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ORIGINAL ARTICLE

Bisphosphonate use and risk of post-operative fracture among patients undergoing a total knee replacement for knee osteoarthritis: a propensity score analysis

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Abstract
Summary We have shown that patients with osteoarthritis are at increased risk of fracture after total knee replacement (TKR). We conducted a population-based cohort study to assess the effect of bisphosphonate use on their post-surgery fracture risk. Cox regression adjusted by propensity score suggested a 50–55% reduction in risk of fracture post-surgery.

Introduction Patients with osteoarthritis have a higher bone mass but similar or higher risk of fracture. We recently demonstrated that patients have an elevated fracture risk after TKR, but it is unknown if bisphosphonate therapy in this patient group would reduce fracture risk. We aimed to assess the effect of bisphosphonate prescription to patients undergoing a TKR, on their risk of fracture after surgery.
Methods From the General Practice Research Database, all patients≥40 years old, who received a TKR from 1986 to 2006 for knee osteoarthritis were eligible. We identified bisphosphonate use (BPU) as the main exposure. Propensity scores (equivalent to the estimated conditional probability of being treated given the individual's covariates) were calculated using logistic regression and used to reduce observed confounding. We fitted Cox models to study the effect of BPU on post-surgery fracture occurrence. Analyses were stratified by history of previous fracture: no fracture, osteoporotic fracture (hip, wrist, humerus, spine), and other fractures.
Results The hazard ratio (HR) associated with BPU in non-previously fractured patients was 0.50 (95% confidence interval, 0.37–0.68; propensity-adjusted model), and 0.48 (0.35–0.65; matched analysis). In subjects with osteoporotic and with other previous fracture, BPU was associated with a propensity-adjusted HR of 0.46 (0.30 to 0.71) and 0.47 (0.26–0.85), respectively, and with a propensity-matched HR of 0.45 (0.29 to 0.70) and 0.45 (0.25–0.82).
Conclusion Our results suggest that BPU in primary prevention could reduce post-operative risk of fracture by 50% and by 55% in secondary prevention.

Keywords Arthroplasty · Bone · Diphosphonates · Epidemiology · Fractures · Knee · Propensity score · Replacement

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Introduction

Osteoarthritis (OA) and osteoporosis (OP) are both common conditions in the elderly, associated with significant morbidity, and health care costs. In 1990, an estimated 1.66 million people suffered a hip fracture, with an estimated cost of more than US $7 billion dollars in the USA alone [1].

Osteoarthritis is the most prevalent arthritis: the prevalence of radiographic knee OA is 33% in people >63 years old [2], and the prevalence of clinically diagnosed knee OA is 18.1% in those who are >55 years old [3]. Moreover, OA accounted for 97% from a total of 71,527 primary total knee replacement (TKR) procedures in the UK in 2008 [4], with reported costs of more than US $20,000 per patient [5].

A possible association between OA and OP (and fragility fractures) has been studied and reported in recent years, with discordant results. Firstly, observations [6] showed that patients with hip fracture rarely had OA, and so suggested a protective effect of OA for OP and subsequent fractures. Several studies demonstrated later an increased bone mass in patients with OA, even measuring it at sites distant to the OA affected joints. This association appeared to be stronger for knee and hip OA than for generalized OA or OA in other sites [7, 8], though studies using more accurate bone mineral density (BMD) measuring tools, such as peripheral quantitative computed tomography, have been inconsistent [9]. Prospective cohort studies, have suggested an increased risk of fracture in patients with OA [10, 11]. Furthermore, a recent prospective study which included more than 6,500 men and women ages >75 years, and followed them for 3 years, demonstrated that patients with a clinical diagnosis of knee OA have double the risk of hip fracture [12].

In addition, we have recently demonstrated an increased risk of hip fracture in patients with knee OA who subsequently went on to receive a TKR (adjusted RR 1.58 (95% confidence interval (CI), 1.14 to 2.19) in the first year post-surgery) [13]. This study suggests that the risk varies according to the clinical stage of disease, as defined by time before and after their operation. Fracture rate starts to increase in the year before and is greatest for a year and a half following a total knee replacement, only returning to normal after 3 years. However, it is not known if bisphosphonate therapy in this patient group would reduce fracture risk.

Effective oral treatments (bisphosphonates [14, 15] raloxifene [16] and strontium ranelate [17]) are available that reduce the risk of future clinical fracture by up to 50% in osteoporotic populations. Bisphosphonates have also been suggested as potential therapeutic agents for disease modification in osteoarthritis [18]. The available evidence shows that they can produce a decrease in biochemical markers of cartilage degradation, but are not useful to improve symptoms or to attenuate radiographic progression in patients with knee osteoarthritis [19].

Whilst several studies have demonstrated the effect of bisphosphonate use on fracture risk [14, 15] as OA is associated with higher BMD, the mechanism of fracture is likely to be different and so the efficacy of osteoporosis treatments to reduce fracture in patients with OA is not known.

We aimed to test the hypothesis that bisphosphonate use attenuates the increased risk of fracture among patients undergoing a TKR.

Materials and methods

Study population

The data was obtained from the General Practice Research Database (GPRD). The GPRD comprises of computerized medical records of a sample of patients attending 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. GPs in the UK play a key role in the delivery of healthcare by providing primary care and referral to specialist hospital services. Patients are registered with one practice that stores medical information from primary care and hospital attendances. The GPRD is administered by the Medicines and Healthcare products Regulatory Agency (MHRA) [20].

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 their major outcomes. Data is stored using “OXMIS” and “Read” codes for diseases that are cross-referenced to the International Classification of Diseases (ICD-9). Only practices that pass quality control are used as part of the GPRD database. Deleting or encoding personal and clinic identifiers ensures the confidentiality of information in the GPRD.

We identified all patients in the database with a medical diagnosis code for knee replacement from 1986 to the end of 2006. Read/OXMIS codes were used to identify primary total knee replacements (see Appendix 1, available online, for the list of codes used to ascertain TKR). Patients were included in the analysis if aged 40 years or over at the time of the replacement. Subjects with a diagnosis of rheumatoid arthritis and oral corticosteroid users were excluded. Patients receiving a second TKR within the period of observation (n=1,308) were censored at the time of this operation. Subjects of study were followed-up from 0.09 to 5 years after TKR (median, 3.23 years). In order to avoid selection bias and interaction between exposure (bisphosph-

onate therapy) and outcome, we repeated the analyses in the group of subjects without and with previous fracture. The latter were further divided in two groups: those with an antecedent of osteoporotic fracture and those with a previous fracture of any other site. "Osteoporotic fractures" were defined based on fracture site: humerus, wrist/forearm, and clinical spine fractures have been defined as "major osteoporotic fractures" in the FRAX model [21]. Hip fractures are the other fracture site considered in the FRAX tool. The epidemiology of these fracture sites has been widely studied in the UK, and in primary care settings, which are the source of GPRD data [22].

Ascertainment of fractures

Fractures were identified using the GPRD Medical Codes for any site of fracture, which are based on the "Read/OXMIS" codes (see list of codes used at Appendix 2, available online). Previous studies have demonstrated good validity of fractures within the GPRD [23]. When a same subject appeared to have two (or more) fractures at the same site with less than a week difference between them, they were considered duplicated registers, and first date was taken into consideration for the analysis. The date of fracture is the date entered by the GP on which the fracture occurred.

Identification of bisphosphonate users

Among the population with no previous fracture (n= 14,223), 934 (6.6%) patients were identified as *bisphosphonate users*. We defined bisphosphonate use as follows: a patient was identified as bisphosphonate user if she had been prescribed bisphosphonates by her General Practitioner, either before or after their TKR, for at least 6 months before having any fracture. Similarly, from the eligible patients who had had an osteoporotic fracture prior to surgery (n=1,491), 287 (19.2%) were identified as *bisphosphonate users*. Finally, amongst the total of participants with any other previous fracture (n=2,407), we found 218 (9.1%) *bisphosphonate users*.

