

Incidence and Predictors of Multiple Fractures Despite High Adherence to Oral Bisphosphonates: A Binational Population-Based Cohort Study

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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 oral BP treatment failure, defined as the incidence of two or more fractures while on treatment (≥ 2 FWOT) among users with high adherence. Fractures were considered from 6 months after treatment initiation and up to 6 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 ≥ 6 months with overall medication possession ratio (MPR) $\geq 80\%$. Incidence of ≥ 2 FWOT was 2.4 (95% confidence interval [CI], 1.8 to 3.2) and 1.7 (95% CI, 1.2 to 2.2) per 1000 patient-years (PYs) within Catalonia and Denmark, respectively. Older age was predictive of ≥ 2 FWOT in both Catalanian and Danish cohorts: subhazard ratio (SHR) = 2.28 (95% CI, 1.11 to 4.68) and SHR = 2.61 (95% CI, 0.98 to 6.95), respectively, for 65 to <80 years; and SHR = 3.19 (95% CI, 1.33 to 7.69) and SHR = 4.88 (95% CI, 1.74 to 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 to 19.4) (SIDIAP); and history of recent or older fracture, SHR = 3.40 (95% CI, 1.50 to 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. © 2015 American Society for Bone and Mineral Research.

KEY WORDS: OSTEOPOROSIS; BISPHOSPHONATES; TREATMENT FAILURE; EPIDEMIOLOGY; FRACTURES

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

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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 one-half of patients discontinuing treatment in the first 3 to 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 nonadherence and inadequate response in the incidence of new fractures among users of BPs. This is especially true for observational studies where data on antiosteoporosis medications is usually scarce and often self-reported.

Subsequently, the issue of defining and characterizing 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).⁽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; eg, a decrease in β CTX and P1NP in response to antiresorptives that is less than the LSC.⁽¹¹⁾

A recent International Osteoporosis Foundation (IOF) consensus paper⁽¹¹⁾ has likewise provided pragmatic criteria for defining treatment failure in osteoporosis. Its authors recommend that two or more fragility fractures while on antiresorptive 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% to 90% for treated versus 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 two or more fractures while on treatment (≥ 2 FWOT), data on the incidence and predictors of such occurrences in the general population are scarce. Treatment failure among BP users has consequences both for the patient, who remains at increased risk of fracture, and for healthcare providers because this phenomenon reduces cost-efficacy of treatment.⁽¹⁷⁾ This is particularly relevant given the estimated 23% increase in osteoporosis prevalence (as defined using the World Health Organization [WHO] diagnostic criteria) within Europe from 2010 to 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] $\geq 80\%$).

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 (general practitioners [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 1, 2000 to December 31, 2001, and January 1, 2006 to December 31, 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 antio-osteoporosis 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 because of 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 $\geq 80\%$) 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 [DDD] 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 ≥ 2 FWOT

Osteoporotic fractures (of any site except fingers, toes, and skull/face) were identified in Danish Health Registries and SIDIAP data using International Classification of Diseases (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, 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 “washout” after treatment discontinuation (given the known carryover 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 6 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 [≤ 6 months before starting therapy]), concomitant medications (proton pump inhibitors [PPIs], oral

corticosteroids [equivalent to prednisolone 5 mg daily for 3 months or more], and hormone replacement therapy [HRT]; and clinical diagnosis of preexisting comorbid conditions (inflammatory arthritis, a neurological condition [stroke, Parkinson's disease or multiple sclerosis], and dementia). Body mass index (BMI) (<25, 25 to 35, and ≥ 35 kg/m²) and smoking status (current, ex-smoker, and nonsmoker) were included for the SIDIAP analysis only because these variables were unavailable for Denmark.

