ORAL BISPHOSPHONATES MAY NOT DECREASE HIP FRACTURE RISK IN ELDERLY SPANISH WOMEN

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TITLE

ORAL BISPHOSPHONATES MAY NOT DECREASE HIP FRACTURE RISK IN ELDERLY SPANISH WOMEN

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ARTICLE SUMMARY

Article Focus

. The hypothesis of this study is that oral bisphosphonates may not be effective in reducing hip fracture risk in clinical practice in the long-term use.

Key messages

. Ever use of oral bisphosphonates was not associated with a decreased risk of hip fracture in women aged 65 or older as compared to never use.

. No association between hip fracture risk and cumulative duration of bisphosphonate treatment was observed.

. When treatment duration is analysed as time since first prescription, a statistically significant increased risk for hip fracture was observed in patients exposed to bisphosphonates over 3 years.

Strengths and limitations

. The main strength of this study is that it sheds light on the effects of oral bisphosphonates on hip fracture risk in clinical practice in a Mediterranean population.

. One of the main limitations is the relatively short follow-up period.

ABSTRACT

Objectives

To evaluate the association between long-term use of bisphosphonates and the risk of hip fracture compared to never use among women aged 65 years or older.

Design

Case-control study nested in a cohort.

Setting

General practice research database operated by the Spanish Medicines Agency.

Participants:

Cases of hip fracture were defined as women aged 65 years or older with a validated first diagnosis of hip fracture between 2005 and 2008. Five controls free of hip fracture were matched on age and calendar year with each case.

Interventions

Information on bisphosphonate use, hip fractures, comedication, and comorbidities was collected.

Primary outcomes

Hip fracture risk comparing bisphosphonate users vs never users

Secondary outcomes

Hip fracture risk comparing bisphosphonate users vs never users by individual drugs

Results

The study included 2,009 incident hip fractures and 10,045 matched controls. Hip fracture risk did not differ between bisphosphonate users and never users, adjusted OR = 1.09 (95% CI, 0.94-1.27). No association between hip fracture risk and cumulative duration of bisphosphonate treatment was observed. However, when treatment duration is analysed as time since first prescription, hip fracture risk of the different subgroups compared to never users obtained were as follows: <1 year, OR 0.85 (95%CI, 0.60-1.21); 1 to <3 years, OR 1.02 (95%CI 0.82-1.26); ≥ 3 years, OR 1.32 (95%CI 1.05-1.65) (p for trend = 0.03).

Conclusions

Ever use of oral bisphosphonates was not associated with a decreased risk of hip fracture in women aged 65 or older as compared to never use. No association between hip fracture risk and cumulative duration of bisphosphonate treatment was observed. However, when treatment duration is analysed as time since first prescription, a statistically significant increased risk for hip fracture was observed in patients exposed to bisphosphonates over 3 years.

Trial Registration

Spanish Ministry of Health. TRA-071

INTRODUCTION

Background

When bisphosphonates came onto the market, they had demonstrated efficacy in the improvement of bone density, but there was no evidence for reduction of hip fractures. They were introduced on the theoretical assumption that the increase in bone density implied strengthening of the bone structure, and therefore a reduction in the risk of fracture.

In most pivotal trials comparing the effects of alendronate,[1-4] risedronate, [5-7] or ibandronate[8] versus placebo hip fractures were considered as secondary endpoints and outcomes did not show any clear potential benefit in decreasing hip fracture risk. Several meta-analyses of alendronate and risedronate have been carried out and a statistically significant benefit of these drugs over placebo is claimed. However, the clinical significance of the findings is debateable and methodology biases are also present in the reviews.[9] A recent meta-analysis obtained similar results. However, trials' quality assessment was carried out and revealed an unclear or high risk of bias in approximately 75% of the trials. This means that the small significant reduction in hip fracture may not be real, or at best, is an exaggeration of the real benefit.[10]

In 2006 the longest ever clinical trial evaluating the effects of bisphosphonates was published. After 5 years under alendronate, women were randomized to either continue taking the drug or receive placebo for another five years. Discontinuation of alendronate for up to five years did not increase fracture risk.[11] However no comparison between alendronate use versus no use was established. This prompted us to carry out the present study.[12]

The long-term use of bisphosphonates has been associated with deleterious effects on bone structure such as osteonecrosis of the jaw, atypical

fractures and bone pain that prompted several safety communications issued by both the FDA and EMA.[13,14]

In 2008 a cohort study in Danish women with no previous hip fracture was published. The incidence of hip fractures increased in the group treated with alendronate by 50% in relative terms and by 6 cases per 1,000 women–years in absolute terms[15]. Updated information from this Danish cohort was published in 2010 and the increased incidence of hip fractures in women taking alendronate was confirmed.[16]

Objective

The aim of this study is to evaluate the association between long-term use of bisphosphonates and the risk of hip fracture compared to never use among women aged 65 years or older.

METHODS

Study design and setting

We carried out a case-control study nested in a cohort in Spain using the information from BIFAP (*Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria,* Database for Pharmacoepidemiologic Research in Primary Care). This is a longitudinal population-based database kept by the Spanish Agency for Medicines and Medical Devices that collates, from 2001 onwards, the computerized medical records of more than 1,800 physicians throughout Spain. It includes anonymized information on over 3.2 million patients, totalling over 13.7 million person-years of follow up.[17,18]

This project was approved by the Navarre Research Ethics Board, Pamplona, Spain. All data were anonymized and no written consent was necessary for this type of study according to the Spanish regulations (law 41/2002, article 16).

Participants

Cases were defined as women aged 65 years or older with a first diagnosis of hip fracture, using the ICPC-1 codes, recorded between 01/01/2005 and 31/12/2008, and with at least 1 year of follow-up in BIFAP before the event date. The date of hospitalization served as the index date. All hip fracture cases were double-checked and validated by both BIFAP and the research team. We excluded women with any history of cancer, Paget disease,

prevalent hip fracture and fractures resulting from trauma or motor vehicle collisions. For each case, 5 controls with no history of hip fracture by the time of the index date of their corresponding case were selected, matched by same age and calendar year of enrolment in BIFAP.

Medication use and other covariates

Use of bisphosphonates before the index date was obtained from the computerized database. Duration of bisphosphonate exposure was evaluated by examining prescriptions for oral alendronate, risedronate, ibandronate or etidronate from the beginning of therapy to the index date or the corresponding date among controls (ATC codes: alendronate, M05BA04; alendronate plus vitamin D, M05BB; risedronate, M05BA07 and ibandronate, M05BA06).

Individuals were classified as ever vs never users. Ever users were also divided into *current users* (if most recent prescription lasted through index date or ended in the month before it), *recent users* (if most recent prescription ended between 1 and 6 months before index date) and *past users* (if most recent prescription ended more than 6 months before index date).

In order to assess the effects of treatment length on the outcomes two criteria were used: a) Cumulative duration of actual treatment; and b) Time since first prescription. In both, three different subgroups were considered, namely <1 year; 1 to 3 years and over 3 years.

Information on comorbilities (ICPC-1 codes) and use of other medications (ATC codes) was obtained. Patients were considered exposed if the most recent prescription lasted through index date or ended in the month before it. Other variables such as weight (kg), height (cm), body mass index (kg/m^2) and smoking status (yes/no/past smoker) were obtained as well.

Statistical methods

Between 2005 and 2008 we expected to find some 2,000 cases and 10,000 controls in our database. This would provide statistical power >90% to detect a change >20% in the risk of having hip fracture associated to biphosphonate use with an alpha risk of 5% and a prevalence of exposure of 20%.

We used conditional logistic regression to estimate the odds ratios (ORs) and 95 percent confidence intervals (CIs) for the association between bisphosphonate exposure and hip fractures. Bisphosphonate use was categorized as ever vs never. In separate analyses, current, recent, or past use was also evaluated. Treatment duration was assessed as well and results were tested to identify a trend. The level of significance was established at $p = 0.05$. In the duration analysis adjusted for exposure, never users was considered as the reference group. The results were also

compared to bisphosphonate users for less than one year as a sensitivity analysis in case of selection bias.

An initial "model 1" adjusted only for matching variables. A second "model 2" adjusted additionally for smoking, BMI, alcoholism, previous fracture, kidney disease, malabsorption, stroke, dementia, rheumatoid arthritis, diabetes, epilepsy, Parkinson disease, thyroid disease, PPI (no use, <=1 yr, >1 yr), anxiolytics, sedatives, antidepressants, antihypertensives, oral corticosteroids (no use, <=1 yr, >1 yr), raloxifene, hormone replacement therapy, and thiazolidinediones.

RESULTS

Participants

Between 2005 and 2008, 3,181 potentially eligible cases were registered. Out of them we validated 2,069 hip fractures and 45 atypical fractures (31 subtrochanteric and 14 shaft fractures). Of the remainder 1,067 records were classified as "no case", 718 "other diagnoses" and 349 "lacking information". Sixty cases were excluded due to lack of matching controls. A total of 2,009 cases were obtained and 10,045 matching controls were selected (figure 1).

The average age of cases was 82.4 ± 6.6 years. In general terms co-morbidities and drug use was more prevalent in cases while smoking status and BMI were similar between cases and controls (table 1).

Outcome data

Hip fractures were more frequent among bisphosphonate users, 283 (14.1%) compared to never users, 1207 (12.0%). Results according to timing, duration, and bisphosphonate exposure are described in table 2.

Main results

Ever users of bisphosphonates had a higher risk of hip fracture compared to never users (unadjusted OR = 1.21, 95%CI, 1.05-1.39). After adjusting for co-medication and pathologies no significant differences were found between bisphosphonate users and never users, OR = 1.09 (95%CI, 0.94-1.27).

No association between hip fracture risk and cumulative duration of bisphosphonate treatment was observed: <1 year, OR 1.20 (95% CI, 0.97-1.47); 1 to <3 years, OR 0.94 (95% CI, 0.74-1.20); ≥ 3 years, OR 1.15 (95%CI, 0.82-1.60) (p for trend = 0.63). However, when treatment duration is analysed as time since first prescription, hip fracture risk of the different subgroups compared to never users obtained were as follows: <1

year, OR 0.85 (95%CI, 0.60-1.21); 1 to <3 years, OR 1.02 (95%CI 0.82-1.26); ≥ 3 years, OR 1.32 (95%CI 1.05-1.65) (p for trend = 0.03). If women exposed to bisphosphonates during less than one year was considered as the reference group, hip fracture risk observed in the different subgroups were: 1 to <3 years, OR 1.56 (95%CI 0.73-3.31); ≥ 3 years, OR 2.31 (95%CI 1.00-5.36) (p for trend = 0.03) (tables 2 and 3).

No significant trend was observed for timing (past, recent and current use). Past use of bisphosphonates was associated with a statistically significant increase in hip fracture risk (OR = 1.50, 95%CI 1.19-1.89) while current or recent use was not (table 2).

No protective effect on hip fracture risk was observed when the results were analysed by individual drugs. On the contrary, a statistically significant increased risk was found for ibandronate users (OR = 3.67, 95%CI 1.31-10.3) and for switchers as welll (OR = 1.63, 95%CI 1.07-2.47) (table 4).