Subjects with a first prescription of bisphosphonates after a post-surgery fracture were considered as *non-users*, to avoid reverse causality (bisphosphonates appearing related with a higher number of fractures, when what really happens is that they are prescribed to prevent further fractures). In addition, subjects who never were prescribed bisphosphonates were considered as *non-users* as well.

Compliance with bisphosphonates

The level of compliance with bisphosphonates was assessed among bisphosphonate users using a standard measurement: the medication possession ratio (MPR). MPR has been used elsewhere to assess compliance in GPRD data [24], and was defined in our study as the proportion of days within the first and the last prescription registered for which patients had prescription cover. Bisphosphonate non-users were imputed an MPR value of null.

Propensity score methods

As bisphosphonate prescription was not randomly allocated in our study, potential confounding by indication was accounted for by using a propensity score for bisphosphonate use. The background and methods underlying propensity score use for the assessment of causality in epidemiological studies has been previously described [25–27].

The propensity score for bisphosphonate use represents the probability that a patient is prescribed bisphosphonate therapy, and was estimated separately for each of the three strata defined by pre-surgery fracture antecedents (no previous fracture, prior osteoporotic fracture and other previous fracture), using multivariate logistic regression modeling. Any prescription of bisphosphonates (yes/no) at least 6-months prior to fracture was used as a binary outcome variable. Potential confounding variables considered were age, gender, body mass index (BMI), drinking status, smoking status, bone active drugs, hormone replacement therapy-selective estrogen receptor modulator (HRT-SERM), calcium/vit D supplements, comorbid conditions. The propensity score for bisphosphonate use was calculated from the estimated probability for each patient, based on the logistic regression equation. The calculated score represents the predicted probability that a subject would be prescribed bisphosphonates. For instance, in this case, female gender, older age and lower BMI (amongst other predictors) appeared associated with a higher probability of being a bisphosphonate user. Hence, an older thinner lady had a higher propensity score than a younger obese male.

Propensity score was used as a covariate in further two separate models: firstly we performed a multivariate models (*propensity score adjustment*), as proposed by Austin et al. [28]; secondly, using the Matching package in R (available at http://cran.r-project.org/web/packages/Matching/index.html), we matched on the propensity scores each bisphosphonate user to the three non-users with most similar propensity score (*propensity-matched analysis*).

Statistical analyses

Differences between bisphosphonate users and non-users (as defined above) 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. The covariates included in the model were those with clinically plausible confounders, and/or which presented at least borderline significance ($p \leq 0.1$) in the multivariate analysis.

As a sensitivity analysis, compliance with bisphosphonates (MPR) was tested as a predictor of fracture occurrence using uni and multivariable Cox regression models, controlling for the same confounders as described above.

The proportional hazards assumption was checked using the Schoenfeld residuals formal test and the smoothing splines in time plots. The linearity of quantitative covariates was assessed by inspection of the Martingale's residuals plots. Deltabeta plots were used to look for possible influential cases.

To give a clinical effect size, we calculated Number Needed to Treat to avoid one fracture at 5 years of follow-up, based on the survival probability function and the Hazard Ratio [29].

All these analyses were performed separately for each group previously defined by stratification on previous fracture.

As an additional analysis, the same models were fitted using the occurrence of major fractures (as defined by Center and Eisman, based on the mortality associated to them (30)) as the main outcome. The list of fracture sites accounted for in these analyses included: hip, clinical spine, pelvic, distal femoral, proximal tibial, multiple rib, and proximal humeral fracture. GPRD codes used to ascertain these fractures are shown in Appendix 3 (available online). Due to a reduced number of outcomes, matched models and analyses where compliance was the main exposure were underpowered. Hence, only propensity-adjusted multivariate models, using bisphosphonate use as a binary exposure, are presented.

Results

Patient characteristics

Among 18,121 eligible patients, 14,223 (78.49%) had no fracture antecedent prior to TKR, and the remaining 3,898 (21.51%) had suffered at least one fracture prior to surgery. In the latter group, 1,491 (38.3%) had previously had an osteoporotic fracture, and 2,407 (61.7%) a fracture at any other site. From the non-previously fractured group, 934 (6.57%) were *bisphosphonate users*, as were 287 (19.2%) from those with an osteoporotic fracture, and 218 (9.1%) from those with any other previous fracture. See population flow-chart (Fig. 1). Baseline characteristics for treated and non-treated subjects in these three subpopulations are summarized in Table 1. *Bisphosphonate users* were significantly older, had lower BMI, were more likely to be women, and to be prescribed fracture-associated medications (from the following: antiarrhythmics, anticonvulsants, antidepressants, antiparkinson agents, anxiolytics, or proton pump inhibitors), HRT, SERM or calcium/vitamin D supplements. They were also more likely to suffer from comorbid conditions (asthma, malabsorptive syndromes, inflammatory bowel disease, hypertension, hyperlipidemia, ischemic heart disease, cerebro-vascular disease, chronic renal failure, cancer). In contrast, *bisphosphonate non-users* were more likely to be current smokers. This applied to all the subgroups.

After matching on propensity score, *bisphosphonate users* and *matched non-users* became more comparable (see Table 1). A bias reduction of more than 90% was achieved in most of the observed potential confounders. The corresponding propensity score logistic models for the population of no fracture, osteoporosis fracture, and any other previous fracture, respectively, achieved a *c* statistic (corresponding to the area under the ROC curve) of 0.74 (95% CI, 0.73 to 0.76), 0.76 (95% CI, 0.73 to 0.80), and 0.77 (95% CI, 0.74 to 0.81), indicating a good ability to differentiate between bisphosphonate users and non-users.

Bisphosphonate use and post-TKR fractures

Patients with no fracture prior to TKR

In the 5 years following knee replacement, 646 (4.5%) subjects had a first fracture. Among bisphosphonate users, first fractures occurred in 50 (5.4%) patients, while in non-users, they appeared in 596 (4.5%) subjects. In a crude Cox analysis, there was no association between bisphosphonate use and fracture occurrence (hazard ratio (HR), 1.08; 95% CI, 0.81 to 1.44). In the propensity-matched analysis, 244 (8.71%) of the matched controls had a first fracture during the 5 years follow-up post-surgery. In bisphosphonate users, fractures occurred in 50 (5.36%) patients in the same period. Crude Cox analysis suggested a significant decrease in fracture risk associated with bisphosphonate use (HR, 0.56; 95% CI, 0.42 to 0.76; $p<0.001$) that persisted significant event after adjustment for age, gender, BMI, drinking status, smoking status, bone active drugs, HRT-SERMs, calcium/vitamin D supplements, and comorbid conditions (HR, 0.48; 95% CI, 0.35 to 0.65; $p<0.001$) (see Table 2). The findings from the propensity-adjusted analyses did not differ substantially from these and are shown in Table 2.

In the same time period, 270 (1.9%) subjects had a major fracture, as defined by Center and Eisman [30]. Propensity-adjusted multivariate Cox models showed a significant reduction in the risk of occurrence of these fractures

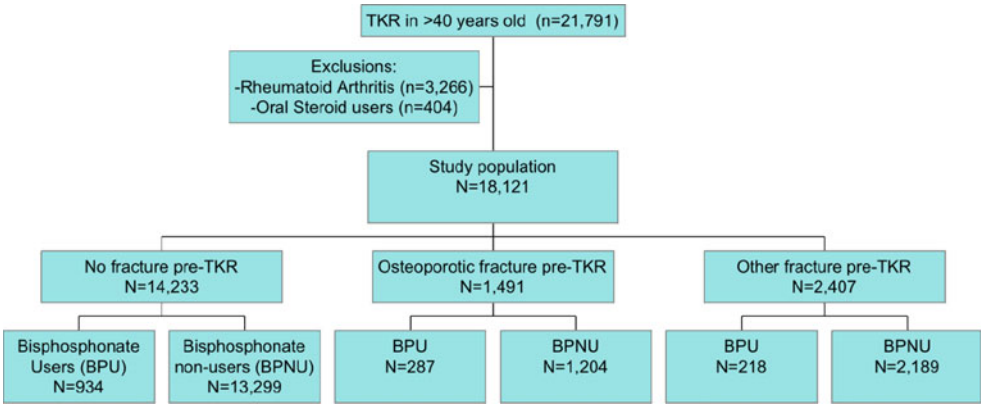

Fig. 1 Population flow-chart

associated to bisphosphonate use (HR, 0.55; 95% CI, 0.36 to 0.86; p=0.008).

