# The Association of Oral Bisphosphonate Use With Mortality Risk Following a Major Osteoporotic Fracture in the United Kingdom

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Original Study

# The Association of Oral Bisphosphonate Use With Mortality Risk Following a Major Osteoporotic Fracture in the United Kingdom: Population-Based Cohort Study

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A B S T R A C T

*Objectives:* Bisphosphonates (BPs) might have extra benefits in reducing mortality because of their anti-atherosclerotic effects, but studies reported conflicting results. We investigated the association between oral BP use and mortality risk following a major osteoporotic fracture (MOF) in the United Kingdom.
*Design:* This was a population-based cohort study.
*Setting and Participants:* In total, 163,273 adults aged 50 years and older with an MOF between 2000 and 2018 from the Clinical Practice Research Datalink in the United Kingdom.
*Methods:* Cox proportional hazards models were used to estimate the risk of all-cause mortality in current (0–6 months), recent (7–12 months), and past (>1 year) exposures to oral BPs after nonhip MOF and hip fracture. In addition, stratification by sex, BP type, and duration of follow-up was performed.
*Results:* Compared with never users of oral BPs, current BP use was associated with a 7% higher all-cause mortality risk after nonhip MOF, whereas a 28% lower all-cause mortality risk was observed after hip fracture. Past BP exposure was associated with a 14% and 42% lower risk after nonhip MOF and hip fracture, respectively. When considering only the first 5 years of follow-up, mortality risk associated with current BP use was significantly lower for both fracture groups, and the greatest reduction in mortality risk was observed within the first year. Women had slightly lower risk compared with men.

Dr. Frank de Vries is the guarantor of this study, accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. He attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

This study was reviewed and approved by the Independent Scientific Advisory Committee of the Clinical Practice Research Datalink (reference 18_115), which is responsible for reviewing protocols for scientific quality.

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All authors have completed the ICMJE uniform disclosure form (available on request from the corresponding author) at www.icmje.org/coi_disclosure.pdf and declare: SA, AMB, PG declare no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

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*Conclusions and Implications:* We found a slight increased risk of all-cause mortality with current BP exposure after a nonhip MOF; however, a protective effect was observed following a hip fracture. Both the timing and the effect size of an association based on the anti-atherosclerotic hypothesis of BPs are not supported by our results. The decreasing trend of the mortality risk with shorter durations of follow-up suggests that the observed association is likely due to unknown distortion or unknown pleiotropic properties of BPs.



Major osteoporotic fractures (MOFs) are the main consequence of osteoporosis, with devastating results for the affected patients, including a significant increased risk of mortality.[1] Occurrence of a hip fracture markedly increases the risk of subsequent fractures (relative risks of 2–7 compared with the general population).[2,3] This may increase mortality after fracture even more.[4] Approximately 33% of men and 22% of women suffering a hip fracture will die within 1 year, and 51% of men and 39% of women sustaining an MOF will die within 5 years.[5–7] But the reasons of this high mortality risk and the ways to prevent it are still not fully understood.

Secondary fracture prevention with anti-osteoporotic treatment, such as bisphosphonates (BPs), can prevent subsequent fractures.[8,9] Given the strong association between fracture and mortality in older individuals, it has been hypothesized that use of BPs may lower the risk of mortality after a fracture. Apart from preventing secondary fractures, the main underlying potential mechanism that could explain the mortality-reducing benefits of BPs is protection against cardiovascular events. This may mostly be the result of lowering lipid profile and decreasing arterial wall calcification.[10–14] However, data from randomized clinical trials (RCTs) yield conflicting evidence.[15,16] Although a post-hoc analysis of the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) trial showed a 28% statistically significant mortality reduction among users of zoledronic acid after hip fracture,[15] the design, analysis, and conduct of this study have been heavily criticized.[17]

Because the underlying mechanism for mortality reduction is likely similar for various BPs, we sought to further test the hypothesis of an association between all-cause mortality and the initiation of oral BPs following an MOF in a large representative real-life cohort study. Thus, the aim of this study was to examine if oral BP treatment was associated with a lower all-cause mortality risk after a nonhip MOF or hip fracture.

