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Risk of medical complications following total hip or knee arthroplasty in patients with rheumatoid arthritis

A register-based cohort study from Denmark

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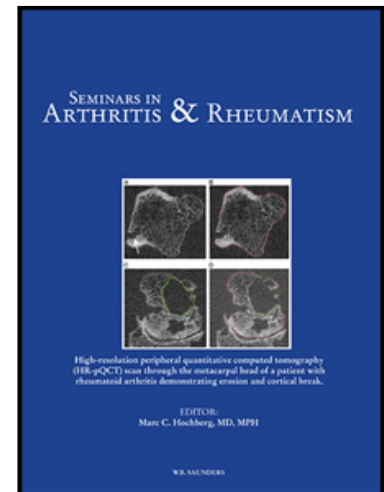
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Risk of Medical Complications following Total Hip or Knee Arthroplasty in Patients with Rheumatoid Arthritis: A Register-Based Cohort Study from Denmark

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Title:

Risk of Medical Complications following Total Hip or Knee Arthroplasty in Patients with Rheumatoid Arthritis: A Register-Based Cohort Study from Denmark

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Abstract (271 words):

Objective: To investigate the risk of medical complications following total hip and knee arthroplasty (THA/TKA) among rheumatoid arthritis (RA) compared with osteoarthritis (OA) patients; and, to assess the risk of complications among biologics-treated RA patients.

Methods: In a nationwide register-based study, patients with RA and OA with THA/TKA surgery between 2000 and 2015 were identified and followed up to 90 days after surgery for venous thromboembolism (VTE), myocardial infarction and stroke, and non-surgical infections, respectively. Information on treatment with biologics was obtained in the DANBIO rheumatology register to compare risks of complications with non-biologics treated.

Results: A total of 2,899 and 112,571 patients with RA and OA had THA/TKA. RA was associated with a hazard ratio (HR) of 1.29 (1.03 to 1.61) for infection following THA/TKA, but a HR of 0.60 (0.26 to 0.98) for VTE following TKA. Biologics treated patients had a HR of 1.35 (0.65 to 2.80) for infection and 4.82 (1.67 to 13.90) for VTE compared with non-biologics treated RA patients. RA patients had no increased risk of post-surgical myocardial infarction and stroke (HR 1.16, 0.76 to 1.78) compared with OA, but a higher incidence proportion was observed in biologics treated compared with non-biologics treated (1.0 vs 0.6 %); however, the number of events were too small to estimate a HR.

Conclusion: In this study, RA was a risk factor for infection after THA/TKA, and RA patients treated with biologics had a slightly increased risk compared with non-biologics treated RA patients. Compared with OA, RA patients had a lower risk of VTE following THA/TKA, but our finding of increased incidences of VTE in biologics-treated patients warrants further studies.

1. INTRODUCTION

In non-surgical settings, patients with rheumatoid arthritis (RA) are at increased risk of infections, myocardial infarction, stroke and venous thromboembolism (VTE) compared with the general population [1–6].

Total hip and total knee arthroplasty (THA/TKA) are regular procedures in patients with RA, and the increased risks of VTE, myocardial infarction and stroke, and infections could be further exacerbated following such major surgery.

Patients selected for treatment with biological DMARDs (biologics) are at increased risk of infections with a time-dependent risk peaking immediately following treatment commencement but subsequently decrease to the level of RA patients not treated with biologics [7–9]. Perioperative adverse events in users of biologics is a major concern and the scientific literature has not provided clear answers as to whether that concern should be merited, but recent studies indicate no clear increased risk of prosthetic joint infection and mortality in those exposed to these drugs prior to surgery [10–12]. However, very few have looked at the risk of other infections than prosthetic joint infection while at the same time adjusting for disease activity and glucocorticoids, the two other major confounders when assessing these relations. Likewise, the potential impact of biologics on the risk of VTE and other cardiovascular events in a surgical setting is unknown.