Statistical analysis

Independent risk factors of time to second fracture while on oral BP treatment were identified for users within the 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 analyzed separately and all potential predictors (as described in the previous paragraph) were assessed in univariate models and using backward-stepwise selection, whereby a parsimonious multivariable model was identified from the full model using cutoffs of *p*-entry 0.049 and *p*-exit 0.10. Index date for these models was 6 months after treatment initiation and only fractures sustained during continued persistence to treatment, or up to 6 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 (StataCorp, College Station, TX, USA) 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 (Fig. 1) to investigate treatment failure as defined by two or more fractures from at least 6 months after treatment initiation and during continued follow up, irrespective of persistence or refill 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; ie, 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 the Danish Health Registries and 22,355 within SIDIAP during the 2 years of recruitment for each study cohort. A total of 13,949 (Denmark) and 21,385 (SIDIAP) patients were remaining who met the inclusion criteria (Fig. 1). Of these, 7885 (56.5%) and 7449 (34.8%), for Denmark and

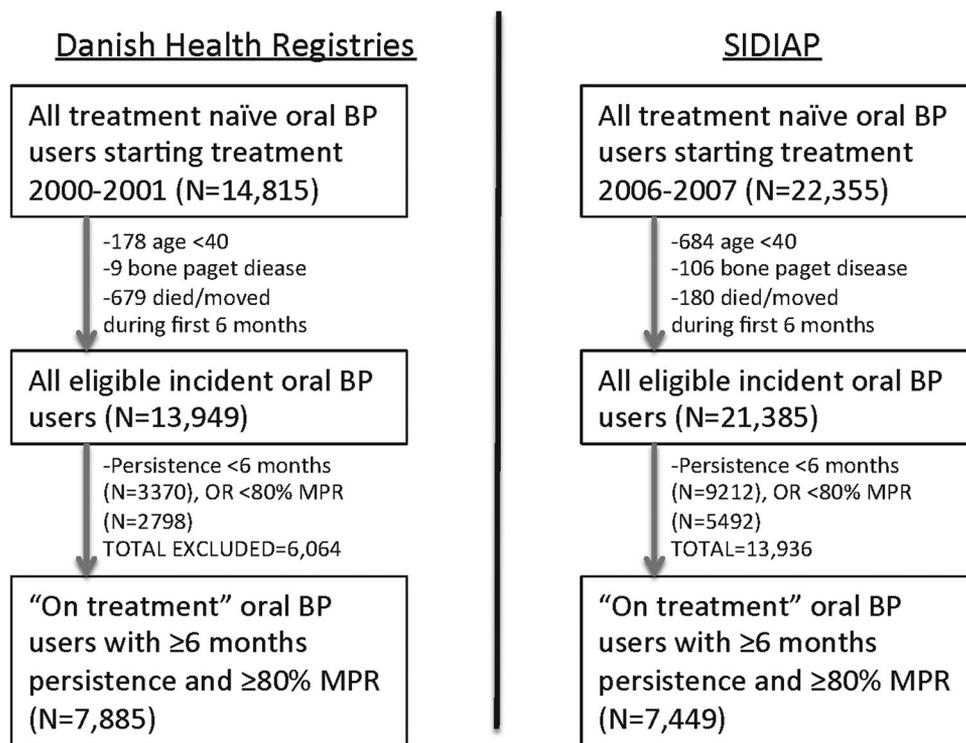


Fig. 1. Population flow diagram.

Table 1. Baseline Characteristics Among Incident Oral Bisphosphonate Users Within the SIDIAP Database and Danish Health Registries

	SIDIAP (n = 7449)				Danish Health Registries (n = 7885)			
	All incident users ^a (n = 21,385)		Adherent users ^b (n = 7449)		All incident users ^a (n = 13,949)		Adherent users ^b (n = 7885)	
	n	% ^c	n	% ^c	n	% ^c	n	% ^c
Sex, male	5119	24	750	10	2202	16	1251	16
Age								
<65 years	8782	41	2866	39	3814	27	2268	29
65 to <80 years	9543	45	3619	49	7149	51	4113	52
≥80 years	3060	14	964	13	2986	21	1504	19
Previous fracture								
No	18,308	86	6088	82	10,266	74	6042	77
>6 months ago	2018	9	885	12	2551	18	1336	17
≤6 months ago	1059	5	476	6	1132	8	507	6
PPI user	12,804	60	4546	61	2145	15	1106	14
Oral corticosteroid user	3266	15	1245	17	3630	26	2059	26
HRT user	567	3			2034	15	1144	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 kg/m ²	3121	15	1221	16	–	–	–	–
25–35 kg/m ²	9295	44	3336	45	–	–	–	–
>35 kg/m ²	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	–	–	–	–

PPI = proton pump inhibitor; HRT = hormone-replacement therapy; MPR = medication possession ratio.

