Cessation rate of anti-osteoporosis treatments and risk factors in Spanish primary care settings: a population-based cohort analysis

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Mini-abstract

Among 95,057 patients ≥50 years with new anti-osteoporosis medications (AOM) (2001-2013) in primary care: 1-y cessation was 51% (28%-68%), higher in men, smokers, patients with missing lifestyle data, and out normal BMI, and lower in aged 60-79, with recent fractures or other anti-osteoporotics. Suggesting non-severe osteoporosis, and less risk awareness.

Abstract

Purpose

Low compliance to anti-osteoporosis medications (AOM) has been previously reported. We aimed to estimate one-year cessation rates of different AOMs as use in Spanish healthcare settings, and to identify associated risk factors.

Methods

A cohort study was performed using primary care records data (BIFAP). Patients entered the cohort when aged 50 years in 2001-2013, with ≥1 year of data available, and identified as incident users of AOM (one-year wash out). Participants were divided in 6 cohorts: alendronate, other oral bisphosphonates, selective estrogen receptor modulators, strontium ranelate, teriparatide, and denosumab. Patients were followed from therapy initiation to the earliest of cessation (90-day refill gap), switching (to alternative AOM), lost, death, or end of 2013. One-year therapy cessation was estimated using life tables. Hazard Ratios (of cessation) according to age, sex, lifestyle factors, morbidity and comedication were estimated after stepwise backwards selection.

Results

95,057 AOM users were identified (91% women; mean age 68). One-year cessation was 51% overall, highest for strontium ranelate (68%), and lowest for denosumab (28%). Cessation probability was higher in men (14%-2.1-fold), smokers (>6%), and patients with missing BMI (19-28%) or smoking (6-20%) data, and overweight/obese/underweight (7% to 2.6-fold increase compared to normal weight). Patients aged 60-79 years, with a recent fracture or other drugs used for osteoporosis had better persistence.

Conclusions

Over half of the patients initiating AOM stopped therapy within the 1st year after initiation. The described risk factors for cessation could be proxies for non-severe osteoporosis, and/or disease/risk awareness, which could inform the targeting of high-risk patients for monitoring and/or interventions aimed at improving persistence.

Key words: anti-osteoporosis medication; cessation; risk factors; primary care.

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Introduction

Multiple randomized controlled trials (RCT) (1–7) and independent meta-analyses of RCT (8,9) have confirmed the anti-fracture efficacy of anti-osteoporosis medications (AOM). However, recent studies suggest that baseline characteristics of actual users of these drugs differ significantly from those of pivotal RCT study participants, potentially affecting both compliance and 'real world' effectiveness (10).

A high compliance of over 80% and long-term therapy duration of at least 3 years (11) is needed to achieve maximum therapeutic benefits with most AOM. Conversely, current data suggest a lack of persistence with AOM in the community (12).

AOM treatment cessation may be consequence of several reasons such as patients scepticism or uncertainty to their osteoporosis diagnosis (13), willingness to take prescribed medications (13), posology and daily dosage regimen (12,14), side effects (13–15), safety concerns (13), and consequently may vary among type of drugs (15) and also be associated to certain identifiable patients characteristics. It might be also influenced by a number of recent safety alerts (16).

Interventions such as biomarker or motivational feedback packages to patients on AOM, may reduce significantly the cessation of treatment (17). However, such interventions are costly and cannot be applied to all patients under treatment. Identification of high risk (for therapy cessation) patients may hence help to target and optimize efforts to promote adherence.

We therefore aimed to estimate different AOMs cessation rates when used in actual primary care practice and settings, by year after therapy initiation, focusing on early (first year) cessation. Secondly, we aimed to identify AOM user patient features associated with early (first year) cessation risk for the different AOM independently.

Methods

Source of data

BIFAP (Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria), is a longitudinal population-based database of anonymized electronic medical records of primary care practitioners (PCP) and pediatricians from 9 different regions in Spain (18). BIFAP is fully funded by the Spanish Agency on Medicines and Medical Devices (AEMPS), belonging to the Department of Health. Spain has a public national health service (named SNS) where PCPs act as gatekeepers for and receiver of information from primary and secondary care. Almost all population is registered with a local PCP under the Spanish SNS. The database includes anonymized information from patients assisted by 2324 physicians (84% PCP and 15% pediatricians). Data available include patient demographics, clinical events (coded through ICPC medical terms dictionary (19)), free text notes, specialist referrals and laboratory test results of around 4 million patients (19 million patient-years) covering around 8.9% of the Spanish population (19.1% of the total population from participating regions). Prescriptions are issued by PCP to the patients and automatically recorded in BIFAP once written.

Study design and cohort

A cohort study was performed using BIFAP database. Patients aged ≥50 years, with at least 1 year of information (inclusion criteria) and newly prescribed with AOM* by the practitioner (one-year wash out) between 2001-2013 were identified and divided in 6 cohorts according to first prescription: alendronate (N=36,182), other bisphosphonates (N=37,594), selective estrogens receptor modulators (SERM: raloxifene and bazedoxifene; N=11,7223), strontium ranelate (N=7,978), teriparatide (N=1287) and denosumab (N=293). There were a total of 95,057 AOM new users. Treatment initiation was the date of first AOM prescription. Patients receiving several AOM on treatment initiation date (assumed as not clear final treatment), as well as those censored on the start date (0 days contribution to follow-up) were excluded. Patients prescribed with AOM will be referred to as "AOM users" onwards.

