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Effect of bisphosphonates on knee replacement surgery

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Abstract

Purpose—Bone remodelling as a therapeutic target in knee osteoarthritis (OA) has gained much interest, but the effects of antiresorptive agents on knee OA have been conflicting, with no studies to date examining the effects of bisphosphonate use on the clinically relevant endpoint of knee replacement (KR) surgery.

Methods—We used data from The Health Improvement Network (THIN), a general practitioner electronic medical records representative of the general UK population. We identified older women who had initiated bisphosphonate use after their incident knee OA diagnosis. Each bisphosphonate initiator was propensity score-matched with a non-initiator within each 1-year cohort accrual block. The effect of bisphosphonates on the risk of KR was assessed using Cox proportional hazard regression. Sensitivity analyses to address residual confounding were also conducted.

Results—We identified 2006 bisphosphonate initiators, who were matched to 2006 non-initiators (mean age 76, mean body mass index 27), with mean follow-up time of 3 years. The crude incidence rate of KR was 22.0 per 1000 person-years among the initiators, and 29.1 among the non-initiators. Bisphosphonate initiators had 26% lower risk of KR than non-initiators (HR 0.74, 95% CI 0.59 to 0.93); these results were similar when additionally adjusted for potential confounders in the propensity score (HR 0.76, 95% CI 0.60 to 0.95). Results of sensitivity analyses supported this protective effect.

Conclusions—In this population-based cohort of older women with incident knee OA, those with incident bisphosphonate users had lower risk of KR than non-users of bisphosphonates, suggesting a potential beneficial effect of bisphosphonates on knee OA.

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Contributors All authors: participated in the study design, interpretation of results and manuscript preparation. TN: additionally drafted and revised the manuscript. CP: additionally extracted and analysed the data.

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Data sharing statement The Health Improvement Network (THIN) dataset is a subscription-based dataset with a legal contract requiring data to remain onsite and be analysed at Boston University Medical Center. We are therefore not legally able to make these data available publicly. We would be happy to collaborate with potential external collaborators to address research questions of interest using THIN if appropriate resources are provided.

INTRODUCTION

Knee osteoarthritis (OA) is a leading cause of disability,^{1–4} with no approved agents proven to alter the disease course. Joint replacement surgery remains the only definitive for end-stage disease, with knee OA accounting for 97% of all knee replacement (KR) surgeries, the numbers and costs of which are rising each year.⁵ Thus, there is an urgent need for new effective treatment options for knee OA.

Bone plays an important role in OA pathophysiology and is considered an important treatment target. Since mechanical factors play a central role in OA development,^{6–8} and bone adapts readily to mechanical stresses,⁹ it is essential to understand the long-term effects of modulating bone remodelling via antiresorptive agents on the course of OA. Trials of antiresorptive agents have had conflicting results.^{10–15} For bisphosphonates, trials have focused primarily on medium-term and short-term structural endpoints, such as joint-space width on radiograph and bone marrow lesions on MRI, with the majority not finding a protective effect.^{10–12}¹⁴ Observational studies have also focused primarily on structural changes, but their interpretation is limited by potential confounding and selection bias.¹⁶¹⁷ Additionally, efficacy of bisphosphonates in an animal model of OA suggests that it varies based on stage of disease at which it is initiated.¹⁸

While bisphosphonates may have beneficial articular cartilage effects, there are theoretical concerns about their long-term effects related to decreasing bone turnover. Because of its high bone turnover state, OA bone may be relatively hypomineralised and weaker, and thus more easily deformed,¹⁹²⁰ but may also have increased stiffness overall due to increased subchondral bone thickness and volume.²¹ Whether bisphosphonates could increase stiffness and interfere with bone adaptation to mechanical stresses, which could be detrimental in OA in the long term, requires clarification before further pursuit of this as an OA treatment.

The most clinically relevant long-term sequela of knee OA is end-stage disease leading to joint replacement surgery. If bisphosphonates could reduce the risk of KR, it would suggest that these agents have a beneficial effect on the disease process, and in turn, can prevent or delay a costly surgical intervention. On the other hand, if long-term bisphosphonate use has a negative impact on bone's mechanical properties, then this class of drugs should not be pursued for further development for OA management. We therefore evaluated the relation of bisphosphonate use to KR surgery.