DISCUSSION

Key results

According to our findings oral bisphosphonates may not decrease hip fracture risk in elderly women. In order to reduce selection bias, results were adjusted for co-pathologies and medication. However, residual selection bias may still occur. In a cohort study in Danish women with a previous fracture but with no previous hip fracture, the risk of hip fracture was increased in the group treated with alendronate.[15,16] This study was performed on alendronate only whereas in our study all oral bisphosphonates were included. Our findings are in line with the Danish study in which a higher hip fracture risk was observed.

A recent meta-analysis of clinical trials assessed the effects of bisphosphonates on hip and wrist fracture risk. Similar results to previous meta-analyses were observed, namely a 1% absolute reduction of hip fracture risk in bisphosphonate users. What is new about this publication is that trials' quality assessment was carried out and revealed an unclear or high risk of bias in approximately 75% of the trials. This means that the small significant reduction in hip fracture may not be real, or at best, is an exaggeration of the real benefit[10**Error! Bookmark not defined.**] which is in line with our findings.

We evaluated the effects of treatment length and the results by individual drugs as secondary outcomes. No association between hip fracture risk and cumulative duration of bisphosphonate treatment was observed. However,

fracture risk increased with longer exposure to bisphosphonates. A statistically significant trend for increased risk of hip fracture was observed among bisphosphonate users irrespective of whether the reference group was never users or women under treatment for less than one year. Results were tested against the two different reference groups because of the possible selection bias in any of them. The results were consistent in both analyses.

According to the results by individual drugs, no protective effect was observed. On the contrary, a statistically significant increased risk was found for ibandronate users and for switchers as well. Probably ibandronate results in our study are conditioned by a small sample size.

No significant trend was observed for timing (past, recent and current use). Past users showed a statistically significant higher fracture risk when compared to never users while current or recent users did not. This could be interpreted as if bisphosphonates provided a protective effect on hip fracture risk that disapears after drug withdrawal. However there are some other possible explanations for this. First, treatment withdrawal could be more frequent in patients suffering from drug adverse reactions, in those who did not tolerate treatment, or had a poorer clinical status. All these patients have a higher fracture risk and selection bias is another possible explanation for a higher fracture risk in patients who stopped taking bisphosphonates.

Second, bisphosphonates accumulate in bone structure and past users are exposed to the drug effects for many years after withdrawal. Given the relatively short follow-up period in this study, all patients are exposed to the drug effects irrespective of whether they are past, recent or current users. Thereby interpreting results according to these subgroups may be meaningless. The FLEX trial shows that there is no difference in hip fracture risk between past and current users. Past users had been under treatment for 5 years and had stopped taking the drug 5 years before assessment. This trial supports that alendronate accumulates in bone and past users are exposed to the drug effects for many years after withdrawal. Thereby it makes sense to consider exposure to bisphosphonates in the results analysis. Also we must take into account that in the FLEX trial there is no selection bias due to randomization, and consequently its findings support that the higher risk observed in the past users in our study may be related to a selection bias and a longer exposure to bisphosphonates in this subgroup as well.

A recent article published by FDA researchers analysed the results of three long-term extension trials on alendronate, risedronate and zoledronic acid. Pooled data pertaining to patients who received continuous bisphosphonate

treatment for 6 or more years resulted in fracture rates ranging from 9.3 to 10.6%, whereas the rate for patients switched to placebo was 8.0 to 8.8%. These data raise the question on whether long-term use of bisphosphonates is beneficial for patients.[19]

With long-term use it is widely accepted that bisphosphonates may cause osteonecrosis of the jaw and atypical fractures as well. Recently, a self-controlled case series analysis showed that bisphosphonate use was associated with osteonecrosis at any site.[20] Deleterious effects on bone structure have been observed with bisphosphonates and denosumab as well but not with other osteoporosis drugs. Both type of drugs inhibit bone turnover and thereby bone strength may be weaker as a result of treatment. Besides bisphosphonates prolong secondary mineralization leading to increased bone density but decreased bone toughness due to a higher mineral content (brittle bones). Since there is biological rationale to explain the harmful effects of bisphosphonates on bone, more long-term studies are needed to test our findings.

Limitations

One of the main limitations in our study is the relatively short follow-up period. Besides, we relied on prescription data to determine duration of bisphosphonate exposure. It is sensible to think that real exposure will likely be lower than registered. In the clinical records included in the BIFAP database, X-ray images are not available which might occasionally lead to misclassification of cases. However we believe this may not be a relevant limitation yet hip fracture cases are described in detail in the surgical procedures.

Another aspect to be pointed out is that ibandronate was marketed in Spain in January 2007 and in our study we included incident cases of hip fracture that occurred between 2005 and 2008. Thereby the exposure of both cases and controls to ibandronate is rather short-term.

Confounding by indication is a possible bias of this study. Theoretically women in a poor baseline condition could be prescribed bisphosphonates to a greater extent when compared to women with a better health status. In order to minimize this bias, results were adjusted for previous fractures, comorbidities and use of other medications.

Bone mineral density determination is not a standard test available in the public health system in Spain. Thereby information on BMD in clinical records was rather scarce. However, this test has a very poor fracture risk predictive value and its clinical relevance can be challenged. When it comes

to adjusting crude data we used other bone-related variables instead such as prevalence of previous fractures.

Conclusions

Ever use of oral bisphosphonates was not associated with a decreased risk of hip fracture in women aged 65 or older as compared to never use. No association between hip fracture risk and cumulative duration of bisphosphonate treatment was observed. However, when treatment duration is analysed as time since first prescription, a statistically significant increased risk for hip fracture was observed in patients exposed to bisphosphonates over 3 years.

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Disclaimer:

The Spanish Agency of Medicines and Medical Devices (AEMPS) provided the crude data from BIFAP to the researchers according to an agreement with the Health Department of Navarre Government but did not take part in the design or in the study development. Authors are fully responsible for the analysis, results and opinions appearing in the paper and do not represent the position of the AEMPS. The views expressed are those of the authors only and do not represent necessarily the position of their respective institutions.

Footnotes

- Contributors JE, AA, JG and AL were responsible for developing of study concept and design, data validation and interpretation of the results. AA performed the statistical analyses. JE drafted the manuscript. All authors have been involved in revising and elaborating it critically in the intellectual context.
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- Competing interests: None.
- Ethics approval: Navarre Research Ethics Board, Pamplona, Spain.
- Data sharing statement: There are no additional data sharing to other parties.

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Table 1. Characteristics of cases and controls

	Cases	Controls
N	2009	10045
Age, years (±SD)	82.4 (6.6)	82.4 (6.6)
Smoking		
Non-current smoker, %	69.5	73.4
Current smoker, %	2.7	2.0
Not recorded, %	27.8	24.6
Alcoholism, %	0.4	0.2
Body mass index, kg/m^2 (±SD)	27.2 (5.0)	29.0 (5.0)
<20 kg/m^2, %	2.7	1.0
20-<25 kg/m^2, %	17.6	12.2
25-<30 kg/m^2, %	25.5	28.9
≥30 kg/m^2, %	19.8	30.8
Not recorded, %	34.4	27.1
Comorbidities		
Previous fracture, %	17.2	10.1
Kidney disease, %	4.9	3.6
Malabsorption, %	2.3	2.1
Stroke, %	10.7	6.2
Dementia, %	14.6	6.2
Rheumatoid arthritis, %	2.3	1.3
Diabetes, %	22.2	17.7
Epilepsy, %	1.4	0.9
Parkinson disease, %	4.9	1.9
Thyroid disease, %	10.2	10.8
Use of medication		
PPI or H2 receptor blocker, %	38.2	34.0
Anxiolytic, %	29.1	24.8
Antidepressants, %	22.6	13.8
Antihypertensives, %	56.8	61.6
Oral corticosteroids, %	8.0	7.4
Sedatives, %	11.8	9.3
Raloxifene, %	0.3	0.5
Hormone replacement therapy, %	0.0	0.0
Thiazolidinedione, %	0.3	0.2

Values correspond to percentage or means (standard deviation)

Table 2. Association of any bisphosphonate use with the risk of hip fracture.

	Cases	Controls	Average cumulative duration (days)	Time since first BP prescription (days)	Model 1	Model 2
	n (%)	n (%)	Mean (SD)	Mean (SD)	OR (95% CI)	OR (95% CI)
Use						
No use	1726 (85.9)	8838 (88.0)	-	-	1 (ref.)	1 (ref.)
Ever use	283 (14.1)	1207 (12.0)	600 (556)	968 (622)	1.21 (1.05-1.39)	1.09 (0.94-1.27)
Timing						
No use	1726 (85.9)	8838 (88.0)	-	-	1 (ref.)	1 (ref.)
Past use	111 (5.5)	347 (3.5)	315(415)	1164 (601)	1.63 (1.31-2.04)	1.50 (1.19-1.89)
Recent use	43 (2.1)	127 (1.3)	515(521)	774 (599)	1.74 (1.22-2.47)	1.34 (0.92-1.95)
Current use	129 (6.4)	733 (7.3)	769(563)	903 (612)	0.90 (0.74-1.10)	0.84 (0.68-1.03)
p for trend					0.54	0.53
Duration						
Never use	1726 (85.9)	8838 (88.0)	-	-	1 (ref.)	1 (ref.)
≤1 yr	139 (6.9)	533 (5.3)	147 (106)	687 (590)	1.34 (1.10-1.63)	1.20 (0.97-1.47)
>1 yr - ≤3 yr	92 (4.6)	458 (4.6)	684 (211)	956 (419)	1.03 (0.82-1.30)	0.94 (0.74-1.20)
>3 yr	52 (2.6)	216 (2.2)	1566 (375)	1698 (437)	1.25 (0.91-1.70)	1.15 (0.82-1.60)
p for trend					0.16*	0.63*
Time since first BP use						
No use	1726 (85.9)	8838 (88.0)	-	-	1 (ref.)	1 (ref.)
<1 yr	41 (2.0)	222 (2.2)	140 (99)	194 (103)	0.95 (0.67-1.33)	0.85 (0.60-1.21)
1 - <3 yr	120 (6.0)	546 (5.4)	454 (299)	727 (209)	1.13 (0.92-1.38)	1.02 (0.82-1.26)
≥3 yr	122 (6.1)	439 (4.4)	990 (660)	1618 (445)	1.44 (1.17-1.78)	1.32 (1.05-1.65)
p for trend**					0.0008	0.03

Model 1: Conditional logistic regression model; Model 2: Conditional logistic regression model adjusted for smoking, BMI, alcoholism, previous fracture, kidney disease, malabsorption, stroke, dementia, rheumatoid arthritis, diabetes, epilepsy, Parkinson disease, and thyroid disease, PPI (no use, <=1 yr, >1 yr), anxiolytics, sedatives, antidepressants, antihypertensives, oral corticosteroids (no use, <=1 yr, >1 yr), raloxifene, hormone replacement therapy, and thiazolidinediones

* Modeled as the median duration of use in each category; ** Modeled as time in days since first bisphosphonate prescription (0 for no users)

Table 3. Risk of hip fracture by time since first prescription for bisphosphonates

	Cases	Controls	Average cumulative duration (days)	Time since first BP prescription (days)	Model 1	Model 2
	n (%)	n (%)	Mean (SD)	Mean (SD)	OR (95% CI)	OR (95% CI)
Time since first BP use						
<1 yr	41 (14.5)	222 (18.4)	157 (133)	194 (103)	1 (ref)	1 (ref)
1 - <3yr	120 (42.4)	546 (45.2)	535 (451)	727 (209)	1.23 (0.68-2.23)	1.49 (0.71-3.13)
≥3 yr	122 (43.1)	439 (36.4)	1138 (873)	1618 (445)	1.79 (0.94-3.40)	2.21 (0.96-5.09)
p for trend*					0.03	0.03

Model 1: Conditional logistic regression model

Model 2: Conditional logistic regression model adjusted for smoking, BMI, alcoholism, previous fracture, kidney disease, malabsorption, stroke, dementia, rheumatoid arthritis, diabetes, epilepsy, Parkinson disease, and thyroid disease, PPI (no use, <=1 yr, >1 yr), anxiolytics, sedatives, antidepressants, antihypertensives, oral corticosteroids (no use, <=1 yr, >1 yr), raloxifene, hormone replacement therapy, and thiazolidinediones

* Modeled as time in days since first bisphosphonate prescription

Table 4. Association of ever use of individual bisphosphonates with the risk of hip fracture.