## Methods

### *Data Source*

This was a cohort study using the Clinical Practice Research Datalink (CPRD; www.cprd.com). The CPRD contains medical records of 674 practices in the United Kingdom representing approximately 6.9% of the total population.[18] Recorded data includes patient demographics, lifestyle parameters, medical history, laboratory test results, prescription details, specialist referrals, hospital admissions, and major outcomes since 1987. Previous studies showed a high validity of using CPRD data regarding MOF.[19]

### *Study Population*

The study population included all patients aged 50 years and older with a record of their first fracture between January 1, 2000 and December 31, 2018. The index date (start of study follow-up) was defined as the date of first recorded MOF (ie, a fracture of the hip/femur, vertebrae, humerus, or radius/ulna). We further classified fractures by hip or nonhip MOF (ie, vertebral, humerus, radius/ulna, or femur excluding hip). Patients with any fracture prior to age 50 years and those with use of oral BPs prior to the index date were excluded (adhering to new-user design). Also, to allow for at least 1 year of follow-up, we excluded those with an index fracture in 2018.

### *Exposure and Outcome*

The exposure of interest was the use of oral BPs after index date, which was assessed time-dependently. First, the total follow-up time for each patient was established by considering the time he/she had entered the study (ie, index date) and the time follow-up ends, which could be the end of study period, the date of transfer out of the practice area, or death (the outcome of interest), whichever came first. The total follow-up time was then divided into 180-day "periods" starting from the index date. Exposure status to BPs was defined as the following: "current exposure" means that the patient has received his most recent BP prescription during the past 6 months before the start of a period. "Recent exposure" means that the patient has taken his most recent BP prescription 7–12 months before, and "past exposure" means that the patient has stopped taking BPs for >1 year before. Using this model, patient exposure is then classified in a dynamic time-dependent manner, meaning they can move between exposure groups (current, recent, past) throughout time. However, once a patient is classified as a current user, he cannot return to the never user group. The total person-time in each category is accounted for and contributes to the Cox proportional hazards model. In addition, BP use was broken down into nitrogen-containing BPs (n-BP, alendronate, and risedronate) and the non-nitrogen-containing BP (non-n-BP) etidronate. The outcome of interest was all-cause mortality as recorded in the CPRD.

### *Potential Confounders*

Age was considered time dependently, whereas sex, smoking status, alcohol use, and body mass index were determined at index date. A history of the following comorbidities was assessed at the start of each interval: cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, dementia, diabetes mellitus, epilepsy, heart failure, ischemic heart disease, major infections (sepsis, meningitis, upper and lower respiratory tract infections), or malignant neoplasms (excluding nonmelanoma skin cancers). In addition, the use of following medications in the 6 months prior was included: antihypertensives, anti-Parkinson's medications, glucocorticoids, loop diuretics, psychotropic drugs (antipsychotics, anxiolytics, hypnotics, and sedatives), and statins. Confounders were included in the final model if they changed the beta coefficient of the association >5% or based on expert opinion. Collinearity between potential confounders was assessed.

### *Statistical Analysis*

Cox proportional hazards models were used to assess the risk of all-cause mortality following fracture associated with current BP use vs never use (using the SAS PHREG procedure). To avoid immortal

time bias, all patient time in each exposure status was incorporated into the model and all patient time prior to first BP use was defined as never use. Analyses were stratified by index fracture type (nonhip MOF vs hip) and sex.

In secondary analyses, current BP exposure was stratified by type of oral BP (n-BP or non-n-BP). A sensitivity analysis assessed 1-year and 5-year all-cause mortality risk, censoring the total follow-up period at 1 or 5 years, respectively.

Data were analyzed using SAS v 9.3 (SAS Institute Inc, Cary, NC).

## Results

A total of 163,273 patients were included in our cohort with a first MOF between 2000 and 2018 (Figure 1). Of the eligible fractures, 119,107 (72.9%) were nonhip MOF and 44,166 (27.1%) were hip fractures (Table 1). The mean age of patients with a nonhip MOF and hip fracture were 70 and 81 years, respectively. Female patients accounted for 74% of the nonhip MOF and 69% of hip fracture patients. A similar pattern of smoking was observed among both fracture groups, with less than one quarter of patients being current smokers. Frequent comorbidity and comedication included major infections and antihypertensives. The nonhip MOF comprised 16,378 vertebral fractures (13.8%), 5294 femur fractures (4.4%), 33,665 humerus fractures (28.3%), and 63,770 radius/ulna fractures (53.5%). The follow-up time for BP users was 7.6 years in the nonhip MOF and 5.7 years in the hip fracture group. The average duration of BP use was 3.3 years among nonhip MOF patients and 2.7 years among hip fracture patients.