Figure 2 shows a Kaplan–Meier plot, representing the probability of not having a fracture in the follow-up period of 5 years and 95% CI among bisphosphonate users and non-users, in the matched cohort.

Patients with fracture antecedents prior to TKR

In the group of patients with history of an osteoporotic fracture prior to TKR, and during the 5 years post-surgery, 201 (13.5%) subjects had a new fracture, being 43 (2.9%) of them identified as major fractures. Among subjects with any other previous fracture, 190 (7.9%) suffered a fracture in the same time period, and 36 (1.5%) of these were major fractures.

In the first group, among *bisphosphonate users* (n=287), 29 (10.1%) suffered a new fracture in the 5 years post-TKR, and of the *propensity-matched bisphosphonate non-users* (n=861), 127 (14.8%) had a new fracture in the same period. Cox analysis showed a significantly lower risk of fracture in *bisphosphonate users* (HR, 0.45; 95% CI, 0.29 to 0.70; p<0.001), which did not change in propensity-adjusted multivariate analyses (shown in Table 3). In the latter models, when major fractures were defined as the outcome, a similar protective effect was shown for bisphosphonate users (HR, 0.45; 95% CI, 0.20 to 1.00; p=0.05).

In the group of patients with any other fracture prior to TKR, 15 out of 218 *bisphosphonate users* (6.9%) had a new fracture post-surgery, while among *matched bisphosphonate non-users* (n=654), 61 (9.3%) of them fractured in the same 5 years of follow-up. Cox regression showed a significant reduction in risk of fracture after TKR associated to the use of bisphosphonates (HR 0.45, 95% CI, 0.25 to 0.82; p=0.003), which was similar in the propensity-adjusted multivariate model (Table 3). As for the major fractures propensity-adjusted models, a non-significant protective effect was demonstrated (HR, 0.50; 95% CI, 0.17 to 1.50; p=0.2).

Compliance with bisphosphonates and fracture risk

We explored the effect of different levels of exposure to bisphosphonates using MPR as a measurement of compliance. The results showed an increasing protective effect the higher is the MPR, with a maximum effect in those with an MPR >0.8: HR, 0.22 (95% CI, 0.08 to 0.59; p=0.004) in non-previously fractured subjects (Table 2), HR, 0.09 (95% CI, 0.01 to 0.67; p=0.01) in subjects with a prior osteoporotic fracture (Table 3). In the group of patients with any other fracture prior to TKR, the HR related to an MPR >0.8 was not significant (0.47 (95% CI, 0.20 to 1.11; p=0.12)) (Table 3), probably due to a power issue (only 15 of the bisphosphonate users identified amongst them had a fracture).

Figure 3 shows a Kaplan–Meier plot, representing the probability of not having a first fracture in the 5 years post-TKR among bisphosphonate non-users and among three categories of MPR (>0 to 0.4, >0.4 to 0.8, and >0.8 to 1), in the non-previously fractured subjects (matched analysis).

Number needed to treat and sample size estimation

In patients with no fracture antecedent prior to TKR, according to our results, at 5 years follow-up, the number of patients needed to treat to avoid one fracture (NNT) for the matched cohort would be 38.9. The calculated NNT to avoid one major fracture, as previously defined, was of 118.

The estimated NNT to avoid a fracture in subjects with an osteoporotic fracture prior to surgery at 5 years was 13.4 (NNT to avoid one major fracture was 63). In subjects with any other previous fracture, the calculated NNT was 23.2. Assuming that the estimated (non-significant) HR of 0.50 was correct, the NNT to avoid one major fracture in these patients would be 134.

In this context, our results are useful to make a first estimation of the sample size needed to assess the effect of bisphosphonates on post-TKR fracture primary and secondary prevention using a randomized clinical trial (RCT) design: in patients with no previous fracture, with 90%

Table 1 Baseline characteristics of the study population

	No fracture prior to TKR			Osteoporotic fracture prior to TKR			Any other fracture prior to TKR		
	Bisphosphonate users	Non-users	Matched non-users	Bisphosphonate users	Non-users	Matched non-users	Bisphosphonate users	Non-users	Matched non-users
No.	934	13,289	2,802	287	1,204	861	218	2,189	654
Age (years)	73.2 (0.4)	69.9***	73.3	75.5 (0.6)	72.4***	74.7 (0.1)	73.4 (0.6)	68.4***	73.5 (0.01)
Gender (males)	18.84%	46.77%***	17.45%	4.9%	29.2%***	4.6%	18.3%	51.1%***	17.1%
BMI (kg/m^2)	27.6 (0.3)	29.1***	27.7	27.3 (0.3)	28.7***	28.3** (0.2)	27.8	29.2***	28.1 (0.06)
Alcohol drinker	67.35%	74.88%***	67.31%	65.5%	67.7%**	64.1%*	67.4%	73.9%*	69.9%
Smoker	6.64%	9.71%***	7.24%	7.0%	10.7%**	8.4%*	6.9%	11.5%**	7.5%
Bone active drugs user[a]	74.73%	57.69%***	74.91%	77.4%	69.0%**	72.9%	79.8%	64.8%***	78.4%
HRT-SERM user	20.56%	14.85%***	20.63%	21.3%	12.1%***	16.7%	20.6%	13.6%**	20.3%
Calcium/vitamin D supplements user	4.07%	0. 44%***	2.00%**	21.6%	2.7%***	3.7%***	13.8%	0.9%***	2.9%***
Comorbid Conditions[b]	80.30%	74.50%***	80.48%	77.4%	73.8%	74.6%	81.2%	70.5%**	81.7%
Fractured post-TKR	5.35%	4.48%	8.71%	10.1%	11.9%	14.8%*	6.9%	5.9%	9.3%

Mean (standardized mean difference) is shown for continuous variables. Percentage is shown for categorical

*p <0.05, a difference between groups (bisphosphonate users vs. non-users); **p<0.01; ***p<0.001

[a] Bone active drugs: antiarrhythmics, anticonvulsants, antidepressants, antiparkinson agents, anxiolytics, proton pump inhibitors. Oral corticoid users were dropped from the study population

[b] Comorbid conditions: asthma, malabsorptive syndromes, inflammatory bowel disease, hypertension, hyperlipidemia, ischemic heart disease, *COPD* cerebro-vascular disease, chronic renal failure, cancer

Table 2 Effect of bisphosphonate use on post-surgery fracture in patients with no fracture prior to TKR

	Crude model HR (95% CI)	Propensity-score-adjusted model HR (95% CI)	Multivariate matched HR[a] (95% CI)
Use of bisphosphonates, at least 6 months before fracture	1.08 (0.81 to 1.44)	0.50*** (0.37 to 0.68)	0.48*** (0.35 to 0.65)
Use of bisphosphonates: medication possession ratio			
>0 to 0.4	1.27 (0.78 to 2.09)	0.46** (0.27 to 0.76)	0.44** (0.26 to 0.74)
>0.4 to 0.8	1.00 (0.59 to 1.70)	0.52* (0.30 to 0.89)	0.50* (0.29 to 0.86)
≥0.8 to 1	0.39 (0.15 to 1.05)	0.23** (0.09 to 0.62)	0.22** (0.08 to 0.59)

