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ORIGINAL ARTICLE

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 replacements 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,

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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 ± SD years	64 ± 14	71 ± 9	< 0.001*
Women, %	73	69	< 0.001†

* Calculated by the Student's *t*-test.
† Calculated by the chi-square test.

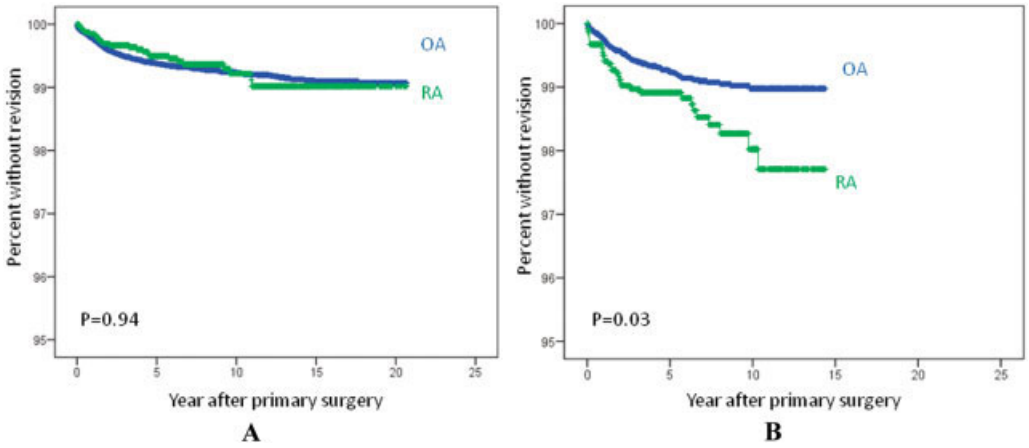

Figure 1. **A**, Kaplan-Meier survival curves for total hip replacement (1987–2008), and **B**, Kaplan-Meier survival curves for total knee replacement (1994–2008), with revision for infection as the end point. *P* values were obtained from Cox regression analyses with adjustment for age, sex, and year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

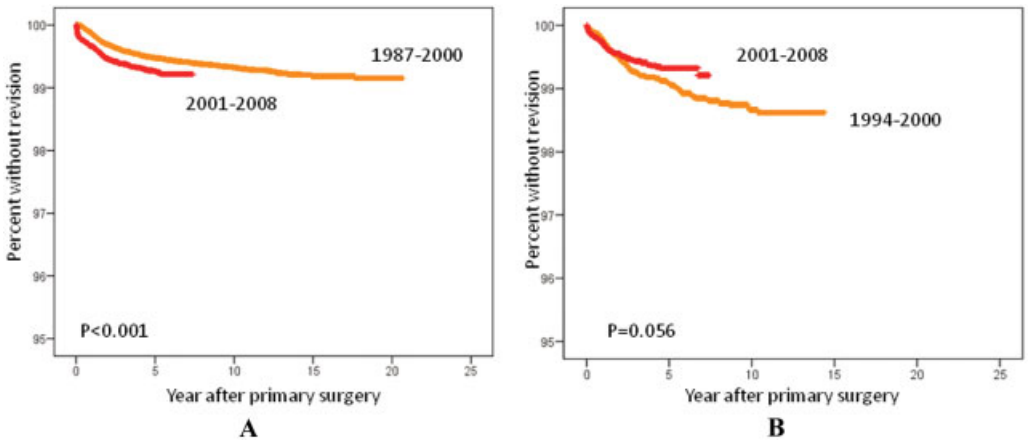

Figure 2. **A**, Kaplan-Meier survival curves of all patients with total hip replacement in the period 2001–2008 versus 1987–2000, and **B**, Kaplan-Meier survival curves of all patients with total knee replacement in the period 2001–2008 versus 1994–2000, with revision for infection as the end point. *P* values were obtained from Cox regression analyses with adjustment for age, sex, and diagnosis.

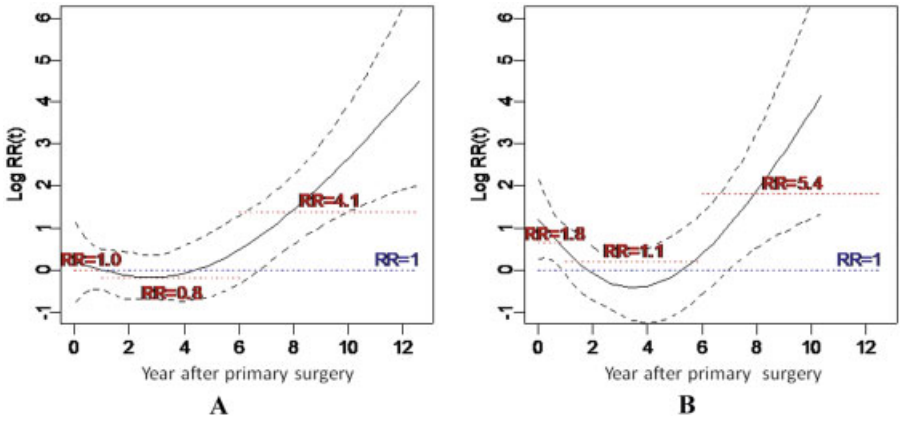

Figure 3. A, Total hip replacement (1994–2008), and **B**, total knee replacement (1994–2008). Log relative risk (RR) estimates of revision for infection for patients with rheumatoid arthritis versus osteoarthritis are shown by year after the primary surgery. Broken lines show the 95% confidence intervals. 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.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Schrama had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Schrama, Fevang.
Acquisition of data. Schrama, Espehaug, Fevang.
Analysis and interpretation of data. Schrama, Espehaug, Hallan, Engesæter, Furnes, Havelin, Fevang.

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