ORIGINAL ARTICLE

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Safety of Oral Bisphosphonates in Moderate-to-Severe Chronic Kidney Disease: A Binational Cohort Analysis

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ABSTRACT

Bisphosphonates are the first-line treatment for preventing fractures in osteoporosis patients. However, their use is contraindicated or to be used with caution in chronic kidney disease (CKD) patients, primarily because of a lack of information about their safety and effectiveness. We aimed to investigate the safety of oral bisphosphonates in patients with moderate to severe CKD, using primary-care electronic records from two cohorts, CPRD GOLD (1997–2016) and SIDIAP (2007–2015) in the UK and Catalonia, respectively. Both databases were linked to hospital records. SIDIAP was also linked to end-stage renal disease registry data. Patients with CKD stages 3b to 5, based on two or more estimated glomerular filtration rate measurements less than 45 mL/min/1.73 m^2, aged 40 years or older were identified. New bisphosphonate users were propensity score–matched with up to five non-users to minimize confounding within this population. Our primary outcome was CKD stage worsening (estimated glomerular filtration rate [eGFR] decline or renal replacement therapy). Secondary outcomes were acute kidney injury, gastrointestinal bleeding/ulcers, and severe hypocalcemia. Hazard ratios (HRs) were estimated using Cox regression and Fine and Gray sub-HRs were calculated for

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competing risks. We matched 2447 bisphosphonate users with 8931 non-users from CPRD and 1399 users with 6547 non-users from SIDIAP. Bisphosphonate use was associated with greater risk of CKD progression in CPRD (sub-HR [95% CI]: 1.14 [1.04, 1.26]) and SIDIAP (sub-HR: 1.15 [1.04, 1.27]). No risk differences were found for acute kidney injury, gastrointestinal bleeding/ulcers, or hypocalcemia. Hence, we can conclude a modest (15%) increased risk of CKD progression was identified in association with bisphosphonate use. No other safety concerns were identified. Our findings should be considered before prescribing bisphosphonates to patients with moderate to severe CKD. © 2020 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR)..

KEY WORDS: ANTIRESORPTIVES; FRACTURE PREVENTION; GENERAL POPULATION STUDIES; OSTEOPOROSIS; STATISTICAL METHODS

Introduction

Moderate to severe (stages 3 to 5) chronic kidney disease (CKD) affects up to 2.8 million people in the United Kingdom (UK)[1] and 2.7 million people in Spain.[2] CKD is associated with low bone mass.[3] Increased fracture risk is associated with increasing CKD severity.[4–7]

Although bisphosphonates are first-line anti-osteoporosis therapies for preventing fractures, their use is contraindicated or to be used with caution in patients with an estimated glomerular filtration rate (eGFR) under 30 mL/min/1.73 m^2. Clinical guidelines[8–10] and drug regulators[11–13] impose similar restrictions.

A systematic review of the benefits and harms of anti-osteoporosis medications, including bisphosphonates, suggested that bisphosphonates did not increase the risk of renal adverse events (373 patients from four trials), gastrointestinal events (179 patients from two trials), or hypocalcemia (93 patients from one trial).[14] The review acknowledged that most of the included studies had possible reporting bias and that the results might not apply to patients with stages 3b to 5 CKD because of scant evidence in this population. Reporting bias was driven by selective reporting of trial outcomes, unclear methods, and restricted study designs (randomized trials with 6 to 36 months of follow-up). The participants in the included trials were also far healthier than bisphosphonate users in actual practice settings.

The most recent (2017) Kidney Disease Outcomes Quality Initiative guidelines[15] proposed that potential kidney progression, the severity of any biochemical abnormalities, fracture risk, and bone and mineral disorders related to CKD should be considered when deciding whether to prescribe bisphosphonates. There is an urgent need for data on the risks and benefits of bisphosphonates for patients with moderate to severe CKD.

Following a commissioned call from the UK National Institute for Health Research, we analyzed routinely collected data from Spain and the UK to establish the safety of bisphosphonates in patients with stages 3b to 5 CKD. Our prespecified list of safety events included CKD worsening (primary outcome), acute kidney injury, gastrointestinal events, and severe hypocalcemia (secondary outcomes).

Materials and Methods

Data sources

This study used a cohort design with data from two primary-care electronic health record databases linked to hospital records.

We used 1997 to 2016 records from the UK's Clinical Practice Research Datalink (CPRD) GOLD linked with Hospital Episode Statistics (HES). CPRD-HES contains anonymized primary- and secondary-care records from 401 English primary-care practices (58% of CPRD-registered practices). In CPRD, practices suitable for research purposes are considered "up to standard". [16]

We also used 2007 to 2015 records from Catalonia's Information System for the Development of Research in Primary Care (SIDIAP) linked with the National Hospital Discharge Database and renal registry. SIDIAP contains information on 5.8 million patients from 279 practices in the Catalonia region of Spain, representing 80% of that population.[17]

Both data sets are representative of their respective populations.[18,19] The replication of analyses from CPRD in SIDIAP was undertaken to check the generalizability of results identified in the UK to other European countries. Differences between CPRD and SIDIAP are mainly due to difference in the population, since the data sets collect data in the same manner. Scientific approval was obtained for CPRD (protocol number 15_153R2) and SIDIAP (protocol number 148). Data were extracted and analyzed by independent statisticians using an agreed common data structure and shared programming codes.

Study population

Our target population was patients with two or more eGFR measurements under 45 mL/min/1.73 m^2, aged 40 years or older. Patients had to be registered with a practice considered "up to standard" by that database for at least 1 year before their first low eGFR measurement. eGFR estimates were obtained directly from biochemistry data and calculated using the CKD Epidemiology Collaboration formula based on serum creatinine if automated laboratory reporting of eGFR was not available.[20]

Patients were excluded if they had used bisphosphonates in the year before their index date (first bisphosphonate use), used non-oral bisphosphonate anti-osteoporotic therapies at any time before their index date, were missing index of multiple deprivation information (social deprivation level in CPRD), or had no follow-up eGFR measurement.

Study exposure: bisphosphonate use

Oral bisphosphonate prescriptions (CPRD) and dispensations (SIDIAP) were identified using previously validated lists of prodcodes in CPRD and anatomic therapeutic chemical classification (ATC) codes in SIDIAP. All participants joined the study unexposed to bisphosphonates on their second eGFR measurement under 45 mL/min/1.73 m^2. Participants could contribute both exposed and unexposed time, as illustrated in Supplemental Fig. S1. Participants were followed until the end of enrollment in the database (moving out, death, or 10 years), an incident record of the outcome of interest, stopping treatment (6 months), or switching treatment (bisphosphonate users only). A washout period of 6 months plus 30 days from the last prescription or dispensation accounted for carry-over effects. Code lists are provided in https://github.com/vystrauss/BisCK/tree/master.

Outcomes

The primary outcome was CKD stage worsening, based on follow-up annual eGFR measurements in primary-care records, dialysis, a kidney transplant recorded in CPRD-HES with relevant codes from the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) or fourth version of the OPCS Classification of Interventions and Procedures (OPCS-4), or a record in the renal registry in SIDIAP. CKD stage worsening included a move from stage 3b (eGFR 30 to 45 mL/min/1.73 m^2) to stage 4 (eGFR 15 to 30 mL/min/1.73 m^2) or 5 (eGFR less than 15 mL/min/1.73 m^2), or from stage 4 to 5.