*$p<0.05$; **$p<0.01$; ***$p<0.001$

[a] Adjusted by: propensity score (when applicable), age, gender, BMI, drinking status, smoking status, bone active drugs (antiarrhythmics, anticonvulsants, antidepressants, antiparkinson agents, anxiolytics, proton pump inhibitors; oral corticoid users were dropped from the study population), calcium/vitamin D supplements, and comorbid conditions (asthma, malabsorptive syndromes, inflammatory bowel disease, hypertension, hyperlipidemia, ischemic heart disease, cerebro-vascular disease, COPD, chronic renal failure, cancer)

power and 5% significance, assuming a probability of fracture of 5% and a 20% of loss to follow-up, and taking into account the estimated HR of 0.47, a total of 1,844 subjects are required in an RCT (922 per arm) to assess the effect of bisphosphonates to reduce the risk of fracture after a TKR; in patients with a previous osteoporotic fracture, with same power and significance, assuming a probability of fracture of 13.6% and the same rate of loss to follow-up, and taking into account the estimated HR of 0.45, a total of 606 subjects (303 per arm) would be needed in a similar RCT. In patients with any other previous fracture, with same power, significance and rate of loss to follow-up, and assuming a probability of fracture of 8.7% and a HR of 0.45, 948 (474 per arm) would be needed to recruit per arm in such RCT. If high compliance (MPR >0.8) was to be assumed (as usual in RCT protocol designs), 230 patients per arm would be needed for a trial in patients with no previous fracture (assumed HR 0.22), and 35 should be assessed per arm for the study in patients with a previous osteoporotic fracture (estimated HR 0.09). In patients with any other previous fracture, the HR related to higher compliance with bisphosphonate therapy was not significant.

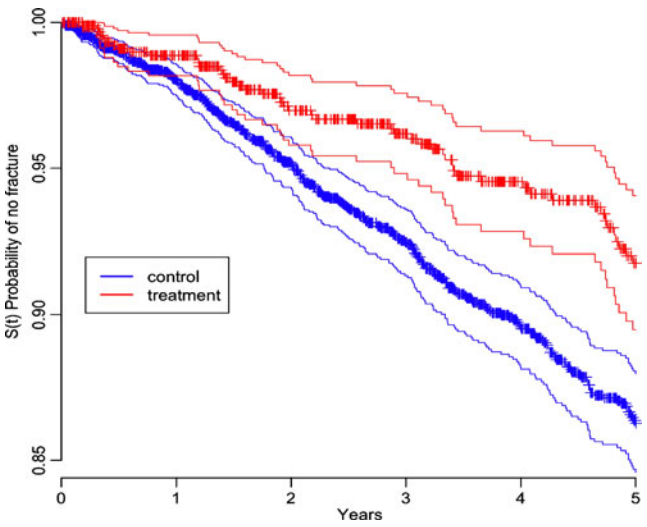

Fig. 2 Kaplan–Meier plot, showing probability of no fracture occurrence in time of follow-up after TKR (S(t)±95% CI) for bisphosphonate users (treatment) and non-users (control) in patients with no fracture prior to TKR. Matched analysis

Discussion

We report, for the first time, a potential beneficial effect of bisphosphonate use against all fractures in a population-based cohort of patients with knee osteoarthritis undergoing TKR. Our data suggest an associated fracture risk reduction of 50% in patients with no previous fracture, and of about 55% in patients with any fracture prior to surgery. The observed reduction in risk of major fractures occurrence observed for bisphosphonate users was similar: 55% in patients with an osteoporotic fracture antecedent prior to TKR, and 45% in patients with no prior fracture. In patients with any other previous fracture, we observed a non-significant major fracture risk reduction of about 50%.

Also, we showed that the higher compliance with bisphosphonate therapy, is associated with higher protective effect achieved. The maximum protective effect observed was shown in patients with an osteoporotic fracture prior to TKR: among them, bisphosphonate use was associated with a reduction of fracture risk of about 90%.

Comparison with previous studies

At least two trials have aimed to assess in the last few years the effect of bisphosphonates on osteoarthritis symptoms and progression, with different results [19, 31]. While observational data raised recently the suspicion that these drugs could have beneficial effects on subchondral bone structure in patients with knee osteoarthritis, as assessed by magnetic resonance imaging [32], a randomized clinical

Table 3 Effect of bisphosphonate use on post-surgery fracture in patients with a previous fracture

	Non-OP fracture prior to TKR		OP fracture prior to TKR	
	Propensity-score-adjusted model HR[a] (95% CI)	Multivariate matched HR (95% CI)	Propensity-score-adjusted model HR[a] (95% CI)	Multivariate matched HR (95% CI)
Use of bisphosphonates, at least 6 months before fracture	0.47* (0.26–0.85)	0.45** (0.25–0.82)	0.46*** (0.30–0.71)	0.45*** (0.29–0.70)
Compliance (medication possession ratio)				
>0 to <0.8	0.54 (0.25–1.17)	0.52 (0.24–1.13)	0.56* (0.35–0.88)	0.55* (0.35–0.88)
≥0.8	0.48 (0.20–1.14)	0.47 (0.20–1.11)	0.10* (0.01–0.68)	0.09* (0.01–0.67)

*$p<0.05$; **$p<0.01$; ***$p<0.001$

[a] Adjusted by: propensity score (when applicable), age, gender, BMI, drinking status, smoking status, bone active drugs (antiarrhythmics, anticonvulsants, antidepressants, antiparkinson agents, anxiolytics, proton pump inhibitors; oral corticoid users were dropped from the study population), Calcium/Vitamin D supplements, and comorbid conditions (asthma, malabsorptive syndromes, inflammatory bowel disease, hypertension, hyperlipidemia, ischemic heart disease, cerebro-vascular disease, COPD, chronic renal failure, cancer)

trial [33] demonstrated that risedronate, when given at high dose (15 mg/day) for 2 years, retained vertical trabecular structure in the medial compartment of the proximal tibia among knee OA affected patients. Also, a small ($n=19$) randomized clinical trial suggested that alendronate may reduce early post-operative periprosthetic bone loss significantly in patients who had undergone a TKR. This would suggest that the expected improvement in bone structure produced by bisphosphonates in osteoporotic patients is also applicable to patients with osteoarthritis, at least locally. If such effect were not only local but also observed at distant sites from the affected joint/s, these reports would be concordant with our findings of a fracture risk reduction after a TKR associated with bisphosphonate use. However, we have not been able to identify any study that addressed the important issue here raised, about the potential effect of these drugs on the risk of fractures in these patients.

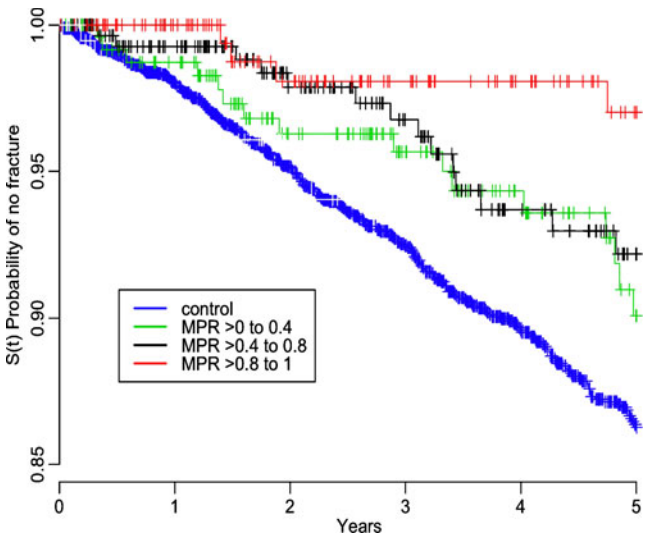

Fig. 3 Kaplan–Meier plot, showing probability of no fracture occurrence in time of follow-up after TKR (S(t)±95% CI) for bisphosphonate non-users (control) and different levels of compliance (*MPR*) with bisphosphonate use in patients with no prior fracture. Matched analysis