Thus, our aim was to investigate the risk of VTE, myocardial infarction and stroke, and non-surgical site infections in patients with RA who had THA/TKA surgery in a population-based nationwide cohort study. Further, we assessed the risk of complications among RA patients treated with biologics.

2. PATIENTS AND METHODS

2.1 Design and setting

This was a nationwide, register-based cohort study from Denmark, investigating the risk of serious medical complications following THA/TKA in patients with RA compared with OA; and, among biologics-treated patients compared with non-biologics treated RA patients. The study period ran from 2000 to the end of 2014. In Denmark healthcare is tax-funded and offers universal access for all residents, and unique personal identifiers assigned to all residents at birth or upon immigration allows for nationwide register-linkage. The study adheres to the STROBE guidelines [13].

2.2 Data sources and study populations

The Danish Hip and Knee Arthroplasty Registers (DHR and DKR) both hold detailed surgical information on > 96 % of primary THA and TKA surgeries performed in Denmark since 1995 and 1997, respectively [14–17]. Among individuals registered with a first primary THA or TKA in the DHR or DKR between 2000 and end of 2014 [14,15], patients with RA were identified by linkage with the DANBIO rheumatology register, and the Danish National Patient Register (DNPR) using validated algorithms (Supplementary Table 1) [18].

DANBIO is a nationwide register used by rheumatologists in routine care of rheumatic patients since 2000 [19]. Registered information includes but is not limited to clinical history and progress along with information on treatment series with biologics, conventional synthetic DMARDs, and glucocorticoids. In DANBIO, the positive predictive value of an RA diagnosis is 96 %. However, the registration of patients not treated with biologics did not become mandatory before 2006. Thus, in order to include patients not treated with biologics within the full study period, the DNPR was also used to identify RA patients. DNPR was established in 1977 and since 1995, all in- and outpatient hospital contacts have been registered [20]. One primary and up to 19 secondary

diagnoses are registered in accordance with the International Classification of Diseases 10th version (ICD-10). In addition, all surgeries and procedures performed during a contact are also registered.

We used a validated algorithm to identify RA patients in DNPR that were not registered in DANBIO: individuals were required to have at least two hospital contacts at a rheumatology or general internal medicine department listing RA as the main diagnosis and no more than 90 days apart. This algorithm has a PPV of at least 79 % [19].

The OA cohort comprised patients registered in DHR/DKR with OA listed as the main diagnosis and surgical indication, but with no previous RA diagnosis listed in DANBIO nor DNPR [21].

Biologics and non-biologics treated RA patients. We used information on start and stop dates for treatment episodes with biologics in DANBIO to identify patients treated with biologics within 90 days prior to surgery. Information was obtained in the same manner for pre-operative exposure to conventional DMARDs and steroid treatments in the 90-day presurgical window. Clinical information on RA disease activity score (DAS28) and physical function (HAQ-DI) registered within 180 days prior to surgery was obtained.

2.3 Outcomes

There were three outcomes of interest: VTE, myocardial infarction and stroke, and infections (non-surgical site). Outcome information was obtained in DNPR (Supplementary table 2 for ICD-10 codes). Most of these outcomes have been validated with PPVs of ~70-90 % [20,22]. The composite infection outcome included occurrences of pneumonia, sepsis, urinary tract infection, and erysipelas. If patients experienced more than one infection, only the first one counted in the composite analysis. We specifically investigated infections that were in no way related to the surgical procedure nor the prosthetic material as this was the subject of a previous publication in this study population [12].

2.4 Follow-up

We obtained vital status information from the Danish Civil Registration System [23]. For all 3 outcomes, follow-up was limited to the first 90 days after surgery. In each analysis, patients were followed from the date of surgery until date of outcome of interest, death, emigration or 90 days post-surgery, whichever occurred first.

