Alarkawi, D., Ali, M. S., Caskey, F. J., Ben-Shlomo, Y., Judge, A., & al., E. (2020). Oral bisphosphonate use and all-cause mortality in patients with moderate-severe (grade 3B-5D) chronic kidney disease: a population-based cohort study. *Journal of Bone and Mineral Research*. https://doi.org/10.1002/jbmr.3961

Peer reviewed version

Link to published version (if available):
10.1002/jbmr.3961

Link to publication record in Explore Bristol Research
PDF-document

Oral bisphosphonate use and all-cause mortality in patients with moderate-severe (grade 3B-5D) chronic kidney disease: a population-based cohort study.

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Disclosure

The authors have no conflicts of interests to declare.

Abstract

Oral Bisphosphonates (oBP) have been associated with reduced fractures and mortality. However, their risks and benefits are unclear in patients with moderate-severe CKD. This study examined the association between oBP and all-cause mortality in G3B-5D CKD. This is a population-based cohort study including all subjects with an eGFR<45/ml/min/1.73m^2 aged 40+ years from the UK Clinical Practice Research Datalink (CPRD) and the Catalan Information System for Research in Primary Care (SIDIAP). Previous and current users of other anti-osteoporosis drugs were excluded. oBP use was modelled as a time-varying exposure to avoid immortal time bias. Treatment episodes in oBP users were created by concatenating prescriptions until patients switched or stopped therapy or were censored or died. A washout period of 180 days was added to (date of last prescription +180 days). Propensity scores (PS) were calculated using pre-specified predictors of mortality including age, gender, baseline eGFR, socio-economic status, co-morbidities, previous fracture, co-medications and number of hospital admissions in the previous year. Cox models were used for PS adjustment before and after PS trimming (the first and last quintiles). In the CPRD, of 19,351 oBP users and 210,954 non-oBP users, 5,234 (27%) and 85,105 (40%) deaths were recorded over 45,690 and 915,867 person-years of follow-up, respectively. oBP users had 8% lower mortality risk compared to non-oBP users (HR 0.92, 95% CI 0.89-0.95). Following PS trimming, this became non-significant (HR 0.98, 95% CI 0.94-1.04). In the SIDIAP, of 4,146 oBP users 86,127 non-oBP users, 1,330 (32%) and 36,513 (42%) died, respectively. oBP were not associated with mortality in PS adjustment and trimming (HR 1.04, 95% CI 0.99-1.1 and HR 0.95, 95% CI 0.89-1.01). In this observational, patient-based cohort study, oBP were not associated with increased mortality amongst patients with moderate-severe CKD. However, further studies are needed on other effects of oBP in CKD patients.

Keywords Chronic kidney disease, osteoporosis, bisphosphonates, epidemiology, mortality

Introduction

Osteoporosis is a common public health problem internationally. Osteoporotic fractures, which are the main complication of osteoporosis lead to increased disability, further fracture risk (1, 2) and premature mortality (3, 4). Similar to osteoporosis, declining kidney function is a common disorder of aging. Moreover, there has been a worldwide epidemic of chronic kidney disease (CKD) over the last decade (5, 6). NHANES data suggest that over 1 in 4 people with osteoporosis have CKD (7). CKD patients are more susceptible to osteoporotic fractures and fracture-related mortality because of the changes in their mineral metabolism and bone structure, which occur early in the course of the disease and worsen with the progressive loss of kidney function (8). CKD patients generally exhibit two broad pathways for bone fragility depending on the stage of renal impairment (9). Traditional osteoporosis as defined by the National Institute of Health (10) is mostly seen in those with early CKD. As CKD progresses, different forms of renal osteodystrophy defined by specific quantitative histomorphometry or chronic kidney disease-mineral and bone disorder (CKD-MBD) become prevalent. (11). Multiple studies have examined the fracture risk for different KDIGO (Kidney Disease Improving Global Outcomes) Grades (G) of CKD. It has been demonstrated that G3 CKD patients had a two-fold increased risk of fracture (8, 12) while those in G4 CKD had four times increased risk of fracture (13) similar to that seen in G5 CKD (end-stage renal disease) or in patients on dialysis (14, 15).

