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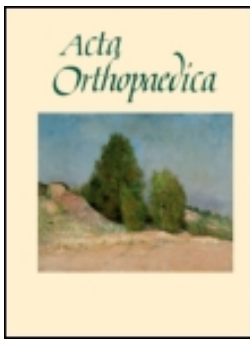
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Increased risk of revision for infection in rheumatoid arthritis patients with total hip replacements

A study of 390,671 primary arthroplasties from the Nordic Arthroplasty Register Association

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Background and purpose — Medical treatment of rheumatoid arthritis (RA) has changed dramatically over the last 15 years, including immune modulation. We investigated the risk of revision for infection after primary total hip replacement (THR) in patients with rheumatoid arthritis over a 16-year period, and compared it with that in THR patients with osteoarthritis (OA).

Patients and methods — We identified 13,384 THRs in RA patients and 377,287 THRs in OA patients from 1995 through 2010 in a dataset from 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) of revision for infection adjusted for age, sex, fixation technique, and year of primary surgery.

Results — RA patients had a 1.3 times (95% CI 1.0–1.6) higher risk of revision for infection. After 2001, this risk 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 fixated with antibiotic-loaded cement than in corresponding OA patients.

Interpretation — We found a slightly higher overall risk of revision for infection in RA patients than in OA patients, but this difference was only present after 2001. In THRs with antibiotic-loaded cement, the risk of very early and late infections leading to revision was higher in RA patients than in OA patients.

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 (Mutru et al. 1985, Doran et al. 2002). The increasing use of immune-modulating agents, particularly biologics, in the treatment of RA during the last decade may increase this risk of infection (Bongartz et al. 2006, Winthrop et al. 2008, Komano et al. 2011). RA often leads to joint destruction, so patients with RA are at risk of requiring joint replacement surgery. Before biologics were used, around 25% of all RA patients with 16–20 years of observation needed at least 1 large joint replacement (Wolfe and Zwillich 1998, Kapetanovic et al. 2008). Around 2–3% of all total hip replacements (THRs) in the Nordic Arthroplasty Register Association (NARA) dataset have been performed on RA patients (Havelin et al. 2009, Makela et al. 2014b).

The frequency of prosthetic joint infection is reported to be as low as 1–2% after hip or knee replacement (Zimmerli et al. 2004), and the frequency of surgical revision due to infection is even lower (Pedersen et al. 2010, Schrama et al. 2010, Dale et al. 2012). In a previous study of RA patients with THRs from the Norwegian Arthroplasty Register, the risk of revision for infection was similar to that in osteoarthritis (OA) patients within 6 years of primary THR, whereas there was a higher risk of revision for infection in RA patients than in patients with OA from 6 years postoperatively. The overall risk of revision for infection was not significantly different in the 2 diagnostic groups (Schrama et al. 2010).

Knowing that treatments for RA patients have improved dramatically in the last 10–15 years, we found it important to assess whether there is increased infection risk, which would require a large patient population to be followed over a long period. The collaboration between the Nordic arthroplasty registers—in the form of the NARA—has resulted in a large dataset on THR (Havelin et al. 2009, Makela et al. 2014a). 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.

Based on what we know about increased infection risk associated with immunosuppressive treatments in general, we hypothesize that the new aggressive treatment strategies for RA that have evolved over the last decades including higher doses (e.g. of methotrexate), frequent use of combination regimes (e.g. methotrexate, hydroxychloroquine, and sulfasalazine), and the use of biologics, may make the patients more susceptible to infections—in this case, prosthesis infections.

The main objective of our study was therefore to estimate the risk of revision for infection after primary THR in RA patients relative to that in patients with OA, to evaluate whether today's RA patients are at greater risk of prosthesis infection. We also wanted to evaluate risk factors for revision because of infection and to study the effect of the length of time from primary THR to revision.

