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Fracture Risk Before and After Total Hip Replacement in Patients With Osteoarthritis

Potential Benefits of Bisphosphonate Use

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Objective. **The association between osteoarthritis (OA) and fractures remains unclear. OA patients have increased bone mass, but no corresponding decrease in fracture rate. This study was undertaken to determine the fracture rates in patients with hip OA undergoing a total hip replacement (THR), as compared with disease-free controls, and to assess the association between bisphosphonate use and postsurgery fracture risk.**

Methods. **We conducted a population-based parallel-cohorts study. All patients in the UK General Practice Research Database undergoing a THR for hip OA between 1986 and 2006 constituted the exposed cohort (n = 14,133). Five disease-free controls were matched with each patient by age, sex, and practice site. Subjects were followed up for 5 years before and after surgery. Fracture rates and rate ratios (RRs) were estimated using Poisson regression. In addition, bisphosphonate use was identified among patients undergoing THR, and the data, stratified by the presence or absence of a previous fracture and by treatment propensity score, were assessed using fitted Cox models to study the effect of bisphosphonate use on the risk of fracture postsurgery.**

Results. **Patients undergoing a THR had a similar fracture risk as that in controls in the 5 years before THR, but had higher rates postsurgery, which peaked at years 2.5–5 (adjusted RR 1.24, 95% confidence interval [95% CI] 1.02–1.52). Use of bisphosphonates lowered the fracture risk among THR patients who received bisphosphonates as primary prevention (hazard ratio [HR] 0.56, 95% CI 0.38–0.82) and also among THR patients who had experienced a previous osteoporotic fracture (HR 0.48, 95% CI 0.23–0.99).**

Conclusion. **This study identified a 25% increase in fracture risk at 2.5–5 years postsurgery among patients undergoing a THR. Bisphosphonate use reduced the post-THR risk of fracture when administered both as primary prevention and as secondary prevention, by 44% and 52%, respectively. This must be further confirmed in randomized controlled trials.**

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Osteoarthritis (OA) and osteoporosis (OP) are the 2 most common joint and bone conditions in the elderly. OP remains asymptomatic until its main complication appears, the fragility fracture. The lifetime risk of any fracture in England is 53.2% at age 50 years among women, and 20.7% at the same age among men (1).

OA is the most prevalent joint disease. The prevalence of clinically diagnosed hip OA is ~7.4% in individuals >60 years old (2), and the prevalence of radiographic hip OA ranges from 0.9% to 27% (3). Moreover, hip OA accounts for 93% of the 64,722 primary total hip replacements (THRs) performed in the UK in 2008 (4), and available evidence supports the notion that the rate of replacement is increasing in the UK (5). The costs of OA to the UK National Health Service included 3.02 million general practice consultations in 2000, and 114,628 hospital admissions for OA in 1999–2000 in the UK (6).

The association between OA and OP has been studied, but results have been conflicting. Although, in the first studies, increased bone mass was observed in patients with OA (7,8), findings from more recent cohort studies have suggested that there is not only no corresponding decrease in fracture risk, but even an increased risk of fracture among patients with OA (9–11).

In addition, we recently demonstrated an increased risk of hip fracture in patients with knee OA who subsequently went on to receive a total knee replacement (TKR) (adjusted rate ratio [RR] 1.58, 95% confidence interval [95% CI] 1.14–2.19 in the first year postsurgery) (12). The results from this previous study suggest that the risk varies according to the clinical stage of disease, as defined by the time point before or after the operation. The fracture rate starts to increase in the year before, and is greatest for a year and a half following a TKR, only returning to normal after 3 years. There is no biologic reason that a similar situation might not occur in patients with hip OA undergoing a THR. Therefore, a postsurgery increase in fracture risk is to be expected in patients after they undergo hip replacement.

Nevertheless, bisphosphonate oral therapies are available that reduce the risk of future clinical fracture by up to 50% in patients with OP (13,14). However, since the mechanism of fracture might be different in subjects with OA, the efficacy of treatments for OP as a strategy to reduce the risk of fracture in patients with OA is still to be studied.

In the present study, we aimed to assess the rates of wrist, humerus, and spine fracture before and after a THR in subjects with severe hip OA, compared to that in disease-free matched controls. Second, we aimed to test the hypothesis that bisphosphonate use attenuates the postulated increased risk of fracture among patients undergoing a THR, for up to 5 years after their surgery.