A growing body of evidence demonstrates that osteoporosis treatment such as bisphosphonates, which are highly effective in preventing osteoporotic fractures, also reduce mortality risk following osteoporotic fractures (16-22) . However, the evidence for the effectiveness and safety of bisphosphonates is scarce in CKD, particularly in those with an eGFR <30ml/min where it is contraindicated (23-25). Patients with moderate-severe kidney disease are under-represented or excluded from most randomised clinical trials of

osteoporosis medications leaving a gap in the current medical knowledge about the potential benefits and risks of those medications in this growing group of the population.

Therefore, the aim of this study was to examine the association between oral bisphosphonates (oBP) and all-cause mortality in patients with moderate-severe CKD [G3B-5D i.e. estimated glomerular filtration rate (eGFR)<45ml/min] using real world data.

Methods

Study population and design

This is a bi-national population-based cohort study that included participants aged 40 years or older with an eGFR < 45 ml/min/1.73m^2 at the time of biochemistry testing with at least one year of follow-up data available. The diagnosis of renal impairment was confirmed by linkage to the renal registry. Participants were excluded if they were users of bisphosphonates in the year prior to eGFR testing and if they were previous or current users of intravenous bisphosphonates or anti-osteoporosis medications other than oBP.

Two study populations from two data sources were included:

1- The CPRD (Clinical Practice Research Datalink) database linked to the Office of National Statistics (ONS) mortality, the Hospital Episodes Statistics Admitted Patient Care (HES) and the UK Renal Registry (UKRR). Established in London in 1987, the small Value-Added Medical Products (VAMP) dataset grew to become the General Practice Research Database (GPRD) in 1993, before expanding to become the CPRD in 2012. The CPRD comprises anonymised computerised records of clinical and referral events (as coded by primary care health professionals) as well as biochemistry results for a representative sample of over 14 million patients registered in more than 400 primary and secondary care health services in the UK (26).

In this study, 230,305 participants with G3B-5D CKD were included (19,351 oBP users and 210,954 non-oBP users). The period of follow up extended from 1996 to 2016.

2- The SIDIAP (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària) database linked to the Catalan Renal Registry and the Minimal Dataset of Hospital Admissions for Catalonia (CMBD-AH). The SIDIAP, created in 2010 under the auspices of the Catalan Institute of Health (CIH) and the Primary Care Research Institute Jordi Gol (IDIAP), contains anonymised clinical information as coded by general practitioners (GP) and community/family nurses in 279 primary care practices in Catalonia, Spain, covering over 5 million patients (80% of the Catalan population) (27). In this study, 90,273 participants with G3B-5D were included (4,146 oBP users and 86,127 non-oBP users). Participants were followed up from 2007 till 2015.

Exposure and study outcome

Use of oral bisphosphonates including alendronate, risedronate and ibandronate was identified from GP prescriptions (CPRD cohort) and pharmacy dispensations (SIDIAP cohort). oBP use was analysed as a time-varying exposure to avoid immortal time bias where bisphosphonate users were classified as "non-oBP users" before the initiation of oBP treatment and as "oBP users" after starting oBP prescription/ dispensation. To account for time-varying confounding, baseline characteristics for non-oBP users were considered at the start of the study and for oBP users at the start of oBP treatment.

Treatment periods (in oBP users) were created by concatenating prescriptions for each patient until the patient switched to another anti-osteoporosis medication or stopped therapy (refill gap in prescriptions of 180+ days) or were censored (end of study or transfer out from the GP clinic) or died. A washout period of 180 days was added.

The CPRD had information about the doses of oBP prescribed. Therefore, as a measure of adherence, the medication possession ratio (MPR) was calculated as the number of WHO defined daily doses divided by the length of time in days for each year of treatment, transferring any excess doses (>365 defined daily doses in a year) into the next year, where it

was added to prescriptions filled. The cohort was highly adherent to oBP use with more than 75% of the patients with an MPR >88%. Hence, the MPR categories (quartiles) were: <=88%, >88% to 97%, >97% to 109% and >109%.

