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TITLE: Incidence and predictors of multiple fractures despite high adherence to oral bisphosphonates: a binational population-based cohort study

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Supplemental data have been included with the submission

ABSTRACT

Oral bisphosphonates (BPs) are highly effective in preventing fractures and are recommended first-line therapies for patients with osteoporosis. We identified the incidence and predictors of treatment failure to oral BP therapy, defined as the incidence of ≥2 fractures while on treatment (≥2 FWOT) among users with high adherence. Fractures were considered after six months from treatment initiation and up to six months after discontinuation. Data from computerized records and pharmacy invoices were obtained from Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària (SIDIAP) (Catalonia, Spain) and Danish Health Registries (Denmark) for all incident users of oral BPs in 2006-2007 and 2000-2001 respectively. Fine and Gray survival models using backward-stepwise selection (p-entry 0.049; p-exit 0.10) and accounting for the competing risk of therapy cessation were used to identify predictors of ≥2 FWOT among patients having persisted with treatment ≥6months with overall medication possession ratio (MPR) ≥80%. Incidence of ≥2 FWOT was 2.4 (95% Confidence Interval (CI): 1.8-3.2) and 1.7 (95% CI: 1.2-2.2) per 1000 Person Years (PYs) within Catalonia and Denmark respectively. Older age was predictive of ≥2FWOT in both Catalonian and Danish cohorts: subhazard ratio (SHR)=2.28 (95% CI: 1.11-4.68) and SHR=2.61 (95% CI: 0.98-6.95) respectively for 65 to <80 years and SHR=3.19 (95% CI: 1.33-7.69) and SHR=4.88 (95% CI: 1.74-13.7) respectively for ≥80 years. Further significant predictors of ≥2 FWOT identified within only one cohort were dementia, SHR=4.46 (95% CI: 1.02-19.4) (SIDIAP) and history of recent or older fracture, SHR=3.40 (95% CI: 1.50-7.68) and SHR=2.08 (95% CI: 1.04-4.15) respectively (Denmark). Even among highly adherent users of oral BP therapy, a minority sustain multiple fractures while on treatment. Older age was predictive of increased risk within both study populations, as was history of recent/old fracture and dementia within one but not

both populations. Additional and/or alternative strategies should be investigated for these patients.

INTRODUCTION

A number of guidelines propose oral bisphosphonates (BPs) as first-line therapies for the prevention of fragility fractures in osteoporotic patients [1], and data from clinical trials suggest they can reduce the risk of fracture by up to 50% [2-4]. Such a large reduction in fracture risk is only achieved in patients persisting with treatment over several years [3], although 12 months has previously been considered sufficient time for BPs to reach efficacy [5] and significant benefits have been reported as early as 6 months after treatment initiation [6]. However in actual practice relatively few patients starting oral BP therapy persist for an adequate length of time, with up to half of patients discontinuing treatment in the first 3-6 months [7] who hence remain at increased risk of fracture [8].

Furthermore, it has been shown in strictly controlled conditions such as randomized controlled trial (RCT) settings that even patients with high adherence to BPs may sustain fractures while on treatment [3, 4, 9, 10]. Indeed, no biological agent prescribed with the goal of fracture prevention can be expected to eliminate the risk of subsequent fracture completely. This makes it difficult to disentangle the individual roles of non-adherence and inadequate response in the incidence of new fractures among users of BPs. This is especially true for observational studies where data on anti-osteoporosis medications is usually scarce and often self-reported.

Subsequently, the issue of defining and characterising inadequate response to osteoporosis therapy has become increasingly topical in recent literature [5, 11-15]. Inadequate response has previously been defined as the occurrence of an incident fragility fracture despite having been on oral BP therapy for a minimum of 12 months [5]. Such a definition was similarly used by investigators of the Observational Study of Severe Osteoporosis (OSSO) in their evaluation of health-related quality of life among inadequate responders to anti-resorptive medications [16]. Other methods to assess response to osteoporosis treatment include a decrease in bone mineral density (BMD) greater than the least significant change (LSC) or insufficient improvement in biochemical markers of bone turnover, e.g. a decrease in βCTX and PINP in response to anti-resporptives that is less than the LSC [11].

A recent IOF consensus paper [11] has likewise provided pragmatic criteria for defining treatment failure in osteoporosis. Its authors recommend that ≥2 fragility fractures while on anti-resorptive drugs be considered indicative of treatment failure. The provided rationale was that data from clinical trials show risk of second or third fracture is reduced by 80-90% for treated vs. placebo and that fracture risk after an index fracture wanes over time.

