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Effect of bisphosphonate use in patients with symptomatic and radiographic knee osteoarthritis: data from the Osteoarthritis Initiative

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ABSTRACT

Objectives: Bisphosphonates have some reported beneficial effects in treating osteoarthritis (OA). This study examined the effects of bisphosphonate use on symptoms and structural progression of knee OA in participants from the NIH Osteoarthritis Initiative cohort.

Methods: People with typical OA trial entry criteria (KL2/3, minimum joint space width (mJSW) 2.5-5.0mm and pain ≥4 on a numerical rating scale [NRS]) were classified as bisphosphonate users (≥3 of the 5 years; n=55) or non-users (no use in the preceding 5 years or during follow-up; n=268). Annual data over 4 years were analysed using linear mixed modelling and generalised estimating equations.

Results: Bisphosphonate compliance was 85% at year 1, reducing to 76% by year 4. NRS pain scores were significantly reduced among bisphosphonate users at years 2 and 3 (Year 3, -0.9 vs -2.2, p=0.004), though not year 4, after adjustment for baseline pain and analgesic use. Differences in WOMAC pain and disability scores did not reach statistical significance at any time point. There was a trend to less joint space narrowing in bisphosphonate users over time (Year 4, 0.51mm vs 0.29mm; p=0.06).

Conclusions: Significant reduction in NRS pain was observed in the first 3 years with bisphosphonate use; diminution of effects by year 4 may reflect reduced compliance. Differences in results obtained using NRS and WOMAC may reflect different constructs measured by these tools. The beneficial trend on structural progression should be considered in terms of the sample size.

Osteoarthritis (OA) is a growing cause of chronic disability and a major problem for health economies[1-4].Current therapies are symptomatic with limited effect size in terms of pain reduction[5], while development of disease modifying OA drugs (DMOADs) has been challenging[6]. There is therefore a major need to develop new, effective therapies.

Recent work has highlighted some beneficial effects of agents with potential for both cartilage and bone-modifying effects in OA of the knee[7-9] and spine[10]. The subchondral bone is known to play an important role in OA pain and structural progression. Bone marrow lesions (BML) seen on magnetic resonance imaging (MRI) have been associated with knee pain and ipsilateral progressive cartilage loss[11-13]. Bone area and elevated bone mineral density (BMD) in the subchondral bone predict cartilage defect development[14, 15] and bone area also predicts cartilage volume loss[15].

Of these potential therapies, bisphosphonate use has been explored in a number of OA studies with apparent mixed results[16]. Effects on bone have generally been positive, with one cross sectional study showing reduction in odds of having a bone marrow abnormality of nearly 90% with the use of alendronate (OR 0.11, $p \leq 0.05$)[17]. Other work demonstrated that risedronate 50 mg weekly prevented an increase in BML size[18], although this did not reach statistical significance. Zoledronic acid has been reported effective in reducing knee pain and the size of BMLs.[7]However, though risedronate (15 mg) reduced markers of cartilage degradation and bone resorption, it did not achieve WOMAC symptom reduction or slowing of radiologic progression of joint space narrowing over 2 years[19, 20].

The NIH Osteoarthritis Initiative (OAI) provides a large, comprehensive dataset which permits exploration of the effects of bisphosphonates over a number of years. We aimed to examine the effect of bisphosphonate use on OA symptom and structural outcomes in people selected from the OAI cohort for typical OA trial inclusion criteria and followed for 4 years.

PATIENTS AND METHODS

Study design, setting and participants

Data used in the preparation of this article were obtained from the Osteoarthritis Initiative (OAI) cohort, a publicly available multi-centre population-based observational cohort study of knee OA which is available for public access at http://www.oai.ucsf.edu/. Specific datasets used are detailed Supplementary Table 1. The OAI comprises data on persons aged 45-79 years within three sub–cohorts, the Progression group (persons with existing knee OA; n=1,390), the Incidence group (persons with risk factors for knee OA; n=3,284) and the non-exposed control group (n=122)[21]. Both knees of 4796 participants were studied annually using 3T MR imaging (not used in these analyses) and fixed flexion radiography[22, 23]at baseline, 1, 2, 3 and 4 years follow-up.

Persons were excluded from the OAI if they had inflammatory arthritis, severe joint space narrowing (JSN) in both knees, unilateral knee joint replacement and severe JSN in the contralateral knee, inability to undergo MRI, or to provide a blood sample, required use of walking aids excepting a single straight cane ≤50% of the time, or were unwilling to provide informed consent. Patients were recruited at four clinical sites, and the study was approved by the institutional review boards at each of the

sites. All participants gave informed consent. Radiological endpoints are now available for four years of observation (79% of population retained) and clinical data to 5 years.

