

# Early (1-year) Discontinuation of Different Anti-osteoporosis Medications Compared: A Population-Based Cohort Study

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**Abstract** Although a number of reports suggest very low persistence with oral bisphosphonates, there is limited data on persistence with other anti-osteoporosis medications. We compare rates of early discontinuation (in the first year) with all available outpatient anti-osteoporosis drugs in Catalonia, Spain. We conducted a population-based retrospective cohort study using data from the SIDIAP database. SIDIAP contains computerized primary care records and pharmacy dispensing data for >80 % of the population of Catalonia (>5 million people). All SIDIAP participants starting an anti-osteoporosis drug between 1/1/2007 and 30/06/2011 (with 2 years wash-out) were included. We modelled persistence as the time between first prescription and therapy discontinuation (refill gap of at least 6 months) using Fine and Gray survival models with competing risk for death. We identified 127,722 patients who started any anti-osteoporosis drug in the study period. The most commonly prescribed drug was weekly alendronate ( $N = 55,399$ ). 1-Year persistence ranges from 40 % with monthly risedronate to 7.7 % with daily risedronate, and

discontinuation was very common [from 49.5 % (monthly risedronate) to 84.4 % (daily risedronate)] as was also switching in the first year of therapy [from 2.8 % (weekly alendronate) to 10 % (daily alendronate)]. Multivariable-adjusted models showed that only monthly risedronate had better one-year persistence than weekly alendronate and teriparatide equivalent, whilst all other therapies had worse persistence. Early discontinuation with available anti-osteoporosis oral drugs is very common. Monthly risedronate, weekly alendronate, and daily teriparatide are the drugs with the best persistence, whilst daily oral drugs have 40–60 % higher first-year discontinuation rates compared to weekly alendronate.

**Keywords** Electronic health records · Epidemiology · Medication adherence · Osteoporosis · Catalonia · Primary health care

## Introduction

The primary challenge in treating chronic illness today is that many patients do not take their medications correctly [1]. There has been much concern about the negative consequences of poor compliance and persistence with oral osteoporosis medications [2, 3].

Prior systematic reviews have documented that many patients discontinue oral medications for osteoporosis soon after treatment initiation, with a rapid drop in persistence in the first 3 months, followed by a slower decline over ensuing months: fewer than half the patients persist with osteoporosis drugs for a full year [4–6], with estimates ranging between 18 and 78 % for bisphosphonates [7]. The effectiveness of anti-osteoporotic drugs is compromised by this poor adherence to treatment: a significant proportion of patients

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abandon their treatment within 6 months of initiation and more than half stop treatment within the first year [8].

Low adherence is associated with less suppression of bone turnover and lower gains in bone mineral density. This in turn leads to higher fractures rates [9–11], medical costs, and greater healthcare utilization, including higher hospitalization [12, 13].

We therefore used a large primary care database that includes pharmacy invoice data and clinical information for more than 5 million people in Catalonia (Spain) to analyse and compare 1-year persistence with all outpatient anti-osteoporosis drugs in primary care settings.

## Methods

### Study Design

This is a population-based retrospective cohort study.

### Source of Data

The Spanish public healthcare system covers practically the whole of the population. General practitioners (GPs) play an essential role, being responsible for primary healthcare, long-term prescriptions and specialist and hospital referrals. The data in this study were obtained from the SIDIAP Database (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària). SIDIAP ([www.sidiap.org](http://www.sidiap.org)) comprises primary care electronic medical records in Catalonia (North-East Spain), covering a population of about 5 million patients (80 % of the total population for the region) from 274 primary care practices (3414 GPs). Health professionals gather this information using ICD-10 codes and structured spreadsheets designed for the collection of variables relevant for primary care clinical management, including the country of origin, gender, age, height, weight, body mass index, smoking and drinking status, blood pressure measurements, preventive care provided, and blood and urine test results. Only GPs who achieve quality control standards can contribute to the SIDIAP database [14]. Encoding personal identifiers ensures the confidentiality of the information in the SIDIAP.