Table 2 shows that current use of oral BPs was associated with a 7% higher risk of all-cause mortality among patients with an index nonhip MOF compared with never use (adjusted hazard ratio [$HR_{adj}$] 1.07, 95% confidence interval [CI] 1.03–1.10). Mortality risk in the recent exposure group was also higher compared with the reference group ($HR_{adj}$ 1.25, 95% CI 1.16–1.36), but past exposure was associated with statistically significant lower risk ($HR_{adj}$ 0.86, 95% CI 0.83–0.90). Among patients who had sustained a hip fracture, current BP exposure was associated with a significant 28% lower mortality risk compared with never BP exposure ($HR_{adj}$ 0.72, 95% CI 0.70–0.75), whereas recent and past exposures were associated with 21% and 42% lower risk, respectively. The HR of past exposure was statistically lower compared with recent and current exposure. In general, mortality risk tended to be slightly lower among women as compared with men.

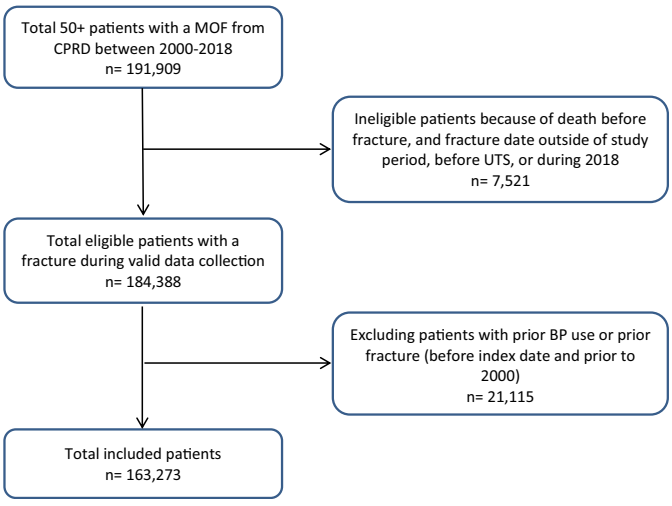


**Fig. 1.** Flowchart on establishment of patient population. All patients aged over 50 years from the CPRD in the UK who had a major osteoporotic fracture between 2000 and 2018, and started bisphosphonate use after the (index, first) fracture are included in the study. *50+ patients*, patients aged over 50 years; UTS, up to standard time of the CPRD practice.

Stratifying our analysis by nitrogen-containing BPs showed similar results to the primary analysis. Analyses with the non-n-BP etidronate lacked statistical power due to low frequency of exposure (data not shown).

The 5-year analysis showed a significant reduction in mortality risk with current BP exposure after nonhip MOF ($HR_{adj}$ 0.91, 95% CI 0.87–0.95) compared with never use (Table 3). Following a hip fracture, all-cause mortality risk associated with current exposure shifted further from the null value with a significant 39% reduction compared to never use ($HR_{adj}$ 0.61, 95% CI 0.59–0.64).

The 1-year mortality risk (data not shown) in the nonhip MOF group showed a 34% lower risk of all-cause mortality with current BP exposure ($HR_{adj}$ 0.66, 95% CI 0.60–0.72), whereas it was not lower with recent exposure ($HR_{adj}$ 0.23, 95% CI 0.03–1.61). The 1-year risk of all-cause mortality among hip fracture patients was considerably lower for current BP exposure ($HR_{adj}$ 0.41, 95% CI 0.37–0.44), but not for recent ($HR_{adj}$ 0.79, 95% CI 0.33–1.90).

## Discussion

This study identified that current oral BP exposure was associated with a 7% higher all-cause mortality risk after a nonhip MOF and with a 28% lower mortality risk after a hip fracture. When the follow-up time was censored at 1 and 5 years, a significant protective effect was observed in both fracture groups, with a trend away from the null with decreasing follow-up time: mortality risk with current BP use in the nonhip MOF group first dropped to a 9% reduction in the 5-year and then to 34% reduction in the 1-year analysis. In the case of hip fracture, mortality risk with current BP use first dropped to a 39% reduction in the 5-year and then to 59% in the 1-year analysis.

