



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****AUTHORS**

Juan Erviti, Álvaro Alonso^{1,2}, Javier Gorricho, Antonio López

Drug Prescribing Service, Navarre Regional Health Service, Pamplona, Navarre, Spain;

¹School of Public Health, University of Minnesota, Minneapolis, Minnesota, United States;

²School of Medicine, University of Navarre, Pamplona, Navarre, Spain.

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

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

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14 Spanish Ministry of Health. TRA-071
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18 **INTRODUCTION**

19 **Background**

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25 When bisphosphonates came onto the market, they had demonstrated
26 efficacy in the improvement of bone density, but there was no evidence for
27 reduction of hip fractures. They were introduced on the theoretical
28 assumption that the increase in bone density implied strengthening of the
29 bone structure, and therefore a reduction in the risk of fracture.
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31
32 In most pivotal trials comparing the effects of alendronate,¹⁻⁴ risedronate,⁵⁻⁷
33 or ibandronate⁸ versus placebo hip fractures were considered as secondary
34 endpoints and outcomes did not show any clear potential benefit in
35 decreasing hip fracture risk. Several meta-analyses of alendronate and
36 risedronate have been carried out and a statistically significant benefit of
37 these drugs over placebo is claimed. However, the clinical significance of the
38 findings is debateable and methodology biases are also present in the
39 reviews.⁹ A recent meta-analysis obtained similar results. However, trials'
40 quality assessment was carried out and revealed an unclear or high risk of
41 bias in approximately 75% of the trials. This means that the small
42 significant reduction in hip fracture may not be real, or at best, is an
43 exaggeration of the real benefit.¹⁰
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48 In 2006 the longest ever clinical trial evaluating the effects of
49 bisphosphonates was published. After 5 years under alendronate, women
50 were randomized to either continue taking the drug or receive placebo for
51 another five years. Discontinuation of alendronate for up to five years did
52 not increase fracture risk.¹¹ However no comparison between alendronate
53 use versus no use was established. This prompted us to carry out the
54 present study.¹²
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58 The long-term use of bisphosphonates has been associated with deleterious
59 effects on bone structure such as osteonecrosis of the jaw, atypical
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3 fractures and bone pain that prompted several safety communications
4 issued by both the FDA and EMA.^{13,14}
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6 In 2008 a cohort study in Danish women with no previous hip fracture was
7 published. The incidence of hip fractures increased in the group treated with
8 alendronate by 50% in relative terms and by 6 cases per 1,000 women-
9 years in absolute terms¹⁵. Updated information from this Danish cohort was
10 published in 2010 and the increased incidence of hip fractures in women
11 taking alendronate was confirmed.¹⁶
12
13

14 15 16 **Objective**

17 The aim of this study is to evaluate the association between long-term use
18 of bisphosphonates and the risk of hip fracture compared to never use
19 among women aged 65 years or older.
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24 25 **METHODS**

26 27 **Study design and setting**

28 We carried out a case-control study nested in a cohort in Spain using the
29 information from BIFAP (*Base de Datos para la Investigación*
30 *Farmacoepidemiológica en Atención Primaria*, Database for
31 *Pharmacoepidemiologic Research in Primary Care*). This is a longitudinal
32 population-based database kept by the Spanish Agency for Medicines and
33 Medical Devices that collates, from 2001 onwards, the computerized
34 medical records of more than 1,800 physicians throughout Spain. It includes
35 anonymized information on over 3.2 million patients, totalling over 13.7
36 million person-years of follow up.^{17,18}
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41 This project was approved by the Navarre Research Ethics Board,
42 Pamplona, Spain. All data were anonymized and no written consent was
43 necessary for this type of study according to the Spanish regulations (law
44 41/2002, article 16).
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49 50 **Participants**

51 Cases were defined as women aged 65 years or older with a first diagnosis
52 of hip fracture, using the ICPC-1 codes, recorded between 01/01/2005 and
53 31/12/2008, and with at least 1 year of follow-up in BIFAP before the event
54 date. The date of hospitalization served as the index date. All hip fracture
55 cases were double-checked and validated by both BIFAP and the research
56 team. We excluded women with any history of cancer, Paget disease,
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3 prevalent hip fracture and fractures resulting from trauma or motor vehicle
4 collisions. For each case, 5 controls with no history of hip fracture by the
5 time of the index date of their corresponding case were selected, matched
6 by same age and calendar year of enrolment in BIFAP.
7

8 **Medication use and other covariates**

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10 Use of bisphosphonates before the index date was obtained from the
11 computerized database. Duration of bisphosphonate exposure was
12 evaluated by examining prescriptions for oral alendronate, risedronate,
13 ibandronate or etidronate from the beginning of therapy to the index date
14 or the corresponding date among controls (ATC codes: alendronate,
15 M05BA04; alendronate plus vitamin D, M05BB; risedronate, M05BA07 and
16 ibandronate, M05BA06).
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19
20 Individuals were classified as ever vs never users. Ever users were also
21 divided into *current users* (if most recent prescription lasted through index
22 date or ended in the month before it), *recent users* (if most recent
23 prescription ended between 1 and 6 months before index date) and *past*
24 *users* (if most recent prescription ended more than 6 months before index
25 date).
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29 In order to assess the effects of treatment length on the outcomes two
30 criteria were used: a) Cumulative duration of actual treatment; and b) Time
31 since first prescription. In both, three different subgroups were considered,
32 namely <1 year; 1 to 3 years and over 3 years.
33

34
35 Information on comorbidities (ICPC-1 codes) and use of other medications
36 (ATC codes) was obtained. Patients were considered exposed if the most
37 recent prescription lasted through index date or ended in the month before
38 it. Other variables such as weight (kg), height (cm), body mass index
39 (kg/m²) and smoking status (yes/no/past smoker) were obtained as well.
40

41 **Statistical methods**

42
43 Between 2005 and 2008 we expected to find some 2,000 cases and 10,000
44 controls in our database. This would provide statistical power >90% to
45 detect a change >20% in the risk of having hip fracture associated to
46 bisphosphonate use with an alpha risk of 5% and a prevalence of exposure
47 of 20%.
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49
50 We used conditional logistic regression to estimate the odds ratios (ORs)
51 and 95 percent confidence intervals (CIs) for the association between
52 bisphosphonate exposure and hip fractures. Bisphosphonate use was
53 categorized as ever vs never. In separate analyses, current, recent, or past
54 use was also evaluated. Treatment duration was assessed as well and
55 results were tested to identify a trend. The level of significance was
56 established at p = 0.05. In the duration analysis adjusted for exposure,
57 never users was considered as the reference group. The results were also
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3 compared to bisphosphonate users for less than one year as a sensitivity
4 analysis in case of selection bias.
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6 An initial "model 1" adjusted only for matching variables. A second "model
7 2" adjusted additionally for smoking, BMI, alcoholism, previous fracture,
8 kidney disease, malabsorption, stroke, dementia, rheumatoid arthritis,
9 diabetes, epilepsy, Parkinson disease, thyroid disease, PPI (no use, <=1 yr,
10 >1 yr), anxiolytics, sedatives, antidepressants, antihypertensives, oral
11 corticosteroids (no use, <=1 yr, >1 yr), raloxifene, hormone replacement
12 therapy, and thiazolidinediones.
13