	Cases	Controls	Average duration	Time since first prescription	Model 1	Model 2
	n (%)	n (%)	(days)	(days)	OR (95% CI)	OR (95% CI)
Never use	1726 (85.9)	8838 (88.0)	-	-	1 (ref.)	1 (ref.)
Alendronate	128 (6.4)	598 (6.0)	599 (566)	956 (603)	1.10 (0.90-1.34)	0.99 (0.81-1.22)
Risedronate	95 (4.7)	438 (4.4)	508 (459)	822 (503)	1.12 (0.89-1.41)	1.02 (0.81-1.30)
Etidronate	19 (1.0)	63 (0.6)	818 (629)	1478 (746)	1.55 (0.92-2.59)	1.56 (0.91-2.65)
Ibandronate	7 (0.4)	9 (0.1)	161 (137)	239 (151)	4.18 (1.55-11.2)	3.67 (1.31-10.3)
Switcher	34 (1.7)	99 (1.0)	898 (676)	1397 (714)	1.80 (1.21-2.68)	1.63 (1.07-2.47)

Model 1: Conditional logistic regression model

Model 2: Conditional logistic regression model adjusted for smoking, BMI, and alcoholism, previous fracture, kidney disease, malabsorption, stroke, dementia, rheumatoid arthritis, diabetes, epilepsy, Parkinson disease, and thyroid disease, PPI (no use, <=1 yr, >1 yr), anxiolytics, sedatives, antidepressants, antihypertensives, oral corticosteroids (no use, <=1 yr, >1 yr), raloxifene, hormone replacement therapy, and thiazolidinediones

Figure 1. Selection of study population

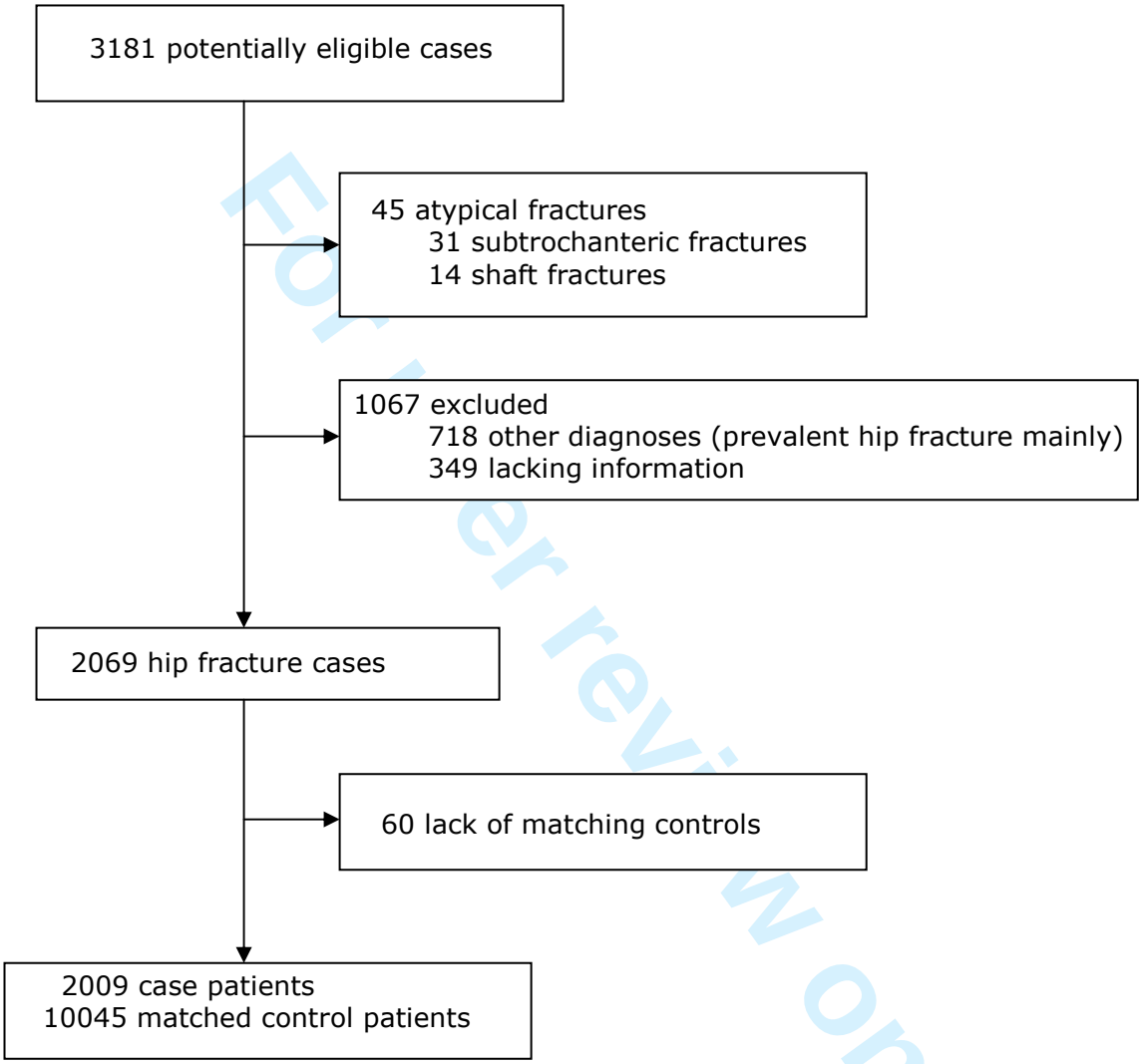
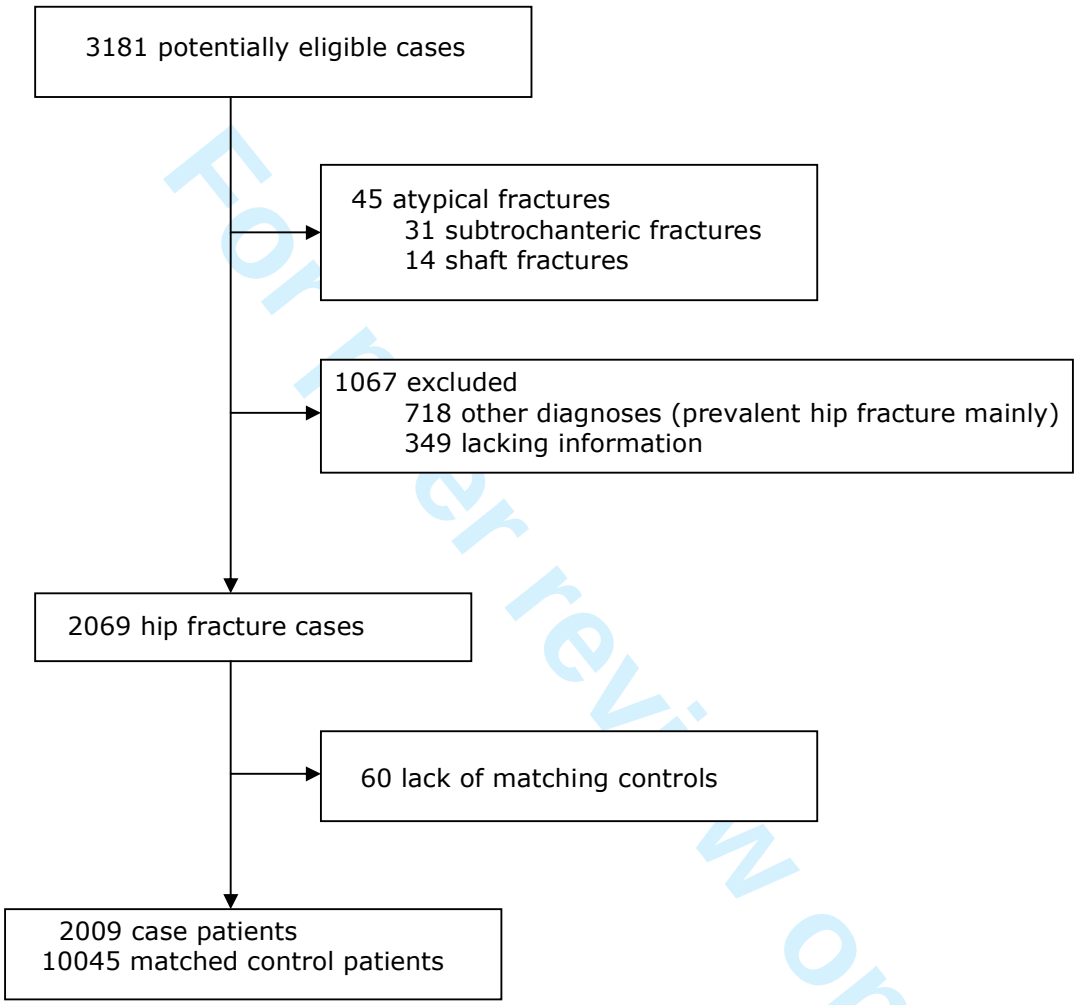


Figure 1. Selection of study population



STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract. **OK**	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **OK**	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **OK**	
Objectives	3	State specific objectives, including any pre-specified hypotheses **OK**	
Methods			
Study design	4	Present key elements of study design early in the paper **OK**	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **OK**	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls **OK** *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case **OK**	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **OK**	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **OK**	
Bias	9	Describe any efforts to address potential sources of bias **OK**	
Study size	10	Explain how the study size was arrived at **OK**	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **OK**	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **OK**	
		(*b*) Describe any methods used to examine subgroups and interactions **OK**	
		(*c*) Explain how missing data were addressed **OK**	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed **OK**	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **OK**	
		(b) Give reasons for non-participation at each stage Not applicable	
		(c) Consider use of a flow diagram Not applicable	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **OK**	
		(b) Indicate number of participants with missing data for each variable of interest **OK**	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure **OK**	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **OK**	
		(*b*) Report category boundaries when continuous variables were categorized **OK**	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **OK**	
Discussion			
Key results	18	Summarise key results with reference to study objectives **OK**	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **OK**	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **OK**	
Generalisability	21	Discuss the generalisability (external validity) of the study results **OK**	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **OK**	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

ORAL BISPHOSPHONATES MAY NOT DECREASE HIP FRACTURE RISK IN ELDERLY SPANISH WOMEN

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TITLE

ORAL BISPHOSPHONATES MAY NOT DECREASE HIP FRACTURE RISK IN ELDERLY SPANISH WOMEN

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ARTICLE SUMMARY

Article Focus

. The hypothesis of this study is that oral bisphosphonates may not be effective in reducing hip fracture risk in clinical practice in the long-term use.

