Osteoporosis International

Comparative risk of acute myocardial infarction for anti-osteoporosis drugs in primary care: a meta-analysis of propensity-matched cohort findings from the UK Clinical Practice Research Database and the Catalan SIDIAP Database.

--Manuscript Draft--

Manuscript Number:	OSIN-D-21-00225R1
Full Title:	Comparative risk of acute myocardial infarction for anti-osteoporosis drugs in primary care: a meta-analysis of propensity-matched cohort findings from the UK Clinical Practice Research Database and the Catalan SIDIAP Database.
Article Type:	Original Article
Funding Information:	National Osteoporosis Society — Prof Daniel Prieto-Alhambra National Institute for Health Research Clinician Scientist award (CS-2013-13-012) — Prof Daniel Prieto-Alhambra NIHR Biomedical Research Centre at the University Hospitals Bristol NHS Foundation Trust and the University of Bristol — Prof Andrew Judge
Abstract:	Purpose To evaluate the comparative safety of AOD based on the observed risk of AMI while on treatment in a primary care setting. Methods Propensity-matched cohort study and meta-analysis. Setting Two primary care records databases covering UK NHS (CPRD) and Catalan healthcare (SIDIAP) patients during 1995-2014 and 2006-2014 respectively. AMI while on treatment was the outcome. Users of alendronate (reference group) were compared to those of 1. other oral bisphosphonates (OBP), 2. strontium ranelate (SR), and 3. Selective estrogen receptor modulator (SERM), after matching on baseline characteristics (socio-demographics, fracture risk factors, co-morbidities, and concomitant drug/s use) using propensity scores. Multiple imputation was used to handle missing data on confounders, and competing risk modelling for the calculation of relative risk (sub-distribution hazard ratios, SHR) according to therapy. Country-specific data were analysed separately and meta-analysed. Results Although there was no difference in any of the treatment groups in either CPRD or SIDIAP, when meta-analysed, there was a 9% increased risk of AMI in other bisphosphonates. Sensitivty analysis showed SERMS users with diabetes and chronic kidney disease were at an elevated risk. Conclusions This study provides new data on the risk of AMI in patients receiving osteoporosis treatment. The results favour the cardiovascular safety of alendronate as a first line choice for osteoporosis treatment.
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Author Comments:	To the Osteoporosis International Journal editor, November 4th, 2021 We would like to thank and acknowledge the work and understanding that the journal, especially the editor John Richard Arrienda, have had with us in extending the period of revision during this uncertain period. In other to answer the reviewers, we had to conduct some additional analyses. Thus, we would like to extraordinary request the inclusion of a new co-author, Marta Pineda-Moncusi, who has conducted the extra analysis to satisfy reviewers comments, revised manuscript, and contributed to the discussion (which makes it substantial contribution enough to meet ICMJE authorship criteria). Yours faithfully, Sara Khalid
Response to Reviewers:	Authors comment: We would like to thank and acknowledge the work and understanding that the journal, especially the editor John Richard Arrienda, have had with us in extending the period of revision during this uncertain period. We would also like to thank the reviewers' effort in evaluating our manuscript and appreciate their contribution, which has improved the quality of our work. Reviewer #1: This is a potentially interesting study using 2 large population databases. However, the statistical analyses are rather messy and unclear, many mistakes in the analysis. Major comments: 1. Most important, osteoporosis diagnosis or BMD was not included in the propensity score. Potential confounding by indication, especially when SERM is not indicated for those people with very low BMD. Thank you very much for pointing out this important consideration. Definition of osteoporotic population by including only osteoporosis (OP) diagnosis and values of BMD is generally insufficient in real-world data since OP is diagnosed at hospitals and OP tag/BMD values can be miss at primary care databases. Thus, use of anti-osteoporotic medication is a common proxy to detect OP population: e.g., Pineda-Moncusí M, et a. 2020 Increased Fracture Risk in Women Treated With Aromatase Inhibitors Versus Tamoxifen: Beneficial Effect of Bisphosphonates. or Khalid et al.2021 Predicting Imminent Fractures in Patients With a Recent Fracture or Starting Oral Bisphosphonate Therapy: Development and International Validation of Prognostic

Models).
Moreover, we aimed to compare the safety of AOD not exclusively to population diagnosed with OP, but to other users, such as osteopenic population that qualifies to be treated with AOD.
Finally, we would like to acknowledge the lack of BMD data as one of the limitations of this study. All attempts were known to eliminate known confounding where data on confounders were available, however the risk of residual confounding/ confounding by indication may remain despite the adjustments. We have included it in the limitations of the study.

2. Another important factor was not included, year of index date. Strontium was progressively not used due to potential cardiac event, thus the difference could be driven by the index year. Nevertheless, year of study was not well described, please clarify.

Thank you for the comment. The study periods were included in the abstract but not to the main manuscript text. Those were 1995-2014 in CPRD and 2006-2014 in SIDIAP. We have included this information in the section Participants and Variables section from Methods.
We decided to analyse data up to 2014 since that was the year that the European Medicines Agency's Pharmacovigilance Risk Assessment Committee warned not to use it. Specifically, this warning message was announced the 1st of October of 2014.

3. For confounders, I am not familiar with SIDIAP, but CPRD should have a wealth of data, more relevant variables should be used to generate propensity score.

We agree with the reviewers that both databases contain a wealth of patient characteristics that can be considered as confounders. The included confounders in the study were decided by a common effort of clinical bone and joint specialist experts and epidemiologists from our group, based on the literature and routine clinical practice. We hope that the expertise, robust methodology, and the consistency of the results across the two datasets validate the obtained results, which were well-matched.

4. Not sure why Charlson comorbidity index and related variables were all included in the PS generation?! Charlson comorbidity index includes several variables that used to generate PS as well. Please clarify

Thank you for this observation. Charlson comorbidity index is a complex indicator (i.e., it tells us the number of concomitant comorbidities/chronic conditions that patients have simultaneously). Patients with higher complexity have higher risk of events. By adding Charlson to the PS adjustment, we are ensuring that patient's complexity will not affect our study outcome, which is independent of the increased risk of AMI events driven by the specific comorbidities included in the adjustment.

Minor comments:
1. Variables: Chronic renal failure and eGFR should be highly correlated, potential collinearity, please also check other related variables

We agree with the reviewers that CRF and EGFR are indeed highly correlated as CRF is derived from EGFR. However, as CRF was coded as a binary variable, it was decided to retain EGFR (since it was available as a continuous variable) in the propensity score matching, to ensure the matched samples were as well matched as possible with all available confounders. Whereas collinearity is an important consideration for e.g., risk prediction modelling, here it was not a concern.

2. P.5 line 55, previous hip fracture.... type 2 diabetes.,, and hip fractures? please clarify.

Thank you for the comment. It was a typing error from the track changes. We have replaced it for the following sentence: "were age, gender, body mass index (BMI), smoking, drinking, Charlson morbidity index, previous hip fracture, previous non hip fracture, and type 2 diabetes".

3. for imputation, how accurate is the imputation?

Multiple imputation is a commonly used strategy to avoid reduction of sample size or the elimination of the incomplete variable in large datasets. It is based in the prediction of the missing values from the known values of the incomplete variable and from its correlation to the rest of the data set variables (i.e., missing values are replaced by imputed values, obtained from their predictive distribution based on the observed data — Bayesian approach).
The validity of results depends on its correct application. For instance, missing data might be normally distributed and initial percentage of missing data should ideally be lower than 80% (our maximum percentage of missing data is 56%).
To avoid a potential bias of single imputation results, this process is repeated several times (in our case we imputed each missing value of the dataset 50 times). Then, the average number of each imputed number is calculated using the Rubin's rules (Rubin D. Multiple imputation for nonresponse in surveys. New York: Wiley, 1987), which take account of the variability in results between the imputed datasets, reflecting the uncertainty associated with the missing values.
We had into account all the key issues before starting the imputation. We have included the number of imputations performed.
"… a series of 50 multiple imputations were performed to impute the missing values for those confounders that were found to have missingness …"

4. For subgroup analysis, please justify the choice of subgroup, e.g. why age of 80?

Thank you for this observation. We decided to analyse the octogenarian population to confirm that there were no differences in the results regarding the most elderly population (i.e., that could be related to end-of-life characteristics).

5. did you check the proportional assumption of the cox regression?

Thank you so much for the comment. The proportional assumption of the cox regression was checked. We have included in the methods.

6. When is the index date?

We appreciate the reviewer's comment. Index date is the date of the first AOD prescription/dispensation. It has been clarified in methods:
"Index date was defined as date of first AOD prescription in CPRD and first AOD dispensation in SIDIAP."

7. Two important papers from Ian Reid on this topic (one in NEJM and one in JBMR) were not mentioned at all, it should be cited and discussed in this study.

Following to the reviewer's advice, we found the following articles from Ian Reid that might be the ones suggested:
Fracture Prevention with Zoledronate in Older Women with Osteopenia – NEJM 2018
Effects of Zoledronate on Cancer, Cardiac Events, and Mortality in Osteopenic Older Women – JBMR 2019.
First article (NEJM 2018) compares Zolendronate vs Placebo and mentions in the discussion that some studies support the possibility that bisphosphonates reduce the risk of vascular disease and MI risk compared to placebo but doesn't include any information about differences across anti-osteoporotic treatments. In the same line, second article (JBMR 2019) evaluates Zolendronate vs Placebo.
If we had mistaken the election of articles, we would appreciate very much if the reviewer can send us further details such as year and/or doi.

Reviewer #2:
The aim of this study was to evaluate the risk of acute myocardial infarction in patients taking osteoporosis drugs.
Patients were taken from the SIDIAP or CPRD database and were matched using propensity scores.

The authors concluded that:
an 10% increased risk of acute myocardial infarction was found in users of other bisphosphonates as compared to alendronate users within CPRD.

