J Korean Med Sci. 2025 May 12;40(18):e72
https://doi.org/10.3346/jkms.2025.40.e72
eISSN 1598-6357·pISSN 1011-8934

JKMS

Original Article
Endocrinology

Check for updates

Factors Associated With Compliance and Persistence With Pharmacotherapy in Patients With Osteoporosis: A Nationwide Cohort Study in Korea

Seong Hee Ahn,[1] **So Young Park**,[2] **Mi Kyung Kwak**,[3] **Yong-Chan Ha**,[4] **Tae-Young Kim**,[5] **and Ha Young Kim** [6]

[1]Department of Endocrinology and Metabolism, Inha University Hospital, Incheon, Korea
[2]Division of Endocrinology and Metabolism, Department of Internal Medicine, Kyung Hee University College of Medicine, Seoul, Korea
[3]Department of Endocrinology and Metabolism, Hallym University Dongtan Sacred Heart Hospital, Hwaseong, Korea
[4]Department of Orthopaedic Surgery, Bumin Hospital, Seoul, Korea
[5]Department of Orthopaedic Surgery, Konkuk University Medical Center, Seoul, Korea
[6]Department of Endocrinology and Metabolism, Gangneung Asan Hospital, University of Ulsan College of Medicine, Gangneung, Korea

OPEN ACCESS

Received: Jul 1, 2024
Accepted: Nov 7, 2024
Published online: Jan 29, 2025

Address for Correspondence:
Ha Young Kim, MD
Department of Endocrinology and Metabolism, Gangneung Asan Hospital, University of Ulsan College of Medicine, 38 Bangdong-gil, Sacheon-myeon, Gangneung 25540, Republic of Korea.
Email: hykimmd@hanmail.net

ORCID iDs
Seong Hee Ahn
https://orcid.org/0000-0003-2558-2118
So Young Park
https://orcid.org/0000-0002-4820-9415
Mi Kyung Kwak
https://orcid.org/0000-0002-8092-2560
Yong-Chan Ha
https://orcid.org/0000-0002-6249-0581

ABSTRACT

Background: Despite the necessity of long-term management for fracture risk reduction, adherence to osteoporosis pharmacotherapy remains poor. We investigated the factors influencing adherence to pharmacotherapy among Korean patients with osteoporosis, with a particular focus on treatment with bisphosphonates (BPs).
Methods: Data from 725,313 osteoporosis patients newly prescribed BPs or selective estrogen receptor modulators (SERMs) between 2012 and 2014, obtained from the Korean National Health Insurance Service, were analyzed. Adherence was assessed based on compliance and persistence over a two-year period, with factors associated with adherence identified using multivariable logistic regression.
Results: Only 14.8% of the patients who started BPs or SERMs sustained medication compliance, with 15.8% persisting with treatment over the two-year follow-up. Compared with BPs, patients receiving SERMs showed better compliance and persistence (odds ratios [ORs], 1.44 and 1.48, respectively; $P < 0.001$); while patients receiving intravenous administration showed higher compliance and persistence (ORs, 2.08 and 1.76, respectively; $P < 0.001$) compared with those taking oral medications. Patients placed on a quarterly dosing schedule showed improved compliance and persistence (ORs, 1.55 and 1.31, respectively; $P < 0.001$) compared with those on other dosing intervals. Male gender, advanced age, living outside metropolitan areas, receiving treatment in non-general hospitals, and a history of previous fractures were associated with poorer two-year adherence.
Conclusion: This study underscores the complex nature of medication adherence among Korean osteoporosis patients, particularly those treated with BPs. These findings accordingly indicate that medication with more convenient administration regimens and fewer side effects, coupled with suitable follow-up durations, could contribute to enhancing treatment adherence.

Keywords: Compliance; Osteoporosis; Pharmacotherapy; Persistence; Korea

Tae-Young Kim
https://orcid.org/0000-0003-2028-0460
Ha Young Kim
https://orcid.org/0000-0002-0651-2213

Funding
This work was supported by the Korean Society for Bone and Mineral Research. National Health Information Database (NHIS-2022-1-406) data was provided by the National Health Insurance Service (NHIS) of Korea. The authors would like to thank the NHIS for the cooperation.

Disclosure
The authors have no potential conflicts of interest to disclose.

Author Contributions
Conceptualization: Ahn SH, Kim HY. Data curation: Ahn SH. Formal analysis: Ahn SH. Investigation: Ahn SH, Park SY, Kwak MK, Ha YC, Kim TY, Kim HY. Methodology: Ahn SH, Park SY, Kwak MK, Ha YC, Kim TY, Kim HY. Validation: Ahn SH, Kim HY. Writing - original draft: Ahn SH. Writing - review & editing: Ahn SH, Park SY, Kwak MK, Ha YC, Kim TY, Kim HY.

INTRODUCTION

The global aging of populations has led to an increase in the incidence of osteoporosis and associated fractures, thereby contributing to significant medical, social, and economic burdens.[1,2] Osteoporosis, as a chronic condition, requires long-term management, including the maintenance of different medications and repeated assessments of fracture risk.[3] Consequently, maintaining adherence to osteoporosis medication is essential for the effective prevention of fractures. Numerous studies have established a link between a poor adherence to medication and reduced gains in bone mineral density (BMD), diminished impact on bone turnover, and higher rates of fragility fractures.[4] However, despite this knowledge, large-scale studies in different countries continue to report inadequate adherence to osteoporosis pharmacotherapy[5,6]; thereby, highlighting the need to identify the clinical factors that influence the adherence to medication in osteoporosis patients and to promote sustained medication usage to meet treatment goals.