All-cause mortality was the primary outcome of the study. In the CPRD dataset death date was obtained from the Office of National Statistics. In the SIDIAP dataset, date of death was registered as available in the source data, as this is provided periodically by the Regional National Health Insurance Database.

Clinical characteristics

In the CPRD data, information was collected by general practitioners and other health professionals in primary care by using Oxford Medical Information Systems (OXMIS) and Read codes for diseases (28). Information collated included: age, gender, baseline eGFR, socio-economic status [Index of Multiple Deprivation (IMD) Q1(most deprived) to Q5 (least deprived)] , number of hospital admissions in the year prior to the study, prior hip and non-hip fractures, current smoking and alcohol drinking status (yes/no), comorbidities including Charlson Index, deep vein thrombosis and hyperlipidemia and number of comedications and comedications including steroids, heparin, aromatase inhibitors, non-steroidal anti-inflammatory drugs, proton pump inhibitors, anxiolytics, antidepressants, statins, anti-epileptics, beta-blockers and digoxin.

In the SIDIAP data, primary care health professionals gather information using structured spreadsheets and ICD-10 codes for diseases. Information collected included all the variables listed previously for the CPRD data (29). For the socio-economic status the Medea Index was used with R and Q± as those with no information available on Medea Index, Q1 as the least deprived and Q5 as the most deprived (30)

The fractures considered in this study were non-incident fractures (fractures that did not occur during the study period) but hip and non-hip fractures that occurred before the study

as was confirmed by the OXMIS and Read codes in CPRD data and the ICD-10 codes in SIDIAP. Prior fractures for non-oBP users were those collected before the start date of the study and for oBP users before the initiation of oBP treatment.

Sample size and power

According to the available participant counts from the CPRD (19,351 oBP users and 210,954 non-users) and the SIDIAP (4,4146 oBP users and 86,127 non-users), in a survival analysis (two-sided test) and accepting 5% type 1 error, the sample size would provide >90% power to detect as significant a ≥10% excess risk in mortality as the outcome.

Statistical analyses

Analyses were performed using R software version 3.2 and SAS software version 9.4. Descriptive statistics for baseline characteristics were performed for oBP users and non-oBP users. The mean and standard deviation were used to describe continuous variables and frequencies and percentages were used to describe categorical variables. The differences between the two groups were compared using a *chi-square* test for categorical variables and a *t-test* for continuous variables.

Body mass index (BMI) and smoking variables had missing data in both datasets. In addition, alcohol drinking variable in the CPRD data had missing information. Missing information for each variable was imputed using multiple imputation by chained equations (MICE). Twenty imputation sets were created for each missing variable in the CPRD data and ten in the SIDIAP data.

Multivariable Cox regression models

CPRD data: Cox regression models were fitted to calculate mortality risk according to oBP use in CKD patients. A priori defined confounders that were adjusted for included the list of variables mentioned previously. Three pre-defined and hypothesized interactions of oBP with gender, history of prior fracture and CKD grade were tested for. In the presence of evidence

of a significant interaction, Cox models were further stratified by each of the previous variables. Cox models were also used to examine the impact of MPR categories on mortality risk.

SIDIAP data: Cox regression models were fitted to test for the three pre-defined interactions as in the CPRD data. The potential confounders adjusted for in the model included all the confounders listed for the CPRD data. Similar to the CPRD data, interactions of oBP with gender, history of prior fracture and CKD grade were tested for.