Key messages

. Ever use of oral bisphosphonates was not associated with a decreased risk of hip fracture in women aged 65 or older as compared to never use.

. No association between hip fracture risk and cumulative duration of bisphosphonate treatment was observed.

. When treatment duration is analysed as time since first prescription, a statistically significant increased risk for hip fracture was observed in patients exposed to bisphosphonates over 3 years.

Strengths and limitations

. The main strength of this study is that it sheds light on the effects of oral bisphosphonates on hip fracture risk in clinical practice in a Mediterranean population.

. One of the main limitations is the relatively short follow-up period.

ABSTRACT

Objectives

To evaluate the association between long-term use of bisphosphonates and the risk of hip fracture compared to never use among women aged 65 years or older.

Design

Case-control study nested in a cohort.

Setting

General practice research database operated by the Spanish Medicines Agency.

Participants:

Cases of hip fracture were defined as women aged 65 years or older with a validated first diagnosis of hip fracture between 2005 and 2008. Five controls free of hip fracture were matched on age and calendar year with each case.

Interventions

Information on bisphosphonate use, hip fractures, comedication, and comorbidities was collected.

Primary outcomes

Hip fracture risk comparing bisphosphonate users vs never users

Secondary outcomes

Hip fracture risk comparing bisphosphonate users vs never users by individual drugs

Results

The study included 2,009 incident hip fractures and 10,045 matched controls. Hip fracture risk did not differ between bisphosphonate users and never users, adjusted OR = 1.09 (95% CI, 0.94-1.27). No association between hip fracture risk and cumulative duration of bisphosphonate treatment was observed. However, when treatment duration is analysed as time since first prescription, hip fracture risk of the different subgroups compared to never users obtained were as follows: <1 year, OR 0.85 (95%CI, 0.60-1.21); 1 to <3 years, OR 1.02 (95%CI 0.82-1.26); ≥ 3 years, OR 1.32 (95%CI 1.05-1.65) (p for trend = 0.03).

Conclusions

Ever use of oral bisphosphonates was not associated with a decreased risk of hip fracture in women aged 65 or older as compared to never use. No association between hip fracture risk and cumulative duration of bisphosphonate treatment was observed. However, when treatment duration is analysed as time since first prescription, a statistically significant increased risk for hip fracture was observed in patients exposed to bisphosphonates over 3 years.

Trial Registration

Spanish Ministry of Health. TRA-071

INTRODUCTION

Background

When bisphosphonates came onto the market, they had demonstrated efficacy in the improvement of bone density, but there was no evidence for reduction of hip fractures. They were introduced on the theoretical assumption that the increase in bone density implied strengthening of the bone structure, and therefore a reduction in the risk of fracture.

In most pivotal trials comparing the effects of alendronate,[1-4] risedronate, [5-7] or ibandronate[8] versus placebo hip fractures were considered as secondary endpoints and outcomes did not show any clear potential benefit in decreasing hip fracture risk. Several meta-analyses of alendronate and risedronate have been carried out and a statistically significant benefit of these drugs over placebo is reported. However, the clinical significance of the findings is debateable and methodology biases are also present in the reviews.[9] A recent meta-analysis obtained similar results. However, trials' quality assessment was carried out and revealed an unclear or high risk of bias in approximately 75% of the trials. This means that the small significant reduction in hip fracture may not be real, or at best, is an exaggeration of the real benefit.[10]

In 2006 the longest ever clinical trial evaluating the effects of bisphosphonates was published. After 5 years under alendronate, women were randomized to either continue taking the drug or receive placebo for another five years. Discontinuation of alendronate for up to five years did not change numerically or statistically either nonspine or hip fracture incidence.[11] However no comparison between alendronate use versus no use was established. This prompted us to carry out the present study.[12]

The long-term use of bisphosphonates has been associated with deleterious effects on bone structure such as osteonecrosis of the jaw, atypical

fractures (subtrochanteric and diaphyseal), and bone pain that prompted several safety communications issued by both the FDA and EMA.[13,14]

In 2008 a cohort study in Danish women with no previous hip fracture was published. The incidence of hip fractures increased in the group treated with alendronate by 50% in relative terms and by 6 cases per 1,000 women–years in absolute terms[15]. Updated information from this Danish cohort was published in 2010 and the increased incidence of hip fractures in women taking alendronate was confirmed.[16]

Objective

The aim of this study is to evaluate the association between long-term use of bisphosphonates and the risk of hip fracture compared to never use among women aged 65 years or older.

METHODS

Study design and setting

We carried out a case-control study nested in a cohort in Spain using the information from BIFAP (*Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria,* Database for Pharmacoepidemiologic Research in Primary Care). This is a longitudinal population-based database kept by the Spanish Agency for Medicines and Medical Devices that collates, from 2001 onwards, the computerized medical records of more than 1,800 physicians throughout Spain. It includes anonymized information on over 3.2 million patients, totalling over 13.7 million person-years of follow up.[17,18]

This project was approved by the Navarre Research Ethics Board, Pamplona, Spain. All data were anonymized and no written consent was necessary for this type of study according to the Spanish regulations (law 41/2002, article 16).

Participants

Cases were defined as women aged 65 years or older with a first diagnosis of hip fracture, using the ICPC-1 codes, recorded between 01/01/2005 and 31/12/2008, and with at least 1 year of follow-up in BIFAP before the event date. The date of hospitalization served as the index date. All hip fracture cases were double-checked and validated by both BIFAP and the research team. We excluded women with any history of cancer, Paget disease,

prevalent hip fracture and fractures resulting from trauma or motor vehicle collisions. For each case, 5 controls with no history of hip fracture by the time of the index date of their corresponding case were selected, matched by same age and calendar year of enrolment in BIFAP.

Medication use and other covariates

Use of bisphosphonates before the index date was obtained from the computerized database. Duration of bisphosphonate exposure was evaluated by examining prescriptions for oral alendronate, risedronate, ibandronate or etidronate from the beginning of therapy to the index date or the corresponding date among controls (ATC codes: alendronate, M05BA04; alendronate plus vitamin D, M05BB; risedronate, M05BA07 and ibandronate, M05BA06).

Individuals were classified as ever vs never users. Ever users were also divided into *current users* (if most recent prescription lasted through index date or ended in the month before it), *recent users* (if most recent prescription ended between 1 and 6 months before index date) and *past users* (if most recent prescription ended more than 6 months before index date).

In order to assess the effects of treatment length on the outcomes four different subgroups were considered based on cumulative duration of actual treatment, namely 30 days or less; >30 days to ≤1 year; >1 to ≤3 years and over 3 years. The effects of time of bisphosphonate exposure on hip fracture risk were also analyzed. Exposure was measured as the time (in days) since the first prescription.

Information on comorbilities (ICPC-1 codes) and use of other medications (ATC codes) was obtained. Patients were considered exposed if the most recent prescription lasted through index date or ended in the month before it. Other variables such as weight (kg), height (cm), body mass index (kg/m^2) and smoking status (yes/no/past smoker) were obtained as well.

Statistical methods

Between 2005 and 2008 we expected to find some 2,000 cases and 10,000 controls in our database. This would provide statistical power >90% to detect a change >20% in the risk of having hip fracture associated to biphosphonate use with an alpha risk of 5% and a prevalence of exposure of 20%.

We used conditional logistic regression to estimate the odds ratios (ORs) and 95 percent confidence intervals (CIs) for the association between bisphosphonate exposure and hip fractures. Bisphosphonate use was categorized as ever vs never. In separate analyses, current, recent, or past use was also evaluated. Treatment duration was assessed as well and results were tested to identify a trend. The level of significance was

established at p = 0.05. In the duration analysis adjusted for exposure, never users was considered as the reference group. The results were also compared to bisphosphonate users for less than one year as a sensitivity analysis in case of selection bias.

An initial "model 1" adjusted only for matching variables. A second "model 2" adjusted additionally for smoking, BMI, alcoholism, previous fracture, kidney disease, malabsorption, stroke, dementia, rheumatoid arthritis, diabetes, epilepsy, Parkinson disease, thyroid disease, PPI (no use, <=1 yr, >1 yr), anxiolytics, sedatives, antidepressants, antihypertensives, oral corticosteroids (no use, <=1 yr, >1 yr), raloxifene, hormone replacement therapy, and thiazolidinediones.

RESULTS

Participants

Between 2005 and 2008, 3,181 potentially eligible cases were registered. Out of them we validated 2,069 hip fractures and 45 atypical fractures (31 subtrochanteric and 14 shaft fractures). Of the remainder 1,067 records were classified as "no case", 718 "other diagnoses" and 349 "lacking information". Sixty cases were excluded due to lack of matching controls. A total of 2,009 cases were obtained and 10,045 matching controls were selected (figure 1).

The average age of cases was 82.4 ± 6.6 years. In general terms co-morbidities and drug use was more prevalent in cases while smoking status and BMI were similar between cases and controls (table 1).

Outcome data

Hip fractures were more frequent among bisphosphonate users, 283 (14.1%) compared to never users, 1207 (12.0%). Results according to timing, duration, and bisphosphonate exposure are described in table 2.

Main results

Ever users of bisphosphonates had a higher risk of hip fracture compared to never users (unadjusted OR = 1.21, 95%CI, 1.05-1.39). After adjusting for co-medication and pathologies no significant differences were found between bisphosphonate users and never users, OR = 1.09 (95%CI, 0.94-1.27).

No association between hip fracture risk and cumulative duration of bisphosphonate treatment was observed: <1 year, OR 1.20 (95% CI, 0.97-1.47); 1 to <3 years, OR 0.94 (95% CI, 0.74-1.20); ≥ 3 years, OR 1.15 (95%CI, 0.82-1.60) (p for trend = 0.63). However, when treatment

duration is analysed as time since first prescription, hip fracture risk of the different subgroups compared to never users obtained were as follows: <1 year, OR 0.85 (95%CI, 0.60-1.21); 1 to <3 years, OR 1.02 (95%CI 0.82-1.26); ≥ 3 years, OR 1.32 (95%CI 1.05-1.65) (p for trend = 0.03). If women exposed to bisphosphonates during less than one year was considered as the reference group, hip fracture risk observed in the different subgroups were: 1 to <3 years, OR 1.56 (95%CI 0.73-3.31); ≥ 3 years, OR 2.31 (95%CI 1.00-5.36) (p for trend = 0.03) (tables 2 and 3).