Despite the expectation that not all oral BP users will remain fracture free and that treatment failure can be inferred from the incidence of ≥2 fractures while on treatment (≥2 FWOT), data on the incidence and predictors of such occurrences in the general population are scarce. Treatment failure among bisphosphonate users has consequences both for the patient who remains at increased risk of fracture, and for healthcare providers as this phenomenon reduces cost-efficacy of treatment [17]. This is particularly relevant given the estimated 23% increase in osteoporosis prevalence

(as defined using the WHO diagnostic criteria) within Europe from 2010-2025 [18]. It would be of expected benefit therefore to be able to identify which patients are most at risk of multiple fractures while adhering to treatment so that suitable alterations to either a proposed or an existing treatment regimen may be considered.

The primary objective of the present analysis was to identify the key predictors of ≥2 FWOT during oral BP therapy in order to further elucidate the mechanisms of treatment failure among users remaining on therapy with high adherence (at least 6 months persistence with overall medication possession ratio (MPR) ≥80%).

MATERIALS AND METHODS

Study population and source of data

Sources of data used were The Danish Health Registries and Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària (SIDIAP) database. These have both been described in detail elsewhere [19, 20], and will therefore only be described briefly here. Danish data incorporates The National Prescriptions Database containing all filled prescriptions in the country since 1995, The National Hospital Discharge Register and National Cause of Death Register. SIDIAP covers a population of about 5 million patients (80% of the total population of Catalonia, Spain) and comprises the clinical and referral events registered by primary care health professionals (GPs and nurses) and administrative staff, demographic information, prescription and corresponding pharmacy invoicing data, specialist referrals, primary care laboratory test results, hospital admissions, and their major outcomes [21].

Both the Danish Health Registries and SIDIAP were searched to identify all incident users of oral BPs (excluding high-dose oral BPs) for the period January 1st 2000 to

December 31st 2001 and January 1st 2006 to December 31st 2007 respectively with no BP prescription in the previous 12 months. Eligible participants aged below 40 years, those with a diagnosis of Paget disease and previous users of any antiosteoporosis drug (except calcium or vitamin D supplements) in the year prior to the first prescription of oral BPs were excluded. Users of intravenous bisphosphonates were not included due to limitations in accurately tracking this form of treatment using prescription data. Only users with a minimum of 6 months treatment persistence and high refill compliance (MPR ≥80%) were included in the main analysis. MPR is calculated as the proportion of days covered with therapy between the first and the last prescription of BPs (total number of defined daily doses [DDDs] purchased divided by the number of days between the first day of the first prescription and last day of the last prescription).

Outcome: Ascertainment of ≥2FWOT

Osteoporotic fractures (of any site except fingers, toes and skull/face) were identified in Danish and SIDIAP data using ICD codes for the period 2000-2008 and 2006-2011 respectively (the list of codes used is provided in Supplementary Table 1). Fractures were included if they occurred after 6 months from starting therapy, so as to account for the delayed effects of BPs on bone, and before the end of study follow-up if remaining on treatment, or before a 6 month 'wash-out' after treatment discontinuation (given the known carry-over effect of BPs on bone metabolism). Treatment discontinuation was defined as last date for which medication was available on the last prescription before a 6-month refill gap in medication. Only fractures sustained on a date with no other incident fracture were considered, the rationale being to avoid inclusion of fractures arising from the same/high trauma event. Second fractures sustained at the same site as the first were only counted if

occurring after the elapse of six months in order to reduce the inclusion of readmissions/duplicate coding.

Potential predictors of ≥2 FWOT

Potential risk factors of ≥2 FWOT were assessed at the time of first oral BP prescription and defined a priori based on previous literature. These included the following: age (<65 years, 65 to <80 years, ≥80 years), gender, history of previous osteoporotic fracture (none, old fracture (≥6 months before starting oral therapy), recent fracture (<6months before starting therapy)), concomitant medications (proton pump inhibitors (PPI), oral corticosteroids (equivalent to prednisolone 5 mg daily for three month or more) and hormone replacement therapy (HRT)) and clinical diagnosis of pre-existing comorbid conditions (inflammatory arthritis, a neurological condition (stroke, Parkinson's disease or multiple sclerosis), and dementia). Body mass index (BMI) (<25, 25-35 and ≥35 kg/m^2) and smoking status (current, Ex- and non-smoker) were included for the SIDIAP analysis only as these variables was unavailable for Denmark.