	Meta-analysis of CPRD and SIDIAP results showed a 9% increased risk in users of other bisphosphonate as compared to alendronate users. Sensitivity analysis showed SERMS users with diabetes and chronic kidney disease were at an elevated risk. My comments: In paper published in Clin Ther. 2011 Sep;33(9):1173-9 entitled Alendronate and Raloxifene Use Related to Cardiovascular Diseases: Differentiation by Different Dosing Regimens of Alendronate by Pei-Yu Lu et al, the authors concluded that Alendronate 10 mg was associated with a higher risk of cardiovascular disease than alendronate 70 mg. In your work there are difference among 10 daily and 70 weekly mg of dose of alendronate administration? Thank you so much for this observation. Unfortunately, data on dose administration were not available and we cannot distinguish between them. We have included it in the limitations: “Differences among higher risk of 10 mg dose of Alendronate versus 70 weekly mg dose reported by Pei-Yu Lu et al. were not evaluated since administration doses were not available [34].” Pag 5, line 30 The authors reported: "The OBP included in this study, were risedronate and ibandronate, as these were most commonly used in both countries. what are the other oral bisphosphonates? We appreciate so much the reviewer’s comment. The most used oral bisphosphonate in both countries is alendronate, reason why we decided to use it as the comparison treatment. The following most frequent - other oral bisphosphonates, OBP - are risedronate and ibandronate. We have clarified this sentence as following: “The OBP included in this study were risedronate and ibandronate, as these were most commonly used in both countries after alendronate”. pag 5 line 55 delete hip fractures after type 2 diabetes because it is reported two time. Thank you for the comment. It was a typing error from the track changes. We have amended the sentence.

Comparative risk of acute myocardial infarction for anti-osteoporosis drugs in primary care: a meta-analysis of propensity-matched cohort findings from the UK Clinical Practice Research Database and the Catalan SIDIAP Database.

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ABSTRACT

Purpose

To evaluate the comparative safety of anti-osteoporosis drugs based on the observed risk of acute myocardial infarction while on treatment in a primary care setting.

Methods

Propensity-matched cohort study and meta-analysis.

Setting Two primary care records databases covering UK NHS (CPRD) and Catalan healthcare (SIDIAP) patients during 1995-2014 and 2006-2014 respectively. The outcome was accute myocardial infarction while on treatment. Users of alendronate (reference group) were compared to those of 1) other oral bisphosphonates (OBP), 2) strontium ranelate (SR), and 3) selective estrogen receptor modulator (SERM), after matching on baseline characteristics (socio-demographics, fracture risk factors, co-morbidities, and concomitant drug/s use) using propensity scores. Multiple imputation was used to handle missing data on confounders, and competing risk modelling for the calculation of relative risk (sub-distribution hazard ratios, SHR) according to therapy. Country-specific data were analysed individually and meta-analysed.

Results

An 10% increased risk of acute myocardial infarction was found in users of other bisphosphonates as compared to alendronate users within CPRD. Meta-analysis of CPRD and SIDIAP results showed a 9% increased risk in users of other bisphosphonate as compared to alendronate users. Sensitivity analysis showed SERMS users with diabetes and chronic kidney disease were at an elevated risk.

Conclusions

This study provides additional data on the risk of acute myocardial infarction in patients receiving osteoporosis treatment. The results favour the cardiovascular safety of alendronate as a first line choice for osteoporosis treatment.

Keywords

Acute Myocardial Infarction, Osteoporosis Treatment, CPRD, SIDIAP

Mini Abstract

The aim of this study was to evaluate the risk of acute myocardial infarction in patients taking osteoporosis medication. Patients were taken from the SIDIAP or CPRD database and were matched using propensity scores. Patients with diabetes and chronic kidney disease taking SERMs, were at an increased risk.

INTRODUCTION

Osteoporosis is characterised by low bone mass and deterioration of bone microarchitecture with an increased susceptibility to fragility fractures and consequent disability, pain, and decrease of quality of life. [1]

Among higher risk women, anti-osteoporosis-drugs (AODs) have proved to be an effective additional treatment to improve bone strength and diminish fracture risk [2]. It has long been speculated that specific AODs also provide additional extra-skeletal benefits.

A 2-year follow-up cohort study analysing the risk of acute myocardial infarction in patients with osteoporotic fractures receiving bisphosphonate treatment found a 65% risk reduction amongst bisphosphonate users (HR 0.36 [0.14-0.84]) [3], but this was not replicated in subsequent meta-analysis and a sequential trial analysis (TSA)[4, 5] . On the other hand, according to the safety update report published by the European Medicines Agency (EMA) in 2013, pooled analyses of SOTI and TROPOS trials showed an increased risk of AMI with strontium ranelate [6, 7]. Latest observational studies have, however, failed to support such findings, which might be attributed to inherent methodological issues, such as confounding by indication, few events and short duration of exposure [8–11]. Amidst safety concerns, since August 2017, strontium ranelate has been discontinued worldwide by manufacturers alluding to commercial reasons based on the limited uses of the drug [12]. As regards the Selective Estrogen Receptor Modulators (SERMs), RUTH and MORE trials have failed to demonstrate any association with increased risk of AMI[13, 14], though the RUTH trial found an increased occurrence of fatal stroke. The available RCTs did not address AMI as the primary endpoint[15, 16].

Population-based studies provide the advantage of assessing the safety of new treatments in much larger populations than those participating in phase 3 trials, and under conditions that reflect current medical practice. Moreover, they allow for including less selected populations than those in clinical trials, providing a better representation of the use of the drug in real life.

The aim was to compare the association between available AODs and the risk of acute myocardial infarction (AMI) utilising “real world” data from the healthcare records from two countries

METHODS

Study Design

A retrospective cohort study was conducted including all registered users of anti-osteoporosis medications. Data from two anonymised primary care outpatient records were used.

Data Sources

SIDIAP comprises of primary care anonymised electronic medical records for a representative >80% of the population of Catalonia [17]. The Catalan healthcare system is universal in coverage with primary care physicians as the gatekeepers to the system and responsible for long-term prescriptions. SIDIAP is linked to community pharmacy dispensations data.

The CPRD database (www.cprd.com) contains anonymised, computerised primary care outpatient records for a representative sample of the UK population. In addition to comprehensive demographic information, data include medication prescriptions by general practitioners (GPs), clinical events, referrals, and hospital admissions with their major outcomes in a sample of >7 million patients [18]. The CPRD is administered by the Medicines and Healthcare products Regulatory Agency (MHRA) and has broad National Research Ethics Service Committee (NRES) ethics approval for purely observational research using the primary care data and established data linkages.

Participants and Variables

Individuals with AOD exposure from 1995-2014 in CPRD and 2006-2014 in SIDIAP, and at least 1 year of data before this index date were recruited. Index date was defined as date of first AOD prescription in CPRD and first AOD dispensation in SIDIAP.

AOD exposure was identified by GP prescriptions in CPRD and dispensations in SIDIAP, considering that in both countries AODs are available only under prescription. A single prescription counted as a user. Alendronate users were considered as the *reference* group, to be compared with the *treatment* group, which could be one of the following: [1] selective estrogen receptor modulators (SERMs) [2] strontium ranelate (SR), and [3] other oral bisphosphonates (OBP). The OBP included in this study were risedronate and ibandronate, as these were most commonly used in both countries after alendronate. Amongst SERMs, Raloxifine was the most widely prescribed drug in both datasets and the only one included in this study. Male SERM users were excluded from both datasets, as SERMs are only licensed for use in women. Parenteral therapies such as zoledronate, denosumab and teriparatide are not well captured in primary care records and were not included.

Outcome was the first occurrence of an AMI event, and *follow-up time* was the duration between the start of treatment (first AOD prescription/dispensation) and end of treatment, where end of treatment was defined as the first-occurring evnet out of the following: (a) a gap in prescription/dispensation of 90 days or more, (b) switching to another AOD treatment, (c) transfer out of the study or loss to follow up, (d) end of study period (2014), (e) death, or (f) AMI.

Confounders included in the analysis for CPRD and SIDIAP were age, gender, body mass index (BMI), smoking, drinking, Charlson morbidity index, previous hip fracture, previous non hip fracture, and type 2 diabetes. CPRD exclusive were corticosteroids, serum cholesterol, marital status, ischeamic heart disease, cerebrovascular disease, chronic renal failure, and EGFR. In the analysis for SIDIAP, additional confounders were also included (which were not available in CPRD (number of systemic glucocorticoids dispensed, LDL cholesterol, ischaemic heart disease, myocardial infarction, temporary ischeamic attack, history of stroke, haemorrhagic stroke, chronic kidney disease diagnosed from lab results, history of chronic kidney failure listed in ICD 10, history of nephrotic syndrome coded in ICD 10 number of packages of HRT dispensed, number of anticoagulants dispensed, deprivation index score, and country of origin in Spanish) as listed in Table 2.

Statistical methods

PS matching

Due to the non-randomised nature of an observational study, the analysis may be subject to confounding such as that posed by baseline characteristics. Propensity score (PS) matching is used to match "comparable" patients from the control and treatment groups, such that matched patients are similar with respect to baseline characteristics. For each drug comparison (i.e. alendronate vs OBP; alendronate vs SERMs; and alendronate vs SR users) PS matching was performed in order to reduce the difference between baseline characteristics (as listed in Table 1 for CPRD and Table 2 for SIDIAP). PS matching was performed with *MatchIt* within the software package R (version 3.3.2) using the nearest neighbours matching algorithm, and a caliper width of 0.2[19] of the standard deviation of the logit of the PS[20] was used to restrict the search for matches within the caliper distance. A subject in the treatment group could be matched to up to 4 subjects in the control group, without replacement. For a given variable, the standardised mean difference (SMD) in the distribution of the variable for the control and treatment groups was used to assess if a good match had been obtained [20]. Control and treatment groups were considered to be well-matched with respect to a variable if the absolute SMD was < 0.1 after matching. Multivariable adjustment was performed for any confounders with a remaining SMD≥0.1 after PS matching.

Missing data

Prior to PS matching, missing information in variables included in the PS model was addressed using multiple imputation with chained equations methods. Assuming that data were missing at random, a series of 50 multiple imputations were performed to impute the missing values for those confounders that were found to have missingness (BMI, smoking, and

drinking status). Confounders, study exposure, time-to-event, and outcome status were included in the multiple imputation models, which also included pre-specified interactions. Multiple imputation by chained equations was performed with ICE library implemented in the Stata software (version 13).

