León Vázquez F[1], Bonis J[2], Bryant Cerezo V[2], Herrero Hernández S[3], Jamart Sánchez L[3], Díaz Holgado A[4]

1 Centro de Salud Universitario San Juan de la Cruz - Dirección Asistencial Noroeste - Gerencia de Atención Primaria - Servicio Madrileño de Salud - Pozuelo de Alarcón (Madrid)

2 BIFAP - Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria - División de Farmacoepidemiología y Farmacovigilancia - Agencia Española de Medicamentos y Productos Sanitarios - Madrid

3 Servicio de Farmacia Atención Primaria - Dirección Asistencial Noroeste - Gerencia de Atención Primaria - Servicio Madrileño de Salud - Majadahonda (Madrid)

4 Dirección Técnica de Sistemas de Información Sanitaria - Gerencia Adjunta de Planificación y Calidad - Servicio Madrileño de Salud - Madrid

Prevention of osteoporotic fracture in Spain: use of drugs before and after a hip fracture

Correspondence: Fernando León Vázquez - Centro de Salud Universitario San Juan de la Cruz - Camino de Alcorcón, 8 - 28224 Pozuelo de Alarcón - Madrid (Spain)
e-mail: fleonvaz@gmail.com

Date of receipt: 04/04/2015
Date of acceptance: 07/07/2015

Summary

Introduction: Treatment of osteoporosis is focussed on the prevention fragility fractures, fractures of the hip being those which produce the highest rates of morbidity and mortality. The existence of a previous fracture is an important predictor of a new fracture.

Objective: we intend to analyse how treatment for osteoporosis varies before and after a hip fracture.

Material and methods: Using the 4,126,030 clinical records in the database for pharmaco-epidemiological research in primary care (Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria [BIFAP]) 2011 for the whole of Spain, information was obtained regarding patients who had a first hip fracture recorded between 2005-2011, having been monitored for at least a year before and after. We analyse the previous and subsequent treatment for osteoporosis (including calcium and vitamin D supplements).

Results: 2,763 patients over 60 years of age (average 81 years) had suffered a hip fracture, of whom 81.6% were women. Before the fracture 26.5% (95% confidence interval [CI]: 24.8-28.1%) had received some antiosteoporotic treatment, of which 12% (95% CI: 11.0-13.5%), were bisphosphonates. 38.6% (95%CI: 36.8-40.4%) received treatment after the fracture, 20.4% (95%: 18.9-22%) treated with bisphosphonates. The factors associated with the initiation of treatment after the fracture were being a woman, being younger and having a previous diagnosis of osteoporosis.

Conclusions: Most of the patients studied were not receiving preventative treatment before their hip fracture. After the fracture the prescription of treatment increased a little. The drugs most commonly added were calcium, vitamin D and bisphosphonates.

Key words: *osteoporosis, hip fracture, secondary prevention.*

Introduction

Osteoporosis is a bone disorder characterised by a deficit in both bone mineral density (quantity) and bone architecture (quality), which results in lower bone strength, greater fragility and a higher risk of fracture after minor trauma (fragility or osteoporotic fracture)[1]. According to the densitometric criteria proposed in 1994 by the World Health Organisation (WHO)[2], in Spain, the prevalence of osteoporosis is around 26% of women aged 50 years or over, increasing with age[3].

Among the osteoporotic fractures, vertebral fractures are those with the highest incidence, along with those of the radius, generating significant morbidity, although little mortality. But it is fractures of the hip, which appear later on, which present the greatest mortality[4], in addition to generating greater dependency and higher health costs. In a third of cases the patient had already had an earlier fragility fracture, with 21% of these even in the other hip[5]. A previous fragility fracture is, along with age, the most significant risk factor for suffering a new osteoporotic fracture. The appearance of a hip fracture due to a low impact trauma in older age permits the establishment with a high degree of suspicion of the diagnosis of established osteoporosis, making its confirmation through the use of other diagnostic measures, such as densitometry, unnecessary[6].