*Note: Anatomical Therapeutic Chemical (ATC) classification for AOM included in the current study were as follows: alendronate (M05BA04 and M05BB03); other oral bisphosphonates (etidronate [M05BA01], clodronate [M05BA02], tiludronate [M05BA05], ibandronate [M05BA06], and risedronate [M05BA07]); selective estrogen receptor modulators (bazedoxifene [G03XC01], and raloxifene [G03XC02]); strontium ranelate (M05BX03), teriparatide (H05AA02), and denosumab (M05BX04). In Spain, zolentronic acid is prescribed and administered in a hospital setting and were not included in the study.

Time to AOM cessation

Patients forming the AOM cohorts were followed from therapy initiation to cessation (i.e. study outcome) of first treatment episode (90 days refill gap; unknown whether PCP decision, patient choice or other reasons), or to the earliest of: 1. switching to an alternative AOM cohort, 2. loss to follow up, 3.death, or 4. end of study period (31st December 2013).

For each AOM cohort, the first treatment episode was defined as a series of subsequent prescriptions issued by PCP during the patient visits, and constructed according to the method-1 of Gardarsdottir et al. (20). In that method, the theoretical end date of each prescription equals the prescription date plus its duration. The duration was calculated by the number of prescribed Defined Daily Dose (DDD; 6 months for denosumab and 1 month for remaining AOM). In case a subsequent prescription with the same drug was collected before the theoretical end date of a previous prescription, the number of overlapping days was disregarded, assuming that overlapping days compensate gaps between prescriptions. Cessation of first treatment episode was defined as 90 days refill gap. Sensitivity analyses using 180 and 30-day refill gaps were performed.

Risk factors of cessation

The following factors were assessed before therapy initiation as potentially associated with 1-year cessation, as they were linked to indication or contraindication according to literature and clinical knowledge:

- sex and age at treatment initiation (categorized by 10-year cut-off as reported in Table 1);
- life style factors including:

- body mass index (BMI in Kg/m2 or missing, analysed according to WHO categories)
- current smoker (categorized as yes, no [including never and former-smoker], or missing)

  BMI and smoking were collected as recorded through treatment initiation year (the closest value to 1st January in case of repeat records in that same year),

- alcohol abuse categorized as yes or no anytime before treatment initiation.

- medication including other AOM (i.e. parathyroid hormone, calcitonin, and elcatonin), calcium-vitamin D, disease modifying anti-rheumatic drugs (DMARD), systemic glucocorticoids, and oral anticoagulant drugs, as recorded anytime before treatment initiation (yes/no), as well as hormone replacement therapy or oestrogen contraceptives (HRT) as recorded during the year before treatment initiation (yes/no);

- morbidity included in Charlson index, i.e. cardiovascular diseases (heart failure (HF), aneurysm, cerebrovascular disease (CVD), myocardial infarction (MI), peripheral arterial disease, and vein insufficiency or phlebitis), peptic ulcer, and other chronic diseases (such as asthma, COPD, malignant cancer, metastatic cancer, dementia, hemiplegia, HIV, liver disorders, renal disorders, and rheumatoid arthritis (RA)), and fracture, as recorded anytime before treatment initiation. Morbidity variables were categorized as yes or no (reference category), but fracture which was categorized as recent (within previous year), past (more than 1 year before; reference category) or no fractures.

Statistical analysis

Kaplan-Meier survival curves to cessation were drawn over all follow-up, by type of AOM. Yearly cessation proportion was estimated using life tables over all follow-up. Overall Kaplan-Meier curve and life table, were estimated for main (90 days gap) and sensitivity analysis (30 and 180 days). Median of treatment duration was also estimated over all follow-up.

We were interested in early (1-year cessation), so results and discussion on survival analysis and risk factors focus on that period.

Cox proportional hazards models were run to estimate Hazard Ratio (HR; 95%CI) of first year cessation according to potential risk factors stratified by AOM cohort, after automatic stepwise backward-selection estimation of categories associated with one-year cessation. A p-value of 0.05 for addition to the model, and p-value of 0.1 for removal from the model were required. Stepwise selection was performed for the variables listed above in risk factor section and tables 1 and 2 footnotes. Reference category is indicated in table 1 for each factor. Risk factors for alendronate and other oral bisphosphonates were merged and analysed together after observing similar cessation proportion in the two cohorts.

Stata/SE 13.1 was utilized for analysis.

Results

Time to cessation

A Kaplan-Meier stratified by drug use and associated life table including all new AOM users is shown in Figure 1. Among them, 46,464 out of 95,057 (51% by life table estimation) stopped therapy during the first year of treatment, and 99.4% at the end of the maximum 13 years of follow-up. Drug-specific one-year cessation probability was estimated (in descending order) at 68% for strontium ranelate, 52% for SERM, 51% for teriparatide, 49% for oral bisphosphonates (similar for alendronate and others), and 28% for denosumab. Overall median of treatment duration was 251 days (range: 1 day to 12.38 years),

Sensitivity analyses using 30 and 180-day gaps showed that 62,315/95,057 (68%) and 40,642/95,057 (45%) of new AOM users stopped treatment during the first year of treatment respectively (see Figures 2, 3).