No significant trend was observed for timing (past, recent and current use). Past use of bisphosphonates was associated with a statistically significant increase in hip fracture risk (OR = 1.50, 95%CI 1.19-1.89) while current or recent use was not (table 2).

No protective effect on hip fracture risk was observed when the results were analysed by individual drugs. On the contrary, a statistically significant increased risk was found for ibandronate users (OR = 3.67, 95%CI 1.31-10.3) and for switchers as welll (OR = 1.63, 95%CI 1.07-2.47) (table 4).

DISCUSSION

Key results

According to our findings oral bisphosphonates may not decrease hip fracture risk in elderly women. In order to reduce selection bias, results were adjusted for co-pathologies and medication. However, residual selection bias may still occur. In a cohort study in Danish women with a previous fracture but with no previous hip fracture, the risk of hip fracture was increased in the group treated with alendronate.[15,16] This study was performed on alendronate only whereas in our study all oral bisphosphonates were included. Our findings are in line with the Danish study in which a higher hip fracture risk was observed.

A recent meta-analysis of clinical trials assessed the effects of bisphosphonates on hip and wrist fracture risk. Similar results to previous meta-analyses were observed, namely a 1% absolute reduction of hip fracture risk in bisphosphonate users. What is new about this publication is that trials' quality assessment was carried out and revealed an unclear or high risk of bias in approximately 75% of the trials. This means that the small significant reduction in hip fracture may not be real, or at best, is an exaggeration of the real benefit[10]Error! Bookmark not defined. which is in line with our findings.

We evaluated the effects of treatment length and the results by individual drugs as secondary outcomes. No association between hip fracture risk and cumulative duration of bisphosphonate treatment was observed. However, fracture risk increased with longer exposure to bisphosphonates. A statistically significant trend for increased risk of hip fracture was observed among bisphosphonate users irrespective of whether the reference group was never users or women under treatment for less than one year. Results were tested against the two different reference groups because of the possible selection bias in any of them. The results were consistent in both analyses.

According to the results by individual drugs, no protective effect was observed. On the contrary, a statistically significant increased risk was found for ibandronate users and for switchers as well. Probably ibandronate results in our study are conditioned by a small sample size.

No significant trend was observed for timing (past, recent and current use). Past users showed a statistically significant higher fracture risk when compared to never users while current or recent users did not. This could be interpreted as if bisphosphonates provided a protective effect on hip fracture risk that disapears after drug withdrawal. However there are some other possible explanations for this. First, treatment withdrawal could be more frequent in patients suffering from drug adverse reactions, in those who did not tolerate treatment, or had a poorer clinical status. All these patients have a higher fracture risk and selection bias is another possible explanation for a higher fracture risk in patients who stopped taking bisphosphonates.

Second, bisphosphonates accumulate in bone structure and past users are exposed to the drug effects for many years after withdrawal. Given the relatively short follow-up period in this study, all patients are exposed to the drug effects irrespective of whether they are past, recent or current users. Thereby interpreting results according to these subgroups may be meaningless. The FLEX trial shows that there is no difference in hip fracture risk between past and current users. Past users had been under treatment for 5 years and had stopped taking the drug 5 years before assessment. This trial supports that alendronate accumulates in bone and past users are exposed to the drug effects for many years after withdrawal. Thereby it makes sense to consider exposure to bisphosphonates in the results analysis. Also we must take into account that in the FLEX trial there is no selection bias due to randomization, and consequently its findings support that the higher risk observed in the past users in our study may be related to a selection bias and a longer exposure to bisphosphonates in this subgroup as well.

A recent article published by FDA researchers analysed the results of three long-term extension trials on alendronate, risedronate and zoledronic acid. Pooled data pertaining to patients who received continuous bisphosphonate treatment for 6 or more years resulted in fracture rates ranging from 9.3 to 10.6%, whereas the rate for patients switched to placebo was 8.0 to 8.8%. These data raise the question on whether long-term use of bisphosphonates is beneficial for patients.[19]

With long-term use it is widely accepted that bisphosphonates may cause osteonecrosis of the jaw and atypical (subtrochanteric and diaphyseal) fractures as well. Recently, a self-controlled case series analysis showed that bisphosphonate use was associated with osteonecrosis at any site.[20] Deleterious effects on bone structure have been observed with bisphosphonates and denosumab as well but not with other osteoporosis drugs. Both type of drugs inhibit bone turnover and thereby bone strength may be weaker as a result of treatment. Besides bisphosphonates prolong secondary mineralization leading to increased bone density but decreased bone toughness due to a higher mineral content (brittle bones).[21] Since there is biological rationale to explain the harmful effects of bisphosphonates on bone, more long-term studies are needed to test our findings.

Limitations

One of the main limitations in our study is the relatively short follow-up period. Besides, we relied on prescription data to determine duration of bisphosphonate exposure. It is sensible to think that real exposure will likely be lower than registered. In the clinical records included in the BIFAP database, X-ray images are not available which might occasionally lead to misclassification of cases. However we believe this may not be a relevant limitation yet hip fracture cases are described in detail in the surgical procedures.

Another aspect to be pointed out is that ibandronate was marketed in Spain in January 2007 and in our study we included incident cases of hip fracture that occurred between 2005 and 2008. Thereby the exposure of both cases and controls to ibandronate is rather short-term.

Confounding by indication is a possible bias of this study. Theoretically women in a poor baseline condition could be prescribed bisphosphonates to a greater extent when compared to women with a better health status. In order to minimize this bias, results were adjusted for previous fractures, comorbidities and use of other medications.

Bone mineral density determination is not a standard test available in the public health system in Spain. Thereby information on BMD in clinical

records was rather scarce. However, this test has a very poor fracture risk predictive value and its clinical relevance can be challenged. When it comes to adjusting crude data we used other bone-related variables instead such as prevalence of previous fractures.

In our study no information on vitamin D plasma levels in our patients was available. However we believe this does not pose any problem since patients were not institutionalized and in Spain the exposure to sunlight is sufficient to ensure adequate levels of vitamin D. Furthermore, almost 90% of women aged 65 or older take supplements of calcium plus vitamin D.[22]

Conclusions

Ever use of oral bisphosphonates was not associated with a decreased risk of hip fracture in women aged 65 or older as compared to never use. No association between hip fracture risk and cumulative duration of bisphosphonate treatment was observed. However, when treatment duration is analysed as time since first prescription, a statistically significant increased risk for hip fracture was observed in patients exposed to bisphosphonates over 3 years.

Acknowledgements

The authors would like to thank the collaboration of general practitioners contributing to BIFAP.

Disclaimer:

The Spanish Agency of Medicines and Medical Devices (AEMPS) provided the crude data from BIFAP to the researchers according to an agreement with the Health Department of Navarre Government but did not take part in the design or in the study development. Authors are fully responsible for the analysis, results and opinions appearing in the paper and do not represent the position of the AEMPS. The views expressed are those of the authors only and do not represent necessarily the position of their respective institutions.

Footnotes

- Contributors JE, AA, JG and AL were responsible for developing of study concept and design, data validation and interpretation of the

results. AA performed the statistical analyses. JE drafted the manuscript. All authors have been involved in revising and elaborating it critically in the intellectual context.

- Funding: The present study is funded by the Spanish Ministry of Health, grant SAS/2481/2009 No TRA-071
- Competing interests: None.
- Ethics approval: Navarre Research Ethics Board, Pamplona, Spain.
- Data sharing statement: There are no additional data sharing to other parties.

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Table 1. Characteristics of cases and controls

	Cases	Controls	P-value*
N	2009	10045	
Age, years	82.4 (6.6)	82.4 (6.6)	1.00
Smoking			0.001
Non-current smoker, %	69.5	73.4	
Current smoker, %	2.7	2.0	
Not recorded, %	27.8	24.6	
Alcoholism, %	0.4	0.2	0.30
Body mass index, kg/m2	27.2 (5.0)	29.0 (5.0)	<0.0001
<20 kg/m2, %	2.7	1.0	<0.0001
20-<25 kg/m2, %	17.6	12.2	
25-<30 kg/m2, %	25.5	28.9	
>=30 kg/m2, %	19.8	30.8	
Not recorded, %	34.4	27.1	
Comorbidities			
Previous fracture, %	17.2	10.1	<0.0001
Kidney disease, %	4.9	3.6	0.006
Malabsorption, %	2.3	2.1	0.54
Stroke, %	10.7	6.2	<0.0001
Dementia, %	14.6	6.2	<0.0001
Rheumatoid arthritis, %	2.3	1.3	0.0006
Diabetes, %	22.2	17.7	<0.0001
Epilepsy, %	1.4	0.9	0.03
Parkinson disease, %	4.9	1.9	<0.0001
Thyroid disease, %	10.2	10.8	0.47
Use of medication			
PPI or H2 receptor blocker, %	38.2	34.0	0.0004
Anxiolytic, %	29.1	24.8	<0.0001
Antidepressants, %	22.6	13.8	<0.0001
Antihypertensives, %	56.8	61.6	<0.0001
Corticosteroids, %	8.0	7.4	0.33
Sedatives, %	11.8	9.3	0.0006
Raloxifene, %	0.3	0.5	0.14
Hormone replacement therapy, %	0.0	0.0	1.00
Thiazolidinedione, %	0.3	0.2	0.43

Values correspond to percentage or means (standard deviation). P-values calculated from chi-square test for categorical values and Student's t test for continuous variables.

Table 2. Association of any bisphosphonate use with the risk of hip fracture.