Currently, various drugs are used for the prevention of osteoporotic fractures such as the bisphosphonates (alendronate, risedronate, etidronate, ibandronate and zoledronate) strontium ranelate (which has recently seen its authorisation for use limited) estrogen receptor modulators (raloxifene and bazedoxifene), denosumab, teriparatide and parathyroid hormone. In the past, hormone replacement therapy or calcitonin were also used, but are now in disuse due to the existence of safer and more efficacious alternatives. The use of calcium[7] and vitamin D supplements[8] was also recommended, associated or not with the aforementioned drugs, to which have been attributed improvements in bone mineral density, whose efficacy in the prevention of fractures is currently compromised when used without being associated with other drugs[9].

The main aim of this study was to analyse, in a primary care setting, the prevalence of the use of pharmacological drugs for the treatment or prevention of osteoporosis before and after a first hip fracture of osteoporotic aetiology. The secondary aim was to analyse the possible factors associated with the decision to initiate treatment with bisphosphonates after a fracture in patients who were not taking them previously.

Material and methods

The study was carried out using the BIFAP database (Database for pharmaco-epidemiological research in primary care [Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria]) 2011, which includes anonymised information from the clinical records of 4,126,030 patients (with an average monitoring period of 4.8 years per patient), recorded by 2,239 family doctors and primary care paediatricians across the whole of Spain[10].

The computerised clinical history for each patient is composed of episodes, each of which has an associated diagnosis, coded according to the International Classification for Primary Care (ICPC)[11]. Each prescription issued for the patient is associated with a specific ICPC episode.

A study of transverse design was carried out of the use of medications for osteoporosis before and after a first episode of fracture. Those patients over 60 years of age with a first record of hip fracture coded as ICPC L75 in the period between 1st January 2005 and 1st January 20011, and with a record covering at least a year before and after the date of the fracture, were included. Those patients with a history of cancer and of Paget's disease were excluded.

For each patient selected, the sex, the age at the time of fracture, the date of the hip fracture and the presence of earlier diagnoses coded using ICPC corresponding to possible absolute or relative contraindications for the use of bisphosphonates, were noted from the medical record (Annex 1), as well as the presence of previous episodes of diabetes mellitus type 1, rheumatoid arthritis, hyperthyroidism, masculine hypogonadism, malabsorption, malnutrition, early menopause and osteoporosis (Annex 2).

The previous use of corticoids was also analysed, with, for the purposes of this study, a previous user being a patient who had had at least 3 prescriptions, and with an estimated 90 days or more of usage (based on the dosage) of prednisolone ≥ 5 mg/day (or equivalent) at any time before the date of the hip fracture.

Lastly, the use before or after the hip fracture of bisphosphonates (etidronate, alendronate, ibandronate, risedronate), vitamin D, calcium, calcitonin, estrogens, parathyroid hormones, teriparatide, raloxifene, bazedoxifene strontium ranelate and denosumab, were considered (Annex 3).

For each of the aforementioned drugs the patient was considered to be under primary prevention if they had received, at any time before the fracture, at least two prescriptions for one of the drugs listed, or in the case of having received a single prescription, if this was issued within 180 days before the fracture. The patient was considered to be under subsequent prevention for hip fracture if they had had at least one prescription of one of the drugs for osteoporosis described within a year after the date of the fracture.

In order to analyse which factors were associated with the initiation of treatment with bisphosphonates after a hip fracture in those who had not received earlier treatment, a logistical regression model was constructed, using as independent variables the year of the fracture, the age of the patient, the sex, the presence of diabetes, rheumatoid arthritis, record of osteoporosis or any contraindication for the use of bisphosphonates, as

well as previous exposure to corticoids. A backward selection strategy was used based on the likelihood ratio model for the selection of variables finally included in the model. For the descriptive analysis the proportion of patients who were receiving each of the treatments studied before, and in the year following, the fracture was calculated, as well as the average age and duration of the monitoring before and after the fracture, with corresponding confidence intervals of 95% (95% CI). For hypothesis testing regarding the differences in the proportion of use of each of the drugs before and after the fracture, the McNemar test for paired data was used.