Propensity score analyses

Propensity scores (PS) represent the probability that a patient will receive oral bisphosphonates according to their baseline socio-demographics and clinical characteristics. Multivariable logistic regression models were used to calculate the PS. The pre-specified predictors of mortality (confounders) were included in the models. The calculated PS were used as a covariate in two separate models: adjustment for PS and PS trimming and adjustment. Adjustment for PS involved using a Cox regression model where mortality was related to BP use and the PS considered as a covariate. PS trimming involved excluding the first and last quintiles of the PS distribution and consequently restricting the range of PS. The rationale for PS trimming is that those subjects in the extreme quintile would have PS distributions with little or no overlap between oBP users and non-oBP users, so treatment effect cannot be accurately estimated (31). A Cox regression model was then fitted with PS and oBP use as covariates. This analysis was also performed using MPR categories in the CPRD data only.

Propensity score trimming has been widely used in observational research and has been recommended as a valid approach for the study of treatment effects especially when addressing the bias of unmeasured confounding. T. Stürmer et al found that in patients who are treated/not treated contrary to prediction, confounding by frailty (one of the most

important unmeasured confounders that also has direct effect on the outcome – mortality), may be most pronounced. These were usually the untreated patients with the highest PS and the treated patients with the lowest PS. Consequently, trimming increasingly greater proportions of those patients at both ends of PS distribution reduced unmeasured confounding and variances and enhanced validity. The results observed were very similar to those derived from other PS methods (32, 33).

Results

Study population characteristics

CPRD cohort: There were 19,351 oBP users and 210,954 non-oBP users followed up for a median of 1.5 years (IQR, 1.0-3.0) and 3.5 (IQR, 1.4-6.6), respectively. oBP users were older (82 years SD 9 years) than non-oBP users (78 years SD10 years). There were four times more women among oBP users than men. oBP users had a significantly higher Charlson Index score, a higher prevalence of diabetes, cardiovascular diseases, and prior hip and non-hip fractures than non-oBP users. There was significantly higher steroid and NSAID use among oBP users than non-oBP users (Table 1).

SIDIAP cohort: There were 4,146 oBP users and 86,127 non-oBP users followed up for a median of 3.0 years (interquartile range 1.7-5.2) and 3.6 years (1.7-6.2), respectively. Similar to the CPRD cohort there were four times more women among the oBP users than men and significantly greater prior hip and non-hip fractures, steroid and NSAID use. However, unlike the CPRD cohort, oBP users had significantly lower Charlson Index score, lower prevalence of diabetes, cardiovascular diseases and cancer than non-oBP users. oBP users were comparable to non-oBP users in their BMI, age and socio-economic status (Table 1).

Mortality risk

CPRD cohort

There were 5,234 (28%) and 85,105 (40%) deaths recorded over 45,690 and 915,867 person-years of follow up in oBP users and non-oBP users, resulting in an absolute mortality rate of 11.5/100 person-years (95% CI 11.2-11.8) and 9.3/100 person-years (95% CI 9.2-9.4), respectively. The unadjusted analysis demonstrated a 25% higher risk of mortality among oBP users than non-oBP users [hazard ratio (HR) 1.25, 95% confidence interval (CI) 1.22-1.29]. However, after multivariable adjustment there was an 8% decreased mortality risk in oBP users compared to non-oBP users (HR 0.92, 95% CI 0.90-0.95).

The three pre-defined interaction terms between oBP use and gender, history of prior fracture and CKD grade were significant (p=<0.0001, p=<0.0001 and p=0.02), respectively. Therefore, multivariable Cox models were stratified by each of these variables. The multivariable adjustment demonstrated 11% decreased mortality risk in female oBP users (HR 0.89, 95% CI 0.85-0.92) while in men, oBP showed no association with mortality (HR 1.03, 95% CI 1.00-1.06). oBP users with a history of prior fracture had a 20% decreased mortality risk compared to 6% in those with no history of prior fracture (HR 0.80, 95% CI 0.74-0.85 and HR 0.94, 95% CI 0.91-0.98, respectively). oBP users with CKD G3B had 4% decreased mortality risk (HR 0.96, 95% CI 0.93-0.99) while those with CKD G4-5D had 30% decreased mortality risk (HR 0.70, 95% CI 0.65-0.72).