PATIENTS AND METHODS

Study population. Data were obtained from the UK General Practice Research Database (GPRD). The GPRD comprises computerized medical records of a sample of patients receiving care from general practitioners (GPs) in the UK, covering a population of 6.5 million patients from 433 contributing practices chosen to be representative of the wider UK population. The GPRD is administered by the Medicines and Healthcare Products Regulatory Agency (15).

The GPRD records contain all clinical and referral events in both primary and secondary care, in addition to comprehensive demographic information, prescription data, clinical events, specialist referrals, hospital admissions, and major outcomes. Data are stored using Read and OXMIS codes for diseases. Only practices that pass quality control are used as part of the GPRD. Encrypting personal and clinic identifiers ensures the confidentiality of information.

We identified all patients in the database with a medical diagnosis code for THR from 1986 to the end of 2006, using Read/OXMIS codes (a full list of the identified codes is available from the corresponding author upon request). Patients were included in the analysis if they were age ≥40 years at the time of the hip replacement, and only subjects undergoing THR in association with a diagnosis of hip OA were studied. Hip OA was identified using the following Read/OXMIS codes: X703K, N05z511, 7130D, 7130DA, N053512, and N05zJ00. Previous studies have shown good validity for the identification of OA in the GPRD. Five controls were identified for each case and matched with patients by age (±5 years), sex, and practice site, and also by index date. All subjects for whom there was never a clinical or referral record for hip arthroplasty or hip OA or hip pain in the database were eligible as controls. Subjects undergoing a hip replacement due to a hip fracture (or with a hip fracture 90 days before or after the replacement), hip dysplasia, or hip osteonecrosis, patients with a medical diagnosis code for rheumatoid arthritis, and patients who had received oral corticosteroids were excluded.

To calculate the rate of wrist, proximal humerus, and clinical spine fracture, patients were followed up for a maximum of 5 years before and after the THR. Controls were assigned the same index date as their matched case. Patients receiving a second THR within the period of observation (n = 143) were censored at the time of this operation, as were their matched controls.

Ascertainment of fractures. Fractures were identified using the GPRD Medical Codes for hip fracture (considered an exclusion criterion in our study), wrist fracture, humerus fracture, and clinical spine fracture, all of which were based on the Read/OXMIS codes. (A full list of the codes used for these fractures, as well as the codes used to identify other fractures in the GPRD, is available from the corresponding author upon request.) Previous studies have demonstrated good validity for the identification of fractures within the GPRD (16). The date of fracture is the date at which the fracture occurred, as entered by the patient's GP. When the same patient appeared

to have 2 (or more) fractures at the same site and these were reported less than 1 week apart, they were considered duplicated registers, and therefore only the first date was taken into consideration as the index date.

Identification of bisphosphonate users. From the total population of eligible subjects undergoing a THR due to hip OA (n = 14,133), 2,322 patients (16.4%) had experienced a fracture before surgery. In order to avoid selection bias and interaction between exposure (bisphosphonate therapy) and outcome, we stratified the patients according to whether or not they had experienced a previous fracture. Subjects who had experienced any fracture prior to undergoing their THR were further divided into 2 groups: 826 patients (35.6%) with an OP fracture (defined by fracture site: hip, wrist, humerus, or clinical spine) and 1,496 patients (64.4%) with a previous fracture at any other site. Overall, 1,159 subjects (8.2%) were identified as bisphosphonate users, according to whether the subject had been prescribed any bisphosphonate by his or her GP for the first time at least 6 months before the occurrence of a fracture postsurgery. Compliance was defined as the proportion of days between the first prescription and the last prescription of bisphosphonates and was measured as the medication possession ratio (MPR). An MPR higher than 80% has been associated with a reduced risk of fracture (17).

Those patients who had received a first prescription of bisphosphonates after the occurrence of a fracture postsurgery were considered to be nonusers. Moreover, subjects who were never prescribed bisphosphonates were also considered nonusers.

Determination of propensity score. Because prescription of bisphosphonates was not randomly allocated in our study, potential confounding was accounted for by determining a propensity score for bisphosphonate use. Use of the propensity score for the assessment of causality in epidemiologic studies has been previously described (18–21).

The propensity score for bisphosphonate use was estimated using multivariate logistic regression models. Bisphosphonate use, as previously defined, was assessed as a binary outcome variable. Potential predictors were designated as "other covariates" in the model. The propensity score for bisphosphonate use was calculated from the estimated probability of biphosphonate use in each patient, based on the logistic regression equation. The calculated score represents the predicted probability that a subject would be prescribed bisphosphonates.