Results

2,763 patients over 60 years of age (average of 81 years) were identified who had presented a first hip fracture in the period of the study, 2,225 of whom were women (81.6%). The average duration of the period of registration prior to the fracture was 5.8 years. The rest of the demographic and comorbidity data are described in Table 1.

A total of 731 patients (26.5%; 95% CI: 24.8-28.1%) had received one of the drugs analysed before the fracture (Table 2). Of these, 338 patients (12.2%; 95% CI: 11.0-13.5%) had received some treatment with bisphosphonates.

In the year following the hip fracture, 1,066 patients (38.6%; 95% CI: 36.8-40.4%) had received some antiosteoporotic treatment (Table 2), of whom 564 (20.4%; 95% CI: 18.9-22.0%) had received a bisphosphonate (Figure 1). The increase in the use of drugs against osteoporosis (p<0.0001), as well as the increase in the use of a bisphosphonate (p<0.0001) were statistically significant according to the McNemar test.

The most commonly prescribed drugs, both before and after the fracture, were calcium (23.2% and 32.4% respectively) and vitamin D (19.6% and 31.0% respectively). Among the bisphosphonates the most common were alendronate (6.6% and 10.4%) and risedronate (5.4% and 8.1%). On the other hand, it was notable that of the 508 men in the study, 11 (2.2%) were receiving alendronate before the fracture, and 29 (5.2%) took them within the year following the fracture.

Of the 338 patients who took bisphosphonates at any time before the fracture, 104 (30.8%) did not take them in the year after it. On the other hand, of the 2,425 patients who had not taken it before, 330 (13.6%) started treatment with bisphosphonates afresh in the year following the fracture. A total of 369 patients (13.4%; 95% CI: 12.1-14.6%) presented some absolute and relative contraindications for the use of bisphosphonates, including any diagnosis of gastritis or dyspepsia (complete criteria in Annex 1). Of the 642 patients who were taking calcium supplements at some point before the fracture, 31% (200 patients) did not receive them in the year after the fracture; while of 2,121 patients who were not taking them, 462 (21.8%) started to receive them after it. We obtained almost identical percentages with vitamin D supplements.

The logistic regression model (Table 3) regarding patients who were not taking treatment before the fracture (n=2,425) showed that the factors associated with a higher probability of initiating a treatment with bisphosphonates after fracture (n=330) were: being a woman (OR=2.44; p<0.0001), having a previous diagnosis of osteoporosis recorded (OR=1.61; p=0.009), being younger (OR per year of age=0.96; p<0.0001) and having some absolute or relative contraindication for the use of bisphosphonates (OR=1.41; p=0.033). No association was observed between the start of treatment with bisphosphonates after fracture and the fact of having diabetes, previous exposure to corticoids, history of rheumatoid arthritis or the year in which the fracture occurred. No significant interactions were observed between the independent variables analysed.

Discussion

The natural course of osteoporosis has a prolonged asymptomatic phase. In this period of primary prevention it is necessary to influence modifiable risk factors[12], although the use of drugs is controversial and the benefits, if any, are of low magnitude[13]. On the other hand, there is a consensus in not recommending population screening of bone mineral density with densitometry, and that this test is reserved for high risk cases and in order to take key therapeutic decisions[14].

After the first fragility fracture the risk of suffering future fractures increases considerably[15,16]. So, after a first vertebral fracture, the risk of a new vertebral fracture increases 4.4 times, and of a hip fracture by 2.3 times[17]. The usefulness of drugs for prevention subsequent to the fracture (which is usually called secondary prevention, but which would strictly be tertiary prevention),[18] has better tests available for its use in primary prevention[6,13].