The secondary outcomes of interest were hospitalization for acute kidney injury; hospitalization for, or a primary-care record of, peptic ulcer or gastrointestinal bleeding; and hospitalization for hypocalcemia, identified with ICD-10 codes.

Covariates

Covariates were identified in a consensus meeting between two clinicians and one epidemiologist using a predefined list of potential confounders identified in the literature. Forty-five covariates were selected, including patient demographics, clinical diagnoses identified with Read codes (CPRD) or ICD-10 (SIDIAP), and previous drug use ascertained using prodcodes (CPRD) or ATC codes (SIDIAP). Covariates are listed in the footnote of Supplemental Fig. S2.

Statistical analyses

A propensity score (PS) was estimated using the 45 covariates with logistic regression. The PS represented the probability of receiving oral bisphosphonates based on the covariates and exact matching on years of follow-up. Missing data for body mass index, smoking category, drinking category (CPRD), and creatinine (SIDIAP) were imputed in 10 data sets using multiple imputation by chained equations, assuming data were missing at random. Exposed participants were PS-matched with up to five unexposed participants on a caliper width of 0.2 standard deviations of the logit of the PS, without replacement. The absolute standardized mean difference (ASMD) was used to evaluate balance, with values below 0.1 indicating good balance.

Incidence rates and their 95% confidence intervals (CIs) were reported per 1000 person-years in the PS-matched and full cohorts. Unadjusted and fully adjusted Cox proportional hazard models were used to calculate hazard ratios (HRs) for each of the outcomes. Fine and Gray sub-HRs were calculated for the PS-matched cohorts to account for any difference in death rate due to PS matching. The proportionality assumption of all models was checked using Schoenfeld Residuals. The proportionality assumption held for all models (data not shown). We combined the results from CPRD and SIDIAP in fixed-effects meta-analyses to produce an overall estimate.

Numbers needed to harm after 3 and 5 years were calculated from Kaplan–Meier curves for the primary outcome. Supplemental Materials and Methods contains the sample size calculation.

Additional and sensitivity analyses

Two predefined interactions with bisphosphonate use were tested, sex and history of fracture at any location except the digits, with a cut-off of $p < .1$. Stratified Fine and Gray regressions were reported if there was evidence of significant interactions. Medication possession ratios (MPR) were calculated as the number of defined daily doses from the first prescription/dispensation until 30 days after the last record, divided by the number of days within this time window. Fine and Gray models were repeated for MPR quartiles (0 versus <0.83, 0.83–0.97, 0.97–1.05, and >1.05) to test the biological gradient of the Bradford-Hill causality criteria.[21]

The effect of potential unmeasured confounding was measured using an array analysis[22] for any significant result in CPRD. The percentage unexposed with the unmeasured confounder was set at 30%, based on unpublished data. The array analysis combined a range of values for the unmeasured variable's exposed prevalence (30% to 80%) and the association with the study outcome (1.0 to 3.0) to adjust the main (estimated) treatment effect size.

Data were analyzed in R version 3.3.2 (CPRD) and 3.5.1 (SIDIAP). Packages used included mice,[23] MatchIT,[24] survival,[25] and survminer.[26]

The reporting guidelines of STROBE were followed when writing this article.

Results

We identified 217,405 patients with an eGFR ≤45 mL/min/1.73 m^2 in CPRD, of whom 53,986 patients contributed unexposed time and 2613 bisphosphonate exposure time. We identified 40,800 unexposed and 1408 exposed patients in SIDIAP. Fig. 1 shows all exclusions. The most common reasons for exclusion were not having two eGFR measurements and not having any follow-up eGFR data available.

Across 10 imputed data sets, on average 2447 bisphosphonate users were matched with 8931 non-users in CPRD and 1399 users were matched with 6547 non-users in SIDIAP. Table 1 reports characteristics after imputation and before and after PS matching.

Participants were well-matched, including on key covariates such as age, body mass index (BMI), and baseline eGFR, with ASMDs of less than 0.1 for all covariates in the PS in both data sets (Supplemental Materials and Methods), although there were differences in rates (Table 1). In CPRD, the average age was 80 years with approximately 27% of patients male, whereas in SIDIAP, the average age was 78 years with approximately 23% of patients male.

In the PS-matched cohorts, participants were followed up for a total of 7287 exposed and 26,731 unexposed person-years in CPRD (median of 3.0 years for both users and non-users) and 3946 exposed and 20,152 unexposed person-years in SIDIAP (median of 4.4 years for users and 4.8 years for non-users), before censoring at an outcome of interest.

The risk of death differed between users and non-users in only the PS-matched cohort from CPRD (HR [95% CI]: 0.67 [0.62, 0.73]).

CKD stage worsening

In CPRD, 2572 events occurred, including 229 dialysis or transplant events. The incidence rate of CKD stage worsening was 89.1 (95% CI: 82.1, 96.7) per 1000 person-years in bisphosphonate users and 85.6 (82.0, 89.5) in non-users (Table 2). Fig. 2 shows the cumulative incidence of stage worsening and death. The number needed to harm was 40.8 after 3 years and 20.7 after 5 years.

Similar results were found in SIDIAP. There were 2482 events, with incidence rates of 118.4 per 1000 person-years in users and