For several decades, bisphosphonates (BPs) have served as the cornerstone of osteoporosis treatment, being administered as the first-line therapy for many patients. BPs are well-documented to effectively increase BMD and prevent both vertebral and non-vertebral fractures.[7] Moreover, given their acknowledged prolonged effects, both orally and intravenously administered BPs are recommended as sequential treatments[3,8-10] following novel parenteral osteoporosis medications such as denosumab, teriparatide, and romosozumab, which tend to lack a sustained effect post-cessation.[11] In this context, the recent COVID-19 pandemic has further highlighted the need for continuous treatment and the availability of accessible alternative BP therapies when other parenteral medications are unavailable, particularly for patients with limited access to healthcare facilities.[12] However, the poor adherence to BP regimens remains a common problem, which to a large extent can be attributed to the associated side effects, including gastrointestinal discomfort and acute phase reaction.[13] Consequently, it is essential to identify approaches that can be adopted to enhance adherence to osteoporosis medications, particularly BPs. To this end, based on a survey of national claims data, we sought in this study to examine the clinical factors associated with the compliance and persistence with osteoporosis medications in Korea, with a particular focus on BPs.

METHODS

Study population

In this study, we utilized data obtained from the Korean National Health Insurance Service (KNHIS), which provides mandatory health insurance coverage to nearly all Koreans. The KNHIS database encompasses a comprehensive set of health information for 50 million individuals, including diagnoses, procedures, and prescription drugs.[14,15] Participants were selected based on having osteoporosis diagnosed according to International Classification of Disease, Tenth Revision (ICD-10) codes M80-82 (n = 1,776,285). Among these, we identified participants aged 50 years or older who had received newly initiated BP or selective estrogen receptor modulator (SERM) therapy between January 2012 and December 2014 (n = 1,378,020). Excluded from the study were those who died within 2 years of initiating therapy and those who changed their osteoporosis medications during the follow-up period, whether by class, ingredient, or dosing interval. To exclude diseases and conditions that may have impacted the use of BP, we also excluded patients with a prior history of hypercalcemia,

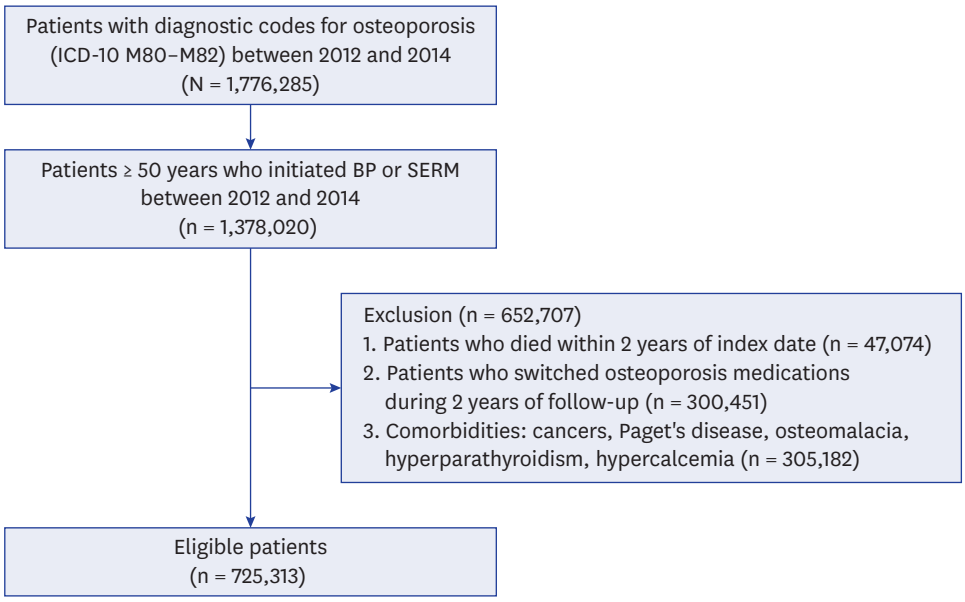

Fig. 1. The enrollment of study participants.
ICD-10 = International Classification of Disease, Tenth Revision, BP = bisphosphonate, SERM = selective estrogen receptor modulator.

hyperparathyroidism, malignancies, osteomalacia, or Paget's disease. Ultimately, 725,313 patients were included in the study (**Fig. 1**).

Osteoporosis medications

As osteoporosis medications, we assessed the usage of BPs (alendronate, risedronate, ibandronate, pamidronate, and zoledronic acid) and SERMs (raloxifene and bazedoxifene), for which we collected the following information: dosing intervals (daily, weekly, monthly, every three months, or yearly) and routes of administration (oral or intravenous).

Study variables

We collected information on demographic factors (sex, age groups, and residence), healthcare system (type of health coverage and medical institution), comorbidities (diabetes, hypertension, chronic kidney disease [CKD], osteoarthritis, coronary artery obstructive disease [CAOD], stroke, chronic obstructive pulmonary disease [COPD], dementia, and gastrointestinal diseases), and Charlson Comorbidity index (CCI) values at the time of the initiation of osteoporosis medication. Concurrent medications that are either known to frequently cause gastrointestinal problems or are commonly used to manage such issues in clinical practice, as well as those frequently prescribed in older adults — including gastroprotective agents, glucocorticoids, and non-steroidal anti-inflammatory drugs (NSAIDs) — were also recorded. Polypharmacy was defined as the use of five or more types of medication, including osteoporosis medications, at the time of initiation. We also collected information on the participants' history of fractures prior to initiating osteoporosis medication.