14 15 16 **RESULTS**

17 ***Participants***

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19 Between 2005 and 2008, 3,181 potentially eligible cases were registered.
20 Out of them we validated 2,069 hip fractures and 45 atypical fractures (31
21 subtrochanteric and 14 shaft fractures). Of the remainder 1,067 records
22 were classified as "no case", 718 "other diagnoses" and 349 "lacking
23 information". Sixty cases were excluded due to lack of matching controls. A
24 total of 2,009 cases were obtained and 10,045 matching controls were
25 selected (figure 1).
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29 The average age of cases was 82.4 ± 6.6 years. In general terms co-
30 morbidities and drug use was more prevalent in cases while smoking status
31 and BMI were similar between cases and controls (table 1).
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34 ***Outcome data***

35 Hip fractures were more frequent among bisphosphonate users, 283
36 (14.1%) compared to never users, 1207 (12.0%). Results according to
37 timing, duration, and bisphosphonate exposure are described in table 2.
38
39

40 ***Main results***

41 Ever users of bisphosphonates had a higher risk of hip fracture compared to
42 never users (unadjusted OR = 1.21, 95%CI, 1.05-1.39). After adjusting for
43 co-medication and pathologies no significant differences were found
44 between bisphosphonate users and never users, OR = 1.09 (95%CI, 0.94-
45 1.27).
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50 No association between hip fracture risk and cumulative duration of
51 bisphosphonate treatment was observed: <1 year, OR 1.20 (95% CI, 0.97-
52 1.47); 1 to <3 years, OR 0.94 (95% CI, 0.74-1.20); ≥ 3 years, OR 1.15
53 (95%CI, 0.82-1.60) (p for trend = 0.63). However, when treatment
54 duration is analysed as time since first prescription, hip fracture risk of the
55 different subgroups compared to never users obtained were as follows: <1
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3 year, OR 0.85 (95%CI, 0.60-1.21); 1 to <3 years, OR 1.02 (95%CI 0.82-
4 1.26); ≥ 3 years, OR 1.32 (95%CI 1.05-1.65) (p for trend = 0.03). If
5 women exposed to bisphosphonates during less than one year was
6 considered as the reference group, hip fracture risk observed in the
7 different subgroups were: 1 to <3 years, OR 1.56 (95%CI 0.73-3.31); ≥ 3
8 years, OR 2.31 (95%CI 1.00-5.36) (p for trend = 0.03) (tables 2 and 3).

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

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17 No protective effect on hip fracture risk was observed when the results were
18 analysed by individual drugs. On the contrary, a statistically significant
19 increased risk was found for ibandronate users (OR = 3.67, 95%CI 1.31-
20 10.3) and for switchers as well (OR = 1.63, 95%CI 1.07-2.47) (table 4).

21 22 23 24 25 **DISCUSSION**

26 27 **Key results**

28
29 According to our findings oral bisphosphonates may not decrease hip
30 fracture risk in elderly women. In order to reduce selection bias, results
31 were adjusted for co-pathologies and medication. However, residual
32 selection bias may still occur. In a cohort study in Danish women with a
33 previous fracture but with no previous hip fracture, the risk of hip fracture
34 was increased in the group treated with alendronate.^{15,16} This study was
35 performed on alendronate only whereas in our study all oral
36 bisphosphonates were included. Our findings are in line with the Danish
37 study in which a higher hip fracture risk was observed.

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40 A recent meta-analysis of clinical trials assessed the effects of
41 bisphosphonates on hip and wrist fracture risk. Similar results to previous
42 meta-analyses were observed, namely a 1% absolute reduction of hip
43 fracture risk in bisphosphonate users. What is new about this publication is
44 that trials' quality assessment was carried out and revealed an unclear or
45 high risk of bias in approximately 75% of the trials. This means that the
46 small significant reduction in hip fracture may not be real, or at best, is an
47 exaggeration of the real benefit¹⁰Error! Bookmark not defined. which is in line with
48 our findings.

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55 We evaluated the effects of treatment length and the results by individual
56 drugs as secondary outcomes. No association between hip fracture risk and
57 cumulative duration of bisphosphonate treatment was observed. However,
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3 fracture risk increased with longer exposure to bisphosphonates. A
4 statistically significant trend for increased risk of hip fracture was observed
5 among bisphosphonate users irrespective of whether the reference group
6 was never users or women under treatment for less than one year. Results
7 were tested against the two different reference groups because of the
8 possible selection bias in any of them. The results were consistent in both
9 analyses.
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12 According to the results by individual drugs, no protective effect was
13 observed. On the contrary, a statistically significant increased risk was
14 found for ibandronate users and for switchers as well. Probably ibandronate
15 results in our study are conditioned by a small sample size.
16

17
18 No significant trend was observed for timing (past, recent and current use).
19 Past users showed a statistically significant higher fracture risk when
20 compared to never users while current or recent users did not. This could be
21 interpreted as if bisphosphonates provided a protective effect on hip
22 fracture risk that disappears after drug withdrawal. However there are some
23 other possible explanations for this. First, treatment withdrawal could be
24 more frequent in patients suffering from drug adverse reactions, in those
25 who did not tolerate treatment, or had a poorer clinical status. All these
26 patients have a higher fracture risk and selection bias is another possible
27 explanation for a higher fracture risk in patients who stopped taking
28 bisphosphonates.
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33 Second, bisphosphonates accumulate in bone structure and past users are
34 exposed to the drug effects for many years after withdrawal. Given the
35 relatively short follow-up period in this study, all patients are exposed to the
36 drug effects irrespective of whether they are past, recent or current users.
37 Thereby interpreting results according to these subgroups may be
38 meaningless. The FLEX trial shows that there is no difference in hip fracture
39 risk between past and current users. Past users had been under treatment
40 for 5 years and had stopped taking the drug 5 years before assessment.
41 This trial supports that alendronate accumulates in bone and past users are
42 exposed to the drug effects for many years after withdrawal. Thereby it
43 makes sense to consider exposure to bisphosphonates in the results
44 analysis. Also we must take into account that in the FLEX trial there is no
45 selection bias due to randomization, and consequently its findings support
46 that the higher risk observed in the past users in our study may be related
47 to a selection bias and a longer exposure to bisphosphonates in this
48 subgroup as well.
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55 A recent article published by FDA researchers analysed the results of three
56 long-term extension trials on alendronate, risedronate and zoledronic acid.
57 Pooled data pertaining to patients who received continuous bisphosphonate
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3 treatment for 6 or more years resulted in fracture rates ranging from 9.3 to
4 10.6%, whereas the rate for patients switched to placebo was 8.0 to 8.8%.
5 These data raise the question on whether long-term use of bisphosphonates
6 is beneficial for patients.¹⁹
7

8
9 With long-term use it is widely accepted that bisphosphonates may cause
10 osteonecrosis of the jaw and atypical fractures as well. Recently, a self-
11 controlled case series analysis showed that bisphosphonate use was
12 associated with osteonecrosis at any site.²⁰ Deleterious effects on bone
13 structure have been observed with bisphosphonates and denosumab as well
14 but not with other osteoporosis drugs. Both type of drugs inhibit bone
15 turnover and thereby bone strength may be weaker as a result of
16 treatment. Besides bisphosphonates prolong secondary mineralization
17 leading to increased bone density but decreased bone toughness due to a
18 higher mineral content (brittle bones). Since there is biological rationale to
19 explain the harmful effects of bisphosphonates on bone, more long-term
20 studies are needed to test our findings.
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24 25 26 **Limitations** 27