Drug-specific cessation risk

In an overall multivariable adjusted stepwise Cox analysis, strontium ranelate (HR 1.57; 95%CI: 1.53-1.62), or SERM (HR: 1.08; 95%CI: 1.05-1.12) users were more likely to cease treatment during first year when compared to alendronate users (reference group), while denosumab was associated with a reduced risk (HR: 0.51; 95%CI: 0.40-0.65). Other oral bisphosphonates users had similar cessation rates to those of alendronate (HR: 0.97; 95%CI: 0.95-1.00). Teriparatide users had similar cessation comparable to alendronate users (p>=0.1000, data not shown).

Risk factors for cessation

Risk of one-year cessation associated with sex, age, recent fractures, other medication used for osteoporosis, and life style factors by AOM is reported in Table 1. Cessation of denosumab was not associated to any of those factors.

Cessation was higher in men than women (14%, 26%, and 2.12-fold increase for SR, BP and SERM), in patients with overweight or obesity (from 7% to 2.58-fold increase), and those with missing smoking or BMI data (6-20% and 19-28% increased risk, respectively), for most AOM. Among BP users, also patients with underweight and current smokers had an increased risk to cease (22% and 6% respectively).

Age was also associated to cessation, i.e. oldest patients among BP and SERM showed the highest risk to cessation, while patients in middle age categories (60-79y in BP, SR and TE) were at lowest risk (8%-20% reduced risk) versus youngest patients.

Regarding co-medication, cessation of BP was lower among patients prescribed with other AOM (HR: 0.89; 95%CI: 0.85-0.93), calcium-D (HR: 0.92; 95%CI: 0.90-0.94), or HRT (HR: 0.85; 95%CI: 0.80-0.91) before therapy initiation. Also, cessation was lower among SR and TE users prescribed with calcium-D (HR: 0.90 (95%CI: 0.85-0.96), and 0.73 (95%CI: 0.62-0.86), respectively), or SERM users prescribed with HRT before therapy initiation (HR: 0.65; 95%CI: 0.59-0.71).

Other morbidity and medication associated to one-year cessation is reported in Table 2, which affected differently to each AOM cessation. BP cessation was mainly reduced among patients with rheumatoid arthritis (HR: 0.83; 95%CI: 0.77-0.89), and increased among patients with liver disease (HR: 1.10; 95%CI: 1.02-1.17) or diabetes (HR: 1.07; 95%CI: 1.04-1.11). SERM cessation was reduced among patients with cerebrovascular disease (HR: 0.73; 95%CI: 0.53-0.99), while increased among those with peripheral arterial disease (HR: 1.54; 95%CI: 1.04-2.28) and patients treated with glucocorticoids (HR: 1.18; 95%CI: 1.08-1.28) or oral anticoagulant drugs (HR: 1.27 ; 95%CI: 0.98-1.65). SR cessation was reduced among patients with dementia (HR: 0.84; 95%CI: 0.70-1.00), cancer (HR: 0.89; 95%CI: 0.81-0.97) and increased among patients with liver diseases (HR: 1.19; 95%CI: 1.00-1.41). TE cessation was reduced among patients with asthma (HR: 0.70; 95%CI: 0.50-0.97).

Variables not reported in tables were removed automatically from model during stepwise run, or were present only in ≤8 patients.

Discussion

Cessation rate

In the current study, half of the patients initiating oral bisphosphonates, SERM or teriparatide therapy, ceased treatment during 90 or more days through the first year of treatment. Cessation was even higher for initiators of strontium ranelate (68%), and lowest for denosumab users (28%). Users of SR or SERM had the highest cessation rates, whilst denosumab ones had the lowest, as confirmed in multivariate (confounder-adjusted) analyses.

These findings support the previously reported high cessation rates of AOM in the community (2,12,14,21–23), i.e. 60.8% for 180-days gap in Catalonia (2), 57.1% for 30 days gap in The Netherlands (14) and 19.4%-26.8% for 90 days gap in smaller studies of Spanish populations (22,23). Such differences may be the result of diverse methodology (including cessation definition, study design, or analysis), or prevalence of risk factors among patients participating in each study.

In term of persistence, we observed that patients persisted with AOM treatment for a median of 8 months (shortest for strontium [4 months] and longest for bisphosphonates [9 months]). This duration is much lower than the published earlier (24) in patients with recent fractures, which are usually more risk aware as expected in any secondary prevention setting.

Adherence to treatment represents a challenge for drug effectiveness (25): a 46% increased risk of fractures in non-adherence versus adherers to bisphosphonates has been reported (26). In term of persistence, the minimum duration of treatment required for reaching a long-term efficacy will depend on the pharmacologic profile of the drugs, and it is not always well-known. In particular for bisphosphonates, the reduced risk of fracture seems to be present as early as six months after initiation (27,28). The median duration observed in the current Spanish data for bisphosphonates (9 months) was probably suboptimal to reach and keep meaningful clinical effect at least for half of the identified AOM new users.

Cessation differences by type of drugs have also been observed by previous authors (15,21), and related to route of administration (12,14) or adverse reactions (15), but also to worry to

live with the treated disease or, on the contrary, with the triggered adverse event (13). The knowledge about specific safety evaluation of drugs and establishment of risk minimization measures may also affect the adherence, such may have happened with dermatological and cardiovascular evaluations of SR since 2007 (29–33), the jaw osteonecrosis with BP since 2005 (34,35) and denosumab since 2014 (36), as well as the novelty in market of teriparatide (2004), strontium ranelate (2005) or denosumab (2010). Also, although the cost of treatments is fully (for retired patients) or partially (for current workers) covered by the Spanish national health system, differential costs (from highest cost to lowest: teriparatide, denosumab, strontium ranelate, raloxifene, other biphosphonates and alendronate) between the study drugs could partially explain our findings.