Study outcomes

Adherence to osteoporosis medications was evaluated by assessing both compliance and persistence during the one- and two-year follow-up periods. Medication possession ratio (MPR), representing the percentage of days an individual possessed prescribed medications during the observation period, was used to assess compliance. For the purposes of this

https://doi.org/10.3346/jkms.2025.40.e72

study, compliance was defined as having an MPR ≥ 80%. Persistence is defined as the duration of time a patient continues taking their prescribed medication as directed, without discontinuation. This concept is quantified by observing the permissible gap in medication use, which is the maximum allowed number of days between refilling prescriptions. In this study, persistence was evaluated based on the length of treatment without exceeding a permissible 90-day interval between prescriptions for both BPs and SERMs, regardless of dosing intervals, from the start of treatment to the final effective date of the medications at discontinuation.[16] Participants who did not exceed the permissible interval during the follow-up period were considered to show persistence. The index date for each participant is the date on which osteoporosis medication was initiated.

Statistical analysis

The compliance and persistence with osteoporosis pharmacotherapy according to class, route of administration, and dosing interval during one- and two-year follow-up periods were analyzed using an analysis of variance. The baseline characteristics of study participants according to compliance or persistence were analyzed using the chi-square test. Multivariable logistic regression analyses were performed to determine the odds ratios (ORs) for compliance or persistence according to different factors over the follow-up periods. The multivariable models included sex, age group, residence, type of health coverage, medical institution, previous history of fractures, comorbidities, concurrent medications, and polypharmacy as confounding variables. SAS for Windows version 9.1 (SAS Institute, Inc., Cary, NC, USA) was used for all statistical analyses, with a *P* value < 0.05 being considered indicative of a statistical significance.

Ethics statement

The Institutional Review Board (IRB) and Ethics Committee of Inha University Hospital approved the study protocol (IRB No. 2020-03-004), which was conducted in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived due to the de-identified nature of the data utilized from the KNHIS database.

RESULTS

Baseline characteristics of the study participants

Among the 725,313 patients with osteoporosis for whom medical therapy with BPs or SERMs was newly initiated between 2012 and 2014, a vast majority (90.1%) were women, and nearly half (47.6%) were aged over 70 (**Table 1**). The majority of these individuals lived in rural areas (59.1%), had health insurance coverage (91.2%), and received their medication prescriptions from primary clinics (80.9%), with 12% having a history of fracture. With respect to comorbidities, 34.0% had one or more CCIs, and there was a notable prevalence of hypertension (42.2%) and gastrointestinal diseases (50.5%). Concurrent prescriptions at the time of osteoporosis medication initiation included gastroprotective agents (28.5%), glucocorticoids (1.2%), and NSAIDs (11.7%), with nearly a third (29.9%) of patients showing signs of polypharmacy. The most frequently initiated osteoporosis medication was weekly oral alendronate (34.7%).

Compliance and persistence with osteoporosis pharmacotherapy

During the two-year follow-up period post-initiation of osteoporosis medications, only a fraction of participants (14.8%) maintained compliance with their prescribed medications,

Table 1. Baseline characteristics of the study participants

Variables	All participants (N = 725,313)
Sex	
Men	72,036 (9.9)
Women	653,277 (90.1)
Age groups, yr	
50–59	144,321 (19.9)
60–69	236,091 (32.6)
70–79	249,800 (34.4)
80–89	87,816 (12.1)
90–99	7,285 (1.0)
Residence	
Metropolis	119,922 (16.5)
Small to medium urban area	176,992 (24.4)
Rural area	428,399 (59.1)
Type of health coverage	
Health insurance	661,678 (91.2)
Medical aid	63,635 (8.8)
Medical institution	
General hospital	53,993 (7.4)
Hospital	66,547 (9.2)
Primary clinic	586,930 (80.9)
Public health center	17,843 (2.5)
Previous fracture history	86,888 (12.0)
CCI	
0	478,867 (66.0)
1	173,502 (23.9)
2	51,406 (7.1)
≥ 3	21,538 (3.0)
Comorbidity	
Diabetes	99,828 (13.8)
Hypertension	306,144 (42.2)
CKD	1,849 (0.3)
Osteoarthritis	19,763 (2.7)
CAOD	10,449 (1.4)
Stroke	24,262 (3.3)
COPD	9,545 (1.3)
Dementia	17,374 (2.4)
Gastrointestinal disease	366,183 (50.5)
Concurrent medications	
Gastroprotective agents	206,658 (28.5)
Glucocorticoid	8,756 (1.2)
NSAIDs	84,795 (11.7)
Polypharmacy	217,193 (29.9)
Osteoporosis medications	
Oral	
Raloxifene 60 mg (daily)	33,520 (4.6)
Bazedoxifene 20 mg (daily)	3,531 (0.5)
Alendronate 10 mg (daily)	23,037 (3.2)
Alendronate 70 mg (weekly)	251,426 (34.7)
Risedronate 5 mg (daily)	351 (0.0)
Risedronate 35 mg (weekly)	216,313 (29.8)
Risedronate 150 mg (monthly)	58,876 (8.1)
Pamidronate 100 mg (daily)	1,034 (0.1)
Ibandronate 150 mg (monthly)	45,475 (6.3)
Intravenous	
Pamidronate 30 mg (every 3 moths)	16,447 (2.3)
Ibandronate 3 mg (every 3 months)	73,666 (10.2)
Zoledronic acid 5 mg (yearly)	1,637 (0.2)

Values are presented as number (%).
CCI = Charlson Comorbidity Index, CKD = chronic kidney disease, CAOD = coronary artery obstructive disease, COPD = chronic obstructive pulmonary disease, NSAID = non-steroidal anti-inflammatory drug.

https://doi.org/10.3346/jkms.2025.40.e72

Table 2. Compliance and persistence according to the characteristics of osteoporosis medications during a 2-year follow-up period