Participants: Inclusion and exclusion criteria for these analyses

For these analyses, we were interested in a group who were in the early stages of clinical OA and who were at increased risk of developing incident OA or of worsening OA over time. Therefore, persons with knee replacements at baseline (n=64) and those in the non-exposed control group (n=122) were excluded from the analysis. To further simulate a population similar to patients commonly included in clinical trials of knee OA, we included participants whose knees were scored as having joint space narrowing of Grade 2 or 3 on the Kellgren and Lawrence grading system [24], medial joint space width of 2.5–5mm, an osteophyte (medial osteophyte grade 1 and above) using the Altman atlas[25], and had pain of 4-10 on a numeric rating scale (NRS). Only one knee was used for each participant. When both knees met the above criteria for an individual patient, the knee with the most severe features of OA was selected by serially choosing the knee with the worst (highest) KL grade, the worst osteophyte(s) (higher grade), the highest pain, and the lowest join space width (JSW).

Bisphosphonate use

Bisphosphonate use was calculated by classifying self-reported use in the last year, then summarising number of years use. Patients were classified as long-term bisphosphonate users if they self-reported bisphosphonate in the past year on 3–5 occasions between baseline and four years of observation. Misclassification due to

missing data was minimised by classifying patients as users on a particular occasion if they had missing data for that occasion, but reported bisphosphonate use in the last year at both the preceding and subsequent year. Non-users of bisphosphonates were defined as persons who reported not using bisphosphonates in the preceding five years at baseline, and did not report use of bisphosphonates in the past year for years 0–5.

Summary of included patients

Participants whose outcomes are described in these analyses had knee OA of KL grade 2 or 3, a definite osteophyte, medial joint space narrowing (2.5 – 5mm), a knee pain score of 4 or more, and reported either non–use or high use of bisphosphonates over our time period. We limited our analysis to women as the prevalence of bisphosphonate use in men was low.

Knee pain severity scale

Global knee pain severity during the past seven days was assessed using an 11 point (0–10) numeric rating scale (NRS).

WOMAC questionnaire

The pain, function and stiffness scales of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) version LK 3.1 (five point Likert scale) were used to assess knee pain and function for right and left knees separately over the preceding seven days.

Knee radiographs

Knee radiographs of both knees were taken annually, using fixed flexion radiographs, filmed in the standing position in posterior–anterior projection with knees flexed to 20–30 degrees and feet internally rotated 10 degrees, with a plexiglass positioning frame (SynaFlexer TM) used to standardise positioning[21]. Trained readers at each clinical centre assessed JSW using the knee radiographs using a classification based on the OARSI atlas grades[25].

Measurement of minimal JSW measures was facilitated by the use of automated software that delineated the femoral and tibial margins of the joint[26]. Measurement of minimum JSW was made by the software at the location of the smallest distance between the femur and tibia margins in the medial compartment[27].

Radiological and radioclinical progression

Participants were considered radiological progressors if minimal JSW reduced by 0.5mm or greater[28]; and radioclinical progressors if JSW reduced by 0.5mm or greater and 20% or less improvement in WOMAC pain scores[29].

Joint replacements

Data on joint replacements was collected at each follow up visit.

Statistical methods

Primary hypotheses were tested using all available data on participants who met the entry criteria at baseline. Statistical significance was determined using a p value ≤0·05 (two–tailed) and using Stata 12.0. Students' t–tests, chi square tests and

Fisher's exact tests were used to compare differences in means and proportions, between bisphosphonate users and non–users.

Linear mixed effect modelling was used to assess the effect of bisphosphonate use on continuous outcomes (pain NRS scores, WOMAC scores, medial JSW). Quadratic and cubic transformations of the time variable were added to each model to allow for non-linear changes, and were retained if statistically significant. We also incorporated a random effect of patient ID to account for the dependence in repeated observations on the same person over time and a random slope for the effect of time, enabling differences in trajectory to be modelled, and adjusting for heteroskedasticity in outcomes over time where applicable (JSW).

Binary outcomes (radiological and radioclinical progression) were assessed using generalised estimating equations for the binomial family and using a log link. Adding study recruitment site as a random effect made no difference to outcomes so site was not included as a random effect in these analyses.

Group, time and the interaction between group and time were entered as predictor variables, and age and BMI were included as covariates. Data on pain outcomes were additionally adjusted for baseline pain and use of analgesia. Yearly estimates were calculated from the model using the linear combination of estimates function (lincom).