STASTICAL ANALYSIS

Independent risk factors of time to second fracture while on oral BP treatment were identified for users within Danish Health Registries and SIDIAP database using multivariable Fine and Gray survival regression models to take into account the competing risk of treatment discontinuation [22]. The two study populations were analysed separately and all potential predictors (as described above) were assessed in univariate models and using backward-stepwise selection, whereby a parsimonious multivariable model was identified from the full model using cut-offs of p-entry 0.049 and p-exit 0.10. Index date for these models was six months after treatment initiation

and only fractures sustained during continued persistence to treatment, or up to six months after discontinuation were considered. Patients were censored at date of death or end of follow-up. Therapy discontinuation was entered into these models as a competing risk given that cessation, by definition, precluded future 'while on treatment' events. Models were also run stratified by gender. STATA v13 was used for all statistical analyses, under permit 702538 from Statistics Denmark for analysis of Danish Health Registries data.

Sensitivity analyses

Two sensitivity analyses of predictors of ≥2 FWOT were carried out, one in which fractures were included if occurring on the same date as other fractures and another where a 12 month instead of 6 month period was used to allow for time to drug efficacy.

Additionally, an analysis of all eligible oral BP users was used (Figure 1) to investigate treatment failure as defined by ≥2 fractures from at least 6 months after treatment initiation and during continued follow up, irrespective of persistence or re-fill compliance (in an intention-to-treat (ITT)-like approach). This alternative approach addressed the broader public health context of treatment failure, incorporating both aspects of failure of drug and failure of adherence in the process of treatment not achieving the goal for which it was prescribed, i.e. fracture prevention. Standard multivariable Cox regression methods were used to identify independent predictors using backward-stepwise selection as used for the main analysis.

RESULTS

The total number of treatment-naïve patients who started oral BP therapy was 14,815 within DHR and 22,355 within SIDIAP during the two years of recruitment into each study cohort. 13,949 (Denmark) and 21,385 (SIDIAP) patients were remaining who met the inclusion criteria (Figure 1). Of these, 7,885 (56.5%) and 7,449 (34.8%) respectively persisted for a minimum of 6 months with an overall high MPR of ≥80% and were thus included in the main analysis (Figure 1). Baseline characteristics among these users and for all eligible treatment naïve oral BP users, irrespective of adherence are included in Table 1.

Mean follow-up "on treatment" was 3.5 years within Denmark and 2.8 years within Catalonia, for a total of 27,870 and 20,598 patient-years (PYs) respectively. Occurrence of ≥2 FWOT was 46 (0.6%) for Denmark and 50 (0.7%) for SIDIAP, corresponding to an unadjusted incidence rate within Danish Health Registries of 1.7/1,000 person years (95% confidence interval [CI]: 1.2-2.2) and within SIDIAP of 2.4/1,000 person years (95% CI: 1.8-3.2). Cumulative incidence function plots are displayed in Figure 2. The majority of the fractures captured were clinical/symptomatic fractures; of the incident second fractures while on treatment, 43 (93%) and 41 (88%) were non-vertebral within Danish Health Registries and SIDIAP respectively, reflecting the general under-reporting of vertebral fractures outside clinical trial settings. Rates remained unchanged in sensitivity analyses using a 12-month lag for time to treatment effect (data not shown), but were higher when same date fracture were included: 2.7/1000 PYs (95% CI: 2.1-3.3) (Denmark) and 3.3/1000 PYs (95% CI: 2.6-4.1) (SIDIAP).

For SIDIAP the incidence rate of second fracture among all incident oral BP users, irrespective of adherence was 2.5/1,000 PYs (95% CI: 2.2-2.9). Within Denmark this rate was 14.2/1,000 PYs (95% CI: 13.4-15.1) (Table 2).

Older age (65 to <80 years and ≥80 years) was identified as an independent predictor of ≥2 FWOT within both Danish and SIDIAP 'on treatment' cohorts (Table 3). Further independent predictors of ≥2 FWOT were previous diagnosis of dementia in SIDIAP (but not Denmark) and history of recent or older fracture in Denmark (but not in SIDIAP) (Table 3). Cumulative incidence function plots stratified by these predictors are provided (Figures 3-5).