METHODS

Study sample

The Health Improvement Network (THIN) is a UK general practitioner (GP) electronic database that has anonymised health data on >12 million patients.²² The information available in THIN is collected by GPs as part of routine patient care, which is deidentified and integrated into a central database for research purposes. THIN contains information on demographic factors, referrals, hospitalisations, laboratory test results and prescriptions ordered by GPs, including the dose, strength and formulation of medication. Diagnoses and test procedures are recorded with read codes. Prescriptions written by GPs are recorded

automatically in the database as drug codes, with the use of a coded drug dictionary (Multilex). Quality is checked regularly and the information from this database has been found to be representative of the UK population.²²

Eligible subjects of the current study consisted of women aged 50–89 years during 2003 to 2012 who were enrolled in THIN for at least 1 year without a diagnosis of knee OA prior to inclusion in the study sample. They were also required to have at least one GP visit or prescription during the year prior to their knee OA diagnosis.

We excluded subjects who were on bisphosphonates prior to their knee OA diagnosis, on non-bisphosphonate antiresorptive agents or on bisphosphonates that are prescribed only for Paget's disease or metastatic disease in the UK (clodronate, tiludronate); those with a KR prior to a knee OA diagnosis; and those with rheumatoid arthritis. We also excluded subjects deemed unlikely to be a candidate for KR surgery, including subjects with body mass index (BMI) $>40 \text{ kg/m}^2$, history of joint infection, high-risk cancer (pancreatic, oesophageal, gastric or metastatic cancer) or comorbidities with poor prognosis (end-stage renal disease on dialysis and severe pulmonary disease requiring supplemental oxygen). In our main analyses, we also excluded individuals with incomplete covariate data for BMI, alcohol and smoking status, with sensitivity analyses conducted in which we used multiple imputation to enable inclusion of such subjects.

Study design

We conducted a sequential (ie, time-stratified) propensity score-matched cohort study to examine the relation of bisphosphonate initiation to the risk of KR among older women with incident knee OA. We divided the study period (1 January 2003–31 December 2012) into ten 1-year cohort accrual blocks. We propensity score-matched each bisphosphonate initiator with a non-initiator within each cohort accrual block using a greedy-matching algorithm.²³ The propensity score for initiating bisphosphonates was computed using logistic regression within each cohort accrual block. For bisphosphonate initiators, the date of the first bisphosphonate prescription was considered the index date. Non-initiators were assigned an index date randomly within the cohort accrual block. The covariate assessment period for the propensity score modelling was prior to the index date. Variables included in the propensity score model were: sociodemographic factors (age, sex, BMI, smoking status, alcohol use and socioeconomic status), knee OA characteristics (duration and analgesic use), potential indications for bisphosphonate (osteoporosis, osteopaenia and fractures (hip, wrist, vertebral, fragility and multiple fractures over time)), bone mineral density assessment, glucocorticoid use, falls and fall risk, comorbidities (see table 1), healthcare usage (GP visits and hospitalisations) and medications (see table 1). Covariate balance was assessed with standardised mean differences, all of which were <0.1 .

Assessment of exposure and outcome

The first bisphosphonate prescription was identified using Multilex drug codes in THIN which have been used in prior studies.^{24,25} We focused on the bisphosphonates approved for use in osteoporosis in the UK, which include etidronate–calcitonin combination therapy, ibandronate, pamidronate, risedronate and zoledronate.

KR was identified using read codes. A similar approach has been used to validly identify joint arthroplasties in other studies using in THIN^{26,27} and Clinical Practice Research Database,^{28–30} which has substantial overlap with THIN.^{31–33}

Statistical analysis

Subjects were followed from the index date until KR, death, loss-to-follow-up (e.g., transfer out of GP practice), age >90 years, last date of data collection by GP or end of study (31 December 2013). To examine the relation of incident bisphosphonate use to KR surgery, we conducted Cox proportional hazards regression using age as the time scale with an intention-to-treat approach, additionally adjusting for the covariates used in the propensity score model.