Survival Analysis

The effect of AOD exposure on the risk of AMI was estimated by directly comparing the outcomes and follow-up times in the treatment and control groups in the matched sample in a survival model. The relative risk of AMI (denoted by sub-hazard ratio (SHR)) in the presence of a competing risk of death was estimated using the proportional hazards regression model described by Fine and Gray[21]using the *cpmrsk* package in R)[22]. The proportional assumption of the cox regression was checked. Cumulative incidence function curves (CIF) of the observed AMI risk over time were produced for the control and treatment groups in the matched sample.

Sub-Group Analyses

Treatment-variable interaction was investigated for the following variables as pre-specified per protocol: octogenarian (age 80 years), obesity (BMI>30), gender, previous glucocorticoid use, and previous fracture history. For this, a treatment–variable interaction term was included in the Fine and Gray model, in addition to the terms included in the primary survival analysis above. Stratified analyses for each sub-group are reported in Supplementary Table 1 (a) and (b) are described in the Discussion where the *p*-value for interaction is borderline or significant (p<0.1) in both CPRD and SIDIAP analyses, and/or the interaction is considered to be of clinical relevance.

Meta-analysis

Meta-analyses were performed to compare and combine results of the survival analysis for the CPRD and SIDIAP datasets. Results for the two datasets analysed individually and then pooled using fixed effects model in case of homogeneity and random effects model if a significant between-study heterogeneity was found. Heterogeneity was assessed using the I^2 test statistic and the χ^2 test (P < 0.01 indicated possible significance). This was performed using Review Manager (RevMan version 5.3; Cochrane, London, UK).

RESULTS

Study population

The cohort consisted of 163,949, and 156,917 patients included from the UK (CPRD) and Catalan (SIDIAP) populations, respectively (Figure 1). Propensity score (PS) matching was done as detailed in the corresponding flowcharts (Figure 1). Patients were followed-up for a median (interquartile range) of years 1.22 (1.83) and 4.82 (4.16) years in CPRD and SIDIAP, respectively. Baseline characteristics of alendronate and other AOD users were similar after propensity matching, with an absolute standardised mean difference (SMD) below 10% for almost all baseline characteristics, as shown in Tables 1 and 2 for CPRD and SIDIAP participants, respectively. However, when comparing each matched sample to one another, SERM users were younger than alendronate, OBP and SR users. We also found a lower prior type 2 diabetes, ischemic cardiopathy, cerebrovascular disease, and chronic kidney failure rate amongst SERM compared to the other AOD users within the CPRD, that was reflected in the SIDIAP. Within CPRD, SR users appeared to have an increased chronic kidney failure rate compared to OB and SERM users.

Outcomes

Alendronate vs SERM users. When analysing the rate of AMI for SERM users as compared to alendronate users in the CPRD database, we identified 0.85 and 1.05 cases of AMI per 100 person-years, respectively (Table 3). Within the SIDIAP, AMI rate per 100 person-years was 0.07 and 0.08 for alendronate and SERM users, respectively. The cumulative incidence of AMI comparing alendronate to SERM of an AMI is shown in S1 (a) for CPRD and (b) for SIDIAP.

After adjusting for the competing risk of mortality, no significant differences in the relative risk of AMI were found either in the CPRD nor in the SIDIAP datasets (SHR 1.21 [95%CI 0.89-1.65] and (SHR 1.05 [95%CI 0.70, 1.55] respectively).

Meta-analysis of the findings from both datasets did not demonstrate any AMI risk difference between alendronate and SERM users (SHR 1.15 [95%CI 0.90, 1.46]) as shown in Figure S3.

Alendronate vs strontium ranelate users. The incidence rate of AMI was 1.41 per 100 person-year in patients who received alendronate and 1.53 per 100 person-years in strontium ranelate users, within the CPRD dataset (Table 3). Patients registered in SIDIAP had an incidence rate of 0.15 per 100 patient-years for both alendronate users and strontium

ranelate users. The cumulative incidence of AMI comparing alendronate to SR of an AMI is shown in Figure S1 (c) and (d). Within the CPRD, AMI risk appeared to be lower but not significant (SHR 0.95 [95%CI 0.71, 1.26]) amongst SR compared to alendronate users, while no significant differences were found amongst patients in SIDIAP identified as SR and alendronate users (SHR 0.97 [95%CI 0.78, 1.20]) Table 3.

Meta-analyses of the results for CPRD and SIDIAP demonstrated no statistically significant difference in risk (SHR 0.82 [95%CI 0.58, 1.16]) as shown in Figure S4.

Alendronate vs other bisphosphonate users. The absolute incidence rate for AMI was 1.96 per 100 patient-years (alendronate users) and 2.86 per 100 patient-years (other bisphosphonate users) within the CPRD dataset (Table 3). In SIDIAP, the incidence rate was 0.17 per 100 patient-years for both alendronate and other bisphosphonate users. The cumulative incidence of AMI comparing alendronate to SR of an AMI is shown in Figure S1 (e) and (f).

When AMI rates in alendronate and other bisphosphonate users within the CPRD dataset were compared, an increased risk (SHR 1.10 [95%CI 1.03, 1.18]) amongst users of OBP was found. An increased risk was also found in SIDIAP (SHR 1.03 [95%CI 0.90, 1.18]) however it was not statistically significant.

Meta-analysing the datasets identified a 9% higher MI risk amongst OBP compared to alendronate users (SHR 1.09 [95%CI 1.02, 1.15]) as shown in Figure S5.

Analysis of Interactions

The only clinically relevant interaction which was consistent across the two datasets was with users of SERMs and previous history of cardiovascular risk factors (diabetes (p-value of significance of interaction = 0.001) and CKD (p-value for significance of interaction p<0.001)). Patients taking SERMs with a history of diabetes were at a greater risk of AMI compared to diabetic users of alendronate , with SHR of 3.69 [95%CI 1.26 -10.80] in CPRD, and 1.54 [0.75-3.15] in SIDIAP (Supplementary Table 1). Similarly, users of SERMs with a previous history of CKD had a significant increase in risk of AMI compared to alendronic acid users with a similar history, with SHR of 6.1 [1.37-27.20] in CPRD, and 2.4 [0.77-7.27] in SIDIAP. The meta-analysed results for these sub-groups is shown in Figure s2.

Sub-group Analysis

Stratified analysis by age showed no statistically significant differences in the risk of AMI between the age groups, in CPRD and SIDIAP (Table 4). In CPRD a reduced risk was seen with SERMS use in patients over 80 (0.59 (0.21 - 1.65)) as compared to those under 80 (1.33 (0.96 - 1.84)), but these risks were not statistically significant.

Similarly, in SIDIAP a reduced risk was seen with SR use in patients over 80 (0.75 (0.45 - 1.24)) as compared to those under 80 (1.03 (0.81 - 1.31)), but these risks were also not statistically significant.

Some differences in the risk of AMI for men and women were seen in both CPRD and SIDIAP, but these risks were not statistically significant (Table 5). SERMS were not included, as they are not indicated for men.

DISCUSSION

In this study, we report on the AMI risk of different AODs utilising "real world" data from the UK and Catalan primary care records. While alendronate appeared to be safer compared to OBP, with a 9% higher AMI risk amongst users of the latter, no significant MI risk difference was found amongst SR and SERM compared to alendronate users.

Differences in baseline risk are known and have been described previously [23] Differences in the incidence rates between CPRD and SIDIAP might be a manifestation of the Mediterranean paradox. Galbete et al., reviewed the evidence and found an inverse relationship between a higher adherence to the Mediterranean diets and reduction in AMI and stroke, amongst other chronic diseases [24]. A stratified analysis by age and gender shows this difference persists.

Studies have demonstrated a lower risk of myocardial infarction or stroke among bisphosphonate users compared to non-users[3, 25]. A retrospective review of medical records by Sing at al. found that alendronate reduced the number of incident MI (HR 0.55 95% CI 0.33-0.89 p=0.014)[26]. They suggested extra-mineral and skeletal effects documented such as reducing cholesterol synthesis via mevalonate pathway, similar to statins, in addition, inhibit vessel pathogenesis and a reduction inflammation[26]. Other beneficial anti-atherosclerotic effects of bisphosphonates have been documented in animal models [27] evidence in human subjects is still inconclusive. Some healthy user bias cannot be dismissed.

On the other hand, a nationwide cohort study in Denmark found an excess risk of AMI amongst users of alendronate, which was not replicated amongst etidronate users when compared to unexposed [28]. Lastly, recent meta-analysis and sequential trial analysis have failed to demonstrate any relation between bisphosphonates and incident MI [4, 5]. Our

findings provide further evidence regarding the AMI risk of oral bisphosphonates and corroborate that alendronate is a safe first-line treatment, as recommended in current NICE guidelines[2].

We found a similar AMI risk amongst alendronate compared to strontium ranelate users after meta-analyzing data from both primary care records, which appears to be consistent with the findings in other observational studies[8–11] . A nested case-control study exploring the cardiac safety of strontium ranelate in the UK CPRD found no association between current or past use of strontium ranelate compared to non-users (OR [95%CI] 1.0 [0.8-1.6]) [8]. In the same sense, a large prospective European 3-year follow-up cohort study aiming to assess the safety and acceptability of strontium ranelate in the management of osteoporosis did not report any association with cardiac events [11]. A population-based 6-year follow-up cohort study of a postmenopausal woman in Denmark also found no evidence of any significant association between use of strontium ranelate and acute coronary syndrome (HR [95%CI] 1.0 [0.5-2.0])[10].

However, recent concerns have been raised about a possible increase in cardiovascular risk associated with strontium ranelate use. A pooled analysis of SOTI and TROPOS trials showed a 62% (RR [95%CI] 1.6 [1.1-2.41) higher risk of AMI amongst strontium ranelate compared to placebo users, which led the European Medicines Agency to modify recommendations for its use, including a contradiction in patients with cardiovascular disease [29]. In this respect, Bolland MJ et al. recently concluded that the number of fractures prevented by strontium use was similar to the number of extra cases of venous thromboembolism, pulmonary embolism and myocardial infarction and suggested full disclosure of the strontium trial data to better characterise its risk/benefit profile [30] . Found cardiovascular risk factors and haemostatic parameters were not affected after 12 months of strontium ranelate treatment. The authors concluded, that this result indicates that myocardial infarction with strontium is mediated through a different mechanism[31]. Our study aims to provide further valuable and population-based evidence on this issue and has failed to demonstrate any significant association between strontium ranelate and AMI.