When fractures occurring on the same days with other fractures were included as a sensitivity analysis, history of recent fracture became predictive of ≥2 FWOT within SIDIAP (sub-hazard ratio (SHR)=2.10 (95% CI: 1.05-4.20)) (Supplementary Table 2). Likewise within Denmark, dementia became a significant risk factor of ≥2 FWOT (SHR=4.30 (95% CI: 1.47-12.60)) although it no longer did within SIDIAP (Supplementary Table 2). Independent predictors from the main analysis remained unchanged when a 12-month period was used for delayed treatment effect; with the exception that dementia was no longer a significant risk factor within the SIDIAP cohort (Supplementary Table 3).

In the analysis of all incident users, irrespective of adherence, several significant predictors were identified in addition to those identified from the 'on treatment' approach (Supplementary Table 4). PPI use was predictive of second fracture within both study populations: HR=1.37 (95% CI: 1.17-1.61) for Denmark, and HR=1.58 (95% CI: 1.13-2.20) for SIDIAP. Rheumatoid arthritis was also predictive in

Denmark: HR=1.61 (95% CI: 1.28-2.04). Conversely, male gender was found to be protective for both Denmark and SIDIAP: HR=0.64 (95% CI: 0.51-0.81) and HR=0.45 (95% CI: 0.29-0.71) respectively, as was HRT use within Denmark only (HR=0.83 (95% CI: 0.69-0.99)). Key findings were unaltered when analyses were run separately by gender, although predictors could not be identified among males only due to insufficient events of interest in this subgroup.

DISCUSSION

This binational retrospective cohort study reports a minority of oral BP users will proceed to suffer at least two fragility fractures, at a rate of between 1.7 (95% CI: 1.2-2.2)/1000 PYs (Denmark) and 2.4 (95% CI: 1.8-3.2)/1000 PYs (Catalonia, Spain), despite remaining adherent to medication. In addition, we report here several key risk factors of ≥2 FWOT as identified among 'on treatment' users either within one or both study populations.

Previous observational studies [14, 23] have reported between 1.3% and 15.5% of persistent BP users fracture at least twice while on treatment over a 3-year period. In terms of RCT settings, the rate of two or more clinical fractures among women while on alendronate treatment within the Fracture Intervention Trial (FIT) was approximately 0.8/100 PYs at risk [24]. Incidence of at least two (radiographic) vertebral fractures after 1 year among Risedronate-treated women within the Vertebral Efficiency with Risedronate Therapy (VERT) trial was 0.3% [25]. To our knowledge this is the first observational study to report on the incidence rate of ≥2 FWOT for oral BP users within the general population. In main analyses we used a conservative definition of fracture - including only fractures sustained on days with no other fracture, after a lag period of six months from first to second fracture if at the

same site and only among users with at least 6 months persistence to treatment with overall high MPR (≥80%).

Incidence rates of ≥2 FWOT were similar between the "on treatment" cohorts from the two countries, although non-significantly higher in Catalonia, Spain. It is worth noting several differences in the baseline characteristics between the "on treatment" cohorts from the two study populations (Table 1). The proportion of females and PPI users was significantly higher in SIDIAP, with less than a fifth of the number of HRT users compared to Denmark. The reason for the higher extent of HRT use in Denmark compared with Catalonia may be a function of time rather than geography as recruitment into the Danish study cohort began six years earlier than in Catalonia and this preceded the decline in worldwide use of HRT that followed on from publication of the Women's Health Initiative RCT results on adverse events with HRT [26]. Secular trends may also have caused the differences in PPI exposure.

Among all incident oral BP users within Denmark, the incidence rate of second fracture was approximately 8-fold higher compared to the Danish cohort of adherent patients considered "on treatment". Conversely, it was surprising to find no significant change in rates between all incident oral BP users and those "on treatment" using the SIDIAP database, although fracture incidence during antiresorptive therapy has elsewhere been reported to be independent of compliance [15].