2.5 Statistics

RA compared with OA. Hazard ratios (HR) with 95 % confidence intervals (95%CI) were estimated in a crude and two multivariable Cox models: Model 1 was stratified by sex and adjusted for age at surgery and calendar period of surgery, whilst Model 2 included the covariates of Model 1 and was further stratified by type of surgery (THA vs TKA) and adjusted for duration of surgery and comorbidities: history of chronic obstructive pulmonary disease (COPD), previous VTE, previous serious infections, cardiovascular disease (CVD), diabetes mellitus (DM) or cancer. Comorbidity information was obtained in DNPR using a 5-year lookback window for infections from the date of surgery and 10-year lookback windows for other comorbidities (Supplementary Table 3 for ICD-10 codes).

Biologics compared with non-biologics treated. The Cox proportional hazards model included only the biologics exposure covariate and the calculated propensity score (PS), i.e. the probability of receiving biologics conditional on confounders at the time of surgery, as a spline covariate with 5 degrees of freedom. Covariates used in calculation of the PS included: age at surgery, sex, calendar period of surgery, pre-operative use of methotrexate, pre-operative use of other conventional DMARDs, pre-operative use of glucocorticoids, DAS28, HAQ-DI, VAS physician, COPD, DM, CVD, previous VTE, cancer, and previous serious infection. Due to few events in the comparison of biologics with non-biologics treated patients, no additional confounders were included in the model.

Multiple imputation. Multiple imputation using chained equations (MICE) was undertaken to account for missing data in the perioperative window. Around 68 and 66 % had no information on DAS28 and HAQ-DI within 180 days prior to THA/TKA surgery. All covariates included in PS calculation were entered in the imputation model. Missing values of DAS28, HAQ-DI, tender and swollen joint count (using 28 joints), visual analogue scores (0-100) for physician assessment of overall disease burden, patient reported pain level, patient reported fatigue level, and CRP level were imputed using predictive mean matching. A total of 100 datasets were imputed and following Cox regression analyses within each dataset, the hazard ratios were combined according to Rubin's Rules. Statistical analyses were performed in R Statistical Software 3.2.3.

Sensitivity analyses. In analyses where the confidence interval did not cross unity, the E-value was calculated [24]. The E-value is a relatively new sensitivity measure that provides an estimate of the magnitude with which any unmeasured confounder would have to be associated with the outcome of interest in order to overcome or dismiss the exposure-outcome association of the presented analysis. It is a sensitivity analysis that requires no assumptions regarding the distribution of the confounder nor if it is a continuous or binary explanatory variable [25].

Due to the non-negligible proportion of DANBIO patients that had missing data on DAS28 and HAQ-DI, we carried out a sensitivity analysis in which these covariates were not included in the propensity score estimation, and subsequently carried out the Cox models estimating the impact of treatment with biologics adjusted for the spline of the propensity score.

3. RESULTS

RA compared with OA.

We identified 2,899 and 112,571 patients with RA and OA who underwent THA or TKA surgery (Supplementary Figure 1 for patient flow-chart). Patients with RA were younger at the time of surgery (66.1 vs 69.1 years), more likely to be female (73 vs 58 %) and have TKA rather than THA surgery (TKA: 63 vs 44 % of surgeries in RA compared with OA) (Table 1). In both cohorts, 99 % of patients received thromboprophylaxis with no difference in the duration of the therapy. RA patients more frequently had a history of COPD, cardiovascular disease including previous VTE events, and hospitalisations due to infection, whereas a higher proportion of OA patients had a history of cancer (Table 1).

Patients with RA had a lower risk of deep vein thrombosis and pulmonary embolism and consequently VTE (Table 2). This decreased risk was only driven by TKA surgery (HR_{TKA} 0.60, 0.26 to 0.98) (Supplementary Table 4). Excluding patients with a history of VTE, cancer or both did not substantially alter the HRs: 0.81 (0.56 to 1.18); 0.81 (0.56 to 1.17); and 0.89 (0.61 to 1.29), respectively. The decreased risk of VTE was more pronounced in male patients with RA (HR 0.48, 95%CI 0.2 to 1.17). The E-value for the association between RA and VTE following TKA was 2.73

The overall risk of post-surgical myocardial infarction and stroke was not increased among RA patients, but increased risk estimates were seen among female RA patients compared with OA (HR 1.53, 0.91 to 2.56).