Using the Matching package in R (available at http://cran.r-project.org/web/packages/Matching/index.html), we matched the propensity score of each bisphosphonate user to that of the 3 nonusers whose propensity score was most similar (propensity-matched analysis). We did this separately for the different groups defined on the basis of previous fracture antecedents.

Other covariates. For assessment of baseline clinical characteristics and further adjustment for potential confounding, we took into consideration age, body mass index (BMI), smoking status, and drinking habits, all recorded closest to the date at which the THR was performed. Data on these covariates were not available (missing values) in a proportion of subjects: 11.5% for BMI, 2.9% for smoking, and 10.4% for drinking habits. Multiple imputation was used to account for these missing values.

In addition, comorbid conditions registered by the physician were identified using the GPRD Medical Codes for asthma, malabsorption syndromes, inflammatory bowel disease, hypertension, hyperlipidemia (22), ischemic heart disease, cerebrovascular disease (23), chronic obstructive pulmonary disease, chronic renal failure, and cancer. Similarly, use of certain drugs was assessed: antiarrhythmics, anticonvulsants, antidepressants (24), anti–Parkinson's disease agents, anxiolytics, proton-pump inhibitors, hormone replacement therapy (HRT)/selective estrogen receptor modulators (SERMs), and calcium/vitamin D supplements. In postsurgery models, adjustment was also made for the antecedent of fracture prior to surgery.

Statistical analysis. *Analyses of hip replacement rates and rates of wrist, humerus, and clinical spine fracture.* A Poisson regression model was fitted to calculate the rate of THR and the rates of wrist, humerus, and clinical spine fracture (separately for cases and for controls) based on the number of fractures and person-years of observation at risk, in time intervals of 2.5–5 years and 0–2.5 years before and after the index THR. RRs (crude and multivariate adjusted) and 95% CIs were calculated using Poisson regression, and the values were plotted against time before and after THR in yearly intervals.

For multivariate analysis, we fitted a zero-inflated Poisson model. The standard error was inflated using the square root of the Pearson's chi-square statistic, because repeat fractures in the same person cannot be assumed to be independent. For the univariable analysis, the main exposure of interest was whether a person had a THR or was a control, and we estimated the rate of fractures in cases versus controls. In multivariate adjustment, the variables listed as other covariate were assessed as potential confounders, based on a priori knowledge. Multiple imputation was used to account for missing values for the BMI and smoking and drinking status, using the Imputation by Chained Equations procedure in Stata (21).

Assessment of fracture risk after surgery, according to bisphosphonate use. Differences between bisphosphonate users and nonusers (before and after propensity matching) were compared using chi-square statistics for categorical variables and *t*-tests for continuous (all normally distributed) variables. Bisphosphonate use and fracture occurrence were tested using univariable and multivariable Cox regression models. We repeated the analysis using the MPR categories of treatment compliance (0, >0 to 0.4, >0.4 to 0.8, and >0.8 to 1) as the main exposure of interest. The proportional hazards assumption was checked using the Schoenfeld residuals formal test and the smoothing splines in time plots. Multivariable models were controlled for the potential confounders designated other covariates.

To determine the clinical effect size, we calculated the number needed to treat (NNT) to avoid 1 fracture at 5 years of followup, based on the survival probability function and the hazard ratio (HR) (25). Furthermore, the estimated HRs and probabilities of fracture were used in order to calculate the sample size required in a randomized clinical trial to assess the effect of bisphosphonates on post-THR occurrence of fractures.

All analyses of bisphosphonate use were performed separately for patients treated in primary prevention and those

Table 1. Baseline clinical characteristics of patients with hip osteoarthritis undergoing total hip replacement (THR) and matched control subjects*