Clinical trials that assessed the effect of alendronate [34] on patients with hip osteoporosis estimated a NNT at 5 years of 11. This would imply that the NNT to avoid one fracture in patients after a TKR with a prior osteoporotic fracture would be similar to that in osteoporotic subjects. However, the NNT is highly influenced by the baseline risk of fracture, and so the NNT is higher for patients with lower fracture risk than those with a high fracture risk. The NNT for fracture prevention among patients with any other previous fracture would double the NNT of these patients, and in subjects with no previous fracture, it would be about three times and a half higher. However, while in the mentioned FIT trial at 4.2 years of follow-up, 81.3% of the treated participants were still taking alendronate [35], in community based studies up to 40% of the patients who start the same drug in actual practice are non-persistent by 12 months [36]. This would lead to significant underestimation of the efficacy of bisphosphonates to reduce post-operative fractures in subjects after a TKR in our study, due to lack of persistence with the treatment. We evaluated the effect of compliance with the treatment on the protective effect of bisphosphonate use, and showed that a higher compliance (MPR >0.8) is related to a higher fracture risk reduction. This is reassuring of the potential effect of bisphosphonates among these patients, and supports the results of studies performed in osteoporotic patients that have shown that increased compliance leads to a higher reduction in fracture risk [37].

In addition, taking into consideration that the costs of knee replacement are high, cost-effectiveness of bisphosphonate therapy to avoid fractures post-surgery (and further complications) among these patients, must be carefully evaluated in the future.

Strengths and limitations

This is a large prospective cohort study using data from general practice across the UK. Potential limitations are the quality of coding of drug use, timing of fractures and confounders. However, the coding of drug use and fracture have been validated in the GPRD. Propensity score matching is a recognized method to address confounding by indication in observational studies [25, 26, 38].

We have looked at the effect of any bisphosphonate use for at least 6 months prior to fracture, so may have underestimated the effect of treatment, which may be stronger in persistents. Also, some bisphosphonates might be more protective than others, but we were unable to assess this in our data, due to the difficulties associated to the use of propensity scores methods to control for treatment allocation when different drugs are compared.

The benefit of a cohort study rather than a trial is it is more likely to reflect clinical practice rather than a trial setting due to less restrictive inclusion criteria. According to this, we report the results of both the propensity-adjusted model, where all the participants were included in the analysis (better external validity), and the propensity-matched model, which only included comparable controls, and so, is more likely to give results similar to clinical trials. A major limitation of this method is it is not able to assess the potential effect of placebo, and so may overestimate the beneficial effect of bisphosphonate use.

Limitations are possible loss to follow-up bias, but right censoring on the date when a patient left the practice and on death date in our Cox models tried to take into account different possible scenarios. Also, quality of coding of outcome variable (measurement bias) could be present in our study, though fractures registration has been shown to be valid [23] in GPRD. Anyway, this should all be non-differential (same across exposure groups).

The calculated NNTs for the different groups are useful both for clinical implications and for future research, but not applicable to populations with relevant differences in baseline characteristics when compared with ours.

Another limitation is the possibility of residual confounding, though the high values of the c statistics calculated for the logistic propensity models suggest a strong ability to differentiate between users and non-users. However, the finding of a significant fracture reduction in patients with low MPR remains unexplained, and could be due to residual confounding, not adjusted for using propensity scores: the main example of such residual confounding in these data is the use of calcium and vitamin D supplements, which remained different among bisphosphonate users and non-users, even after adjusting and matching on propensity scores (see Table 1). The observed higher use of calcium and vitamin D supplements among bisphosphonate users can account for the protective effect demonstrated in subjects with low compliance to bisphosphonate therapy.

Finally, the important issue as to whether patients should be initiated on bisphosphonate therapy before or after surgery remains unanswered, and should be addressed in future randomized clinical trial studies.

Conclusions and clinical implications

The results of our study, despite the mentioned limitations, demonstrate an observed clinically significant reduction by about 50% to 55% in fracture risk after TKR associated with bisphosphonate use. Similar protective effects were shown as well in terms of major fractures risk reduction. These findings should now be confirmed in a randomized clinical trial.

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Conflicts of interest DPA has no conflicts of interest to declare. MKJ, NKA and CC have received honorarium, ad boards and consortium research grants respectively from: Novartis, Alliance for Better Health and Lilly; Merck, MSD, Roche, Novartis, Smith and Nephew, Q-MED, Nicox, Servier, GSK, Schering-Plough, Pfizer and Rottapharm; Alliance for Better Bone Health, Amgen, Novartis, MSD, Servier, Eli Lilly and GSK. The rest of authors have no conflicts of interest to state.

Appendix 1

Table 4 READ/OXMIS codes used for the ascertainment of primary total knee replacement

Read/OXMIS code	Read/OXMIS term
X6060	Total knee replacement
XE08w	Total prosthetic replacement of knee using cement
XE08y	Total prosthetic replacement of knee joint not using cement
XE090	Other total prosthetic replacement of knee joint
XE091	Primary hybrid total knee replacement NEC
7K30.00	Total prosthetic replacement of knee joint using cement

Table 4 (continued)

Read/OXMIS code	Read/OXMIS term
7K30.11	Anametric total replacement of knee joint using cement
7K30.13	Attenborough total replacement of knee joint using cement
7K30.15	Cavendish total replacement of knee joint using cement
7K30.16	Charnley total replacement of knee joint using cement
7K30.17	Deane total replacement of knee joint using cement
7K30.18	Denham total replacement of knee joint using cement
7K30.19	Freeman total replacement of knee joint using cement
7K30.1A	Geomedic total replacement of knee joint using cement
7K30.1B	Geometric total replacement of knee joint using cement
7K30.1C	Guepar hinge replacement of knee joint using cement
7K30.1D	Gunston total replacement of knee joint using cement
7K30.1E	Herbert total replacement of knee joint using cement
7K30.1F	Ilch total replacement of knee joint using cement
7K30.1G	Irving total replacement of knee joint using cement
7K30.1H	Liverpool total replacement of knee joint using cement
7K30.1I	Manchester total replacement of knee joint using cement
7K30.1 J	Marmor total replacement of knee joint using cement
7K30.1 L	Melbourne total replacement of knee joint using cement
7K30.1 N	Polycentric total replacement of knee joint using cement
7K30.1P	Sheehan total replacement of knee joint using cement
7K30.1Q	Shiers total replacement of knee joint using cement
7K30.1R	Stanmore total replacement of knee joint using cement
7K30.1 S	Swanson total replacement of knee joint using cement
7K30.1 T	Uci total replacement of knee joint using cement
7K30.1 V	TKR—total prosthetic replacement of knee joint using cement
7K31.00	Total prosthetic replacement of knee joint not using cement
7K31.12	TKR—total prosthetic replacement knee joint without cement
7K32.00	Other total prosthetic replacement of knee joint

Table 4 (continued)

Read/OXMIS code	Read/OXMIS term
7K32.12	TKR—other total prosthetic replacement of knee joint
7K32000	Primary total knee replacement NEC
7K32011	Primary hybrid total knee replacement NEC
7K37.00	Cemented unicompartmental knee replacement
7K37000	Primary cemented unicompartmental knee replacement
7K38.00	Uncemented unicompartmental knee replacement
7K38000	Primary uncemented unicompartmental knee replacement
7K39.00	Hybrid unicompartmental knee replacement
7K39000	Primary hybrid unicompartmental knee replacement
K812	Total knee replacement
K812 AA	Arthroplasty knee
K812 AB	Knee joint replacement
K812 AC	Knee replacement
7K30000	Primary cemented total knee replacement
7K30y00	Total prosthetic replacement of knee joint using cement OS
7K30z00	Total prosthetic replacement of knee joint using cement NOS
7K31000	Primary uncemented total knee replacement
7K31y00	Total prosthetic replacement knee joint not using cement OS
7K31z00	Total prosthetic replacement knee joint not using cement NOS
7K32y00	Other total prosthetic replacement of knee joint OS
7K32z00	Other total prosthetic replacement of knee joint NOS
X606Q	Prosthetic medial unicompartmental arthroplassty of the knee
X606R	Prosthetic lateral unicompartmental arthroplassty of the knee
X606T	Resurfacing of the patella