^aWith a minimum of 6 months persistence and overall MPR ≥80%.

^bAll incident users, irrespective of persistence or overall MPR.

^cPercentages may not equal 100% because of rounding.

SIDIAP respectively, persisted for a minimum of 6 months with an overall high MPR of ≥80% and were thus included in the main analysis (Fig. 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 1.7/1000 person years (95% confidence interval [CI], 1.2 to 2.2) and within SIDIAP of 2.4/1000 person years (95% CI, 1.8 to 3.2). Cumulative incidence function plots are displayed in Fig. 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 nonvertebral within Danish Health Registries and SIDIAP, respectively, reflecting the general underreporting 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 to 3.3) (Denmark) and 3.3/1000 PYs (95% CI, 2.6 to 4.1) (SIDIAP).

For SIDIAP the incidence rate of second fracture among all incident oral BP users, irrespective of adherence was 2.5/1000

PYs (95% CI, 2.2 to 2.9). Within Denmark this rate was 14.2/1000 PYs (95% CI, 13.4 to 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 (Figs. 3 to 5) and estimates from full models containing all available predictors (Supplementary Table 5).

When fractures occurring on the same day to other fractures were included as a sensitivity analysis, history of recent fracture became predictive of ≥2 FWOT within SIDIAP (subhazard ratio [SHR] = 2.10; 95% CI, 1.05 to 4.20) (Supplementary Table 2). Likewise within Denmark, dementia became a significant risk factor of ≥2 FWOT (SHR = 4.30; 95% CI, 1.47 to 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

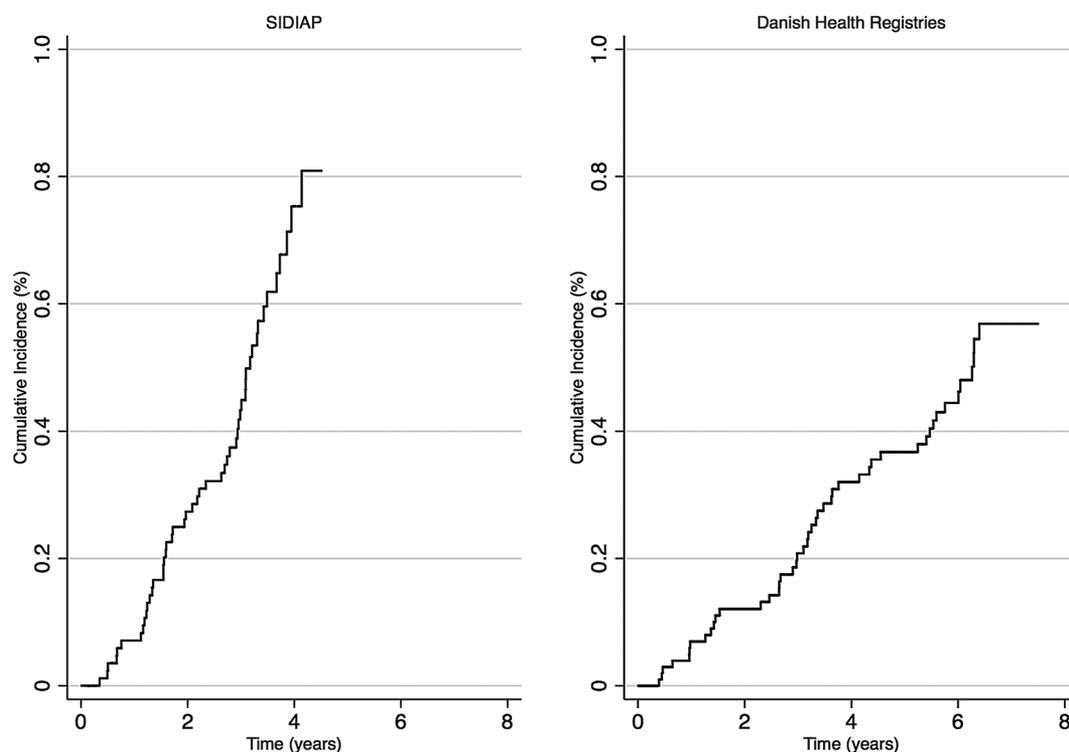


Fig. 2. Cumulative incidence of second fracture while on oral BP treatment within SIDIAP and Danish Health Registries. Estimated using competing risk models adjusted for age and previous fracture history.

