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Trends in postmenopausal osteoporosis treatment in France during the period 2007–2016: A nationwide claims database analysis

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ABSTRACT

Purpose: To describe the trends in the pharmacological management of postmenopausal osteoporosis in France during the period 2007–2016.

Method: This cross-sectional, yearly repeated study of patients in France used the nationwide claims database 'Échantillon Généraliste de Bénéficiaires' (EGB), covering a 1 in 97 representative sample of approximately 600,000 individuals insured by the main French public insurance scheme. For women aged 50–89 years, prescriptions for all anti-osteoporosis medications (AOMs) marketed in France during the study period (bisphosphonates alone or used in combination with calcium, selective estrogen receptor modulators, strontium ranelate, teriparatide or denosumab) were identified in each calendar year. Initiation of any AOM in a calendar year was defined by the absence of a prescription for any AOM within the 2 previous calendar years. Incidence was calculated for all AOM prescriptions and initial prescriptions for AOM.

Results: Marked changes were observed in the rates of women receiving any AOM, with a slight increase from 2007 to 2009 (from 10.22 to 10.42 per 100 patient-years [PY]), then a plateau in 2009–2010, followed by a rapid and more than twofold decrease until 2016 (from 10.39 to 5.02 per 100 PY). The decrease in the overall rate of women initiating an AOM showed a rapid halving from 2007 to 2012 (from 2.56 to 1.15 per 100 PY), followed by a plateau in the range of 0.90–1.0 per 100 PY during the period 2013–2016. In contrast, the use of calcium/vitamin D has been rapidly increasing as the only prevention and exclusive intervention for postmenopausal osteoporosis, from 10.6% of women in 2007 to 47.7% in 2016.

The profile of patients initiating AOM changed substantially over the 10-year period. Despite a stable mean age of approximately 69 years, an increasing proportion of women with severe chronic comorbidities (from 34.9% to 43.3%), history of fractures (from 7.8% to 13.3%) or high-dose steroid use (from 2.9% to 8.4%) was observed. The decline of AOM initiation was associated with a marked reduction of prescriptions during the study period: by 64.2% for primary care physicians; by 36.7% for specialty doctors; and by 18.4% for rheumatologists.

Conclusion: These findings suggest a general trend toward an AOM uptake that is increasingly limited to a fraction of patients who are at high risk of fractures. In the context of an aging population and declining prescription rates

Abbreviations: AOM, anti-osteoporosis medication; ATC, Anatomical Therapeutic Chemical; CCAM, Classification Commune des Actes Médicaux (French national coding system for surgical and interventional procedures); CNAM, Caisse Nationale de l'Assurance Maladie (French national health insurance fund); CIP, Codes Identifiants de Présentation (unique French national registration code); CMU-C, Couverture Maladie Universelle Complémentaire (complementary universal health insurance); CNIL, Commission Nationale de l'Informatique et des Libertés (French national data protection agency); DEXA, dual-energy X-ray absorptiometry; EGB, Échantillon Généraliste de Bénéficiaires (Generalist Sample of Beneficiaries); HAS, Haute Autorité de Santé (French National Authority for Health); ICD-10, International Classification of Disease, 10th Revision; LTD, long-term disease; PY, patient-years; PMSI, Programme de Médicalisation des Systèmes d'Information (Hospital discharge summaries database).

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for AOM, these data highlight an increasing treatment gap among women in France with osteoporosis, which is similar to that seen in other European countries and in the USA.

1. Introduction

Osteoporosis is a progressive bone disease characterized by decreased bone quality and density and increased risk of osteoporotic (fragility) fracture [1]. Owing to its high prevalence and the severe consequences of osteoporotic fractures, osteoporosis has been identified by the World Health Organization as a major public health concern [2]. Fracture risk increases with age; one in three women aged 50 or over will experience a fragility fracture during the rest of their lives. Fractures may be induced by certain treatments, including prolonged corticosteroid therapy, or by certain pathologies. The risk of osteoporotic fractures can be reduced with lifestyle changes, fall preventive measures and pharmaceutical intervention. Before any specific treatment, calcium and/or vitamin D deficiency can be corrected by adjusting dietary intake and/or using calcium/vitamin D supplementation [3]. However, there is no evidence that calcium/vitamin D supplementation alone prevents fragility fractures [4]. Osteoporosis can be treated effectively with anti-resorptive agents, such as bisphosphonates and denosumab, or by anabolic agents, such as parathyroid hormone analogues [5]. Various studies have reported important changes in the pharmacological management of postmenopausal osteoporosis during the past few decades [6–9]. However, none included a national representative sample from France. Furthermore, most studies did not describe the evolving clinical profile of patients initiating anti-osteoporosis medication (AOM) or the use of calcium/vitamin D supplementation alone.

1.1. Objectives

The primary objective was to describe rates of women treated with or initiating an AOM (medication uptake) in France during the period 2007–2016. Other co-primary objectives were to describe prescribers of AOM and the use of calcium/vitamin D supplementation in women not receiving AOM.