RESULTS

Participants

The demographic profile of participants is shown in Table 1. Bisphosphonate users were older, shorter, thinner, less physically active, and more likely to be white than non–users.

Bisphosphonate use

Within our highly compliant bisphosphonate users, compliance peaked early in the observation period (years 1–3) and diminished by year 4 (Table 2). The most commonly used bisphosphonate in years 1–4 was alendronate (Table 3). Most participants classified as bisphosphonate users over years 1–4 were already using bisphosphonates at baseline (78%).

Study outcomes

Numeric rating scale (NRS)

The effect of time on NRS in the non–users was modelled using quadratic and cubic terms, and the effect of bisphosphonate use modelled using quadratic and cubic interaction terms. NRS scores reduced in both groups between baseline and 1 year, with differences between groups largest at years 2 and 3. Differences were statistically significant at both year 2 and 3 (-0.97, p=0.001 at year 2, -1.15, p=0.004 at year 3. By year 4 users and non–users had similar NRS scores (Table 4, Figure 1a).

WOMAC pain, disability and stiffness

WOMAC pain scores reduced over time in both bisphosphonate users and non users, with the rate of change non–linear in both groups (Figure 1b). The effect of time was modelled using a quadratic effect in non–users, and the effect of bisphosphonate use modelled using a quadratic interaction term. Groups were most different at year 2 (-0.72 units for pain; 2.85 units for disability), but differences were not statistically significant. Differences narrowed by year 4. There was no effect of bisphosphonate use on the stiffness score.

WOMAC disability scores were linear over time for non–users, but the effect of bisphosphonate use was modelled using a quadratic interaction term (Figure 1c). Differences in WOMAC disability score were not significant at any time point. WOMAC stiffness scores were modelled using a quadratic effect in non–users, but interaction terms were not significant, with no effect of bisphosphonate use on the stiffness score.

Radiological changes

Joint space width reduced linearly over time in both groups. The difference in JSW between bisphosphonate users and non–users reached 0.35mm by year 4 (p=0.06) (Table 4,Figure 2).

The proportion of participants with radiological and radioclinical progression increased over time both in bisphosphonate users and non–users. Incidence of progression was lower in the bisphosphonate group (IRR of 0.63; p=0.04) after 3 years of observation. There was no difference in the incidence of radioclinical progression was not different between users and non–users (Table 4, Figure 1d).

Joint replacements

Numbers of joint replacements in these cohorts were small and differences in numbers and rates of joint replacement were not statistically significant.

DISCUSSION

This longitudinal study demonstrated reduction in NRS pain , differences in radiological progressors, and trend to reduction of joint space narrowing in OAI participants meeting OA clinical trial inclusion criteria and reporting 3-5 years of bisphosphonate use, compared to similar participants not using bisphosphonates. Compliance in bisphosphonate use diminished by year 4, potentially reducing the effect size for bisphosphonate use. However this study also suggests that bisphosphonate use (predominantly alendronate) does not result in sustained pain relief or structural protection after bisphosphonate discontinuation.

This study provides the longest reported period of observation for examining bisphosphonate effects on OA pain and structural endpoints. Randomised trials observed patients for a maximum of two years[20], and none followed participants once bisphosphonate used ceased, in order to investigate the effect of drug discontinuation on pain and structural outcomes.

Bisphosphonates may work through a variety of mechanisms, including effects on the subchondral bone and osteochondral junction [30] Recently there have been reports of anti-inflammatory actions for bisphosphonates[31, 32]; such effects may play a role in an immediate analgesic benefit, as distinct from that which might arise as a consequence of osteochondral structural alteration, and explain why analgesic benefits in this study did not persist beyond the period of drug use. We observed discrepancies between the two measures of pain, as reduction in pain was significant for the NRS but not WOMAC total pain score. The time reference for these questions was identical (7 days) and both were Likert scales, therefore differences in outcomes either reflect sensitivity to change of the measure, or the

questions may assess different aspects of pain. The NRS may be a more true measure of pain intensity, whereas Rasch analyses of the WOMAC pain subscalehave previously suggested that it measures a combined function–pain construct[33, 34].

The effects of bisphosphonates on bone and cartilage endpoints would be expected to take months or years to be evident. In terms of structural endpoints, we observed a trend to reduction of joint space loss over the 4 year period of observation with reduction in the proportion of progressors in the bisphosphonate group. Clinical trials with structure modification endpoints typically require hundreds of patients per arm to demonstrate a statistically significant effect over time. Therefore the 55 bisphosphonate users and 268 non-users meeting the clinical trial criteria in the OAI result in suboptimal power to assess structural endpoints. Additionally, the reduction in compliance in this cohort diluted differences between bisphosphonate users and non users from Year 4, further reducing available power.