Various studies have analysed the prescription of drugs for osteoporosis after a hip fracture, Some evaluate the treatment prescribed on discharge from hospital after a hip fracture, with levels of treatment which vary between 6%[19] and 19%[20]. Other works address treatment after any osteoporotic fracture over the course of a year, obtaining levels from 15% for treatment after the event[21], in other cases up to 24% after any fracture, with levels of 44% after vertebral fracture and 21% after a hip fracture[22]. In our case we obtained rates somewhat higher than the 38% for osteoporotic treatment, even though our data include treatment initiated up to a year after the fracture, and excluded patients with early mortality (with less than a year of records available after the fracture), which probably limits its comparability with other studies. The majority of the patients (73.5%) in our sample had not received drug treatment for osteoporosis before their hip fracture. After the first fracture, the doctors initiated some treatment afresh in a minority of patients, both with bisphosphonates (13.6%) and calcium-vitamin D (21.8%). By comparing the prevalence of its use before and after the fracture an increase was con-

Table 1. Description of the population. Clinical characteristics, exposure to corticoids and contraindications for the use of bisphosphonates, before a hip fracture

	n		
Total	2,763		
		Average	SD (min-max)
Age (years)		81.6	7.76 (60-105)
Preregistration period (days)		2,130	999 (366-10,909)
	n	Percentages	
Women	2,255	81.6%	
Diabetes mellitus type 2	454	16.4%	
Hyperthyroidism	30	1.1%	
Rheumatoid arthritis	32	1.2%	
Hypogonadism	0	0.0%	
Malabsorption	0	0.0%	
Malnutrition	4	0.1%	
Early menopause	5	0.2%	
Osteoporosis	428	15.5%	
Prior exposure to corticosteroids	144	5.2%	
Contraindications for bisphosphonates	369	13.36%	

firmed in the proportion of patients who received some drug treatment (from 26.5% to 38.6%), which was, furthermore, statistically significant ($p<0.0001$ for the McNemar test). In a north American study[23], the probability of receiving treatment after a hip fracture diminished from 40.2% in 2002 to 20.5% in 2011. Whether this increment is slight or not, is a matter of controversy, although the guides[6,15,17,24] include people with fractures as the target population, who obtain the greatest benefit from pharmacological treatment in normal clinical practice.

The highest consumption of antiresorptive drugs in our setting is found in women at relatively early ages (66 years on average)[25] in whom osteoporotic fracture is less frequent in comparison with the age group of older women, in which fractures are more common and (in the hip) more serious. However, a review concluded that alendronate does reduce clinically and statistically significantly vertebral, non-vertebral, hip and wrist fractures in secondary prevention, without there being statistically significant results for primary prevention, except for vertebral fractures[13], although this is a controversial point[26].

The logistical regression model allows us to analyse the factors related to the decision to initiate a treatment with bisphosphonates after a first hip fracture in patients who were not receiving them previously. The data suggest that doctors in primary care use criteria similar to those used for the initiation of treatment before fracture and in primary prevention. So, being female, younger and having an earlier diagnosis of osteoporosis increases the probability of initiating treatment after a first hip fracture.

Notable among the drugs which have most been used in our analysis, both before and after a fracture, are the bisphosphonates, alendronate and risedronate, similar to other series[27]. On the other hand there are the recommendations in the guides for efficacy, safety and price[10]. The data from the study showed the existence of men in treatment with alendronate; even though alendronate has shown definite efficacy in improving bone mass in males[28], its indication in the data

Table 2. Prevalence of pharmacological treatment for osteoporosis before and after a first hip fracture

	Before fracture (a)		After fracture (b)				
	n	%	n	%	Suspended (c)	Begin (d)	p (e)
Total	2,763		2,763				
Bisphosphonates (f)	338	12.2%	564	20.4%	104	330	<0.0001
Alendronate	183	6.6%	288	10.4%	84	189	<0.0001
Etidronate	21	0.8%	3	0.1%	18	0	<0.0001
Ibandronate	26	0.9%	74	2.7%	9	57	<0.0001
Risedronate	149	5.4%	224	8.1%	66	141	<0.0001
Calcium	642	23.2%	904	32.7%	200	462	<0.0001
Vitamin D	542	19.6%	857	31.0%	167	482	<0.0001
Ca + vitamin D	535	19.3%	828	30.0%	173	466	<0.0001
Calcitonin	91	3.3%	42	1.5%	72	23	<0.0001
Teriparatide/PTH	13	0.5%	58	2.1%	6	51	<0.0001
Estrogens	15	0.5%	6	0.2%	13	4	0.0490
Raloxifene/bazedoxifene	41	1.5%	17	0.6%	29	5	<0.0001
Strontium ranelate	21	0.8%	71	2.6%	14	64	<0.0001
Denosumab	0	0.0%	0	0.0%	0	0	<0.0001
In treatment (g)	731	26.5%	1,066	38.6%	194	529	<0.0001