The secondary objective was to describe the profile of women who initiated any AOM, including their demographics, social characteristics, presence of chronic comorbidities, fracture history and high-dose steroid use.

2. Methods

2.1. Data

The study was performed on a French nationwide claims database: the 'Échantillon Généraliste de Bénéficiaires' (EGB) [French national healthcare system claims database], which covers a 1 in 97 representative sample of the population insured by the main French public health insurance schemes [10] (i.e. approximately 600,000 individuals). At present, healthcare use data are available from 2003 for ambulatory care and from 2005 for hospital data recorded through the 'Programme de Médicalisation des Systèmes d'Information' (PMSI) [hospital discharge summaries database]. A single anonymous identifier is used to link ambulatory care data with the public and private hospital discharge database (PMSI). All details are documented regarding primary and secondary diagnoses relating to each acute care hospital stay (International Classification of Disease, 10th Revision [ICD-10] code), procedures and diagnostic-related group.

The EGB collects all items of medical consumption reimbursed by the public health insurance, with specific identification of the medicinal products ('Codes Identifiants de Présentation' [CIP] [unique French national registration code]) or medical procedures ('Classification Commune des Actes Médicaux' [CCAM] [French national coding system for surgical and interventional procedures]) [11]. For each service (procedure, visit, pharmacy etc.), the dispensing or performance date is specified with the prescribing date, type of prescribing physician and healthcare provider. The EGB also includes the diagnosis (ICD-10 code) of all severe chronic diseases for which patients are eligible for co-payment exemption under the long-term disease (LTD) status. This information may be used as an indirect measure of the presence of chronic comorbidities.

The EGB identifies individuals who benefit from the 'Couverture Maladie Universelle Complementaire' (CMU-C) [universal health insurance], which depends on household annual income and can be considered an indicator of low economic status. These data are supplemented by administrative information on the patient: age, sex, area of residence and, if applicable, date of death.

2.2. Study design

We performed a cross-sectional, yearly, repeated, cohort study over the period January 1, 2007 to December 31, 2016, using the French EGB claims database.

2.3. Study population

Women aged 50–89 years, alive on January 1 of each calendar year, and affiliated to the main French public health insurance scheme ('Caisse Nationale de l'Assurance Maladie' (CNAM) [French national health insurance fund], which covers approximately 90% of the population of France), were included in the first step. Women aged 90 years and over were excluded to preserve database quality (i.e. to prevent possible under-reporting of mortality and because a high proportion of women in nursing homes have no record of medical consumption).

Women were also excluded if they presented with at least one hospitalization for one of the following ICD-10 diagnoses (primary or associate): M88: Paget's disease; C40: malignant neoplasms of bone and articular cartilage of limbs; C41.2: malignant neoplasm of vertebral column; or C79.5: secondary malignant neoplasm of bone and bone marrow. Women with at least one reimbursement for any AOM in a given calendar year were identified as prevalent users in that year. Among them, women with no previous reimbursement for any AOM in the preceding 2 years were also defined as new AOM users.

2.4. Variables

AOMs were identified using Anatomical Therapeutic Chemical (ATC) codes, with at least one reimbursement within the calendar year. Bisphosphonates were split into two categories: monotherapy (ATC: M05BA01 [except etidronate 200 mg], M05BA03, M05BA04, M05BA06 and M05BA07) or combination therapy (ATC: M05BB03 and M05BB04). Bisphosphonates with an injectable formulation (zoledronic acid; ATC: M05BA08) were included but not analyzed separately because usage was low for the duration of the study. Comorbidities were identified using the Charlson Comorbidity Index for women who had LTD status [12,13].

Fragility fractures were identified using selected ICD-10 codes for full hospitalization, or procedures codes (CCAM) [11] for emergency room visits with no full hospitalization (list of codes available on demand). The ICD-10 selected codes were: S22 (rib, sternum and thoracic spine); S32 (lumbar vertebra except S322 and S327); S42 (shoulder and upper arm except S427, S428 and S429); S52 (forearm except S527, S528 and S529); S72 (femur); S82 (lower leg except S827); and M80 (osteoporosis with current pathological fracture).

Among women initiating AOM in each calendar year, the proportion with prior fracture was adjusted for age distribution, using 2007 values as a reference. Use of high-dose steroids (>7.5 mg/day prednisone equivalent for at least 3 months) was identified using medication codes (CIP). Mean dose, in defined daily dose, was calculated based on drug conditioning and dates of deliveries. When reimbursed, data were captured on bone mineral density (measured by dual-energy X-ray absorptiometry [DEXA]), vitamin D assays, and supplementations of calcium, vitamin D and analogues, and calcium associated with vitamin D. It is of note that reimbursement in France requires a medical prescription. In addition, in 2013, the Haute Autorité de Santé (HAS) [French National Authority for Health]) limited vitamin D assays to patients with potential rickets or osteomalacia, older adults with recurrent falls, monitoring of kidney transplantation in adults, and surgical treatment of obesity in adults [14]. Fracture history, use of high-dose steroids, DEXA and vitamin D assays were captured within the 2 calendar years before the year in which AOM was initiated.