	Cases (n = 14,133)	Controls (n = 68,527)	OR (95% CI)	*P*
Followup				
Mean ± SD months	40.33 ± 20.42	36.26 ± 20.96		
Mean (95% CI) difference vs. controls	4.07 (3.69–4.44)			<0.001
Age				
Mean ± SD years	69.33 ± 9.78	69.13 ± 9.73		
Mean (95% CI) difference vs. controls	0.20 (0.03–0.38)			0.02
BMI				
Mean ± SD kg/m^2	27.37 ± 4.71	26.23 ± 4.67		
Mean (95% CI) difference vs. controls	1.24 (1.15–1.33)			<0.001
Male sex, no. (%)	5,698 (40.3)	27,616 (40.3)	1 (0.97–1.03)	0.93
Alcohol drinker, no. (%)				<0.001
Current	10,231 (72.4)	44,457 (64.9)		
Former	779 (5.5)	3,766 (5.5)		
Never	1,659 (11.7)	9,239 (13.5)		
Not reported	1,464 (10.4)	11,065 (16.1)		
Smoker, no. (%)				<0.001
Current	1,677 (11.9)	10,928 (15.9)		
Former	4,268 (30.2)	18,369 (26.8)		
Never	7,778 (55.0)	33,744 (49.2)		
Not reported	410 (2.9)	5,486 (8.1)		
Fracture, no. (%)				
Any fracture prior to THR	2,322 (16.4)	10,230 (14.9)	1.12 (1.07–1.18)	<0.001
Wrist, proximal humerus, or clinical spine fracture				
Prior to THR	826 (5.8)	3,839 (5.6)	1.05 (0.97–1.13)	0.26
After THR	273 (1.9)	970 (1.4)	1.37 (1.20–1.57)	<0.001
Number of comorbid conditions, no. (%)†				0.12
0	13,648 (96.6)	66,453 (97.0)		
1	244 (1.7)	1,119 (1.6)		
2	159 (1.1)	640 (0.9)		
3	61 (0.4)	233 (0.3)		
4	15 (0.1)	60 (0.1)		
≥5	6 (0.0003)	22 (0.0002)		

* OR = odds ratio; 95% CI = 95% confidence interval; BMI = body mass index.
† Includes the following conditions: asthma, malabsorption syndromes, inflammatory bowel disease, hypertension, hyperlipidemia, ischemic heart disease, cerebrovascular disease, chronic obstructive pulmonary disease, chronic renal failure, or cancer.

treated in secondary prevention, as defined previously. All statistical analyses were carried out in Stata SE version 10.1 (StataCorp) and the R program (Mac OS version 2.9.1).

RESULTS

Fracture rates and THR. Among the patients in the GPRD originally identified as having undergone a THR (n = 23,813), 1,789 (7.5%) were excluded due to an occurrence of a hip fracture in the 90 days before or after the date of surgery, 164 (0.7%) were excluded due to a diagnosis of rheumatoid arthritis, 255 (1.1%) were excluded due to a diagnosis of osteonecrosis, and 63 (0.3%) were excluded due to the use of oral corticosteroids. From the remaining 21,542 subjects, we identified 14,133 patients (65.6%) as having undergone a THR due to hip OA. Among their matched controls (n = 70,665), 2,138 control subjects (3.0%) were excluded on the basis of our exclusion criteria, and 68,527 control subjects (97.0%) remained in the study. Following these exclusions, all of the THR patients had at least 3 matched controls remaining, and 12,211 patients (86.4%) still had the 5 initially matched controls. The baseline clinical characteristics of both groups are shown in Table 1.

As shown in Table 2, the fracture rates (per 1,000 person-years at risk) were assessed in 2.5-year intervals, starting from the 5 years prior to THR to the 5 years after surgery, both for patients undergoing a THR and for matched controls. As expected, due to increasing age, controls demonstrated an increase in fracture rate over time. Subjects undergoing surgery had a similar increase in fracture rates before surgery, but experienced a steeper rise in fracture risk immediately after the THR. When fracture rates in THR cases and matched controls were compared, the estimated RR (ratio of the risk in THR patients to that in controls) showed no significant effect, if not a tendency toward a lower risk of fracture associated with hip OA at 2.5–5

Table 2. Occurrence of wrist, proximal humerus, and clinical spine fracture in patients with hip osteoarthritis undergoing total hip replacement (THR), compared with matched control subjects, up to 5 years before and 5 years after the THR*

	Fracture rate (95% CI)	Crude RR	Adjusted RR
Prior to THR			
5–2.5 years (total 74,693 patients)			
THR patients	3.80 (3.53–4.09)	0.88 (0.71–1.08)	0.92 (0.75–1.12)
Controls	4.10 (3.97–4.24)		
2.5 years–surgery date (total 82,638 patients)			
THR patients	4.21 (3.94–4.50)	1.01 (0.83–1.22)	0.90 (0.76–1.07)
Controls	4.54 (4.41–4.67)		
Post-THR			
Surgery date–2.5 years (total 82,629 patients)			
THR patients	5.99 (5.64–6.36)	1.10 (0.93–1.32)	1.01 (0.86–1.19)
Controls	5.16 (5.64–6.36)		
2.5–5 years (total 49,346 patients)			
THR patients	6.81 (6.34–7.31)	1.25 (1.01–1.55)†	1.24 (1.02–1.52)†
Controls	5.24 (5.03–5.46)		