Our finding of a higher mortality risk among nonhip MOF patients with current BP exposure is not in line with findings from 2 meta-analyses of RCTs in 2010 (n = 25,072) and 2018 (n = 63,371), which showed no association between all-cause mortality and BP use vs placebo, yielding a pooled relative risk of 0.91 (95% CI 0.80–1.03) and 0.95 (95% CI 0.86–1.04), respectively.[20,21] However, the 28% lower mortality risk after hip fracture with current BP exposure in our study could be in line with those from the HORIZON trial, which showed a 28% reduced risk of all-cause mortality after 16 months of zoledronic acid use (HR 0.72; 95% CI 0.56–0.93), and was included in both meta-analyses.[15] However, RCTs have normally evaluated BP use in individual patients in a time-fixed model, while we assessed person-time within exposure states in a time-dependent analysis.

Our results in patients with hip fractures are in line with those from other observational studies in the field. In a recent cohort study by van Geel et al, a 21% reduction in mortality risk (HR 0.79, 95% CI 0.64–0.97) was reported with oral BP use compared to calcium and vitamin D use among fracture patients.[22] Using Danish national health register data, Bondo et al observed survival benefits for patients who had taken BP both before and after hip fracture, although their results may be distorted due to channelling or immortal time bias.[23] Sambrook et al found 27% mortality reduction for oral BP use compared to no use in frail older people (mean age = 86 years), and an even higher reduction (80%) in those only after hip fracture, although the number of BP users were very low (n = 17).[24,25]

However, BPs are not always found in literature to be beneficial on mortality risk reduction. Steinbuch et al reported no significant risk reduction in all-cause mortality for risedronate in patients with a history of vertebral or hip fracture or with low bone mass, although there was some benefits in case of stroke and cardiovascular events reduction.[14] In “primary prevention arm” of the HORIZON trial, Black et al reported a small but not statistically significant increase in death

**Table 1**
Baseline Characteristics of Participants According to Index Fracture Site

| | Nonhip MOF | | Hip Fracture | |
|---|---|---|---|---|
| | n | % - SD | n | % - SD |
| Number of events | 119,107 | | 44,166 | |
| Follow-up time (y) | 6.7 | 4.8 | 3.9 | 4.0 |
| Mean age, y | 70.1 | 11.9 | 80.5 | 10.3 |
| Female | 88,415 | 74.2 | 30,645 | 69.4 |
| Mean BMI | 26.6 | 5.5 | 24.3 | 4.9 |
| Smoking status | | | | |
| Never | 70,241 | 59.0 | 25,593 | 57.9 |
| Past | 17,856 | 15.0 | 6878 | 15.6 |
| Current | 29,056 | 24.4 | 9443 | 21.4 |
| Missing | 1954 | 1.6 | 2252 | 5.1 |
| Alcohol use | | | | |
| Yes | 80,188 | 67.3 | 22,786 | 51.6 |
| No | 28,937 | 24.3 | 13,921 | 31.5 |
| Missing | 9982 | 8.4 | 7459 | 16.9 |
| Comorbidities* | | | | |
| Cerebrovascular disease | 10,825 | 9.1 | 7908 | 17.9 |
| Chronic kidney disease | 11,168 | 9.4 | 7850 | 17.8 |
| COPD | 8269 | 6.9 | 4198 | 9.5 |
| Dementia | 4395 | 3.7 | 6142 | 13.9 |
| Diabetes mellitus | 12,820 | 10.8 | 6247 | 14.1 |
| Epilepsy | 3630 | 3.0 | 1520 | 3.4 |
| Heart failure | 3284 | 2.8 | 2626 | 5.9 |
| IHD | 15,268 | 12.8 | 8218 | 18.6 |
| Major infection | 31,928 | 26.8 | 10,660 | 24.1 |
| Malignant neoplasm | 14,816 | 12.4 | 7568 | 17.1 |
| Prior fracture | 0 | 0.0 | 0 | 0.0 |
| Medications† | | | | |
| Antihypertensives‡ | 49,832 | 41.8 | 22,195 | 50.3 |
| Anti-Parkinson's | 1428 | 1.2 | 1325 | 3.0 |
| BP history | 0 | 0.0 | 0 | 0.0 |
| Loop diuretics | 13,933 | 11.7 | 9790 | 22.2 |
| Glucocorticoids | 5944 | 5.0 | 2325 | 5.3 |
| Psychotropics | 16,299 | 13.7 | 9580 | 21.7 |
| Statins | 30,354 | 25.5 | 11,820 | 26.8 |
| Fracture at baseline | | | | |
| Hip | n/a | n/a | 44,166 | 100 |
| Vertebral | 16,378 | 13.8 | n/a | n/a |
| Femur | 5294 | 4.4 | n/a | n/a |
| Humerus | 33,665 | 28.3 | n/a | n/a |
| Radius/ulna | 63,770 | 53.5 | n/a | n/a |