The rates of second fracture among users "on treatment" are not directly comparable with those among all-incident users as these are different groups of users whose baseline risk is unlikely to be the same. However, data from RCTs can be inferred here. The Fracture Intervention Trial indicated a 90% reduction for multiple vertebral fracture associated with Alendronate use [27], as was also found for Risedronate use

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in the VERT trial [25]. In this context, the 88% lower incidence of second fracture among adherent *vs.* all-incident users is not an implausible finding. As previously noted though, comparison of rates should be made with caution given potential non-equivalence of baseline risk. While we identified any differences in baseline gender, age, previous fracture history, PPI, steroids, HRT, dementia and rheumatoid arthritis - and found the all-incident cohort to be slightly frailer - we were not able to examine other potentially confounding factors such as smoking status, parental history of hip fracture, BMI, alcohol or use of Calcium/Vitamin D supplements. These factors may have been unbalanced in the two groups and may have contributed to some of the observed difference in fracture rates in addition to the effects of bisphosphonate adherence. Conversely, within SIDIAP the proportion of men in the "on treatment" cohort is less than half that among all-incident users (Table 1). This suggests a concentration of high-risk patients within the SIDIAP "on treatment" cohort, possibly due to better adherence among those with greater (correct) perception of fracture risk. There is also large potential within SIDIAP for further unobserved non-equivalence in baseline characteristics between all-incident users and those "on treatment" given that approximately two thirds of oral BP users failed the persistence and/or compliance criteria for the main analysis.

Moreover, the Danish all-incident oral BP population contains a more fragile patient mix compared to that in Catalonia (Table 1), which likely contributes to the significantly higher incidence rate of second fracture after treatment initiation within Denmark relative to SIDIAP, irrespective of treatment adherence. Worth noting from the literature is a recent report estimating that Denmark has the highest ten-year probability of major osteoporotic fracture out of 20 European countries; over twice that of Spain that has the lowest (estimated using the FRAX algorithm) [18]. Also of

note within the same report was a 3-fold range in hip fracture incidence, in which Denmark (2004) was highest and Spain (1984-91) third lowest [18].

Incidence (per 1000 PYs) of first fracture has previously been reported among the general population for these study populations [28, 29], and were as follows: hip=4.9, wrist=4.8, forearm=5.9, vertebral=1.3, humerus=4.1 and pelvis=0.7 (Danish Health Registries); hip=2.23, wrist/forearm=2.56, clinical spine=1.98, humerus=1.55 and pelvis=0.04 (SIDIAP).

Using competing risk survival methods to study predictors of ≥2 FWOT we have identified oral BP users of older age to be at greater risk in both of two large study populations. Furthermore, those with a history of recent/older fracture or with dementia were at increased risk within one but not both of the populations under study. All independent predictors identified among users within only one study population (Denmark or SIDIAP) were found to be predictive in the other when fractures occurring on the same date were included as a sensitivity analysis. Failure to identify all such characteristics as risk factors in the main analysis may be due to the comparatively low number of users experiencing a second fracture while on treatment. Independent predictors of ≥2 FWOT reported by other studies [14, 23] have included previous history of fracture, low levels of vitamin D, current smoking status and baseline alkaline phosphatase total activity levels. History of fracture has also been identified as a predictor of single fracture while on BP treatment [5, 13, 19, 20], as has older age [15, 20] and dementia [19].

Previous studies have frequently shown that low compliance leads to higher fracture risk [8]. In parallel, some reports have shown that previous use of HRT is related to better compliance with oral BPs [30]. The appearance of HRT (Denmark) as a

protective factor for second fracture in the analysis of all incident users but not in the competing risk analysis of ≥2 FWOT might therefore be due to an indirect effect on fracture reduction via altered therapy adherence. Similarly, the gender effect (lower risk of second fracture among men treated with oral BPs) identified in both Denmark and SIDIAP could be associated with poorer adherence which would explain why this was not relevant in the main analysis of predictors of ≥ 2FWOT. The finding of PPI use (Denmark and SIDIAP) and rheumatoid arthritis (Denmark only) as significantly predictive of second fracture among all-incident users is clinically plausible and these factors have previously been reported as risk factors of single FWOT within the SIDIAP population [20]. Moreover, it has recently been shown that the anti-fracture efficacy of oral alendronate is significantly reduced when taken concomitantly with PPIs [31]; a finding further confirmed in a more recent report using the Danish data [19]. Lack of association between these variables and greater risk of ≥2 FWOT as reported here may be due to lack of power within our comparatively smaller sample size of those "on treatment" compared to all incident users.