Patients with RA had an increased risk of infection (HR_{Model2} 1.29, 1.03 to 1.64) driven by risks of pneumonia, sepsis and erysipelas but not urinary tract infection. This finding was consistent across both sexes and all age groups (Supplementary Table 4). The E-value for this association was 1.9.

Biologics compared with non-biologics treated RA patients.

A total of 411 patients received treatment with a biologic within 90 days preceding surgery (Table 3). No difference in DAS28 was observed prior to surgery, but biologics-treated had higher median HAQ-DI. Biologics treated more frequently had a history of hospitalisation due to infection, whereas they less frequently had a history of cancer compared with their non-biologics treated counterparts.

Following THA/TKA, biologics-treated had a higher incidence and risk of VTE compared with non-biologics treated (1.9 vs 0.5%; HR 4.82, 1.67 to 13.90) (Table 4). Excluding patients who had a history of cancer, VTE or either of the two, did not change the results: HRs 4.74 (1.64 to 13.75); 4.76 (1.65 to 13.72); and, 4.70 (1.62 to 13.61), respectively. The calculated E-value was 9.1 indicating that any unmeasured confounder would have to be associated with VTE at a relative risk of this magnitude to overcome the association between biologics treatment and VTE.

A higher proportion of biologics-treated also suffered a myocardial infarction or stroke compared with non-biologics treated (1.0 vs 0.6 %), but with < 5 events registered in one group (4 and 8, respectively), no hazard ratio could be estimated.

An increased risk of infection was observed among biologics treated compared with non-biologics treated patients (HR 1.35, 0.65 to 2.80). Excluding patients previously hospitalised due to infection did not alter the HR, 1.38 (0.61 to 3.12).

When omitting DAS28 and HAQ-DI from the propensity score estimation, the subsequent Cox models for VTE and infection resulted in HRs of 6.39 (95% CI 2.12 to 19.30) and 1.10 (95% CI 0.52 to 2.34), respectively, when comparing biologics treated patients with non-biologics treated patients.

4. DISCUSSION

In this nationwide study investigating the risk of serious medical complications following major joint surgery, patients with RA were at increased risk of infections following THA/TKA, and biologics treated RA patients had a higher risk estimate of infections compared with non-biologics treated RA patients. We found a lower risk of VTE among RA patients following TKA, but surprisingly, biologics treated had a ~5-fold increased risk of VTE compared to non-biologics treated RA patients.

The finding of an increased risk of non-surgical site infections among RA patients following major surgery is in line with some [26,27], but not all previous studies.[28] Michaud et al. found no increased risk of infection up to 30 days after THA and TKA in a predominantly male RA cohort compared with OA patients [28]. Possible explanations for different findings could be the different follow-up period (30 vs 90 days in the present study) and/or the differences in sex composition and population size. In contrast, Cancienne et al. reported an odds ratio of 1.5 for infection within 90 days of TKA in RA compared with OA in a study using Medicare data [26].

Biologics treated patients had a HR of 1.35 for infections compared with non-biologics treated RA patients but with wide confidence intervals. To our knowledge, only one study by Somayaji et al. has specifically investigated this matter, and they found no increased risk of non-surgical infections following THA/TKA in 70 TNFi treated compared with 189 non-TNFi treated patients [29].

The lower risk of VTE following TKA is intriguing given that RA is a well-established risk factor for VTE in a non-surgical setting [2,5,6]. The HR remained below 1 even after exclusion of all patients with a history of cancer and/ or previous VTE. In the present study, 99% of patients in both cohorts received thromboprophylaxis. Thus, we have no definite explanation for this finding which has now been shown in a number of studies [30–33]. Theoretical explanations include a possibly

increased prevalence of obesity in the OA cohort, which was at least suggested by the higher mean weight among TKA recipients in the present study. It could also be that OA patients are more frequent users of NSAIDs than patients with RA [34].

