in Norway not giving routinely antibiotic prophylaxis before dental procedures.

Ethical Approval

The study with patient identifiable data was approved by the Regional Committee for Medical Research Ethics, Oslo, Norway (number 2009/856b).

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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

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Abstract

Objectives: The major objective of the present study was to investigate the risk of revision for infection after primary total hip replacements (THRs) in patients with rheumatoid arthritis (RA) during a 16-year period. We compared RA patients with osteoarthritis (OA) patients in order to detect any differences in the risk of revision for infection and to compare change over time in this risk for the two patient groups. Furthermore, we studied the time from primary implantation to revision for infection in the two groups and evaluated the THRs fixed with antibiotic-loaded cement and the uncemented THRs separately.

Methods: We identified 13,384 THRs in RA patients and 377,287 THRs in OA patients from 1995 to 2010 in a dataset of the Nordic Arthroplasty Register Association (NARA). Kaplan-Meier survival curves, with revision for infection as the endpoint, were constructed. Cox regression analyses were performed to calculate the relative risk (RR) with 95% confidence interval (CI) 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: Overall, 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 compared to OA patients with THRs fixed with antibiotic-loaded cement.

Conclusion: Overall, we found a slightly higher risk of revision for infection in RA compared to OA patients, but this difference was only present after 2001. In antibiotic-loaded cement THRs the risk of very early and late infections leading to revision was greater in RA than in OA patients.

Introduction

Rheumatoid arthritis (RA) patients are particularly vulnerable to infections due to the nature of the disease (immunopathy and ongoing inflammation), general disability, comorbidity and medication. [1, 2] The increasing use of immune modulating agents, particularly biologic agents, in the treatment of RA during the last decade may have increased this risk of infection. [3-5] RA often leads to joint destruction and thus patients with RA are at risk of eventually needing joint surgery, especially joint replacement surgery. Before biologic agents were used, around 25% of all RA patients with 16-20 years of observation needed at least one large joint replacement. [6, 7] Around 2-3% of all total hip replacements (THRs) in the NARA dataset were performed on RA patients. [8, 9]

Deep infection with subsequent revision of the implant is a feared but rare complication after joint replacement surgery. The frequency of prosthetic joint infection is reported to be as low as 1-2% after hip or knee replacements [10], and of surgical revision due to infection

even lower. [11-13] In a previous study from the Norwegian Arthroplasty Register of RA patients with THR, the risk of revision for infection was similar to that of OA patients within 6 years of primary THR, whereas there was an increased risk of revision for infection from 6 years postoperatively for RA compared to patients with osteoarthritis (OA). The overall risk of revision for infection did not differ between the two diagnostic groups. [13]

The collaboration between the Nordic arthroplasty registers, the Nordic Arthroplasty Register Association (NARA), has resulted in a large THR dataset. [8, 14] This dataset gives the opportunity to study rare events in selected patient groups, such as revision due to infection after THR in patients with RA.

The main objective of the present study was to estimate the risk of revision for infection after primary THR in RA patients compared to patients with OA. Further aims were to evaluate risk factors of revision for infection and study the impact of the time span from primary THR to revision.

Patients and methods

The Danish Hip Arthroplasty Register was established in 1995, [15] the Finnish Hip Arthroplasty Register in 1980, [16] the Norwegian Hip Arthroplasty Register in 1987 and the Swedish Hip Arthroplasty Register in 1979. [17, 18] Denmark, Finland, Norway and Sweden have similar health care systems, personal identity numbers and census registers. This enables combination and comparison of the arthroplasty registers. The collaboration of the registers, the Nordic Arthroplasty Register Association (NARA), was thus established in 2007. [8, 14] For the present study we defined a common set of parameters, containing only data that all registers could provide, and we reached a consensus on the definition of several variables. From 1995 to 2010 a total of 390,671 primary THRs with the diagnoses RA or OA were identified in the NARA and included in the study. Bilateral THRs were treated as two independent observations since bilaterality has been shown to have a negligible influence on the risk of revision for infection. [11] The outcome measure of the study was revision for infection following primary THR and only infections leading to revision of the prosthesis (removal or exchange of prosthesis parts) were included, since minor soft-tissue procedures were not reported to all national registers.

First we compared the overall risk of revision for infection after primary THR in patients with RA to those with OA during 1995-2010 (Figure 1).