To explore the possibility of residual confounding, we performed additional sensitivity analyses. In the first, we re-ran the above analyses without including BMI in the propensity score to determine indirectly how much of an influence BMI has on the effect estimate. We also did not include alcohol or smoking so that our model was not limited to those with complete data. We also performed multiple imputation by imputing missing BMI, alcohol and smoking data in five blocked datasets that were each used to create propensity score-matched datasets that were analysed separately with a summary effect estimate calculated. Second, we conducted age-matched, BMI-matched and OA duration-matched analyses, in which bisphosphonate initiators were matched 1:4 with non-initiators, adjusting for all other potential confounders used in the propensity score model. Third, this latter analysis was repeated using active comparator drugs as the referent group: (1) oestrogen initiators; (2) initiation of any other bone-modulating agent (eg, strontium, calcitonin, raloxifene, teriparatide and oestrogen). Fourth, to account for potential selection bias due to death or loss to follow-up (eg, individuals transferring out of their GP practice or other issue), we applied inverse probability weighting.^{34,35} To account for competing risk of death, we implemented the Fine and Grey approach.³⁶ Finally, to assess the influence of unmeasured and residual confounding factors, such as bone mineral density, we performed a sensitivity analysis using an array approach, which is helpful for exploring the effect of residual confounding over a wide range of parameter values and effects, and to examine the extent of confounding necessary to fully explain the observed effect estimate.³⁷

All statistical analyses were performed using SAS V.9.3 (SAS Institute, Cary, North Carolina, USA).

RESULTS

From among 27 295 subjects who met our inclusion and exclusion criteria, we identified 2225 bisphosphonate initiators. From these, 2006 bisphosphonate initiators were propensity-score matched to the same number of non-initiators. Eighty-four per cent of the bisphosphonate initiators were prescribed alendronate; the remaining were risedronate (13%), ibandronate (2%) and etidronate–calcitonin combination therapy (1%). The mean age of the cohort was 76, and the mean BMI was 27.3 kg/m². Overall, covariate data were well-balanced among the initiators and non-initiators (table 1). Approximately 60% of the initiators and the non-initiators appeared to have an indication for bisphosphonate use prior

to the index date; however, this proportion increased to 82% among the initiators, and remained fairly steady among the non-initiators (63%) over the follow-up period.

The mean follow-up time for subjects was approximately 3 years for both groups (table 2). During the follow-up period, 208 KR surgeries were performed overall, with 138 in bisphosphonate initiators and 170 in the non-initiators. The mortality rate was similar in both groups (39.7 and 38.2 per 1000 person-years in the initiators and non-initiators, respectively). The crude incidence rate of KR was 22.0 per 1000 person-years among the bisphosphonate initiators and 29.1 per 1000 person-years among the comparator group, with a crude incidence rate ratio of 0.75 (95% CI 0.60 to 0.94) (table 2). The HR for KR related to bisphosphonate initiation was 0.74 (95% CI 0.59 to 0.93), and results did not change materially when additionally adjusted for the potential confounders used in the propensity score (adjusted HR 0.76 (95% CI 0.60 to 0.95)).

Because approximately 15% of subjects had missing values for either BMI, smoking and/or alcohol, we performed a sensitivity analysis in which we created the propensity score without including these variables. In this analysis, with 2379 initiators of bisphosphonates and the same number of propensity score-matched non-initiators, the adjusted HR was similar to the main result (0.79, 95% CI 0.64 to 0.98). In analyses using multiple imputation, the adjusted HR was also similar to the main result (0.72, 95% CI 0.59 to 0.89). We also conducted a sensitivity analysis in which we matched each bisphosphonate initiator to four non-initiators by age (within 2 years), BMI (± 0.5 kg/m²) and OA duration (within 2 years). The adjusted HR from this matched cohort study was 0.35 (95% CI 0.26 to 0.47). To further address confounding by indication, we compared bisphosphonate initiation to that of an active comparator drug (oestrogen and any bone-modulating agent, respectively), matched on age, BMI and OA duration, and obtained results similar to our main results (adjusted HR 0.75 (95% CI 0.30 to 1.87)). The smaller sample sizes and lower number of KR outcomes precluded precise estimation of these effects.

When we accounted for censoring due to loss to follow-up or death with inverse probability weighting, the results remained similar to the main results (HR 0.75, 95% CI: 0.59 to 0.94). The competing risk of death analysis also provided similar results (HR 0.76, 95% CI 0.61 to 0.86). Finally, in a sensitivity analysis to examine the potential effect of residual confounding on our results, we found that in order for an unmeasured confounder to nullify the observed HR, that confounder would need to be associated with a fivefold difference in risk of the outcome (KR) and have a 30% difference in prevalence among bisphosphonate initiators versus non-initiators. Such a scenario would be highly unlikely (figure 1).