28 One of the main limitations in our study is the relatively short follow-up
29 period. Besides, we relied on prescription data to determine duration of
30 bisphosphonate exposure. It is sensible to think that real exposure will likely
31 be lower than registered. In the clinical records included in the BIFAP
32 database, X-ray images are not available which might occasionally lead to
33 misclassification of cases. However we believe this may not be a relevant
34 limitation yet hip fracture cases are described in detail in the surgical
35 procedures.
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39 Another aspect to be pointed out is that ibandronate was marketed in Spain
40 in January 2007 and in our study we included incident cases of hip fracture
41 that occurred between 2005 and 2008. Thereby the exposure of both cases
42 and controls to ibandronate is rather short-term.
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45 Confounding by indication is a possible bias of this study. Theoretically
46 women in a poor baseline condition could be prescribed bisphosphonates to
47 a greater extent when compared to women with a better health status. In
48 order to minimize this bias, results were adjusted for previous fractures,
49 comorbidities and use of other medications.
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54 Bone mineral density determination is not a standard test available in the
55 public health system in Spain. Thereby information on BMD in clinical
56 records was rather scarce. However, this test has a very poor fracture risk
57 predictive value and its clinical relevance can be challenged. When it comes
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3 to adjusting crude data we used other bone-related variables instead such
4 as prevalence of previous fractures.
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8 **Conclusions**

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

23
24 The authors would like to thank the collaboration of general practitioners
25 contributing to BIFAP.
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28

29 **Disclaimer:**

30
31 The Spanish Agency of Medicines and Medical Devices (AEMPS) provided the
32 crude data from BIFAP to the researchers according to an agreement with
33 the Health Department of Navarre Government but did not take part in the
34 design or in the study development. Authors are fully responsible for the
35 analysis, results and opinions appearing in the paper and do not represent
36 the position of the AEMPS. The views expressed are those of the authors
37 only and do not represent necessarily the position of their respective
38 institutions.
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45 **Footnotes**

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- 48 • Contributors JE, AA, JG and AL were responsible for developing of
49 study concept and design, data validation and interpretation of the
50 results. AA performed the statistical analyses. JE drafted the
51 manuscript. All authors have been involved in revising and
52 elaborating it critically in the intellectual context.
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 - 55 • Competing interests: None.
 - 56 • Ethics approval: Navarre Research Ethics Board, Pamplona, Spain.
 - 57 • Data sharing statement: There are no additional data sharing to other
58 parties.
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Table 1. Characteristics of cases and controls

	Cases	Controls
N	2009	10045
Age, years (\pm 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 (\pm 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
\geq 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)

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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

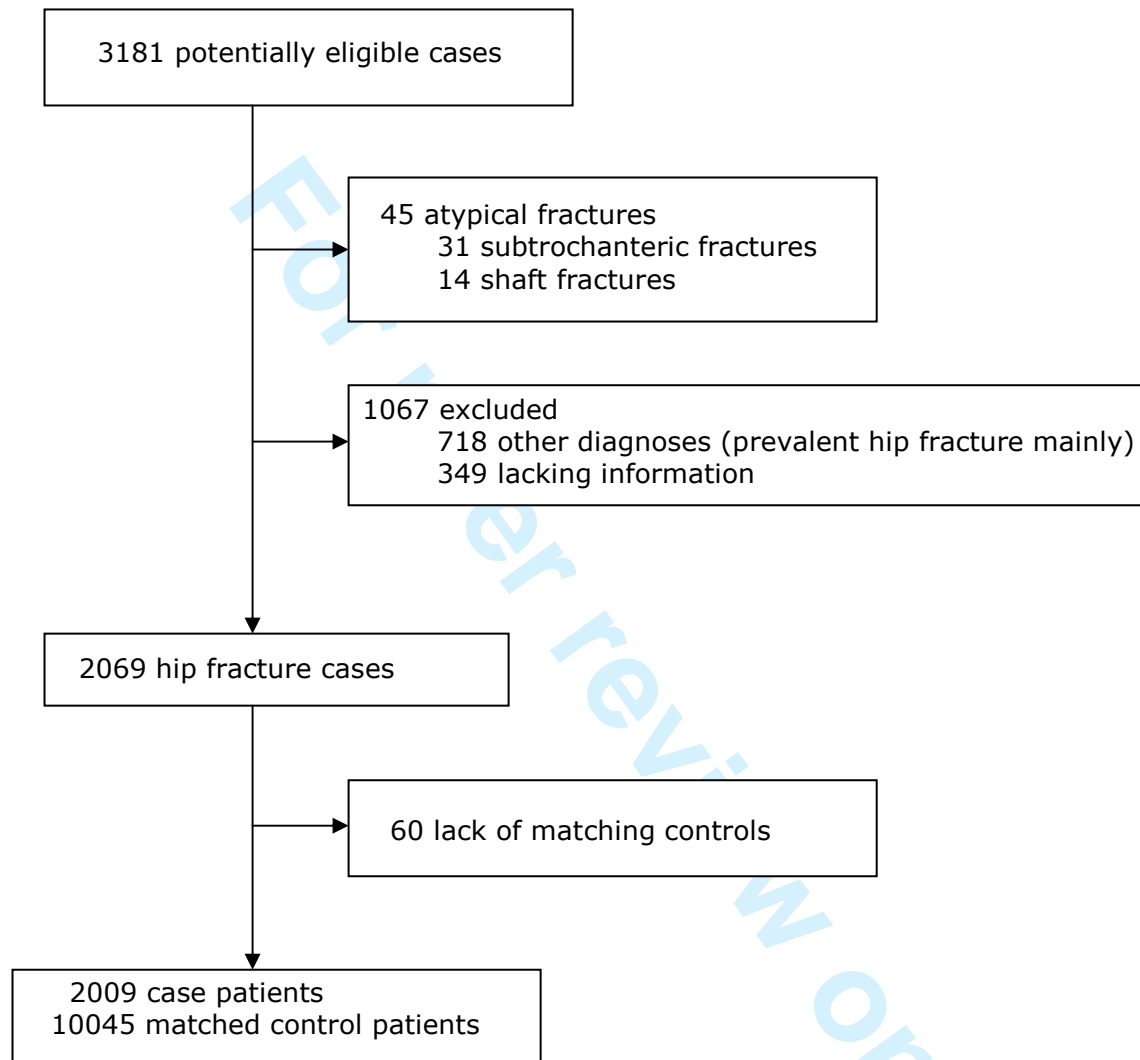
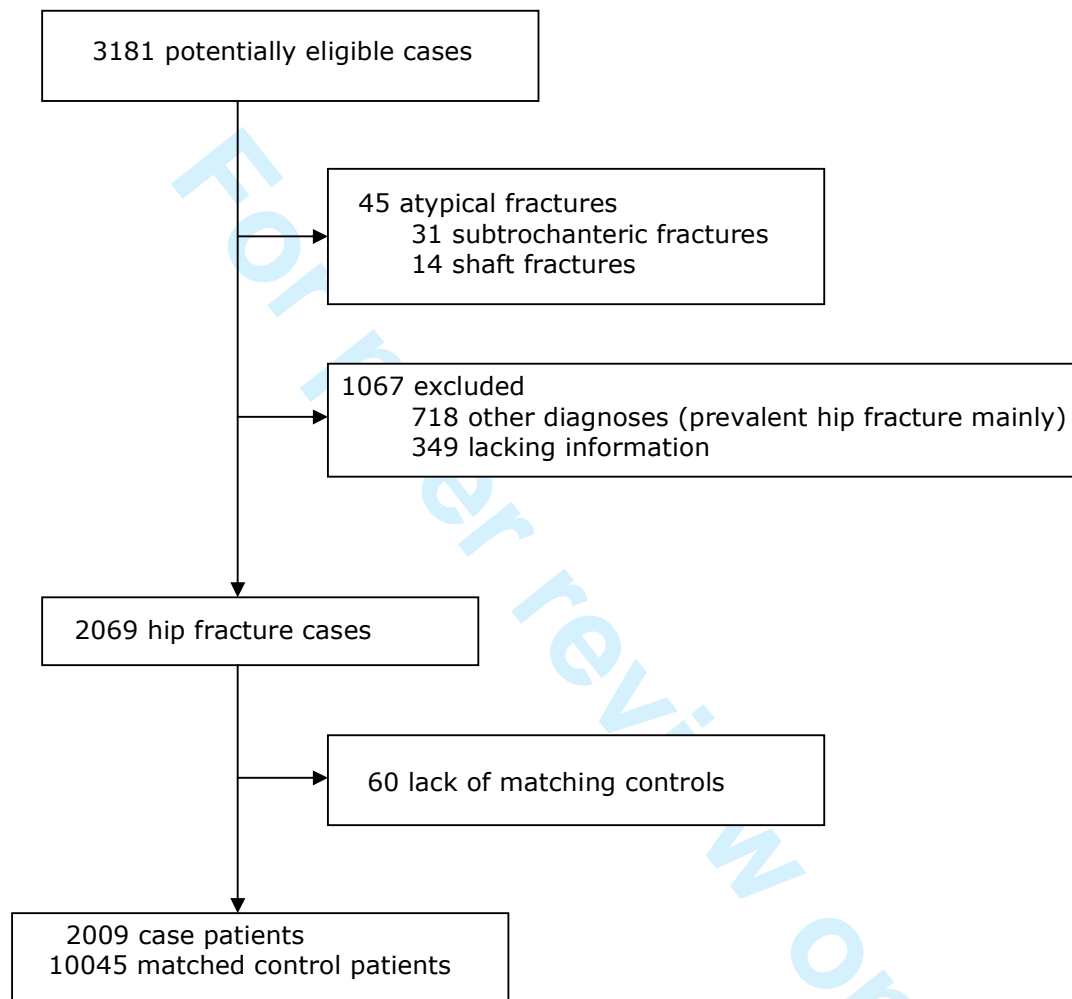