	Cases	Controls	Average cumulative duration (days)	Time since first BP prescription (days)	Model 1	Model 2
	n (%)	n (%)	Mean (SD)	Mean (SD)	OR (95% CI)	OR (95% CI)
Use						
No use	1726 (85.9)	8838 (88.0)	-	-	1 (ref.)	1 (ref.)
Ever use	283 (14.1)	1207 (12.0)	600 (556)	968 (622)	1.21 (1.05-1.39)	1.09 (0.94-1.27)
Timing						
No use	1726 (85.9)	8838 (88.0)	-	-	1 (ref.)	1 (ref.)
Past use	111 (5.5)	347 (3.5)	315(415)	1164 (601)	1.63 (1.31-2.04)	1.50 (1.19-1.89)
Recent use	43 (2.1)	127 (1.3)	515(521)	774 (599)	1.74 (1.22-2.47)	1.34 (0.92-1.95)
Current use	129 (6.4)	733 (7.3)	769(563)	903 (612)	0.90 (0.74-1.10)	0.84 (0.68-1.03)
p for trend					0.54	0.53
Duration						
No use (≤30 d)	1726 (85.9)	8838 (88.0)	-	-	1 (ref.)	1 (ref.)
>30 d ≤1 yr	139 (6.9)	533 (5.3)	147 (106)	687 (590)	1.34 (1.10-1.63)	1.20 (0.97-1.47)
>1 yr - ≤3 yr	92 (4.6)	458 (4.6)	684 (211)	956 (419)	1.03 (0.82-1.30)	0.94 (0.74-1.20)
>3 yr	52 (2.6)	216 (2.2)	1566 (375)	1698 (437)	1.25 (0.91-1.70)	1.15 (0.82-1.60)
p for trend					0.16*	0.63*
Time since first BP use						
No use (≤30 d)	1726 (85.9)	8838 (88.0)	-	-	1 (ref.)	1 (ref.)
>30 d ≤1 yr	41 (2.0)	222 (2.2)	140 (99)	194 (103)	0.95 (0.67-1.33)	0.85 (0.60-1.21)
>1 yr - ≤3 yr	120 (6.0)	546 (5.4)	454 (299)	727 (209)	1.13 (0.92-1.38)	1.02 (0.82-1.26)
>3 yr	122 (6.1)	439 (4.4)	990 (660)	1618 (445)	1.44 (1.17-1.78)	1.32 (1.05-1.65)
p for trend**					0.0008	0.03

Model 1: Conditional logistic regression model; Model 2: Conditional logistic regression model adjusted for smoking, BMI, alcoholism, previous fracture, kidney disease, malabsorption, stroke, dementia, rheumatoid arthritis, diabetes, epilepsy, Parkinson disease, and thyroid disease, PPI (no use, <=1 yr, >1 yr), anxiolytics, sedatives, antidepressants, antihypertensives, oral corticosteroids (no use, <=1 yr, >1 yr), raloxifene, hormone replacement therapy, and thiazolidinediones

* Modeled as the median duration of use in each category; ** Modeled as time in days since first bisphosphonate prescription (0 for no users)

Table 3. Risk of hip fracture by time since first prescription for bisphosphonates

	Cases	Controls	Average cumulative duration (days)	Time since first BP prescription (days)	Model 1	Model 2
	n (%)	n (%)	Mean (SD)	Mean (SD)	OR (95% CI)	OR (95% CI)
Time since first BP use						
>30 d ≤1 yr	41 (14.5)	222 (18.4)	157 (133)	194 (103)	1 (ref)	1 (ref)
>1 yr - ≤3 yr	120 (42.4)	546 (45.2)	535 (451)	727 (209)	1.23 (0.68-2.23)	1.49 (0.71-3.13)
>3 yr	122 (43.1)	439 (36.4)	1138 (873)	1618 (445)	1.79 (0.94-3.40)	2.21 (0.96-5.09)
p for trend*					0.03	0.03

Model 1: Conditional logistic regression model

Model 2: Conditional logistic regression model adjusted for smoking, BMI, alcoholism, previous fracture, kidney disease, malabsorption, stroke, dementia, rheumatoid arthritis, diabetes, epilepsy, Parkinson disease, and thyroid disease, PPI (no use, <=1 yr, >1 yr), anxiolytics, sedatives, antidepressants, antihypertensives, oral corticosteroids (no use, <=1 yr, >1 yr), raloxifene, hormone replacement therapy, and thiazolidinediones

* Modeled as time in days since first bisphosphonate prescription

Table 4. Association of ever use of individual bisphosphonates with the risk of hip fracture.

	Cases	Controls	Average duration	Time since first prescription	Model 1	Model 2
	n (%)	n (%)	(days)	(days)	OR (95% CI)	OR (95% CI)
Never use	1726 (85.9)	8838 (88.0)	-	-	1 (ref.)	1 (ref.)
Alendronate	128 (6.4)	598 (6.0)	599 (566)	956 (603)	1.10 (0.90-1.34)	0.99 (0.81-1.22)
Risedronate	95 (4.7)	438 (4.4)	508 (459)	822 (503)	1.12 (0.89-1.41)	1.02 (0.81-1.30)
Etidronate	19 (1.0)	63 (0.6)	818 (629)	1478 (746)	1.55 (0.92-2.59)	1.56 (0.91-2.65)
Ibandronate	7 (0.4)	9 (0.1)	161 (137)	239 (151)	4.18 (1.55-11.2)	3.67 (1.31-10.3)
Switcher	34 (1.7)	99 (1.0)	898 (676)	1397 (714)	1.80 (1.21-2.68)	1.63 (1.07-2.47)

Model 1: Conditional logistic regression model

Model 2: Conditional logistic regression model adjusted for smoking, BMI, and alcoholism, previous fracture, kidney disease, malabsorption, stroke, dementia, rheumatoid arthritis, diabetes, epilepsy, Parkinson disease, and thyroid disease, PPI (no use, <=1 yr, >1 yr), anxiolytics, sedatives, antidepressants, antihypertensives, oral corticosteroids (no use, <=1 yr, >1 yr), raloxifene, hormone replacement therapy, and thiazolidinediones

TITLE

ORAL BISPHOSPHONATES MAY NOT DECREASE HIP FRACTURE RISK IN ELDERLY SPANISH WOMEN

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ARTICLE SUMMARY

Article Focus

. The hypothesis of this study is that oral bisphosphonates may not be effective in reducing hip fracture risk in clinical practice in the long-term use.

Key messages

. Ever use of oral bisphosphonates was not associated with a decreased risk of hip fracture in women aged 65 or older as compared to never use.

. No association between hip fracture risk and cumulative duration of bisphosphonate treatment was observed.

. When treatment duration is analysed as time since first prescription, a statistically significant increased risk for hip fracture was observed in patients exposed to bisphosphonates over 3 years.

Strengths and limitations

. The main strength of this study is that it sheds light on the effects of oral bisphosphonates on hip fracture risk in clinical practice in a Mediterranean population.

. One of the main limitations is the relatively short follow-up period.

ABSTRACT

Objectives

To evaluate the association between long-term use of bisphosphonates and the risk of hip fracture compared to never use among women aged 65 years or older.

Design

Case-control study nested in a cohort.

Setting

General practice research database operated by the Spanish Medicines Agency.

Participants:

Cases of hip fracture were defined as women aged 65 years or older with a validated first diagnosis of hip fracture between 2005 and 2008. Five controls free of hip fracture were matched on age and calendar year with each case.

Interventions

Information on bisphosphonate use, hip fractures, comedication, and comorbidities was collected.

Primary outcomes

Hip fracture risk comparing bisphosphonate users vs never users

Secondary outcomes

Hip fracture risk comparing bisphosphonate users vs never users by individual drugs

Results

The study included 2,009 incident hip fractures and 10,045 matched controls. Hip fracture risk did not differ between bisphosphonate users and never users, adjusted OR = 1.09 (95% CI, 0.94-1.27). No association between hip fracture risk and cumulative duration of bisphosphonate treatment was observed. However, when treatment duration is analysed as time since first prescription, hip fracture risk of the different subgroups compared to never users obtained were as follows: <1 year, OR 0.85 (95%CI, 0.60-1.21); 1 to <3 years, OR 1.02 (95%CI 0.82-1.26); ≥ 3 years, OR 1.32 (95%CI 1.05-1.65) (p for trend = 0.03).

Conclusions

Ever use of oral bisphosphonates was not associated with a decreased risk of hip fracture in women aged 65 or older as compared to never use. No association between hip fracture risk and cumulative duration of bisphosphonate treatment was observed. However, when treatment duration is analysed as time since first prescription, a statistically significant increased risk for hip fracture was observed in patients exposed to bisphosphonates over 3 years.

Trial Registration

Spanish Ministry of Health. TRA-071

INTRODUCTION

Background

When bisphosphonates came onto the market, they had demonstrated efficacy in the improvement of bone density, but there was no evidence for reduction of hip fractures. They were introduced on the theoretical assumption that the increase in bone density implied strengthening of the bone structure, and therefore a reduction in the risk of fracture.

In most pivotal trials comparing the effects of alendronate,[1-4] risedronate,[5-7] or ibandronate[8] versus placebo hip fractures were considered as secondary endpoints and outcomes did not show any clear potential benefit in decreasing hip fracture risk. Several meta-analyses of alendronate and risedronate have been carried out and a statistically significant benefit of these drugs over placebo is ~~claimed~~reported. However, the clinical significance of the findings is debateable and methodology biases are also present in the reviews.[9] A recent meta-analysis obtained similar results. However, trials' quality assessment was carried out and revealed an unclear or high risk of bias in approximately 75% of the trials. This means that the small significant reduction in hip fracture may not be real, or at best, is an exaggeration of the real benefit.[10]

In 2006 the longest ever clinical trial evaluating the effects of bisphosphonates was published. After 5 years under alendronate, women were randomized to either continue taking the drug or receive placebo for another five years. Discontinuation of alendronate for up to five years did not ~~increase fracture risk~~change numerically or statistically either nonspine or hip fracture incidence.[11] However no comparison between alendronate use versus no use was established. This prompted us to carry out the present study.[12]

The long-term use of bisphosphonates has been associated with deleterious effects on bone structure such as osteonecrosis of the jaw, atypical fractures (subtrochanteric and diaphyseal), and bone pain that prompted several safety communications issued by both the FDA and EMA.[13,14]

In 2008 a cohort study in Danish women with no previous hip fracture was published. The incidence of hip fractures increased in the group treated with alendronate by 50% in relative terms and by 6 cases per 1,000 women–years in absolute terms[15]. Updated information from this Danish cohort was published in 2010 and the increased incidence of hip fractures in women taking alendronate was confirmed.[16]

Objective

The aim of this study is to evaluate the association between long-term use of bisphosphonates and the risk of hip fracture compared to never use among women aged 65 years or older.

METHODS

Study design and setting

We carried out a case-control study nested in a cohort in Spain using the information from BIFAP (*Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria,* Database for Pharmacoepidemiologic Research in Primary Care). This is a longitudinal population-based database kept by the Spanish Agency for Medicines and Medical Devices that collates, from 2001 onwards, the computerized medical records of more than 1,800 physicians throughout Spain. It includes anonymized information on over 3.2 million patients, totalling over 13.7 million person-years of follow up.[17,18]

This project was approved by the Navarre Research Ethics Board, Pamplona, Spain. All data were anonymized and no written consent was necessary for this type of study according to the Spanish regulations (law 41/2002, article 16).

Participants

Cases were defined as women aged 65 years or older with a first diagnosis of hip fracture, using the ICPC-1 codes, recorded between 01/01/2005 and 31/12/2008, and with at least 1 year of follow-up in BIFAP before the event date. The date of hospitalization served as the index date. All hip fracture

cases were double-checked and validated by both BIFAP and the research team. We excluded women with any history of cancer, Paget disease, prevalent hip fracture and fractures resulting from trauma or motor vehicle collisions. For each case, 5 controls with no history of hip fracture by the time of the index date of their corresponding case were selected, matched by same age and calendar year of enrolment in BIFAP.

Medication use and other covariates

Use of bisphosphonates before the index date was obtained from the computerized database. Duration of bisphosphonate exposure was evaluated by examining prescriptions for oral alendronate, risedronate, ibandronate or etidronate from the beginning of therapy to the index date or the corresponding date among controls (ATC codes: alendronate, M05BA04; alendronate plus vitamin D, M05BB; risedronate, M05BA07 and ibandronate, M05BA06).