* Values are the fracture rate (95% confidence interval [95% CI]) per 1,000 person-years at risk, as well as the crude rate ratio (RR) for the fracture rate in THR patients relative to matched controls and the RRs adjusted for the use of bisphosphonates (>6 months), age, body mass index, drinking status, smoking status, use of bone-active drugs, use of hormone replacement therapy/selective estrogen receptor modulators, use of calcium/vitamin D supplements, and long-term conditions (asthma, malabsorption syndromes, inflammatory bowel disease, hypertension, hyperlipidemia, ischemic heart disease, cerebrovascular disease, chronic obstructive pulmonary disease, chronic renal failure, or cancer). The postsurgery models at both time points were also adjusted for the antecedent of fracture presurgery.
† $P < 0.05$ versus controls.

years before the surgery. However, such protection from fractures decreased over time, and THR patients showed higher fracture rates after surgery, which became significant only at 2.5–5 years after surgery (adjusted RR 1.24, 95% CI 1.02–1.52). Estimated RRs (crude and adjusted) during the time before surgery and the time after surgery, plotted against time, are shown in Figure 1.

Bisphosphonate use and fracture risk after THR. For the purpose of assessing the effect of bisphosphonate use on postsurgery fracture risk, we stratified the subjects according to fracture antecedents. We identified 873 bisphosphonate users with no previous fracture, and we then matched them to the 3 control subjects with the closest propensity score, thus obtaining 2,619 comparable bisphosphonate nonusers. In the same way, we identified 140 bisphosphonate users with an OP fracture prior to THR, and also identified 146 bisphosphonate users with any other previous fracture, and thus obtained 420 and 438 matched controls as nonusers, respectively. Bisphosphonate users were significantly older, had a lower BMI, and were more likely to be women, to be prescribed fracture-associated medications (antiarrhythmics, anticonvulsants, antidepressants, anti-Parkinson's agents, anxiolytics, or proton-pump inhibitors), and to be prescribed HRT/SERMs or calcium/vitamin D supplements.

The propensity-matching procedure made groups comparable, with the exception of use of HRT/SERMs, which remained higher in matched bisphosphonate nonusers in the group of patients with an OP

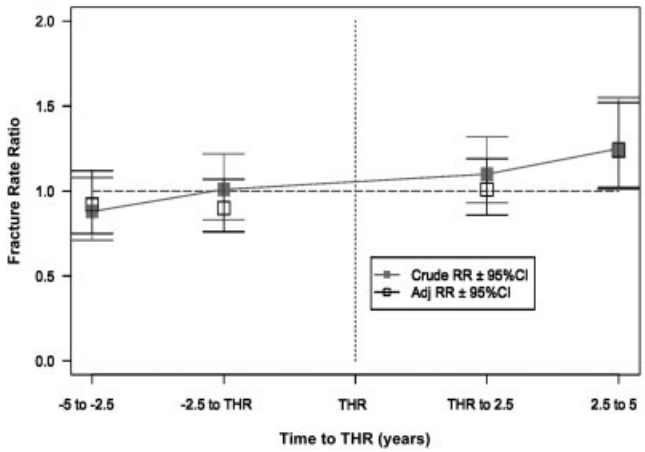

Figure 1. Rate ratio (RR) for the occurrence of wrist, proximal humerus, and clinical spine fracture up to 5 years before and 5 years after total hip replacement (THR) in patients with hip osteoarthritis, relative to that in disease-free controls. RRs are the crude values, as well as the values adjusted (Adj) for the use of bisphosphonates (>6 months), age, body mass index, drinking status, smoking status, use of bone-active drugs, use of hormone replacement therapy/selective estrogen receptor modulators, use of calcium/vitamin D supplements, and long-term conditions (asthma, malabsorption syndromes, inflammatory bowel disease, hypertension, hyperlipidemia, ischemic heart disease, cerebrovascular disease, chronic obstructive pulmonary disease, chronic renal failure, or cancer). 95% CI = 95% confidence interval.