We then evaluated the potential influence of biologic drugs on the infection risk in patients with RA. Since we had no data on drug use in these patients, the risk of revision for infection was analysed in two different time periods; from 1995 to 2001, and from 2002 to 2010. TNF-alpha inhibitors were introduced as treatment for RA in a few patients in Denmark, Finland, Norway and Sweden in 1999/2000. [19-21] From 2000, the use of TNF-alpha inhibitors increased steadily. [19, 21] Using 2001 as the cut-off, we attempted to divide the patients into one group (n=6,337) (2002-2010) in which a considerable proportion of RA patients (20-30%) received biologic treatment and one group (n=7,047) (1995-2001) in which few or no RA patients had

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such treatment. [22] RA and OA patients were compared in the two time periods, and the risk of revision for infection in the two diagnostic groups was compared in order to evaluate the possible influence of important changes in medical treatment in the second time period. Finally, separate analyses were performed for the evaluation of fixation method in THR.

Statistics

Survival analyses with revision for infection as the end point were performed for the total study population, for the THRs in RA and OA separately. A revision of the implant was defined as the surgical removal or exchange of the whole or any part of the implant. Follow-up was calculated from primary THR until first revision for infection or until the patient was censored at death or emigration, until date of revision if the THR was revised for other causes than infection, or until the end of the period studied on December 31, 2010. Survival curves were generated using the Kaplan-Meier method. Cox regression analyses were performed to estimate the relative risk (RR with 95% confidence interval) of revision for infection adjusted for age (continuous), sex, year of primary surgery and method of fixation (Table 2). The RR is an estimate of the relative difference in revision risk between the groups at any given time throughout the observation period and all given RRs are adjusted estimates. Additional Schoenfeld residual analyses were performed to detect any changes in revision risk with increasing time since the primary surgery, in uncemented THRs and where antibiotic-loaded cement was used, comparing RA and OA patients (Figures 3 and 4). Adjusted RR estimates were further established for predefined follow-up intervals, i.e. the first 3 months, 3 months-2 years, 2-8 years and longer than 8 years, using an extended Cox model including time-dependent covariates. This largely follows the widely used Coventry's prosthetic joint infection classification into early (<3 months), delayed (3 months-2 years) and late (>2 years) infections. [23] The cut-off at 8 years was based on an examination of the course of the curve in Figure 4. P-values of 0.05 or less were considered statistically significant. The statistical analysis was performed using the statistical software programmes SPSS, version 20.0 (SPSS, Chicago, IL), and the R statistical software package (version 3.0.2). [24]

Results

Patient characteristics are given in Table 1. Patients with OA were on average older than the RA patients. We found no important difference in mean age for the two diagnostic groups when comparing the two time periods (mean age for RA patients 61 and 62 years in the first

and second period, respectively, and unchanged at 69 years in OA patients). In our study no influence of increasing age on the risk of revision for infection was found (Table 2).

Overall results RA versus OA

Of the 390,671 THRs included, 2,315 were revised for infection, of which 2,228 were OA patients and 87 were RA patients. The incidence of revision for infection was 0.6% in OA patients and 0.7% in RA patients. The overall risk of revision for infection was higher in RA patients than in OA patients (RR 1.3 (1.0-1.6), Table 2 and Figure 1). Men had a significantly higher risk of revision for infection compared to women (RR 1.9 (1.8-2.1)).

Infection risk associated with RA according to time of primary surgery

For all patients and within both RA and OA, the risk of revision for infection in the second period (2002-2010) was significantly higher than in the first period (1995-2001) (RR 1.4 (1.3-1.6), Table 2, Figure 2). For both diagnoses this increase in infection risk was significant. In the first period the risk of revision for infection was no higher for RA patients than for OA patients (RR 1.1 (0.8-1.5) Figure 2, Table 3) whereas in the second period RA patients showed a higher risk of revision for infection than OA patients (RR 1.4 (1.0-1.8) Figure 2, Table 3).

Impact of fixation mode

There was no difference in frequency between the RA and OA groups in terms of method of implant fixation (cemented, hybrid, cementless, Table 1). A higher risk of revision for infection was seen in THRs where cement without antibiotics was used compared to THRs with antibiotic-loaded cement (RR 1.4 (1.2-1.6) Table 2). Additional analysis also revealed a higher risk of revision for infection in THRs with cement without antibiotics compared to uncemented THRs (RR 1.5 (1.2-1.8)).