Patients and methods

The Danish Hip Arthroplasty Register was established in 1995 (Lucht 2000), the Finnish Hip Arthroplasty Register in 1980 (Paavolainen et al. 1991), the Norwegian Hip Arthroplasty Register in 1987, and the Swedish Hip Arthroplasty Register in 1979 (Havelin et al. 2000, Malchau et al. 2002). Denmark, Finland, Norway, and Sweden (with 25 million inhabitants) have similar healthcare systems, personal identity numbers, and census registries. This enables combination and comparison of the arthroplasty registries. The collaboration between the registries, the NARA, was established in 2007 (Havelin et al. 2009, Makela et al. 2014a). For the present study, we defined a common set of parameters containing only data that all the registries could provide, and we reached a consensus on the definition of several variables. In all the registries, reporting of infection as the cause of revision reflects the surgeon's opinion based on clinical information and findings at surgery. The data are not edited according to postoperative culture results. From 1995 through 2010, a total of 390,671 primary THRs with the diagnoses RA or OA were identified in the NARA and included in the study (Table 1). Bilateral THRs were treated as 2 independent observations, since bilaterality has been shown to have a negligible influence on the risk of revision for infection (Lie et al. 2004, Ranstam and Robertsson 2010, Dale et al. 2012). The primary outcome measure

Table 1. Patient characteristics

	RA	OA	p-value
No. of THRs	13,384	377,287	
Mean age (SD), years	62 (14)	69 (9.6)	< 0.001
% females	76%	60%	< 0.001
No. of primary THRs			< 0.001
1995–2001	7,047	130,613	
2002–2010	6,337	246,674	
Type of fixation, n (%)			0.3
Cemented	8,633 (65)	245,464 (65)	
Uncemented	3,034 (23)	83,547 (22)	
Hybrid ^a	1,143 (8.5)	31,619 (8.4)	
Inverse hybrid	574 (4.3)	16,657 (4.4)	
Mean follow-up (SD), years	7.0 (4.3)	6.1 (4.1)	< 0.001

^a Hybrid: cemented stem and uncemented cup.

was revision for infection following primary THR and only infections leading to revision of the prosthesis (removal or exchange of prosthetic parts) were included, since minor soft-tissue procedures were not reported to all national registries.

Firstly, we compared the overall risk of revision for infection after primary THR in patients with RA to that in patients with OA during 1995–2010 (Figure 1). We then evaluated the potential influence of biologics 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 analyzed in 2 different time periods: from 1995 to 2001, and from 2002 to 2010. TNF- α inhibitors were introduced as treatment for RA in a few patients in Denmark, Finland, Norway, and Sweden in 1999–2000 (Hjardem et al. 2005, Nordstrom et al. 2006, Soderlin and Geborek 2008). From 2000, the use of TNF- α inhibitors increased steadily (Hjardem et al. 2005, Soderlin and Geborek 2008). Using 2001 as the cutoff, we attempted to divide the patients into 1 group (n = 6,337) (2002–2010) in which a considerable proportion of RA patients (20–30%) (Kvien et al. 2005) received treatment with biologics and 1 group (n = 7,047) (1995–2001) in which few or no RA patients had such treatment. RA and OA patients were compared in the 2 time periods, and the risk of revision for infection in the 2 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 evaluation of the prosthetic fixation method on revision rate.

Statistics

Survival analyses with revision for infection as the end point were performed for the total study population and for the THRs in RA patients and OA patients separately. Revision of the implant was defined as surgical removal or exchange of the whole or any part of the implant. Follow-up time was calculated from primary THR until first revision for infection, until the patient was censored at death or emigration, until date of

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

	No. of revisions	RR	95% CI	p-value
Age	2,315	1.0	0.99–1.01	0.1
Sex				
Female	1,044	1 (ref.)		
Male	1,271	1.9	1.8–2.1	< 0.001
Diagnosis				
OA	2,228	1 (ref.)		
RA	87	1.3	1.0–1.6	0.04
Year of primary surgery				
1995–2001	858	1 (ref.)		
2002–2010	1,457	1.4	1.3–1.5	< 0.001
Fixation				
AB+ cement ^a	1,632	1 (ref.)		
Uncemented	490	0.9	0.8–1.0	0.1
AB– cement ^a	193	1.4	1.2–1.6	< 0.001

^a AB+ cement: antibiotic-loaded cement. AB– cement: cement without antibiotics.