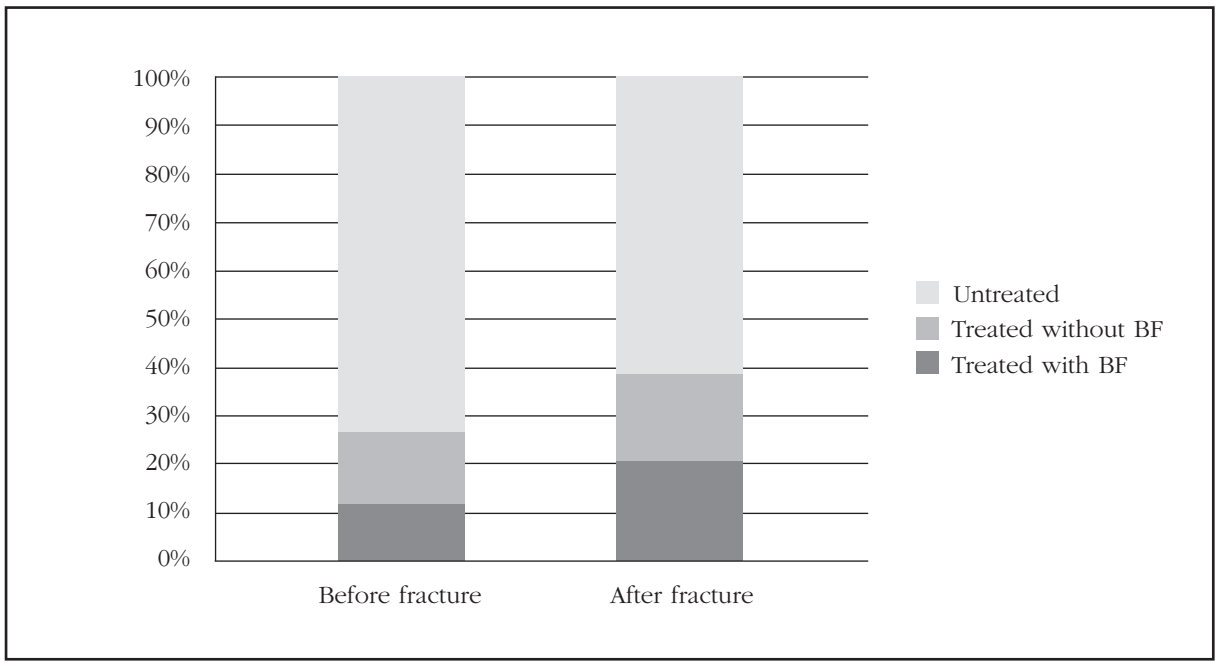
(a): at any time before the first hip fracture; (b): within the 365 days subsequent to the first hip fracture; (c): treatment stopped after the hip fracture; (d): treatment initiated after the hip fracture; (e): McNemar test for paired data; (f): in treatment with at least one bisphosphonate; (g): in treatment with one of the earlier drugs.

sheet is restricted to postmenopausal osteoporosis[29,30]. Only 15.5% of those patients with hip fracture had included in their diagnosis "osteoporosis", although they had received treatment with antiresorptive drugs, which suggests an additional problem of under-registration.

Our study has some limitations. It does not distinguish as to whether the treatment before the fracture was for primary prevention, given that the patient could have had a previous fragility fracture, as long as it was different from the hip. Neither does it analyse the dose or duration of the drugs used, since after the fracture there could have been patients treated for a short period, as against others who could have been treated for the whole period of the study after the hip fracture. The prescription of drugs subsequent to the fracture reflects the preoccupation by the professional with the risk of new fractures, which results in the initiation of treatment aimed at secondary prevention. However, it does not tell us about its persistence over time.