In addition, we showed that biologics treated patients had a higher incidence of VTE compared with non-biologics treated patients, and the calculated E-value for this association was 9.1, suggesting that any unmeasured confounder would need to be associated with the outcome at this magnitude to overcome the presented result. A time-dependent increased risk of VTE has been reported for patients with RA commencing biologics treatment with a subsequent gradually normalisation of the risk [35]. Following orthopaedic surgery, a study using data from the BSRBR-RA in the UK showed TNF-inhibitor treatment was associated with a statistical non-significant elevated odds ratio for VTE compared with non-biologics treated RA patients; the same pattern was observed in a study from Japan by Kawakami et al. [36,37]. The cumulative incidence of 1.9 % among biologics treated in our study is even higher than the 1.3 % observed in the OA cohort indicating that the risk is not merely “normalised” from the lower incidence of the entire RA cohort to an average level of the OA cohort, but that a possibly elevated risk truly exists. With the present results it is not possible to conclude if this risk is due to treatment with biologics or confounded by RA-severity markers for which we were unable to fully adjust, although interestingly, the DAS28 did not differ between biologics and non-biologics treated.

In line with some, [28] but not all previous studies [31,38], no short-term increased risk of myocardial infarction and stroke following THA/TKA was observed among patients with RA. Burn et al. recently reported an increased risk of myocardial infarction in patients with RA compared with OA up to 90 days following THA and TKA (adjusted HR 3.54, 1.44 to 8.73) [31]. The cumulative incidence of myocardial infarction in that RA cohort was 0.75 %, the same proportion of RA and OA patients who suffered either a myocardial infarction or stroke in our cohort. Thus,

the different outcome definitions (with and without stroke, respectively) and validity, as well as different origins of the RA populations (hospital vs general practice, respectively) are more likely to explain the different results. We do, however, also find it surprising that no increased risk of myocardial infarction and stroke was seen among patients with RA in the present study.

There are limitations to the present study that needs mentioning. One such is the definition of biologics exposure used: Currently no validation exists of the start and stop dates for treatment series in DANBIO. This is also the reason why we did not investigate the impact on complications with presurgical continued or withholding of biologics. Further, the DANBIO data on DAS28 and HAQ-DI suffered from a non-negligible degree of missingness. Primarily, we carried out multiple imputation to account for this, but in a sensitivity analysis we omitted these confounders from the propensity score estimation, which did not change the direction of the risk estimates in the subsequent Cox models.

Including and adjusting for the PS as a spline covariate is another limitation, although given the low number of events and the many important confounders, this was the most reasonable alternative. Another possible pitfall is the risk of misclassification bias in the subset of our RA cohort from DNPR. Whereas the positive predictive value (PPV) of an RA diagnosis in DANBIO has been estimated to ~97 %, a less strict definition of RA in DNPR than the one used in the present study had a PPV of ~80 % (Supplementary Table 1) [18].

The strengths of the present study include the nationwide design with independent reporting to health care registers and no loss to follow-up. The VTE and cardiovascular outcomes from DNPR have been validated and found to have high PPVs ranging from 70-100 % in DNPR [22]. Lastly, the detailed information on thromboprophylaxis in DHR and DKR along with the information on VTE and cancer history allowed us ensure that the results of lower risk of VTE in patients with RA were robust.

In conclusion, we found that following THA/TKA surgery, RA was associated with increased risk of infections, mainly pneumonia, sepsis and erysipelas, compared with OA. RA patients treated with biologics had a slightly increased risk of infections compared with non-biologics treated RA patients. The risk of VTE was lower among RA compared with OA patients following TKA. Nonetheless, the increased risk of postoperative VTE among patients receiving biologics needs to be investigated further.

ETHICS

According to Danish legislation, publication of data from registers and databases does not require patient consent or ethics approval. Approval was given by the Danish Data Protection Agency (GEH-2014-043, I-Suite: 03166).