Table 3. Propensity-matched analysis of the effect of bisphosphonate use (primary and secondary) on occurrence of fracture postsurgery in patients with hip osteoarthritis undergoing total hip replacement (THR)*

Bisphosphonate use	No fracture prior to THR	Osteoporotic fracture prior to THR	Other fracture prior to THR
Overall	0.56 (0.38–0.82)†	0.48 (0.23–0.99)‡	0.72 (0.23–1.45)
MPR			
>0.4 to 0.8	0.43 (0.24–0.80)†	0.40 (0.15–1.04)	1.00 (0.13–7.58)
>0.8 to 1	0.42 (0.21–0.86)‡	0.13 (0.02–0.99)‡	0.31 (0.04–2.29)

* Bisphosphonate use was defined as use of bisphosphonates for at least 6 months before occurrence of the fracture. Values are the hazard ratio (95% confidence interval) for the fracture risk overall and stratified by medication possession ratio (MPR) as a measure of treatment compliance, adjusted for age, sex, body mass index, drinking status, smoking status, use of bone-active drugs (antiarrhythmics, anticonvulsants, antidepressants, anti–Parkinson's disease agents, anxiolytics, and proton-pump inhibitors; oral corticosteroid users were dropped from the study population), use of calcium/vitamin D supplements, and comorbid conditions (asthma, malabsorption syndromes, inflammatory bowel disease, hypertension, hyperlipidemia, ischemic heart disease, cerebrovascular disease, chronic obstructive pulmonary disease, chronic renal failure, or cancer).
† $P < 0.01$.
‡ $P < 0.05$.

fracture prior to THR, and the exception of use of calcium/vitamin D supplements, which remained significantly higher in bisphosphonate users, even after matching for the 3 groups. In the logistic models with inclusion of the propensity score, a c statistic, corresponding to the area under the receiver operating characteristic curve, was obtained. The c statistic for the patients with no previous fracture, for those with an OP fracture, and for those with any other previous fracture was 0.73 (95% CI 0.71–0.75), 0.76 (95% CI 0.72–0.80), and 0.77 (95% CI 0.72–0.81), respectively, indicating a good ability to differentiate between bisphosphonate users and nonusers.

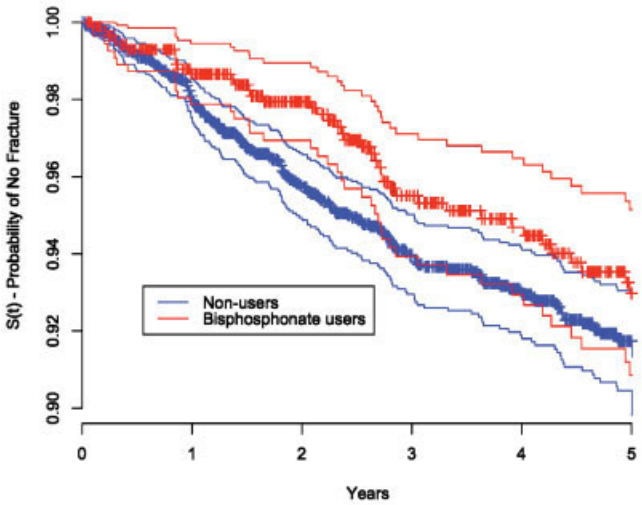

Figure 2. Kaplan-Meier plot showing the probability (S[t]) of the occurrence of no fractures during the 5 years of followup in bisphosphonate users (patients receiving bisphosphonates in primary prevention) compared with nonusers. Probabilities are shown with 95% confidence intervals.

Propensity-matched Cox regression analysis showed a lower fracture risk post-THR among the group of bisphosphonate users in whom there was no previous fracture (HR 0.56, 95% CI 0.38–0.82; $P = 0.003$) and among bisphosphonate users who had experienced an OP fracture prior to THR (HR 0.48, 95% CI 0.23–0.99; $P = 0.04$), but there was no significant effect of bisphosphonate use in subjects with any other previous fracture (HR 0.72, 95% CI 0.23–1.45; $P = 0.35$). Higher compliance with bisphosphonate treatment (MPR >0.8) was related to a more important reduction in fracture risk among patients receiving bisphosphonates as primary prevention (HR 0.42, 95% CI 0.21–0.86; $P = 0.01$) and among patients with a previous OP fracture (HR 0.13, 95% CI 0.02–0.99; $P = 0.04$), but there was a nonsignificant decrease in fracture risk in subjects with any other previous fracture (HR 0.31, 95% CI 0.04–2.29; $P = 0.25$). Table 3 shows the propensity-matched HRs for fracture occurrence among bisphosphonate users in these specifically defined groups according to fracture antecedents. The probability of not having a fracture in the followup period of 5 years after THR was compared between bisphosphonate users (those receiving bisphosphonates as primary prevention) and matched nonusers, as shown in the Kaplan-Meier plot in Figure 2.

The NNT to avoid 1 fracture at 5 years of followup associated with bisphosphonate use was calculated to be 39 in subjects with no previous fracture. For those subjects with a previous OP fracture, the NNT would be 17, and for patients with any other fracture antecedent (assuming the estimated HR of 0.72 to be accurate), the estimated NNT would be 47.