However, the choice of the AOM type, i.e. first line (bisphosphonates), second line (denosumab) or third line (SERM, teriparatide, strontium ranelate) (37) depend on the patient baseline characteristics, including indication, osteoporosis severity and others. So, we evaluated the factors associated with cessation of each AOM separately, with the aim to assess groups of patients comparable in terms of indication.

Risk factors for cessation

We observed that AOM cessation differs by certain baseline characteristics, without large variations among users of different AOM. Overall, cessation was more likely among youngest and oldest users, men, patients with naïve osteoporosis medication, and those without recent fractures or life style record.

Increasing age (21,24,38) has been previously identified as a determinant of one-year discontinuation of BP and raloxifene (21,24,38). Treatment cessation among the elderly might be affected by the high co-morbidity, and poly-pharmacy, increasing the risk to adverse events or interactions, and review of treatment. Also patients with dependence (38), who are bed-bound (requiring SERM stopping for instance), or living in nursing home residence (21), were reported associated with cessation in this population.

In the literature, cessation of AOM was also higher among patients with no recent fractures (21), and men (21), although association with gender has not always been found (38).

Men, young patients and those with no recent fractures, overweight or obesity, or naïve osteoporosis medication, might be describing patients with less severe osteoporosis, slower progression, or less aware of the disease than reference groups. Less severe osteoporosis or awareness were observed by other authors as determinants of cessation (13).

Also, missing lifestyle information (i.e. BMI or smoking status) showed an increased risk to cessation versus normal BMI or non-current smoking status in the current study. Missing may reflect less frequent consultations by patients or monitoring. No studies have been found for comparison.

In the current study, other diseases or medications were also associated with AOM cessation, differing by AOM. Most factors were at borderline significance or had low statistical power, and difficult to interpret, so we will discuss those we found more clinically relevant or interpretable.

Overall, therapy appropriateness of AOM may be re-assessed (39–41), and consequently early-cessations of treatments indicated when non tolerated, deemed inappropriate, in the context of poly-pharmacy, no adequate response, or bothering dosage regimen (12–15,42,43), as mentioned above for the elderly. For instance, the increased risk of SERM early cessation among patients with history of peripheral arterial disease or anticoagulant drugs, may be related to SERM contraindication. On the other hand, reducing the number of drugs might be –both in some clinicians' and patients' opinion- more important than keeping the benefit of AOM in patients with co-morbidities such as diabetes, or liver diseases in patients with BP.

On the contrary, as hypothesized above regarding risk awareness, patients with rheumatoid arthritis may be more observed and/or concerned about the effects of that disease on bone fragility, as well as patients with asthma about their risk of osteoporosis when treated with glucocorticoids (44), or patients with peptic ulcer about following instructions to avoid gastrointestinal effects with bisphosphonates, resulting in better persistence to AOM therapy. Also, although the presentation of high DDD AOM officially indicated for cancer or metastasis, were not included in the current study, patients with malignant cancer may have been receiving AOM for indications related to cancer rather than conventional osteoporosis treatment, and so being more adherent to treatment.

Furthermore, we do not have any reason to explain the slight reduced cessation of some AOM treatment in patients with cerebrovascular diseases (SERM and BP), cancer (BP and SR), vein insufficiency or phlebitis (BP) or dementia (SR), or increased risk with glucocorticoids (SERM). The estimators found must be interpreted with caution because many had low statistical power. Dementia, glucocorticoids, upper gastrointestinal disorders, alcoholism, or DMARD, were not -or poorly- associated with AOM cessation in our study, as observed before (38).

The aforementioned baseline determinants are not intended to explain completely the cessation episodes but the patterns of patients with higher probability to early cessation.

It is worth mentioning that, in the current study, 15% of patients ceasing 90 days re-started AOM in the following 180 days (temporary cessations). Also, 8.55% of new users switched among AOM cohorts during the first year (N=8129), most of them to bisphosphonates or among them (64.88%) as expected (38) being first line therapy, following by strontium ranelate (19.51%). As explain in Time to AOM cessation section, switching to an alternative AOM cohort was a stop reason to follow-up, and was not considered a cessation episode in the current study.