2.5. Statistical analysis

Patient-years (PY) of exposure were calculated for each calendar year using the distribution of deaths in that year. For each calendar year, the incidence of first AOM prescription was calculated by dividing the number of women with a first prescription by the total number of women at risk in that year and presented per 10,000 PY (expressed per 100 PY in the abstract). This was calculated overall and for each specific medication. Owing to possible switches from one AOM to another within the same calendar year, the rates of first prescription of any AOM are lower than the sum of the rates of each specific medication.

The rate of AOM prescriptions was calculated by dividing the number of women with any prescription in a given calendar year by the total number of women at risk in that calendar year (rate per 100 PY).

2.6. Ethical considerations

Because this study was a retrospective analysis of an anonymized database and had no influence on patient care, ethics committee approval was not required. Access to the EGB database was authorized by the Commission Nationale de l'Informatique et des Libertés (CNIL) [French national data protection agency] : decision DR-2018-110, dated July 31, 2018.

3. Results

3.1. Population selection

Fig. 1 shows patient selection for 2016. The same algorithm was used for each calendar year in the study. Demographic data and the number of deaths in each calendar year are reported in Table 1.

3.2. Change over time of the annual rate of women receiving any specific AOMs

The rates per 100 PY of women aged 50–89 years receiving any specific AOM over the study period is shown in Fig. 2.

The rates were highest in 2009 (10.42 per 100 PY) and decreased thereafter. Rates were halved over the entire study period, from 10.22 to 5.02 per 100 PY. A small increase (from 10.22 to 10.42 per 100 PY) was observed over the period 2007–2009: this was driven by the medication class 'bisphosphonates in association' (ATC codes M05BB03 and M05BB04: alendronic acid and colecalciferol; risedronic acid, calcium and colecalciferol, sequential). Overall, rates of all other medication classes decreased over this period. From 2011, the rate for most AOM classes declined steadily. Between 2013 and 2016, there was a small increase in the rate for denosumab (0.06 to 0.51 per 100 PY), which coincided with its commercial launch in 2013. Rates for teriparatide remained steadily low over the whole study period, at approximately 0.8 per 100 PY.

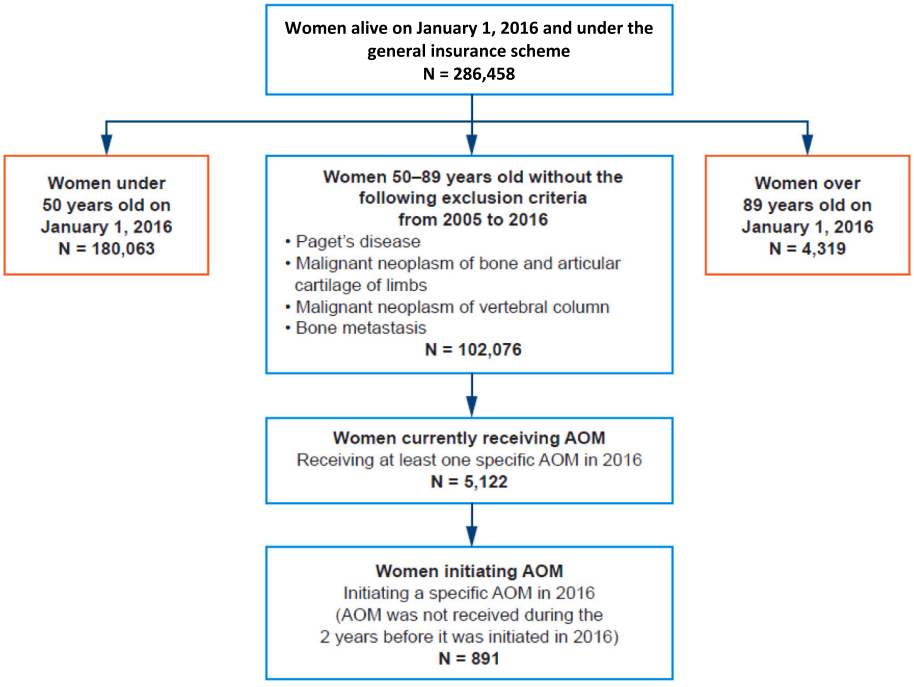

Fig. 1. Flowchart of population selection (2016 shown as an example).
Abbreviations: AOM, anti-osteoporosis medication.

Table 1
Demographics of women aged 50–89 years and prescription rates of AOM in each calendar year.