Appendix 2

Table 5 READ/OXMIS codes used for the ascertainment of fractures

Read/OXMIS code	Read/OXMIS term
S30..00	Fracture of neck of femur
8210	Fracture femur
S31z.00	Fracture of femur, NOS
820 B	Fracture neck of femur
820 A	Fracture hip
S30..11	Hip fracture
S31..00	Other fracture of femur

Table 5 (continued)

Read/OXMIS code	Read/OXMIS term
S310.00	Closed fracture of femur, shaft or unspecified part
S314.00	Fracture of shaft of femur
7K1L400	Closed reduction of fracture of hip
S10B400	Fracture of acetabulum
S30y.11	Hip fracture NOS
S30y.00	Closed fracture of neck of femur NOS
808 A	Fracture acetabulum
S302400	Closed fracture of femur, intertrochanteric
14G7.00	H/O: hip fracture
820T	Fracture trochanter
S312300	Closed fracture distal femur, supracondylar
S310100	Closed fracture shaft of femur
S130.00	Closed fracture acetabulum
S302.00	Closed fracture of proximal femur, pertrochanteric
S305.00	Subtrochanteric fracture
S3x2.00	Multiple fractures of femur
SC3D400	Sequelae of fracture of femur
S310000	Closed fracture of femur, unspecified part
S310011	Thigh fracture NOS
S10x.00	Closed fracture of spine, unspecified,
8056AA	Fracture vertebral column
S104.00	Closed fracture lumbar vertebra
S15..00	Fracture of thoracic vertebra
S10..12	Fracture of vertebra without spinal cord lesion
L8056LV	Fracture lumbar vertebra
8054C	Fracture coccyx
S104100	Closed fracture lumbar vertebra, wedge
S10..00	Fracture of spine without mention of spinal cord injury
S10B200	Fracture of coccyx
S102.00	Closed fracture thoracic vertebra
S100.00	Closed fracture of cervical spine
8050	Fracture cervical spine
S10B000	Fracture of lumbar vertebra
N331800	Osteoporosis+pathological fracture lumbar vertebrae
N331900	Osteoporosis+pathological fracture thoracic vertebrae
8056C	Fracture compression vertebra
N1y1.00	Fatigue fracture of vertebra
14G8.00	H/O: vertebral fracture
8054A	Fracture sacrum
S106.00	Closed fracture sacrum
S1...00	Fracture of neck and trunk
S1...00	Fracture of neck and trunk
S102100	Closed fracture thoracic vertebra, wedge
S150.00	Multiple fractures of thoracic spine
S10B100	Fracture of sacrum

Table 5 (continued)

Read/OXMIS code	Read/OXMIS term
S10B600	Multiple fractures of lumbar spine and pelvis
8052D	Fracture dorsal vertebra
S10A200	Multiple fractures of cervical spine
8056	Spinal fracture
7 J43.00	Fixation of fracture of spine
7 J43.00	Fixation of fracture of spine
S10..11	Fracture of transverse process spine—no spinal cord lesion
S10B.00	Fracture of lumbar spine and pelvis
S10B.00	Fracture of lumbar spine and pelvis
S100200	Closed fracture axis
S10A.00	Fracture of neck
S234100	Closed Colles' fracture
8130R	Fracture radius
S23x111	Fracture of radius NOS
814W	Fracture wrist
8230T	Fracture tibia
S23..00	Fracture of radius and ulna
S234.11	Wrist fracture—closed
S23B.00	Fracture of lower end of radius
S234200	Closed fracture of the distal radius, unspecified
8130RU	Fracture radius and ulnar
7K1LL00	Closed reduction of fracture of radius and or ulna
8134C	Fracture Colles'
S230600	Closed fracture radius, head
S242.00	Fracture at wrist and hand level
S23x100	Closed fracture of radius (alone), unspecified
7K1LM00	Closed reduction of fracture of wrist
S23z.00	Fracture of radius and ulna, NOS
S23x300	Closed fracture of the radius and ulna
8134R	Fracture radius lower end
S234.00	Closed fracture of radius and ulna, lower end
S237.00	Fracture of upper end of radius
S239.00	Fracture of shaft of radius
7K1LE00	Closed reduction of fracture of elbow
8130RH	Fracture radius head
S234B00	Closed fracture radial styloid
S23..11	Forearm fracture
S234700	Closed Smith's fracture
8134RA	Smiths fracture
S235.11	Wrist fracture—open
S4C..00	Fracture–dislocation or subluxation of wrist
S4C..00	Fracture–dislocation or subluxation of wrist
S234z00	Closed fracture of forearm, lower end, NOS
S24..00	Fracture of carpal bone
S230700	Closed fracture radius, neck
S235100	Open Colles' fracture
S232.00	Closed fracture of radius and ulna, shaft
S240300	Closed fracture triquetral

Table 5 (continued)

Read/OXMIS code	Read/OXMIS term
S23C.00	Fracture of lower end of both ulna and radius
S234600	Closed fracture radius and ulna, distal
S352.11	March fracture
S293.00	Multiple fractures of forearm
S230.00	Closed fracture of proximal radius and ulna
S232100	Closed fracture of the radial shaft
814 C	Fracture carpal
S23x.00	Closed fracture of radius and ulna, unspecified part
S240800	Closed fracture hamate
S23A.00	Fracture of shafts of both ulna and radius
S240.00	Closed fracture of carpal bone
S24z.00	Fracture of carpal bone NOS
S234000	Closed fracture of forearm, lower end, unspecified
S232000	Closed fracture of radius, shaft, unspecified
S230900	Closed fracture of the proximal radius
S234900	Closed volar Barton's fracture
S22..00	Fracture of humerus
8122	Fracture humerus
S224100	Closed fracture distal humerus, supracondylar
8120HN	Fracture humerus neck
S220.00	Closed fracture of the proximal humerus
8124SH	Supracondylar fracture humerus
7K1LG00	Closed reduction of fracture of shoulder
7K1LF00	Closed reduction of fracture of humerus
S22z.00	Fracture of humerus NOS
S228.00	Fracture of lower end of humerus
S224.00	Closed fracture of the distal humerus
811 B	Fracture shoulder blade
8120	Fracture humerus upper end
S4A..00	Fracture–dislocation or subluxation shoulder
S220100	Closed fracture proximal humerus, neck
S226.00	Fracture of upper end of humerus
S292.00	Multiple fractures of clavicle, scapula, and humerus
S220300	Closed fracture proximal humerus, greater tuberosity
S227.00	Fracture of shaft of humerus
S222100	Closed fracture of humerus, shaft
S4A0.00	Closed fracture–dislocation shoulder
S222000	Closed fracture of humerus NOS
8124SC	Fracture humerus supra condylar
S222.00	Closed fracture of humerus, shaft or unspecified part
S220000	Closed fracture of proximal humerus, unspecified part
S221.11	Shoulder fracture—open
S20..00	Fracture of clavicle
S34..00	Fracture of ankle

Table 5 (continued)