Another limitation is that, given the nature of the record from which the data was obtained, it is not possible to differentiate with certainty between absolute contraindications and precautions for the use of bisphosphonates. The association between the existence of an earlier contraindication before the fracture and the start of treatment after the fracture (OR=1.41) should be interpreted within this context. A possible hypothesis would suggest that the professionals, faced with precaution on use, don't initiate preventative treatment with bisphosphonates, but that once the fracture occurs, reconsider the risk-benefit balance in favour of pharmacological treatment. It is important to note that in our study only those patients with a survival of at least one year after fracture were included. This selection criterion adds consistency to our data and facilitates their interpreta-

Figura 1. Evolución del tratamiento antes y después de la fractura de cadera



tion, but makes it difficult to compare them with the results of other studies in which patients with early mortality after a fracture are included.

Notable among the strengths of the study is the high number of hip fractures analysed (n=2,763) and the variety of drugs studied. The fact that the clinical record was used as a source of data retrospectively, and the inclusion of treatment initiated up to a year after the date of the fracture, and not only immediately after it, means that the results are probably a good refection of real clinical practice in the primary care context. Using episodes of hip fractures in people over 60 years of age as a marker for established osteoporosis offers advantages since, given its gravity, it is not usually omitted from their record, and it rarely has a different origin from bone fragility[6]. Contrarily, the analysis of other types of fracture such as of the wrist or vertebrae are less specific, since they may have other origins, may pass unnoticed, or be variable in the register. A piece of data in favour of the external validity of the study is that the average age at fracture in our sample, 81 years, coincides with other Spanish studies with different methodologies, and coincides also in the ratio between women and men of 4:1[4,5].

The majority of patients in our study were not in treatment before suffering their hip fracture. After it there was a moderate increase in the prescription of drugs for osteoporosis. There are currently no data on the efficacy of these drugs in the prevention of hip fracture in patients who have already suffered a previous hip fracture, and it would therefore be very interesting to carry out new studies to determine whether the preventative treatment after a first hip fracture is effective or not in preventing new fractures.

Acknowledgements: The authors would like to thank the inestimable collaboration of the family doctors and paediatricians in primary care participating in BIFAP, whose contribution of a high quality record of their daily activity has made the realisation of this study possible.

Source of funding: This work was carried out without external funding.

Bibliography

1. National Institutes of Health (USA). Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. JAMA 2001;285:785-95.
2. World Health Organization: Assessment of Fracture Risk and its application to screening for postmenopausal Osteoporosis. Report of WHO Study group (Technical report series 843: 1-129). Geneva Switzerland; 1994.
3. Díaz-Curiel M, García JJ, Carrasco JL, Honorato J, Pérez-Cano R, Rapado A, et al. Prevalencia de osteoporosis determinada por densitometría en la población femenina española. Medicina Clínica (Barcelona) 2001;116:86-8.
4. Serra JA, Garrido G, Vidán M, Marañón E, Brañas F, Ortiz J. Epidemiología de la fractura de cadera en ancianos en España. Ann Med Intern (Madrid) 2002;19:389-95.
5. Herrera A, Martínez AA, Ferrández L, Gil E, Moreno A. Epidemiology of osteoporotic hip fractures in Spain. Int Orthop 2006;30:11-4.
6. National Institute for Health and Care Excellence. Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (amended) (TA161). NICE, 2010 http://www.nice.org.uk/guidance/ta161.
7. Shea B, Wells G, Cranney A, Zytaruk N, Robinson V, Griffith L, et al. Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group. Meta-

Table 3. Factors related to the initiation of bisphosphonate therapy after first hip fracture (a)

	OR adjusted (b)	IC 95%
Woman	2.44	1.69 - 3.52
Prior osteoporosis	1.61	1.13 - 2.30
Contraindication prior bisphosphonate (c)	1.41	1.03 - 1.94
Age	0.96	0.94 - 0.97

(a): logistical regression model with 2,425 patients who did not receive primary prevention with bisphosphonates prior to the fracture; (b): dependent variable: receiving secondary prevention with bisphosphonates in the 365 days subsequent to a first hip fracture; (c) absolute or relative contraindication for the use of bisphosphonates.