Variables	No.	Compliant group[a]		MPR, %		Persistent group[b]		Persistent duration, days	
		No.	%	Mean	SD	No.	%	Median	1st, 3rd quartiles
All participants	725,313	107,344	14.8	33.3	31.2	114,472	15.8	168	42–372
Class									
SERM	37,051	7,857	21.2	39.9	34.1	8,438	22.8	210	60–548
Bisphosphonate	688,262	99,487	14.5	32.9	31.0	106,034	15.4	166	36–369
P values[c]		< 0.001		< 0.001		< 0.001		< 0.001	
Route									
Oral	633,563	84,942	13.4	31.4	30.5	93,012	14.7	140	28–364
Intravenous	91,750	22,402	24.4	46.4	32.5	21,460	23.4	270	90–566
P values[c]		< 0.001		< 0.001		< 0.001		< 0.001	
Dosing interval									
Daily	61,473	11,016	17.9	35.4	33.5	11,953	19.4	164	31–433
Weekly	467,739	57,544	12.3	30.2	30.0	62,874	13.4	135	28–353
Monthly	104,351	16,382	15.7	34.4	30.6	18,185	17.4	168	56–392
Every 3 months	90,113	22,245	24.7	46.2	32.7	21,315	23.7	270	90–578
Yearly	1,637	157	9.6	54.6	13.8	145	8.9	365	365–365
P values[c]		< 0.001		< 0.001		< 0.001		< 0.001	

MPR = medication possession ratio, SERM = selective estrogen receptor modulator.
[a]Compliant group: MPR ≥ 80%.
[b]Persistent group: Patients who were continuously prescribed osteoporosis medications without more than 90 days of gap during a 2-year follow-up period.
[c]*P* values were obtained using χ^2 and Student's *t* tests.

with a mean MPR of 33.3% (**Table 2**). Comparatively, a relatively higher compliance was detected for the one-year follow-up period, with 27.3% maintaining their medications with a mean MPR of 46.3% (**Supplementary Table 1**). Persistence with pharmacotherapy was similarly low, with only 15.8% of participants persisting with their treatment over the two-year period, with a median persistence duration of 168 days (interquartile range [IQR], 42–372 days) (**Table 2**). Similar to compliance, the 1-year persistence was somewhat higher at 34.4%, with a median duration of 142 days (IQR, 42–361 days) (**Supplementary Table 1**).

Patients administered SERMs generally showed better compliance and persistence than those administered BPs, and those receiving intravenous medication tended to be more compliant and persistent in their usage than those on oral medications. Additionally, patients starting a dosing regimens at three-month intervals were more compliant and persistent than those on other dosing intervals (**Table 2**, **Supplementary Table 1**).

Clinical characteristics of study participants according to compliance and persistence with osteoporosis pharmacotherapy

On the basis of our analysis of the clinical characteristics of study participants, we established that both compliant and persistent groups at the two-year follow-up consisted predominantly of women (94.5% in compliant vs. 89.3% in non-compliant, and 94.5% in persistent vs 89.2% in non-persistent, both $P < 0.001$), individuals aged under 70 (56.4% vs. 51.8% and 56.4% vs. 51.7%, respectively, $P < 0.001$), those living in metropolitan areas (18.9% vs. 16.1% and 18.4% vs. 16.2%, respectively, $P < 0.001$), those covered by medical aid (9.3% vs. 8.7% and 9.5% vs. 8.6%, respectively, $P < 0.001$) and prescribed from a general hospital (8.1% vs. 7.3% and 7.7% vs. 7.4%, respectively, $P < 0.001$), those having one or more CCI (35.2% vs. 33.8%, both, $P < 0.001$) and prescribed concurrent gastroprotective agents (31.5% vs. 28.0% and 31.4% vs. 27.9% respectively, $P < 0.001$), and patients characterized by polypharmacy (35.7% vs. 28.9% and 35.2% vs. 29.0%, respectively, $P < 0.001$) (**Table 3**). These groups generally contained fewer patients with a history of previous fractures (10.6% vs. 12.2% and 10.3% vs. 12.3%, respectively, $P < 0.001$). Similar demographic trends were observed at the one-year follow-up (**Supplementary Table 2**).

https://doi.org/10.3346/jkms.2025.40.e72

Table 3. Characteristics of study participants according to the compliance and persistence with osteoporosis pharmacotherapy after 2 years of follow-up