Adjusted RR estimates for predefined follow-up intervals revealed a trend towards higher risk of revision in the RA group than the OA group for uncemented THRs, throughout the study period (Figure 3). For the antibiotic-loaded cement group a higher relative risk of revision for infection was observed for RA patients compared to OA patients during the first 3 postoperative months (RR 1.8 (1.1-3.0, p=0.01)), and after 8 years (RR 2.7 (1.2-6.3, p=0.02), Figure 4).

Discussion

One finding of the present study was an increased risk of revision for infection in RA compared to OA patients. This was not found in a previous publication from the Norwegian Arthroplasty Register. In that study the RA population was considerably smaller (n = 4,167, with only 25 patients revised for infection). [13] However, the current finding has been confirmed in other publications. [25-27] Furthermore, in a previous study total knee replacements (TKR) were included as well as THR and a significantly higher risk of revision for

infection of TKR was seen in RA patients compared to OA patients. [13]

Another finding was the increased risk of revision for infection from the first to the second time period demonstrated in both patient groups. This has previously been shown and discussed in a recent paper on infection in THRs from the NARA dataset by Dale et al. [11]

More revisions for infection in RA patients in 2002-2010

We found that the difference in risk of revision for infection between RA and OA patients emerged after 2002. In the period 1995-2001 no difference was seen. A general development towards accepting patients with more comorbidity for THR surgery may have taken place during the study period, but we have little reason to believe this to have occurred to a greater extent in the RA population than in the OA population. It has been shown that the use of joint replacement surgery in RA patients has declined during recent years [28, 29] and those still needing such treatment would be patients with a long disease duration or non-responders to treatment, who may have particularly high disease activity. The latter group would have an increased risk of infection in general [30] due to ongoing inflammation. Furthermore, the use of steroids would probably be greater in this group, possibly contributing to the increased infection risk. [31] Another possible reason for the increased risk of revision for infection among RA patients in the latter period is the use of immune modulating biologic drugs, although studies on the impact of these drugs in the context of joint replacement surgery have so far been conflicting. [32-41]

A change in treatment strategy of RA with early intensive treatment aimed at remission was adopted during the last study period. [42, 43] Superior results have been shown with this strategy but patients generally use higher doses of Methotrexate and are often on combination regimes (with or without biologic drugs and/or steroids); this might have led to a greater impairment of the immune system, rendering patients more susceptible to prosthetic joint infection.

A 40% (RA 2002-2010: RR 1.4, Table 3) increase in risk of revision for infection for RA versus OA in 2002-2010 of an already uncommon outcome (0.6% revision for infection in our study) still renders the absolute risk low.

Many factors influencing the risk of infection leading to revision (treatment policy, operating technique, diagnostics, awareness, etc.) may have changed over time. The possible changes in these factors are unlikely to differ between RA and OA patients undergoing THR. By comparing RA to the large OA group we sought to control for these factors, when evaluating the risk of revision for infection in the two time periods. We studied here the possible influence of the changed medical treatment of RA over time on the risk of revision for infection.

Impact of fixation mode

Another finding of this study was that in RA patients with antibiotic-loaded cement, no difference in revision risk compared to OA patients was seen (except for the first three months) until an increased risk was evident in RA patients from 8 years postoperatively (Figure 4). It seems as if the antibiotics protected the THRs in RA patients against infection during the period from 3 months till 8 years postoperatively. This concurs with the findings of Josefsson et al. that gentamicin-loaded cement is effective in infection prophylaxis for longer than 5 years but shorter than 10 years postoperatively. [44]

After 8 years the risk of revision for infection increases in the RA patients, probably because of the higher susceptibility to blood-borne infections connected to the diagnosis and possibly due to the immune modulating medical treatment. [45, 46] Not only the extra volume but probably also the surface properties regarding bacterial adherence and colonization of the now inactive bone cement might reinforce this susceptibility .[47] There may also have been a selection of low-risk RA patients for uncemented THRs, which could explain the difference between the uncemented and antibiotic-loaded cement THRs in risk of revision in the first 3 months postoperatively.