According to the literature, SERMs have not been shown to affect the risk of myocardial infarction [28, 32] which is consistent with our findings. Neither RUTH nor MORE trials have demonstrated any significant higher AMI risk amongst SERM compared to placebo users (RR [95%CI] 0.95 [0.8-1.1] and 0.9 [0.6-1.2] respectively)[13, 14]. Lastly, a nationwide retrospective cohort study in Denmark has also failed to demonstrate any excess risk of AMI amongst users of Raloxifene compared to the unexposed (HR [95%CI] 0.9 [0.5-1.7]) [14]. They found there was no difference in the incidence of AMI in patients with breast cancer (Raloxifene 183 (0.69%) placebo= 208 (0.8))[33].

In secondary analyses after stratification by pre-specified risk factors, SERMs use appeared associated with an excess risk of MI amongst subjects with a previous history of diabetes and/or CKD. Meta –analysis (Figure s2) demonstrates in both type 2 diabetes, and CKD alendronate is more favourable compared to SERMs. There is little evidence specifically addressing how SERMs may affect the risk of AMI in patients taking antiosteoporosis medication in patients with diabetes.

There are some limitations in this study. This study was observational in nature, and there was no randomization, which can result in confounding. Although some possible confounders (such as bone mineral density, physical activity and family history of ischemic cardiac events) are not recorded in CPRD, we have sought to minimise known confounding by using propensity score matching methods as much as possible with the available variables recorded in the two datasets. All attempts were known to eliminate known confounding where data on confounders were available, however the risk of residual confounding/ confounding by indication may remain despite the adjustments. In order to minimize any residual confounding all of the information available from the databases was used. Also, head-to-head comparisons of different available AODs offer the advantage of a high likelihood of patients in the study cohorts having osteoporosis. The decision of treating patients with strontium ranelate might have been based on a previous lack of effectiveness with alendronate, which would shift strontium ranelate towards a more fragile subgroup of patients. However, the alleged reduced risk of AMI amongst alendronate users (reference group) would have made any potential AMI increased risk within strontium ranelate or SERMs users become more visible. Some differences may be explained by the presence of variables which were available in one database and not the other, for example country of origin was present in SIDIAP and not in CPRD. Conversely marital status was present in CPRD and not in SIDIAP. Differences among higher risk of 10 mg dose of Alendronate versus 70 weekly mg dose reported by Pei-Yu Lu et al. were not evaluated since administration doses were not available [34].

The advantages of the present meta-analysis are both the large sample size and the extended duration of follow-up, which allow us to assess the AMI risk of the AODs as used by potentially all NHS patients in actual practice conditions. Moreover, the accuracy of both CPRD and SIDIAP datasets have been previously confirmed[35, 36], as well as their validity for cardiac events, including MI [37, 38]. Lastly, we used propensity score adjustment to accurately estimate

relative risks, which is currently recognised as the best analytical approach to reducing the effects of confounding by indication [39].

Conclusion

In this multi-country study, compared to alendronate we found a 9% increase in AMI with other bisphosphonates, a similar risk with strontium ranelate, and no difference in SERMS. We analysed the interactions between cardiovascular risk factors. Patients with history of Diabetes and CKD taking SERMs showed impact on the risk in both CPRD and SIDIAP compared to those without. Further head to Head RCTs would help to confirm these findings.

Declarations

Funding

This work was partially funded by a Project Grant from the National Osteoporosis Society. This work was 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). Andrew Judge was supported by the NIHR Biomedical Research Centre at the University Hospitals Bristol NHS Foundation Trust and the University of Bristol. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health. This study has been approved by the Independent Scientific Advisory Committee (ISAC, protocol number 14_110). This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone.

Role of funding source: The study funder had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. All authors had full access to all of the data in the study and take responsibility for the integrity of such data and the accuracy of the data analysis.

Authors' contributions

DPA, AJ, CC, TVS, NA, MKJ, BA conceived and planned the study. SK, DPA, SCL, SH extracted and/or prepared the data for the statistical analyses. SK, SH, SCL, MPM conducted the statistical analysis. SK, DPA, SH, SCL, AS, completed the interpretation of the results with contributions from all authors. SK, SCL, AS, DPA, MPM drafted of the manuscript, which was reviewed, commented and approved by all authors. The corresponding author attests that all listed authors meet authorship criteria and

Ethics approval (include appropriate approvals or waivers)

This study has been approved by the Independent Scientific Advisory Committee (ISAC, protocol number 14_110). Ethics approval was not required.

Consent to participate (include appropriate statements)

Not applicable

Consent for publication (include appropriate statements)

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COMPETING INTERESTS

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare Cyrus Cooper reports Personal fees from Alliance for Better Bone Health, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier, Takeda and UCB. Kassim Javaid reports Honoraria, unrestricted research grants, travel and/or subsistence expenses from: Amgen, Lilly UK, Shire, Internis, Consilient Health, Stirling

Anglia Pharmaceuticals, Mereo Biopharma, Optasia Medical, Zebra Medical Vision, Kyowa Kirin Hakin, UCB. Andrew Judge reports Consultancy fees, lecture fees and honoraria from Servier, UK Renal Registry, Oxford Craniofacial Unit, IDIAP Jordi Gol and Freshfields Bruckhaus Deringer, is a member of the Data Safety and Monitoring Board (which involved receipt of fees) from Anthera Pharmaceuticals, Inc., and received consortium research grants from Roche.Bo Abrahamsen reports Institutional research grants UCB and Novartis. Advisory board and consulting fees UCB.Daniel Prieto Alhambra reports DPA's institution received speaker fees from AMGEN and UCB Biopharma, consultancy fees from UCB Biopharma, research grants from UCB, Amgen and Les Laboratoires Servier, and financial support to organise educational activities from Janssen (on behalf of IMI-funded EHDEN and EMIF consortiums) and Synapse Management Partners.Sara Khalid, Sara Calderon-Larranaga, Marta Pineda-Moncusí, Arvind Sami, Samuel Hawley, Tjeerd P Van Staa declare that they have no conflict of interest.

DATA SHARING STATEMENT

The different data sources have provided the research team with data subject to different licenses, which do not allow sharing.

TRANSPARENCY STATEMENT

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

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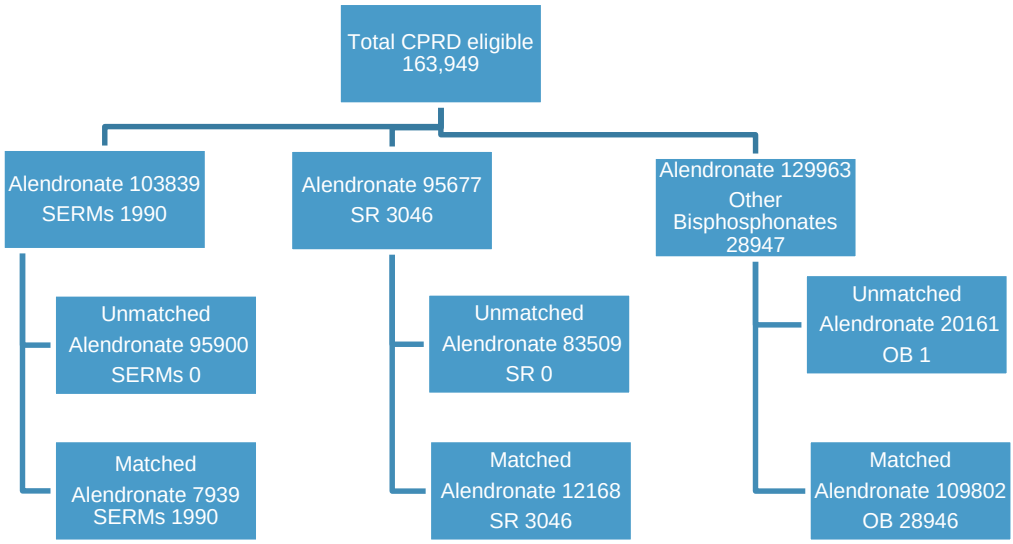
Tables And Figures

Figure 1 Recruitment of patients through the study within the (a) CPRD and (b) SIDIAP

(a)



(b)

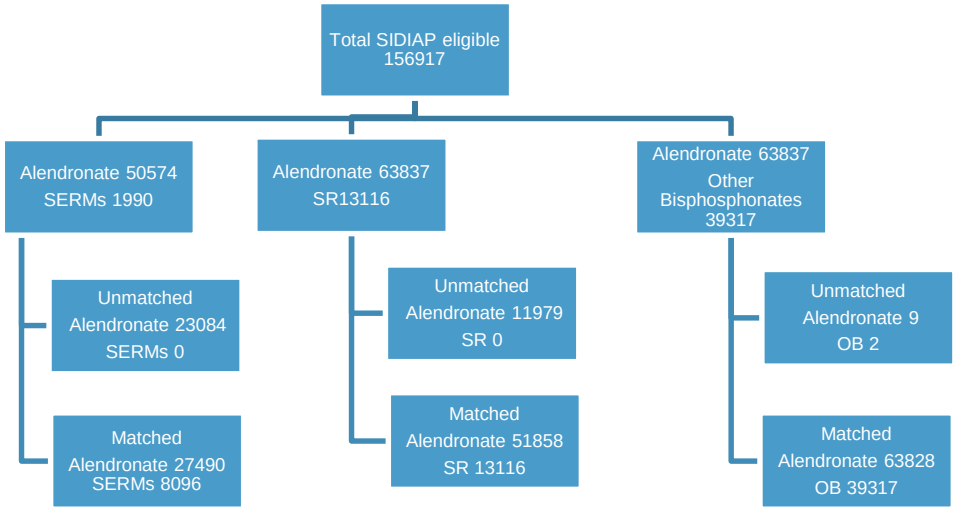


Table 1 Baseline Characteristics for the CPRD dataset after propensity score matching