Variables	Compliant group[a] (n = 107,344)		Non-compliant group (n = 617,969)		*P* value[c]	Persistent group[b] (n = 114,472)		Non-persistent group (n = 610,841)		*P* value[c]
	No.	%	No.	%		No.	%	No.	%	
Sex					< 0.001					< 0.001
Men	5,926	5.5	66,110	10.7		6,264	5.5	65,772	10.8	
Women	101,418	94.5	551,859	89.3		108,208	94.5	545,069	89.2	
Age groups, yr					< 0.001					< 0.001
50–59	20,263	18.9	124,058	20.1		21,858	19.1	122,463	20.0	
60–69	40,254	37.5	195,837	31.7		42,656	37.3	193,435	31.7	
70–79	36,890	34.4	212,910	34.5		39,321	34.3	210,479	34.5	
80–89	9,443	8.8	78,373	12.7		10,103	8.8	77,713	12.7	
90–99	494	0.5	6,791	1.1		534	0.5	6,751	1.1	
Residence					< 0.001					< 0.001
Metropolis	20,287	18.9	99,635	16.1		21,064	18.4	98,858	16.2	
Small to medium urban area	27,302	25.4	149,690	24.2		29,051	25.4	147,941	24.2	
Rural area	59,755	55.7	368,644	59.7		64,357	56.2	364,042	59.6	
Type of health coverage					< 0.001					< 0.001
Health insurance	97,344	90.7	564,334	91.3		103,651	90.5	558,027	91.4	
Medical aid	10,000	9.3	53,635	8.7		10,821	9.5	52,814	8.6	
Medical institution					< 0.001					< 0.001
General hospital	8,663	8.1	45,330	7.3		8,826	7.7	45,167	7.4	
Hospital	8,103	7.5	58,444	9.5		8,467	7.4	58,080	9.5	
Primary clinic	88,697	82.6	498,233	80.6		95,163	83.1	491,767	80.5	
Public health center	1,881	1.8	15,962	2.6		2,016	1.8	15,827	2.6	
Previous fracture history	11,410	10.6	75,478	12.2	< 0.001	11,780	10.3	75,108	12.3	< 0.001
CCI					< 0.001					< 0.001
0	69,457	64.7	409,410	66.3		74,214	64.8	404,653	66.2	
1	26,439	24.6	147,063	23.8		28,223	24.7	145,279	23.8	
2	8,204	7.6	43,202	7.0		8,630	7.5	42,776	7.0	
≥ 3	3,244	3.0	18,294	3.0		3,405	3.0	18,133	3.0	
Comorbidity										
Diabetes	15,231	14.2	84,597	13.7	< 0.001	16,079	14.0	83,749	13.7	< 0.001
Hypertension	48,242	44.9	257,902	41.7	< 0.001	51,068	44.6	255,076	41.8	< 0.001
CKD	249	0.2	1,600	0.3	< 0.001	257	0.2	1,592	0.3	0.014
Osteoarthritis	3,141	2.9	16,622	2.7	< 0.001	3,357	2.9	16,406	2.7	< 0.001
CAOD	1,533	1.4	8,916	1.4	0.710	1,600	1.4	8,849	1.4	0.349
Stroke	3,820	3.6	20,442	3.3	< 0.001	3,941	3.4	20,321	3.3	0.012
COPD	1,215	1.1	8,330	1.3	< 0.001	1,311	1.1	8,234	1.3	< 0.001
Dementia	2,143	2.0	15,231	2.5	< 0.001	2,229	1.9	15,145	2.5	< 0.001
Gastrointestinal disease	55,773	52.0	310,410	50.2	< 0.001	59,664	52.1	306,519	50.2	< 0.001
Concurrent medications										
Gastroprotective agents	33,804	31.5	172,854	28.0	< 0.001	35,971	31.4	170,687	27.9	< 0.001
Glucocorticoid	1,911	1.8	6,845	1.1	< 0.001	2,041	1.8	6,715	1.1	< 0.001
NSAIDs	13,044	12.2	71,751	11.6	< 0.001	14,166	12.4	70,629	11.6	< 0.001
Polypharmacy	38,295	35.7	178,898	28.9	< 0.001	40,276	35.2	176,917	29.0	< 0.001

CCI = Charlson Comorbidity Index, CKD = chronic kidney disease, CAOD = coronary artery obstructive disease, COPD = chronic obstructive pulmonary disease, NSAID = non-steroidal anti-inflammatory drug.
[a]Compliant group: medication possession ratio ≥ 80%.
[b]Persistent group: Patients who were continuously prescribed osteoporosis medications without more than 90 days of gap during a 2-year follow-up period.
[c]*P* values were obtained using χ^2 test.

Medication-related factors associated with compliance and persistence with osteoporosis pharmacotherapy

Multivariable logistic regression analysis revealed that compliance and persistence differed according to the characteristics of osteoporosis medication prescribed (**Table 4**). Compared with BPs, SERMs (ORs, 1.44 and 1.48, respectively; $P < 0.001$) had higher odds for both compliance and persistence. In terms of administration, we found that compared with oral medications, intravenous administration (ORs, 2.08 and 1.76, respectively; $P < 0.001$) was associated with higher odds for both compliance and persistence, whereas compared with

https://doi.org/10.3346/jkms.2025.40.e72

Table 4. Multivariate logistic regression analyses for the odds of compliance and persistence with osteoporosis pharmacotherapy after 2 years of follow-up according to the characteristics of osteoporosis medications

Characteristics of osteoporosis medications	Compliance[a]			Persistence[b]		
	ORs	95% CI	*P* value[c]	ORs	95% CI	*P* value[c]
Class						
SERM	1.44	1.40–1.48	< 0.001	1.48	1.44–1.51	< 0.001
Bisphosphonate	1.00			1.00		
Route						
Oral	1.00			1.00		
Intravenous	2.08	2.05–2.18	< 0.001	1.76	1.73–1.80	< 0.001
Dosing interval						
Daily	1.00			1.00		
Weekly	0.67	0.66–0.69	< 0.001	0.67	0.66–0.69	< 0.001
Monthly	0.83	0.81–0.86	< 0.001	0.85	0.83–0.87	< 0.001
Every 3 months	1.55	1.51–1.59	< 0.001	1.31	1.28–1.35	< 0.001
Yearly	0.56	0.47–0.66	< 0.001	0.47	0.39–0.55	< 0.001

OR = odds ratio, CI = confidence interval, SERM = selective estrogen receptor modulator.
[a]Compliant group: medication possession ratio ≥ 80%.
[b]Persistent group: Patients who were continuously prescribed osteoporosis medications without more than 90 days of gap during a 2-year follow-up period.
[c]*P* values were obtained using logistic regression analysis after adjusting for age groups, sex, residence, medical institution, years of medication initiation, previous fracture history, Charlson Comorbidity Index, comorbidities, concurrently prescribed medications, and polypharmacy.

other intervals, significantly higher odds for compliance and persistence were obtained for those on a quarterly dosing schedule (ORs, 1.55 and 1.31, respectively; all $P < 0.001$). The findings at the one-year follow-up period were similar to those obtained at the two-year follow-up period (**Supplementary Table 3**).