A variety of factors likely contribute to the process of treatment failure among oral BP users. While we have addressed the issue of discontinuation to therapy and low refill compliance in our main analysis, the failure of treatment as reported here might be the result of poor absorption due to users not taking medications as per instructions of prescription. Another reason may be divergent responses of bone to BPs due to variation in severity of bone structural damage [11, 23]. In the presence of continuous bone remodeling with negative balance, weakening in the microarchitecture of bone may have become too advanced for antiresorptives to be effectual in restoring bone mechanical competence. In other words, the oral BPs are prescribed "too late" in the natural history of bone deterioration in order to adequately reduce fracture risk. Also, though anti-resorptives reduce the number of stress risers on the surface of bone

trabeculae and cortices, which is a prominent issue in high turnover states, they are likely ineffective when it comes to reversing accumulation of microdamage and advanced glycation end products as seen in low turnover states and bone ageing [32, 33]. Other risk factors such as recurrent falls or adverse hip geometry are also unlikely to be modified by bisphosphonates.

The IOF CSA Inadequate Response Working Group state that if treatment adherence cannot be further improved then treatment should be changed under the circumstances of two or more incident fragility fractures [11]. There is a need for further studies to demonstrate whether a patient failing on one treatment will respond favorably to an alternative, and our findings here can inform investigations into more personalized strategies for reducing fracture risk for high risk individuals. In the present absence of such evidence for effectiveness of alternatives, three general rules were recommended by the working group: 1) a weaker anti-resorptive is reasonably replaced by a more potent drug of the same class, 2) an oral drug is reasonably replaced by an injected drug and 3) a strong anti-resorptive is reasonably replaced by an anabolic agent.

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Strengths of our study are the representativeness of the data used: Danish Health Registries covers the whole of Denmark while SIDIAP covers a highly representative sample of more than 80% of the total population of Catalonia [21]. The definition of second fracture used was conservative, addressing the issues of trauma events (same-date fracture not included) and re-coding (second fracture only included if at different site or after a 6 month lag). In addition, the information gathered on dispensed BPs is detailed, and likely to be more reliable than patient reports or GP prescriptions.

The main limitation in our analysis is the lack of individual x-ray validation of the fractures observed in SIDIAP and Denmark, although coding of clinical fractures in both data sources has been validated and shown to be highly specific [28, 34].

Another is the use of MPR as a measure of adherence which assumes the drug is taken once dispensed, although MPR has been widely used elsewhere [12, 14, 19, 20, 35]. As noted in a previous analysis using the Danish data, there is the possibility such a finding as dementia being predictive of fracture while on treatment may be an artifact of an artificially inflated MPR among dementia patients due to medications being delivered to them yet who in actual practice may fail to take them as prescribed. Also, the nature of our study unfortunately did not permit the analysis of bone turnover markers or bone mineral density decline that may otherwise have provided insight into the biological mechanisms of inadequate response to BPs. Finally, the risk reductions found in the original RCT of alendronate [27] was calculated after exclusion of high impact fractures while our analysis included fractures irrespective of trauma mechanism (except multiple fractures occurring on the same date, suggesting high impact trauma). Inclusion of some high impact fractures in the analysis may conservatively bias our risk reduction estimates.

CONCLUSION

We conclude that oral BP therapy fails for a small proportion of users, as defined by the incidence of ≥2 FWOT. Older age was associated with higher risk in both Catalonia and Denmark. History of recent/old fracture and previous diagnosis of dementia were predictive of ≥2 FWOT within one but not both study populations. A number of clinical variables were additionally predictive of two or more fractures, irrespective of adherence. Information on all these variables is readily available in actual practice conditions and could be used to facilitate the identification of patients at higher risk of experiencing treatment failure. Additional and/or alternative strategies should be investigated for these patients.

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AUTHORS' ROLES

Authors' roles: Study design: DPA, BA and SH. Study conduct: SH, BA and DPA. Data management and statistical analyses: SH, KHR, BA and DPA. Data interpretation: All the authors. Drafting manuscript: SH, DPA and BA. Revising manuscript content: All the authors. Approving final version of manuscript: All the authors. SH takes responsibility for the integrity of the data analysis. BA and DPA supervised the study and are joint senior authors.

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FIGURE LEGENDS

Figure 1: Population flow diagram

Figure 2: Cumulative incidence function plots of second fracture while on oral BP treatment within SIDIAP and Denmark. Estimated using competing risk model adjusting for age and previous fracture history

Figure 3: Cumulative incidence function plots of second fracture while on oral BP treatment within SIDIAP and Denmark, by age category. Estimated using competing risk model adjusting for previous fracture history

Figure 4: Cumulative incidence function plots of second fracture while on oral BP treatment within SIDIAP and Denmark, by previous fracture history. Estimated using competing risk model adjusting for age.