	Alendronate	SERMs	SMD	Alendronate	SR	SMD	Alendronate	OBP	SMD ****
n	7939	1990		12180	3046		109802	28946	
Age (mean (sd))	65.3 (9.5)	64.7 (9.33)	0.07	78.9 (10.1)	79.3 (10.3)	0.04	73.2 (10.5)	73.3 (10.5)	0.01
Female n (%)	7939 (100%)	1990 (100%)	NA	10353 (85%)	2589 (85%)	0.01	89252 (81.3)	23711 (81.9)	0.02
*BMI (mean (sd))	25.7 (5.3)	25.7 (5.2)	0.01	24.2 (5.2)	24.1 (5.4)	0.01	25.4 (5.4)	25.4 (5.4)	0.01
**Smoking (%)			0.01			0.07			0.02
Never n (%)	4675 (58.9)	1167 (58.6)		7067 (58.0)	1761 (57.8)		58146 (53.0)	15543 (53.7)	
Current n (%)	2084 (26.3)	520 (26.1)		3709 (30.5)	937 (30.8)		35544 (32.4)	9219 (31.8)	
Ex n (%)	1177 (14.8)	303 (15.2)		1404 (11.5)	348 (11.4)		16112 (14.7)	4184 (14.5)	
***Drinker			0.02			0.01			0.029
No n (%)	1598 (20.1)	389 (19.5)		4700 (38.6)	1183 (38.8)		30062 (27.4)	8305 (28.7)	
Mild n (%)	232 (2.9)	59 (3.0)		606 (5.0)	157 (5.2)		4712 (4.3)	1218 (4.2)	
Heavy n (%)	6109 (76.9)	1542 (77.5)		6874 (56.4)	1706 (56.0)		75028 (68.3)	19423 (67.1)	
Charlson Co morbitiy Index (%)			0.04			0.01			0.03
Charlson Co morbitiy Index ==0 n (%)	6087 (76.7)	1546 (77.7)		5868 (48.2)	1477 (48.5)		60632 (55.2)	15651 (54.1)	
Charlson Co morbitiy Index ==1 n (%)	1022 (12.9)	259 (13.0)		2099 (17.2)	520 (17.1)		21133 (19.2)	5840 (20.2)	
Charlson Co morbitiy Index >=2 n (%)	830 (10.5)	185 (9.3)		4213 (34.6)	1049 (34.4)		28037 (25.5)	7455 (25.8)	
Hip Fracture n (%)	40 (0.5)	5 (0.3)	0.04	1488 (12.2)	393 (12.9)	0.02	3505 (3.2)	934 (3.2)	0.00
Non hip Fracture n (%)	66 (0.8)	13 (0.7)	0.02	451 (3.7)	109 (3.6)	0.01	2734 (2.5)	693 (2.4)	0.01
Type 2 Diabetes n (%)	246 (3.1)	45 (2.7)	0.02	1334 (11.0)	333 (10.9)	0.00	8066 (7.3)	2106 (7.3)	0.00
Corticosteroids n (%)	925 (11.7)	219 (11.0)	0.02	1894 (15.6)	467 (15.3)	0.01	34668 (31.6)	9293 (32.1)	0.01
Serum cholestrol (mean (sd))	5.56 (1.1)	5.57 (1.1)	0.00	5.1 (1.1)	5.2 (1.2)	0.01	5.3 (1.2)	2.3 (1.2)	0.00
Marital status = married n (%)	1547 (19.5)	380 (19.1)	0.01	1632 (13.4)	404 (13.3)	0.00	18456 (16.8)	4762 (16.5)	0.01
Ischeamic Heart Disease n (%)	638 (8.0)	162 (8.1)	0.00	2258 (18.5)	561 (18.4)	0.00	17849 (16.3)	5068 (17.5)	0.03
Cerebro Vascular disease n (%)	239 (3.0)	59 (3.0)	0.00	1604 (13.2)	412 (13.5)	0.01	9194 (8.4)	2516 (8.7)	0.01
Chronic Renal Failure (%)n (%)	145 (1.8)	24 (1.2)	0.05	2646 (21.7)	662 (21.7)	<0.00	8211 (7.5)	2023 (7.0)	0.02
EGFR (mean (sd))	0.31 (0.1)	0.31 (0.1)	0.02	0.28 (0.09)	0.28 (0.0)	0.00	0.30 (0.1)	0.29 (0.1)	0.09

*after imputing 45% missing data for BMI in CPRD

** after imputing for 22% missing data for smoking in CPRD

*** after imputing for 54% missing data for drinking in CPRD

Table 2 Baseline characters for SIDIAP after propensity score matching

	Alendronate	SERMs	SMD	Alendronate	SR	SMD	Alendronate	OBP	SMD
n	27484	8096		51858	13116		63828	39317	0.06
Age	63.3 (11.3)	61.9 (11.3)	0.19	69.2 (11.3)	69.04 (11.3)	0.01	69.6 (11.3)	69.00 (11.3)	0.06
Female n (%)	27484 (100%)	8096(100%)	NA	41815 (80.6)	10629 (81)	0.01	50567 (79.2)	29878 (76.0)	0.08
*BMI (mean (sd))	27.65 (5.0)	27.51 (4.8)	0.03	28.27 (4.9)	28.48 (5.0)	0.04	27.97 (4.9)	28.21 (4.9)	0.05
**Smoke n (%)			0.02			0.02			0.02
0	21760 (79.2)	6357 (78.5)		41096 (79.2)	10477 (79.9)		49009 (76.8)	30495 (77.6)	
1	2906 (10.6)	874 (10.8)		5969 (11.5)	1468 (11.2)		8641 (13.5)	5076 (12.9)	
2	2818 (10.8)	865 (10.7)		4793 (9.2)	1171 (8.9)		6178 (9.7)	3746 (9.5)	
***Alcohol n (%)	5978 (21.8)	1805 (22.3)	0.01	12659 (24.4)	3185 (24.3)	0	15626 (24.5)	10102 (25.7)	0.03
Carlson Morbidity Category n (%)						0.01			0.07
1	19944 (72.6)	6187 (76.4)		32319 (62.3)	8251 (62.9)		35885 (56.2)	23399 (59.5)	
2	4752 (17.3)	1258 (15.5)		11373 (21.9)	2858 (21.8)		14678 (23.0)	8746 (22.2)	
3	2788 (10.1)	651 (8.0)		816 (15.7)	2007 (15.3)		13265 (20.8)	7172 (18.2)	
Previous history of hip fracture n (%)	220 (0.8)	52 (0.6)	0.02	1654 (3.2)	418 (3.2)	<0.00	2093 (3.3)	833 (2.1)	0.07
Previous history of non-hip fracture n (%)	2249 (8.2)	533 (6.6)	0.06	6635 (12.8)	1642 (12.5)	0.01	8953 (14.0)	3952 (10.1)	0.12
Type 2 diabetes (%)	2003 (7.3)	511 (6.3)	0.04	6964 (13.4)	1768 (13.5)	0	8665 (13.6)	5349 (133.6)	0
Number of systemic glucocorticoids dispensed n (%)	1619 (5.9)	390 (4.8)	0.05	4327 (8.3)	1085 (8.3)	0	7876 (12.3)	167(11.9)	0.01
LDL Cholesterol (mean (sd)	136.49 (32.5)	136.94 (32.41)	0.01	130.70 (33.3)	130.86 (33.2)	0.01	129.52 (33.5)	130. 15 (334)	0.02
Ischaemic heart disease n (%)	353 (1.3)	85 (1.0)	0.02	1896 (3.7)	469 (3.6)	0	2800 (4.4)	1728 (4.4)	<0.00
Myocardial Infarction n (%)	90 (0.3)	22 (0.3)	0.01	697 (1.3)	168 (1.3)	0.01	1045 (1.6)	669 (1.7)	0.01
Temporary Ischaemic Stroke/Attack aka TIA n (%)	117 (0.4)	25 (0.3)	0.02	293 (0.6)	75 (0.6)	0	577 (0.9)	246 (0.6)	0.03
History of stroke n (%)	331 (1.2)	86 (1.1)	0.01	1405 (2.7)	352 (2.7)	0	2068 (3.2)	1123 (2.9)	0.02
Haemorrhagic stroke n (%)	48 (0.2)	13 (0.2)	0	96 (0.2)	22 (0.2)	0	141 (0.2)	89 (0.2)	0
Chronic kidney failure diagnosed from lab results n (%)	911 (3.3)	213 (2.6)	0.04	3343 (6.4)	848 (6.5)	0.01	4538 (7.1)	2486 (6.3)	0.03
History of chronic kidney failure (coded in ICD10 code/s) n (%)	441 (1.6)	107 (1.3)	0.02	1534 (3.0)	385 (2.9)	0	2454 (3.8)	1278 (3.3)	0.03
History of nephrotic syndrome (coded in ICD10 code/s) n (%)	8 (0.0)	1 (0.0)	0.01	19 (0.0)	5 (0.0)	0	27 (0.0)	24 (0.1)	0.01
Number of packages of HRT n (%)	2348 (8.5)	798 (9.9)	0.05	3240 (6.2)	918 (7.0)	0.03	3473 (5.4)	2366 (6.0)	0.03
Number of anticoagulants dispensed n (%)	429 (1.6)	106 (1.3)	0.02	2322 (4.5)	586 (4.5)	<0.00	3202 (5.0)	1873 (4.8)	0.01
Deprivation index score in quintiles n (%)						0.022			0.1
1	3723 (13.5)	1217 (15.0)		6106 (11.8)	1507 (11.5)		7825 (12.3)	5663 (14.4)	
2	5165 (18.8)	1626 (20.1)		9093 (17.5)	2275 (17.3)		11020 (17.3)	7083 (18.0)	
3	5332 (19.4)	1514 (18.7)		9943 (19.2)	2488 (19.0)		12491 (19.6)	7430 (18.9)	
4	4591 (16.7)	1298 (16.0)		9188 (17.7)	2329 (17.8)		11051 (17.3)	6188 (15.7)	
5	3549 (12.9)	1479 (18.3)		6690 (12.9)	1665 (12.7)		8959 (14.0)	4769 (12.1)	
6	5124 (18.6)	1479 (18.3)		10838 (20.9)	2852 (21.7)		12482 (19.6)	8184 (20.8)	
Country of origin==Spanish n (%)	27048 (98.4)	7989 (98.7)	0.02	51299 (98.9)	12983 (99.0)	0.01	62722 (98.3)	38911 (99.0)	0.06

*after imputing 26% missing data for BMI in SIDIAP

** after imputing 16% missing data for smoking in SIDIAP

*** after imputing 56% missing data for drinking in SIDIAP

Table 3: Incidence rate (IR) per 100 person-years (PY) and sub-hazard ratio (SHR) with 95% confidence interval (CI) for AMI risk in the propensity-matched population.