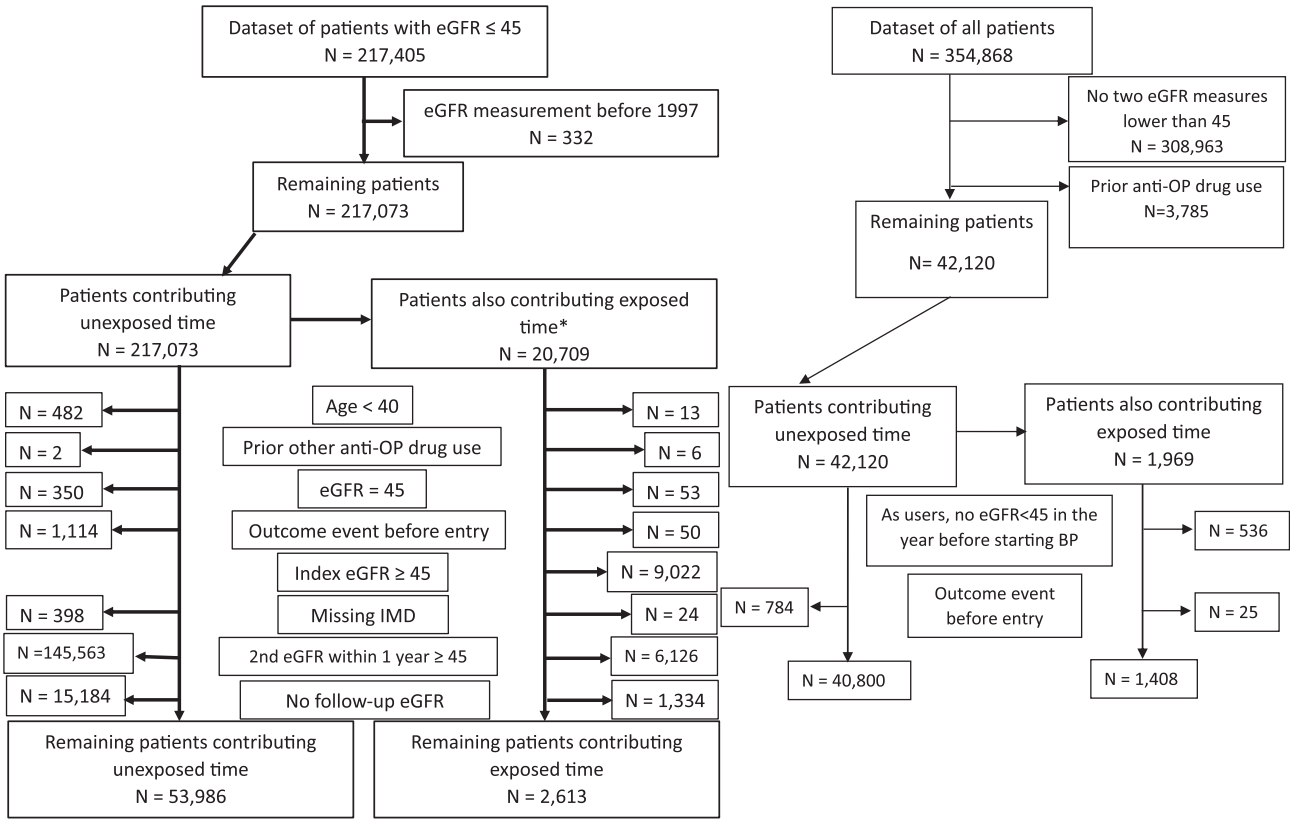


Fig 1. Flow diagrams for patient exclusions in CPRD (left) and SIDIAP (right) identifying when and why patients were excluded from each data set. *Patients contribute both unexposed and exposed time. See Supplemental Fig. S1 for full explanation. eGFR = estimated glomerular filtration rate in mL/min/1.73 m^2; IMD = index of multiple deprivation.

100.0 in non-users. The number needed to harm was 29.4 after 3 years and 28.6 after 5 years.

Combining results from CPRD and SIDIAP gave a PS-matched cohort sub-HR (95% CI) of 1.14 (1.07, 1.23) and a whole cohort HR of 1.18 (1.11, 1.26) (Table 2). Supplemental Table S1 gives the full results of the multiple regression model for CPRD.

In CPRD, significant interactions were identified with history of fracture ($p = .03$) and sex ($p = .04$). Those with a history of fracture were more likely to experience stage worsening (sub-HR [95% CI]: 1.36 [1.08, 1.71]) than those without a history of fracture (1.10 [0.99, 1.22]), although the CIs overlapped. Women were more likely to experience stage change (1.24 [1.11, 1.38]) than men (1.00 [0.83, 1.21]).

Those in the highest MPR quartile ratio category were at highest risk of CKD stage worsening and those with the lowest ratio were at least risk, although the CIs overlapped (Supplemental Fig. S3).

The array analysis (Fig. 3*A*, *B*) showed that unmeasured confounding was unlikely to negate the identified risk of sub-HR 1.14 (1.04, 1.26). For the risk identified to be negated, more than 50% of the bisphosphonate users needed to have the confounder, with an sub-HR of 3.0 between the confounder and CKD stage worsening. The presented results would be more than 25% biased. The results would also be negated if more than 80% of the participants had the confounder, with an association (sub-HR) of 1.75 (results 20% biased).

Acute kidney injury

The PS-matched CPRD and SIDIAP cohorts contained 482 and 597 acute kidney injury events, respectively. There was no significant difference in the risk of developing an acute kidney injury between bisphosphonate users and non-users, with a combined sub-HR (95% CI) of 0.92 (0.78, 1.08) (Table 2).

No significant interactions were identified in sensitivity analyses. Less than 15% of the participants experienced an acute kidney injury within 10 years (Supplemental Fig. S4). Participants exposed to bisphosphonates with an MPR between 97% and 105.2% had a lower risk of acute kidney injury than if matched to unexposed patients (sub-HR [95% CI]: 0.55 [0.32, 0.94]). However, no dose-response effect was found.

Gastrointestinal events

The rates of gastrointestinal events were 5.5 (4.0, 7.5) per 1000 patient-years for users and 6.4 (5.5, 7.4) for non-users in the CPRD PS-matched cohort and 1.9 (0.9, 3.5) for users and 1.9 (1.4, 2.5) for non-users in the SIDIAP PS-matched cohort. No difference was found between users and non-users in any of the cohorts (Table 2).

No interactions were identified in sensitivity analyses. More than 95% of participants did not experience a gastrointestinal event within 10 years (Supplemental Fig. S5).