Figure 5: Cumulative incidence function plots of second fracture while on oral BP treatment within SIDIAP and Denmark, by baseline dementia status. Estimated using competing risk model adjusting for age and previous fracture history.

TABLES

Table 1: Baseline characteristics among incident oral bisphosphonate users within the SIDIAP database and Danish Health Registries

	SIDIAP (N=7,449)				Danish Health Registries (N=7,885)			
	all incident users[1] (N=21,385)		adherent users[2] (N=7,449)		all incident users[1] (N=13,949)		adherent users[2] (N=7,885)	
	n	%*	n	%*	n	%*	n	%*
Sex, male	5119	24%	750	10%	2202	16%	1,251	16%
Age, years								
<65 years	8782	41%	2866	39%	3814	27%	2,268	29%
65 to ≤80 years	9543	45%	3619	49%	7149	51%	4,113	52%
≥80 years	3060	14%	964	13%	2986	21%	1,504	19%
Previous fracture								
No	18,308	86%	6088	82%	10,266	74%	6,042	77%
>6m ago	2,018	9%	885	12%	2,551	18%	1,336	17%
<6m ago	1,059	5%	476	6%	1,132	8%	507	6%
PPI user	12,804	60%	4546	61%	2,145	15%	1,106	14%
Oral corticosteriod user	3,266	15%	1245	17%	3,630	26%	2,059	26%
HRT user	567	3%			2034	15%	1,144	15%
Dementia	276	1%	53	1%	126	1%	66	1%
Neurological conditions	860	4%	245	3%	666	5%	379	5%
Rheumatoid arthritis	496	2%	221	3%	795	6%	465	6%
BMI								
<25	3121	15%	1221	16%	-	-	-	-
25-35	9295	44%	3336	45%	-	-	-	-
>35	1307	6%	468	6%	-	-	-	-
Missing	7662	36%	2424	33%	-	-	-	-
Smoking								
Never	15219	71%	5852	79%	-	-	-	-
Ex-Smoker	2126	10%	488	7%	-	-	-	-
Current	1636	8%	395	5%	-	-	-	-
Missing	2404	11%	714	10%	-	-	-	-

[1] with a minimum of 6 months persistence and overall MPR ≥80%,

[2] all incident users, irrespective of persistence or overall MPR

* percentages may not equal 100% due to rounding

Table 2: Incidence of first and second fracture among all-incident users of oral bisphosphonates and those on treatment*, within SIDIAP and Danish Health Registries

	SIDIAP				Danish Health Registries			
	All Users (N=21,385)		On Treatment (N=7,449)		All Users (N=13,949)		On Treatment (N=7,885)	
	1st fracture	2nd fracture	1st fracture	2nd fracture	1st fracture	2nd fracture	1st fracture	2nd fracture
Events	1725	180	507	50	3,446	995	493	46
Total Follow-up (yrs)	69,643	72,323	19,918	20,598	62,480	70,027	27,663	27,870
Mean Follow-up (yrs)	3.26	3.38	2.67	2.77	4.48	5.02	3.51	3.54
Rate (per 1000 PYs);	24.7	2.5	25.5	2.4	55.2	14.2	17.8	1.7
95% Confidence Interval	(23.6-26.0)	(2.2-2.9)	(23.3-27.8)	(1.8-3.2)	(53.3-57.0)	(13.3-15.1)	(16.3-19.5)	(1.2-2.2)

*Bisphosphonate users with a minimum of 6 months persistence and overall MPR ≥80%. Fractures considered after 6 months from treatment initiation, during continued persistece with therapy and up to date of death, end of follow-up or 6 months after discontinuation

Table 3: Estimated sub-hazard ratios (SHR) for 2-25 fractures while on oral bisphosphonate treatment* within SIDIAP and Danish Health Registries