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 to 1.61) for Denmark, and HR = 1.58 (95% CI, 1.13 to 2.20) for SIDIAP. Rheumatoid arthritis was also predictive in Denmark: HR = 1.61 (95% CI, 1.28 to 2.04). Conversely, male gender was found to be protective within both Denmark and SIDIAP: HR = 0.64 (95% CI, 0.51 to 0.81) and HR = 0.45 (95% CI, 0.29 to 0.71), respectively, as was HRT use within Denmark only (HR = 0.83; 95% CI, 0.69 to 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 to 2.2)/1000 PYs (Denmark) and 2.4 (95% CI, 1.8 to 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,

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 = 7449)		All users (n = 13,949)		On treatment (n = 7885)	
	1st fracture	2nd fracture	1st fracture	2nd fracture	1st fracture	2nd fracture	1st fracture	2nd fracture
Events	1725	180	507	50	3446	995	493	46
Total follow-up (years)	69,643	72,323	19,918	20,598	62,480	70,027	27,663	27,870
Mean follow-up (years)	3.26	3.38	2.67	2.77	4.48	5.02	3.51	3.54
Rate (per 1000 PYs) (95% confidence interval)	24.7 (23.6–26.0)	2.5 (2.2–2.9)	25.5 (23.3–27.8)	2.4 (1.8–3.2)	55.2 (53.3–57.0)	14.2 (13.3–15.1)	17.8 (16.3–19.5)	1.7 (1.2–2.2)

“On treatment” users are bisphosphonate users with a minimum of 6 months persistence and overall MPR $\geq 80\%$. Fractures considered from 6 months after treatment initiation, during continued persistence with therapy and up to date of death, end of follow-up or 6 months after discontinuation. PY = patient-years; MPR = medication possession ratio.

Table 3. Estimated SHRs for Two or More Fractures While on Oral Bisphosphonate Treatment Within SIDIAP and Danish Health Registries

Characteristic	SIDIAP (n = 7449)				Danish Health Registries (n = 7885)			
	Unadjusted		Final model		Unadjusted		Final model	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Gender								
Female	Ref				Ref			
Male	0.80 (0.29–2.23)	0.67			0.68 (0.27–1.73)	0.42		
Age								
<65 years	Ref		Ref		Ref		Ref	
65 to <80 years	2.32 (1.13–4.77)	0.022	2.28 (1.11–4.68)	0.025	2.83 (1.08–7.39)	0.034	2.61 (0.98–6.95)	0.054
≥80 years	3.50 (1.48–8.25)	0.004	3.19 (1.33–7.69)	0.01	5.97 (2.22–16.1)	<0.001	4.88 (1.74–13.7)	0.003
Previous fracture history								
None	Ref				Ref		Ref	
Old fracture	2.06 (1.02–4.17)	0.045			2.42 (1.24–4.76)	0.009	2.08 (1.04–4.15)	0.039
Recent fracture	2.34 (0.98–5.58)	0.054			4.05 (1.83–8.98)	0.001	3.40 (1.50–7.68)	0.003
PPI user								
No	Ref				Ref			
Yes	1.08 (0.61–1.92)	0.79			1.37 (0.64–2.93)	0.42		
Rheumatoid arthritis								
No	Ref				Ref			
Yes	1.38 (0.34–5.67)	0.66			1.47 (0.53–4.11)	0.46		
Neurological condition								
No	Ref				Ref		Ref	
Yes	1.30 (0.31–5.33)	0.72			2.71 (1.07–6.85)	0.035	2.23 (0.87–5.74)	0.094
HRT user								
No	Ref				Ref			
Yes	–	–			0.68 (0.27–1.73)	0.42		
Dementia								
No	Ref		Ref		Ref			
Yes	6.48 (1.56–26.9)	0.01	4.46 (1.02–19.4)	0.047	6.17 (1.48–25.8)	0.013		
Oral corticosteroid user								
No	Ref				Ref			
Yes	1.47 (0.75–2.87)	0.26			0.54 (0.24–1.20)	0.13		
BMI								
<25 kg/m ²	Ref				–	–	–	–
25–35 kg/m ²	1.40 (0.61–3.21)	0.43			–	–	–	–
>35 kg/m ²	1.10 (0.29–4.27)	0.89			–	–	–	–
Unknown	0.91 (0.36–2.27)	0.84						
Smoking								
Never	Ref				–	–	–	–
Ex-smoker	0.37 (0.05–2.66)	0.32			–	–	–	–
Current	0.89 (0.27–2.86)	0.84			–	–	–	–
Unknown	1.03 (0.41–2.61)	0.95			–	–	–	–