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% CI) 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 RRs given are adjusted estimates. We chose to adjust for age as a continuous variable as opposed to performing stratified analyses for age categories, due to the low number of events in the RA population. 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 (Figure 3). The hybrids and reverse hybrids were included in these analyses together with the fully cemented prostheses in the antibiotic-loaded cement group. Adjusted RR estimates were further established for predefined follow-up intervals, i.e. the first 3 months, 3 months to 2 years, 2 to 8 years, and longer than 8 years, using an extended Cox model including time-dependent covariates. This largely follows the widely used Coventry prosthetic joint infection classification into early infections (< 3 months), delayed infections (3 months to 2 years), and late infections (> 2 years) (Coventry 1975). The cutoff at 8 years was based on examination of the course of the curve in Figure 3B. Any p-values of 0.05 or less were considered to be statistically significant. The statistical analysis was performed using SPSS version 20.0 and the R statistical software package, version 3.0.2.

Revised for infection (%)

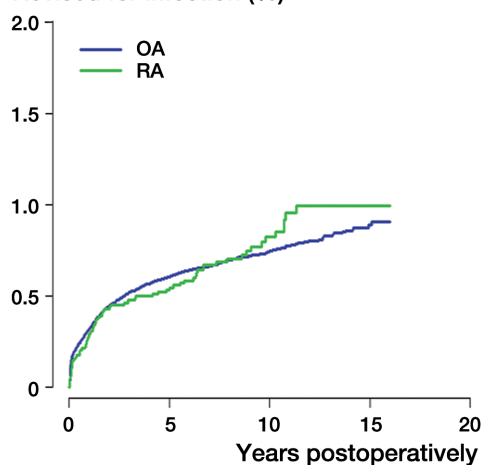


Figure 1. Kaplan-Meier failure curves with revision for infection as the endpoint for rheumatoid arthritis (RA) and osteoarthritis (OA) patients.

Results

Patients with OA were generally older than the RA patients. We found no important difference in mean age in the 2 diagnostic groups when comparing the 2 time periods (mean age for RA patients was 61 years in the first period and 62 years in the second, and in OA patients it was unchanged at 69 years). We found no influence of increasing age on the risk of revision for infection (Table 2).

Overall results for RA and OA patients

Of the 390,671 THRs included (377,287 in the OA group and 13,384 in the RA group), 2,315 were revised for infection. Of these revisions, 2,228 were in OA patients and 87 were in 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, 95% CI: 1.0–1.6) (Table 2 and Figure 1). Men had a statistically significantly higher risk of revision for infection than women (RR = 1.9, CI: 1.8–2.1).

Infection risk associated with RA according to time of primary surgery

For all patients and in both groups (RA and OA), the risk of revision for infection in the second period (2002–2010) was statistically significantly higher than in the first period (1995–2001) (RR = 1.4, CI: 1.3–1.6) (Table 2 and 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, CI: 0.8–1.5) (Figure 2 and Table 3) whereas in the second period, RA patients had a higher risk of revision for infection than OA patients (RR = 1.4, CI: 1.0–1.8) (Figure 2 and Table 3).

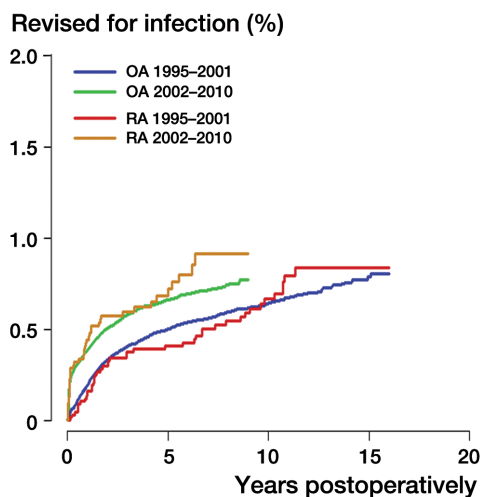


Figure 2. Kaplan-Meier failure curves for rheumatoid arthritis (RA) and osteoarthritis (OA) patients in the periods 1995–2001 and 2002–2010 with revision for infection as the end-point.