	CPRD		**SIDIAP**	
Drug	IR (100 PYs)	SHR [95% CI]	IR (100 PYs)	SHR [95% CI]
Alendronate	0.85	ref	0.07	ref
SERMs	1.05	1.21 (0.89-1.65)	0.08	1.05 (0.70-1.55)
Alendronate	1.41	ref	0.15	ref
Strontium ranelate	1.52	0.95 (0.72-1.26)	0.15	0.97 (0.78-1.20)
Alendronate	1.96	ref	0.17	ref
Other bisphosphonates	2.86	1.10 (1.03-1.18)	0.17	1.03 (0.90-1.18)

Table 4. Incidence Rates of AMI Stratified by Age

	CPRD				SIDIAP			
	Age>=80		**Age<80**		**Age>=80**		**Age<80**	
Treatment	IR (100 PYs)	SHR [95% CI]	IR (100 PYs)	SHR [95% CI]	IR (100 PYs)	SHR [95% CI]	IR (100 PYs)	SHR [95% CI]
Alendronate	2.39	ref	1.40	ref	0.33	ref	0.14	Ref
Other bisphosphonates	2.72	1.08 (0.97, 1.2)	1.69	1.11 (1.03 - 1.21)	0.29	0.94 (0.70 - 1.26)	0.15	1.07 (0.92 - 1.25)
Alendronate	2.23	Ref	1.42	Ref	0.30	ref	0.14	Ref
Strontium ranelate	1.73	0.66 (0.46 - 0.94)	1.30	0.76 (0.49 - 1.17)	0.22	0.75 (0.45 - 1.24)	0.14	1.03 (0.81 - 1.31)
Alendronate	1.85	Ref	0.74	Ref	0.23	Ref	0.06	Ref
SERMs	1.12	0.59 (0.21-1.65)	1.05	1.33 (0.96 - 1.84)	0.32	1.28 (0.45 - 3.61)	0.07	1.07 (0.70 1.65)

Table 5. Incidence Rates of AMI Stratified by Gender

	CPRD				SIDIAP			
	Men		**Women**		**Men**		**Women**	
Treatment	IR (100 PYs)	SHR [95% CI]	IR (100 PYs)	SHR [95% CI]	IR (100 PYs)	SHR [95% CI]	IR (100 PYs)	SHR [95% CI]
Alendronate	2.75	Ref	1.43	Ref	0.39	ref	0.11	Ref
Other bisphosphonates	3.17	1.08 (0.95 - 1.23)	1.73	1.11 (1.03- 1.20)	0.38	1.00 (0.83 - 1.22)	0.11	1.02 (0.84- 1.23)
Alendronate	2.34	Ref	1.39	Ref	0.35	Ref	0.11	Ref
Strontium ranelate	2.70	1.05 (0.60- 1.84)	1.32	0.84 (0.61 - 1.16)	0.41	1.2 (0.88 - 1.63)	0.09	0.85 (0.63- 1.15)
Alendronate	na	na	na	na	na	na	na	na
SERMs	na	na	na	na	na	na	na	na

Supplementary Figures and Tables

Figure S1 Cumulative Fracture Incidence comparing Alendronate v SERMs (a: CPRD, b: SIDIAP) Alendronate v Strontium Ranelate (c: CPRD, b: SIDIAP) and Alendronate v OBP (e: CPRD, f: SIDIAP).

(B)

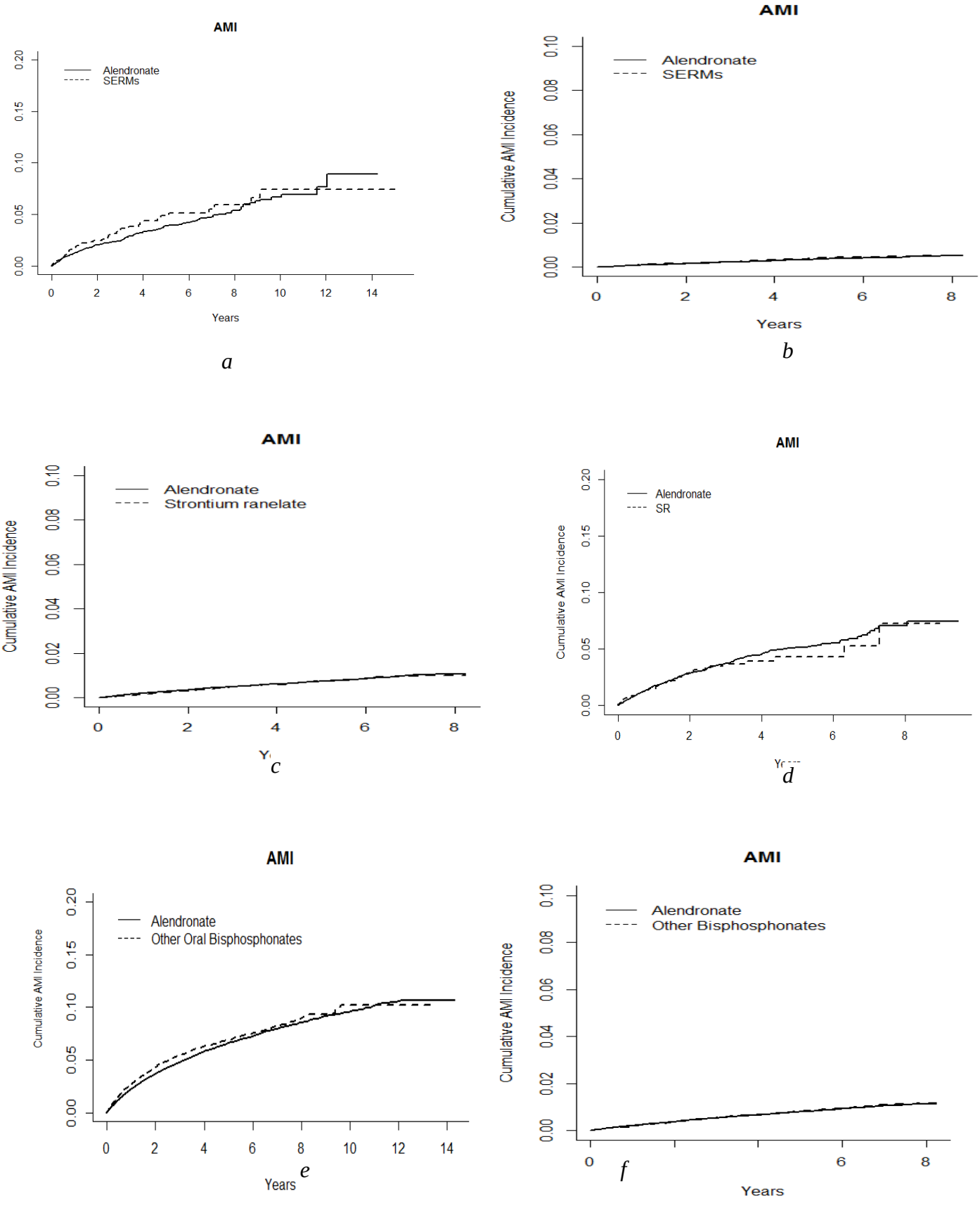
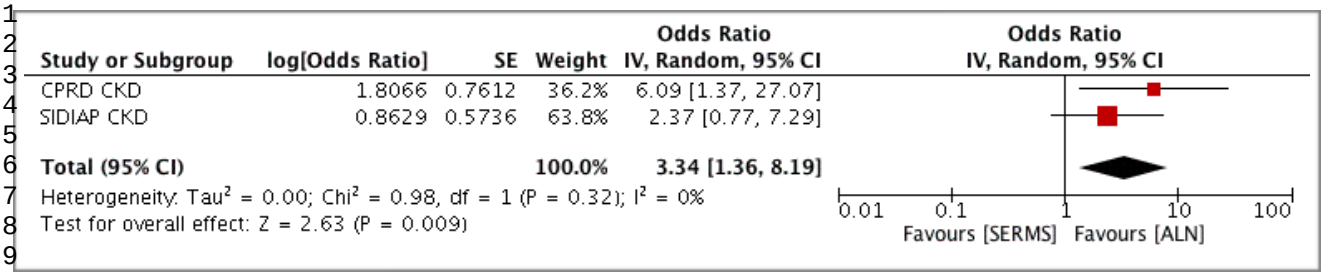


Figure s2 Stratified Forrest Plots for Meta analysis for a subgroup of patients with (a) CKD and with (b) DM



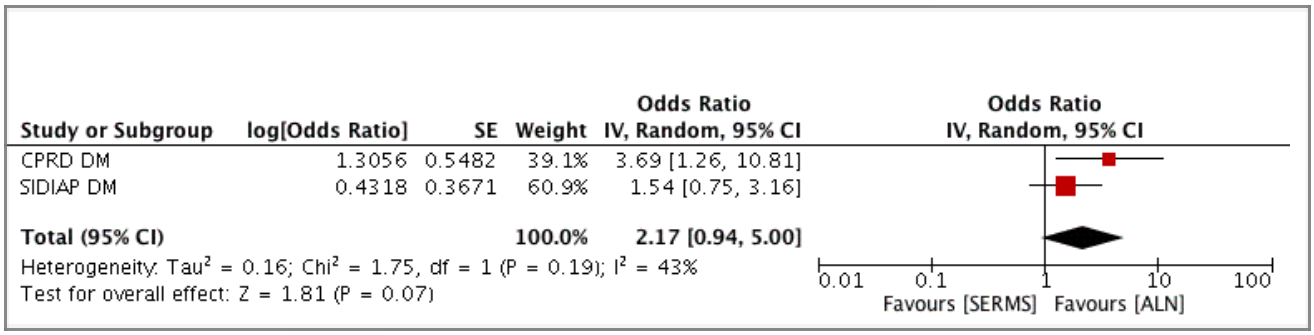


Table S1Comparison of interactions between CPRD (a)and SIDIAP (b)