Strengths and weaknesses

A strength of this study is that it was based on a population of about 25 million inhabitants in 4 countries, with high data completeness and coverage in the registers. [48-50] The positive predictive value of the registered RA diagnosis is also high. [49] Consequently, the population of THR patients was large, rendering a large cohort of RA patients with THRs for the evaluation of prosthetic joint infections, a rare complication. Furthermore, this register-based study enables a long follow-up period which would be difficult in e.g. an RCT.

Some limitations of the study have to be considered. We lack information as to what medical treatment was used in the individual patient. We may only assume that patients in this study were treated in accordance with the recommendations for patients with RA at the time. [51] In addition, the number of revisions for infections performed in RA patients was relatively low (n = 87 in 13,384 RA patients) but even so, our material on hip replacements in RA patients is among the largest published. We lack information on comorbidity prior to THR, which is well known to differ between RA and OA patients and may affect the risk of revision due to infection following THR. [52] However, we have no reason to believe that this difference has changed over time. If there is any difference, we might expect a reduction in comorbidity with time in RA patients due to improved medical treatment.

In conclusion, we found an increased risk for revision caused by prosthetic joint infection in patients with RA compared to those with OA. The difference was only present from 2002. The increased risk of revision for infection in RA coincided with the introduction and increased use of TNF-α inhibitors, but other factors may also have contributed. For THRs with antibiotic-loaded cement an increased risk of very early and late infections leading to revision was seen in RA patients compared to OA patients.

Table 1. Patient characteristics

		RA	OA	P
Number of THRs		13,384	377,287	
Mean age (SD), in years		62.3 (13.9)	69.3 (9.6)	<0.001
% females		76%	60%	<0.001
Number primary THRs	1995-2001	7,047	130,613	
	2002-2010	6,337	246,674	<0.001
Type of fixation	Cemented n	8,633 (65%)	245,464 (65%)	
	Uncemented n	3,034 (23%)	83,547 (22%)	
	Hybrid* n	1,143 (8.5%)	31,619 (8.4%)	
	Inverse hybrid n	574 (4.3%)	16,657 (4.4%)	0.33
Mean follow up (SD), in years		7.0 (4.3)	6.1 (4.1)	<0.001

*Hybrid: cemented stem and uncemented cup

Table 2. Relative risk of revision for infection according to gender, age, diagnosis, year of surgery and type of fixation, calculated using Cox regression analysis.

		Revisions (n)	RR	95% CI	p
Age		2,315	1.0	0.99-1.01	0.12
Gender	Female	1,044	1		
	Male	1,271	1.9	1.8-2.1	<0.001
Diagnosis	OA	2,228	1		
	RA	87	1.3	1.0-1.6	0.04
Year of primary surgery	1995-2001	858	1		
	2002-2010	1,457	1.4	1.3-1.5	<0.001
Fixation	AB+ cement*	1,632	1		
	Uncemented	490	0.9	0.8-1.0	0.12
	AB- cement*	193	1.4	1.2-1.6	<0.001

*AB+ cement is antibiotic-loaded cement. AB- cement is cement without antibiotics.

Table 3. Relative risk of revision for infection according to age, gender and type of fixation for both diagnoses and time periods, calculated using Cox regression analysis.

	Revisions (n)	RR	95% CI	p
RA 1995-2001	44	1		
RA 2002-2010	43	1.9	1.2-3.1	0.006
OA 1995-2001	814	1		
OA 2002-2010	1,414	1.4	1.3-1.5	<0.001
OA 1995-2001	814	1		
RA 1995-2001	44	1.1	0.8-1.5	0.52
OA 2002-2010	1,414	1		
RA 2002-2010	43	1.4	1.0-1.8	0.05