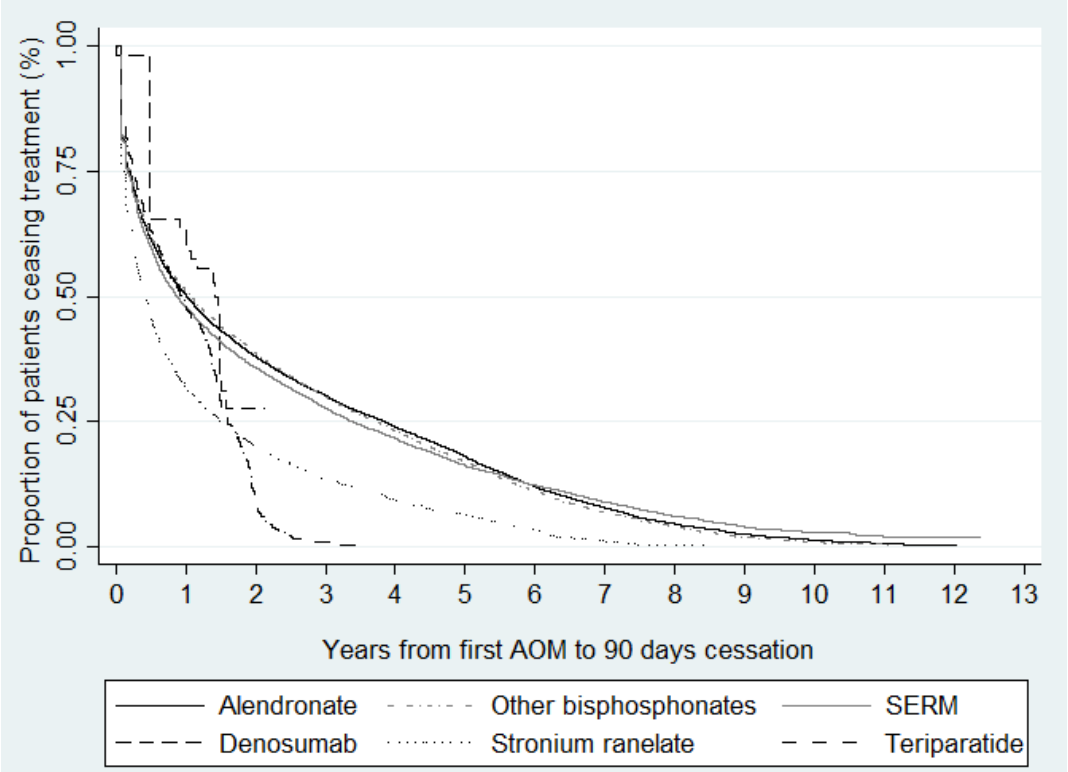
Some limitations must be mentioned. First, according to a published study, around the half of all AOM prescribed treatments for osteoporosis, initiates in primary care settings in Spain (23), so we could have missed first prescriptions recorded only in specialist setting. This would lead to underestimation of both, the cessation proportion (if many patients stop after first prescription) and the time from first real exposure to cessation, especially in denosumab, which is administered each six months. Second, we did not validate compliance to the first prescription nor cessation or its reason by asking physician or patient (which could be the gold-standard). Third, compliance was based on prescription duration accounted for as exposed time by default (6 months for denosumab and 1 month for others AOM consistent with prescribed DDD) which could affect the shorter cessation proportion on denosumab versus

other AOM. Fourth, prescriptions overlaps were disregarded which may have influenced the median of treatment duration. Fifth, cessation definition derived from frequency and duration of the prescriptions, required assumptions for interpreting both, gaps of information between prescriptions dates as well as overlapping of their supplies (20). For this reason, sensitivity analysis using different gaps were performed, which provided a range of cessation that may contain the actual one. Sixth, residual confounding by severity among patients receiving different AOM, might still be present in our estimation of risk cessation associated with each AOM, even after adjusting by recent fractures or additional medication (used as proxies for severity). In particular, higher osteoporosis severity (i.e. lower bone mineral density or higher estimated fracture risk) among denosumab and teriparatide users could therefore lead to either closer physician monitoring or higher risk awareness, which might (at least partially) explain the different risk of cessation, and support the idea to identify its determinants separated by AOM. Also, a lack of power to detect significant determinants of cessation may be happened in small cohorts, such as teriparatide or denosumab. Finally, discontinuation trend over the calendar years was not assessed, which could reflect the potential effect of the marketing of new drugs, officially published warnings or news in the media in particular dates. Only patients' characteristics present at first prescription were assessed as determinants of cessation, factors occurring during treatment (such as fractures while on treatment) were not assessed. We do not know whether the discontinuation was a physician decision to cease the prescriptions or patient choice to not request further refill, or other reasons.

The strength of the current study includes the high number of patients included, the representation of real world primary care data, the novel estimation of cessation rate and risk factors for some AOM scarcely or not published previously in the literature (such as teriparatide or denosumab).

In conclusion, over half of the patients initiating AOM in primary care ceased treatment during the first year of therapy. Overall, cessation probabilities increased among men, young patients, and patients with no recent fractures, overweight or obesity, naïve osteoporosis medication, or missing lifestyle recorded information. These factors could be proxies for non-severe osteoporosis, its progression, and/or disease/risk awareness. On the contrary, awareness could be higher among patients with rheumatoid arthritis or asthma, who persisted more on AOM treatment. Higher cessation of SERM associated to a history of cardiovascular diseases could be related to late identification of contraindication/s or precautions of use. Other diseases such as diabetes, or liver disease slightly increased the risk of cessation which may be related to poly-pharmacy among those patients.

Figure 1. Kaplan-Meier survival curves to cessation (defined as a gap of 90 days without supply) by type of anti-osteoporosis medication and life table over all AOM



Life table over all AOM:													
Interval, years	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-11	11-12	12-13
Patient at risk	95057	40270	26051	17477	11538	7036	3785	1932	886	343	113	30	3
Lost	8323	4424	3185	2371	1810	1153	647	367	214	119	52	20	3
Cessation	46464	9795	5389	3568	2692	2098	1206	679	329	111	31	7	0
Cum. cessation,%	51.1	63.7	71.7	77.9	83.5	88.9	92.7	95.6	97.4	98.4	99.0	99.4	99.4

Table 1. Risk* of one-year cessation associated to demographics, history of fractures, osteoporosis medication and life style factors, by AOM cohort.