“On treatment” users are 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 and Gray survival models accounting for competing risk of therapy discontinuation. Final model estimates adjusted for significant predictors ($p < 0.10$) retained in backward stepwise procedure. Estimates from models containing all potential predictors are reported in Supplementary Table 5.

SHR = subhazard ratio; PPI = proton pump inhibitor; HRT = hormone-replacement therapy; MPR = medication possession ratio.

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 6 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 nonsignificantly 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

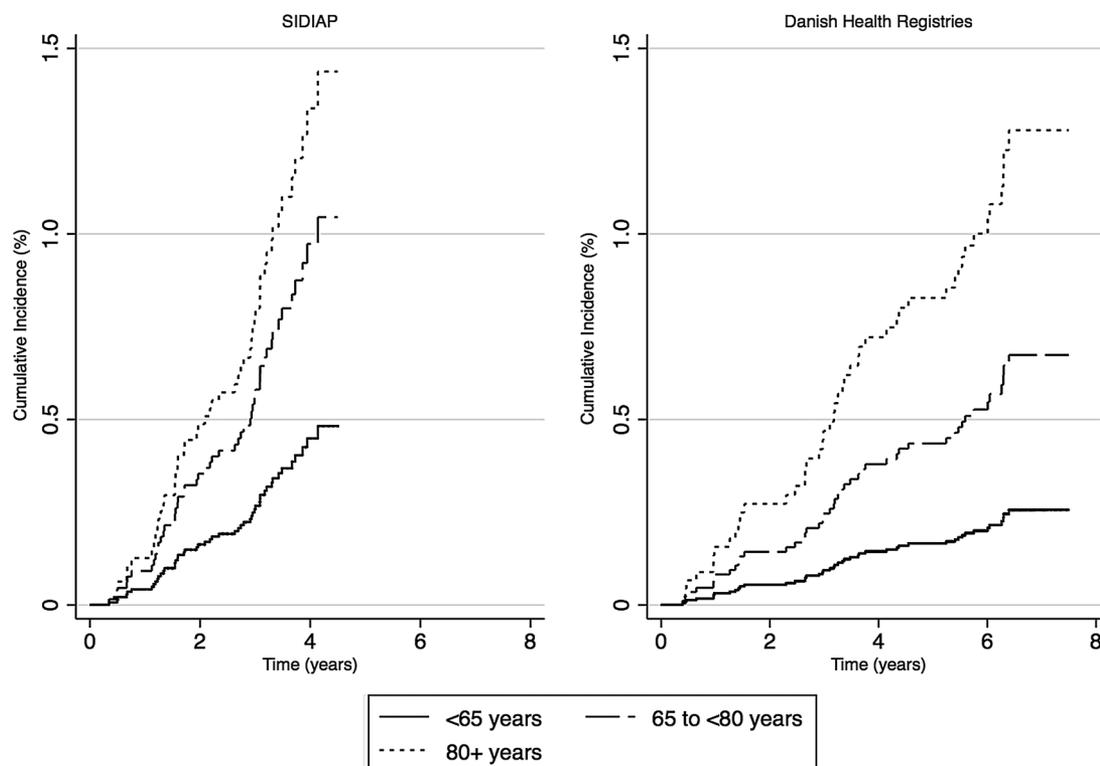


Fig. 3. Cumulative incidence of second fracture while on oral BP treatment within SIDIAP and Danish Health Registries, by age category. Estimated using competing risk models adjusted for previous fracture history.

in SIDIAP, with less than one-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 because recruitment into the Danish study cohort began 6 years earlier than in Catalonia and this preceded the decline in worldwide use of HRT that occurred after 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 eightfold 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⁾