DISCUSSION

Subjects with hip OA have a similar rate of fracture (of the wrist, humerus, and clinical spine) as that in matched disease-free controls 5 years before surgery, but the risk of fracture becomes significantly higher in the 2.5–5 years post-THR, with an increase in fracture risk of up to 25%. The results of our study demonstrate that the association between hip OA and fractures is time-dependent, and this might explain the controversial evidence in the current literature. This association is modified by hip replacement, since patients who have undergone the surgery are at an increasing risk of fracture from 2.5 years up to 5 years after surgery, and therefore these patients may need to be properly assessed for fracture risk before or at the time of surgery.

The second part of our study assessed the effect of bisphosphonate use on risk of fracture in the 5 years following the date of THR. Our results suggest a significant reduction in fracture risk, with a decrease in fracture risk of 44%, among bisphosphonate users in whom there was no fracture antecedent prior to surgery, as compared to propensity-matched nonusers. The fact that higher compliance appeared to be associated with a higher risk reduction, with a decrease in risk of up to 58% in patients with an MPR >0.8, makes causality more plausible. Among bisphosphonate users who received the treatment in secondary prevention, those with a previous OP fracture had a risk of post-THR fracture that was reduced by 52% when compared to that in nonusers, and by 87% when high compliance (MPR >0.8) was achieved. We did not find a significant reduction in fracture risk associated with bisphosphonate use in patients with any other fracture antecedent.

Several studies showed that patients with OA had increased bone mass (7,8), which was expected to reduce their risk of fragility fractures. Nonetheless, not only did cohort studies fail to demonstrate a reduced fracture risk among such patients, but some have even shown an increase in the rates of OP fracture (9–11). A possible explanation for this paradox might be the increased number and severity of falls sustained by subjects with lower-limb OA, as has been observed by some investigators (26,27).

The present study shows that the association between OA and OP fracture is time-dependent, with an equivalent rate of fractures before THR and an increasing rate 2.5–5 years after the date of the surgery. This may be attributed to an increased risk of falling due to more severe arthralgia, leading to immobility and, consequently, to a loss in muscle mass and lower-limb function. It has been recently suggested that THR-related hip, knee, and calf muscle atrophy can persist for at least 2 years after a hip replacement (28). In addition, altered balance, gait, and proprioception have been related to hip arthroplasty (29–31), and this might play a role in the present findings. These observations may explain some of the discrepancies between studies.

Furthermore, bone loss can appear as a consequence of immobility associated with joint pain, and might explain the increase in fracture rates in the immediate postoperative period, which may last for longer periods than surgery-related joint pain. Some studies have demonstrated an increase in the prevalence of OP among patients awaiting hip replacement (32), particularly at the forearm, one of the sites of fracture explored in this study.

These hypotheses are supported by our recent findings in subjects undergoing a TKR due to knee OA. We have demonstrated an increased risk of hip fracture postsurgery among these subjects, when compared to disease-free matched controls (adjusted RR 1.58, 95% CI 1.14–2.19 in the first year after TKR) (12). The main difference with the current study is that, in patients undergoing a TKR, fracture rates started to increase before the TKR was performed, and were highest for 1.5 years following the TKR, returning to normal after 3 years. In contrast, the fracture risk continued to increase further in subjects after their THR, and became significant at 2.5–5 years postsurgery, with the rates never returning to those in controls during the 5 years of followup. Although one might anticipate that the rate of falls would increase during the immediate postoperative period, the data do not support the hypothesis that this translates to an increased risk of fractures. It would be of interest in future studies to ascertain rates of falls before and after THR.

We also report a potentially beneficial effect of bisphosphonate use on the increase in risk fracture after THR. The low rate of bisphosphonate therapy in those subjects with a history of fracture is due, principally, to 3 factors. Bisphosphonates were licensed in 1995, roughly midway through the period of observation, which may affect the findings. Second, it is well recognized that despite clinical trial evidence, only a minority of patients eligible for therapy for OP are identified and treated, even in those with a previous history of fracture. Finally, the risk factors for OA do not overlap with the traditional risk factors for OP, and therefore few patients would be screened for OP.