analyses of therapies for postmenopausal osteoporosis. VII. Meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. Endocr Rev 2002;23:552-9.
8. Papadimitropoulos E, Wells G, Shea B, Gillespie W, Weaver B, Zytaruk N, et al. Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group. Meta-analyses of therapies for postmenopausal osteoporosis. VIII: Meta-analysis of the efficacy of vitamin D treatment in preventing osteoporosis in postmenopausal women. Endocr Rev 2002;23:560-9.
9. Moyer VA. U.S. Preventive Services Task Force. Vitamin D and calcium supplementation to prevent fractures in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2013;158:691-6.
10. Salvador-Rosa A, Moreno-Pérez JC, Sonego D, García-Rodríguez LA, de Abajo-Iglesias FJ. El Proyecto BIFAP: Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria. Aten Primaria 2002;30:655-61.
11. Lamberts H, Wood M (Eds.). Clasificación Internacional de la Atención Primaria (CIAP). Barcelona: Masson/SG; 1990.
12. National Clinical Guideline Centre (UK). Osteoporosis: Fragility Fracture Risk: Osteoporosis: Assessing the risk of fragility fracture. London: Royal College of Physicians (UK); 2012.
13. Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, et al. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev 2008;(1):CD001155.
14. Malabanan AO, Rosen HN, Vokes TJ, Deal CL, Alele JD, Olenginski TP, et al. Indications of DXA in women younger than 65 yr and men younger than 70 yr: The 2013 Official Positions. J Clin Densitom 2013;16:467-71.
15. Grupo de trabajo de la Guía de Práctica Clínica sobre Osteoporosis y Prevención de Fracturas por Fragilidad. Guía de Práctica Clínica sobre Osteoporosis y Prevención de Fracturas por Fragilidad. Plan de Calidad para el Sistema Nacional de Salud del Ministerio de Sanidad y Política Social. Agència d Avaluació de Tecnologia i Recerca Mèdiques de Cataluña (AATRM). Madrid, 2010.
16. Akesson K, Marsh D, Mitchell PJ, McLellan AR, Stenmark J, Pierroz DD, et al. IOF Fracture Working Group. Capture the Fracture: a Best Practice Framework and global campaign to break the fragility fracture cycle. Osteoporos Int 2013;24:2135-52.
17. Dirección General de Farmacia y Productos Sanitarios. Recomendaciones para la valoración y tratamiento de la osteoporosis primaria en mujeres de la Comunidad de Madrid. Madrid: Consejería de Sanidad; 2007.
18. Martínez-González MA, Guillén-García F, Delgado-Rodríguez M. Conceptos en Salud Pública. En:

Annex 1. Absolute or relative contraindications to the bisphosphonates

Gastric pathology:

- Oesophagitis: oesophagitis, caustic oesophagitis, reflux oesophagitis.
- Duodenal ulcer: duodenal ulcer, duodenal ulceration.
- Gastric ulcer: stomach ulcer, stomach ulceration, perforated stomach ulceration, gastrointestinal ulceration, peptic ulceration.
- Gastritis: disturbance in stomach function, dyspepsia, duodenitis

Annex 2. Other clinical characteristics analysed

- Hyperthyroidism
- Diabetes mellitus type 2
- Malabsorption syndrome
- Malnutrition
- Masculine hypogonadism
- Early menopause
- Rheumatoid arthritis
- Osteoporosis