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Table 1. Demographic, clinical and surgical characteristics of patients with rheumatoid arthritis (RA) and osteoarthritis (OA) who had a first primary elective total hip or total knee arthroplasty (THA and TKA) between 2000 and end of 2014.

	RA	OA	p	Missing data
N	2899	112 571		
Female sex, n (%)	2115 (73.0)	65 664 (58.3)	<0.001	
Age at surgery, mean (sd)	66.1 (11.0)	69.1 (9.7)	<0.001	0%
2000 to 2002	531 (18.3)	16 110 (14.3)	<0.001	0%
2003 to 2005	554 (19.1)	18 797 (16.7)		
Calendar period of surgery, n (%)	547 (18.9)	23 463 (20.8)		
2006 to 2008	638 (22.0)	27 928 (24.8)		
2009 to 2011	629 (21.7)	26 273 (23.3)		
2012 to 2014				
Surgical characteristics				
Type of arthroplasty, n (%)				
THA	1062 (36.6)	62 637 (55.6)	<0.001	0%
TKA	1837 (63.4)	49 934 (44.4)		
Duration of surgery in minutes, median (IQR)	68 (59 to 83)	65 (55 to 80)	<0.001	0%
Duration of hospital stay in days, median (IQR)	5 (3 to 9)	4 (3 to 8)	<0.001	0%
Preoperative weight in kilograms (only reported for TKA recipients), mean (sd)	75.7 (18.1)	83.4 (18.4)	<0.001	12% (of TKA recipients)
Received thromboprophylaxis, %	2858 (99)	111 331 (99)	0.25	0%
Duration of thromboprophylaxis in days, median (IQR)	7 [4, 30]	7 [4, 30]	0.56	33%
Comorbidities				
Chronic obstructive pulmonary disease, n (%)	197 (6.8)	4727 (4.2)	<0.001	0%
Previous VTE, n (%)	96 (3.3)	2624 (2.3)	0.001	0%
Diabetes mellitus, n (%)	201 (6.9)	7603 (6.8)	0.51	0%
Cardiovascular disease, n (%)	480 (16.6)	16 593 (14.7)	0.007	0%
Previously diagnosed with cancer, n (%)	171 (5.9)	7819 (6.9)	0.03	0%
Previously hospitalised due to infection, n (%)	279 (9.6)	4804 (4.3)	<0.001	0%

Abbreviations: IQR, interquartile range; sd, standard deviation; VTE, venous thromboembolism

Table 2: Risk of complications after total hip and knee arthroplasty in rheumatoid arthritis compared with osteoarthritis patients.

Outcome	Rheumatoid arthritis, N = 2899		Osteoarthritis, N = 112 571		Crude	Model 1*	Model 2**
	Events	Cum. incidence, %	Events	Cum. incidence, %	HR (95%CI)	HR (95%CI)	HR (95%CI)
Deep vein thrombosis or pulmonary embolism	30	1.03	1464	1.30	0.80 (0.55 to 1.14)	0.83 (0.58 to 1.19)	0.74 (0.52 to 1.07)
- Deep vein thrombosis	25	0.86	1169	1.04	0.83 (0.56 to 1.23)	0.86 (0.58 to 1.28)	0.79 (0.53 to 1.17)
- Pulmonary embolism	5	0.17	331	0.29	0.59 (0.24 to 1.42)	0.61 (0.25 to 1.48)	0.52 (0.21 to 1.26)
Myocardial infarction and stroke	22	0.76	851	0.76	1.00 (0.66 to 1.53)	1.28 (0.83 to 1.95)	1.16 (0.76 to 1.78)
Any non-surgical site infection	79	2.73	2394	2.13	1.28 (1.01 to 1.61)	1.50 (1.19 to 1.90)	1.29 (1.03 to 1.64)
- Pneumonia	32	1.10	740	0.66	1.68 (1.18 to 2.39)	2.14 (1.50 to 3.05)	1.72 (1.20 to 2.45)
- Sepsis	13	0.45	383	0.34	1.32 (0.76 to 2.29)	1.66 (0.96 to 2.90)	1.42 (0.81 to 2.47)
- Urinary tract infection	24	0.83	973	0.86	0.96 (0.64 to 1.44)	1.06 (0.70 to 1.59)	0.95 (0.63 to 1.43)
- Erysipelas	17	0.59	496	0.44	1.40 (0.7 to 2.55)	1.63 (0.89 to 2.98)	1.34 (0.74 to 2.46)