CPRD (a)									
	Alen	OBP		Alen	SR		Alen	SERMs	
Interaction	IR	IR	SHR (95% CI)	IR	IR	SHR (95% CI)	IR	IR	SHR (95% CI)
Obese	1.50	1.86	1.13, 1.04-1.24	1.13	1.07	0.818, 0.521-1.28	0.86	0.94	1.1, 0.738-1.64
Not Obese	1.84	2.10	1.07, 0.971-1.18	1.92	2.08	0.903, 0.633-1.29	0.73	1.28	1.71 , 1.05 -2.79
Steroid User	2.25	2.59	1.07, 0.963-1.19	2.26	0.80	0.295, 0.108-0.802	1.17	1.86	1.57,0.773-3.17
Non Steroid User	1.41	1.71	1.12,1.03-1.22	1.73	1.64	0.779, 0.585-1.04	0.82	0.95	1.14,0.813-1.6
Previous Fracture	1.74	2.01	1.1,0.834-1.46	1.93	0.99	0.426, 0.186-0.977	0.41	3.42	6.58, 0.452 -95.9
No Previous Fracture	1.64	1.96	1.1, 1.03-1.18	1.78	1.63	0.759, 0.567-1.01	0.86	1.04	1.19, 0.873-1.62
Chronic Kid Fail	2.61	2.52	0.951,0.748-1.21	1.95	1.44	0.645, 0.337-1.23	1.34	7.36	6.09, 1.37-27.2
No Chronic Kid Fail	1.59	1.93	1.12, 1.04-1.2	1.28	1.55	1.06, 0.776-1.45	0.85	0.98	1.14, 0.829-1.57
Has diabetes	2.57	2.91	1.09,0.886-1.34	2.83	3.06	0.903, 0.477-1.71	1.05	3.91	3.69, 1.26-10.8
No Diabetes	1.58	1.89	1.1 , 1.03 -1.18	1.70	1.36	0.662, 0.488-0.897	0.85	0.96	1.11, 0.803-1.54
Has Dementia	1.42	1.20	0.873,0.458-1.66	1.22	0.87	0.686, 0.194-2.42	0.00	0.00	na
No Dementia	1.59	1.98	1.18, 1.1-1.26	1.53	1.59	0.928, 0.697-1.24	0.81	1.06	1.33, 0.968-1.81

SIDIAP (b)									
	Alen	OBP		Alen	SR		Alen	SERMs	
Interaction	IR	IR	SHR (95% CI)	IR	IR	SHR (95% CI)	IR	IR	SHR (95% CI)
Obese	0.19	0.15	0.792, 0.622-1.01	0.18	0.15	0.841, 0.588-1.2	0.12	0.09	0.808, 0.428-1.53
Not Obese	0.16	0.18	1.18, 0.998-1.39	0.14	0.15	1.05, 0.8-1.38	0.05	0.07	1.27, 0.758-2.11
Steroid User	0.22	0.24	1.14, 0.797-1.64	0.21	0.30	1.52, 0.841-2.75	0.04	0.10	2.39, 0.418-13.6
Non Steroid User	0.16	0.16	1.02, 0.878-1.18	0.15	0.13	0.908, 0.719-1.15	0.07	0.07	1.01, 0.668-1.51
Previous Fracture	0.19	0.21	1.2, 0.838-1.73	0.17	0.14	0.897, 0.489-1.65	0.06	0.16	2.45, 0.691-8.69
No Previous Fracture	0.16	0.16	1.01, 0.876-1.18	0.15	0.15	0.98, 0.777-1.24	0.07	0.07	0.966, 0.635-1.47
Chronic Kid Fail	0.34	0.30	0.922, 0.634-1.34	0.29	0.25	0.881, 0.469-1.65	0.16	0.39	2.37, 0.422-0.772
No Chronic Kid Fail	0.15	0.16	1.06, 0.913-1.2	0.15	0.14	0.978, 0.777-1.23	0.07	0.07	0.956, 0.624-1.47
Has diabetes	0.38	0.40	1.1, 0.857-1.42	0.37	0.34	0.936, 0.626 -1.4	0.27	0.41	1.54, 0.752-3.15
No Diabetes	0.14	0.13	1.01, 0.856-1.18	0.12	0.12	0.981, 0.759-1.27	0.06	0.05	0.927, 0.574-1.5
Has Dementia	0.32	0.27	0.887, 0.398-1.97	0.11	0.42	3.24, 0.242-43.3	0.32	0.28	0.951, 0.271-3.34
No Dementia	0.16	0.17	1.04, 0.905-1.19	0.07	0.07	1.04, 0.694-1.55	0.15	0.14	0.977, 0.784-1.22

Figure S3: AMI relative risk (SHR) amongst SERM users compared to alendronate users, after meta-analyzing data from CPRD and SIDIAP datasets

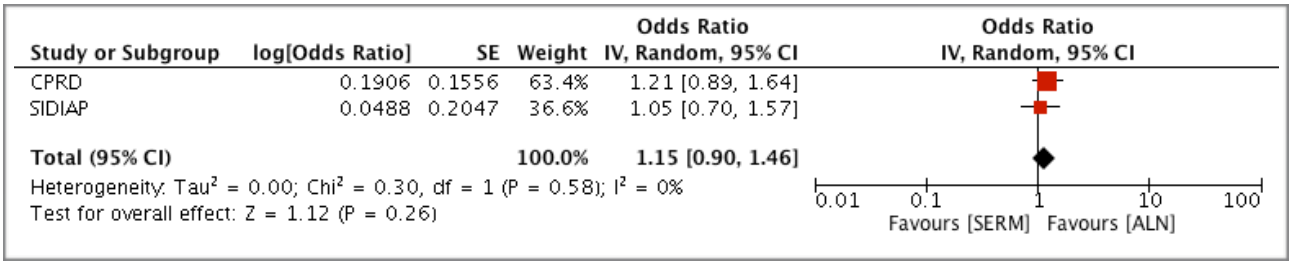


Figure S4: AMI relative risk (SHR) amongst strontium ranelate users compared to alendronate users, after meta-analyzing data from CPRD and SIDIAP datasets.

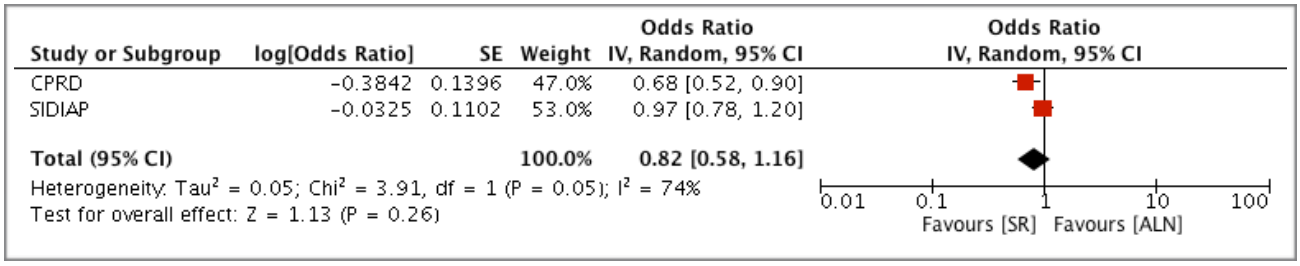
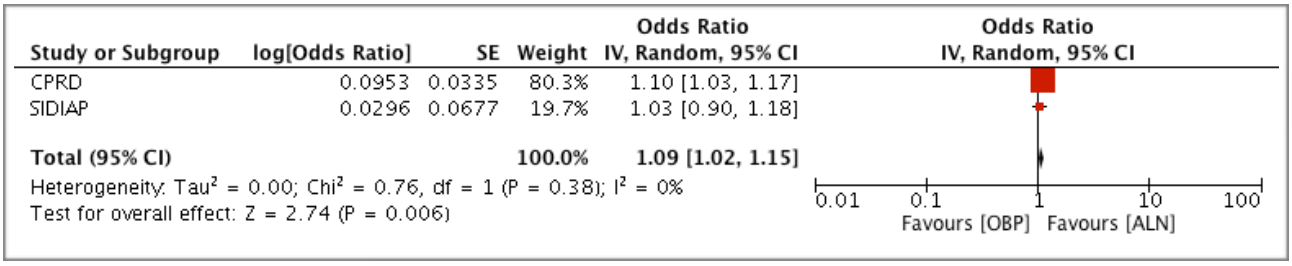


Figure S5: AMI relative risk (SHR) amongst other bisphosphonate users compared to alendronate users, after meta-analyzing data from CPRD and SIDIAP datasets



Authors comment:

We would like to thank and acknowledge the work and understanding that the journal, especially the editor John Richard Arrienda, have had with us in extending the period of revision during this uncertain period. We would like to extraordinary request the inclusion of a new co-author, *Marta Pineda-Moncusi*, who has conducted the extra analysis to satisfy reviewers comments, revised manuscript, and contributed to the discussion (which makes it substantial contribution enough to meet ICMJE authorship criteria)

We would also like to thank the reviewers' effort in evaluating our manuscript and appreciate their contribution, which has improved the quality of our work.

Reviewer #1: This is a potentially interesting study using 2 large population databases. However, the statistical analyses are rather messy and unclear, many mistakes in the analysis.

Major comments:

1. Most important, osteoporosis diagnosis or BMD was not included in the propensity score. Potential confounding by indication, especially when SERM is not indicated for those people with very low BMD.