SIDIAP data have been used in many previous publications reporting of musculoskeletal conditions including osteoporosis and the epidemiology of fragility fracture in patients treated with oral bisphosphonates [15–19].

### Study Population

We identified incident users of oral or subcutaneous anti-osteoporosis drugs [as available in primary care settings in

Catalonia (Spain)] in the SIDIAP database between 01/01/2007 and 30/06/2010 and followed them up for at least 1 year.

Users of any anti-osteoporosis medications (excluding calcium or vitamin D supplements) in previous 2 years were excluded.

### Drugs of Interest

We included oral drugs that can we use in primary care setting: daily (alendronate, risedronate, raloxifene, bazedoxifene and strontium ranelate), weekly (alendronate and risedronate), and monthly (ibandronate and risedronate). We also included subcutaneous daily teriparatide. We do not include zoledronic acid because it is hospital dispensed in our country and denosumab because it was not in the market in the study period. In Catalonia and during the study period, the presentations of these drugs were monthly (for example, a box of weekly alendronate contains four pills which covers 4 weeks, approximately 1 month).

### Outcome

The main outcomes were rates of treatment cessation in the first year following therapy initiation.

As the best gap to identify the patients with bad compliance is not well defined, we decide to define persistence as time from initiation to discontinuation of therapy. Therapy cessation was defined on the basis of therapy dispensation refill gaps: if the gap between consecutive dispensing dates was more than 6 months, the gap based on the period over which repeat prescriptions was scheduled, and the last prescription of the drug before this gap was considered as the last prescription date. Our definition of persistence based on 6-month refill gap is an arbitrary decision based on two reasons: we have previously published on a cohort of oral bisphosphonate users extracted from the same data source using this gap [15] as have other authors using different datasets [20] and the nature of the local (catalan) GP prescription and reimbursement system—in our universal healthcare, GP provides repeat prescriptions every 3 months, and therefore, short gaps (<3–4 months) would artificially overestimate therapy cessation rates. One-year persistence (primary study outcome) was defined as the proportion of patients who received continuous drug dispensations for at least 365 days without a  $\geq 6$  month refill and without switching to another oral anti-osteoporosis drug. But since we are aware of the variability of adherence definitions, a sensitivity analysis using a 12-month gap (secondary definition) and another using de total dose prescribed [Daily Defined Doses (DDDs)] instead of time prescription was done.

## Potential Confounders

A list of pre-specified potential confounders were considered and adjusted for in multivariable models (see below): age, gender, body mass index, smoking, alcohol drinking, Charlson co-morbidity index, number of previous fracture/s, use of oral corticosteroids, and concomitant therapy with aromatase inhibitors.

## Statistical Analyses

We estimated persistence using Kaplan–Meier survival analysis. Risk of early (in the first year since therapy initiation) therapy discontinuation according to drug used was modelled using multivariable Fine and Gray regression models, accounting for a potential competing risk with death. In such models, unadjusted and multivariate-adjusted (for all confounders above) subhazard ratios (SHR) and 95 % confidence intervals (95 % CI) for one-year therapy cessation according to therapy group were estimated.

All statistical analyses were performed using Stata for Mac version 12.

## Results

We identified 127,722 incident users of anti-osteoporosis drugs in the SIDIAP database between 01/01/2007 and 30/06/2010. Only 1689 patients were followed less than 6 months (approximately 1 %). These patients were censored at end of follow-up, as usual in survival analyses. 118,829 (93.0 %) completed the study period, 970 (0.8 %) were lost to follow-up because they transferred out of the region, and 7923 (6.2 %) died in this period. Baseline characteristics of the study population according to follow-up status at the end of study (completed, lost to follow-up, or dead) are shown in Table 1. Patients who completed the study were as expected younger and with a lower Charlson co-morbidity index.