Figure 1. Selection of study population



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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed OK	

		<i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure OK	
		<i>Cross-sectional study</i> —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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Keywords:	CLINICAL PHARMACOLOGY, EPIDEMIOLOGY, PRIMARY CARE

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

Juan Erviti, Álvaro Alonso^{1,2}, Javier Gorricho, Antonio López

Drug Prescribing Service, Navarre Regional Health Service, Pamplona, Navarre, Spain;

¹School of Public Health, University of Minnesota, Minneapolis, Minnesota, United States;

²School of Medicine, University of Navarre, Pamplona, Navarre, Spain.

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

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

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14 Spanish Ministry of Health. TRA-071
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17 **INTRODUCTION**

18 **Background**

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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 ibandronate⁸ 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

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3 fractures (subtrochanteric and diaphyseal), and bone pain that prompted
4 several safety communications issued by both the FDA and EMA.^{13,14}
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6 In 2008 a cohort study in Danish women with no previous hip fracture was
7 published. The incidence of hip fractures increased in the group treated with
8 alendronate by 50% in relative terms and by 6 cases per 1,000 women-
9 years in absolute terms¹⁵. Updated information from this Danish cohort was
10 published in 2010 and the increased incidence of hip fractures in women
11 taking alendronate was confirmed.¹⁶
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14 15 16 **Objective**

17 The aim of this study is to evaluate the association between long-term use
18 of bisphosphonates and the risk of hip fracture compared to never use
19 among women aged 65 years or older.
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24 25 **METHODS**

26 27 **Study design and setting**

28 We carried out a case-control study nested in a cohort in Spain using the
29 information from BIFAP (*Base de Datos para la Investigación*
30 *Farmacoepidemiológica en Atención Primaria*, Database for
31 *Pharmacoepidemiologic Research in Primary Care*). This is a longitudinal
32 population-based database kept by the Spanish Agency for Medicines and
33 Medical Devices that collates, from 2001 onwards, the computerized
34 medical records of more than 1,800 physicians throughout Spain. It includes
35 anonymized information on over 3.2 million patients, totalling over 13.7
36 million person-years of follow up.^{17,18}
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41 This project was approved by the Navarre Research Ethics Board,
42 Pamplona, Spain. All data were anonymized and no written consent was
43 necessary for this type of study according to the Spanish regulations (law
44 41/2002, article 16).
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49 50 **Participants**

51 Cases were defined as women aged 65 years or older with a first diagnosis
52 of hip fracture, using the ICPC-1 codes, recorded between 01/01/2005 and
53 31/12/2008, and with at least 1 year of follow-up in BIFAP before the event
54 date. The date of hospitalization served as the index date. All hip fracture
55 cases were double-checked and validated by both BIFAP and the research
56 team. We excluded women with any history of cancer, Paget disease,
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3 prevalent hip fracture and fractures resulting from trauma or motor vehicle
4 collisions. For each case, 5 controls with no history of hip fracture by the
5 time of the index date of their corresponding case were selected, matched
6 by same age and calendar year of enrolment in BIFAP.
7

8 **Medication use and other covariates**

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10 Use of bisphosphonates before the index date was obtained from the
11 computerized database. Duration of bisphosphonate exposure was
12 evaluated by examining prescriptions for oral alendronate, risedronate,
13 ibandronate or etidronate from the beginning of therapy to the index date
14 or the corresponding date among controls (ATC codes: alendronate,
15 M05BA04; alendronate plus vitamin D, M05BB; risedronate, M05BA07 and
16 ibandronate, M05BA06).
17

18
19 Individuals were classified as ever vs never users. Ever users were also
20 divided into *current users* (if most recent prescription lasted through index
21 date or ended in the month before it), *recent users* (if most recent
22 prescription ended between 1 and 6 months before index date) and *past*
23 *users* (if most recent prescription ended more than 6 months before index
24 date).
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29 In order to assess the effects of treatment length on the outcomes four
30 different subgroups were considered based on cumulative duration of actual
31 treatment, namely 30 days or less; >30 days to ≤ 1 year; >1 to ≤ 3 years
32 and over 3 years. The effects of time of bisphosphonate exposure on hip
33 fracture risk were also analyzed. Exposure was measured as the time (in
34 days) since the first prescription.
35

36
37 Information on comorbidities (ICPC-1 codes) and use of other medications
38 (ATC codes) was obtained. Patients were considered exposed if the most
39 recent prescription lasted through index date or ended in the month before
40 it. Other variables such as weight (kg), height (cm), body mass index
41 (kg/m^2) and smoking status (yes/no/past smoker) were obtained as well.
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43