Furthermore, the PS adjustment demonstrated an 8% decreased mortality risk in oBP users (HR 0.92, 95% CI 0.89-0.95). Following PS trimming at the first and last quintiles, oBP were no longer associated with mortality (HR 0.98, 95% CI 0.94-1.04) (Figure 1).

Notably, patients' adherence to oBP use was high with more than 75% of the CPRD cohort with an MPR >88%. Not surprisingly, the multivariable adjustment, the PS adjustment and trimming using the MPR categories (quartiles) <=88%, >88% to 97%, >97% to 109% and >109% demonstrated no association between the level of adherence to oBP and mortality risk.

SIDIAP cohort

There were 1,330 (32%) and 36,513 (42%) deaths recorded over 14,374 and 344,389 person-years of follow up in oBP users and non-oBP users, yielding absolute mortality rates of 9.3/100 person-years (95% CI 8.8-9.8) and 10.6/100 person-years (95% CI 10.5-10.7), respectively, similar to that seen in the CPRD UK population. The unadjusted analysis showed an 11% reduced mortality risk (HR 0.89, 95% CI 0.84-0.93) in oBP users. The three pre-defined interactions between oBP use and gender, history of prior fracture and CKD grade were not significant (p=0.6, p=0.1 and p=0.1, respectively). Therefore, stratified analyses were not performed.

The PS adjusted results showed no association between oBP use and mortality risk: PS adjustment (HR 1.04, 95% CI 0.99-1.10) and PS adjustment following trimming of the first and last quintiles of PS (HR 1.02, 95% CI 0.94-1.10) (Figure 1).

Discussion

This study demonstrated no overall increased mortality risk with oBP use in patients with moderate-severe chronic kidney disease (G3B-5D) in two different cohorts from the UK and Spain. However, oBP use in the CPRD cohort was associated with decreased mortality risk by 8% in the whole cohort, 11% in women, 20% in those with prior history of fracture and 30% in those with CKD G4-5D.

The available literature for the management of osteoporosis in CKD G1-3A suggests that patients should be treated similarly to patients without CKD as long as there are no biochemical markers suggestive of CKD-MBD (34, 35). However, there is limited information about the safety and efficacy of anti-osteoporosis treatment in patients with moderate-severe CKD (G4-5D). Bisphosphonates, the most commonly used anti-osteoporosis treatment, are usually contraindicated in patients with moderate-severe CKD for two main reasons: 1) the mechanism of action of bisphosphonates is to reduce bone turnover and

remodelling by osteoclast death. Hence, their use in moderate-severe CKD where bone turnover is often low (36) and prevalence of adynamic bone disease is high (37) is controversial and, 2) bisphosphonates are cleared by the kidneys and therefore may worsen kidney function and exacerbate other adverse events already present in CKD patients on renal replacement therapy including hypocalcemia, hypophosphatemia (38, 39) and upper gastro-intestinal events (40, 41). However, it is unclear whether these adverse events are exacerbated with oBP use and consequently contribute to mortality risk in these patients.

Patients with significant renal damage are usually excluded from clinical trials of osteoporosis treatments or under-represented. However, over the past decade, evidence based on growing anecdotal experience and post-hoc analyses about the safety and efficacy of oBP in CKD has been expanding such as the use of alendronate and risedronate in patients with eGFR <45ml/min/1.73m2 and no evidence of adynamic bone disease (42, 43). In the light of this evidence, the KDIGO revised its guidelines and no longer recommended bone biopsy prior to the use of oBP to prevent fractures in patients with G3A-5D CKD (44). oBP have also not been shown to cause acute kidney injury (45). However, intravenous (IV) BP, have been reported to cause acute kidney injury. Although the mechanism of toxicity is uncertain, kidney biopsies have shown tubular injury after IV BP (46, 47). Therefore, zoledronic acid has been contraindicated in those with an eGFR<35ml/min/1.73m^2 due to an increase in serum creatinine observed in a small but significant number of patients (48).