DISCUSSION

In this large cohort of older women with incident knee OA derived from the general population, we found that bisphosphonate initiation was associated with a ~25% lower risk of KR surgery than those who did not initiate bisphosphonates. Our findings were consistent across several sensitivity analyses that were performed to address potential residual confounding, missing data and selection bias, suggesting that it is unlikely for unaddressed biases to result in bisphosphonate initiation to have a detrimental effect.

Trials of bisphosphonates in knee OA have not been able to examine the risk of KR surgery due to the longer duration of follow-up required to examine this clinically relevant endpoint. Interestingly, though the clinical scenario and mechanisms are distinct from that of OA, bisphosphonates have been demonstrated to reduce the risk of revision surgery after joint replacement, potentially through antiresorptive effects minimising periprosthetic bone loss and osteolysis.³⁰ Nonetheless, while there are potentially beneficial effects of bisphosphonates and other bone-modulating agents on bone and cartilage,³⁸ study results in OA have been conflicting to date. We previously demonstrated in a spinal OA trial that alendronate reduced spinal osteophyte and disc space narrowing progression,³⁹ and an observational study also noted less bone pathology on knee imaging by MRI (bone marrow lesions and subchondral bone attrition) and knee pain.¹⁶ A trial of risedronate with 1-year follow-up suggested symptom benefits, and minimal non-significant structure benefits based on joint-space width on radiograph.¹⁰ However, a subsequent larger trial with 2-year follow-up failed to demonstrate any symptom or structure (joint-space width) benefits,¹¹ and a small subset (<5%) of this trial that had MRIs demonstrated no difference in bone marrow lesions between treatment and placebo.¹² Analysis of prevalent bisphosphonate users in the Osteoarthritis Initiative (OAI) cohort demonstrated no significant difference in joint-space width versus non-users¹⁷; this may be partly related to the prevalent drug user study design used and analytic approach.⁴⁰ More recently, a trial evaluating intravenous zoledronic acid demonstrated significant differences in bone marrow lesion volume and pain between treatment and placebo arms at 6 months, but not at the 12-month follow-up.¹⁴ Taken together, these studies have raised questions about whether potential benefits are being missed by use of relatively insensitive radiographs. Additionally, another concern is whether there are potential adverse longer term effects of bisphosphonates on OA pathology, such as may arise from inhibiting bone turnover, which may in turn lead to increased bone stiffness due to increased mineralisation and subsequent theoretical adverse biomechanical consequences.

Our findings indicate that bisphosphonates do not appear to have long-term adverse effects on the course of knee OA, and may in fact reduce the risk of KR surgery, suggesting that the clinical course may be less severe and/or have a slower rate of progression. In the OAI, bisphosphonate use was associated with a slower trajectory of joint-space width loss and of MRI-based three-dimensional bone shape change, an imaging biomarker predictive of OA onset.^{41,42} Thus, there does not appear to be a reason for bisphosphonates to be avoided in those with knee OA, and in fact, their use may be beneficial, supporting the ongoing investigation of bone modulation as an OA therapeutic target.

Potential limitations of this study deserve comment. Because THIN does not have bone density results, there is a concern for residual confounding by indication since individuals with lower bone mineral density are more likely to be on a bisphosphonate and are also more likely to have a lower BMI. We attempted to address this by including factors in the propensity score that are likely reflective of bone mineral density and risk of osteoporosis. The diagnostic code for osteoporosis and osteopaenia were not as frequently recorded as one would expect for individuals on bisphosphonates, likely reflecting the fact that GPs do not always record the condition for which bisphosphonates are being prescribed. In a manual review of patient profiles, we noted that all patients on bisphosphonates without an

osteoporosis code (including those who had an osteopaenia code) were universally on full-strength doses of a bisphosphonate, usually with 1 bone mineral density test and/or 1 fracture suspicious for an osteoporotic fracture. Further, the code for osteoporosis and/or osteopaenia often occurred well after initial bisphosphonate prescription. Additionally, existing published literature provides some reassurance that bone mineral density status is unlikely to importantly affect our study results. Low systemic bone mineral density has either been associated with increased risk of knee OA progression or no increased risk.^{43–46} Based on such data, one would expect bisphosphonate initiators, who presumably may have lower bone mineral density, to have potentially either no or increased risk of knee OA progression. In contrast, we found that bisphosphonate initiators experienced a protective effect even while accounting for BMI. Additionally, vitamin D, which is commonly taken as over-the-counter medication without prescription, particularly in multivitamins, is not reliably recorded within THIN in a standardised fashion, and was low but well balanced between the two groups in our study sample. Nonetheless, their use is unlikely to importantly confound our results given the lack of association of vitamin D with knee OA in two recent rigorously conducted clinical trials.^{47,48} Though effects on KR cannot be determined from these trials, some studies have suggested that joint-space width may be predictive of KR surgery.

