

The association between renal function and BMD response to bisphosphonate treatment: real-world cohort study using linked national registers.

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Abstract 386 words

Background: Management of osteoporosis given reduced renal function is one of the largest challenges in the bone clinic.

Objectives: Identify the cut-off for renal function below which there would be no overall BMD benefit associated with bisphosphonate use. Track safety outcomes resulting in hospital encounters.

Methods: Population-based, observational register-linked study of BMD trajectories in adults from the island of Funen (pop 465,000) as a function of estimated creatinine clearance (CKD-epi), treatment and adherence to oBP. One laboratory performed all the biochemical analyses for the area while all DXA scans were in a central facility. For inclusion, patients were required to have both a DXA scan and an eGFR measurement (CKD-EPI) within 1 year prior to their study index date. Medication Possession Ratio (MPR) was calculated from national data.

Results: Out of 6,176 incident BP users, 1,789 had eGFR and DXA measurements at appropriate timepoints for the planned analysis, while this was the case for 3,908 of 29,336 non-users. Users of oBPs exhibited progressively smaller gains in BMD with decreasing renal function. However, for CKD stage 3A and better, the annual change in BMD was significantly more positive than in the non-user group at similar levels of renal function. In non-users, the average annual change in BMD was negative but largely unaffected by renal function down to stage 3B. There were no new cases of acute renal injury, glomerulonephritis or dialysis. The rate of new kidney transplantation was zero in non-users and 0.26 per 1000 PY in the BP user population. Hypocalcaemia encounters did not differ significantly from that seen in non-users.

Conclusions: The BMD changes observed in real-world users of oBP in this population based single-clinic are consistent with those observed in the original RCTs of alendronate. We noted a gradual decrease in the absolute gains in BMD in oBP users with decreasing renal function though there was no significant interaction – largely explained by low numbers of treated patients with poor renal function - between CKD stage and adherence driven BMD change. There were no cases of acute renal injury resulting in hospital encounters. More data is needed on the efficacy and safety of

bisphosphonates in CKD stage 3B to 5 and prescribers should reconsider the low use of DXA in patients with renal function impairment now that a wider range of treatment options are available.

Keywords: Osteoporosis – Bisphosphonates – Renal Disease – Bone Mineral Density - Epidemiology

Conflicts of interest

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Background

Management of osteoporosis in patients with moderate or severe reductions in renal function is one of the largest challenges in the bone clinic[1–4]. Bisphosphonates are not metabolized but cleared from the circulation exclusively and rapidly by renal filtration and by deposition in the skeleton. For oral bisphosphonates, prescribing information generally advise against use in patients with an estimated creatinine clearance below 30 or 35 mL/min, depending on the compound. While oral bisphosphonates have not been shown to effect renal function, too rapid infusion of intravenous zoledronic acid has been shown to impair GFR, though recovery in time of renal function is often seen [5,6] and data on renal outcomes with intravenous ibandronate have been reassuring[7]In a subanalysis of the zoledronic acid HORIZON-PFT trial, an increase in serum creatinine above 0.5 mg/dL was observed in 4.7% of the 75+ age group with zoledronic acid treatment and 3.5% in the placebo group, a difference that was short of statistical significance ($p=0.08$)[8]. Because raised serum creatinine was an exclusion criterion in the RCTs, we have very little information about the tolerability and efficacy of bisphosphonates in more advanced stages of chronic kidney disease (CKD). Concerns – whether justified or not - include a worsening of CKD itself (not a concern if the patient is already at the dialysis stage), and triggering of adynamic bone disease in advanced CKD[9]. The best RCT tolerability and efficacy data in osteoporosis patients with reduced renal function for bisphosphonates come from the risedronate trials demonstrating vertebral fracture risk reductions across strata of renal function impairment and good safety even in stage 4 CKD (CKD 4). A pooled analysis of nine trials[10] from the US, Europe and Japan reached a treated subcohort of 301 patients with severe CKD (clearance 15 to 30 mL/min) while the placebo subcohort included 271 patients with similarly reduced renal function. There is also some support for safety based on real-world data in fracture patients from Canada[11] where safety appeared to be good in 149 BP users with eGFR below 45 mL/min, including 35 patients with eGFR under 30 mL/min. Taken together, RCTs have provided us with some reassurance in CKD4 for risedronate specifically while RCT data on safety and efficacy is lacking for the globally most widely prescribed bisphosphonates insofar as patients with clearance below 30-35 mL/min are concerned. We therefore conducted a real-world observational

study linking successive BMD changes to exposure to oral bisphosphonates in a population-based clinical setting, where one laboratory performed all the biochemical analyses for the area and all DXA scans were also conducted at one facility.

The primary aim was, if possible, to identify the cut-off for renal function below which there would be no overall BMD benefit. It was anticipated that some patients would have begun bisphosphonate treatment despite impaired renal function, either because plasma creatinine was not appropriately interpreted in an older person with low muscle mass or because renal function had worsened in the time period between prescription and the patient actually filling the prescription. A secondary aim was to identify events of in- or outpatient treatment of renal complications or hypocalcaemia in the observation period.