Table 1. Baseline Characteristics Before and After Matching for CPRD and SIDIAP

	CPRD				SIDIAP			
	Before matching, after imputation		After matching		Before matching, after imputation		After matching	
Category	Non-BP (*n* = 53,986)	BP (*n* = 2613)	Non-BP (*n* = 8931)	BP (*n* = 2447)	Non-BP (*n* = 40,800)	BP (*n* = 1408)	Non-BP (*n* = 6547)	BP (*n* = 1399)
Age (years), mean (SD)	77.6 (9.8)	80.6 (8.8)	80.3 (9.1)	80.4 (8.8)	78.9 (10.0)	78.8 (7.7)	78.7 (10.0)	78.8 (7.7)
Sex (male), *n* (%)	23,280 (43.1)	595 (22.8)	2669 (29.9)	584 (23.9)	15,366 (37.7)	314 (22.3)	1609 (24.6)	314 (22.4)
Socioeconomic deprivation, *n* (%)								
1 (least deprived)	11,949 (22.1)	637 (24.4)	2127 (23.8)	587 (24.0)	5325 (13.1)	211 (15.0)	935 (14.3)	210 (15.0)
2	12,649 (23.4)	620 (23.7)	2089 (23.4)	585 (23.9)	5318 (13.0)	194 (13.8)	944 (14.4)	193 (13.8)
3	11,539 (21.4)	550 (21.0)	1881 (21.1)	517 (21.1)	5342 (13.1)	170 (12.1)	816 (12.5)	169 (12.1)
4	10,771 (20.0)	480 (18.4)	1654 (18.5)	452 (18.5)	4967 (12.2)	161 (11.4)	734 (11.2)	161 (11.5)
5 (most deprived)	7078 (13.1)	326 (12.5)	1180 (13.2)	306 (12.5)	4789 (11.7)	181 (12.9)	792 (12.1)	178 (12.7)
Urban (deprivation level undefined)	N/A	N/A	N/A	N/A	4879 (12.0)	201 (14,3)	934 (14.3)	200 (14.3)
Rural					10,180 (25.0)	290 (20.6)	1392 (21.3)	288 (20.6)
BMI, mean (SD)[a]	27.6 (5.5)	26.7 (5.2)	26.9 (5.4)	26.8 (5.3)	29.1 (5.2)	29.1 (5.1)	29.1 (5.4)	29.1 (5.1)
Smoking category, *n* (%)[b]								
No	28,093 (52.0)	1423 (54.5)	4784 (53.6)	1329 (54.3)	30,904 (75.7)	1159 (82.3)	5324 (81.3)	1150 (82.2)
Ex	19,910 (36.9)	966 (37.0)	3295 (36.9)	906 (37.0)	6515 (16.0)	158 (11.2)	776 (11.9)	158 (11.3)
Yes	5983 (11.1)	224 (8.6)	852 (9.5)	212 (8.7)	3381 (8.3)	91 (6.5)	447 (6.8)	91 (6.5)
Drinking category, *n* (%)[c]								
No	14,621 (27.1)	781 (29.9)	2663 (29.8)	734 (30.0)	NA	NA	NA	NA
Ex	2117 (3.9)	126 (4.8)	400 (4.5)	118 (4.8)	NA	NA	NA	NA
Yes	37,248 (69.0)	1706 (65.3)	5868 (65.7)	1595 (65.2)	NA	NA	NA	NA
eGFR category (mL/min/1.73 m^2), *n* (%)								
0–4.9	67 (0.1)	<5 (<0.1)	5 (0.1)	<5 (<0.1)	74 (0.2)	<5 (<0.1)	8 (0.1)	<5 (<0.1)
5–9.9	362 (0.7)	16 (0.6)	60 (0.7)	16 (0.7)	388 (1.0)	7 (0.5)	51 (0.8)	7 (0.5)
10–14.9	616 (1.1)	29 (1.1)	116 (1.3)	29 (1.2)	785 (1.9)	15 (1.1)	114 (1.7)	15 (1.1)
15–19.9	1278 (2.4)	81 (3.1)	263 (2.9)	73 (3.0)	1568 (3.8)	37 (2.6)	207 (3.2)	37 (2.6)
20–24.9	2541 (4.7)	164 (6.3)	537 (6.0)	149 (6.1)	2814 (6.9)	99 (7.0)	425 (6.5)	98 (7.0)
25–29.9	4665 (8.6)	327 (12.5)	996 (11.2)	299 (12.2)	4983 (12.2)	172 (12.2)	759 (11.6)	172 (12.3)
30–34.9	8417 (15.6)	542 (20.7)	1709 (19.1)	498 (20.4)	7741 (19.0)	272 (19.3)	1126 (17.2)	269 (19.2)
35–39.9	14,415 (26.7)	704 (26.9)	2378 (26.6)	657 (26.8)	10,830 (26.5)	399 (28.3)	1807 (27.6)	397 (28.4)
40–44.9	21,625 (40.1)	749 (28.7)	2867 (32.1)	725 (29.6)	11,617 (28.5)	406 (28.8)	2050 (31.3)	403 (28.8)
Hospital visits, *n* (%)								
0	33,367 (61.8)	1,022 (39.1)	4066 (45.5)	988 (40.4)	NA	NA	NA	NA
1	10,968 (20.3)	737 (28.2)	2368 (26.5)	683 (27.9)	NA	NA	NA	NA
2	4971 (9.2)	399 (15.3)	1170 (13.1)	367 (15.0)	NA	NA	NA	NA
3–5	3876 (7.2)	371 (14.2)	1078 (12.1)	340 (13.9)	NA	NA	NA	NA
6+	804 (1.5)	84 (3.2)	249 (2.8)	69 (2.8)	NA	NA	NA	NA

(Continues)

Table 1. Continued

Category	CPRD				SIDIAP			
	Before matching, after imputation		After matching		Before matching, after imputation		After matching	
	Non-BP (*n* = 53,986)	BP (*n* = 2613)	Non-BP (*n* = 8931)	BP (*n* = 2447)	Non-BP (*n* = 40,800)	BP (*n* = 1408)	Non-BP (*n* = 6547)	BP (*n* = 1399)
Charlson score, *n* (%)								
0	30,485 (56.5)	682 (26.1)	3107 (34.8)	671 (27.4)	7392 (18.1)	313 (22.2)	1339 (20.5)	308 (22.0)
1	7723 (14.3)	364 (13.9)	1366 (15.3)	350 (14.3)	7,605 (18.6)	297 (21.1)	1330 (20.3)	293 (20.9)
2	7719 (14.3)	604 (23.1)	1905 (21.3)	565 (23.1)	9604 (23.5)	318 (22.6)	1501 (22.9)	318 (22.7)
3–5	6468 (12.0)	746 (28.5)	2001 (22.4)	666 (27.2)	14,375 (35.2)	450 (32.0)	2212 (33.8)	450 (32.2)
6+	1591 (2.9)	217 (8.3)	552 (6.2)	195 (8.0)	1824 (4.5)	30 (2.13)	165 (2.5)	30 (2.1)
Rheumatoid arthritis, *n* (%)	532 (1.0)	148 (5.7)	171 (1.9)	136 (5.6)	478 (1.2)	49 (3.48)	206 (3.2)	49 (3.5)
Varices, *n* (%)	3323 (6.2)	316 (12.1)	886 (9.9)	281 (11.5)	4674 (11.5)	206 (14.6)	933 (14.3)	204 (14.6)
DVT, *n* (%)	1895 (3.5)	113 (4.3)	388 (4.3)	108 (4.4)	<5 (<0.1)	<5 (<0.1)	<5 (<0.1)	<5 (<0.1)
Type 2 diabetes, *n* (%)	6172 (11.4)	404 (15.5)	1304 (14.6)	371 (15.2)	14,524 (35.6)	473 (33.6)	2202 (33.6)	470 (33.6)
Dementia, *n* (%)	944 (1.7)	79 (3.0)	263 (2.9)	74 (3.0)	2968 (7.27)	97 (6.9)	472 (7.2)	97 (6.9)
CKD, *n* (%)	8245 (15.3)	1381 (52.9)	3479 (39.0)	1225 (50.1)	17,649 (43.3)	810 (57.5)	3568 (54.5)	801 (57.3)
Cerebral vascular disease, *n* (%)	4193 (7.8)	320 (12.2)	976 (10.9)	299 (12.2)	5890 (14.4)	196 (13.9)	920 (14.1)	192 (13.7)
Peripheral vascular disease, *n* (%)	1246 (2.3)	88 (3.4)	266 (3.0)	80 (3.3)	2848 (6.98)	89 (6.3)		
Hypertension, *n* (%)	23,630 (43.8)	1518 (58.1)	4628 (51.8)	1391 (56.8)	33,622 (82.4)	1182 (83.9)	5495 (83.9)	1176 (84.1)
Hyperlipidemia, *n* (%)	5788 (10.7)	459 (17.6)	1289 (14.4)	415 (17.0)	17,206 (42.2)	660 (46.9)	2934 (44.8)	657 (47.0)
Liver disease, *n* (%)	224 (0.4)	32 (1.2)	73 (0.8)	28 (1.1)	1528 (3.75)	62 (4.4)	277 (4.2)	61 (4.4)
Peptic ulcer, *n* (%)	816 (1.5)	65 (2.5)	187 (2.1)	58 (2.4)	1620 (3.97)	63 (4.5)	186 (2.8)	63 (4.5)
Osteomalacia/rickets, *n* (%)	15 (0.0)	<5 (<0.1)	5 (0.1)	<5 (<0.1)	NA	NA	NA	NA
Cancer, *n* (%)	5415 (10.0)	454 (17.4)	1374 (15.4)	416 (17.0)	5790 (14.2)	212 (15.1)	956 (14.6)	209 (14.9)
Hip fracture, *n* (%)	440 (0.8)	33 (1.3)	125 (1.4)	32 (1.3)	1175 (2.9)	97 (6.9)	406 (6.2)	93 (6.7)
Non-hip fracture, *n* (%)	2088 (3.9)	577 (22.1)	1070 (12.0)	482 (19.7)	2981 (7.3)	264 (18.8)	1102 (16.8)	257 (18.4)
Prescriptions, *n* (%)								
0	1527 (2.9)	<5 (<0.2)	72 (0.9)	<5 (<0.2)	501 (5.2)	<5 (<0.1)	45 (0.7)	<5 (<0.1)
1–3	6880 (13.3)	61 (2.5)	360 (4.3)	61 (2.7)	1869 (4.6)	10 (0.7)	208 (3.2)	10 (0.7)
4–6	12,453 (24.0)	230 (9.4)	1104 (13.3)	226 (9.9)	8252 (20.2)	102 (7.2)	1049 (16.0)	102 (7.3)
7–9	12,408 (23.9)	468 (19.2)	1763 (21.2)	451 (19.7)	13,982 (34.3)	336 (23.9)	2165 (33.1)	336 (24.0)
10–12	9019 (17.4)	548 (22.5)	1906 (22.9)	519 (22.7)	11,025 (27.0)	486 (34.5)	1894 (28.9)	481 (34.4)
13+	9524 (18.4)	1129 (46.3)	3125 (37.5)	1026 (44.9)	5171 (12.7)	474 (33.7)	1186 (18.1)	470 (33.6)
Hormone replacement therapy, *n* (%)	2979 (5.5)	244 (9.3)	714 (8.0)	228 (9.3)	857 (2.1)	53 (3.8)	257 (3.7)	51 (3.9)
Contraceptive, *n* (%)	38 (0.1)	<5 (<0.1)	5 (0.1)	<5 (<0.1)	7 (0.0)	<5 (<0.1)	<5 (<0.1)	<5 (<0.1)
Calcium supplements, *n* (%)	3996 (7.4)	782 (29.9)	1818 (20.4)	680 (27.8)	485 (1.2)	25 (1.8)	95 (1.4)	24 (1.7)
Bisphosphonate use more than 1 year before index date, *n* (%)	996 (1.8)	136 (5.2)	486 (5.4)	122 (5.0)	1831 (4.5)	99 (7.0)	450 (6.9)	98 (7.0)
Steroids, *n* (%)	9194 (17.0)	1311 (50.2)	3509 (39.3)	1179 (48.2)	3996 (9.8)	301 (21.4)	1263 (19.3)	296 (21.2)
Anticoagulants, *n* (%)	7078 (13.1)	486 (18.6)	1567 (17.5)	455 (18.6)	22,876 (56.1)	832 (59.1)	3818 (58.3)	824 (58.9)