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Women aged 50–89 years alive on January 1, n	84,484	86,688	88,615	91,606	92,648	94,516	96,550	98,346	100,261	102,076
Deaths, n	1198	1310	1275	1364	1305	1323	1372	1459	1334	1424
Duration of exposure, PY	83,881	86,041	87,964	90,916	92,004	93,845	95,859	97,622	99,561	101,371
Rate of AOM per 100 PY										
Bisphosphonates	6.04	5.88	5.74	5.52	5.01	3.81	3.34	2.93	2.66	2.38
Bisphosphonates in association	2.27	2.67	2.45	2.32	2.62	2.59	2.22	1.93	1.69	1.52
Strontium ranelate	1.56	1.36	1.71	1.94	1.71	0.46	0.34	0.17	0.07	0.00
Denosumab	0.00	0.00	0.00	0.00	0.00	0.00	0.06	0.27	0.45	0.51
Raloxifene	1.62	1.43	1.35	1.29	1.31	1.27	1.10	0.96	0.84	0.73
Teriparatide	0.05	0.05	0.08	0.08	0.08	0.08	0.08	0.09	0.08	0.07
Any AOM	10.22	10.22	10.42	10.39	9.64	7.80	6.82	6.05	5.53	5.02

Abbreviations: AOM, anti-osteoporosis medication; PY, patient-years.

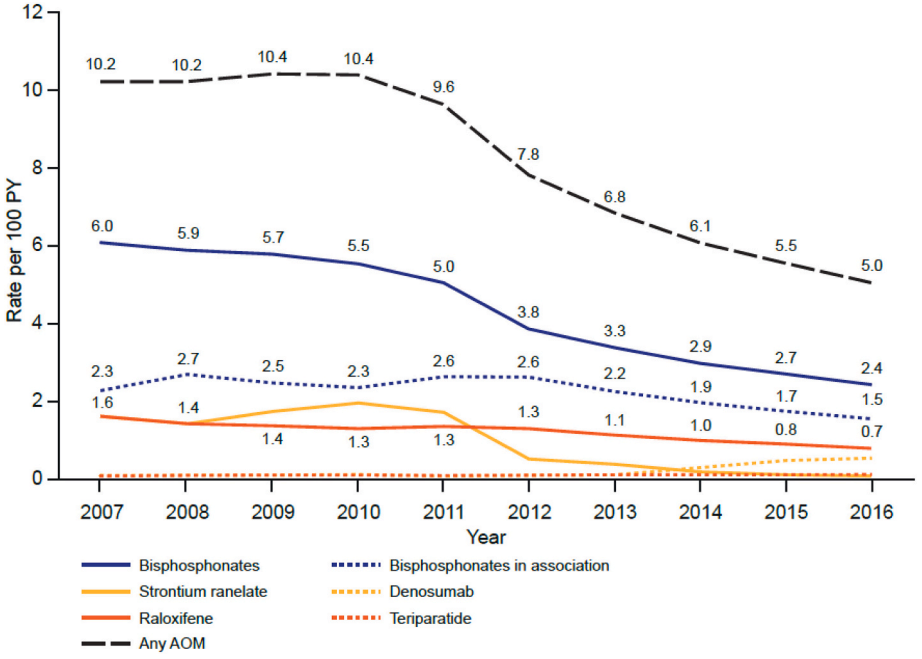

Fig. 2. Prescription rates for specific AOMs in each calendar year.
Abbreviations: AOM, anti-osteoporosis medication; PY, patient-years. Dotted lines represent trends based on a linear model.

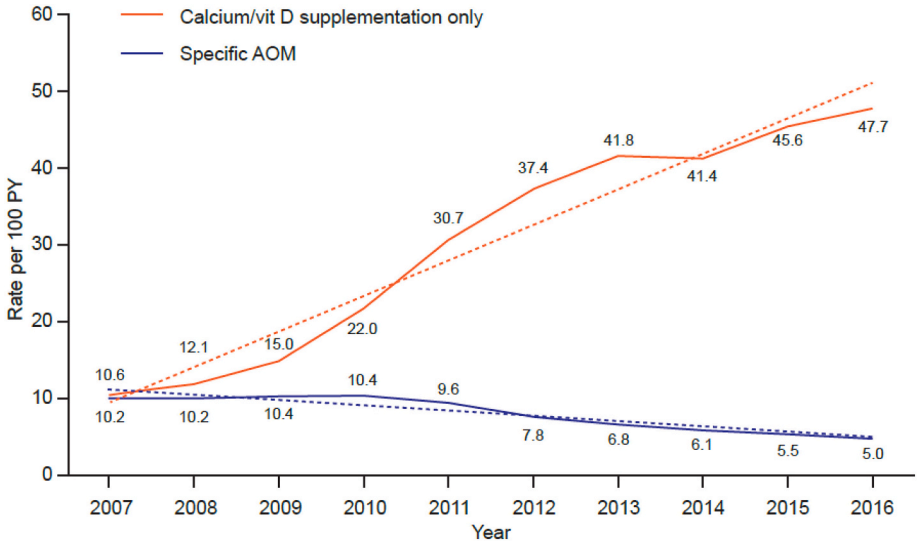

Fig. 3. Prescription rate for women receiving specific AOM or calcium/vit D supplementation only, in each calendar year.
Abbreviations: AOM, anti-osteoporosis medication; PY, patient-years; vit D, vitamin D. Dotted lines represent trends based on a linear model.