	Bisphosphonates							Strontium ranelate							SERM							Teriparatide							Denosumab						
	No cessation N=38970		Cessation N=34806		HR*	LCI	UCI	No cessation N=2874		Cessation N=5104		HR*	LCI	UCI	No cessation N=5846		Cessation N=5877		HR*	LCI	UCI	No cessation N=674		Cessation N=613		HR*	LCI	UCI	No cessation N=229		Cessation N=64		HR*	LCI	UCI
	N	%	N	%				N	%	N	%				N	%	N	%				N	%	N	%				N	%	N	%			
Sex																																			
Females	35451	91.00	30629	88.00	Ref.	-	-	2626	91.40	4565	89.40	Ref.	-	-	5823	99.60	5792	98.60	Ref.	-	-	546	81.00	491	80.10	Ref.	-	-	207	90.40	57	89.10	Ref.	-	-
Males	3519	9.00	4177	12.00	1.26	1.21	1.30	248	8.60	539	10.60	1.14	1.04	1.25	23	0.40	85	1.40	2.12	1.71	2.64	128	19.00	122	19.90	-	-	-	22	9.60	7	10.90	-	-	-
Age (years)																																			
50-59	8594	22.10	8654	24.90	Ref.	-	-	621	21.60	1257	24.60	Ref.	-	-	3495	59.80	3337	56.80	Ref.	-	-	71	10.50	80	13.10	Ref.	-	-	40	17.50	11	17.20	Ref.	-	-
60-69	11789	30.30	9667	27.80	0.89	0.87	0.92	833	29.00	1382	27.10	0.91	0.85	0.97	1818	31.10	1745	29.70	-	-	-	150	22.30	123	20.10	0.8	0.65	0.99	60	26.20	26	40.60	-	-	-
70-79	13085	33.60	10826	31.10	0.92	0.9	0.95	910	31.70	1542	30.20	0.93	0.87	0.99	448	7.70	633	10.80	1.27	1.17	1.38	279	41.40	226	36.90	0.83	0.7	0.99	64	27.90	13	20.30	-	-	-
>=80	5502	14.10	5659	16.30	1.09	1.05	1.13	510	17.70	923	18.10	-	-	-	85	1.50	162	2.80	1.58	1.35	1.86	174	25.80	184	30.00	-	-	-	65	28.40	14	21.90	-	-	-
Fractures												-	-	-																					
≤1y before	3088	7.90	2540	7.30	0.92	0.88	0.96	314	10.90	506	9.90	-	-	-	113	1.90	137	2.30	-	-	-	132	19.60	136	22.20	-	-	-	35	15.30	8	12.50	-	-	-
>1y before	2865	7.40	2426	7.00	Ref.	-	-	212	7.40	369	7.20	Ref.	-	-	210	3.60	204	3.50	Ref.	-	-	94	13.90	69	11.30	Ref.	-	-	38	16.60	9	14.10	Ref.	-	-
No fracture	33017	84.70	29840	85.70	-	-	-	2348	81.70	4229	82.90	-	-	-	5523	94.50	5536	94.20	-	-	-	448	66.50	408	66.60	-	-	-	156	68.10	47	73.40	-	-	-
Medication (yes vs. no)																																			
Other AOM	3148	8.10	2283	6.60	0.89	0.85	0.93	235	8.20	375	7.30	-	-	-	134	2.30	173	2.90	-	-	-	100	14.80	91	14.80	-	-	-	27	11.80	12	18.80	-	-	-
Calcium-D	14463	37.10	11548	33.20	0.92	0.9	0.94	1066	37.10	1643	32.20	0.9	0.85	0.96	1527	26.10	1471	25.00				311	46.10	231	37.70	0.73	0.62	0.86	155	67.70	38	59.40	-	-	-
HRT 1-Year	1237	3.20	917	2.60	0.85	0.8	0.91	84	2.90	114	2.20	-	-	-	985	16.80	596	10.10	0.65	0.59	0.71	6	0.90	3	0.50	-	-	-	0	-	0	-	-	-	-
Life style																																			
BMI																																			
<18.5	112	0.30	105	0.30	1.22	1.00	1.48	5	0.20	13	0.30	-	-	-	12	0.20	10	0.20	-	-	-	6	0.90	3	0.50	-	-	-	1	0.40	1	1.60	-	-	-
18.5-24.9	3641	9.30	2681	7.70	Ref.	-	-	272	9.50	357	7.00	Ref.	-	-	497	8.50	427	7.30	Ref.	-	-	61	9.10	48	7.80	Ref.	-	-	27	11.80	4	6.30	Ref.	-	-
25-29.9	7219	18.50	5117	14.70	-	-	-	514	17.90	753	14.80	-	-	-	957	16.40	738	12.60	0.91	0.83	1.01	113	16.80	88	14.40	-	-	-	35	15.30	5	7.80	-	-	-