(Continues)

Table 1. Continued

	CPRD				SIDIAP			
	Before matching, after imputation		After matching		Before matching, after imputation		After matching	
Category	Non-BP (*n* = 53,986)	BP (*n* = 2613)	Non-BP (*n* = 8931)	BP (*n* = 2447)	Non-BP (*n* = 40,800)	BP (*n* = 1408)	Non-BP (*n* = 6547)	BP (*n* = 1399)
Heparin, *n* (%)	432 (0.8)	61 (2.3)	160 (1.8)	51 (2.1)	2224 (5.5)	119 (8.5)	521 (8.0)	116 (8.3)
Aromatase inhibitors, *n* (%)	265 (0.5)	58 (2.2)	122 (1.4)	45 (1.8)	330 (0.8)	20 (1.4)	91 (1.4)	19 (1.4)
Nonsteroidal anti-inflammatories, *n* (%)	30,095 (55.7)	1873 (71.7)	5862 (65.6)	1737 (71.0)	15,187 (37.2)	714 (50.7)	3116 (47.6)	707 (50.5)
Proton pump inhibitors, *n* (%)	19,596 (36.3)	1593 (61.0)	4795 (53.7)	1465 (59.9)	26,547 (65.1)	1114 (79.1)	5018 (76.6)	1105 (79.0)
Anxiols/sedatives/hypnotics, *n* (%)	10,488 (19.4)	726 (27.8)	2429 (27.2)	668 (27.3)	NA	NA	NA	NA
Antidepressants, *n* (%)	14,578 (27.0)	1118 (42.8)	3386 (37.9)	1032 (42.2)	7268 (17.8)	349 (24.8)	1530 (23.4)	346 (24.7)
Statins, *n* (%)	21,548 (39.9)	1402 (53.7)	4368 (48.9)	1293 (52.8)	17,835 (43.7)	644 (45.7)	2949 (45.0)	642 (45.9)
Calcium channel blockers, *n* (%)	23,668 (43.8)	1507 (57.7)	4683 (52.4)	1392 (56.9)	370 (0.9)	6 (0.4)	32 (0.5)	6 (0.4)
ACE inhibitors, *n* (%)	32,246 (59.7)	1907 (73.0)	6142 (68.8)	1773 (72.5)	18774 (46.0)	572 (40.6)	2714 (41.5)	568 (40.6)
Antiepileptics, *n* (%)	2251 (4.2)	207 (7.9)	631 (7.1)	192 (7.8)	3466 (8.50)	166 (11.8)	720 (11.0)	163 (11.7)
Diuretics, *n* (%)	38,403 (71.1)	2164 (82.8)	7139 (79.9)	2023 (82.7)	NA	NA	NA	NA
Beta blockers, *n* (%)	25,175 (46.6)	1395 (53.4)	4461 (49.9)	1302 (53.2)	10,625 (26.0)	379 (26.9)	1782 (27.2)	375 (26.8)
Digoxin, *n* (%)	5839 (10.8)	319 (12.2)	1152 (12.9)	310 (12.7)	2946 (7.2)	99 (7.0)	476 (7.3)	97 (7.0)
Antihypertensives, *n* (%)	8608 (15.9)	588 (22.5)	1770 (19.8)	548 (22.4)	NA	NA	NA	NA
Antiarrythmics, *n* (%)	7010 (13.0)	447 (17.1)	1418 (15.9)	417 (17.0)	2386 (5.9)	84 (6.0)	436 (6.7)	84 (6.0)
Insulin, *n* (%)	2359 (4.4)	127 (4.9)	421 (4.7)	120 (4.9)	5417 (13.3)	197 (14.0)	871 (13.3)	196 (14.0)

ACE = angiotensin-converting enzyme; BMI = body mass index; BP = bisphosphonate; CKD = chronic kidney disease; CPRD = Clinical Practice Research Datalink; DVT = deep vein thrombosis; eGRF = estimated glomerular filtration rate; SIDIAP = Information System for the Development of Research in Primary Care; NA = not available in this data set.

[a]BMI missing in 468 (17.9%) exposed and 17,915 (33.2%) unexposed patients in CPRD and 677 (47.2%) exposed and 20,402 (49.1%) unexposed patients in SIDIAP before imputation.