Table 2 shows the number and proportion of participants persisting, discontinuing, switching, and dead in the first year after therapy initiation and according to treatment group. The drugs with best 1-year persistence were monthly risedronate and weekly alendronate with persistence rates of 40 and 39.9 % respectively, whilst the one with lowest was daily risedronate (7.7 %). Discontinuation was common ranging from 84.4 % (daily risedronate) to 49.5 % (monthly risedronate), and when we studied therapy switching (to an alternative anti-osteoporosis drug) in the first year of treatment, the most commonly changed drug was daily alendronate (10.0 %) followed (in order) by monthly risedronate (9.9 %) and daily risedronate (7.9 %);

in contrast, weekly alendronate (2.8 %), raloxifene (4.0 %), and bazedoxifene (4.3 %) were the less commonly changed medications.

Detailed results for the Fine and Gray models to study the association between drug group and first-year therapy cessation risk are shown in Table 3. Monthly risedronate was the only drug with lower risk of discontinuation compared to weekly alendronate, with adjusted SHR 0.86 (95 % CI 0.83–0.89). Teriparatide users had similar risk of one-year discontinuation to users of weekly alendronate [adjusted SHR 1.02 (0.98–1.07)], and the rest of drugs showed an increased cessation risk. The drugs with the highest risk of discontinuation were those taken orally on a daily basis: adjusted SHR was 1.86 (1.74–1.99) for daily risedronate, 1.64 (1.52–1.77) for daily alendronate, 1.43 (1.40–1.45) for raloxifene, 1.41 (1.22–1.59) for bazedoxifene, and 1.51 (1.48–1.53) for strontium ranelate. Consistent with these results, Fig. 1 shows Kaplan–Meier curves for 1-year therapy persistence according to recommended drug.

Finally, Table 4 shows the results of the sensibility analysis using the primary definition of cessation (6-month gap), the secondary definition (12-month gap), and on the basis of days covered treatment (DDD). There were no significant differences when using different methods, only monthly risedronate shows worst compliance using the DDT definition but not with de secondary definition, and teriparatide shows worst compliance using both the 12-month gap and de DDT definition.

## Discussion

This is the first study in Spain that compares persistence with all available anti-osteoporosis drugs in the same cohort.

We found that a substantial portion of patients (one-third to half) do not persist on treatment as initially recommended. Both cessation and therapy switching occur soon (in the first 1–3 months) after treatment initiation. Our findings are consistent with previously published studies [15, 21], but most of the studies published include only oral bisphosphonates.

According to our data, 1-year persistence with daily drugs therapy varies from 7.5 to 32 %. Amongst users of weekly oral bisphosphonates, one-year persistence is slightly better, ranging between 30 and 40 %, and teriparatide seems to have similar persistence but still clearly insufficient to achieve therapeutic coverage. In the literature, one study in the United States reported some improvement in persistence with monthly bisphosphonate therapy [22]. But this is not consistent with our results, where users of monthly risedronate were likely to stop