There are other limitations to this study. This is an observational study rather than a randomised clinical trial; therefore there were baseline differences between bisphosphonate users and non-users, and we cannot be certain that the groups were otherwise statistically equivalent. Bisphosphonate use was self reported simply as use or non-use and we have no method to validate compliance. While bisphosphonate users mostly used alendronate, use of other bisphosphonates occurred, and the existing sample size precluded further subgroup analyses. These agents have slightly different mechanisms of action, which could affect the pain and structural modification outcomes.

In summary, this paper further strengthens the concept that treatment with bisphosphonates may have beneficial symptomatic and perhaps structural benefits for people with OA. Therapeutic agents with bone-modifying potential require further exploration for a field lacking effective therapeutic options.

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Competing interests: None of the authors have any conflicts of interests to declare

Authors Contributions

PGC and MB conceived the study. LL, SRK, EMAH, MB and PGC analysed and interpreted the data. LLL, SRK, EMAH and PGC drafted the manuscript. LLL, SRK, EMAH, MB and PGC approved the final version for submission.

Figure Legends

Figure 1: Relationship between bisphosphonate use and clinical outcomes. a) Pain scores (numeric rating scale) over four years of observation, by bisphosphonate use (unadjusted data) b) WOMAC pain scores over four years of observation, by bisphosphonate use (unadjusted data) c) WOMAC disability scores over four years of observation, by bisphosphonate use (unadjusted data) d) Radioclinical progression over four years of observation, by bisphosphonate use (unadjusted data).Legend: Solid line: Non–users; dashed line: bisphosphonate users

Figure 2: Relationship between bisphosphonate use and radiological outcomes. a) Medial minimum joint space width over 4 years of observation, by bisphosphonate use b) Radiological progression over four years of observation, by bisphosphonate use (unadjusted data)

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TABLES

Table 1: Demographic profile of study patients, by use of bisphosphonates

	Non-users Mean (sd) n=268	Users Mean (sd) n=55	p
Age	59.8 (8.0)	66.7 (7.4)	**<0.001**
Height	162.6 (6.3)	160.4 (5.6)	**0.033**
Weight	85 (14.7)	71 (12.0)	**<0.001**
BMI	32.3 (5.4)	27.9 (4.4)	**<0.001**
Race (%)			**0.048**
White or Caucasian	54.1	69.1	
Black or African American	42.2	30.9	
Other non-white	2.2	0.0	
Asian	1.5	0.0	
Current smoking prevalence (%)	6.4	5.5	0.170
Physical activity (PASE)	154.4 (84.7)	135.9 (65.3)	**0.006**
Severity of knee OA (KL grade) (%)			0.453
Grade 2	65.7	70.9	
Grade 3	34.3	29.1	
WOMAC pain score	6.5 (4.3)	5.6 (3.5)	0.118
WOMAC disability score	21.6 (14)	19 (10.9)	0.201
WOMAC stiffness score	3.2 (1.7)	2.9 (1.4)	0.298
Pain score (numerical rating scale)	6.0 (1.7)	5.5 (1.6)	0.059
Proportion of patients using analgesia (%)	33.6	29.1	0.520

*Bisphosphonate use reported in the last year on 3, 4 or 5 occasions in over 5 years

Table 2:Bisphosphonate use in patients reporting bisphosphonate use on 3-5 occasions over 5 years, by year

	n	Proportion (95% CI)
Baseline	55	76.4 (64.8 to 88.0)
Year 1	53	84.9 (74.9 to 94.9)
Year 2	53	86.8 (77.4 to 96.2)
Year 3	54	88.9 (80.2 to 97.5)
Year 4	54	75.9 (64.1 to 87.7)
Year 5*	51	70.6 (57.6 to 83.5)

*Year 5 not included in models as JSW measurements only available to Year 4.
Some data based on previous and subsequent year if data missing

Table 3: Bisphosphonate medication used in past five years

	Baseline n (%)	Year 1 n (%)	Year 2 n (%)	Year 3 n (%)	Year 4 n (%)
None	12 (21.8)	6 (11.1)	2 (3.6)	3 (5.6)	7 (13.0)
Alendronate	33 (60)	36 (66.7)	39 (70.9)	38 (70.4)	36 (66.7)
Risedronate	9 (16.4)	10 (18.5)	12 (21.8)	9 (16.7)	5 (9.3)
Alendronate plus risedronate	1 (1.8)	1 (1.9)	1 (1.8)	1 (1.9)	2 (3.7)
Other	0 (0)	1 (1.9)	1 (1.8)	3 (5.6)	4 (7.4)
Total	55 (100)	54 (100)	55 (100)	54 (100)	54 (100)