Methods and study population

Study Population

The Odense Bisphosphonate Safety Study (Statistics Denmark reference 705079, <http://tinyurl.com/obpsafety>) is a single-centre, population-based observational cohort which includes DXA scans from 35,917 adult persons from the island of Funen (pop 465,000), linked to small panel of clinical biochemistry tests that are pertinent to the use and safety of bisphosphonates for osteoporosis, all analysed at the same clinical biochemistry lab which is the sole clinical biochemistry laboratory for the uptake area. Linkage to the National Patient Discharge Register and the National Prescription Database enabled further clinical characterization of baseline conditions, co-medications (used in the last 12 month before the index date), medication possession ratio (please see below) as well as any non-biochemical safety outcomes. The cohort of eligible patients for this report consisted of all patients with a DXA scan, who did not have a prior diagnosis of cancer (except low malignancy neoplasms of the skin, ICD-10 code C44) or Paget's disease.

Plasma creatinine was analysed in routine practice throughout the study period on an Architect instrument (Abbott, Wiesbaden, Germany) using an enzymatic colorimetric method with end-up reaction. The measurement range was 8.8-3536 $\mu\text{mol/L}$. Quality control was assured with internal (SERO, Norway) and external (Ringversuche, Germany) control programmes in the entire study period. CV for inter- and intra-assay variation was <3.6%.

We estimated eGFR using the CKD-EPI formula[12]. PTH levels or other serum biochemistry was not available for this study. The DXA procedure and quality control is described under outcomes below.

Oral BP users

From within the DXA cohort above, the cohort of incident oral bisphosphonate (BP) users were identified as the probands for the analysis (fig 1). The date of *first oral BP prescription* was defined as the *index date*, which had to be between 2006 and 2012 to allow sufficient follow-up time to calculate

a BMD rate of change. Further, patients were excluded if they did not have both a DXA scan and an eGFR measurement (CKD-EPI) within 1 year prior to the index date.

Non-users

In order to compare BMD changes in the absence of bisphosphonate treatment, a non-user cohort was similarly extracted, also requiring patients to have an eGFR measurement within 1 year prior to a DXA scan. The first DXA meeting this condition was identified. Starting BPs less than 3 years after this DXA scan was an exclusion criterion. To achieve alignment of observation time in non-users with that of BP users, we added the average lag time in BP users between DXA data and *index date* to define an index date in the non-users (fig 2). This is one of the validated approaches available to avoid immortal time bias in pharmaco-epidemiology[13].

The study design intentionally allowed patients to contribute risk time to both cohorts, provided they had sufficient BMD observation time (1 to 3 years) first as a non-user and then as a BP-user.

MPR

A mean medication possession ratio (MPR) for oral BP use was calculated for a maximum of 3 years after initiation. Death or treatment with denosumab or a teriparatide prior the 3-year period would censor the timeframe for calculating MPR and BMD changes.

Outcome

Annualized percent change in total hip BMD was calculated based on one to three years of follow-up from the index date. This window of time is in order to accommodate variation in scheduling of what would have been intended by the referring physician to be a DXA visit approximately two years into treatment. Femoral neck BMD change was also tracked and results, which were very similar, reported in the supplementary table S1. Patients were examined on Hologic Discovery devices and the procedure

was for patients receiving follow-up DXA to be examined on the same device as their initial assessment. The short term precision error for femoral neck and total hip in the clinic is 1.5%[14]. Longitudinal stability was monitored using internal QC-curves and daily scans of a Hologic Spine phantom. Renal and endocrine safety outcomes were tracked through in- and outpatient hospital encounters.

Covariates

We defined comedications as any prescription filled in the last year before the index date. For comorbid conditions and prior major osteoporotic fractures (hip, spine, humerus or forearm), we included all prior hospital contacts. In addition, recent major osteoporotic fractures (last 12 mo) were also tabulated separately. Baseline BMD contributes directly to the outcome estimation (percent and absolute annualized change in BMD from baseline) with no additional adjustments done for baseline BMD itself in the statistical analysis.

Statistics

A non-matched approach was used. Thus, associations between change in BMD as a function of eGFR and treatment status were examined by least squares linear regression, with and without adjustment for key covariates. Similarly, changes in BMD not accounted for by sex or by baseline age, prior Major Osteoporotic Fracture (MOF) or recent GC use were calculated from the linear regression analyses as the individual residuals from data models including the baseline terms as predictors. In simple terms, this adjusts the BMD change for changes that can be statistically explained by baseline differences between BP users and non-users. Multiplicative interaction terms between baseline eGFR, treatment status and BMD change was also tested within the regression analyses.