It should be noted that the rates of second fracture among users "on treatment" are not directly comparable with those among all-incident users because these are different groups of users whose baseline risk is unlikely to be the same. Given the limitations of a nonrandomized study design, any comparison of rates between these groups should be made with caution given the high likelihood of nonequivalence of baseline risk and presence of confounding by indication. Particularly, although we identified any differences between the adherent and all-incident cohorts within the Danish Health Registries in terms of baseline gender, age, previous fracture history, PPI, steroids, HRT, dementia, and rheumatoid arthritis (Table 1), we were not able to examine other factors among the Danish oral

BP users such as smoking status, parental history of hip fracture, BMI, alcohol, or use of calcium/vitamin D supplements. These and other factors may have been unbalanced between the adherent and all-incident cohorts and may have contributed to the observed difference in fracture rates in addition to any effect of bisphosphonate adherence. Conversely, within SIDIAP the proportion of men in the "on treatment" cohort is less than one-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 nonequivalence 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 10-year probability of major osteoporotic fracture out of 20 European countries; over twice that of Spain that has the lowest (estimated using the Fracture Risk Assessment Tool [FRAX] algorithm).⁽¹⁸⁾ Also of note within the same report was a threefold range in hip fracture incidence, in which Denmark (2004) was highest and Spain (1984–1991) third lowest.⁽¹⁸⁾

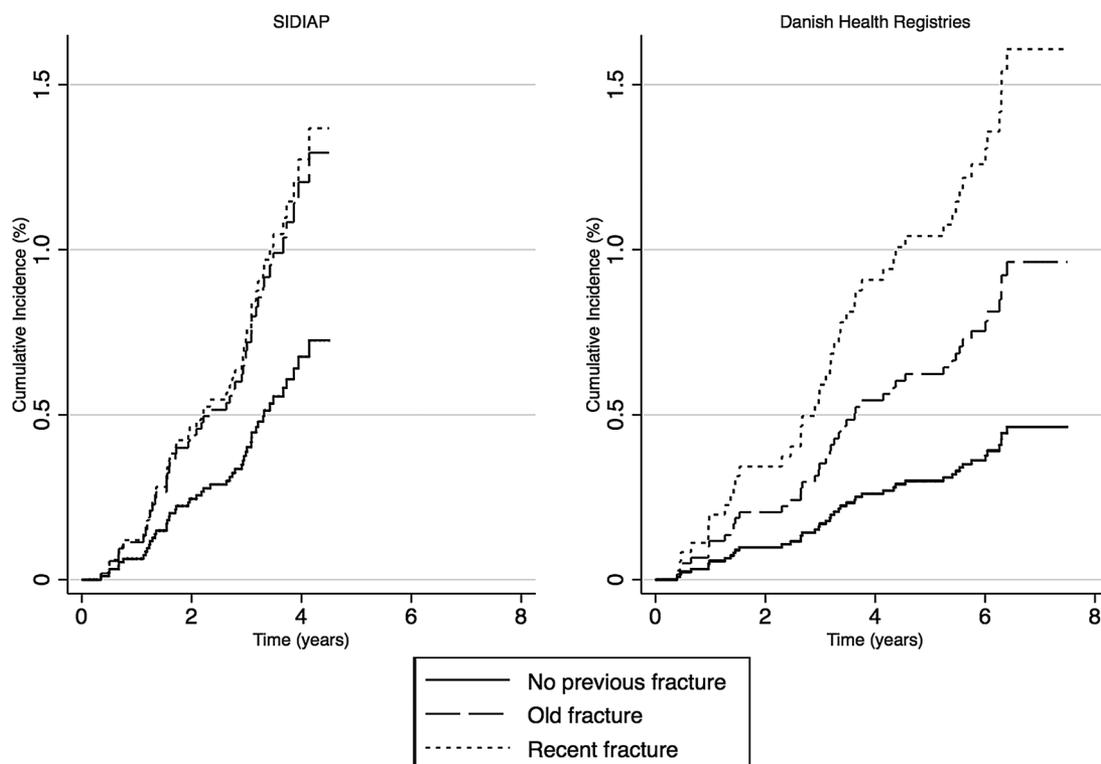


Fig. 4. Cumulative incidence of second fracture while on oral BP treatment within SIDIAP and Danish Health Registries, by previous fracture history. Estimated using competing risk models adjusted for age.