Statistically significant results are in **bold**. *Model 1: Stratified by sex, adjusted for age and calendar period of surgery
 **Model 2: Stratified by sex and type of surgery (THA vs TKA), adjusted for age and calendar period of surgery, duration of surgery, history of chronic obstructive pulmonary disease, previous VTE, previous serious infections, cardiovascular disease, diabetes mellitus or cancer. Abbreviations: HR, hazard ratio; 95%CI, 95% confidence interval.

Table 3: Characteristics and risk of complications after total hip and knee arthroplasty among biologics-treated compared with non-biologics treated rheumatoid arthritis patients at time of surgery.

	Biologics treated	Non-biologics treated	p-value
N	411	1391	
Female sex (%)	298 (72.5)	1028 (73.9)	0.62
Age at surgery, mean (sd)	61.5 (11.6)	65.3 (10.4)	<0.001
Joint replaced (% within cohort)			
Hip	134 (32.6)	519 (37.3)	0.09
Knee	277 (67.4)	872 (62.7)	
Received thromboprophylaxis (%)	398 (97)	1379 (99)	0.002
Treated with csDMARD	328 (79.8)	645 (46.4)	<0.001
Non-user	315 (76.6)	1256 (90.3)	<0.001
Prednisolone use			
2.5 to 5.0 milligrams	49 (11.9)	80 (5.8)	
7.5 to 15.0 milligrams	36 (8.8)	46 (3.3)	
> 15 milligrams	11 (2.7)	9 (0.6)	
DAS28-CRP, mean (sd)	3.6 (1.2)	3.4 (1.2)	0.12
HAQ-DI, median (IQR)	1.38 (0.75 to 1.88)	1.12 (0.62 to 1.62)	0.004
VAS pain, median (IQR)	47 (22 to 70)	50 (29 to 70)	0.50
Chronic obstructive pulmonary disease, n (%)	25 (6.1)	72 (5.2)	0.55
Previous VTE, n (%)	12 (2.9)	54 (3.9)	0.45
Cancer, n (%)	15 (3.6)	88 (6.3)	0.05
History of hospitalisation due to infection, n (%)	51 (12.4)	117 (8.4)	0.02

Abbreviations: s.d, standard deviation; csDMARD, conventional synthetic disease modifying anti-rheumatic drug; DAS28-CRP, disease activity score using 28-joint count and C-reactive protein; HAQ-DI, health assessment questionnaire; VAS, visual analogue scale; VTE, venous thromboembolism.

Table 4. Numbers and hazard ratios (HR) of complications within 90 days of total hip or total knee arthroplasty surgery in patients with rheumatoid arthritis treated with biologics compared with non-biologics treated.

	<u>Venous thromboembolism</u>		<u>Myocardial infarction and stroke</u>		<u>Infections (non-surgical site)</u>	
	N (%)	HR (95% CI)	N (%)	HR (95% CI)	N (%)	HR (95% CI)
Biologics treated	8 (1.9)	4.82 (1.67 to 13.90)	4 (1.0)	NA *	11 (2.7)	1.35 (0.65 to 2.80)
Non-biologics treated	7 (0.5)	1 (Ref.)	8 (0.6)	NA *	35 (2.5)	1 (Ref.)

Results in bold indicate $p < 0.05$. * The number of events were < 5 in one group and thus no Cox regressions analysis was carried out.

Abbreviations: 95 % CI, 95 % confidence interval.