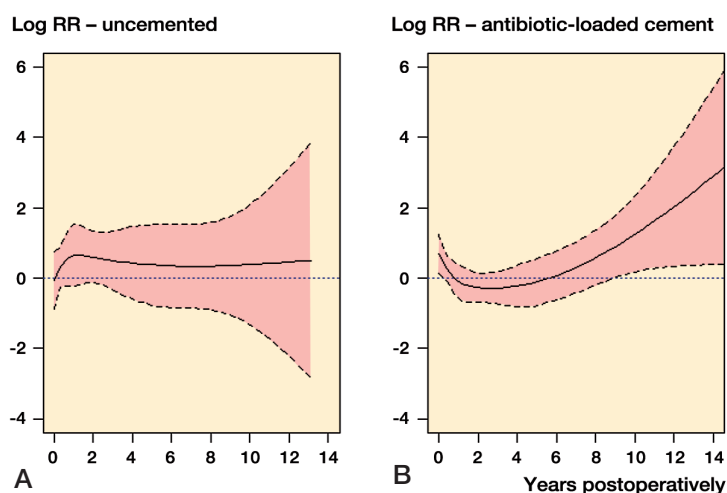


Figure 3. Log relative risk (RR) estimates of revision for infection in patients with rheumatoid arthritis (solid line) vs. osteoarthritis (0-line, reference) are shown by year after the primary surgery. Broken lines show the 95% confidence intervals. A. Uncemented total hip replacements with 22 revisions for infection in RA. B. Total hip replacements with antibiotic-loaded cement as fixation and 55 revisions for infection in RA.

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

	No. of revisions	RR	95% CI	p-value
RA 1995–2001	44	1 (ref.)		
RA 2002–2010	43	1.9	1.2–3.1	0.006
OA 1995–2001	814	1 (ref.)		
OA 2002–2010	1,414	1.4	1.3–1.5	< 0.001
OA 1995–2001	814	1 (ref.)		
RA 1995–2001	44	1.1	0.8–1.5	0.5
OA 2002–2010	1,414	1 (ref.)		
RA 2002–2010	43	1.4	1.0–1.8	0.05

Effect of mode of fixation

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

Adjusted RR estimates for predefined follow-up intervals revealed a trend of a higher risk of revision in the RA group than in the OA group for uncemented THRs, throughout the study period (Figure 3A). For the antibiotic-loaded cement group, a higher relative risk of revision for infection was found for RA patients than for OA patients during the first 3

postoperative months (RR = 1.8, CI: 1.1–3.0; $p = 0.01$), and after 8 years (RR = 2.7, CI: 1.2–6.3; $p = 0.02$) (Figure 3B).

Discussion

We found an increased risk of revision for infection in RA patients than in OA patients. This was not found in a previous publication from the Norwegian Arthroplasty Register (Schrama et al. 2010). In that study, the RA population was considerably smaller ($n = 4,167$, with only 25 patients revised for infection). However, the current finding has been confirmed in other publications (Fitzgerald et al. 1977, Poss et al. 1984, Bongartz et al. 2008). Furthermore, in a previous study, total knee replacements (TKRs) were included in addition to THRs and a higher risk of revision of TKRs for infection was seen in RA patients than in OA patients (Schrama et al. 2010).

Another finding was the increased risk of revision for infection from the first to the second time period in both patient groups. This has also been shown and discussed in a recent paper on infection in THRs from the NARA dataset by Dale et al. (2012).

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; no difference was seen in the period 1995–2001. A move towards accepting patients with more comorbidity for THR surgery may have taken place during the study period, but we have little reason to believe that this would have occurred to a greater extent in the RA population than in the OA popula-

tion. However, joint replacement surgery in RA patients has declined during recent years (Fevang et al. 2007, Jansen et al. 2013), and those still needing surgery 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 (Au et al. 2011), due to ongoing inflammation. Furthermore, the use of steroids would probably be greater in this group, possibly contributing to the increased infection risk (Akkara Veetil and Bongartz 2012). Another possible reason for the increased risk of revision for infection in 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 (Talwalkar et al. 2005, Wendling et al. 2005, Giles et al. 2006, den Broeder et al. 2007, Ruysen-Witrand et al. 2007, Gilson et al. 2010, Kawakami et al. 2010, Momohara et al. 2011, Suzuki et al. 2011, Berthold et al. 2013).