Results

Out of 6,176 incident BP users, 1,789 had eGFR and DXA measurements as specified above, while this was the case for 3,908 of 29,336 non-users (fig 1). Of the initial DXA population (table 1A), 95% had an estimated creatinine clearance of 45 mL/min or above, corresponding to normal renal function or CKD stage 1 to 3A, with CKD4 and CKD5 only accounting for as little as 1% of the total population. Further, relatively fewer patients with severely reduced renal function had follow-up BMD measurements. Hence, among patients with sequential BMD measurements (table 1B), the BP non-user population had a median eGFR of 85 mL/min and consisted of 79% women and 21% men. A total of 179 persons contributed risk time in both arms. The median eGFR in both the high adherence and the low adherence bisphosphonate groups was closely similar at 86 mL/min. Among non-users with BMD follow-up data, 19 (0.5%) were in CKD stage 4 compared with 7 (0.4%) in BP users. The median age of the population with sequential BMD information was also very similar, 65 years for the 3,908 non-users, 66 years for users with high adherence (N=1,121, MPR \geq 80%) and 65 years for users with low adherence (N=668, table 1). The former group had 16% men and the latter group 24% men. The great majority of persons in all three groups had a hospital encounter based Charlson score of 0, i.e. very low comorbidity. However, use of PPIs, NSAID, statins and anti-hypertensives had a high prevalence in all three groups. Systemic glucocorticoid use was more prevalent in the BP groups. Though baseline BMD was, as would be expected, significantly lower in those beginning BPs ($p < 0.001$ for each of the BP subgroups compared with non-users) , the three groups differed little in terms of MOF history. Most patients were fracture naive while prior MOF was present in 19.4% in those starting BPs and 17.4% in the non-user group.

BMD changes, groupwise comparison

The absolute, annualized change in total hip BMD by treatment group, stratified by CKD stage, is shown in the upper half of table 2. Users of oral BPs exhibited progressively smaller gains in BMD with decreasing renal function (fig 3 and table 2, lower half). However, for CKD stage 3A and better ($\text{eGFR} \geq 45 \text{ mL}$), the annual change in BMD was significantly more positive than in the non-user group at similar levels of renal function. The annual change in BMD was largely unaffected by renal

function down to stage 3B (eGFR ≥ 30 mL) in non-users, while modest decreases in BMD gains could be observed at stage 3A in BP users. Because of the small but significant difference in baseline BMD between the groups we also calculated the absolute BMD change in addition to the more commonly used percent BMD change and this confirmed the above findings. Results for the femoral neck were closely similar (supplementary table S1)

BMD changes, predictors of response in BP users

The following analysis focused on BP users only and addressed the change in BMD associated with adherence (MPR $\geq 80\%$). First, interaction tests (table 3) revealed no significant adherence-by-covariate interaction with age and sex, prednisolone exposure or, notably, eGFR. An interaction with MOF could not be entirely refuted (interaction $p=0.19$). The effect of adherence on BMD change was only marginally, non-significantly attenuated when adjusting for eGFR.

Safety data (hospital encounters)

We did a separate tabulation of new events (not present before baseline) and all events (including events that the patient had also experienced at some point in their medical history before the baseline date). In addition, a subgroup analysis was done for CKD3B or worse renal function at baseline. No safety events were significantly different between BP users and non-users. Readers are referred to table 1 for a more detailed break-down of events that also includes recurrent diagnoses.

Non-renal safety

New hypocalcaemia events leading to hospital contact on an in- or outpatient basis (table 4) was rare both in BP users (0.80 per 1,000 patient years, PY) and non-users (0.75 per 1,000 PY). For CKD stages 3B or 4 ($n=149$) specifically, no events were observed in non-users while there were 12.3 events per 1,000 PY in BP users ($p=0.09$).

Renal safety

There were no new cases of acute renal injury in the study, and no new cases of glomerulonephritis or dialysis (table 4). The rate of new kidney transplantation was zero in non-users and 0.26 per 1000 PY in the BP user population. The subgroup analysis of 40 BP users with CK3B or lower renal function

found a rate of kidney transplantation of 12.2 per 1000 PY ($p=0.08$ compared with non-users in the same subanalysis).

Discussion

This population-based observational study finds a low prevalence of patients with renal function impairment among those referred for osteoporosis diagnosis and treatment to a major public osteoporosis centre and DXA service in Denmark. The study suggests that practitioners in our area show considerable restraint in terms of initiating bisphosphonates in patients with moderate or severe reductions in renal function. We found a negative BMD trajectory in non-users across all levels of renal function with no apparent worsening at down to CKD stage 3B (30-44 mL/min) but more rapid BMD decreases in the small number of sequentially DXA scanned subjects with CKD4 or 5. For CKD stage 3A and better, BP users had significantly better BMD trajectories than non-users but this was not significant at lower levels of renal function, partly due to smaller BMD increments but also due to a low number of BP users having pre-existing moderate or severe renal function impairments. The more favourable BMD changes in BP users was not explained by the overall lower initial BMD and it occurred despite a higher exposure to glucocorticoids in the users compared with non-users. Reassuringly, the absolute magnitude of the BMD changes found in this real-world population confirmed the BMD rates of change observed in the original RCTs as discussed in more detail below.