44 **Statistical methods**

45
46 Between 2005 and 2008 we expected to find some 2,000 cases and 10,000
47 controls in our database. This would provide statistical power >90% to
48 detect a change >20% in the risk of having hip fracture associated to
49 bisphosphonate use with an alpha risk of 5% and a prevalence of exposure
50 of 20%.
51

52
53 We used conditional logistic regression to estimate the odds ratios (ORs)
54 and 95 percent confidence intervals (CIs) for the association between
55 bisphosphonate exposure and hip fractures. Bisphosphonate use was
56 categorized as ever vs never. In separate analyses, current, recent, or past
57 use was also evaluated. Treatment duration was assessed as well and
58 results were tested to identify a trend. The level of significance was
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3 established at $p = 0.05$. In the duration analysis adjusted for exposure,
4 never users was considered as the reference group. The results were also
5 compared to bisphosphonate users for less than one year as a sensitivity
6 analysis in case of selection bias.
7

8 An initial "model 1" adjusted only for matching variables. A second "model
9 2" adjusted additionally for smoking, BMI, alcoholism, previous fracture,
10 kidney disease, malabsorption, stroke, dementia, rheumatoid arthritis,
11 diabetes, epilepsy, Parkinson disease, thyroid disease, PPI (no use, ≤ 1 yr,
12 > 1 yr), anxiolytics, sedatives, antidepressants, antihypertensives, oral
13 corticosteroids (no use, ≤ 1 yr, > 1 yr), raloxifene, hormone replacement
14 therapy, and thiazolidinediones.
15

16 17 18 **RESULTS**

19 ***Participants***

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21
22 Between 2005 and 2008, 3,181 potentially eligible cases were registered.
23 Out of them we validated 2,069 hip fractures and 45 atypical fractures (31
24 subtrochanteric and 14 shaft fractures). Of the remainder 1,067 records
25 were classified as "no case", 718 "other diagnoses" and 349 "lacking
26 information". Sixty cases were excluded due to lack of matching controls. A
27 total of 2,009 cases were obtained and 10,045 matching controls were
28 selected (figure 1).
29

30
31 The average age of cases was 82.4 ± 6.6 years. In general terms co-
32 morbidities and drug use was more prevalent in cases while smoking status
33 and BMI were similar between cases and controls (table 1).
34

35 ***Outcome data***

36
37
38 Hip fractures were more frequent among bisphosphonate users, 283
39 (14.1%) compared to never users, 1207 (12.0%). Results according to
40 timing, duration, and bisphosphonate exposure are described in table 2.
41

42 ***Main results***

43
44
45 Ever users of bisphosphonates had a higher risk of hip fracture compared to
46 never users (unadjusted OR = 1.21, 95%CI, 1.05-1.39). After adjusting for
47 co-medication and pathologies no significant differences were found
48 between bisphosphonate users and never users, OR = 1.09 (95%CI, 0.94-
49 1.27).
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53 No association between hip fracture risk and cumulative duration of
54 bisphosphonate treatment was observed: < 1 year, OR 1.20 (95% CI, 0.97-
55 1.47); 1 to < 3 years, OR 0.94 (95% CI, 0.74-1.20); ≥ 3 years, OR 1.15
56 (95%CI, 0.82-1.60) (p for trend = 0.63). However, when treatment
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3 duration is analysed as time since first prescription, hip fracture risk of the
4 different subgroups compared to never users obtained were as follows: <1
5 year, OR 0.85 (95%CI, 0.60-1.21); 1 to <3 years, OR 1.02 (95%CI 0.82-
6 1.26); ≥ 3 years, OR 1.32 (95%CI 1.05-1.65) (p for trend = 0.03). If
7 women exposed to bisphosphonates during less than one year was
8 considered as the reference group, hip fracture risk observed in the
9 different subgroups were: 1 to <3 years, OR 1.56 (95%CI 0.73-3.31); ≥ 3
10 years, OR 2.31 (95%CI 1.00-5.36) (p for trend = 0.03) (tables 2 and 3).

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

18
19
20 No protective effect on hip fracture risk was observed when the results were
21 analysed by individual drugs. On the contrary, a statistically significant
22 increased risk was found for ibandronate users (OR = 3.67, 95%CI 1.31-
23 10.3) and for switchers as well (OR = 1.63, 95%CI 1.07-2.47) (table 4).

24 25 26 27 **DISCUSSION**

28 29 **Key results**

30
31 According to our findings oral bisphosphonates may not decrease hip
32 fracture risk in elderly women. In order to reduce selection bias, results
33 were adjusted for co-pathologies and medication. However, residual
34 selection bias may still occur. In a cohort study in Danish women with a
35 previous fracture but with no previous hip fracture, the risk of hip fracture
36 was increased in the group treated with alendronate.^{15,16} This study was
37 performed on alendronate only whereas in our study all oral
38 bisphosphonates were included. Our findings are in line with the Danish
39 study in which a higher hip fracture risk was observed.

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43 A recent meta-analysis of clinical trials assessed the effects of
44 bisphosphonates on hip and wrist fracture risk. Similar results to previous
45 meta-analyses were observed, namely a 1% absolute reduction of hip
46 fracture risk in bisphosphonate users. What is new about this publication is
47 that trials' quality assessment was carried out and revealed an unclear or
48 high risk of bias in approximately 75% of the trials. This means that the
49 small significant reduction in hip fracture may not be real, or at best, is an
50 exaggeration of the real benefit¹⁰[Error! Bookmark not defined.](#) which is in line with
51 our findings.
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3 We evaluated the effects of treatment length and the results by individual
4 drugs as secondary outcomes. No association between hip fracture risk and
5 cumulative duration of bisphosphonate treatment was observed. However,
6 fracture risk increased with longer exposure to bisphosphonates. A
7 statistically significant trend for increased risk of hip fracture was observed
8 among bisphosphonate users irrespective of whether the reference group
9 was never users or women under treatment for less than one year. Results
10 were tested against the two different reference groups because of the
11 possible selection bias in any of them. The results were consistent in both
12 analyses.
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16 According to the results by individual drugs, no protective effect was
17 observed. On the contrary, a statistically significant increased risk was
18 found for ibandronate users and for switchers as well. Probably ibandronate
19 results in our study are conditioned by a small sample size.
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22 No significant trend was observed for timing (past, recent and current use).
23 Past users showed a statistically significant higher fracture risk when
24 compared to never users while current or recent users did not. This could be
25 interpreted as if bisphosphonates provided a protective effect on hip
26 fracture risk that disappears after drug withdrawal. However there are some
27 other possible explanations for this. First, treatment withdrawal could be
28 more frequent in patients suffering from drug adverse reactions, in those
29 who did not tolerate treatment, or had a poorer clinical status. All these
30 patients have a higher fracture risk and selection bias is another possible
31 explanation for a higher fracture risk in patients who stopped taking
32 bisphosphonates.
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36 Second, bisphosphonates accumulate in bone structure and past users are
37 exposed to the drug effects for many years after withdrawal. Given the
38 relatively short follow-up period in this study, all patients are exposed to the
39 drug effects irrespective of whether they are past, recent or current users.
40 Thereby interpreting results according to these subgroups may be
41 meaningless. The FLEX trial shows that there is no difference in hip fracture
42 risk between past and current users. Past users had been under treatment
43 for 5 years and had stopped taking the drug 5 years before assessment.
44 This trial supports that alendronate accumulates in bone and past users are
45 exposed to the drug effects for many years after withdrawal. Thereby it
46 makes sense to consider exposure to bisphosphonates in the results
47 analysis. Also we must take into account that in the FLEX trial there is no
48 selection bias due to randomization, and consequently its findings support
49 that the higher risk observed in the past users in our study may be related
50 to a selection bias and a longer exposure to bisphosphonates in this
51 subgroup as well.
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3 A recent article published by FDA researchers analysed the results of three
4 long-term extension trials on alendronate, risedronate and zoledronic acid.
5 Pooled data pertaining to patients who received continuous bisphosphonate
6 treatment for 6 or more years resulted in fracture rates ranging from 9.3 to
7 10.6%, whereas the rate for patients switched to placebo was 8.0 to 8.8%.
8 These data raise the question on whether long-term use of bisphosphonates
9 is beneficial for patients.¹⁹
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12 With long-term use it is widely accepted that bisphosphonates may cause
13 osteonecrosis of the jaw and atypical (subtrochanteric and diaphyseal)
14 fractures as well. Recently, a self-controlled case series analysis showed
15 that bisphosphonate use was associated with osteonecrosis at any site.²⁰
16 Deleterious effects on bone structure have been observed with
17 bisphosphonates and denosumab as well but not with other osteoporosis
18 drugs. Both type of drugs inhibit bone turnover and thereby bone strength
19 may be weaker as a result of treatment. Besides bisphosphonates prolong
20 secondary mineralization leading to increased bone density but decreased
21 bone toughness due to a higher mineral content (brittle bones).²¹ Since
22 there is biological rationale to explain the harmful effects of
23 bisphosphonates on bone, more long-term studies are needed to test our
24 findings.
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31 **Limitations**