Read/OXMIS code	Read/OXMIS term
810	Fracture clavicle
815 A	Fracture metacarpal bone(s)
816 F	Fracture finger
824	Fracture ankle
S25..00	Fracture of metacarpal bone
S250.00	Closed fracture of metacarpal bone(s)
S242000	Fracture of scaphoid
S26..11	Finger fracture
8070	Fracture ribs
S0...00	Fracture of skull
S36..11	Toe fracture
826	Fracture toe(s)
S26..00	Fracture of one or more phalanges of hand
S33..00	Fracture of tibia and fibula
825M	Fracture metatarsal
S120.00	Closed fracture rib
8020	Fracture nose
S35..11	Metatarsal bone fracture
S242200	Fracture of other metacarpal bone
814 A	Fracture scaphoid carpal
S240100	Closed fracture of the scaphoid
S224.11	Elbow fracture - closed
S33x000	Closed fracture of tibia, unspecified part, NOS
824 M	Fracture malleolus
8230F	Fracture fibula
S263.00	Fracture of other finger
8124E	Fracture elbow
S352700	Closed fracture metatarsal
S26z.00	Fracture of one or more phalanges of hand NOS
816 T	Fracture thumb
818 F	Fracture arm
827 A	Fracture foot
S32..00	Fracture of patella
S36..00	Fracture of one or more phalanges of foot
S356.00	Fracture of metatarsal bone
S2...11	Arm fracture
8230TF	Fracture tibia and fibula
S339.00	Fracture of fibula alone
S342.00	Closed fracture ankle, lateral malleolus
S13..00	Fracture or disruption of pelvis
8130L	Fracture ulna
S23x211	Fracture of ulna NOS
815 H	Fracture hand
816 PH	Fracture phalanges
S360.00	Closed fracture of one or more phalanges of foot
S262.00	Fracture of thumb
S349.00	Fracture of lateral malleolus

Table 5 (continued)

Read/OXMIS code	Read/OXMIS term
S024100	Closed fracture zygoma
822	Fracture patella
S127.00	Fracture of rib
8022	Fracture mandible
7K1L700	Closed reduction of fracture of tibia and or fibula
S35..00	Fracture of one or more tarsal and metatarsal bones
S33x100	Closed fracture of fibula, unspecified part, NOS
7J03100	Reduction of fracture of nasal bones NEC
S337.00	Fracture of shaft of tibia
827 B	Fracture leg
S25..11	Hand fracture—metacarpal bone
S340.00	Closed fracture ankle, medial malleolus
8020C	Fracture nasal bones closed
S3...11	Leg fracture
8024A	Fracture zygoma
S132.00	Closed fracture pubis
S127000	Multiple fractures of ribs
7K1LA00	Closed reduction of fracture of toe
S342000	Closed fracture ankle, lateral malleolus, low
S26..12	Thumb fracture excluding base
S260.00	Closed fracture of one or more phalanges of hand
8130B	Fracture olecranon
S3z2.00	Stress fracture
7K1LJ00	Closed reduction of fracture of thumb
S362.00	Fracture of great toe
S350.00	Closed fracture of calcaneus
S21..00	Fracture of scapula
7K1LH00	Closed reduction of fracture of finger
S264.00	Multiple fractures of fingers
S33x200	Closed fracture of tibia and fibula, unspecified part
S363.00	Fracture of other toe
S120000	Closed fracture of rib, unspecified
S10B500	Fracture of pubis
S230100	Closed fracture olecranon, extra-articular
7K1L800	Closed reduction of fracture of ankle
S344.00	Closed fracture ankle, bimalleolar
S242300	Multiple fractures of metacarpal bones
S132000	Closed fracture pelvis, single pubic ramus
S339000	Closed fracture of distal fibula
S028300	Fracture of mandible
S122.00	Closed fracture sternum
825 HC	Fracture calcaneum
S348.00	Fracture of medial malleolus
8072	Fracture sternum
S334.00	Closed fracture distal tibia

Table 5 (continued)

Read/OXMIS code	Read/OXMIS term
8070C	Ribs fracture closed
S352100	Closed fracture of talus
S020.11	Closed fracture nasal bone
S33z.00	Fracture of tibia and fibula, NOS
811	Fracture scapula
S3x4.00	Multiple fractures of foot
S355.00	Fracture of talus
S00..00	Fracture of vault of skull
S234300	Closed fracture of ulna, styloid process
S354.00	Fracture of calcaneus
S34x.00	Closed fracture ankle, unspecified
S00..12	Parietal bone fracture
S352300	Closed fracture cuboid
S352200	Closed fracture navicular
S12z.11	Rib fracture NOS
S338.00	Fracture of lower end of tibia
803	Skull fracture
8290SF	Stress fracture
S20..11	Collar bone fracture
S34z.00	Fracture of ankle, NOS
S238.00	Fracture of shaft of ulna
S250400	Closed fracture finger metacarpal neck
S4D..00	Fracture–dislocation/subluxation finger/thumb
S4D..00	Fracture–dislocation/subluxation finger/thumb
S128.00	Fracture of sternum
S260D00	Closed fracture finger proximal phalanx
S360000	Closed fracture proximal phalanx, toe
S28..11	Ill-defined fracture of arm
S242100	Fracture of first metacarpal bone
S024.00	Fracture of malar or maxillary bones, closed
7J03200	Reduction of fracture of zygomatic bones
S2z..00	Fracture of upper limb NOS
S250z00	Closed fracture of metacarpal bone(s) NOS
S24..11	Hand fracture—carpal bone
S2B..00	Fracture of bone of hand
S02z.11	Jaw fracture NOS
8024B	Fracture maxilla
8024RB	Fracture orbit
8024 M	Fracture malar
S13y.00	Closed fracture of pelvis NOS
S23x200	Closed fracture of ulna (alone), unspecified
S132100	Closed fracture pelvis, multiple pubic rami—stable
S336.00	Fracture of upper end of tibia
S260R00	Closed fracture finger distal phalanx
S330300	Closed fracture proximal tibia, medial condyle (plateau)
S200.00	Closed fracture of clavicle
7 J03.00	Reduction of fracture of facial bone

Table 5 (continued)

Read/OXMIS code	Read/OXMIS term
810 CB	Fracture collar bone
S20z.00	Fracture of clavicle NOS
S346.00	Closed fracture ankle, trimalleolar
S4B..00	Fracture–dislocation or subluxation elbow
S4B..00	Fracture–dislocation or subluxation elbow
S108.00	Closed fracture pelvis, coccyx
815	Fracture metacarpus
S35z.00	Fracture of tarsal and metatarsal bones NOS
S352B00	Closed fracture metatarsal base
S3x3.00	Multiple fractures of lower leg
S29..12	Multiple rib fractures
S292.00	Multiple fractures of clavicle, scapula and humerus
S024000	Closed fracture maxilla
S21..11	Shoulder blade fracture
S02x100	Fracture of orbit NOS, closed
S250600	Closed fracture finger metacarpal
N331.00	Pathological fracture
S260K00	Closed fracture finger middle phalanx
S4H..00	Fracture–dislocation or subluxation foot
S4H..00	Fracture–dislocation or subluxation foot
825 B	Fracture cuboid
S260E00	Closed fracture finger proximal phalanx, base
S01..15	Occiput bone fracture
S230B00	Closed fracture olecranon, intra-articular
S01..00	Fracture of base of skull
S332000	Closed fracture shaft of tibia
S250300	Closed fracture finger metacarpal shaft
S36z.00	Fracture of one or more phalanges of foot NOS
7239B	Pathological fracture
S021.00	Open fracture nose
S028100	Fracture of orbital floor
S120900	Closed fracture multiple ribs
S350.11	Heel bone fracture
S260000	Closed fracture of phalanx or phalanges, unspecified
S250200	Closed fracture finger metacarpal base
S225.11	Elbow fracture—open
S362000	Closed fracture of great toe
S224700	Closed fracture distal humerus, medial epicondyle
S210300	Closed fracture scapula, glenoid
8124	Fracture humerus lower end
S120A00	Cough fracture
S330400	Closed fracture proximal tibia, lateral condyle (plateau)
S224600	Closed fracture distal humerus, lateral epicondyle
S200200	Closed fracture clavicle, shaft
S4D0100	Closed fracture–dislocation, metacarpophalangeal joint

Table 5 (continued)