Annex 3. Drug study

• Corticosteroids:	
H02AB01	Betamethasone
H02AB13	Deflazacort
H02AB02	Dexamethasone
H02AB09	Hydrocortisone
H02AB04	Methylprednisolone
H02AB06	Prednisolone
H02AB07	Prednisolone
H02AB08	Triamcinolone
• Vitamin D	
A11CC05	Cholecalciferol
• Calcium supplements	
A12AA01	Calcium phosphate
A12AA04	Calcium phosphate
A12AA10	Calcium glucoheptonate
A12AA12	Calcium acetate, anhydrous
A12AA20	Calcium (different salts in combination)
A12AA91	Calcium pidolate
A12AA92	Oseina-hydroxyapatite complex
• Calcium + vitamin D partnerships	
A12AX91	Calcium phosphate + cholecalciferol
A12AX92	Calcium lactate + cholecalciferol
A12AX93	Calciocarbonato + cholecalciferol
A12AX94	Calcium glucoheptonate + cholecalciferol
A12AX96	Calcium pidolate + cholecalciferol
• Estrogens	
G03CA03	Estradiol
G03CA04	Estriol
G03CA57	Conjugated estrogens
• Selective estrogen receptor modulators	
G03XC01	Raloxifene
G03XC02	Bazedoxifene
• Calcitonins	
H05BA01	Calcitonin (salmon, synthetic)
H05BA03	Calcitonin (human synthetic)
• Bisphosphonates	
M05BA01	Etidronic acid
M05BA04	Alendronate acid
M05BA06	Ibandronic acid
M05BA07	Risedronic acid
M05BA91	Alendronate acid + cholecalciferol
• Other endocrine drugs	
H05AA02	Teriparatide
H05AA03	Parathyroid hormones
• Other drugs bone diseases	
M05BX03	Strontium ranelate
M05BX04	Denosumab

Martínez-González MA (Ed). Conceptos de Salud Pública y Estrategias Preventivas. Un manual para Ciencias de la Salud. Barcelona: Elsevier; 2013:9-13.
19. Rabenda V, Vanoverloop J, Fabri V, Mertens R, Sumkay F, Vannecke C, et al. Low incidence of anti-osteoporosis treatment after hip fracture. J Bone Joint Surg Am 2008;90:2142-8.
20. Andrade SE, Majumdar SR, Chan KA, Buist DS, Go AS, Goodman M, et al. Low frequency of treatment of osteoporosis among postmenopausal women following a fracture. Arch Intern Med 2003;163:2052-7.
21. Ensrud KE, Schousboe JT. Clinical practice. Vertebral fractures. N Engl J Med 2011;364:1634-42.
22 Panneman MJ, Lips P, Sen SS, Herings RM. Undertreatment with anti-osteoporotic drugs after hospitalization for fracture. Osteoporos Int 2004;15:120-4.
23. Solomon DH, Johnston SS, Boytsov NN, McMorrow D, Lane JM, Krohn KD. Osteoporosis medication use after hip fracture in U.S. patients between 2002 and 2011. J Bone Miner Res 2014;29:1929-37.
24. Guías de actuación. Osteoporosis Manejo: prevención, diagnóstico y tratamiento. 1ª Edición. Barcelona: Semfyc Ediciones, 2014.
25. De Felipe R, Cáceres C, Cimas M, Dávila G, Fernández S, Ruiz T. Características clínicas de los pacientes con tratamiento para la osteoporosis en un centro de Atención Primaria: ¿a quién tratamos en nuestras consultas? Aten Primaria 2010;42:559-63.
26. Erviti J, Alonso A, Oliva B, Gorricho J, López A, Timoner J, et al. Oral bisphosphonates are associated with increased risk of subtrochanteric and diaphyseal fractures in elderly women: a nested case-control study. BMJ Open 2013 30;3(1).
27. Carbonell-Abella C, Guañabens-Gay N, Regadera-Anechina L, Marín-Rives JA, Taverna-Llauradó E, Ayechu-Redín MP. Análisis del cumplimiento terapéutico en mujeres con osteoporosis. Reumatol Clin 2011;7:299-304.
28. Orwoll E, Ettinger M, Weiss S, Miller P, Kendler D, Graham J, et al. Alendronate for the treatment of osteoporosis in men. N Engl J Med 2000;343:604-10.
29. Centro de Información online de Medicamentos CIMA. Agencia Española de Medicamentos y Productos Sanitarios. Ficha técnica del Alendronato. Disponible en http://www.aemps.gob.es/cima/pdfs/es/ft/69193/FT_69193.pdf [Consultada el 4/04/2015].
30. León-Vázquez F, Herrero-Hernández S, Cuerpo-Triguero C, Andrés-Prado MJ,Cabello-Ballesteros L. Prescripción de ácidos alendrónico y risedrónico en varones: uso fuera de la ficha técnica en un área de salud. Reumatol Clin 2015;11:64-7.