Individuals were classified as ever vs never users. Ever users were also divided into *current users* (if most recent prescription lasted through index date or ended in the month before it), *recent users* (if most recent prescription ended between 1 and 6 months before index date) and *past users* (if most recent prescription ended more than 6 months before index date).

In order to assess the effects of treatment length on the outcomes four different subgroups were considered based on cumulative duration of actual treatment, namely 30 days or less; >30 days to ≤1 year; >1 to ≤3 years and over 3 years. The effects of time of bisphosphonate exposure on hip fracture risk were also analyzed. Exposure was measured as the time (in days) since the first prescription.

~~In order to assess the effects of treatment length on the outcomes two criteria were used: a) Cumulative duration of actual treatment; and b) Time since first prescription. In both, three different subgroups were considered, namely <1 year; 1 to 3 years and over 3 years.~~

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Information on comorbilities (ICPC-1 codes) and use of other medications (ATC codes) was obtained. Patients were considered exposed if the most recent prescription lasted through index date or ended in the month before it. Other variables such as weight (kg), height (cm), body mass index (kg/m^2) and smoking status (yes/no/past smoker) were obtained as well.

Statistical methods

Between 2005 and 2008 we expected to find some 2,000 cases and 10,000 controls in our database. This would provide statistical power >90% to detect a change >20% in the risk of having hip fracture associated to biphosphonate use with an alpha risk of 5% and a prevalence of exposure of 20%.

We used conditional logistic regression to estimate the odds ratios (ORs) and 95 percent confidence intervals (CIs) for the association between bisphosphonate exposure and hip fractures. Bisphosphonate use was categorized as ever vs never. In separate analyses, current, recent, or past use was also evaluated. Treatment duration was assessed as well and results were tested to identify a trend. The level of significance was established at p = 0.05. In the duration analysis adjusted for exposure, never users was considered as the reference group. The results were also compared to bisphosphonate users for less than one year as a sensitivity analysis in case of selection bias.

An initial "model 1" adjusted only for matching variables. A second "model 2" adjusted additionally for smoking, BMI, alcoholism, previous fracture, kidney disease, malabsorption, stroke, dementia, rheumatoid arthritis, diabetes, epilepsy, Parkinson disease, thyroid disease, PPI (no use, <=1 yr, >1 yr), anxiolytics, sedatives, antidepressants, antihypertensives, oral corticosteroids (no use, <=1 yr, >1 yr), raloxifene, hormone replacement therapy, and thiazolidinediones.

RESULTS

Participants

Between 2005 and 2008, 3,181 potentially eligible cases were registered. Out of them we validated 2,069 hip fractures and 45 atypical fractures (31 subtrochanteric and 14 shaft fractures). Of the remainder 1,067 records were classified as "no case", 718 "other diagnoses" and 349 "lacking information". Sixty cases were excluded due to lack of matching controls. A total of 2,009 cases were obtained and 10,045 matching controls were selected (figure 1).

The average age of cases was 82.4 ± 6.6 years. In general terms co-morbidities and drug use was more prevalent in cases while smoking status and BMI were similar between cases and controls (table 1).

Outcome data

Hip fractures were more frequent among bisphosphonate users, 283 (14.1%) compared to never users, 1207 (12.0%). Results according to timing, duration, and bisphosphonate exposure are described in table 2.

Main results

Ever users of bisphosphonates had a higher risk of hip fracture compared to never users (unadjusted OR = 1.21, 95%CI, 1.05-1.39). After adjusting for co-medication and pathologies no significant differences were found between bisphosphonate users and never users, OR = 1.09 (95%CI, 0.94-1.27).

No association between hip fracture risk and cumulative duration of bisphosphonate treatment was observed: <1 year, OR 1.20 (95% CI, 0.97-1.47); 1 to <3 years, OR 0.94 (95% CI, 0.74-1.20); ≥ 3 years, OR 1.15 (95%CI, 0.82-1.60) (p for trend = 0.63). However, when treatment duration is analysed as time since first prescription, hip fracture risk of the different subgroups compared to never users obtained were as follows: <1 year, OR 0.85 (95%CI, 0.60-1.21); 1 to <3 years, OR 1.02 (95%CI 0.82-1.26); ≥ 3 years, OR 1.32 (95%CI 1.05-1.65) (p for trend = 0.03). If women exposed to bisphosphonates during less than one year was considered as the reference group, hip fracture risk observed in the different subgroups were: 1 to <3 years, OR 1.56 (95%CI 0.73-3.31); ≥ 3 years, OR 2.31 (95%CI 1.00-5.36) (p for trend = 0.03) (tables 2 and 3).

No significant trend was observed for timing (past, recent and current use). Past use of bisphosphonates was associated with a statistically significant increase in hip fracture risk (OR = 1.50, 95%CI 1.19-1.89) while current or recent use was not (table 2).

No protective effect on hip fracture risk was observed when the results were analysed by individual drugs. On the contrary, a statistically significant increased risk was found for ibandronate users (OR = 3.67, 95%CI 1.31-10.3) and for switchers as welll (OR = 1.63, 95%CI 1.07-2.47) (table 4).

DISCUSSION

Key results

According to our findings oral bisphosphonates may not decrease hip fracture risk in elderly women. In order to reduce selection bias, results were adjusted for co-pathologies and medication. However, residual selection bias may still occur. In a cohort study in Danish women with a previous fracture but with no previous hip fracture, the risk of hip fracture was increased in the group treated with alendronate.[15,16] This study was performed on alendronate only whereas in our study all oral bisphosphonates were included. Our findings are in line with the Danish study in which a higher hip fracture risk was observed.

A recent meta-analysis of clinical trials assessed the effects of bisphosphonates on hip and wrist fracture risk. Similar results to previous meta-analyses were observed, namely a 1% absolute reduction of hip fracture risk in bisphosphonate users. What is new about this publication is that trials' quality assessment was carried out and revealed an unclear or high risk of bias in approximately 75% of the trials. This means that the small significant reduction in hip fracture may not be real, or at best, is an

exaggeration of the real benefit[10]**Error! Bookmark not defined.** which is in line with our findings.

We evaluated the effects of treatment length and the results by individual drugs as secondary outcomes. No association between hip fracture risk and cumulative duration of bisphosphonate treatment was observed. However, fracture risk increased with longer exposure to bisphosphonates. A statistically significant trend for increased risk of hip fracture was observed among bisphosphonate users irrespective of whether the reference group was never users or women under treatment for less than one year. Results were tested against the two different reference groups because of the possible selection bias in any of them. The results were consistent in both analyses.

According to the results by individual drugs, no protective effect was observed. On the contrary, a statistically significant increased risk was found for ibandronate users and for switchers as well. Probably ibandronate results in our study are conditioned by a small sample size.

No significant trend was observed for timing (past, recent and current use). Past users showed a statistically significant higher fracture risk when compared to never users while current or recent users did not. This could be interpreted as if bisphosphonates provided a protective effect on hip fracture risk that disapears after drug withdrawal. However there are some other possible explanations for this. First, treatment withdrawal could be more frequent in patients suffering from drug adverse reactions, in those who did not tolerate treatment, or had a poorer clinical status. All these patients have a higher fracture risk and selection bias is another possible explanation for a higher fracture risk in patients who stopped taking bisphosphonates.

Second, bisphosphonates accumulate in bone structure and past users are exposed to the drug effects for many years after withdrawal. Given the relatively short follow-up period in this study, all patients are exposed to the drug effects irrespective of whether they are past, recent or current users. Thereby interpreting results according to these subgroups may be meaningless. The FLEX trial shows that there is no difference in hip fracture risk between past and current users. Past users had been under treatment for 5 years and had stopped taking the drug 5 years before assessment. This trial supports that alendronate accumulates in bone and past users are exposed to the drug effects for many years after withdrawal. Thereby it makes sense to consider exposure to bisphosphonates in the results analysis. Also we must take into account that in the FLEX trial there is no selection bias due to randomization, and consequently its findings support that the higher risk observed in the past users in our study may be related

to a selection bias and a longer exposure to bisphosphonates in this subgroup as well.

A recent article published by FDA researchers analysed the results of three long-term extension trials on alendronate, risedronate and zoledronic acid. Pooled data pertaining to patients who received continuous bisphosphonate treatment for 6 or more years resulted in fracture rates ranging from 9.3 to 10.6%, whereas the rate for patients switched to placebo was 8.0 to 8.8%. These data raise the question on whether long-term use of bisphosphonates is beneficial for patients.[19]

With long-term use it is widely accepted that bisphosphonates may cause osteonecrosis of the jaw and atypical (subtrochanteric and diaphyseal) fractures as well. Recently, a self-controlled case series analysis showed that bisphosphonate use was associated with osteonecrosis at any site.[20] Deleterious effects on bone structure have been observed with bisphosphonates and denosumab as well but not with other osteoporosis drugs. Both type of drugs inhibit bone turnover and thereby bone strength may be weaker as a result of treatment. Besides bisphosphonates prolong secondary mineralization leading to increased bone density but decreased bone toughness due to a higher mineral content (brittle bones).[21] Since there is biological rationale to explain the harmful effects of bisphosphonates on bone, more long-term studies are needed to test our findings.

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Limitations

One of the main limitations in our study is the relatively short follow-up period. Besides, we relied on prescription data to determine duration of bisphosphonate exposure. It is sensible to think that real exposure will likely be lower than registered. In the clinical records included in the BIFAP database, X-ray images are not available which might occasionally lead to misclassification of cases. However we believe this may not be a relevant limitation yet hip fracture cases are described in detail in the surgical procedures.

Another aspect to be pointed out is that ibandronate was marketed in Spain in January 2007 and in our study we included incident cases of hip fracture that occurred between 2005 and 2008. Thereby the exposure of both cases and controls to ibandronate is rather short-term.

Confounding by indication is a possible bias of this study. Theoretically women in a poor baseline condition could be prescribed bisphosphonates to a greater extent when compared to women with a better health status. In

order to minimize this bias, results were adjusted for previous fractures, comorbidities and use of other medications.

Bone mineral density determination is not a standard test available in the public health system in Spain. Thereby information on BMD in clinical records was rather scarce. However, this test has a very poor fracture risk predictive value and its clinical relevance can be challenged. When it comes to adjusting crude data we used other bone-related variables instead such as prevalence of previous fractures.

In our study no information on vitamin D plasma levels in our patients was available. However we believe this does not pose any problem since patients were not institutionalized and in Spain the exposure to sunlight is sufficient to ensure adequate levels of vitamin D. Furthermore, almost 90% of women aged 65 or older take supplements of calcium plus vitamin D.[22]

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Conclusions

Ever use of oral bisphosphonates was not associated with a decreased risk of hip fracture in women aged 65 or older as compared to never use. No association between hip fracture risk and cumulative duration of bisphosphonate treatment was observed. However, when treatment duration is analysed as time since first prescription, a statistically significant increased risk for hip fracture was observed in patients exposed to bisphosphonates over 3 years.