30-34.9	4534	11.60	3570	10.30	1.07	1.03	1.11	361	12.60	570	11.20	1.09	0.99	1.21	486	8.30	457	7.80	-	-	-	79	11.70	62	10.10	-	-	-	23	10.00	10	15.60	-	-	-
35-39.9	1414	3.60	1177	3.40	1.13	1.06	1.20	105	3.70	200	3.90	1.23	1.06	1.43	128	2.20	163	2.80	1.24	1.05	1.47	26	3.90	20	3.30	-	-	-	3	1.30	1	1.60	-	-	-
>=40	482	1.20	406	1.20	1.12	1.01	1.24	25	0.90	74	1.40	1.47	1.16	1.86	37	0.60	57	1.00	1.34	1.03	1.76	4	0.60	11	1.80	2.58	1.39	4.78	0	-	0	-			
Missing	21568	55.30	21750	62.50	1.28	1.25	1.32	1592	55.40	3137	61.50	1.24	1.15	1.33	3729	63.80	4025	68.50	1.19	1.11	1.28	385	57.10	381	62.20				140	61.10	43	67.20	-	-	-
Current smoker																																			
No	17587	45.10	14409	41.40	Ref.	-	-	1285	44.70	2178	42.70	Ref.	-	-	2355	40.30	2289	38.90	Ref.	-	-	298	44.20	261	42.60	Ref.	-	-	97	42.40	26	40.60	Ref.	-	-
Yes	5181	13.30	4284	12.30	1.06	1.02	1.10	384	13.40	611	12.00	-	-	-	838	14.30	756	12.90				77	11.40	66	10.80	-	-	-	31	13.50	4	6.30	-	-	-
Missing	16202	41.60	16113	46.30	1.09	1.07	1.12	1205	41.90	2315	45.40	1.06	1	1.12	2653	45.40	2832	48.20				299	44.40	286	46.70	1.2	1.01	1.41	101	44.10	34	53.10	-	-	-

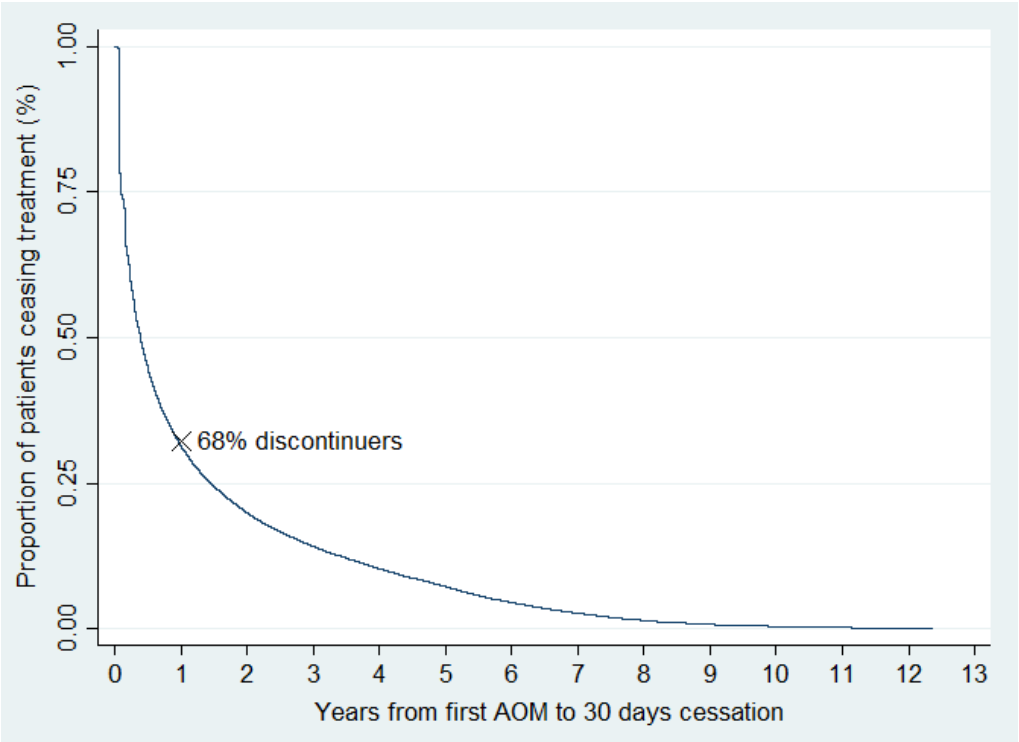
*Stepwise performed backward-selection estimation of categories associated to one-year cessation with a p-value=0.05 for addition to the model, and p-value=0.1 for removal to the model. Stepwise selection was performed for the following variables added together to Cox model: sex, age at treatment initiation, venous thromboembolism, alcohol abuse, aneurysm , asthma , cancer , COPD , cerebrovascular disease, dementia , diabetes, hemiplegia , HF , HIV , liver disease, myocardial infarction, peripheral arterial disease, peptic ulcer, rheumatoid arthritis, renal, vein insufficiency or phlebitis as anytime before treatment initiation, other AOM, calcium-D, glucocorticoids, heparin, oral anticoagulant drugs, hormone replacement therapy (HRT) during previous year, previous fractures, BMI, and smoking (as recorded at year of treatment initiation).

Table 2. Risk* of one-year cessation associated to morbidity and medication (ever versus never before), by AOM cohort.