Similar to bisphosphonates, the information on the use of other osteoporosis therapies in moderate-severe CKD has been obtained from post-hoc analyses of clinical trials. Denosumab, a potent antiresorptive, is not cleared by the kidneys and hence renal impairment is not a contraindication for its use in CKD. However, studies where it has been shown to reduce fracture risk did not have enough participants with G4-5 CKD limiting their power to detect its safety and efficacy in those with severe CKD (49, 50). Denosumab use in CKD has

been associated with severe cases of hypocalcemia and therefore, it should be used with caution especially in those with G5 CKD (51). In addition, being a potent anti-resorptive bone treatment its use in those who may have adynamic bone may actually be counterintuitive. Therefore, more studies are needed to examine the efficacy and safety of Denosumab in CKD.

In this study, the propensity score analyses demonstrated no consistent association between oBP and all-cause mortality in either the CPRD or the SIDIAP cohorts. In the CPRD cohort, the multivariable modelling showed an 8% reduced mortality risk in oBP users, and the interaction terms between oBP use and gender, prior history of fracture and CKD grade were significant. Therefore, the stratified analyses demonstrated an 11% reduced mortality risk in women, 20% in those with prior history of fracture and 30% in patients with G4-5D CKD. Those results were not observed in the SIDIAP cohort which may be explained by the heterogeneity in the baseline characteristics of the two cohorts, the unresolved confounding which could be of higher relevance in patients with more severe CKD as they are most often managed in secondary care, or by the smaller sample size of the SIDIAP cohort leading to lower statistical power.

The characteristics of the oBP users and non-oBP users in the CPRD and the SIDIAP cohorts were different in many ways. In the CPRD cohort, oBP users were older, had higher Charlson Index, higher prevalence of comorbidities and higher absolute mortality rate than non-oBP users. However, in the SIDIAP cohort, oBP users had similar age to non-oBP users, had lower Charlson Index, lower prevalence of comorbidities and lower absolute mortality rate than non-oBP users. The available evidence has demonstrated that the reduction in mortality following bisphosphonate use was mainly observed in older, frail individuals with higher mortality rates and higher risk of fracture (18, 22). Hence, the mortality risk reduction in the CPRD cohort was specifically observed in women, those with prior fracture and in G4+ CKD as they all have higher risk of fractures and G4+ CKD patients are usually frail and have more

comorbidities. Furthermore, the median follow-up time of oBP users in the CPRD cohort was shorter compared to non-oBP users (1.5 versus 3.5 years) while in the SIDIAP cohort the median follow-up times were similar between oBP users and non-oBP users (3 versus 3.6 years). This may also be explained by the fact that oBP users in the CPRD cohort were generally sicker and had higher mortality rates.

The strengths of this study include the two large heterogenous cohorts from two different countries. Both the CPRD and SIDIAP cohorts are excellent "real-world" data sources and their linkage to other sources including renal registries, hospital admissions and mortality registries increased their accuracy and completeness. However, this study has its limitations such as potential sources of bias that are difficult to account for in observational studies including residual confounding, drug misclassifications and further confounding by indication. Moreover, this study explored only mortality as an outcome with oBP use in patients with moderate-severe CKD although the inter-associations between incident fracture and mortality are integral to studying the overall effects of oBP in CKD. However, this study is part of a bigger project that explores other outcomes of the use of oral bisphosphonates in people with CKD including fracture outcomes. In this study the effects of oBP were studied collectively. However, different types of oBP with their different potencies could have variable effects in CKD. In addition, mortality in CKD patients is mainly caused by cardiovascular events, however information about those events was not available, hence, the outcome was restricted to all-cause mortality and cardiovascular mortality was not analysed separately.

In conclusion, oral bisphosphonate treatment in patients with G3B-5D CKD was not associated with increased mortality risk. It may be associated with a decreased mortality risk especially in women, those with prior history of fracture and those with G4-5D CKD.

However, more studies are needed to explore other effects of oral bisphosphonates in this population with high fracture risk and limited options of treatment for fracture prevention.