BMI, body mass index; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; SD, standard deviation.
*Disease comorbidities happened ever before.
†Medications taken 6 months before index fracture.
‡Excluding loop diuretics.

numbers by using zoledronic acid and raised risk of serious atrial-fibrillation adverse events.[16] This might be comparable with our findings regarding the 7% higher mortality risk with current BP use in nonhip MOF patients. Although similar results regarding atrial-fibrillation events have been reported from the Fracture Intervention Trial by using alendronate, this unconfirmed association has no apparent biologic plausibility, and we do not expect this happening to our patients.[26]

There is some evidence from the literature regarding the anti-atherosclerotic effects of BPs, such as lowering low-density lipoprotein (LDL) cholesterol levels, decreasing arterial wall calcification, enhancing endothelial nitric oxide production, and reducing monocytes and platelets interactions with epithelial cells.[12,13,27–30] If cardiovascular effects of BPs would be comparable to those of statins, there should be (indirect) evidence of comparability of the timing and size of the effect. Large RCTs showed that the statin-induced reductions of mortality occurred after 11–24 months of use, which suggests that the mortality reduction starting after 16 months of BP use in the HORIZON trial may be plausible.[31–34] If we assume this timing to be true, part of our observations, such as the lower mortality among hip fracture patients (with 2.7 years of BP use) might be in line with the explained anti-atherosclerotic hypothesis of BPs. However, even among hip fracture patients, we observed the lowest mortality risk within 1-year analysis, which does not support this hypothesis as the proper timing has not been met. Also, the expected effect size is not comparable: large meta-analyses of RCTs comparing statin use with placebo reported an overall 13% reduction of all-cause mortality, or 9% mortality reduction per 1.0 mmol/L reduction of LDL cholesterol.[35,36] BPs have been shown to lower LDL in a range from no effect up to a reduction of approximately 0.34 mmol/L, after 6–12 months of use.[12,37,38] In the best-case scenario, this would then translate into a 3% lower risk of all-cause mortality,[36] which is around 9 times lower than the observed 28% reduction in the HORIZON trial and results of our study in the hip fracture patients.[15] Nevertheless, BPs could have other anti-atherosclerotic effects. A meta-analysis showed BPs have decreased aortic calcification by 11.2% compared with untreated individuals,[13] and coronary artery calcification is a well-known risk factor for all-cause mortality.[39,40]

Although some causal effect of BPs on all-cause mortality cannot be excluded, it is more likely that unmeasured distortion explains the largest proportion of the observed risk reductions in the HORIZON trial and our study. The HORIZON trial was later criticized because of some inconsistencies regarding the interpretation of data, early termination of the trial, and the high number of withdrawal or loss to follow-up.[17] Observational studies may have been confounded by selective prescribing of BPs to patients at lower risk of mortality.[41] Physicians rarely prescribe oral BPs to very ill and hospitalized patients. This can culminate in a spurious survival benefit for exposure drug as the very ill patients are unlikely to receive preventative medication. Moreover, healthy user and healthy adherer bias could also play a role.[42,43] Previous studies have suggested that patients who start a preventative medication or who are more adherent are generally healthier than patients who are not, and therefore may be at lower risk of mortality.[44] These bias scenarios, in addition to the high mortality rates in the early days after a fracture, could best explain the lowest HRs with 1-year analysis and the observed decreasing trend of HRs with shorter durations of follow-up. Moreover, assuming these bias scenarios, the generally lower HRs among the hip fracture patients, compared with the nonhip MOF patients, could be partly explained by longer hospitalization and higher mortality rates after a hip fracture compared with other MOFs.[45] Hip fracture patients are generally sicker with higher chance of mortality and, hence, are less likely to receive BPs.