Incidence (per 1000 PYs) of first fracture has previously been reported among the general population for these study populations,^(27,28) and was 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). The rate of first fracture among all-incident oral BP users within the Danish Health Registries (55.2/1000 PYs) is comparable with previous work⁽²⁹⁾ and would appear to be representative of Danish BP users.

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 ≥ 2 FWOT. 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 antifracture 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. Although 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

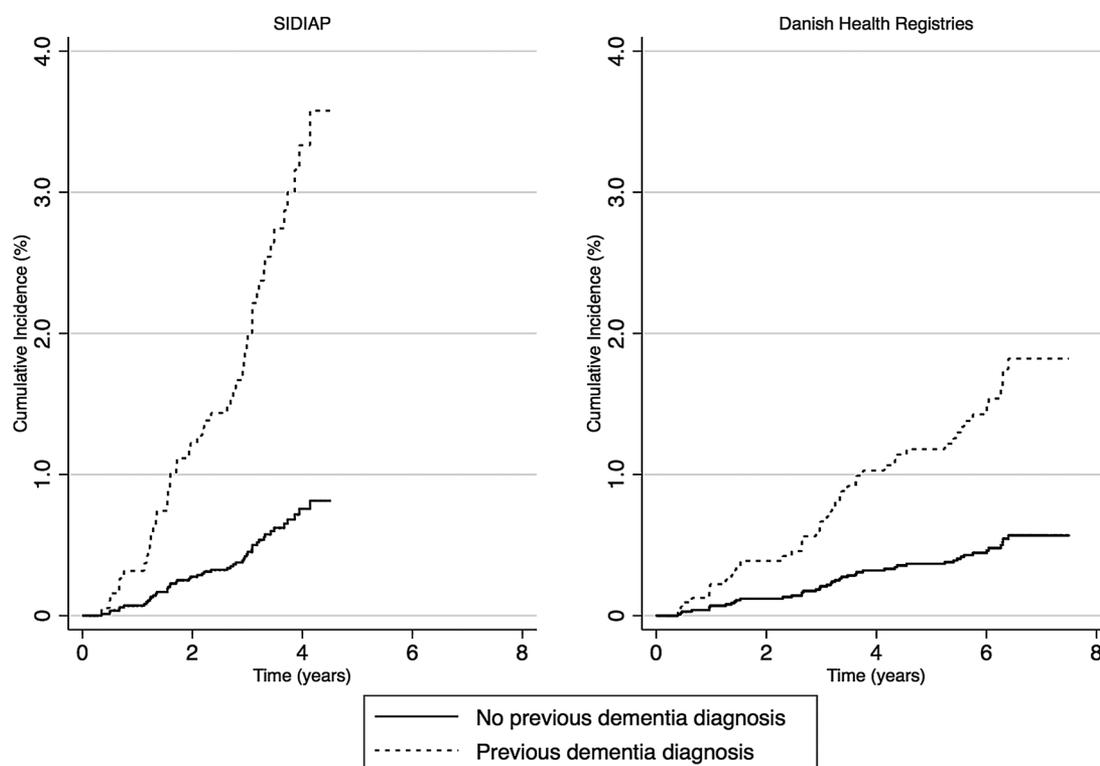


Fig. 5. Cumulative incidence of second fracture while on oral BP treatment within SIDIAP and Danish Health Registries, by baseline dementia status. Estimated using competing risk models adjusted for age and previous fracture history.

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 antiresorptives 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 aging.^(32,33) Other risk factors such as recurrent falls or adverse hip geometry are also unlikely to be modified by BPs.

The IOF Committee of Scientific Advisors (CSA) Inadequate Response Working Group stated 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 antiresorptive 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 antiresorptive is reasonably replaced by an anabolic agent.

The strengths of our study are the representativeness of the data used: the Danish Health Registries covers the whole of

Denmark whereas 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 recoding (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.^(27,34) 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 because medications may have been delivered to them yet in actual practice they may fail to take them as prescribed. Also, the nature of our study unfortunately did not permit the analysis of bone turnover markers or BMD 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⁽³⁶⁾ was calculated after exclusion of high-impact fractures whereas 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 have conservatively biased the risk reduction observed.

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.

Disclosures

All authors state that they have no conflicts of interest.

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