Previous trials have aimed at assessing different

effects of bisphosphonates in patients with OA, with controversial results with regard to the effects on OA symptoms and progression (33,34) and with one study showing a possible effect on subchondral bone structure (35). In our previous population-based cohort study, we showed a clinically significant reduction in fracture risk, of ~50%, after TKR in patients receiving bisphosphonates in primary prevention, and a reduction in risk of 55% in those treated in secondary prevention (36,37). This would support the fact that bisphosphonates could have a potential effect on fracture risk reduction up to 5 years after surgery among patients with lower-limb OA who undergo a joint replacement. It is important to stress that the increase in fractures among patients with lower-limb OA is thought to be due to falls and, given that lower-limb OA is associated with increased bone mineral density, the protective effect of bisphosphonates is unexpectedly relevant.

Our results must be confirmed, either by replication in a different cohort study or in a randomized clinical trial setting, which would represent the real test for causality. For the latter, we can make a first estimation of the sample size needed to assess the effect of bisphosphonates on post-THR fracture. In primary prevention (with 90% power and 5% significance and assuming a 20% loss to followup), a total of 2,650 subjects (1,325 per arm) would be required. Similarly, in patients with a previous OP fracture undergoing a THR, we would need to recruit 428 subjects per arm, and in subjects with any other previous fracture, 3,121 patients per arm would be needed. If high compliance was to be achieved in such trials (as is usual in randomized controlled trials), we could assume a risk reduction similar to that observed in patients with an MPR >0.8, and then the corresponding estimated sample sizes would be 591, 56, and 246 per arm, respectively.

The main strength of our study is the nature of the data gathered to perform it. The GPRD is highly representative of the whole UK population and contains comprehensive data on patients with hip OA before and after a THR. Furthermore, both the main exposure and the outcome of interest have been studied using data from the GPRD, and these have been found to be accurately registered in the data set (16,38). Moreover, large samples of data from the GPRD, similar to the data set used herein, have previously been successfully used to assess fracture risk (39) and to study the epidemiology of fractures in England and Wales (1). The longitudinal nature of this data set allows the temporal trends in the association between hip OA and fracture to be explored accurately.

For the first part of our study, in which we assessed fracture rates before and after THR in subjects with hip OA, the most important limitation is that there were some missing data on fractures in our data set. The GPRD is highly specific for fracture (90.7% of coded fractures have been confirmed by GPs, and 86.5% of them have also been confirmed on discharge summaries), but the data lack sensitivity for fracture (40). However, this is likely to be nondifferential, and would not affect the calculated rate ratio. Furthermore, the GPRD has limited individual information on falls or bone mineral density; therefore, we could not assess these factors as potential links in the postulated causal chain between hip OA and fractures. Nevertheless, the unexpectedly delayed increase in fracture risk observed herein could be attributable to the true effect of post-surgery rehabilitation (leading to recovery and to a later rise in activities, and, thus, to a higher risk of falls), but it might also be related to a nonaccurate coding of surgery and fracture dates in our data. Therefore, further exploration is needed to confirm this.

With regard to our study of the effect of bisphosphonate use on fracture risk post-THR, the main limitation is the study design. We used a prospective cohort to assess the effect of interventions, and this could be a source of potential confounding, due to the fact that it involves nonrandom allocation. However, we also used propensity score matching, which has been proposed and repeatedly used to study the effect of treatments in observational studies (41,42). Nevertheless, a randomized clinical trial should be carried out, in order to demonstrate causality and assess safety. Regardless, the benefit of a cohort study, as compared with a trial, is that it is more likely to reflect actual practice than would a trial setting, due to less restrictive inclusion criteria. A drawback is that our study could not assess the potential effect of placebo, and so the beneficial effect of bisphosphonate use might be overestimated.

We have shown that patients with hip OA undergoing a THR are at a higher risk of fracture (of the clinical spine, wrist, and humerus) after their surgery than are matched controls, with an up to 25% increase in fracture risk at 2.5–5 years post-THR. The presence of arthralgia and the consequent immobilization, leading to muscle atrophy and bone loss, could explain these findings.

Moreover, we have demonstrated that bisphosphonates could play a therapeutic role in this scenario. We found that bisphosphonate use was associated with a reduced risk of fracture in these patients and in the same period, among subjects who received bisphosphonates in primary prevention (NNT 39) and in subjects with a

previous OP fracture (NNT 17). This should be confirmed in a randomized clinical trial, which would need to recruit 1,325 subjects for primary prevention and 428 subjects for secondary prevention.

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 published. Dr. Arden 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. Prieto-Alhambra, de Vries, Cooper.
Acquisition of data. Prieto-Alhambra, Maskell, de Vries, Cooper.
Analysis and interpretation of data. Prieto-Alhambra, Javaid, Judge, Maskell, Kiran, de Vries, Cooper, Arden.

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Merck, Sharp & Dohme and Novartis had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval from these study sponsors.

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