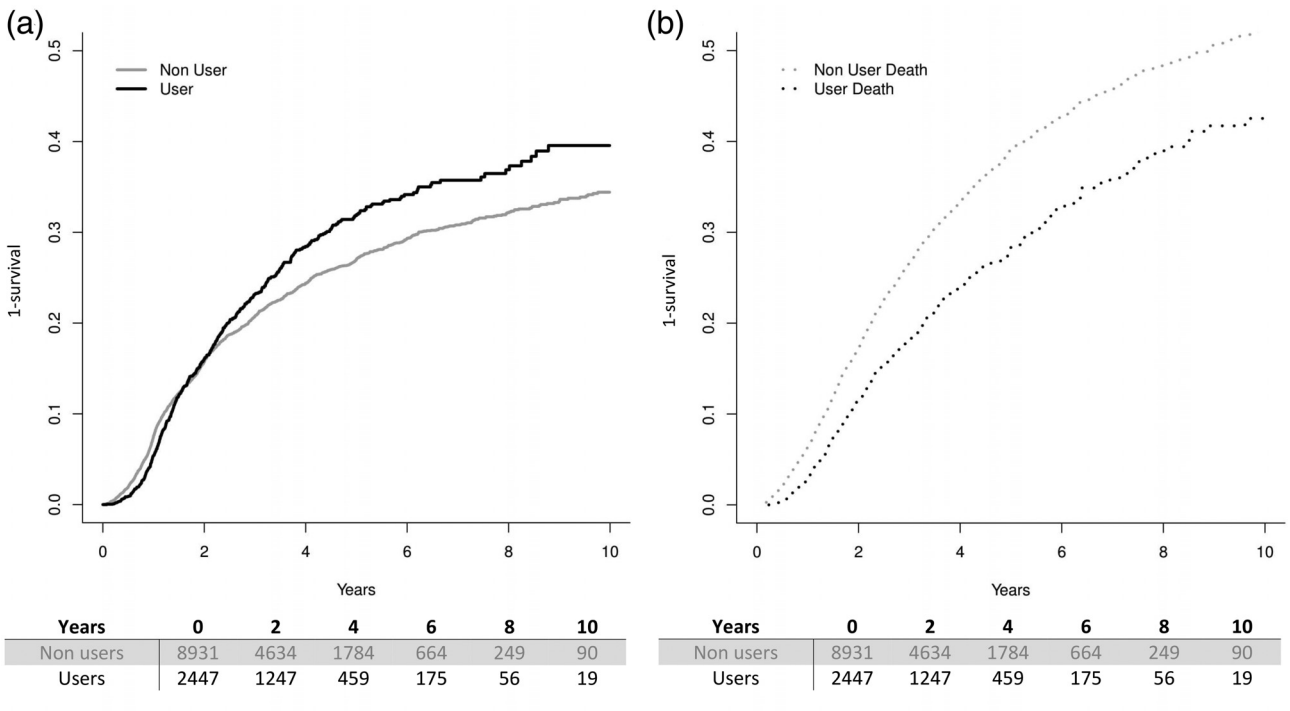
[b]Smoking category missing in 238 (9.1%) exposed and 13,239 (24.5%) unexposed patients in CPRD and 294 (20.5%) exposed and 7124 (17.1%) unexposed patients in SIDIAP before imputation.

[c]Drinking category missing in 665 (25.5%) exposed and 21,581 (40.0%) unexposed patients in CPRD before imputation.

Table 2. Numbers of Events, Incidence Rates, and Hazard Ratios per 1000 person-years for All Analyses

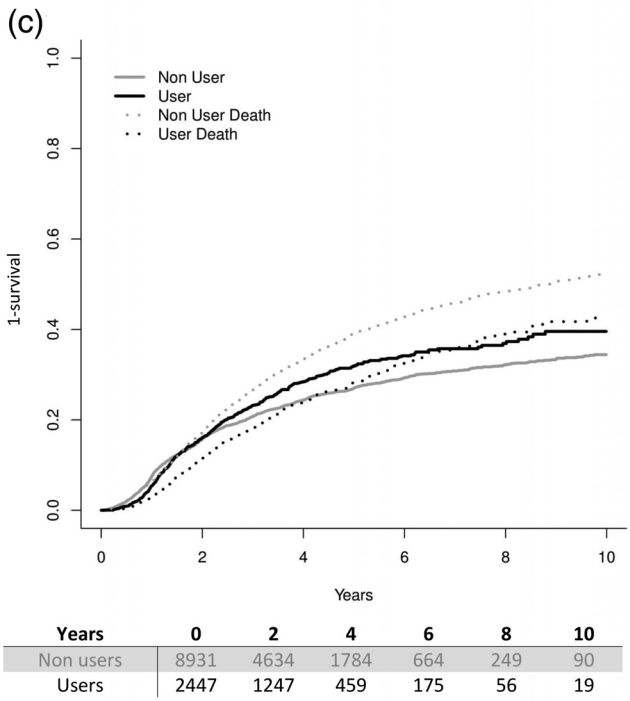
		CPRD		SIDIAP		
		BP	Non-BP	BP	Non-BP	Combined
Chronic kidney disease progression	Unmatched no. events	614	15,411	471	13,462	
	Unmatched incidence rates	90.8 (83.9, 98.3)	73.3 (72.1, 74.4)	119.0 (108.5,130.2)	104.7 (102.9,106.5)	
	Unadjusted HR	**1.25 (1.15, 1.36)**		**1.13 (1.03, 1.23)**		**1.19 (1.12, 1.27)**
	Fully adjusted HR	**1.18 (1.08, 1.29)**		**1.19 (1.08, 1.31)**		**1.18 (1.11, 1.26)**
	PS-matched no. events	576	1996	467	2015	
	PS-matched incidence rates	89.1 (82.1, 96.7)	85.6 (82.0, 89.5)	118.4 (107.9,129.6)	100.0 (95.7,104.5)	
	PS-matched sub-HR	**1.14 (1.04, 1.26)**		**1.15 (1.04, 1.27)**		**1.14 (1.07, 1.23)**
Acute kidney injury	Unmatched no. events	83	2,739	101	3,203	
	Unmatched incidence rates	11.7 (9.5, 14.6)	11.2 (10.8, 11.6)	19.8 (16.1, 24.0)	19.6 (18.9, 20.3)	
	Unadjusted HR	1.11 (0.89, 1.38)		1.01 (0.83, 1.23)		1.05 (0.91, 1.22)
	Fully adjusted HR	0.84 (0.66, 1.05)		1.07 (0.88, 1.31)		0.97 (0.83, 1.12)
	PS-matched no. events	80	402	99	498	
	PS-matched incidence rates	15.2 (13.8, 16.8)	12.0 (9.7, 14.9)	19.5 (15.9, 23.8)	19.6 (17.9, 21.4)	
	PS-matched sub-HR	0.86 (0.67, 1.09)		0.97 (0.78, 1.21)		0.92 (0.78, 1.08)
Gastrointestinal event	Unmatched no. events	38	1294	10	338	
	Unmatched incidence rates	5.3 (3.9, 7.3)	5.3 (5.0, 5.6)	1.9 (0.9, 3.5)	2.0 (1.8, 2.2)	
	Unadjusted HR	0.97 (0.71, 1.35)		0.97 (0.52, 1.82)		0.97 (0.73, 1.29)
	Fully adjusted HR	1.00 (0.71, 1.41)		1.18 (0.62, 2.22)		1.04 (0.77, 1.40)
	PS-matched no. events	37	160	10	49	
	PS-matched incidence rates	5.5 (4.0, 7.5)	6.4 (5.5, 7.4)	1.9 (0.9, 3.5)	1.9 (1.4, 2.5)	
	PS-matched sub-HR	0.96 (0.67, 1.39)		0.99 (0.50, 1.96)		0.97 (0.70, 1.33)
Hypocalcemia	Unmatched no. events	<5	155	<5	14	
	Unmatched incidence rates	0.3 (0.1, 1.1)	0.6 (0.5, 0.7)	0.2 (0.0, 1.1)	0.1 (0.0, 0.1)	
	Unadjusted HR	0.45 (0.11, 1.82)		NA		NA
	Fully adjusted HR	0.28 (0.07, 1.17)		NA		NA
	PS-matched no. events	<5	26	<5	6	
	PS-matched incidence rates	0.3 (0.1, 1.2)	1.1 (0.8, 1.6)	0.2 (0, 1.1)	0.2 (0.1, 0.5)	
	PS-matched sub-HR	0.34 (0.08, 1.43)		NA		NA

BP = bisphosphonate; CPRD = Clinical Practice Research Datalink; HR = hazard ratio; PS = propensity score; SIDIAP = Information System for the Development of Research in Primary Care; NA = analysis not undertaken due to lack of events.