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33 One of the main limitations in our study is the relatively short follow-up
34 period. Besides, we relied on prescription data to determine duration of
35 bisphosphonate exposure. It is sensible to think that real exposure will likely
36 be lower than registered. In the clinical records included in the BIFAP
37 database, X-ray images are not available which might occasionally lead to
38 misclassification of cases. However we believe this may not be a relevant
39 limitation yet hip fracture cases are described in detail in the surgical
40 procedures.
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44 Another aspect to be pointed out is that ibandronate was marketed in Spain
45 in January 2007 and in our study we included incident cases of hip fracture
46 that occurred between 2005 and 2008. Thereby the exposure of both cases
47 and controls to ibandronate is rather short-term.
48

49 Confounding by indication is a possible bias of this study. Theoretically
50 women in a poor baseline condition could be prescribed bisphosphonates to
51 a greater extent when compared to women with a better health status. In
52 order to minimize this bias, results were adjusted for previous fractures,
53 comorbidities and use of other medications.
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56 Bone mineral density determination is not a standard test available in the
57 public health system in Spain. Thereby information on BMD in clinical
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3 records was rather scarce. However, this test has a very poor fracture risk
4 predictive value and its clinical relevance can be challenged. When it comes
5 to adjusting crude data we used other bone-related variables instead such
6 as prevalence of previous fractures.
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9 In our study no information on vitamin D plasma levels in our patients was
10 available. However we believe this does not pose any problem since
11 patients were not institutionalized and in Spain the exposure to sunlight is
12 sufficient to ensure adequate levels of vitamin D. Furthermore, almost 90%
13 of women aged 65 or older take supplements of calcium plus vitamin D.²²
14

15 16 17 **Conclusions**

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19 Ever use of oral bisphosphonates was not associated with a decreased risk
20 of hip fracture in women aged 65 or older as compared to never use. No
21 association between hip fracture risk and cumulative duration of
22 bisphosphonate treatment was observed. However, when treatment
23 duration is analysed as time since first prescription, a statistically significant
24 increased risk for hip fracture was observed in patients exposed to
25 bisphosphonates over 3 years.
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29 30 31 **Acknowledgements**

32
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34 contributing to BIFAP.
35
36

37 38 39 **Disclaimer:**

40
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42 crude data from BIFAP to the researchers according to an agreement with
43 the Health Department of Navarre Government but did not take part in the
44 design or in the study development. Authors are fully responsible for the
45 analysis, results and opinions appearing in the paper and do not represent
46 the position of the AEMPS. The views expressed are those of the authors
47 only and do not represent necessarily the position of their respective
48 institutions.
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51 52 53 **Footnotes**

- 54
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56 • Contributors JE, AA, JG and AL were responsible for developing of
57 study concept and design, data validation and interpretation of the
58
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3 results. AA performed the statistical analyses. JE drafted the
4 manuscript. All authors have been involved in revising and
5 elaborating it critically in the intellectual context.

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- 8 • Competing interests: None.
- 9 • Ethics approval: Navarre Research Ethics Board, Pamplona, Spain.
- 10 • Data sharing statement: There are no additional data sharing to other
11 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/m ²	27.2 (5.0)	29.0 (5.0)	<0.0001
<20 kg/m ² , %	2.7	1.0	<0.0001
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	<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 H ₂ 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.

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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****AUTHORS**

Juan Erviti, Álvaro Alonso^{1,2}, Javier Gorricho, Antonio López

Drug Prescribing Service, Navarre Regional Health Service, Pamplona, Navarre, Spain;

¹School of Public Health, University of Minnesota, Minneapolis, Minnesota, United States;

²School of Medicine, University of Navarre, Pamplona, Navarre, Spain.

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

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

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16 Spanish Ministry of Health. TRA-071
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20 **INTRODUCTION**

21 **Background**

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25 When bisphosphonates came onto the market, they had demonstrated
26 efficacy in the improvement of bone density, but there was no evidence for
27 reduction of hip fractures. They were introduced on the theoretical
28 assumption that the increase in bone density implied strengthening of the
29 bone structure, and therefore a reduction in the risk of fracture.
30

31
32 In most pivotal trials comparing the effects of alendronate,¹⁻⁴ risedronate,⁵⁻⁷
33 or ibandronate⁸ versus placebo hip fractures were considered as secondary
34 endpoints and outcomes did not show any clear potential benefit in
35 decreasing hip fracture risk. Several meta-analyses of alendronate and
36 risedronate have been carried out and a statistically significant benefit of
37 these drugs over placebo is claimed reported. However, the clinical
38 significance of the findings is debateable and methodology biases are also
39 present in the reviews.⁹ A recent meta-analysis obtained similar results.
40 However, trials' quality assessment was carried out and revealed an unclear
41 or high risk of bias in approximately 75% of the trials. This means that the
42 small significant reduction in hip fracture may not be real, or at best, is an
43 exaggeration of the real benefit.¹⁰
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46 In 2006 the longest ever clinical trial evaluating the effects of
47 bisphosphonates was published. After 5 years under alendronate, women
48 were randomized to either continue taking the drug or receive placebo for
49 another five years. Discontinuation of alendronate for up to five years did
50 not increase fracture risk change numerically or statistically either nonspine
51 or hip fracture incidence.¹¹ However no comparison between alendronate
52 use versus no use was established. This prompted us to carry out the
53 present study.¹²
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6 The long-term use of bisphosphonates has been associated with deleterious
7 effects on bone structure such as osteonecrosis of the jaw, atypical
8 fractures (subtrochanteric and diaphyseal), and bone pain that prompted
9 several safety communications issued by both the FDA and EMA.^{13,14}
10