**Table 1** Baseline characteristics of the study population

	Completed follow-up		Lost to follow-up		Died	
	<i>N</i>	(%)	<i>N</i>	(%)	<i>N</i>	(%)
Total <i>N</i> = 127,722	118,829	93.0	970	0.8	7923	6.2
Sex						
Female	91,315	76.8	767	79.1	4543	57.3
Male	27,514	23.1	203	20.9	338	42.7
BMI						
N/A	60,342	50.8	668	68.9	4381	55.3
<18.5 kg/m <sup>2</sup>	345	0.3	2	0.2	72	0.9
18.5–24.9	12,774	10.7	68	7.0	995	12.6
25.0–29.9	24,742	20.8	141	14.5	1402	17.7
30.0–34.9	14,839	12.5	62	6.4	803	10.1
>35.0	5787	4.8	29	3	270	3.4
Smoking						
N/A	25,292	21.3	359	37.0	1981	25.0
Never	70,477	59.3	444	45.8	4216	53.2
Current	11,978	10.1	97	10.0	647	8.2
Ex	11,082	9.3	70	7.2	1079	13.6
Alcohol drinking						
N/A	75,195	63.3	749	77.2	5244	66.2
Never	33,085	27.8	174	17.9	2218	28.0
Mild	9.93	8.4	42	4.3	430	5.4
Severe	619	0.5	5	0.5	31	0.4
Socio-economic deprivation <sup>a</sup>						
N/A	22,514	18.9	8	0.8	1529	19.3
1	22,525	19.00	12	1.2	1504	19.0
2	22,588	19.0	8	0.8	1489	18.8
3	22,618	19.0	4	0.4	1356	17.1
4	22,662	19.0	5	0.5	1529	19.3
Charlson						
0	75,044	63.1	568	58.6	2393	30.2
1	25,951	21.8	202	20.8	2216	28.0
2	11,404	9.6	117	12.1	1539	19.4
3	4031	3.4	50	5.1	879	11.1
4	2399	2.0	33	3.4	896	11.3
Previous fracture						
No	103,562	87.1	839	86.5	6549	82.7
Yes	15,267	12.8	131	13.5	1374	17.34
Age	Mean ± SD	66.90 ± 11.0		72.60 ± 12.9		79.84 ± 9.9

N/A not available

<sup>a</sup> As calculated using the MEDEA Index [22], where higher score is equivalent to poorer socio-economic status

treatment compared to users of weekly alendronate (reference groups), but users of monthly ibandronate had worse persistence.

Our study presents worse medication-taking behaviour (1-year persistence of 33.7 %), which could be explained by a greater percentage of patients in primary prevention, and a greater percentage of men in the sample compared to

similar ones. For example, Hadji et al. [21] found 1-year persistence with oral bisphosphonates of 27.9 % (using a shorter refill gap than ours, of >30 days), with no differences between monthly and weekly administration; Netelembos et al. [20] found 1-year persistence of 43 %: 46 % with monthly, 42–53 % for weekly, and 23–40 % for daily medications, and they included patients with similar age to

**Table 2** Number and % of included participants according to 1-year status: persistence, cessation, switching, or death

Drug	Persist	Discont	Dead	Switch
Weekly ALN	22.012 (39.9 %)	31.158 (56.5 %)	417 (0.8 %)	1.530 (2.8 %)
Daily ALN	70 (14.1 %)	373 (75.1 %)	4 (0.8 %)	50 (10.0 %)
Monthly IBAN	4.750 (35.8 %)	7.658 (57.7 %)	84 (0.6 %)	778 (5.9 %)
Weekly RIS	7.892 (31.2 %)	15.668 (61.9 %)	153 (0.6 %)	1.599 (6.3 %)
Daily RIS	33 (7.7 %)	363 (84.4 %)	0 (0 %)	34 (7.9 %)
Monthly RIS	2.042 (40.0 %)	2.525 (49.5 %)	28 (0.6 %)	505 (9.9 %)
Teriparatide	765 (34.0 %)	1.285 (57.1 %)	23 (1.0 %)	176 (7.9 %)
Raloxifene	2.357 (22.7 %)	7.598 (73.2 %)	12 (0.1 %)	410 (4.0 %)
Bazedoxifene	173 (31.4 %)	354 (64.3 %)	0 (0 %)	24 (4.3 %)
Strontium ranelate	2.768 (19.5 %)	10.347 (73.0 %)	62 (0.4 %)	996 (7.1 %)
TOTAL	42.862 (33.7 %)	77.329 (60.8 %)	783 (0.6 %)	6.102 (4.8 %)