		SIDIAP (N=7,449)						Danish Health Registries (N=7,885)					
		Unadjusted		Fully adjusted		Final Model		Unadjusted		Fully adjusted		Final Model	
Characteristic		HR [95% C.I.]	P-value	HR [95% C.I.]	P-value	HR [95% C.I.]	P-value	HR [95% C.I.]	P-value	HR [95% C.I.]	P-value	HR [95% C.I.]	P-value
Gender	Female	ref		ref				ref		ref			
	Male	0.80 (0.29-2.23)	0.67	0.81 (0.32-2.09)	0.67			0.68 (0.27-1.73)	0.42	0.80 (0.31-2.11)	0.65		
Age	<65 years	ref		ref				ref		ref		ref	
	65 to ≤80 years	2.32 (1.13-4.77)	0.022	2.09 (0.95-4.59)	0.066	2.28 (1.11-4.68)	0.025	2.83 (1.08-7.39)	0.034	2.61 (0.97-7.01)	0.057	2.61 (0.98-6.95)	0.054
	≥80 years	3.50 (1.48-8.25)	0.004	2.75 (1.12-6.78)	0.028	3.19 (1.33-7.69)	0.01	5.97 (2.22-16.1)	<0.001	4.61 (1.58-13.5)	0.005	4.88 (1.74-13.7)	0.003
Previous fracture history	None	ref		ref				ref		ref		ref	
	Old fracture	2.06 (1.02-4.17)	0.045	1.80 (0.88-3.67)	0.11			2.42 (1.24-4.76)	0.009	1.91 (0.94-3.89)	0.074	2.08 (1.04-4.15)	0.039
	Recent fracture	2.34 (0.98-5.58)	0.054	1.87 (0.83-4.23)	0.13			4.05 (1.83-8.98)	0.001	3.12 (1.37-7.09)	0.007	3.40 (1.50-7.68)	0.003
User of proton pump	No	ref		ref				ref		ref			
	Yes	1.08 (0.61-1.92)	0.79	0.81 (0.44-1.51)	0.51			1.37 (0.64-2.93)	0.42	1.28 (0.59-2.81)	0.53		
rheumatoid arthritis	No	ref		ref				ref		ref			
	Yes	1.38 (0.34-5.67)	0.66	1.18 (0.28-4.96)	0.82			1.47 (0.53-4.11)	0.46	2.38 (0.85-6.62)	0.097		
neurological condition	No	ref		ref				ref		ref		ref	
	Yes	1.30 (0.31-5.33)	0.72	0.98 (0.23-4.10)	0.98			2.71 (1.07-6.85)	0.035	2.13 (0.80-5.66)	0.13	2.23 (0.87-5.74)	0.094
HRT user	No	ref		ref				ref		ref			
	Yes	-	-	-	-			0.68 (0.27-1.73)	0.42	0.69 (0.27-1.78)	0.45		
Dementia	No	ref		ref				ref		ref			
	Yes	6.48 (1.56-26.9)	0.01	4.14 (0.93-18.4)	0.063	4.46 (1.02-19.4)	0.047	6.17 (1.48-25.8)	0.013	2.99 (0.66-13.5)	0.16		
Oral corticosteroid user	No	ref		ref				ref		ref			
	Yes	1.47 (0.75-2.87)	0.26	1.41 (0.72-2.75)	0.31			0.54 (0.24-1.20)	0.13	0.50 (0.23-1.12)	0.094		
BMI	<25	ref		ref				-	-	-	-	-	-
	25-35	1.40 (0.61-3.21)	0.43	1.33 (0.57-3.08)	0.51			-	-	-	-	-	-
	>35	1.10 (0.29-4.27)	0.89	1.11 (0.28-4.37)	0.88			-	-	-	-	-	-
	Unknown	0.91 (0.36-2.27)	0.84	0.95 (0.37-2.46)	0.91								
Smoking	Never	ref		ref				-	-	-	-	-	-
	Ex-smoker	0.37 (0.05-2.66)	0.32	0.43 (0.06-2.93)	0.39			-	-	-	-	-	-
	Current	0.89 (0.27-2.86)	0.84	1.35 (0.41-4.42)	0.62			-	-	-	-	-	-
	Unknown	1.03 (0.41-2.61)	0.95	1.14 (0.45-2.90)	0.78			-	-	-	-	-	-

*Bisphosphonate users with a minimum of 6 months persistence and overall MPR>80%. Fractures considered after 6 months from treatment initiation, during continued persistence with therapy and up to date of death, end of follow-up or 6 months after discontinuation. SHRs estimated using Fine&Gray survival models accounting for competing risk of therapy discontinuation. Selectively adjusted estimates adjusted for significant predictors (P<0.10) retained in backward stepwise procedure.