Patients with impaired renal function made up only a small subset of the DXA scanned population. Hence, despite a median age of 65 years only 85 referrals out of more than 27,000 individuals had CKD stage 5 and 243 CKD stage 4. At first, this seemed to be unexpectedly low numbers compared with the literature. Certainly, in the NHANES BMD dataset 24% of patients with T-score below -2.5 had a creatinine clearance below 35 mL/min, i.e. in the lower half of CKD3B or worse[1]. Second, poor renal function was not at all uncommon in BP users in Ontario with 13.5% being in stage 3B and 4.1% being in stages 4 or 5[11]. This seven-fold difference in the prevalence of moderate or severe reduction in renal function between the two populations of BP users is less surprising given that the Ontario based analysis was restricted to a more fragile population of patients with a mean age fifteen years higher than in the present study and confined to patients who were discharged after a fragility fracture. The low prevalence of moderately or severely reduced renal function in patients referred to DXA in our area is not reassuring because it suggests that while physicians are very cautious about

prescribing bisphosphonates in the presence of renal function issues, patients with low eGFR are also unlikely to be referred for DXA. This is unfortunate as this is a missed opportunity to make appropriate treatment decisions to prevent worsening of skeletal status and because the treatment options for osteoporosis increasingly include medications where reduced renal function has less concern than is the case for the bisphosphonates[15,16]. It should be added that most patients with severe CKD in the uptake area are followed in one nephrology department and the pattern may reflect the clinical views of small number of doctors. Further, the prevalence of CKD is also affected by the mean age of the population, which at 65 is relatively young compared with the average age in the alendronate FIT trial[17], and the average age of Danish bisphosphonate initiators, which is known from past studies to be 72 years[18].

In BP users, multiple regression analysis found adherence to BP treatment to be by far the strongest driver of total hip BMD gains with no statistically significant interaction with eGFR. As summarized above, in non-users, a small annual loss of about 0.3% (total hip) was observed irrespective of renal function, down to and including CKD stage 3B with a non-significant acceleration in bone loss rates at lower renal function. This may coexist with elevated PTH levels as renal function progresses; in the present study we do not have information on PTH measurements but only on plasma creatinine.

In patients with pre-existing vertebral fractures in the original alendronate FIT trial[17], hip BMD at three years increased by 3% (1% per year) in the active arm, corresponding to the change observed in this real-world population for adherent BP users with CKD stages 1 and 2. For the full FIT trial [19], where the observation period was 3 years in the vertebral fracture arm and 4 years in the clinical fracture arm, a total total hip change of 4.8% was seen for an estimated creatinine clearance below 45 mL/min and 5.6% for clearance above 45 mL/min again very similar to what was observed in the real-world setting. However, in the FIT trial, no blunting of BMD gains by renal function level was apparent.

There are limitations to the present study due to its observational nature. Though adjustments were made for any unbalanced measured confounders, the decision to treat or not treat were made by

prescribers based on clinical information rather than on randomization. Further, this study considered only oral bisphosphonates and while we removed persons whose initial treatment was an intravenous bisphosphonate, we did not exclude non-users of bisphosphonates who began other osteoporosis drugs such as raloxifene or who started estrogen therapy. While this does not affect the BMD changes observed in the user population it may underestimate the relative difference against the comparator group.

Strengths of the study include the population based clinical setting with complete capture of all creatinine measurements in the uptake area and all prescriptions filled, even if patients filled their prescriptions at pharmacies outside the region. The prescription databases capture all filled prescriptions irrespective of whether they originate in public or private healthcare. Further, prescriptions issued but never used by the patients will not lead to misclassifying non-users as users.

This study focused on changes in hip BMD. While this site is less responsive to osteoporosis treatment than the lumbar spine, in the sense that the percentual increment is smaller, it removes the complications of ensuring that sequential BMD measurements included the same lumbar vertebrae, that the numbering was consistent and that no degenerative changes or fractures had occurred to cause potential misinterpretation of BMD trends. Certainly, in the real world clinical setting outside trials, changes in femoral BMD have been shown to be more reliable predictors of fracture risk reduction than changes at the lumbar spine[20]. Hip BMD changes are routinely reported in clinical trials in the osteoporosis area so comparison of real-world data with that achieved in the more selected[21] populations in clinical trials is straightforward. The changes in BMD of the femoral neck and the total hip were very similar, both in the RCTs referenced and in the present study so for simplicity of presentation the femoral neck outcomes are shown in the supplement only.