We also examined the relation of incident bisphosphonate use to hip fracture to determine whether we could replicate the findings from existing published data; such a replication would suggest that the propensity score model likely adequately captured most important confounders. In this analysis, we found the HR to be similar to the effect noted for clinical fractures in the Fracture Intervention Trial.⁴⁹ Finally, we performed a sensitivity analysis to address the degree of unmeasured confounding that would have to be present to nullify our results. For bone mineral density and/or vitamin D to result in a fivefold alteration in the risk of KR while also having a prevalence differential of 30% between the two groups is highly unlikely. Thus, at minimum, it appears that bisphosphonates do not have a detrimental effect and may indeed have a potential beneficial effect.

Secular trends precluded robust active user comparator analyses, particularly as many women initiated oestrogens prior to knee OA diagnosis. Further, these results are primarily of relevance to older women; whether there should be different biological effects in middle-aged women or in men is not clear, but cannot be extrapolated from this study.

Our approach to addressing this clinically important question also illustrates a number of methodological strengths. We used a new user design to avoid selection bias related to the study of prevalent users of bisphosphonates.⁴¹ We addressed potential secular trends in bisphosphonate use and KR surgery by matching using a time-stratified approach in which the exposed (bisphosphonate initiators) and unexposed (non-initiators) were matched within the same calendar year. We addressed residual confounding in sensitivity analyses focusing on BMI and OA duration, important risk factors for KR, which did not alter the interpretation of our findings. Our approach to minimising potential confounding by indication was twofold: propensity score-matched cohort approach and use of an active comparator design. We also have reassurance that a competing risk of death did not adversely affect our ability to estimate these effects as the mortality rate was similar in both

groups, and inverse probability weighting to account for death and loss to follow-up did not alter the main findings. Finally, we examined the potential effect of unmeasured residual confounding and found our results to be robust and unlikely to be plausibly nullified by important unmeasured (or unaccounted for) confounding.

In summary, bisphosphonate use in older women with incident knee OA did not have a detrimental effect on risk of KR and appears to have a potential beneficial effect. These findings, taken together with other studies' findings, support the ongoing evaluation of bone modulation as a potentially promising therapeutic target for knee OA.

Acknowledgements

This study protocol was approved by the THIN Scientific Review Committee (SRC15THIN023) and judged exempt from review by the Boston University Medical Campus Institutional Review Board (protocol H-32821).

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Figure 1.

A sensitivity analysis illustrates that it would be under only a very extreme scenario that the observed HR of 0.76 would be wholly due to unmeasured and residual confounding. The curved surface represents the ‘true’ risk ratio, assuming an ARR of 1.0, and ‘true’ prevalence of the unmeasured confounder in the unexposed (non-initiator) group (P_{C0}) of 0.5. P_{C1} refers to the prevalence of the unmeasured confounder in the exposed (initiator) group, and is varied from 0.1 to 1.0 on the x -axis. RR_{CD} represents the relative risk of the association between the confounder and disease/outcome (KR), such that the ‘back wall’ of the figure represents no association between the confounder and outcome. If the prevalence of the confounder differs by 30% in the two groups, and the relation between the confounder and outcome has a fivefold differential effect compared with the exposure–outcome relationship, then the observed effect could be nullified, which is highly implausible. ARR, apparent relative risk; KR, knee replacement.