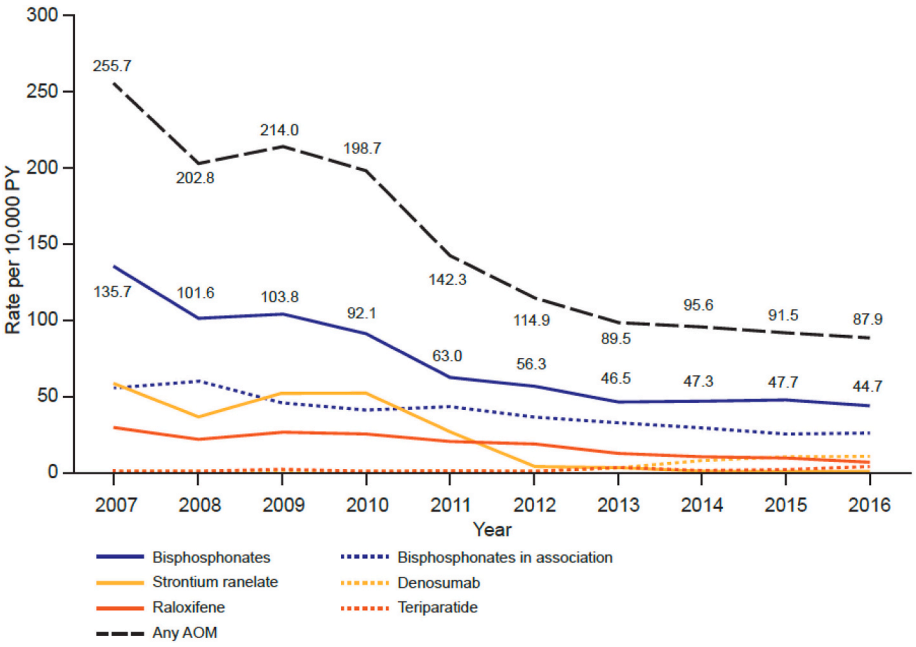

Fig. 4. Rates of first prescription for AOMs in each calendar year.
Abbreviations: AOM, anti-osteoporosis medication; PY, patient-years. Dotted lines represent trends based on a linear model.

3.3. Change in the rate of women treated exclusively with nonspecific AOMs

Rates of prescriptions for nonspecific AOMs (calcium/vitamin D: ATC codes A11CC, A12AA and A12AX) and for specific AOMs are shown in Fig. 3. The change in the rate of women aged 50–89 years receiving only nonspecific AOMs strongly contrasts with the specific AOMs (Fig. 3).

In 2007, similar rates of women aged 50–89 years were treated with specific and nonspecific AOMs (10.2% and 10.6%, respectively) and 79.2% received no AOM (either specific or not). In 2016, these rates were 5.0% (i.e. a halved rate of women aged 50–89 years using specific AOM) and 47.7%, respectively (i.e. a 4.5-fold increase in the rate of women aged 50–89 years using only vitamin D, calcium or combination calcium/vitamin D), and 52.7% received no AOM (either specific or not).

3.4. Initiation of AOM

An approximately threefold decrease in the initiation of any AOM (from 255.7 to 87.9 per 10,000 PY) was observed over the study period (Fig. 4 and Table 2 with detailed results by AOM). This is aligned with the progressive withdrawal of strontium ranelate, and the decline of bisphosphonate (alone or in association) and raloxifene use. Among women receiving any AOM in each calendar year, 15–25% were initiating AOM for the first time (data not shown).

3.5. Profile of women initiating a specific AOM

Characteristics of women initiating a specific AOM in each calendar year are summarized in Table 3.

In the context of the rapid decline of specific AOM initiation over the study period, the age distribution of women initiating a specific AOM changed markedly, with an increase in the 60–69 years sub-group from 26.2% in 2007 to 35.2% in 2016. In contrast, a decrease was seen for women aged 50–60 years (24.6% to 19.9%) and those aged 70–80 years (32.8% to 25.0%), both at a mean annual rate of 0.5–0.6%.

The proportion of women benefitting from CMU-C and initiating any AOM remained stable (approximately 2.5%) over the study period. The Charlson Comorbidity Index scores increased over time, as did, as expected, the proportion of women with LTD status. From 2013 onwards, the mean Charlson Comorbidity Index score increased, which suggests that women initiating any AOM presented with more comorbidities than before 2013.

The proportion of women with prior fractures or high-dose steroid use (within the 2 calendar years before the year of first prescription for any specific AOM) and initiating any AOM is shown in Fig. 5. Among women with prior fractures, the proportion initiating any AOM increased from 7.8% in 2007 to 13.3% in 2016 (1.7-fold increase). The proportion of women with a history of high-dose steroid use initiating

Table 2
Rates of first prescription for AOMs in each calendar year.