Figure 1. Kaplan-Meier failure curves with revision for infection as the endpoint for rheumatoid arthritis (RA) and osteoarthritis (OA) patients.
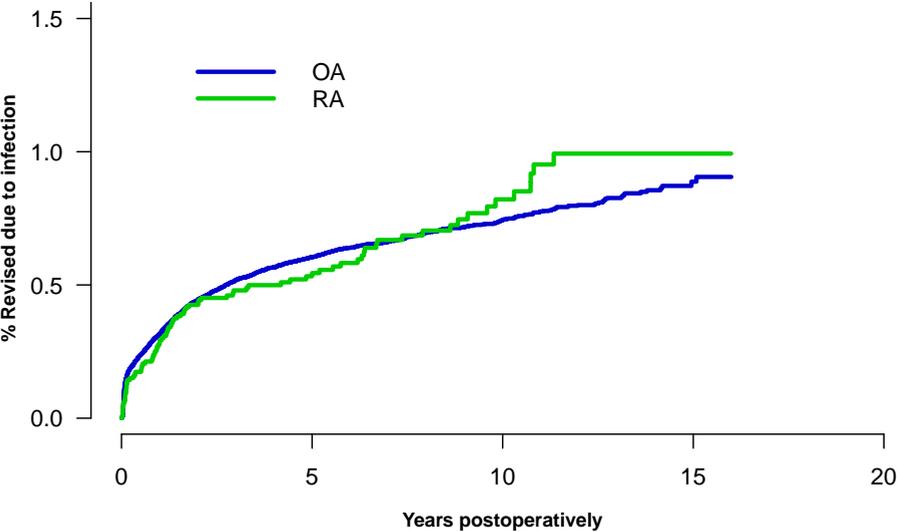
Figure 2. Kaplan-Meier failure curves for rheumatoid arthritis (RA) and osteoarthritis (OA) patients in the periods 1995-2001 and 2002-2010 with revision for infection as the endpoint.
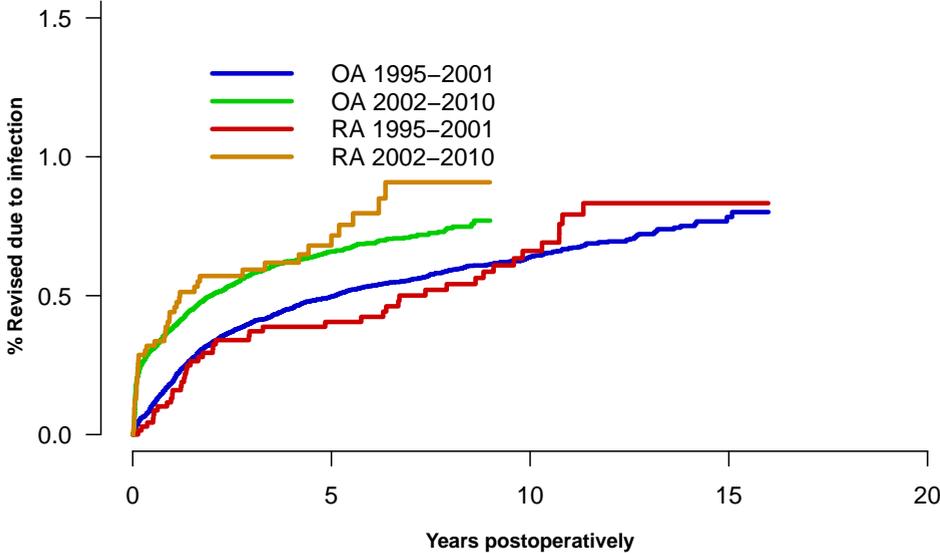
Figure 3. Uncemented total hip replacements. Log relative risk (RR) estimates of revision for infection in patients with rheumatoid arthritis (solid line) versus osteoarthritis (0-line, reference) are shown by year after the primary surgery. Broken lines show the 95% confidence intervals. (22 revisions for infection in RA)
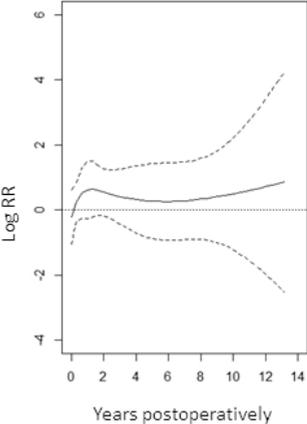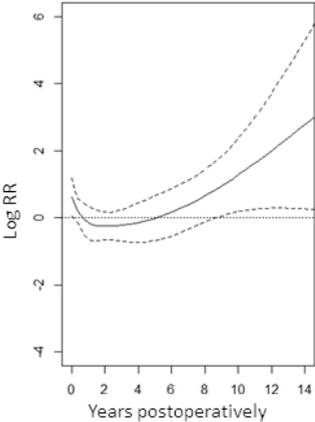

Figure 4. Total hip replacements with antibiotic-loaded cement as fixation. Log relative risk (RR) estimates of revision for infection for patients with rheumatoid arthritis (solid line) versus osteoarthritis (0-line, reference) are shown by year after the primary surgery. Broken lines show the 95% confidence intervals. (55 revisions for infection in RA)

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