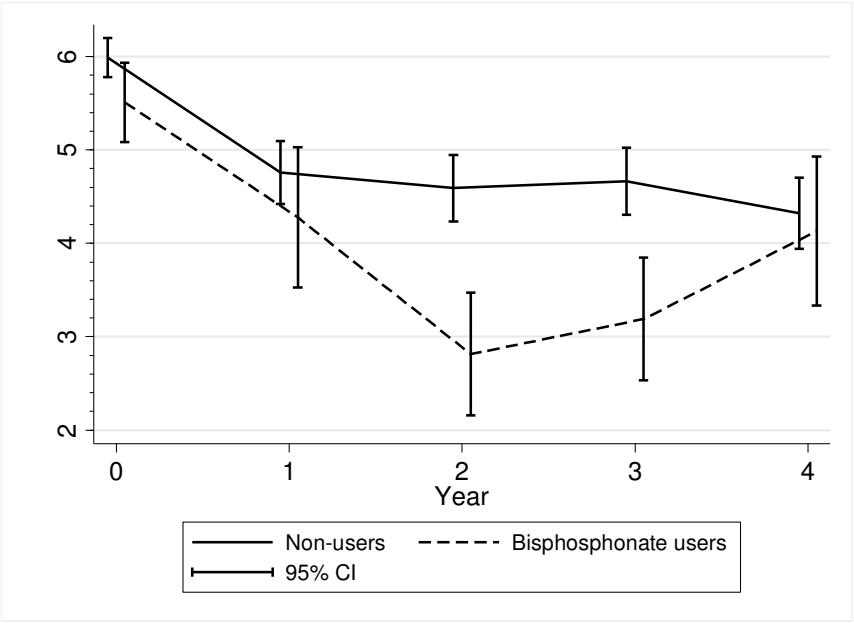
Table 4: Effect of bisphosphonate use on radiographic and clinical measures of knee osteoarthritis over four years of observation

		Non-users Mean change (sd)[§] n=258	Bisphosphonate users Mean change (sd)[§] n=55	Effect size (95% CI) (adjusted for ageand BMI)[¥]	p
Pain score (numerical rating score)	Year 1	-0.9 (2.8)	-1.1 (2.9)	-0.23 (-0.87 to 0.42)	0.491
	Year 2	-1.0 (2.9)	-2.3 (2.5)	**-0.97 (-1.55 to -0.38)**	**0.001**
	Year 3	-0.9 (3.2)	-2.2 (2.7)	**-1.15 (-1.94 to -0.36)**	**0.004**
	Year 4	-1.1 (3.2)	-1.3 (2.8)	0.30 (-0.58 to 1.19)	0.503
WOMAC pain score	Year 1	-0.7 (4.3)	-1.5 (3.8)	-0.44 (-1.30 to 0.42)	0.316
	Year 2	-0.9 (4.2)	-2.2 (3.8)	-0.72 (-1.67 to 0.23)	0.137
	Year 3	-0.8 (4.9)	-2.0 (3.8)	-0.34 (-1.33 to 0.64)	0.492
	Year 4	-1.3 (4.5)	-1.2 (4.0)	0.69 (-0.54 to 1.92)	0.271
WOMAC disability score	Year 1	-2.3 (12.1)	-3.7 (11.4)	-1.62 (-5.08 to 1.85)	0.361
	Year 2	-3.1 (12.3)	-7.6 (11.8)	-2.85 (-6.30 to 0.61)	0.107
	Year 3	-3.2 (13.9)	-5.8 (14.0)	-2.29 (-5.70 to 1.12)	0.188
	Year 4	-4.5 (13.9)	-6.7 (10.8)	0.05 (-3.85 to 3.95)	0.982
WOMAC stiffness score	Year 1	-0.3 (2.0)	-0.4 (1.7)	-0.06 (-0.46 to 0.34)	0.773
	Year 2	-0.4 (2.1)	-1.2 (1.7)	-0.12 (-0.51 to 0.27)	0.552
	Year 3	-0.5 (2.1)	-1.1 (1.8)	-0.18 (-0.61 to 0.25)	0.417
	Year 4	-0.6 (2.2)	-1.0 (1.5)	-0.24 (-0.75 to 0.27)	0.358
Change in JSW	Year 1	-0.15 (0.63)	-0.09 (0.4)	0.13 (-0.11 to 0.38)	0.292
	Year 2	-0.35 (0.73)	-0.12 (0.52)	0.20 (-0.07 to 0.48)	0.144
	Year 3	-0.50 (0.78)	-0.24 (0.61)	0.28 (-0.04 to 0.59)	0.083
	Year 4	-0.51 (0.83)	-0.29 (0.75)	0.35 (-0.01 to 0.70)	0.057
Radiological progression(n (%))	Year 1	45 (18.7)	6 (12.0)	0.59 (0.30 to 1.13)	0.111
	Year 2	70 (31.8)	11 (21.6)	0.61 (0.36 to 1.03)	0.063
	Year 3	82 (39.2)	11 (22.9)	**0.63 (0.41 to 0.98)**	**0.041**
	Year 4	82 (40.6)	13 (28.3)	0.66 (0.43 to 1.01)	0.057
Clinical progression (%)	Year 1	17 (25.0)	3 (6.0)	0.65 (0.25 to 1.72)	0.385
	Year 2	25 (11.6)	5 (9.8)	0.70 (0.34 to 1.44)	0.328
	Year 3	39 (19.4)	6 (12.5)	0.75 (0.42 to 1.33)	0.323
	Year 4	41 (20.9)	9 (19.6)	0.80 (0.43 to 1.48)	0.474
Joint replacement	Year 1-4	16 (6)	2 (3.6)	0.73 (0.15 to 3.48)	0.688