Table 1

Baseline participant characteristics in the propensity score-matched cohort

	Bisphosphonate initiators (N=2006)	Non-initiators (N=2006)
<i>Sociodemographics</i>		
Age (mean±SD)	76.0±8.2	76.4±8.6
BMI (mean±SD)	27.3±4.5	27.3±4.5
Townsend Deprivation Index (n (%))		
Quintile 1 (lowest)	469 (23.4%)	477 (23.8%)
Quintile 2	450 (22.4%)	426 (21.2%)
Quintile 3	473 (23.6%)	496 (24.7%)
Quintile 4	371 (18.5%)	352 (17.5%)
Quintile 5 (highest)	243 (12.1%)	255 (12.7%)
Alcohol use (n (%))		
Current drinker	1315 (65.6%)	1333 (66.5%)
Ex-drinker	71 (3.5%)	74 (3.7%)
Non-drinker	620 (30.9%)	599 (29.9%)
Smoking (n (%))		
Current smoker	187 (9.3%)	166 (8.3%)
Ex-smoker	550 (27.4%)	516 (25.7%)
Non-smoker	1269 (63.3%)	1324 (66.0%)
Knee OA duration (mean±SD)	4.4±3.5	4.4±3.5
<i>Comorbidities (n (%))</i>		
Atrial fibrillation	182 (9.1%)	197 (9.8%)
Cancer	328 (16.4%)	334 (16.7%)
Cellulitis	422 (21.0%)	422 (21.0%)
COPD	168 (8.4%)	159 (7.9%)
Dementia/cognitive Impairment	41 (2.0%)	41 (2.0%)
Depression	637 (31.8%)	643 (32.1%)
Diabetes	286 (14.3%)	280 (14.0%)
Fall/risk of falls	732 (36.5%)	733 (36.5%)
Fragility fracture	346 (17.2%)	317 (15.8%)
Hip fracture	209 (10.4%)	169 (8.4%)
Hypertension	1204 (60.0%)	1231 (61.4%)
Hyperlipidaemia	460 (22.9%)	468 (23.3%)
Inflammatory arthritis	93 (4.6%)	98 (4.9%)
Ischaemic heart disease		
None	1668 (83.2%)	1669 (83.2%)
Angina	209 (10.4%)	216 (10.8%)
Myocardial infarction	76 (3.8%)	76 (3.8%)
Postsurgery for coronary artery disease	53 (2.6%)	45 (2.2%)
Liver disease	53 (2.6%)	46 (2.3%)
Osteoporosis/osteopaenia	689 (34.3%)	670 (33.4%)

	Bisphosphonate initiators (N=2006)	Non-initiators (N=2006)
Peptic ulcer	306 (15.3%)	312 (15.6%)
Pneumonia/influenza	190 (9.5%)	179 (8.9%)
Renal disease	418 (20.8%)	419 (20.9%)
Seizure disorder	47 (2.3%)	59 (2.9%)
Stroke	100 (5.0%)	100 (5.0%)
Venous thromboembolism	121 (6.0%)	120 (6.0%)
Wrist fracture	369 (18.4%)	376 (18.7%)
Investigations, healthcare use:		
BMD measured (n (%))	515 (25.7%)	524 (26.1%)
Albumin level (mg/dL)	4.1±0.4	4.1±0.4
GP visits (n (%))	9±8	9±9
Hospitalisations(n (%))	1±1	1±2
Relevant medication use (n (%))		
Paracetamol	978 (48.8%)	982 (49.0%)
NSAIDs	741 (36.9%)	751 (37.4%)
Opioids	1176 (58.6%)	1190 (59.3%)
Antihypertensive medications	1367 (68.1%)	1397 (69.6%)
Lipid-lowering drugs	775 (38.6%)	739 (36.8%)
Oral diabetics	168 (8.4%)	165 (8.2%)
Insulin	46 (2.3%)	50 (2.5%)
Glucocorticoids inhaled	347 (17.3%)	372 (18.5%)
Glucocorticoids oral	524 (26.1%)	545 (27.2%)
Oestrogen	127 (6.3%)	120 (6.0%)
Antiseizure medications	120 (6.0%)	133 (6.6%)

BMD, bone mineral density; BMI, body mass index; COPD, chronic obstructive pulmonary disease; GP, general practitioner; NSAIDs, non-steroidal anti-inflammatory drug; OA, osteoarthritis.

Table 2

Relation of incident bisphosphonate use to KR surgery

	Bisphosphonate initiators (n=2006)	Non-initiators (n=2006)
KR (n)	138	170
Total follow-up time (person-years)	6283	5835
Mean follow-up time (years)	3.13	2.91
Incidence rate of KR/1000 person-years	21.96	29.13
Crude incidence rate ratio	0.75 (95% CI 0.60 to 0.94.)	
HR	0.74 (95% CI 0.59 to 0.93)	

KR, knee replacement.