11 In 2008 a cohort study in Danish women with no previous hip fracture was
12 published. The incidence of hip fractures increased in the group treated with
13 alendronate by 50% in relative terms and by 6 cases per 1,000 women-
14 years in absolute terms¹⁵. Updated information from this Danish cohort was
15 published in 2010 and the increased incidence of hip fractures in women
16 taking alendronate was confirmed.¹⁶
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20 **Objective**

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

29 **Study design and setting**

30 We carried out a case-control study nested in a cohort in Spain using the
31 information from BIFAP (*Base de Datos para la Investigación*
32 *Farmacoepidemiológica en Atención Primaria*, Database for
33 Pharmacoepidemiologic Research in Primary Care). This is a longitudinal
34 population-based database kept by the Spanish Agency for Medicines and
35 Medical Devices that collates, from 2001 onwards, the computerized
36 medical records of more than 1,800 physicians throughout Spain. It includes
37 anonymized information on over 3.2 million patients, totalling over 13.7
38 million person-years of follow up.^{17,18}
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42 This project was approved by the Navarre Research Ethics Board,
43 Pamplona, Spain. All data were anonymized and no written consent was
44 necessary for this type of study according to the Spanish regulations (law
45 41/2002, article 16).
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49 **Participants**

50 Cases were defined as women aged 65 years or older with a first diagnosis
51 of hip fracture, using the ICPC-1 codes, recorded between 01/01/2005 and
52 31/12/2008, and with at least 1 year of follow-up in BIFAP before the event
53 date. The date of hospitalization served as the index date. All hip fracture
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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.~~

Information on comorbidities (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/m²) 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 bisphosphonate use with an alpha risk of 5% and a prevalence of exposure of 20%.

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

17
18 An initial "model 1" adjusted only for matching variables. A second "model
19 2" adjusted additionally for smoking, BMI, alcoholism, previous fracture,
20 kidney disease, malabsorption, stroke, dementia, rheumatoid arthritis,
21 diabetes, epilepsy, Parkinson disease, thyroid disease, PPI (no use, ≤ 1 yr,
22 > 1 yr), anxiolytics, sedatives, antidepressants, antihypertensives, oral
23 corticosteroids (no use, ≤ 1 yr, > 1 yr), raloxifene, hormone replacement
24 therapy, and thiazolidinediones.

25 26 **RESULTS**

27 ***Participants***

28
29 Between 2005 and 2008, 3,181 potentially eligible cases were registered.
30 Out of them we validated 2,069 hip fractures and 45 atypical fractures (31
31 subtrochanteric and 14 shaft fractures). Of the remainder 1,067 records
32 were classified as "no case", 718 "other diagnoses" and 349 "lacking
33 information". Sixty cases were excluded due to lack of matching controls. A
34 total of 2,009 cases were obtained and 10,045 matching controls were
35 selected (figure 1).
36

37
38 The average age of cases was 82.4 ± 6.6 years. In general terms co-
39 morbidities and drug use was more prevalent in cases while smoking status
40 and BMI were similar between cases and controls (table 1).
41

42 ***Outcome data***

43
44 Hip fractures were more frequent among bisphosphonate users, 283
45 (14.1%) compared to never users, 1207 (12.0%). Results according to
46 timing, duration, and bisphosphonate exposure are described in table 2.
47

48 ***Main results***

49
50 Ever users of bisphosphonates had a higher risk of hip fracture compared to
51 never users (unadjusted OR = 1.21, 95%CI, 1.05-1.39). After adjusting for
52 co-medication and pathologies no significant differences were found
53 between bisphosphonate users and never users, OR = 1.09 (95%CI, 0.94-
54 1.27).
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8 No association between hip fracture risk and cumulative duration of
9 bisphosphonate treatment was observed: <1 year, OR 1.20 (95% CI, 0.97-
10 1.47); 1 to <3 years, OR 0.94 (95% CI, 0.74-1.20); ≥ 3 years, OR 1.15
11 (95%CI, 0.82-1.60) (p for trend = 0.63). However, when treatment
12 duration is analysed as time since first prescription, hip fracture risk of the
13 different subgroups compared to never users obtained were as follows: <1
14 year, OR 0.85 (95%CI, 0.60-1.21); 1 to <3 years, OR 1.02 (95%CI 0.82-
15 1.26); ≥ 3 years, OR 1.32 (95%CI 1.05-1.65) (p for trend = 0.03). If
16 women exposed to bisphosphonates during less than one year was
17 considered as the reference group, hip fracture risk observed in the
18 different subgroups were: 1 to <3 years, OR 1.56 (95%CI 0.73-3.31); ≥ 3
19 years, OR 2.31 (95%CI 1.00-5.36) (p for trend = 0.03) (tables 2 and 3).

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21
22 No significant trend was observed for timing (past, recent and current use).
23 Past use of bisphosphonates was associated with a statistically significant
24 increase in hip fracture risk (OR = 1.50, 95%CI 1.19-1.89) while current or
25 recent use was not (table 2).

26
27 No protective effect on hip fracture risk was observed when the results were
28 analysed by individual drugs. On the contrary, a statistically significant
29 increased risk was found for ibandronate users (OR = 3.67, 95%CI 1.31-
30 10.3) and for switchers as well (OR = 1.63, 95%CI 1.07-2.47) (table 4).

31 32 33 **DISCUSSION**

34 **Key results**

35
36 According to our findings oral bisphosphonates may not decrease hip
37 fracture risk in elderly women. In order to reduce selection bias, results
38 were adjusted for co-pathologies and medication. However, residual
39 selection bias may still occur. In a cohort study in Danish women with a
40 previous fracture but with no previous hip fracture, the risk of hip fracture
41 was increased in the group treated with alendronate.^{15,16} This study was
42 performed on alendronate only whereas in our study all oral
43 bisphosphonates were included. Our findings are in line with the Danish
44 study in which a higher hip fracture risk was observed.

45
46 A recent meta-analysis of clinical trials assessed the effects of
47 bisphosphonates on hip and wrist fracture risk. Similar results to previous
48 meta-analyses were observed, namely a 1% absolute reduction of hip
49 fracture risk in bisphosphonate users. What is new about this publication is
50 that trials' quality assessment was carried out and revealed an unclear or
51 high risk of bias in approximately 75% of the trials. This means that the
52 small significant reduction in hip fracture may not be real, or at best, is an
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6 exaggeration of the real benefit¹⁰Error! Bookmark not defined. which is in line with
7 our findings.
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11 We evaluated the effects of treatment length and the results by individual
12 drugs as secondary outcomes. No association between hip fracture risk and
13 cumulative duration of bisphosphonate treatment was observed. However,
14 fracture risk increased with longer exposure to bisphosphonates. A
15 statistically significant trend for increased risk of hip fracture was observed
16 among bisphosphonate users irrespective of whether the reference group
17 was never users or women under treatment for less than one year. Results
18 were tested against the two different reference groups because of the
19 possible selection bias in any of them. The results were consistent in both
20 analyses.
21