Clinical factors associated with compliance and persistence with osteoporosis pharmacotherapy

In addition to medication-related factors, we found that demographic and clinical variables also influenced adherence. Women, medical aid coverage, one or two CCIs, certain comorbidities, such as hypertension, concurrent prescription of specific medications, such as gastroprotective agents or glucocorticoids, and polypharmacy were all factors associated with higher ORs for compliance and persistence (**Table 5**). In contrast, being over 70 years old, living outside metropolitan areas, treatment in non-general hospitals, a previous history of fractures, or having certain comorbidities, such as diabetes, CKD, CAOD, and dementia, were identified as being associated with lower odds for compliance and persistence over two-year follow-ups (**Table 5**). The findings at the one-year follow-up period were similar to those obtained at the two-year follow-up period (**Supplementary Table 4**).

DISCUSSION

Our findings in this study revealed that Korean patients with osteoporosis showed a generally poor adherence to pharmacotherapy, including BPs and SERMs. Only 14.8% of the patients undergoing newly initiated treatment maintained their medication compliance, and a mere 15.8% persisted with their medications throughout the two-year period of follow-up. We found that, in terms of medication adherence, SERMs performed better than BPs, intravenous administration was more effective than oral routes, and a longer dosing interval (every three months) was associated with better adherence than daily dosing. Clinical factors, including male gender, advanced age, residence outside metropolitan areas, treatment in non-general hospitals, and a history of previous fractures, were also linked to lower adherence to osteoporosis pharmacotherapy. Conversely, factors such as medical aid

Table 5. Clinical factors associated with increased odds for compliance and persistence with osteoporosis pharmacotherapy after 2 years of follow-up in the multivariable models including dosing interval of osteoporosis medications

Variables	Compliance[a]			Persistence[b]		
	ORs	95% CI	*P* value[c]	ORs	95% CI	*P* value[c]
Dosing interval						
Daily	1.00			1.00		
Weekly	0.67	0.66–0.69	< 0.001	0.67	0.66–0.69	< 0.001
Monthly	0.83	0.81–0.86	< 0.001	0.85	0.83–0.87	< 0.001
Every 3 months	1.55	1.51–1.59	< 0.001	1.31	1.28–1.35	< 0.001
Yearly	0.56	0.47–0.66	< 0.001	0.47	0.39–0.55	< 0.001
Sex						
Men	1.00			1.00		
Women	1.75	1.70–1.80	< 0.001	1.81	1.76–1.86	< 0.001
Age groups, yr						
50–59	1.00			1.00		
60–69	1.18	1.16–1.20	< 0.001	1.17	1.14–1.19	< 0.001
70–79	0.96	0.95–0.98	< 0.001	0.97	0.95–0.99	< 0.001
80–89	0.65	0.63–0.67	< 0.001	0.66	0.65–0.68	< 0.001
90–99	0.40	0.36–0.44	< 0.001	0.41	0.38–0.45	< 0.001
Residence						
Metropolis	1.00			1.00		
Small to medium urban area	0.89	0.88–0.91	< 0.001	0.92	0.90–0.94	< 0.001
Rural area	0.82	0.80–0.83	< 0.001	0.85	0.84–0.87	< 0.001
Type of health coverage						
Health insurance	1.00			1.00		
Medical aid	1.09	1.06–1.12	< 0.001	1.12	1.10–1.15	< 0.001
Medical institution						
General hospital	1.00			1.00		
Hospital	0.71	0.68–0.75	< 0.001	0.77	0.73–0.80	< 0.001
Clinic	0.87	0.83–0.91	< 0.001	0.95	0.91–0.99	0.030
Public health center	0.66	0.62–0.71	< 0.001	0.72	0.67–0.77	< 0.001
Previous fracture history	0.88	0.86–0.90	< 0.001	0.86	0.84–0.88	< 0.001
CCI						
0	1.00			1.00		
1	1.03	1.01–1.05	0.002	1.04	1.02–1.05	< 0.001
2	1.06	1.03–1.09	< 0.001	1.06	1.03–1.10	< 0.001
≥ 3	1.00	0.95–1.04	0.823	1.00	0.95–1.04	0.847
Comorbidity						
Diabetes	0.87	0.85–0.89	< 0.001	0.86	0.84–0.88	< 0.001
Hypertension	1.09	1.07–1.10	< 0.001	1.07	1.06–1.09	< 0.001
CKD	0.79	0.69–0.91	< 0.001	0.79	0.69–0.91	0.001
Osteoarthritis	1.01	0.97–1.05	0.615	1.01	0.97–1.05	0.532
CAOD	0.88	0.83–0.93	< 0.001	0.87	0.82–0.92	< 0.001
Stroke	1.00	0.96–1.03	0.807	0.97	0.94–1.01	0.149
COPD	0.94	0.88–0.99	0.041	0.95	0.90–1.01	0.124
Dementia	0.86	0.82–0.90	< 0.001	0.85	0.81–0.88	< 0.001
Gastrointestinal disease	1.00	0.99–1.02	0.545	1.01	1.00–1.03	0.089
Concurrent medications						
Gastroprotective agents	1.06	1.04–1.07	< 0.001	1.06	1.05–1.08	< 0.001
Glucocorticoid	1.44	1.36–1.52	< 0.001	1.44	1.37–1.52	< 0.001
NSAIDs	0.93	0.91–0.95	< 0.001	0.96	0.94–0.98	< 0.001
Polypharmacy	1.40	1.37–1.42	< 0.001	1.36	1.34–1.39	< 0.001

CCI = Charlson Comorbidity Index, CKD = chronic kidney disease, CAOD = coronary artery obstructive disease, COPD = chronic obstructive pulmonary disease, NSAID = non-steroidal anti-inflammatory drug.
[a]Compliant group: medication possession ratio ≥ 80%.
[b]Persistent group: Patients who were continuously prescribed osteoporosis medications without more than 90 days of gap during a 2-year follow-up period.
[c]*P* values were obtained using logistic regression analysis in the multivariable model.