Acknowledgments

This work was supported by the National Health Medical Research Council Australia (NHMRC project ID; DA 1114676, DB 1073430, and JRC 1008219). This work was partially supported by the NIHR Biomedical Research Centre, Oxford. DPA is funded by a National Institute for Health Research Clinician Scientist award (CS-2013-13-012). AJ is funded by the Bristol NIHR Biomedical Research Centre. This article presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the authors and not necessarily those of the NHMRC and the NIHR.

Authors' roles: Study design: DA, SA, DB, NP, CT, FC, NKA, YBS, BA, ADP, JP, MJPS, JRC, AJ, CC, KMJ AND DPA. Data analysis and interpretation: DA, SA, DB, NP, CT, LE, JRC and DPA. Drafting manuscript: DA, DB, JRC and DPA. Revising manuscript content: all authors. Approving final version of manuscript: all authors.

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Table 1 Baseline characteristics for oBP users and oBP non-users in CPRD and SIDIAP cohorts

Characteristics		CPRD		SIDIAP	
		oBP user * n=19,351 (8%)	**oBP non-user n=210,954 (92%)**	**oBP user * n=4,146 (5%)**	**oBP non-user n=86,127 (95%)**
Females		15,378 (79%)	122,460 (58%)	3,245 (78%)	51,944 (60%)
Males		3,973 (21%)	88,494 (42%)	901 (22%)	34,183 (40%)
BMI, kg/m^2		26.4 (5.4)	27.8 (5.6)	29.4 (5.2)	29.1 (5.3)
Age, y		81.7 (8.8)	78 (10.1)	77.6 (8.5)	78.1 (10.5)
eGFR, ml/min/1.73^2		39.1 (6.5)	38.3 (7.4)	36.7 (7.6)	35.5 (8.4)
Medea Index$^{\pm}$	**IMD$^{\pm}$**				
R$^{\pm}$				820 (20%)	21,092 (25%)
Q$^{\pm}$				548 (13%)	9,846 (11%)
Q1	Q1	4,580 (24%)	46,751 (22%)	578 (14%)	11,102 (13%)
Q2	Q2	4,523 (23%)	49,641 (24%)	552 (13%)	11,272 (13%)
Q3	Q3	4,047 (21%)	44,690 (21%)	557 (14%)	11,584 (13%)
Q4	Q4	3,637 (19%)	41,559 (20%)	542 (13%)	10,796 (13%)
Q5	Q5	2,564 (13%)	28,313 (13%)	549 (13%)	10,435 (12%)
Smoking (yes)		1,533 (8%)	23,511 (11%)	268 (6%)	7,908 (9%)
Alcohol drinking (yes)		12,432 (64%)	146,092 (69%)	12,432 (64%)	146,092 (69%)
CKD Grade					
3B		17,647 (91%)	185,607 (88%)	3,469 (84%)	67,562 (78%)
4		1,464 (8%)	21,106 (10%)	584 (14%)	15,647 (18%)
5		113 (0.5%)	4,241 (2%)	78 (1.7%)	2,260 (3%)
5D		127 (0.6%)	N/A[a]	15 (0.3%)	658 (1%)
Kidney transplant		65 (0.3%)	N/A[a]	14 (0.3%)	396 (0.5%)
Charlson Index					
0		6,495 (34%)	117,981(56%)	1,009 (24%)	16,423 (19%)
1-2		7,337 (38%)	61,729 (29%)	1,825 (44%)	36,836 (43%)
≥3		5,519 (29%)	17,615 (8%)	1,312 (32%)	32,868 (38%)
Incident fracture		2,441 (13%)	27,581 (13%)	354 (9%)	6,236 (7%)
Diabetes		2,554 (13%)	23,909 (11%)	1,160 (28%)	28,210 (33%)
Cardiovascular disease		6,167 (32%)	51,369 (24%)	523 (13%)	13,446 (16%)
Cancer		3,641 (19%)	26,138 (12%)	491 (12%)	11,537 (13%)