Thank you very much for pointing out this important consideration. Definition of osteoporotic population by including only osteoporosis (OP) diagnosis and values of BMD is generally insufficient in real-world data since OP is diagnosed at hospitals and OP tag/BMD values can be miss at primary care databases. Thus, use of anti-osteoporotic medication is a common proxy to detect OP population: e.g., *Pineda-Moncusí M, et a. 2020 Increased Fracture Risk in Women Treated With Aromatase Inhibitors Versus Tamoxifen: Beneficial Effect of Bisphosphonates.* or *Khalid et al.2021 Predicting Imminent Fractures in Patients With a Recent Fracture or Starting Oral Bisphosphonate Therapy: Development and International Validation of Prognostic Models*).

Moreover, we aimed to compare the safety of AOD not exclusively to population diagnosed with OP, but to other users, such as osteopenic population that qualifies to be treated with AOD.

Finally, we would like to acknowledge the lack of BMD data as one of the limitations of this study. All attempts were known to eliminate known confounding where data on confounders were available, however the risk of residual confounding/ confounding by indication may remain despite the adjustments. We have included it in the limitations of the study.

2. Another important factor was not included, year of index date. Strontium was progressively not used due to potential cardiac event, thus the difference could be

driven by the index year. Nevertheless, year of study was not well described, please clarify.

Thank you for the comment. The study periods were included in the abstract but not to the main manuscript text. Those were 1995-2014 in CPRD and 2006-2014 in SIDIAP. We have included this information in the section *Participants and Variables* section from *Methods*.

We decided to analyse data up to 2014 since that was the year that the European Medicines Agency's Pharmacovigilance Risk Assessment Committee warned not to use it. Specifically, this warning message was announced the 1st of October of 2014.

3. For confounders, I am not familiar with SIDIAP, but CPRD should have a wealth of data, more relevant variables should be used to generate propensity score.

We agree with the reviewers that both databases contain a wealth of patient characteristics that can be considered as confounders. The included confounders in the study were decided by a common effort of clinical bone and joint specialist experts and epidemiologists from our group, based on the literature and routine clinical practice. We hope that the expertise, robust methodology, and the consistency of the results across the two datasets validate the obtained results, which were well-matched.

4. Not sure why Charlson comorbidity index and related variables were all included in the PS generation?! Charlson comorbidity index includes several variables that used to generate PS as well. Please clarify

Thank you for this observation. Charlson comorbidity index is a complex indicator (i.e., it tells us the number of concomitant comorbidities/chronic conditions that patients have simultaneously). Patients with higher complexity have higher risk of events. By adding Charlson to the PS adjustment, we are ensuring that patient's complexity will not affect our study outcome, which is independent of the increased risk of AMI events driven by the specific comorbidities included in the adjustment.

Minor comments:

1. Variables: Chronic renal failure and eGFR should be highly correlated, potential collinearity, please also check other related variables

We agree with the reviewers that CRF and EGFR are indeed highly correlated as CRF is derived from EGFR. However, as CRF was coded as a binary variable, it was decided to retain EGFR (since it was available as a continuous variable) in the propensity score matching, to ensure the matched samples were as well matched as possible with all available confounders. Whereas collinearity is an important consideration for e.g., risk prediction modelling, here it was not a concern.

2. P.5 line 55, previous hip fracture.... type 2 diabetes.,, and hip fractures? please clarify.

Thank you for the comment. It was a typing error from the track changes. We have replaced it for the following sentence: "were age, gender, body mass index (BMI), smoking, drinking,

Charlson morbidity index, previous hip fracture, previous non hip fracture, and type 2 diabetes".

3. for imputation, how accurate is the imputation?

Multiple imputation is a commonly used strategy to avoid reduction of sample size or the elimination of the incomplete variable in large datasets. It is based in the prediction of the missing values from the known values of the incomplete variable and from its correlation to the rest of the data set variables (i.e., missing values are replaced by imputed values, obtained from their predictive distribution based on the observed data — Bayesian approach).

The validity of results depends on its correct application. For instance, missing data might be normally distributed and initial percentage of missing data should ideally be lower than 80% (our maximum percentage of missing data is 56%).

To avoid a potential bias of single imputation results, this process is repeated several times (in our case we imputed each missing value of the dataset 50 times). Then, the average number of each imputed number is calculated using the Rubin's rules (*Rubin D. Multiple imputation for nonresponse in surveys. New York: Wiley, 1987*), which take account of the variability in results between the imputed datasets, reflecting the uncertainty associated with the missing values.

We had into account all the key issues before starting the imputation. We have included the number of imputations performed.

"… a series of 50 multiple imputations were performed to impute the missing values for those confounders that were found to have missingness …"

4. For subgroup analysis, please justify the choice of subgroup, e.g. why age of 80?

Thank you for this observation. We decided to analyse the octogenarian population to confirm that there were no differences in the results regarding the most elderly population (i.e., that could be related to end-of-life characteristics).

5. did you check the proportional assumption of the cox regression?

Thank you so much for the comment. The proportional assumption of the cox regression was checked. We have included in the methods.

6. When is the index date?

We appreciate the reviewer's comment. Index date is the date of the first AOD prescription/dispensation. It has been clarified in methods:

"Index date was defined as date of first AOD prescription in CPRD and first AOD dispensation in SIDIAP."

7. Two important papers from Ian Reid on this topic (one in NEJM and one in JBMR) were not mentioned at all, it should be cited and discussed in this study.

Following to the reviewer's advice, we found the following articles from Ian Reid that might be the ones suggested:

- Fracture Prevention with Zoledronate in Older Women with Osteopenia – NEJM 2018
- Effects of Zoledronate on Cancer, Cardiac Events, and Mortality in Osteopenic Older Women – JBMR 2019.

First article (NEJM 2018) compares Zolendronate vs Placebo and mentions in the discussion that some studies support the possibility that bisphosphonates reduce the risk of vascular disease and MI risk compared to placebo but doesn't include any information about differences across anti-osteoporotic treatments. In the same line, second article (JBMR 2019) evaluates Zolendronate vs Placebo.

If we had mistaken the election of articles, we would appreciate very much if the reviewer can send us further details such as year and/or doi.

Reviewer #2:

The aim of this study was to evaluate the risk of acute myocardial infarction in patients taking osteoporosis drugs.

Patients were taken from the SIDIAP or CPRD database and were matched using propensity scores.

The authors concluded that:

an 10% increased risk of acute myocardial infarction was found in users of other bisphosphonates as compared to alendronate users within CPRD.

Meta-analysis of CPRD and SIDIAP results showed a 9% increased risk in users of other bisphosphonate as compared to alendronate users.

Sensitivity analysis showed SERMS users with diabetes and chronic kidney disease were at an elevated risk.

My comments:

In paper published in Clin Ther. 2011 Sep;33(9):1173-9 entitled Alendronate and Raloxifene Use Related to Cardiovascular Diseases: Differentiation by Different Dosing Regimens of Alendronate by Pei-Yu Lu et al, the authors concluded that Alendronate 10 mg was associated with a higher risk of cardiovascular disease than alendronate 70 mg.

In your work there are difference among 10 daily and 70 weekly mg of dose of alendronate administration?

Thank you so much for this observation. Unfortunately, data on dose administration were not available and we cannot distinguish between them. We have included it in the limitations:

"Differences among higher risk of 10 mg dose of Alendronate versus 70 weekly mg dose reported by Pei-Yu Lu et al. were not evaluated since administration doses were not available [34]."

Pag 5, line 30

The authors reported: "The OBP included in this study, were risedronate and ibandronate, as these were most commonly used in both countries.

what are the other oral bisphosphonates?

We appreciate so much the reviewer's comment. The most used oral bisphosphonate in both countries is alendronate, reason why we decided to use it as the comparison treatment. The following most frequent - other oral bisphosphonates, OBP - are risedronate and ibandronate. We have clarified this sentence as following:

"The OBP included in this study were risedronate and ibandronate, as these were most commonly used in both countries after alendronate".

pag 5 line 55

delete hip fractures after type 2 diabetes because it is reported two time.

Thank you for the comment. It was a typing error from the track changes. We have amended the sentence.

Table S2 Number of events (N) for each outcome, and median (IQR) follow-up duration for CPRD

	Outcome		
	Censored	Death	AMI
Alend (N)	7412	367	188
Alend follow-up (days)	531 (1326)	680 (1257)	469 (1081)
Serms (N)	1872	69	51
Serms follow-up (days)	345 (1169)	916 (1390)	376 (919)
Alend (N)	9972	1808	394 (3.23%)
Alend follow-up (days)	451 (964)	439 (829)	393 (686)
SR (N)	2588	401	57 (1.87%)
SR follow-up (days)	195 (485)	242 (578)	229 (537)
Alend (N)	93776	11960	4066
Alend follow-up (days)	466 (1059)	513 (984)	400 (791)
OBP (N)	24688	3142	1116
OBP follow-up (days)	427 (932)	481 (892)	293 (591)

Table S3 Number of events (N) for each outcome, and median (IQR) follow-up duration for SIDIAP

	Outcome		
	Censored	Death	AMI
Alend (N)	33997	2012	249
Alend follow-up (days)	2094 (1340)	958 (1092)	852 (1191)
Serms (N)	9927	614	78
Serms follow-up (days)	2459 (1157)	1000 (1157)	995 (1137)
Alend (N)	39575	4557	362
Alend follow-up (days)	2247 (1036)	908 (1058)	841 (1184)
SR (N)	11316	1362	105
SR follow-up (days)	2398 (1004)	1000 (1094)	953 (1134)
Alend (N)	56878	6469	480
Alend follow-up (days)	1974 (1431)	849 (1044)	790 (1138)
OBP (N)	34248	4704	365
OBP follow-up (days)	2367 (790)	960 (1063)	973 (1155)

To the Osteoporosis International Journal editor,

November 4th, 2021

We would like to thank and acknowledge the work and understanding that the journal, especially the editor John Richard Arrienda, have had with us in extending the period of revision during this uncertain period.

In other to answer the reviewers, we had to conduct some additional analyses. Thus, we would like to extraordinary request the inclusion of a new co-author, *Marta Pineda-Moncusi*, who has conducted the extra analysis to satisfy reviewers comments, revised manuscript, and contributed to the discussion (which makes it substantial contribution enough to meet ICMJE authorship criteria).

Yours faithfully,

Sara Khalid