22 According to the results by individual drugs, no protective effect was
23 observed. On the contrary, a statistically significant increased risk was
24 found for ibandronate users and for switchers as well. Probably ibandronate
25 results in our study are conditioned by a small sample size.
26

27 No significant trend was observed for timing (past, recent and current use).
28 Past users showed a statistically significant higher fracture risk when
29 compared to never users while current or recent users did not. This could be
30 interpreted as if bisphosphonates provided a protective effect on hip
31 fracture risk that disappears after drug withdrawal. However there are some
32 other possible explanations for this. First, treatment withdrawal could be
33 more frequent in patients suffering from drug adverse reactions, in those
34 who did not tolerate treatment, or had a poorer clinical status. All these
35 patients have a higher fracture risk and selection bias is another possible
36 explanation for a higher fracture risk in patients who stopped taking
37 bisphosphonates.
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40 Second, bisphosphonates accumulate in bone structure and past users are
41 exposed to the drug effects for many years after withdrawal. Given the
42 relatively short follow-up period in this study, all patients are exposed to the
43 drug effects irrespective of whether they are past, recent or current users.
44 Thereby interpreting results according to these subgroups may be
45 meaningless. The FLEX trial shows that there is no difference in hip fracture
46 risk between past and current users. Past users had been under treatment
47 for 5 years and had stopped taking the drug 5 years before assessment.
48 This trial supports that alendronate accumulates in bone and past users are
49 exposed to the drug effects for many years after withdrawal. Thereby it
50 makes sense to consider exposure to bisphosphonates in the results
51 analysis. Also we must take into account that in the FLEX trial there is no
52 selection bias due to randomization, and consequently its findings support
53 that the higher risk observed in the past users in our study may be related
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6 to a selection bias and a longer exposure to bisphosphonates in this
7 subgroup as well.
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11 A recent article published by FDA researchers analysed the results of three
12 long-term extension trials on alendronate, risedronate and zoledronic acid.
13 Pooled data pertaining to patients who received continuous bisphosphonate
14 treatment for 6 or more years resulted in fracture rates ranging from 9.3 to
15 10.6%, whereas the rate for patients switched to placebo was 8.0 to 8.8%.
16 These data raise the question on whether long-term use of bisphosphonates
17 is beneficial for patients.¹⁹
18

19 With long-term use it is widely accepted that bisphosphonates may cause
20 osteonecrosis of the jaw and atypical (subtrochanteric and diaphyseal)
21 fractures as well. Recently, a self-controlled case series analysis showed
22 that bisphosphonate use was associated with osteonecrosis at any site.²⁰
23 Deleterious effects on bone structure have been observed with
24 bisphosphonates and denosumab as well but not with other osteoporosis
25 drugs. Both type of drugs inhibit bone turnover and thereby bone strength
26 may be weaker as a result of treatment. Besides bisphosphonates prolong
27 secondary mineralization leading to increased bone density but decreased
28 bone toughness due to a higher mineral content (brittle bones).²¹ Since
29 there is biological rationale to explain the harmful effects of
30 bisphosphonates on bone, more long-term studies are needed to test our
31 findings.
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34 35 36 **Limitations**

37 One of the main limitations in our study is the relatively short follow-up
38 period. Besides, we relied on prescription data to determine duration of
39 bisphosphonate exposure. It is sensible to think that real exposure will likely
40 be lower than registered. In the clinical records included in the BIFAP
41 database, X-ray images are not available which might occasionally lead to
42 misclassification of cases. However we believe this may not be a relevant
43 limitation yet hip fracture cases are described in detail in the surgical
44 procedures.
45
46

47 Another aspect to be pointed out is that ibandronate was marketed in Spain
48 in January 2007 and in our study we included incident cases of hip fracture
49 that occurred between 2005 and 2008. Thereby the exposure of both cases
50 and controls to ibandronate is rather short-term.
51

52 Confounding by indication is a possible bias of this study. Theoretically
53 women in a poor baseline condition could be prescribed bisphosphonates to
54 a greater extent when compared to women with a better health status. In
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6 order to minimize this bias, results were adjusted for previous fractures,
7 comorbidities and use of other medications.
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9 Bone mineral density determination is not a standard test available in the
10 public health system in Spain. Thereby information on BMD in clinical
11 records was rather scarce. However, this test has a very poor fracture risk
12 predictive value and its clinical relevance can be challenged. When it comes
13 to adjusting crude data we used other bone-related variables instead such
14 as prevalence of previous fractures.
15

16 In our study no information on vitamin D plasma levels in our patients was
17 available. However we believe this does not pose any problem since
18 patients were not institutionalized and in Spain the exposure to sunlight is
19 sufficient to ensure adequate levels of vitamin D. Furthermore, almost 90%
20 of women aged 65 or older take supplements of calcium plus vitamin D.²²
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22 23 24 **Conclusions**

25
26 Ever use of oral bisphosphonates was not associated with a decreased risk
27 of hip fracture in women aged 65 or older as compared to never use. No
28 association between hip fracture risk and cumulative duration of
29 bisphosphonate treatment was observed. However, when treatment
30 duration is analysed as time since first prescription, a statistically significant
31 increased risk for hip fracture was observed in patients exposed to
32 bisphosphonates over 3 years.
33

34 35 36 **Acknowledgements**

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38 The authors would like to thank the collaboration of general practitioners
39 contributing to BIFAP.
40

41 42 43 **Disclaimer:**

44
45 The Spanish Agency of Medicines and Medical Devices (AEMPS) provided the
46 crude data from BIFAP to the researchers according to an agreement with
47 the Health Department of Navarre Government but did not take part in the
48 design or in the study development. Authors are fully responsible for the
49 analysis, results and opinions appearing in the paper and do not represent
50 the position of the AEMPS. The views expressed are those of the authors
51 only and do not represent necessarily the position of their respective
52 institutions.
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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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- 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/m ²	27.2 (5.0)	29.0 (5.0)	<0.0001
<20 kg/m ² , %	2.7	1.0	<0.0001
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	<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 H ₂ 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

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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.

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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)

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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)

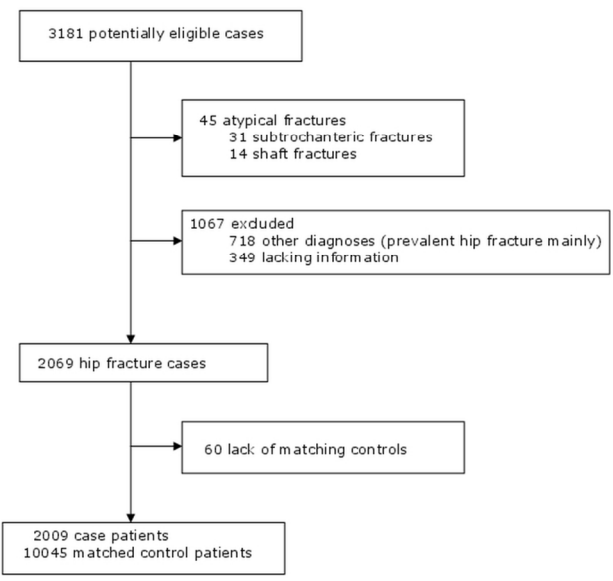
Model 1: Conditional logistic regression model

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

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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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed OK	

		<i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure OK	
		<i>Cross-sectional study</i> —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.