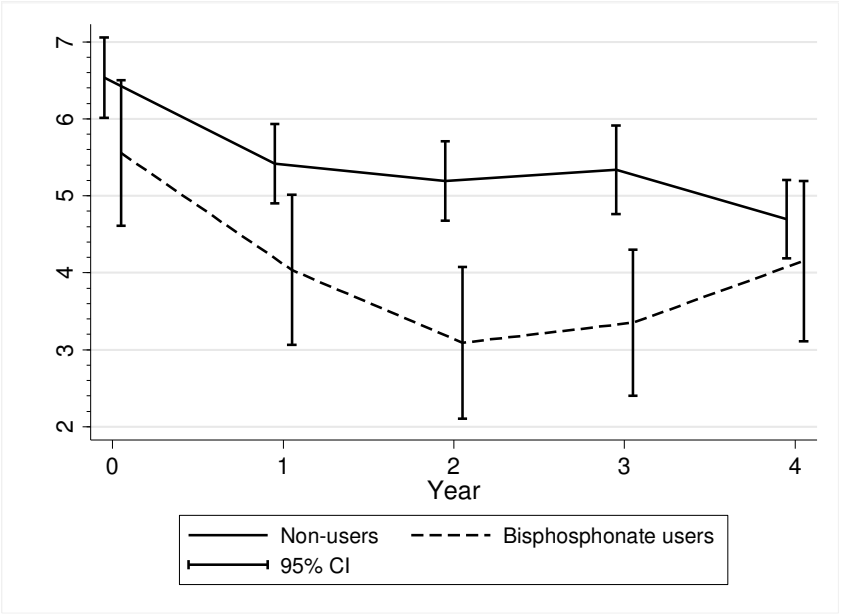
[¥]Effect size is beta coefficient, except in the case of binary outcomes (radiological and clinical progression, joint replacement) where it is an incidence rate ratio.
[§]Mean change is from baseline unless otherwise specified
The effect size is equivalent to differences in the unit on the y axis for continuous outcomes, using the beta coefficient (eg mm JSW for X-ray), and equivalent to ratios of the differences for binary outcomes, using incident rate ratios.
NRS change and womac pain change further adjusted for analgesic use and baseline pain score score