In conclusion, the BMD changes observed in real-world users of oral bisphosphonates in this population based single-clinic are consistent with those observed in the original RCTs of alendronate. The use of DXA and subsequent bisphosphonate treatment was very low as regards patients with moderate or severe reductions in renal function. We noted a gradual decrease in the absolute gains in BMD in oral bisphosphonate users with decreasing renal function though there was no significant

interaction – largely explained by low numbers of treated patients with poor renal function - between CKD stage and adherence driven BMD change. There were no cases of acute renal injury resulting in hospital encounters and the rate of hypocalcaemia encounters did not differ significantly from that seen in non-users. More data is needed on the efficacy and safety of bisphosphonates in CKD stage 3B to 5 and prescribers should reconsider the low use of DXA in patients with renal function impairment now that a wider range of treatment options have become available.

Legends

Fig 1

Study chart for inclusion of exclusion with numbers of patients.

Fig 2

Principle of alignment of index dates for BP-users and non-users for subsequent BMD change.
Please see methods section for details.

Fig 3

Annualized percent change (y-axis) in total hip BMD as a function of CKD stage (x-axis) and treatment status / adherence (markers). Non-users shown as dashed lines and clear diamonds, all BP users as dotted lines and black dots, BP users with $\text{MPR} \geq 80\%$ shown as solid lines and black squares. Asterisks indicate $p < 0.05$

	Total Study Population			
	Non-user	MPR≥80%	MPR<80%	ALL MPR
All	(n=23,375)	(n=2,219)	(n=1,861)	(n=4,080)
eGFR, median (IQR)	85 (71-96)	83 (70-94)	84 (68-95)	83 (69-94)
eGFR, mean (SD)	83.3 (20.5)	81.4 (18.2)	81.3 (20.9)	81.4 (19.4)
Age, median (IQR)	65 (54-74)	69 (61-77)	69 (59-77)	69 (60-77)
Gender, N(%)				
Females	17,560 (75.1%)	1,818 (81.9%)	1,357 (72.9%)	3,175 (77.8%)
Males	5,815 (24.9%)	401 (18.1%)	504 (27.1%)	905 (22.2%)
CKD stages				
CKD stage 1	9,302 (39.8%)	803 (36.2%)	670 (36.0%)	1,473 (36.1%)
CKD stage 2	11,092 (47.5%)	1,113 (50.2%)	879 (47.2%)	1,992 (48.8%)
CKD stage 3A	1,903 (8.1%)	229 (10.3%)	213 (11.4%)	442 (10.8%)
CKD stage 3B	786 (3.4%)	59 (2.7%)	79 (4.2%)	138 (3.4%)
CKD stage 4	212 (0.9%)	13 (0.6%)	18 (1.0%)	31 (0.8%)
CKD stage 5	80 (0.3%)	(n<5)	(n<5)	(n<5)
Total Hip BMD g/cm2 mean (SD)	0.788 (0.140)	0.744 (0.109)	0.758 (0.131)	0.749 (0.118)
Total Hip T-score mean (SD)	-1.318 (1.061)	-1.845 (0.828)	-1.653 (0.944)	-1.773 (0.878)
Charlson Score, N(%)				
0	18,864 (80.7%)	1,613 (72.7%)	1,250 (67.2%)	2,863 (70.2%)
1	2,775 (11.9%)	400 (18.0%)	403 (21.7%)	803 (19.7%)
2	1,107 (4.7%)	118 (5.3%)	131 (7.0%)	249 (6.1%)
≥3	629 (2.7%)	88 (4.0%)	77 (4.1%)	165 (4.0%)
Fracture history				
Major ost fracture, any	3,882 (16.6%)	513 (23.1%)	384 (20.6%)	897 (22.0%)
Major ost fracture, last 12 mo	1,424 (6.1%)	222 (10.0%)	147 (7.9%)	369 (9.0%)
Drugs, N(%)				
Non-BP osteoporosis medications	355 (1.5%)	27 (1.2%)	98 (5.3%)	125 (3.1%)
Systemic glucocorticoids	4,473 (19.1%)	648 (29.2%)	721 (38.7%)	1,369 (33.6%)
NSAID	6,085 (26.0%)	728 (32.8%)	577 (31.0%)	1,305 (32.0%)
PPI	5,356 (22.9%)	491 (22.1%)	523 (28.1%)	1,014 (24.9%)
Anxiolytics	4,357 (18.6%)	552 (24.9%)	492 (26.4%)	1,044 (25.6%)
SSRI	2,319 (9.9%)	245 (11.0%)	244 (13.1%)	489 (12.0%)
Statins	5,362 (22.9%)	603 (27.2%)	473 (25.4%)	1,076 (26.4%)
Anti-Epileptic	1,165 (5.0%)	113 (5.1%)	103 (5.5%)	216 (5.3%)
Anti-Diabetes	1,753 (7.5%)	124 (5.6%)	145 (7.8%)	269 (6.6%)
Anti-hypertensives	8,807 (37.7%)	923 (41.6%)	809 (43.5%)	1,732 (42.5%)
Anti-arrhythmics	775 (3.3%)	87 (3.9%)	99 (5.3%)	186 (4.6%)
Diagnoses, N(%)				
Collagen disorders	2,075 (8.9%)	299 (13.5%)	277 (14.9%)	576 (14.1%)
Diabetes w/o complications	1,947 (8.3%)	135 (6.1%)	154 (8.3%)	289 (7.1%)
Diabetes w/complications	574 (2.5%)	36 (1.6%)	48 (2.6%)	84 (2.1%)
Dementia	412 (1.8%)	51 (2.3%)	31 (1.7%)	82 (2.0%)
CVD	2,000 (8.6%)	188 (8.5%)	191 (10.3%)	379 (9.3%)
PVD	1,099 (4.7%)	103 (4.6%)	114 (6.1%)	217 (5.3%)