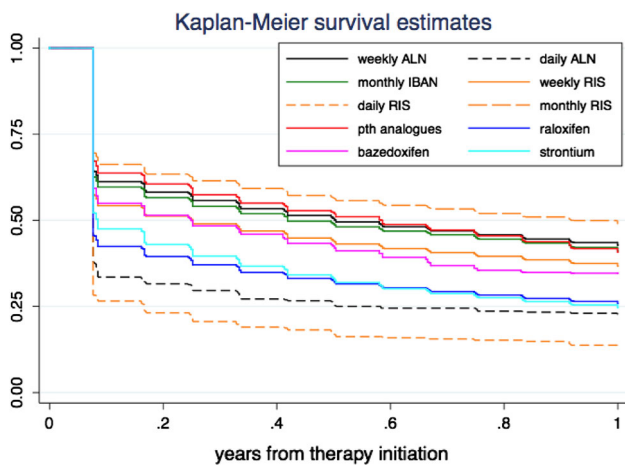
**Table 3** Risk of 1-year discontinuation according to drug prescribed (fine and gray survival model results)

	UNADJ SHR	95 % CI	MV SHR <sup>a</sup>	95 % CI
Weekly ALN	REF		REF	
Daily ALN	1.67***	1.54 1.80	1.64***	1.52 1.77
Monthly IBAN	1.04***	1.02 1.06	1.06***	1.04 1.09
Weekly RIS	1.16***	1.14 1.18	1.12***	1.10 1.14
Daily RIS	2.00***	1.87 2.13	1.86***	1.74 1.99
Monthly RIS	0.86***	0.83 0.89	0.89***	0.86 0.92
Teriparatide	1.02	0.97 1.07	1.02	0.98 1.07
Raloxifene	1.49***	1.46 1.52	1.43***	1.40 1.45
Bazedoxifene	1.22***	1.12 1.33	1.41***	1.29 1.54
Strontium ranelate	1.48***	1.46 1.51	1.51***	1.48 1.53

UNADJ unadjusted, MV multivariate, SHR subhazard ratio, CI confidence interval, REF reference group, ALN alendronate, IBAN ibandronate, RIS risedronate

\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$

<sup>a</sup> Adjusted for age, gender, body mass index, smoking, alcohol drinking, Charlson co-morbidity index, previous fracture, use of oral corticosteroids, and concomitant therapy with aromatase inhibitors



**Fig. 1** Kaplan-Meier estimates: cumulative probability of 1-year persistence with each individual drug/group

our study participants (69.2 years), or Confavreux et al. [8] found 1-year overall persistence of 34 % (50 % at best with monthly and 37 % for weekly). In addition, Lo et al.

[23] studied persistence using the General Practice Research Database in women who had a first prescription for an oral bisphosphonate, oral raloxifene, or oral strontium ranelate in the study period: 44 % of women were continuing with osteoporosis therapy after 6 months, 32 % after 1 year, 16 % at 3 years, and 9 % at 5 years from initiation. Finally, Burden et al. [24] found better persistence: 63 % at one year, but participants were older (75.6 years), in the second-year persistence was 46 and 12 % at 9 years.

Finally, an underreported finding is that many patients who discontinue bisphosphonate therapy reinitiate treatment after an extended gap [25], but little is known about the extent to which patients after discontinuing treatment in the routine care restart or switch to other drugs in the same class. One previous study [24] identified that the proportion of patients that persisted with therapy declined from 63 % at 1 year to 12 % after 9 years. They also identified that most patients experienced one or more extended gaps in bisphosphonate therapy. For example, amongst the 213,029

**Table 4** Comparison of the different HR using 6-month gap, 12-month gap, and DDD definition

	6-month gap			12-month gap			DDD
	MV SHR <sup>a</sup>	95 % CI		MV SHR <sup>a</sup>	95 % CI		MV SHR <sup>a</sup>
Weekly ALN	REF			REF			REF
Daily ALN	1.64 ***	1.52	1.76	1.74 ***	1.61	1.88	2.29
Monthly IBAN	1.06 ***	1.04	1.08	1.11 ***	1.09	1.14	1.15
Weekly RIS	1.12 ***	1.10	1.14	1.15 ***	1.13	1.17	1.26
Daily RIS	1.85 ***	1.73	1.99	1.98 ***	1.84	2.12	2.61
Monthly RIS	<b>0.89</b> ***	0.86	0.92	<b>0.96</b> *	0.93	0.99	<b>1.08</b>
Teriparatida	<b>1.03</b>	0.98	1.08	<b>1.10</b> ***	1.05	1.16	<b>1.58</b>
Raloxifene	1.43 ***	1.40	1.45	1.46 ***	1.43	1.49	1.67
Bazedoxifene	1.41 ***	1.29	1.54	1.53 ***	1.39	1.67	1.82
Strontium ranelate	1.50 ***	1.48	1.53	1.56 ***	1.53	1.59	1.82