Figure 1

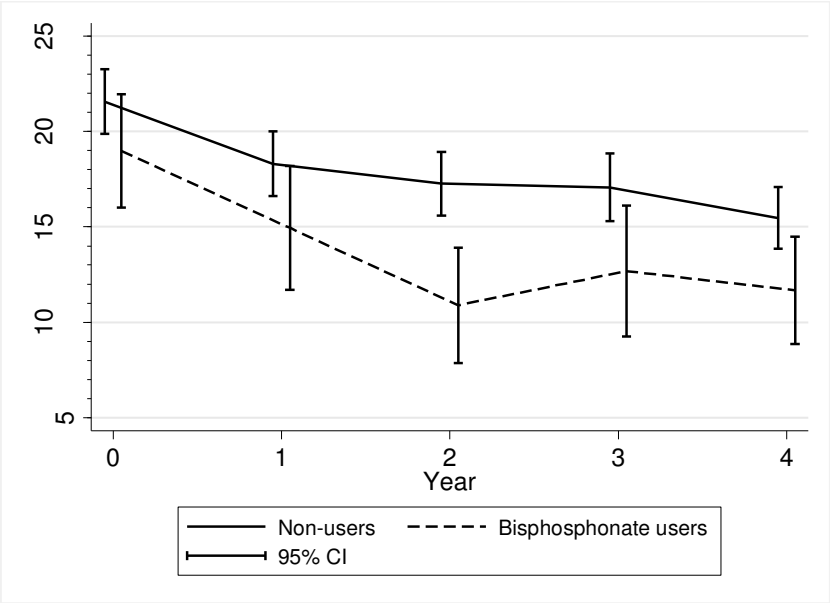
a



b



c



d

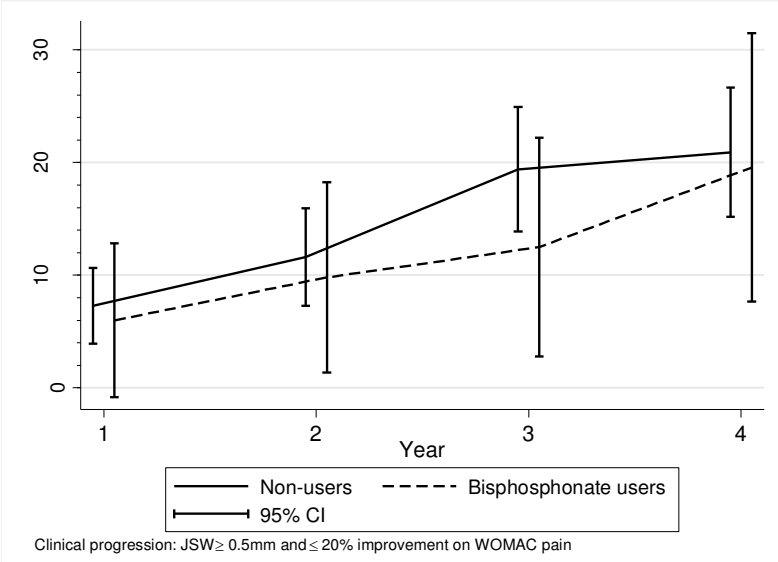
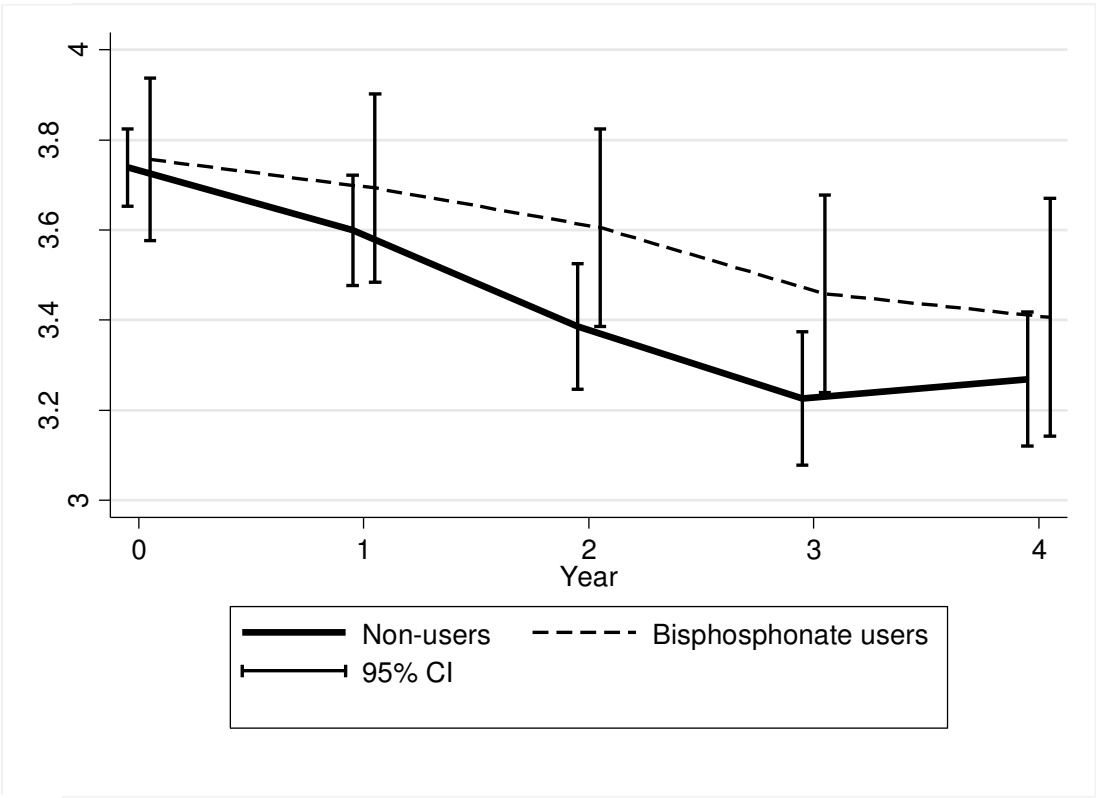
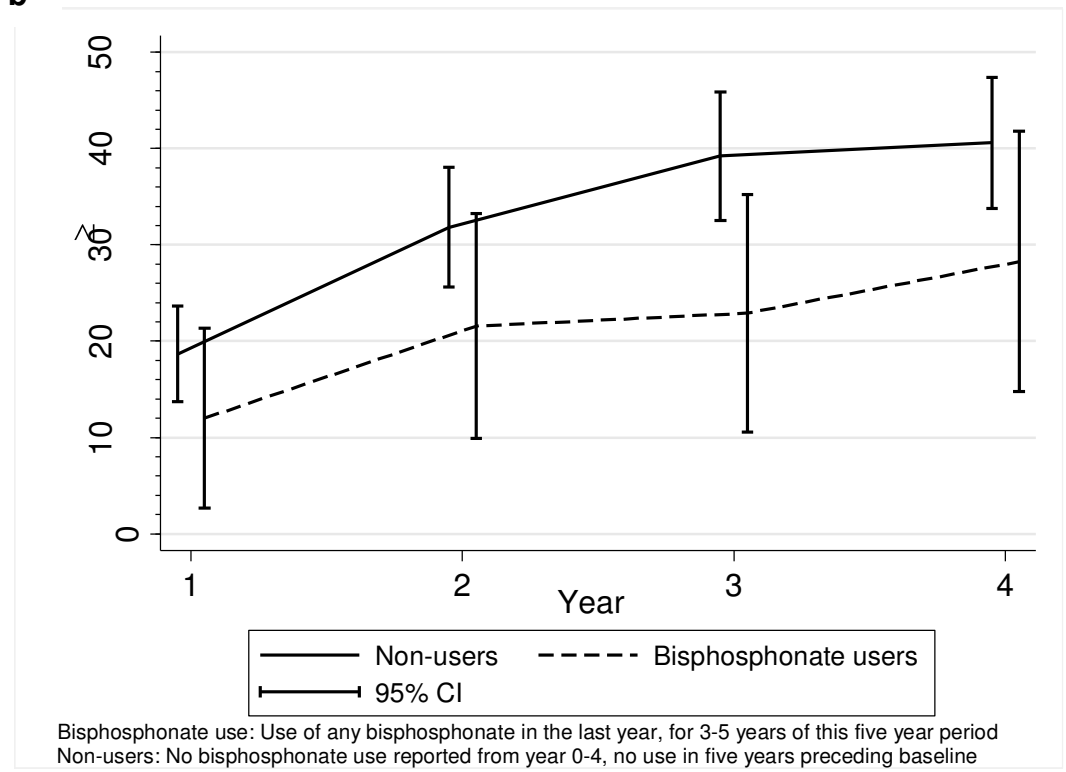


Figure 2:

a



b



Bisphosphonate use: Use of any bisphosphonate in the last year, for 3-5 years of this five year period
Non-users: No bisphosphonate use reported from year 0-4, no use in five years preceding baseline

Supplementary Table 1: Data sources from the Osteoarthritis Initiative

OAI dataset	Version number
Enrolees	17
Subject characteristics	0.2.2
Baseline physical exam	0.2.2
Knee X-ray data (kXR_SQ)	
Baseline	0.5
Year 1	1.5
Year 2	3.4
Year 3	5.4
Year 4	6.2
Knee x-ray quantitative measures of joint space width (Duryea)	
Baseline	0.5
1 year	1.5
2 year	3.4
3 year	5.2
4 year	6.2
Medical history	
Baseline	0.2.2
1 year	1.2.1
2 years	3.2.1
3 years	5.2.1
4 years	6.2.1
Joint symptoms	
Baseline	0.2.2
Year 1	1.2.1
Year 2	3.2.1
Year 3	5.2.1
Year 4	6.2.1
Outcomes	2