Mild liver disease	522 (2.2%)	28 (1.3%)	60 (3.2%)	88 (2.2%)
Severe liver disease	123 (0.5%)	5 (0.2%)	15 (0.8%)	20 (0.5%)
Peptic ulcer	1,019 (4.4%)	110 (5.0%)	119 (6.4%)	229 (5.6%)
COPD	2,875 (12.3%)	341 (15.4%)	342 (18.4%)	683 (16.7%)
HIV/AIDS	18 (0.1%)	(n<5)	(n<5)	5 (0.1%)
CHF	5,512 (23.6%)	505 (22.8%)	489 (26.3%)	994 (24.4%)
Hemiplegia	95 (0.4%)	7 (0.3%)	(n<5)	11 (0.3%)
Renal transplant	120 (0.5%)	9 (0.4%)	11 (0.6%)	20 (0.5%)
Dialysis	104 (0.4%)	(n<5)	(n<5)	(n<5)

Table 1B

Baseline demographics for the subjects in the total study population.

	Study population with sequential BMD			
	Non-user	MPR≥80%	MPR<80%	All MPR
N	(n=3,908)	(n=1,121)	(n=668)	(n=1,789)
eGFR, median (IQR)	85 (72-96)	86 (72-95)	86 (72-97)	86 (72-96)
eGFR, mean (SD)	84.2 (19.2)	83.7 (17.0)	84.4 (18.8)	84.0 (17.7)
Age, median (IQR)	65 (56-72)	66 (59-73)	65 (57-73)	66 (58-73)
Gender, N(%)				
Females	3,088 (79.0%)	942 (84.0%)	507 (75.9%)	1,449 (81.0%)
Males	820 (21.0%)	179 (16.0%)	161 (24.1%)	340 (19.0%)
CKD stages				
CKD stage 1	1,558 (39.9%)	457 (40.8%)	271 (40.6%)	728 (40.7%)
CKD stage 2	1,935 (49.5%)	557 (49.7%)	328 (49.1%)	885 (49.5%)
CKD stage 3A	304 (7.8%)	85 (7.6%)	50 (7.5%)	135 (7.5%)
CKD stage 3B	90 (2.3%)	18 (1.6%)	15 (2.2%)	33 (1.8%)
CKD stage 4	19 (0.5%)	(n<5)	(n<5)	7 (0.4%)
CKD stage 5	(n<5)	(n<5)	-	(n<5)
Total Hip BMD g/cm2 mean (SD)	0.789 (0.140)	0.744 (0.108)	0.758 (0.131)	0.749 (0.118)
Total Hip T-score mean (SD)	-1.314 (1.059)	-1.840 (0.824)	-1.654 (0.945)	-1.771 (0.876)
Charlson Score, N(%)				
0	3,154 (80.7%)	910 (81.2%)	517 (77.4%)	1,427 (79.8%)
1	511 (13.1%)	155 (13.8%)	117 (17.5%)	272 (15.2%)
2	170 (4.4%)	43 (3.8%)	20 (3.0%)	63 (3.5%)
≥3	73 (1.9%)	13 (1.2%)	14 (2.1%)	27 (1.5%)
Fracture history				
Major ost fracture, any	681 (17.4%)	243 (21.7%)	104 (15.6%)	347 (19.4%)
Major ost fracture, last 12 mo	246 (6.3%)	98 (8.7%)	38 (5.7%)	136 (7.6%)
Drugs, N(%)				
Non-BP osteoporosis medications	51 (1.3%)	19 (1.7%)	6 (0.9%)	25 (1.4%)
Systemic glucocorticoids	920 (23.5%)	261 (23.3%)	261 (39.1%)	522 (29.2%)
NSAID	1,083 (27.7%)	361 (32.2%)	209 (31.3%)	570 (31.9%)
PPI	903 (23.1%)	205 (18.3%)	174 (26.0%)	379 (21.2%)
Anxiolytics	827 (21.2%)	255 (22.7%)	147 (22.0%)	402 (22.5%)
SSRI	357 (9.1%)	82 (7.3%)	71 (10.6%)	153 (8.6%)
Statins	926 (23.7%)	272 (24.3%)	165 (24.7%)	437 (24.4%)
Anti-epileptics	158 (4.0%)	36 (3.2%)	30 (4.5%)	66 (3.7%)
Anti-diabetes drugs	245 (6.3%)	49 (4.4%)	50 (7.5%)	99 (5.5%)
Anti-hypertensives	1,464 (37.5%)	416 (37.1%)	243 (36.4%)	659 (36.8%)
Anti-arrhythmics	102 (2.6%)	25 (2.2%)	20 (3.0%)	45 (2.5%)
Diagnoses, N(%)				
Collagen disorders	456 (11.7%)	125 (11.2%)	91 (13.6%)	216 (12.1%)
Diabetes w/o complications	272 (7.0%)	52 (4.6%)	50 (7.5%)	102 (5.7%)
Diabetes w/complications	72 (1.8%)	10 (0.9%)	10 (1.5%)	20 (1.1%)
Dementia	23 (0.6%)	(n<5)	(n<5)	5 (0.3%)
CVD	267 (6.8%)	74 (6.6%)	50 (7.5%)	124 (6.9%)
PVD	155 (4.0%)	41 (3.7%)	18 (2.7%)	59 (3.3%)
Mild liver disease	71 (1.8%)	13 (1.2%)	17 (2.5%)	30 (1.7%)
Severe liver disease	8 (0.2%)	(n<5)	5 (0.7%)	7 (0.4%)