	Bisphosphonates						
	No cessation N=38970		**Cessation N=34806**		**HR***	**LCI**	**UCI**
	No.	%	No.	%			
Rheumatoid arthritis	1068	2.7	760	2.2	0.83	0.77	0.89
Malignant cancer	4070	10.4	3404	9.8	0.93	0.90	0.96
Cerebrovascular disease	1083	2.8	924	2.7	0.94	0.88	1.00
Vein insufficiency or phlebitis	8067	20.7	6469	18.6	0.94	0.92	0.97
Peptic ulcer	1624	4.2	1380	4.0	0.95	0.90	1.00
Glucocorticoids	7685	19.7	6572	18.9	0.98	0.95	1.00
Heart failure	918	2.4	898	2.6	1.06	0.99	1.13
Diabetes	4612	11.8	4193	12.0	1.07	1.04	1.11
Liver disease	851	2.2	863	2.5	1.10	1.02	1.17
	Strontium ranelate						
	No cessation N=2874		**Cessation N=5104**		**HR***	**LCI**	**UCI**
	No.	%	No.	%			
Dementia	87	3.0	124	2.4	0.84	0.70	1.00
Cancer	330	11.5	501	9.8	0.89	0.81	0.97
Liver disease	61	2.1	136	2.7	1.19	1.00	1.41
	SERM						
	No cessation N=5846		**Cessation N=5877**		**HR***	**LCI**	**UCI**
	No.	%	No.	%			
Cerebrovascular disease	51	0.9	42	0.7	0.73	0.53	0.99
Glucocorticoids	478	8.2	597	10.2	1.18	1.08	1.28
Oral anticoagulant drugs	35	0.6	60	1.0	1.27	0.98	1.65
Peripheral arterial disease	13	0.2	25	0.4	1.54	1.04	2.28
	Teriparatide						
	No cessation N=674		**Cessation N=613**		**HR***	**LCI**	**UCI**
	No.	%	No.	%			
Asthma	67	9.9	38	6.2	0.70	0.50	0.97

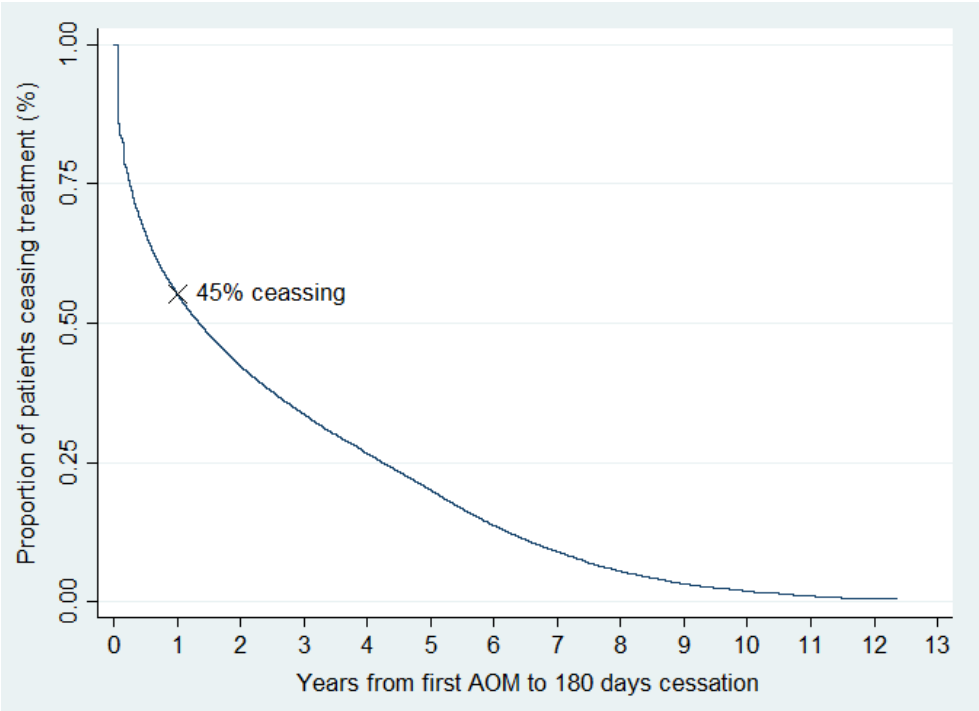
*Stepwise performed backward-selection estimation of categories associated to 1 year cessation with a p-value=0.05 for addition to the model, and p-value=0.1 for removal to the model. Stepwise selection was performed for the following variables added together: sex, age at treatment initiation, venous thromboembolism, alcohol abuse, aneurysm , asthma , cancer , COPD , cerebrovascular disease, dementia , diabetes, hemiplegia , HF , HIV , liver disease, myocardial infarction, peripheral arterial disease, peptic ulcer, rheumatoid arthritis, renal, vein insufficiency or phlebitis as anytime before treatment initiation, other AOM, calcium-D, glucocorticoids, heparin, oral anticoagulant drugs, hormone replacement therapy (HRT) during previous year, previous fractures, BMI, and smoking (as recorded at year of treatment initiation).

Figure 2. Kaplan-Meier survival curves and life table to cessation (defined as a gap of 30 days without supply) over all AOM



Life table over all AOM:													
Interval, years	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-11	11-12	12-13
Patients at risk	95057	25730	14224	8749	5481	3233	1671	808	357	131	43	10	2
Lost	7012	2591	1622	1059	743	430	244	108	73	37	21	6	2
Cessation	62315	8915	3853	2209	1505	1132	619	343	153	51	12	2	0
Cum. cessation,%	68.1	79.9	85.7	89.5	92.6	95.4	97.2	98.5	99.2	99.6	99.7	99.8	99.8

Figure 3. Kaplan-Meier survival curves and life table to cessation (defined as a gap of 180 days without supply) over all AOM



Life table over all AOM:													
Interval, years	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-11	11-12	12-13
Patients at risk	58469	45752	30721	21113	14145	8768	4807	2492	1149	457	156	37	3
Lost	8663	4951	3727	2866	2199	1433	831	488	288	154	68	24	3
Cessation	40642	10080	5881	4102	3178	2528	1484	855	404	147	51	10	0
Cum. cessation,%	44.8	57.6	66.3	73.3	79.8	86.1	90.8	94.3	96.6	97.9	98.8	99.3	99.3

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