Bold: discordant

MV multivariate, SHR subhazard ratio, CI confidence interval, REF reference group, ALN alendronate, IBAN ibandronate, RIS risedronate

\*  $p < 0.05$ ; \*\*\*  $p < 0.001$

<sup>a</sup> Adjusted for: age, gender, body mass index, smoking, alcohol drinking, Charlson co-morbidity index, previous fracture, use of oral corticosteroids, and concomitant therapy with aromatase inhibitors

new users with at least 5 years of follow-up, 25 % persisted with therapy for the full 5 years, 61 % experienced one (24 %) or more (37 %) extended gaps in therapy, and 14 % discontinued treatment without returning to bisphosphonate therapy. Using a more lenient 120-day permissible gap to define non-persistence, they note that persistence rates increased and fewer users were identified to have experienced extended gaps in drug therapy. For example, persistence at 1 year increased from 63 % using a 60-day permissible gap to 77 % when using a 120-day permissible gap. They found that 7 % of new bisphosphonate users switched to a different bisphosphonate within 1 year of treatment initiation, and this increased to more than a third of patients (37 %) over the entire duration of follow-up (5 years). Knowing this findings, and taking into account the nature of prescription in Catalonia, we chose de 6-month gap and compared with 12-month gap and also with de DDDs; this sensitivity analysis showed that the results were robust, and the definition chosen for assessment of persistence (length of refill gaps) was not relevant for estimating persistence.

Our study has several limitations. First, we cannot ensure that patients who receive treatment from community pharmacies (dispensations) actually take the purchased medication/s nor can we know the reason/s for therapy switching and/or cessation, which might also include medical decisions and patient issues (for examples concerns about medication or difficulties in remembering to take it). Second, this is an observational study, and although we adjusted for a number of co-variables, residual confounding is likely. Of special concern in pharmaco-

epidemiological studies is confounding by indication, where patients receiving some specific therapies are given those for a reason (e.g., higher disease severity or contraindications). In addition, channelling bias due to “special” patient characteristics amongst users of recently launched medications in the study period (i.e., bazedoxifene or monthly risedronate) is likely. This would, however, partially explain the observed findings for these medications but not for all the other drugs included. Given all this, we cannot test for causality between treatment prescribed and resulting persistence, which would require experimental (randomized controlled) studies.

Strengths of our study are the high sample size and the representativeness of the data used: SIDIAP covers over 80 % of the total population of Catalonia, and the information is coded in actual practice conditions, different to the restrictive settings required for randomized controlled trials. In addition, the information gathered on community pharmacy dispensations is detailed and likely to be more reliable than patient reports or GP prescriptions.

## Conclusions

Early discontinuation with available therapies for Osteoporosis is very common. In our data, users of monthly risedronate, weekly alendronate, and teriparatide have best persistence: about 40 % of patients on these therapies continue after 1 year. In contrast, users of oral daily drugs (bisphosphonates, SERMs, and strontium ranelate) have a 40–60 % higher one-year cessation risk than weekly ALN.



### Compliance with Ethical Standards

**Conflict of interest** The authors, C Carbonell-Abella, A. Pages-Castella, MK Javaid, X Nogués, AJ Farmer, C Cooper, A Díez-Pérez, and D Prieto-Alhambra, declare that they have no conflict of interest.

**Statement of Human and Animal Rights and Informed Consent** This article does not contain any studies with human participants or animals performed by any of the authors.

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