Peptic ulcer	154 (3.9%)	44 (3.9%)	29 (4.3%)	73 (4.1%)
COPD	448 (11.5%)	134 (12.0%)	87 (13.0%)	221 (12.4%)
HIV/AIDS	(n<5)	(n<5)	(n<5)	(n<5)
CHF	751 (19.2%)	188 (16.8%)	124 (18.6%)	312 (17.4%)
Renal transplant	19 (0.5%)	(n<5)	(n<5)	8 (0.4%)
Renal dialysis	11 (0.3%)	(n<5)	(n<5)	(n<5)

Table 1B
Baseline demographics for the subjects in the sequential BMD analysis

Unadjusted for baseline differences			
	Non-users	BP users, all	BP users, MPR ≥ 80%
	(N=3,908)	(N=1,789)	(N=1,121)
CKD 1	-0.2 (-0.3 ; -0.1) [N=1558]	1.0 (0.9 ; 1.2) [N=729]*	1.4 (1.2 ; 1.5) [N=458]*
CKD 2	-0.3 (-0.4 ; -0.2) [N=1935]	1.0 (0.9 ; 1.2) [N=883]*	1.4 (1.3 ; 1.6) [N=555]*
CKD 3A	-0.5 (-0.8 ; -0.2) [N=304]	0.6 (0.2 ; 0.9) [N=136]*	1.0 (0.6 ; 1.2) [N=86]*
CKD 3B	-0.7 (-1.7 ; 0.4) [N=90]	0.1 (-0.7 ; 0.9) [N=33]	0.3 (-0.6 ; 1.2) [N=18]
CKD 4	-1.9 (-3.6 ; 0.4) [N=19]	1.4 (-1.3 ; 4.1) [N=7]	[N<5]
CKD 5	[N<5]	[N<5]	[N<5]
Adjusted for age, sex, prior MOF, recent GC use			
	Non-users	BP users, all	BP users, MPR ≥ 80%
	(N=3,908)	(N=1,789)	(N=1,121)
CKD 1	-0.4 (-0.5 ; -0.2) [N=1558]	0.9 (0.8 ; 1.1) [N=729]*	1.2 (1.1 ; 1.4) [N=458]*
CKD 2	-0.4 (-0.5 ; -0.3) [N=1935]	1.0 (0.7 ; 1.1) [N=883]*	1.3 (1.2 ; 1.5) [N=555]*
CKD 3A	-0.6 (-0.8 ; -0.3) [N=304]	0.6 (-0.2 ; 0.9) [N=136]*	1.0 (0.6 ; 1.4) [N=86]*
CKD 3B	-0.6 (-1.7 ; 0.4) [N=90]	0.2 (-1.3 ; 0.9) [N=33]	0.4 (-0.5 ; 1.2) [N=18]
CKD 4	-2.0 (-3.7 ; -0.3) [N=19]	1.5 (-1.0 ; 4.0) [N=7]	[N<5]
CKD 5	[N<5]	[N<5]	[N<5]

Table 2 Annualized change in total hip BMD as a function of BP treatment status and baseline CKD stage. BP users and non-users. To reduce selection bias, we allowed overlap so that the same person could be followed as non-users until osteoporosis treatment was initiated. Results not shown for cells with fewer than five subjects for regulatory reasons.