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Bisphosphonates	135.7	101.6	103.8	92.1	63.0	56.3	46.5	47.3	47.7	44.7
Bisphosphonates in association	55.3	60.3	45.6	41.4	43.7	37.8	33.1	30.0	25.1	25.9
Strontium ranelate	59.0	37.3	52.5	53.3	27.4	4.7	4.0	0.9	0.3	0.0
Denosumab	0.0	0.0	0.0	0.0	0.0	0.0	4.0	8.9	10.8	10.5
Raloxifene	30.3	22.1	26.3	24.9	20.2	19.4	12.6	10.7	9.4	7.7
Teriparatide	0.8	1.2	2.4	1.3	1.4	1.4	3.3	2.8	2.3	3.0

Abbreviations: AOM, anti-osteoporosis medication; PY, patient-years.
Rates are per 10,000 PY.

Table 3
Profile of women initiating a specific AOM and specialty of prescribers in each calendar year.

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Mean age, years (SD)	68.6 (10.1)	68.3 (10.2)	68.7 (10.4)	68.2 (10.4)	67.6 (10.4)	68.0 (10.2)	68.5 (10.2)	69.0 (10.0)	67.9 (9.8)	69.1 (10.1)
Aged 50–<60 years, %	24.6	25.2	24.8	26.0	26.9	24.6	23.4	19.4	23.8	19.9
Aged ≥60–<70 years, %	26.2	27.9	27.0	28.7	31.2	33.6	31.2	34.7	34.2	35.2
Aged ≥70–<80 years, %	32.8	29.6	29.8	28.5	24.4	24.3	26.7	27.3	26.5	25.0
Aged ≥80–89 years, %	16.4	17.3	18.4	16.8	17.5	17.5	18.7	18.5	15.5	19.9
Women with LTD status, %	34.9	36.6	35.7	35.0	37.3	34.2	39.2	41.1	36.7	43.3
Women with comorbidities,[a] mean (SD)	0.52 (1.15)	0.53 (1.14)	0.56 (1.23)	0.52 (1.15)	0.53 (1.16)	0.52 (1.18)	0.65 (1.41)	0.65 (1.36)	0.58 (1.23)	0.78 (1.56)
Women in CMU-C, %	2.7	2.6	2.3	2.4	1.5	2.4	2.4	1.3	3.1	2.4
Women with a DEXA scan within the past 2 years, %	0.7	0.6	0.8	0.8	1.0	1.7	1.6	1.9	1.6	2.4
Women with a vitamin D assay during the previous 2 years, %	13.3	19.9	26.3	34.5	46.6	53.0	55.7	57.3	41.9	38.9
Women given prescriptions by										
PCP, n (%)	1698 (79.2)	1377 (78.9)	1455 (77.3)	1444 (79.5)	992 (75.8)	819 (76.0)	714 (74.8)	647 (69.3)	672 (73.8)	608 (68.2)
Rheumatologist, n (%)	239 (11.1)	203 (11.6)	223 (11.8)	193 (10.6)	171 (13.1)	144 (13.4)	143 (15.0)	190 (20.4)	166 (18.2)	195 (21.9)
Gynecologist, n (%)	81 (3.8)	71 (4.1)	69 (3.7)	52 (2.9)	54 (4.1)	45 (4.2)	28 (2.9)	25 (2.7)	22 (2.4)	22 (2.5)
Endocrinologist, n (%)	76 (3.5)	52 (3.0)	66 (3.5)	59 (3.2)	49 (3.7)	28 (2.6)	21 (2.2)	25 (2.7)	20 (2.2)	13 (1.5)
Other HCP, n (%)	51 (2.4)	42 (2.4)	69 (3.7)	68 (3.7)	43 (3.3)	42 (3.9)	48 (5.0)	46 (4.9)	31 (3.4)	53 (5.9)

Abbreviations: AOM, anti-osteoporosis medication; CMU-C, Couverture Maladie Universelle Complémentaire (universal health insurance); DEXA, dual-energy X-ray absorptiometry; HCP, healthcare provider; LTD, long-term disease; PCP, primary care physician; SD, standard deviation.

[a] As measured by the Charlson Comorbidity Index [12].

any specific AOM also increased, from 2.9% in 2007 to 8.4% in 2016, with a similar mean annual increase as that observed for women with prior fractures (Fig. 5).

The absolute numbers of prescriptions for initiation of any AOM during the period was associated with a marked reduction of 64.2% (1698 to 608) for primary care physicians, whereas the reduction in prescriptions by all specialty healthcare providers was 36.7% (447 to 283) and by rheumatologists was only 18.4% (239 to 195). This contrasted evolution increased accordingly the share of specialist physicians, especially of rheumatologists, who represented 21.9% of prescribers in 2016.

The proportion of women with a bone mineral density measurement (measured by a DEXA scan) within 2 years before initiation of any AOM was low: 0.7% from 2007 to 2011, increasing to 2.4% in 2016. This proportion is in line with guidelines regarding reimbursed indications for DEXA scan in postmenopausal women: history of femoral fracture in a first-degree relative; BMI <19 kg/m^2; menopause before 40 years of age; or history of high-dose steroids use (dose >7.5 mg/day equivalent prednisone over 3 months).

The proportion of women who had a vitamin D assay (serum 25-hydroxyvitamin D assay) increased considerably during the study period, from 13.3% in 2007 to a peak of 57.3% in 2014, before declining to 38.9% in 2016 [15]. This reflects the introduction of restrictions for the reimbursed indications of the test in 2013.