coverage, a mild CCI, concurrent use of gastroprotective agents and glucocorticoids, and polypharmacy were associated with an enhanced adherence.

https://doi.org/10.3346/jkms.2025.40.e72

As evidenced in our study and mirrored in the worldwide reality of osteoporosis management, adherence to osteoporosis pharmacotherapy is generally poor[17-19] and this lack of adherence poses a significant hurdle in the effective, lifelong management of osteoporosis.[20] For osteoporosis medications, adherence issues have been particularly prevalent in BPs,[13] while the recently developed parenteral osteoporosis medications such as denosumab has shown better adherence compared to BPs due to its convenience in administration methods and fewer side effects.[21,22] Consistent with this, adherence to osteoporosis pharmacotherapy has improved over the past decade in Korea, likely due to the increasing popularity of denosumab in osteoporosis treatment.[23] Nevertheless, clinical considerations when treating patients with osteoporosis using BPs should especially include the choice of BP type, ensuring correct medication intake, determining when to discontinue these medications, and managing their side effects.[24] In this context, our study indicated that while BPs had lower adherence rates compared to SERMs, intravenous administration and quarterly dosing intervals showed relatively better adherence.

This aligns with previous studies conducted in other countries that compared adherence between oral and intravenous BPs,[25] and it suggests that medication-related factors, such as more convenient regimens and reduced gastrointestinal side effects, contribute to better adherence in the use of BPs for treating osteoporosis. However, it is noteworthy that in our study, zoledronic acid demonstrated lower adherence rates at the two-year follow-up, despite being an annual intravenous BP. This observation might suggest that a once-yearly follow-up is too infrequent to encourage regular hospital visits for osteoporosis treatment. Therefore, encouraging patients to consistently visit the hospital is crucial in managing osteoporosis. Lower adherence of zoledronic acid may also be attributed to various factors including side effects like acute phase reactions, discontinuation due to improvements in BMD, and the medication's limited use during our study period.[26] Moreover, the lower adherence to BPs compared to SERMs might stem from the discontinuation of BPs due to unexpected dental procedures.

Our findings also revealed several clinical factors associated with adherence to osteoporosis pharmacotherapy. Among these factors, males, older age groups, those living outside metropolitan areas, or those treated in medical institutions other than general hospitals typically have poorer adherence. This is consistent with clinical expectations for osteoporosis and other conditions, not only in Korea but also in other countries.[13,27,28] Consistent with this, reports from Korea have indicated that both the health service utilization rate and the treatment rate for osteoporosis are lower among men and very elderly patients.[29] Additionally, the Health Insurance Review & Assessment service of Korea has found that the incidence of BMD measurements is significantly lower in rural areas, where primary clinics and public health centers are more common compared to metropolitan areas, which host many general hospitals.[30] Therefore, elderly male osteoporosis patients, especially those living outside metropolitan areas, require special attention to ensure the continuity of their treatment. Interestingly, patients with a history of previous fractures demonstrated poorer adherence in our study. There was no clear evidence that a history of fractures was associated with adherence to osteoporosis pharmacotherapy, as only a minority of studies found a statistically significant association.[28,31-33] Generally, it is possible that patients with fractures may be more motivated to continue therapy but may also be frailer and, for this reason, more likely to discontinue treatment. However, what should be clearly considered is that targeted management is especially needed in this high-risk group. Additionally, patients with mild CCI conditions, as well as those concurrently using gastroprotective agents or

glucocorticoids and engaging in polypharmacy, demonstrated better adherence in our study. Although these findings are inconsistent with the results of previous studies conducted in other countries,[13,27,28,34] they may suggest that patients with more complex health conditions or those managing multiple medications are more actively engaged in their healthcare in Korea. Conversely, certain comorbidities, such as diabetes, CAOD, COPD, and dementia, were associated with poorer adherence, consistent with findings from previous studies in other countries.[13,28] This highlights the need for careful management of these populations in Korea. Overall, these findings underscore the importance of considering the broader healthcare environment when initiating and maintaining osteoporosis treatment, with approaches tailored to the specific conditions in each country.

Previous studies have demonstrated the effectiveness of patient and doctor education in improving long-term adherence to osteoporosis pharmacotherapy. Specifically, reports have shown that intensive group education only within four weeks is associated with improved adherence at a two-year follow-up, compared to the control group.[35,36] Moreover, a recent study from Australia revealed that a national education program for general practitioners on patient adherence to osteoporosis medications led to changes in primary care prescribing behavior and enhanced long-term treatment adherence over nine years.[37] Its effectiveness was particularly notable in patients who were prescribed oral BPs rather than denosumab. Therefore, ongoing efforts for patient and doctor education are essential for improving adherence to osteoporosis pharmacotherapy. Furthermore, findings in our study identifying factors associated with poor adherence to osteoporosis pharmacotherapy (males, older age groups, those living outside metropolitan areas, or those treated in non-general hospitals) offer guidance on whom to target and what points to emphasize during educational interventions.

The strength of this study lies in the fact that our investigation covered the entire Korean population who initiated osteoporosis medication between 2012 and 2014, utilizing data from the KNHIS, thereby providing an accurate representation of the adherence to osteoporosis pharmacotherapy in Korea. However, although we performed comprehensive analyses of different treatment-related and clinical factors, the study does have certain limitations, notably the use of national claims data, which lack information on BMD, thereby limiting our ability to assess the impact of osteoporosis severity on the adherence to medication. Moreover, the restriction of the study period to the years from 2012 to 2014 means that we were unable to evaluate data relating to some of the more recently introduced osteoporosis medications, such as denosumab, teriparatide, and romosozumab. Furthermore, the follow-up periods were limited to one and two years, and the cohort of patients for whom treatment with zoledronic acid was initiated was too small to draw definitive conclusions. Lastly, we did not evaluate the relationship between osteoporosis medication adherence and fracture outcomes in this study, which could have provided further evidence of the importance of adherence in osteoporosis treatment.