Our study had several strengths. First, we used the CPRD for data collection, which is one of the world's largest primary care databases. Second, as our study period was relatively long (ie, 19 years [2000-2018]), we could include more than 163,000 patients in the study cohort, which is by far the largest study sample among observational studies in this topic. Also, we considered not only hip but all MOFs, making this the first study to our knowledge to evaluate the mortality after nonhip MOF with BP use. Furthermore, the statistical analysis was performed time-dependently, which means it incorporated all person time, avoiding immortal time bias.[46] Moreover, we used different approaches to test the underlying hypothesis of a causal effect,[47] such as assessing the same research question in 2 cohorts with different fracture sites and testing the underlying pharmacologic hypothesis with analyses that evaluated the onset and ending of the effect, which the other observational studies did not do.[14,22–25]

This study had also some limitations. One objective was to differentiate between n-BP or non-n-BP respecting their effect on mortality reduction, which was not feasible due to low numbers of non-n-BP use in the United Kingdom. As mentioned above, we could not exclude those dying shortly after having a fracture, and this could result in

**Table 2**
Risk of All-Cause Mortality Following an Index Fracture (Nonhip MOF and Hip), Stratified by Fracture Type, Sex, and Oral BP Exposure Status

| | Events | IR per 1000 Pys | Age (/Sex) Adjusted Model HR (95%CI)* | Final Adjusted Model HR (95% CI)† |
|---|---|---|---|---|
| Nonhip MOF | | | | |
| BP Never exposure‡ | 21,940 | 34.6 | Reference | Reference |
| BP Past exposure | 2341 | 36.1 | 0.85 (0.81–0.89) | 0.86 (0.83–0.90)§ |
| BP Recent exposure | 627 | 57.9 | 1.40 (1.30–1.52) | 1.25 (1.16–1.36)§ |
| BP Current exposure‖ | 5219 | 57.4 | 1.32 (1.28–1.37) | 1.07 (1.03–1.10)§ |
| Female** | | | | |
| BP Never exposure | 14,535 | 31.4 | Reference | Reference |
| BP Past exposure | 1933 | 33.2 | 0.82 (0.78–0.86) | 0.85 (0.81–0.89)§ |
| BP Recent exposure | 480 | 50.2 | 1.30 (1.19–1.43) | 1.19 (1.09–1.31)§ |
| BP Current exposure‖ | 4003 | 50.1 | 1.25 (1.21–1.30) | 1.04 (1.01–1.08)§ |
| Male** | | | | |
| BP Never exposure | 7405 | 43.2 | Reference | Reference |
| BP Past exposure | 408 | 61.7 | 0.93 (0.84–1.03) | 0.88 (0.80–0.98)§ |
| BP Recent exposure | 147 | 115.1 | 1.81 (1.53–2.13) | 1.47 (1.25–1.73)§ |
| BP Current exposure‖ | 1216 | 109.7 | 1.61 (1.52–1.72) | 1.14 (1.07–1.21)§ |
| Hip Fracture | | | | |
| BP Never exposure‡ | 16,977 | 152.3 | Reference | Reference |
| BP Past exposure | 1440 | 62.5 | 0.51 (0.48–0.53) | 0.58 (0.55–0.62) |
| BP Recent exposure | 398 | 96.2 | 0.75 (0.68–0.83) | 0.79 (0.71–0.87)†† |
| BP Current exposure‖ | 3778 | 103.5 | 0.76 (0.73–0.78) | 0.72 (0.70–0.75)†† |
| Female** | | | | |
| BP Never exposure | 10,942 | 145.1 | Reference | Reference |
| BP Past exposure | 1123 | 59.3 | 0.50 (0.47–0.54) | 0.58 (0.54–0.61)§ |
| BP Recent exposure | 305 | 91.8 | 0.76 (0.68–0.85) | 0.81 (0.72–0.90)§ |
| BP Current exposure‖ | 2738 | 92.4 | 0.71 (0.68–0.74) | 0.69 (0.66–0.72)§ |
| Male** | | | | |
| BP Never exposure | 6035 | 167.5 | Reference | Reference |
| BP Past exposure | 317 | 77.0 | 0.49 (0.43–0.55) | 0.58 (0.52–0.65) |
| BP Recent exposure | 93 | 114.5 | 0.69 (0.56–0.85) | 0.73 (0.59–0.89) |
| BP Current exposure‖ | 1040 | 151.2 | 0.87 (0.81–0.93) | 0.80 (0.75–0.85)†† |

IR, incidence rate; Pys, person years.