4. Discussion

This study observed decreases in prescription rates of all studied AOMs except denosumab among women with postmenopausal osteoporosis in France between 2010 and 2016. These data highlight an increasing treatment gap among women in France with osteoporosis, which is similar to that observed in other European countries and in the USA.

4.1. Comparison with similar international studies

To compare these results with those of other studies, differences in time periods, populations and methods must be considered. Most existing studies analyzed retrospective periods starting earlier than 2007 [16,17] and ending generally before 2012–2013. Owing to a lack of relevant clinical data, comparisons of treatment uptake across countries and time periods are generally based on sales data, which are expressed in value (€) or volume (defined daily dose) [17–20]. Also, their results cannot be easily disaggregated between men and women. Moreover, these approaches are likely to overestimate the number of patients treated because few patients are completely adherent to therapy [21]. In the most comprehensive study of a European population that has been published, the proportion of patients who were at least 50 years old and receiving AOM was <4% before 2006 and 4–5% between 2006 and 2011 [18]. However, large variability across countries was observed. In many countries, including France, these figures reached 6–9%. The results for France during the period 2001–2011 showed a rapid increase from 1% in 2001 to 7% in 2008–2009, followed by a slight decrease in 2010–2011. Although we observed a higher proportion of women receiving AOM during 2008–2009 (10%), this difference may be explained by our method for measuring prevalence. Our study considered a woman 'treated' if she had received at least one AOM prescription during that calendar year, which should provide a higher result than sales data. Despite this different approach, trends over time were consistent with our data, and a similar decreasing trend in the later years of the study period was also evident in Austria, Finland, Latvia and Luxembourg [18].

Most previous studies used cohort analysis to define initiation of treatment [22,23]. In contrast, we used an absence of any previous treatment over a retrospective period of 2 years. This has limitations,

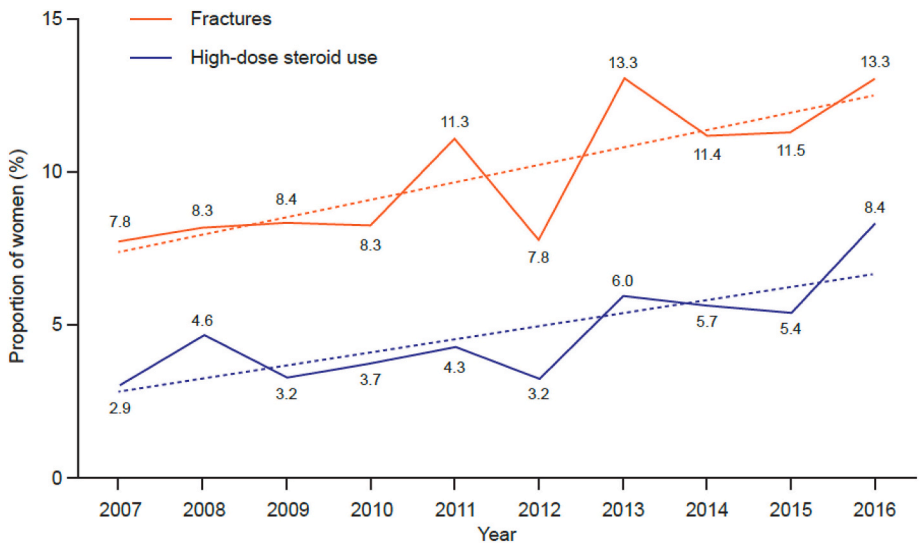

Fig. 5. Proportion of women initiating an AOM with a history of fractures (age-adjusted) or with high-dose steroid use within the past 2 years. Abbreviations: AOM, anti-osteoporosis medication. Dotted lines represent trends based on a linear model.

because an unknown proportion of women may have received AOM before this 2-year period. In the case of denosumab, for example, which is reimbursed in France as second-line treatment after a bisphosphonate, our definition may have underestimated its incidence [24]. Despite these methodological differences, the changes in AOM uptake in the UK [23] and Spain [22] are similar to our findings. Peak uptake was generally around 2009, followed by a rapid decline that plateaued from 2011 to 2012 on. Similar findings were also observed in a US study that used data from the Medical Expenditure Panel Survey for oral bisphosphonate among patients aged at least 55 years from 1996 to 2012 [25].

4.2. Main results

These results must be considered in the context of the evolving AOM landscape and reimbursement requirements in France. It is important to note that in France, drugs will not be prescribed if they are not reimbursed.

Strontium ranelate was reimbursed in France starting in March 2005 [26]. However, given the addition of contraindications and warnings on the product label, and restrictions on the approved indication, the HAS stopped reimbursement for strontium ranelate in March 2015 [27] and the manufacturer withdrew the product from the French market in 2017. Reimbursement for both ibandronic acid [28] and etidronate [29] was stopped in December 2010.