A change in strategy in treatment of RA with early intensive treatment aimed at remission was adopted during the last study period (Smolen et al. 2010a, Vermeer et al. 2011). 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 biologics and/or steroids). This might have led to greater impairment of the immune system, making patients more susceptible to prosthetic joint infection.

A 40% increase in risk of revision for infection in RA patients relative to OA patients (RR = 1.4, Table 3) in 2002–2010 of an already uncommon outcome (0.6% revision for infection in our study) still makes the absolute risk low.

Many factors that influenced the risk of infection leading to revision (treatment policy, operating technique, diagnostics, awareness, etc.) may have changed with time. The possible changes in these factors are unlikely to have differed between RA and OA patients undergoing THR. By comparing RA patients with the large OA group, we tried to control for these factors when evaluating the risk of revision for infection in the 2 time periods. We studied the possible influence of the changed medical treatment of RA over time on the risk of revision for infection.

Effect of mode of fixation

Another finding of this study was that in RA patients with antibiotic-loaded cement, no difference in revision risk was seen compared to OA patients (except for the first 3 months), until an increased risk was evident in RA patients from 8 years postoperatively (Figure 3B). It appears that the antibiotics protected the THRs in RA patients against infection during the period from 3 months to 8 years postoperatively, although we cannot explain why this would not also be the case during the first 3 months. Our results concur with the findings of Josefsson and Kolmert (1993) that gentamicin-loaded cement is effective in infection prophylaxis for longer than 5 years but shorter than 10 years postoperatively.

After 8 years, the risk of revision for infection increased 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 (Stinchfield et al. 1980, Ainscow and Denham 1984). 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 (Oga et al. 1988).

Strengths and limitations

One strength of our study was that it was based on a population of about 25 million inhabitants in 4 countries, with high completeness of data and coverage in the registries (Soderman et al. 2000, Pedersen et al. 2004, Espehaug et al. 2006). The positive predictive value of the registered RA diagnosis is also high (Pedersen et al. 2004). Consequently, the population of THR patients was large, giving a large cohort of RA patients with THRs for the long-term evaluation of the rare prosthetic joint infections.

Some limitations of the study must also be considered. We lack information on 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 (Smolen et al. 2010b). In addition, the number of revisions for infection performed in RA patients was low ($n = 87$ in 13,384 RA patients), but even so, our material on hip replacements in RA patients is among the largest published. Another limitation is that in a recent study from the Swedish Hip Arthroplasty Register, the completeness of reporting of early infection after THR was found to be 67% (Lindgren et al. 2014). However, we believe that the completeness of reporting is most likely the same for patients with different diagnoses. With the use of OA patients as controls, a difference detected between the 2 patient groups can be considered reliable. We lacked information on comorbidity before THR, which is well known to differ between RA and OA patients, and may affect the risk of revision due to infection following THR (Rud-Sorensen et al. 2010). 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. Finally, no information on antibiotic prophylaxis was included in the study. Such data have been shown to vary widely—within countries as well as between them. We cannot rule out the possibility of RA patients having different prophylactic antibiotic regimens from OA patients, although this is not the case in our department.

In conclusion, we found a higher risk of revision caused by prosthetic joint infection in patients with RA than in those with OA. The difference was only present from 2002 onward. The increased risk of revision for infection in RA patients coincided with a change in treatment strategy for these patients, with more aggressive immunomodulating therapy. For THRs

with antibiotic-loaded cement, a higher risk of very early and late infections leading to revision was seen in RA patients than in OA patients.

JCS, BTF, and AMF performed the analyses. JCS and BTF wrote the manuscript. All the authors contributed to interpretation of the analyses and to critical revision of the manuscript.

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No competing interests declared.

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