Prior hip fracture	322 (2%)	2,301 (1%)	412 (10%)	2,199 (3%)
Prior non-hip fracture	5,116 (26%)	9,719 (5%)	780 (19%)	6,027 (7%)
Steriods	8,679 (45%)	38,730 (18%)	590 (14%)	8,168 (9%)
NSAIDs	13,877 (72%)	123,687 (59%)	1,959 (47%)	30,528 (35%)

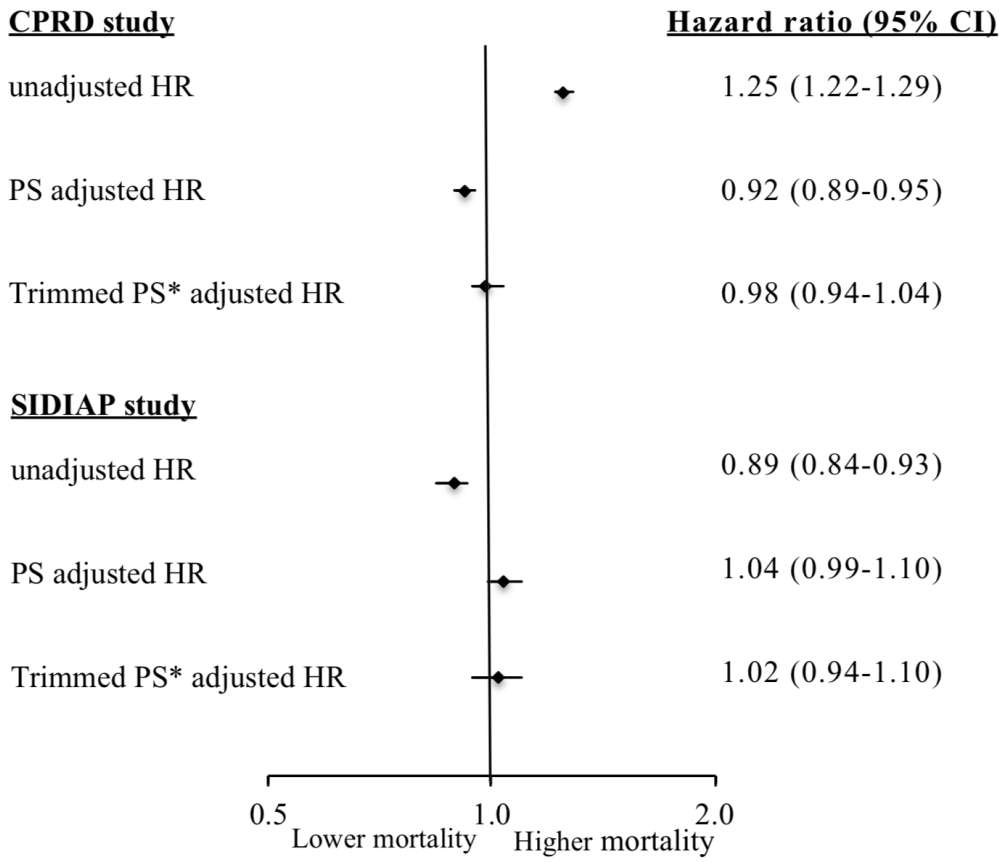
BMI = body mass index, *IMD* = index of multiple deprivation, eGFR = estimated glomerular filtration rate, *NSAIDs* = non-steriodal anti-inflammatory drugs

*p<0.001, difference between oBP users and non-oBP users except for IMD in CPRD and age, BMI and Medea Index in SIDIAP which weren't significant between oBP users and non-oBP users

±Medea Index levels only present in SIDIAP data. "R" means those with no information on Medea Index, "Q" means those with information but not specific and "Q5" are those who are the most deprived. IMD for the CPRD cohort with "Q5" being the least deprived.

[a] The numbers for who were on dialysis or had a kidney transplant were not known at baseline.

Figure 1 Forest plot of hazard ratios and 95% CI for the association of oBP use with mortality in moderate-severe CKD



*****Trimming of PS range at the first and last quintiles