*Adjusted only for age where stratified by sex.

†Adjusted for sex, body mass index, smoking status and alcohol use at baseline, and the following variables time dependently: age and use of antihypertensives, anti-Parkinson's medications, loop diuretics, glucocorticoids, psychotropics, and statins in the previous 6 months, and history of malignant neoplasm, dementia (for hip fracture group), and chronic obstructive pulmonary disease (for nonhip MOF group).

‡Never exposure denotes to no known use of oral BPs, whereas past, recent, and current exposures refer to taking oral BPs in the time window >12 months, 6–12 months, and 0–6 months prior to the start of a period, respectively.

§HR from each BP exposure status is statistically different from the other exposure status in the same model, by Wald test, $P < .05$.

‖Not stratified by nitrogen containing agents because of small cell sizes and reporting restrictions in the CPRD for privacy reasons.

**Patients from each sex are compared only with same sex cohorts.

††HR is statistically different from the past exposure status, by Wald test, $P < .05$.

distortion (ie, higher estimates of drug effect than what it should be, especially with shorter durations of follow-up). Moreover, we could not measure or adjust for healthy user or healthy adherer effect, and we had no information about the cause of death, socioeconomic status of patients, or other similar indicators from CPRD. Nonetheless, we tried to overcome this by running multiple analyses that tested the same hypothesis indirectly in different ways, taking into account the hypothesized pharmacologic effect.

**Table 3**
Five-Year Risk of All-Cause Mortality Following an Index Fracture (Nonhip MOF and Hip), by Oral BP Exposure Status

| | Events | IR per 1000 Pys | Age/Sex Adjusted Model HR (95% CI) | Final Adjusted Model* HR (95%CI) |
|---|---|---|---|---|
| Nonhip MOF | | | | |
| BP Never exposure† | 16,162 | 42.5 | Reference | Reference |
| BP Past exposure | 753 | 43.2 | 0.73 (0.68–0.79) | 0.76 (0.70–0.82) |
| BP Recent exposure | 342 | 55.9 | 1.00 (0.90–1.12) | 0.98 (0.88–1.09)‡ |
| BP Current exposure | 3135 | 56.5 | 1.03 (0.99–1.07) | 0.91 (0.87–0.95)‡ |
| Hip Fracture | | | | |
| BP Never exposure† | 14,946 | 183.1 | Reference | Reference |
| BP Past exposure | 644 | 75.7 | 0.43 (0.40–0.47) | 0.50 (0.47–0.55) |
| BP Recent exposure | 279 | 95.7 | 0.56 (0.50–0.64) | 0.62 (0.55–0.70)‡ |
| BP Current exposure | 2831 | 103.3 | 0.60 (0.58–0.63) | 0.61 (0.59–0.64)‡ |

IR, incidence rate; Pys, person years.

*Adjusted for sex, body mass index, smoking status and alcohol use at baseline, and the following variables time dependently: age and use of antihypertensives, anti-Parkinson's medications, loop diuretics, glucocorticoids, psychotropics, and statins in the previous 6 months, and history of: malignant neoplasm, dementia (for hip fracture group), and chronic obstructive pulmonary disease (for nonhip MOF group).

†Never exposure denotes to no known use of oral bisphosphonates, whereas past, recent, and current exposures refer to taking oral bisphosphonates in the time window >12 months, 6–12 months, and 0–6 months prior to the start of a period, respectively.

‡HR is statistically different from the past exposure status, by Wald test, $P < .05$.

## Conclusions and Implications

In conclusion, although we found a higher risk of all-cause mortality with current BP exposure after nonhip MOF, a protective effect was observed with 1 and 5 years of follow-up. After a hip fracture, current BP exposure was associated with lower mortality risk in all analyses. Compared to statin studies and the effect of BPs on LDL reduction or arterial calcification, both the timing and the effect size of such an association is not supported by our results. Rather, the substantially lower mortality risk in the 1-year analysis and the decreasing trend of HRs with shorter durations of follow-up suggest that the vast majority of the observed association between BP use and mortality risk after fracture is explained by unknown distortion or unknown pleiotropic properties of BPs. We recommend that future studies focus on evaluation of these hypotheses to elucidate alternative mechanisms of potential pleiotropic effects of BPs, and on explaining potential unmeasured distortion.

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