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Disclaimer:

The Spanish Agency of Medicines and Medical Devices (AEMPS) provided the crude data from BIFAP to the researchers according to an agreement with the Health Department of Navarre Government but did not take part in the design or in the study development. Authors are fully responsible for the analysis, results and opinions appearing in the paper and do not represent the position of the AEMPS. The views expressed are those of the authors only and do not represent necessarily the position of their respective institutions.

Footnotes

- Contributors JE, AA, JG and AL were responsible for developing of study concept and design, data validation and interpretation of the results. AA performed the statistical analyses. JE drafted the manuscript. All authors have been involved in revising and elaborating it critically in the intellectual context.
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- Competing interests: None.
- Ethics approval: Navarre Research Ethics Board, Pamplona, Spain.
- Data sharing statement: There are no additional data sharing to other parties.

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Table 1. Characteristics of cases and controls

	Cases	Controls	P-value*
N	2009	10045	
Age, years	82.4 (6.6)	82.4 (6.6)	1.00
Smoking			0.001
Non-current smoker, %	69.5	73.4	
Current smoker, %	2.7	2.0	
Not recorded, %	27.8	24.6	
Alcoholism, %	0.4	0.2	0.30
Body mass index, kg/m2	27.2 (5.0)	29.0 (5.0)	<0.0001
<20 kg/m2, %	2.7	1.0	<0.0001
20-<25 kg/m2, %	17.6	12.2	
25-<30 kg/m2, %	25.5	28.9	
>=30 kg/m2, %	19.8	30.8	
Not recorded, %	34.4	27.1	
Comorbidities			
Previous fracture, %	17.2	10.1	<0.0001
Kidney disease, %	4.9	3.6	0.006
Malabsorption, %	2.3	2.1	0.54
Stroke, %	10.7	6.2	<0.0001
Dementia, %	14.6	6.2	<0.0001
Rheumatoid arthritis, %	2.3	1.3	0.0006
Diabetes, %	22.2	17.7	<0.0001
Epilepsy, %	1.4	0.9	0.03
Parkinson disease, %	4.9	1.9	<0.0001
Thyroid disease, %	10.2	10.8	0.47
Use of medication			
PPI or H2 receptor blocker, %	38.2	34.0	0.0004
Anxiolytic, %	29.1	24.8	<0.0001
Antidepressants, %	22.6	13.8	<0.0001
Antihypertensives, %	56.8	61.6	<0.0001
Corticosteroids, %	8.0	7.4	0.33
Sedatives, %	11.8	9.3	0.0006
Raloxifene, %	0.3	0.5	0.14
Hormone replacement therapy, %	0.0	0.0	1.00
Thiazolidinedione, %	0.3	0.2	0.43

Values correspond to percentage or means (standard deviation). P-values calculated from chi-square test for categorical values and Student's t test for continuous variables.

Table 2. Association of any bisphosphonate use with the risk of hip fracture.

	Cases	Controls	Average cumulative duration (days)	Time since first BP prescription (days)	Model 1	Model 2
	n (%)	n (%)	Mean (SD)	Mean (SD)	OR (95% CI)	OR (95% CI)
Use						
No use	1726 (85.9)	8838 (88.0)	-	-	1 (ref.)	1 (ref.)
Ever use	283 (14.1)	1207 (12.0)	600 (556)	968 (622)	1.21 (1.05-1.39)	1.09 (0.94-1.27)
Timing						
No use	1726 (85.9)	8838 (88.0)	-	-	1 (ref.)	1 (ref.)
Past use	111 (5.5)	347 (3.5)	315(415)	1164 (601)	1.63 (1.31-2.04)	1.50 (1.19-1.89)
Recent use	43 (2.1)	127 (1.3)	515(521)	774 (599)	1.74 (1.22-2.47)	1.34 (0.92-1.95)
Current use	129 (6.4)	733 (7.3)	769(563)	903 (612)	0.90 (0.74-1.10)	0.84 (0.68-1.03)
p for trend					0.54	0.53
Duration						
No use (≤30 d)	1726 (85.9)	8838 (88.0)	-	-	1 (ref.)	1 (ref.)
>30 d ≤1 yr	139 (6.9)	533 (5.3)	147 (106)	687 (590)	1.34 (1.10-1.63)	1.20 (0.97-1.47)
>1 yr - ≤3 yr	92 (4.6)	458 (4.6)	684 (211)	956 (419)	1.03 (0.82-1.30)	0.94 (0.74-1.20)
>3 yr	52 (2.6)	216 (2.2)	1566 (375)	1698 (437)	1.25 (0.91-1.70)	1.15 (0.82-1.60)
p for trend					0.16*	0.63*
Time since first BP use						
No use (≤30 d)	1726 (85.9)	8838 (88.0)	-	-	1 (ref.)	1 (ref.)
>30 d ≤1 yr	41 (2.0)	222 (2.2)	140 (99)	194 (103)	0.95 (0.67-1.33)	0.85 (0.60-1.21)
>1 yr - ≤3 yr	120 (6.0)	546 (5.4)	454 (299)	727 (209)	1.13 (0.92-1.38)	1.02 (0.82-1.26)
>3 yr	122 (6.1)	439 (4.4)	990 (660)	1618 (445)	1.44 (1.17-1.78)	1.32 (1.05-1.65)
p for trend**					0.0008	0.03

Model 1: Conditional logistic regression model; Model 2: Conditional logistic regression model adjusted for smoking, BMI, alcoholism, previous fracture, kidney disease, malabsorption, stroke, dementia, rheumatoid arthritis, diabetes, epilepsy, Parkinson disease, and thyroid disease, PPI (no use, <=1 yr, >1 yr), anxiolytics, sedatives, antidepressants, antihypertensives, oral corticosteroids (no use, <=1 yr, >1 yr), raloxifene, hormone replacement therapy, and thiazolidinediones

* Modeled as the median duration of use in each category; ** Modeled as time in days since first bisphosphonate prescription (0 for no users)

Table 3. Risk of hip fracture by time since first prescription for bisphosphonates

	Cases	Controls	Average cumulative duration (days)	Time since first BP prescription (days)	Model 1	Model 2
	n (%)	n (%)	Mean (SD)	Mean (SD)	OR (95% CI)	OR (95% CI)
Time since first BP use						
>30 d ≤1 yr	41 (14.5)	222 (18.4)	157 (133)	194 (103)	1 (ref)	1 (ref)
>1 yr - ≤3 yr	120 (42.4)	546 (45.2)	535 (451)	727 (209)	1.23 (0.68-2.23)	1.49 (0.71-3.13)
>3 yr	122 (43.1)	439 (36.4)	1138 (873)	1618 (445)	1.79 (0.94-3.40)	2.21 (0.96-5.09)
p for trend*					0.03	0.03

Model 1: Conditional logistic regression model

Model 2: Conditional logistic regression model adjusted for smoking, BMI, alcoholism, previous fracture, kidney disease, malabsorption, stroke, dementia, rheumatoid arthritis, diabetes, epilepsy, Parkinson disease, and thyroid disease, PPI (no use, <=1 yr, >1 yr), anxiolytics, sedatives, antidepressants, antihypertensives, oral corticosteroids (no use, <=1 yr, >1 yr), raloxifene, hormone replacement therapy, and thiazolidinediones

* Modeled as time in days since first bisphosphonate prescription

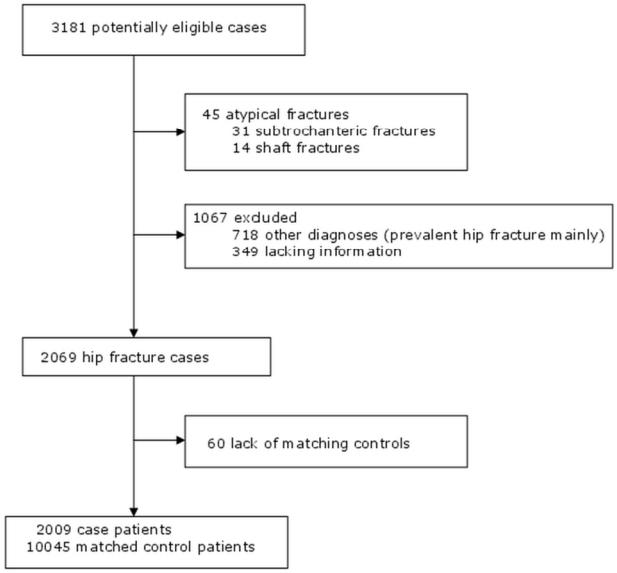
Table 4. Association of ever use of individual bisphosphonates with the risk of hip fracture.

	Cases	Controls	Average duration	Time since first prescription	Model 1	Model 2
	n (%)	n (%)	(days)	(days)	OR (95% CI)	OR (95% CI)
Never use	1726 (85.9)	8838 (88.0)	-	-	1 (ref.)	1 (ref.)
Alendronate	128 (6.4)	598 (6.0)	599 (566)	956 (603)	1.10 (0.90-1.34)	0.99 (0.81-1.22)
Risedronate	95 (4.7)	438 (4.4)	508 (459)	822 (503)	1.12 (0.89-1.41)	1.02 (0.81-1.30)
Etidronate	19 (1.0)	63 (0.6)	818 (629)	1478 (746)	1.55 (0.92-2.59)	1.56 (0.91-2.65)
Ibandronate	7 (0.4)	9 (0.1)	161 (137)	239 (151)	4.18 (1.55-11.2)	3.67 (1.31-10.3)
Switcher	34 (1.7)	99 (1.0)	898 (676)	1397 (714)	1.80 (1.21-2.68)	1.63 (1.07-2.47)

Model 1: Conditional logistic regression model

Model 2: Conditional logistic regression model adjusted for smoking, BMI, and alcoholism, previous fracture, kidney disease, malabsorption, stroke, dementia, rheumatoid arthritis, diabetes, epilepsy, Parkinson disease, and thyroid disease, PPI (no use, <=1 yr, >1 yr), anxiolytics, sedatives, antidepressants, antihypertensives, oral corticosteroids (no use, <=1 yr, >1 yr), raloxifene, hormone replacement therapy, and thiazolidinediones

Figure 1. Selection of study population



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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract. **OK**	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **OK**	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **OK**	
Objectives	3	State specific objectives, including any pre-specified hypotheses **OK**	
Methods			
Study design	4	Present key elements of study design early in the paper **OK**	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **OK**	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls **OK** *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case **OK**	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **OK**	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **OK**	
Bias	9	Describe any efforts to address potential sources of bias **OK**	
Study size	10	Explain how the study size was arrived at **OK**	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **OK**	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **OK**	
		(*b*) Describe any methods used to examine subgroups and interactions **OK**	
		(*c*) Explain how missing data were addressed **OK**	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed **OK**	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **OK**	
		(b) Give reasons for non-participation at each stage Not applicable	
		(c) Consider use of a flow diagram Not applicable	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **OK**	
		(b) Indicate number of participants with missing data for each variable of interest **OK**	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure **OK**	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **OK**	
		(*b*) Report category boundaries when continuous variables were categorized **OK**	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **OK**	
Discussion			
Key results	18	Summarise key results with reference to study objectives **OK**	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **OK**	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **OK**	
Generalisability	21	Discuss the generalisability (external validity) of the study results **OK**	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **OK**	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.