Read/OXMIS code	Read/OXMIS term
S4D0100	Closed fracture–dislocation, metacarpophalangeal joint
S360200	Closed fracture distal phalanx, toe
808 P	Fracture pubis
S330000	Closed fracture of the proximal tibia
N331M00	Fragility fracture due to unspecified osteoporosis
7K1Gz00	Other primary open reduction of fracture of bone NOS
826 P	Phalanx distal fracture
S224200	Closed fracture distal humerus, lateral condyle
825 MA	March fracture
S260L00	Closed fracture finger middle phalanx, base
14G6.00	H/O: fragility fracture
S33x.00	Closed fracture of tibia and fibula, unspecified part, NOS
S120100	Closed fracture of one rib
S026.00	Closed orbital blow-out fracture
S0z..00	Fracture of skull NOS
S10B600	Multiple fractures of lumbar spine and pelvis
S250000	Closed fracture of metacarpal bone (s), site unspecified
S240500	Closed fracture trapezium
S332.00	Closed fracture of tibia/fibula, shaft
7J12100	Open reduction of fracture of mandible NEC
S01..19	Temporal bone fracture
S028200	Fracture of malar and maxillary bones
S210100	Closed fracture scapula, acromion
S02z.00	Fracture of facial bone NOS
801 TM	Fracture temporal bone
S12z.00	Fracture of rib(s), sternum, larynx or trachea NOS
811 A	Fracture acromion
801 C	Fracture occiput
S32z.00	Fracture of patella, NOS
S332100	Closed fracture shaft of fibula
808	Pelvis fracture
S35..12	Tarsal bone fracture
S234500	Closed fracture distal ulna, unspecified
S200z00	Closed fracture of clavicle NOS
S134600	Closed fracture pelvis, iliac wing
8021	Fracture nasal bones open
S236.00	Fracture of upper end of ulna
S224000	Closed fracture of elbow, unspecified part
S200000	Closed fracture of clavicle, unspecified part
S320.00	Closed fracture of the patella
S250500	Closed fracture finger metacarpal head
825 CA	Fracture scaphoid tarsal
S4J0100	Closed fracture–dislocation of pelvis
S4J0100	Closed fracture–dislocation of pelvis

Table 5 (continued)

Read/OXMIS code	Read/OXMIS term
S127100	Cough fracture of ribs
K2196	Zygoma fracture reduction
S022.12	Fracture of lower jaw, closed
S12z.12	Sternum fracture NOS
S260300	Closed fracture thumb proximal phalanx
S250800	Closed fracture of thumb metacarpal
S225100	Open fracture distal humerus, supracondylar
S03z.00	Skull fracture NOS
S335.00	Open fracture distal tibia
S260z00	Closed fracture of one or more phalanges of hand NOS
S261.00	Open fracture of one or more phalanges of hand
S025100	Open fracture zygoma
825T	Fracture tarsal
808 R	Pubic rami fracture
S231100	Open fracture olecranon, extra-articular
S261R00	Open fracture finger distal phalanx
S332200	Closed fracture of tibia and fibula, shaft
S352400	Closed fracture medial cuneiform
814 TR	Fracture trapezium
S210400	Closed fracture scapula, blade
800 P	Fracture skull parietal
S345.00	Open fracture ankle, bimalleolar
S352C00	Closed fracture metatarsal shaft
S231B00	Open fracture olecranon, intra-articular
S260800	Closed fracture thumb distal phalanx
S240200	Closed fracture lunate
S330100	Closed fracture proximal fibula
S120200	Closed fracture of two ribs
S10B300	Fracture of ilium
S230200	Closed fracture of ulna, coronoid
7J02200	Elevation of depressed fracture of cranium
S37..00	Fracture of lower limb, level unspecified
S4C0100	Closed fracture–dislocation radiocarpal joint
S4C0100	Closed fracture–dislocation radiocarpal joint
S022z00	Fracture of mandible, closed, NOS
S4D0400	Closed fracture–dislocation, proximal interphalangeal joint
S4G0.00	Closed fracture–dislocation, ankle joint
S120z00	Closed fracture of rib(s) NOS
9N0X.00	Seen in fracture clinic
S3z..11	Fracture NOS
829N	Fracture
S3z0000	Greenstick fracture
S020.00	Closed fracture nose
S2...00	Fracture of upper limb
S3z..00	Fracture of unspecified bones
14G9.00	H/O: fracture

Table 5 (continued)

Read/OXMIS code	Read/OXMIS term
829 A	Greenstick fracture
S3...00	Fracture of lower limb
S022.00	Fracture of mandible, closed
7K1D.00	Primary open reduction fracture bone & intramedull fixation
8HB9.00	Fracture therapy follow-up
S028000	Fracture of nasal bones
S02..00	Fracture of face bones
8022N	Fracture jaw
829	Fracture dislocation
S350.12	Os calcis fracture
S3z1.00	Open fracture of bones, unspecified
S344.12	Pott's fracture—ankle
K780 AA	Manipulation fracture
7K1L.00	Other closed reduction of fracture of bone
825 C	Fracture os calcis
824 P	Pott's fracture
S3zz.00	Fracture of bones NOS
7K1G.00	Other primary open reduction of fracture of bone
7K1L600	Closed reduction of fracture of knee
822 KC	Fracture knee cap
S28z.00	Ill-defined fractures of upper limb NOS
7206100	Open reduction of fracture of orbit
TC7..00	Fracture, cause unspecified
825 HL	Fracture heel bone
S3xz.00	Other, multiple and ill-defined fractures of lower limb NOS
S4F..00	Fracture–dislocation or subluxation knee
S4F..00	Fracture–dislocation or subluxation knee
829 C	Fracture compound
S00..11	Frontal bone fracture
S4G..00	Fracture–dislocation or subluxation ankle
S4G..00	Fracture–dislocation or subluxation ankle
7403600	Outfracture of turbinates of nose
S312.11	Closed fracture of femur, distal end
S33x.11	Lower leg fracture NOS
S315.00	Fracture of lower end of femur
S230300	Closed Monteggia's fracture
SR1..00	Fractures involving multiple body regions
S3X..00	Fracture of lower leg, part unspecified
S312100	Closed fracture of femoral condyle, unspecified
S312200	Closed fracture of femur, lower epiphysis
S312.00	Closed fracture distal femur
S023.00	Fracture of mandible, open
S03z.11	Depressed skull fracture NOS
Q202.00	Fracture of clavicle due to birth trauma
S224800	Closed fracture distal humerus, capitellum

Appendix 3

Table 6 Fracture occurrence among different bisphophonate users

	No fracture prior to TKR			OP fracture prior to TKR			Any other previous fracture		
	N (% BP users)	Propensity-adjusted HR (95% CI)	*p* value	*N* (% BP users)	Propensity-adjusted HR (95% CI)	*p* value	*N* (% BP users)	Propensity-adjusted HR (95% CI)	*p* value
Alendronate	389 (41.7)	0.60 (0.29–1.23)	0.16	136 (47.4)	0.66 (0.22–1.96)	0.45	96 (44.0)	1.18 (0.30–4.27)	0.81
Etidronate	215 (23.0)	0.68 (0.28–1.66)	0.40	54 (18.8)	0.67 (0.15–2.93)	0.60	46 (21.1)	0.00 (0.00–infinity)[a§]	0.98
Risedronate	117 (12.5)	0.74 (0.18–3.00)	0.68	25 (8.7)	0.00 (0.00–infinity)[a]	0.99	19 (8.7)	0.00 (0.00–infinity)[a]	0.99
Other BP	14 (1.5)	2.38 (0.33–17.08)	0.39	1 (0.3)	0.00 (0.00–infinity)[a]	0.99	5 (2.3)	0.00 (0.00–infinity)[a]	0.99
Switch	199 (21.3)	0.81 (0.39–1.69)	0.57	71 (24.7)	0.36 (0.08–1.62)	0.19	52 (23.9)	0.79 (0.10–6.37)	0.82

Propensity-adjusted Cox models

[a] No events (fractures) in one of the groups (BP users or non-users)

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