Years	0	2	4	6	8	10
Non users	8931	4634	1784	664	249	90
Users	2447	1247	459	175	56	19

Years	0	2	4	6	8	10
Non users	8931	4634	1784	664	249	90
Users	2447	1247	459	175	56	19



Years	0	2	4	6	8	10
Non users	8931	4634	1784	664	249	90
Users	2447	1247	459	175	56	19

Fig 2. Survival plots for stage change with renal replacement therapy showing the (*A*) cumulative incidence of the outcome in CPRD data, (*B*) cumulative incidence of competing risk (death) in CPRD data, and (*C*) cumulative incidence of the outcome and competing risk in CPRD. These figures are calculated as part of a competing risk model using Fine and Gray survival analysis.

Hypocalcemia

Hospitalization for hypocalcemia was rare. There was no difference in risk in CPRD, with an sub-HR of 0.34 (0.08, 1.43) for the PS-matched cohort. The sub-HR was not calculated for the SIDIAP cohort due to the few events. More than 99% of participants did not experience hypocalcemia within 10 years (data not shown) in both cohorts.

Discussion

Statement of principal findings

We used routinely collected data from primary-care practices and hospitals in the UK and Spain and linked renal registry information (Spain only) to assess the safety of bisphosphonate use in patients with stages 3b to 5 CKD. Our analyses included nearly

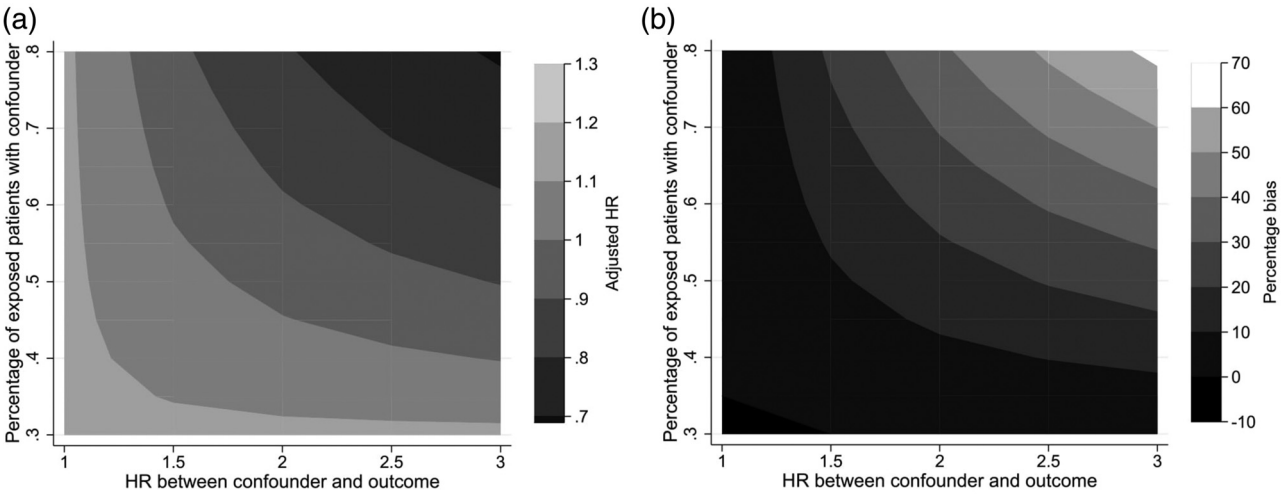


Fig 3. Array of unmeasured confounding based on a sub-hazard ratio (HR) of 1.14 and an unexposed incident of the outcome of 30%: (*A*) adjusted sub-HR; (*B*) percentage bias. (*A*) Darker gray regions show situations when the result would be nullified since the combination of percentage of exposed patients with the confounder and high risk of association induce a large enough amount of bias to affect the results. (*B*) Lighter gray regions suggest more bias and therefore are less likely to be realistic situations. The same position of *A* and *B* can be taken together to identify the amount of bias and corresponding effect to the HR.

4000 bisphosphonate users with at least two measurements of eGFR under 45 mL/min/1.73 m^2, PS-matched to more than 15,000 non-users.

Bisphosphonate users had a 14% higher risk of CKD stage progression (including dialysis and transplant) than non-users. Stage progression was a common event, experienced by approximately 1 in 10 patients. In CPRD, the increased risk was equivalent to a number needed to harm of 20: For every 20 patients treated for 5 years, 1 additional patient would progress in CKD stage.

Bisphosphonates, an analogue of pyrophosphate, have been shown, in vivo, not to affect the calcification of certain tissues including the kidney.[27] However, bisphosphonates are eliminated through the kidney by both passive glomerular filtration and active transportation in renal proximal tubular cells as explained by Miller.[28] High doses given in animal models have shown a variety of adverse renal events. However, no bisphosphonate trial has identified an increased risk of CKD progression,[29] although most trials were limited to patients with an eGFR >30. There is anecdotal evidence (case reports and case series) suggesting that bisphosphonates can cause various types of kidney injury.[30,31] Finally, because of the reduced ability of patients diagnosed with CKD to excrete bisphosphonates, Torregrosa and colleagues[32] have suggested that patients with CKD stage 4 or 5 should have their bisphosphonates reduced to 50% the dose to prevent renal toxicity, which would speed up CKD progression.

It has previously been shown that CKD progression occurs later for women than men, potentially explaining the increased risk identified in the interaction analysis for women but not men.[33] The differences identified in the interaction analysis with fracture are potentially an artifact of the data due to a lack of patients with a history of fracture as shown by the overlapping confidence intervals. This interaction should be replicated.

A dose-response relationship was identified between bisphosphonate use and CKD progression in sensitivity analyses. The array analysis showed that the identified result would only be nullified in extreme situations.[22]

We found no association between bisphosphonate use and acute kidney injury, gastrointestinal events, or hypocalcemia.

Limitations

This work was undertaken using observational data, whereas previous studies have used data from randomized control trials. However, the strengths of using these different data sources have previously been compared.

Although differences between bisphosphonate users and non-users were minimized with PS matching, differences may have remained. This is particularly true for unidentified confounders not included in the PS. An array analysis of hypothetical unmeasured confounders suggested the results would only be nullified if they were biased more than 20%, which is unlikely.