Teriparatide was first reimbursed in France in August 2004 [30] with a restriction to women presenting with a history of at least two vertebral fractures. It was granted 'drug of exception' status (specific prescription form required) and, in April 2008, obtained an extension of indication in corticoid-induced osteoporosis [31]. In 2009, a maximum treatment duration of 2 years was specified [32]. Taking into account these various modifications, a small increase was observed in the rate of teriparatide initiation, from 0.8 per 10,000 PY in 2012 to 3 per 10,000 PY in 2016.

Denosumab obtained European Medicines Agency Marketing Authorization in 2010 for the treatment of postmenopausal osteoporosis in women at high risk of fracture. In 2011, the HAS restricted its reimbursement to second-line therapy after bisphosphonates in patients with postmenopausal osteoporosis who are at high risk of fracture [33]. Access to the French market (i.e. reimbursement) occurred in October 2013. Patients at high risk of fracture were defined as those who had a fracture caused by bone fragility or, in the absence of fracture, a substantial decrease in bone density (T-score <-3), or a T-score of ≤-2.5 combined with other risk factors for fracture, particularly: age >60 years; previous or current systemic corticosteroid therapy at a dose of ≥ 7.5 mg/day prednisone equivalent; body mass index <19 kg/m^2; previous fracture of the femoral neck in a first-degree relative (the patient's mother); or early menopause (before the age of 40 years).

In this study, a decrease in prescriptions for specific AOMs was observed, which contrasted with an increase in the use of only calcium/vitamin D supplementation for osteoporosis treatment; however, the study design does not allow us to determine whether this is a causal relationship. This supports the conclusions of previous studies performed in France. In a multicenter randomized controlled trial evaluating the impact of a population-based, patient-centered, post-fracture care program, only 56% of women with a low bone mineral density who required treatment according to French guidelines received a prescription, although 90% received a calcium/vitamin D supplementation [34]. This may suggest that physicians perceive calcium/vitamin D supplementation as adequate treatment for osteoporosis, despite current French guidelines [1] and existing data that do not support the routine use of this supplementation to prevent fractures [35]. The fear among primary care physicians of adverse events associated with AOMs may be another possible contributing factor [36,37].

These data show that the typical profile of women initiating AOM is changing toward patients with the highest risk of fracture and multiple comorbidities. The aging population could be a contributing factor, but mean age in this study remained fairly stable. Also, the findings do not imply that all high-risk patients are correctly treated. Our findings here highlight that fewer primary care physicians are prescribing initiation of AOM. Indeed, data from other French studies show that the management of patients with recent fractures remains poor in general practice [36,38]. Prescription of AOM is increasingly restricted to a limited number of high-risk patients in the secondary prevention setting. Considering the low number of specialist physicians in France who treat osteoporosis, especially rheumatologists, it would be important to improve both the identification of high-risk patients (through early detection programs) and secondary fracture prevention in this setting.

4.3. Strengths and limitations

The main strength of our study is that we were able to collect data from a representative sample of the French population. This database

contains data for all healthcare reimbursements in France and is validated for use in pharmacoepidemiology studies [10]. Our study had several limitations. First, the study was conducted only in France, thereby limiting the generalizability of the results. Given the low Charlson Comorbidity Index scores reported for the study population, it is difficult to interpret the importance of the increase in the mean Charlson Comorbidity Index score among women initiating any AOM from 2013 onwards. Other limitations include those associated with the use of claims databases, such as incomplete, inaccurate or missing data, and the data may be subject to selection bias or confounding.

5. Conclusions

This study showed marked changes in prescription rates of AOMs among women with postmenopausal osteoporosis, which halved between 2007 and 2016. The decline in the overall rate of women initiating AOM was even greater, with a threefold decrease between 2007 and 2012 that plateaued from 2013 to 2016. In contrast, prescription rates increased rapidly for calcium/vitamin D supplementation as the only AOM, despite French guidelines and existing evidence that do not support the routine use of this supplementation to prevent fractures.

The profile of patients initiating AOMs changed substantially over the 10-year study period, despite a stable mean age of approximately 69 years. An increasing proportion of women presented with multiple comorbidities, a history of fracture or high-dose steroid use. Our data show that much fewer primary care physicians are prescribing initiation of AOM. Collectively, our findings suggest that prescription of AOM is increasingly restricted to a limited number of high-risk patients in the secondary prevention setting.

CRediT authorship contribution statement

BC participated to the conceptualization, the methodology and review of the manuscript.

AMS participated to the conceptualization and review of the manuscript.

GD, JVC, PS participated to the conceptualization and review of the manuscript.

CE participated to the conceptualization, data curation, formal analysis and review of the manuscript.

FF participated to the conceptualization, methodology, project administration, writing and review of the manuscript.

Declaration of competing interest

BC reports grants and sponsorship from MSD, fees for occasional interventions as an expert or speaker for Amgen, Expanscience, Ferring, Lilly, MSD, Mylan, Novartis, Roche Diagnostics, Theramex and UCB. AMS declares that she has no conflict of interest. GD, JVC, and PS own stock in and are full-time employees of Amgen. CE and FF are employees of CEMKA.

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