¹Adjusted for baseline differences in age, sex prior MOF, recent GC use

Hip	Annual %change in	P _{interact}
Adherence	1.00 (0.80-1.19)	N/A
+ adjustment for age and sex	1.02 (0.82-1.21)	.280
+ adjustment for prior MOF	1.02 (0.82-1.21)	.190
+ adjustment for recent prednisolone	0.93 (0.73-1.12)	.639
+ adjustment for eGFR	0.93 (0.73-1.12)	.529

Table 3 Adherence driven total hip BMD change. Multiple regression steps and interaction analysis (BP users only, N=1,789)

Any renal function at baseline		Non-users (n=3,908)	Bisphosphonate Treated (n=1,789)	
Safety Outcome (any)	<u>N with event</u>	<u>Rate per 1,000 PY</u>	<u>N with event</u>	<u>Rate per 1,000 PY</u>
Acute renal injury	n<5	0.25	n<5	0
Glomerulonephritis	n<5	0	n<5	0
Kidney transplant	n<5	0.62	5	0.26
Dialysis	n<5	0	n<5	0
Hypocalcaemia	n<5	0.75	6	0.80
Safety Outcome (new)	<u>N with event</u>	<u>Rate per 1,000 PY</u>	<u>N with event</u>	<u>Rate per 1,000 PY</u>
Acute renal injury	n<5	0.25	n<5	0
Glomerulonephritis	n<5	0	n<5	0
Kidney transplant	n<5	0	n<5	0.26
Dialysis	n<5	0	n<5	0
Hypocalcaemia	n<5	0.75	6	0.80
CKD3B or worse at baseline		Non-users (n=109)	Bisphosphonate Treated (n=40)	
Safety Outcome (any)	<u>N with event</u>	<u>Rate per 1,000 PY</u>	<u>N with event</u>	<u>Rate per 1,000 PY</u>
Acute renal injury	n<5	0	n<5	0
Glomerulonephritis	n<5	0	n<5	0
Kidney transplant	n<5	4.53	n<5	12.19
Dialysis	n<5	0	n<5	0
Hypocalcaemia	n<5	0	n<5	12.30 ⁺
Safety Outcome (new)	<u>N with event</u>	<u>Rate per 1,000 PY</u>	<u>N with event</u>	<u>Rate per 1,000 PY</u>
Acute renal injury	n<5	0	n<5	0
Glomerulonephritis	n<5	0	n<5	0
Kidney transplant	n<5	0	n<5	12.19 ⁺
Dialysis	n<5	0	n<5	0
Hypocalcaemia	n<5	0	n<5	12.30 ⁺

⁺ p < 0.10, * p < 0.05, ** p < 0.01

Table 4
Safety outcomes for subjects with follow-up BMD information.

SUPPLEMENTARY TABLES

Unadjusted for baseline differences			
	Non-users	BP users, all	BP users, MPR ≥ 80%
	(N=3,908)	(N=1,789)	(N=1,121)
CKD 1	-0.3 (-0.4 ; -0.1) [N=1558]	0.8 (0.7 ; 1.0) [N=729]*	1.2 (1.0 ; 1.3) [N=458]*
CKD 2	-0.3 (-0.4 ; -0.2) [N=1935]	1.0 (0.8 ; 1.1) [N=883]*	1.3 (1.1 ; 1.6) [N=555]*
CKD 3A	-0.4 (-0.7 ; -0.1) [N=304]	0.3 (-0.2 ; 0.8) [N=136]*	0.7 (0.1 ; 1.3) [N=86]*
CKD 3B	-0.4 (-1.3 ; 0.5) [N=90]	-0.3 (-1.3 ; 0.7) [N=33]	0.2 (-1.1 ; 1.5) [N=18]
CKD 4	-1.3 (-3.0 ; 0.4) [N=19]	-0.3 (-2.1 ; 1.5) [N=7]	[N<5]
CKD 5	[N<5]	[N<5]	[N<5]
Adjusted for age, sex, prior MOF, recent GC use			
	Non-users	BP users, all	BP users, MPR ≥ 80%
	(N=3,908)	(N=1,789)	(N=1,121)
CKD 1	-0.3 (-0.5 ; -0.1) [N=1558]	0.8 (0.6 ; 1.0) [N=729]*	1.1 (0.9 ; 1.3) [N=458]*
CKD 2	-0.4 (-0.5 ; -0.3) [N=1935]	0.9 (0.7 ; 1.1) [N=883]*	1.2 (1.0 ; 1.5) [N=555]*
CKD 3A	-0.5 (-0.8 ; -0.1) [N=304]	0.2 (-0.2 ; 0.7) [N=136]*	0.6 (0.0 ; 1.2) [N=86]*
CKD 3B	-0.5 (-1.4 ; 0.5) [N=90]	-0.3 (-1.3 ; 0.8) [N=33]	0.2 (-1.1 ; 1.5) [N=18]
CKD 4	-1.4 (-3.1 ; 0.3) [N=19]	-0.3 (-2.0 ; 1.4) [N=7]	[N<5]
CKD 5	[N<5]	[N<5]	[N<5]

Table S1 Annualized change in femoral neck BMD as a function of BP treatment status and baseline CKD stage. BP users and non-users. To reduce selection bias, we allowed overlap so that the same person could be followed as non-users until osteoporosis treatment was initiated. Results not shown for cells with fewer than five subjects for regulatory reasons.

¹Adjusted for baseline differences in age, sex prior MOF, recent GC use

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