There was potential for exposure misclassification. Although we could confirm whether patients had been prescribed (CPRD) and dispensed (SIDIAP) bisphosphonates, we could not confirm whether they had taken those prescriptions.

There was potential for confounding by indication in the eGFR stage change outcome, as patients with low eGFR who were on bisphosphonates may have had their eGFR measured more frequently.

The reduced risk of death found for bisphosphonate users in CPRD suggested the existence of residual unmeasured confounding. However, no effect on death was identified in SIDIAP, and multiple regressions in the two databases gave similar results. It is therefore unlikely that the reduced risk of death in CPRD substantially affected the results after the cause-specific hazards were calculated. Furthermore, other studies[34] have demonstrated a reduced risk of mortality in bisphosphonate users compared to non-users in the general population, suggesting that any residual confounding will not significantly bias the results. The differential risk of death between databases may

be due to the propensity score matching itself. Reasons for this difference are beyond the scope of the study.

There were no data available on injectable bisphosphonates—which are administered in a hospital setting—in the two data sets. Our results are only generalizable to oral bisphosphonates prescribed in primary care, reflecting the individuals included in the two data sets.

The eGFR was calculated using the CKD-EPI formula when estimated eGFR was not available. These measurements have previously been criticized because they may not be accurate in certain patient subgroups. Other measurements for CKD stage, such as the Kidney Disease Improving Global Outcomes classification, could not be used because they rely on general practitioners to collect multiple tests during routine care. Furthermore, unlike the FDA, the EMA bases their advice for the restricted use of bisphosphonates in patients with low kidney function on eGFR instead of creatinine clearance. This may mean there is an overestimation in patients with an eGFR <30 mL/min/1.73 m^2. However, we would expect the rate of difference in results to be equal between users and non-users.

A high proportion of patients (approximately 75%) were female in our study, meaning there may be questions about how meaningful results are for men. This proportion is representative of osteoporosis patients (for which bisphosphonates are the first-line treatment). Hence, we can say that these results are representative of a population of bisphosphonate users.

This analysis only investigated first change of eGFR stage instead of sustained eGFR stage change. However, when those with eGFR stage change were assessed for sustained change between calendar years, it was found that 75% of bisphosphonate users and 64% of non-users had sustained eGFR stage change, suggesting that bisphosphates are associated with more permanent damage. Further research is needed into this area, but this remains outside the scope of the original aim of the study.

Finally, an interaction between eGFR starting class and stage change was not undertaken. The reasons for this were twofold: First the opportunity for patients with CKD stages 3b and 4 to experience stage change is much higher than those in CKD stage 5 because patients with CKD stage 5 can only undergo dialysis and transplant to experience a stage change. Second, there were only 45 patients who started with CKD stage 5, meaning this sensitivity analysis would be substantially underpowered and may lead to misleading results.

Meaning of this study

Because there is little information available on the safety of bisphosphonates in patients with moderate to severe CKD, this study makes a significant addition to the body of knowledge. Reassuringly, we found no excess risk for acute kidney injury, gastrointestinal events, or hypocalcemia with bisphosphonate use. However, these results must be considered alongside the excess risk identified in CPRD and SIDIAP for CKD stage progression. The moderate number needed to harm identified for CPRD suggests that bisphosphonates, which are currently contraindicated or used with caution in patients with an eGFR under 30 mL/min/1.73 m^2, should continue to be used with caution in this population.

The results of this study support previous findings that bisphosphonate use is not related to acute kidney injuries, gastrointestinal events, or hypocalcemia.[14] Because CKD progression due to bisphosphonate use alone has not previously been researched, comparison with prior studies is difficult. Both data sets are from high-income, predominantly white settings.

It is the suggestion of the authors that clinicians should carefully consider the risk-benefit of initiating bisphosphonate therapy in patients with an eGFR between 30 and 45. Once started, it would be advisable to monitor renal function and keep evaluating the potential trade-off in light of clinical data. Clinicians should follow their local/regional guidelines as to which measure of eGFR they should use. A recent European consensus[35] on the diagnosis and management of osteoporosis in severe CKD provides useful guidance for clinical practice.

Unanswered questions and future research

Although the results demonstrated an increased risk of CKD stage change with bisphosphonate use, the mechanisms behind this decreasing eGFR are unclear. We investigated a first decrease in CKD stage, rather than changes in the eGFR trajectory over time. We identified an increased risk of CKD stage change in patients with eGFR under 45 mL/min/1.73 m^2 who use bisphosphonates. We have not yet answered the question "Do bisphosphonates increase the risk of CKD stage decreasing in patients with an eGFR between 45 and 60 mL/min/1.73 m^2 (CKD stage 3a)?"

In a PS-matched analysis of two electronic primary-care data sets linked to hospital records, an increased rate of CKD progression was identified for bisphosphonate users with CKD stages 3b to 5 compared with non-users. Bisphosphonate use was not associated with a higher rate of acute kidney injuries, gastrointestinal events, or hypocalcemia.

Disclosures

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: DPA reports grants and other from AMGEN; grants, non-financial support, and other from UCB Biopharma; grants from Les Laboratoires Servier, outside the submitted work. DPA also reports that Janssen, on behalf of the IMI-funded EHDEN and EMIF consortiums, and Synapse Management Partners have supported training programs that are organized by DPA's department and are open to external participants. AJ reports personal fees from Freshfields Bruckhaus Derringer and Anthera Pharmaceuticals Inc., outside the submitted work. CC reports personal fees from Alliance for Better Bone Health, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier, Takeda, and UCB. KJ reports grants from NIHR HTA during the conduct of the study and personal fees from UCB and AMGEN, outside the submitted work. NA reports grants from Merck and personal fees from Merck, Regeneron, Pfizer/Eli Lilly, and Flexion, outside the submitted work. VS reports consultancy fees from Janssen Pharmaceutica NV, during the conduct of the study. XN reports advisory boards for Amgen, Eli Lilly, and Formation, and talks for Amgen, Eli Lilly, FAES, and ITALFARMACO. ADP reports personal fees from AMGEN-UCB, Eli Lilly, Gilead, and Sandoz; other from Active Life Sci; and personal fees and non-financial support from EchoLight, outside the submitted work. BA reports institutional research contracts and personal consulting fees from UCB Biopharma sprl, institutional research contracts from Novartis, personal speaker's fees from Eli Lilly and Amgen, and personal consulting fees from Kyowa-Kirin Plc. CT reports personal fees from Boehringer Ingelheim and Amgen, outside the submitted work.

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This study was approved by the CPRD Independent Scientific Advisory Committee (protocol number 15_53R2A). The interpretation and conclusions contained in this study are those of the authors alone. We acknowledge two public and patient involvement representatives (Denisse Abbott from the National Kidney Federation and Fizz Thompson from the National Osteoporosis Society) and English language editing by Dr Jennifer A de Beyer of the Centre for Statistics in Medicine, University of Oxford.

Scientific approval was obtained for use of CPRD (ISAC 15_153R2) and SIDIAP data (148). The study protocol was registered in the EU PAS Register for pharmaco-epidemiological studies (ref 10029).

Data were obtained from CPRD under the Oxford University CPRD license and ISAC approval and SIDIAP by IDIBELL. Direct data sharing is not allowed. Data access can be obtained from CPRD, conditional on ISAC approval and SIDIAP after protocol approval.

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PEER REVIEW

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