In conclusion, our findings in this study highlight the multifaceted nature of the adherence to medication among Korean patients with osteoporosis, particularly those receiving treatment with BPs. These findings indicate that osteoporosis medication administered with more convenient regimens and associated with fewer side effects, along with appropriate follow-up intervals, can contribute to enhancing the adherence to treatment in osteoporosis management. Moreover, clinical characteristics such as male gender, advanced age, and residing outside metropolitan areas warrant increased attention through targeted education and regular follow-up strategies. These insights underscore the significance of personalized

https://doi.org/10.3346/jkms.2025.40.e72

treatment approaches and patient-centered care in improving the long-term adherence to prescribed medication and reducing the risk of fractures in patients with osteoporosis.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Compliance and persistence according to the characteristics of osteoporosis medications during a one-year follow-up period

Supplementary Table 2

Characteristics of study participants according to compliance and persistence with osteoporosis pharmacotherapy after one year of follow-up

Supplementary Table 3

Multivariate logistic regression analyses for determining the odds of compliance and persistence with osteoporosis pharmacotherapy after one year of follow-up according to the characteristics of osteoporosis medications

Supplementary Table 4

Clinical factors associated with increased odds for compliance and persistence with osteoporosis pharmacotherapy after one year of follow-up determined using multivariable models including dosing interval of osteoporosis medications

REFERENCES

1. Wright NC, Looker AC, Saag KG, Curtis JR, Delzell ES, Randall S, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. *J Bone Miner Res* 2014;29(11):2520-6. PUBMED | CROSSREF
2. Ahn SH, Park SM, Park SY, Yoo JI, Jung HS, Nho JH, et al. Osteoporosis and osteoporotic fracture fact sheet in Korea. *J Bone Metab* 2020;27(4):281-90. PUBMED | CROSSREF
3. Ramchand SK, Leder BZ. Sequential therapy for the long-term treatment of postmenopausal osteoporosis. *J Clin Endocrinol Metab* 2024;109(2):303-11. PUBMED | CROSSREF
4. Siris ES, Selby PL, Saag KG, Borgström F, Herings RM, Silverman SL. Impact of osteoporosis treatment adherence on fracture rates in North America and Europe. *Am J Med* 2009;122(2 Suppl):S3-13. PUBMED | CROSSREF
5. Cramer JA, Gold DT, Silverman SL, Lewiecki EM. A systematic review of persistence and compliance with bisphosphonates for osteoporosis. *Osteoporos Int* 2007;18(8):1023-31. PUBMED | CROSSREF
6. Huybrechts KF, Ishak KJ, Caro JJ. Assessment of compliance with osteoporosis treatment and its consequences in a managed care population. *Bone* 2006;38(6):922-8. PUBMED | CROSSREF
7. Anastasilakis AD, Polyzos SA, Makras P. Therapy of endocrine disease: denosumab vs bisphosphonates for the treatment of postmenopausal osteoporosis. *Eur J Endocrinol* 2018;179(1):R31-45. PUBMED | CROSSREF
8. Saul D, Drake MT. Update on approved osteoporosis therapies including combination and sequential use of agents. *Endocrinol Metab Clin North Am* 2021;50(2):179-91. PUBMED | CROSSREF
9. Chandran M. The why and how of sequential and combination therapy in osteoporosis. A review of the current evidence. *Arch Endocrinol Metab* 2022;66(5):724-38. PUBMED | CROSSREF
10. Foessl I, Dimai HP, Obermayer-Pietsch B. Long-term and sequential treatment for osteoporosis. *Nat Rev Endocrinol* 2023;19(9):520-33. PUBMED | CROSSREF
11. Khosla S, Hofbauer LC. Osteoporosis treatment: recent developments and ongoing challenges. *Lancet Diabetes Endocrinol* 2017;5(11):898-907. PUBMED | CROSSREF

12. Yu EW, Tsourdi E, Clarke BL, Bauer DC, Drake MT. Osteoporosis management in the era of COVID-19. *J Bone Miner Res* 2020;35(6):1009-13. PUBMED | CROSSREF
13. Fatoye F, Smith P, Gebrye T, Yeowell G. Real-world persistence and adherence with oral bisphosphonates for osteoporosis: a systematic review. *BMJ Open* 2019;9(4):e027049. PUBMED | CROSSREF
14. Lee YK, Yoon BH, Koo KH. Epidemiology of osteoporosis and osteoporotic fractures in South Korea. *Endocrinol Metab (Seoul)* 2013;28(2):90-3. PUBMED | CROSSREF
15. Choi HJ, Shin CS, Ha YC, Jang S, Jang S, Park C, et al. Burden of osteoporosis in adults in Korea: a national health insurance database study. *J Bone Miner Metab* 2012;30(1):54-8. PUBMED | CROSSREF
16. Reyes C, Tebe C, Martinez-Laguna D, Ali MS, Soria-Castro A, Carbonell C, et al. One and two-year persistence with different anti-osteoporosis medications: a retrospective cohort study. *Osteoporos Int* 2017;28(10):2997-3004. PUBMED | CROSSREF
17. Weycker D, Macarios D, Edelsberg J, Oster G. Compliance with drug therapy for postmenopausal osteoporosis. *Osteoporos Int* 2006;17(11):1645-52. PUBMED | CROSSREF
18. Kothawala P, Badamgarav E, Ryu S, Miller RM, Halbert RJ. Systematic review and meta-analysis of real-world adherence to drug therapy for osteoporosis. *Mayo Clin Proc* 2007;82(12):1493-501. PUBMED | CROSSREF
19. Morley J, Moayyeri A, Ali L, Taylor A, Feudjo-Tepie M, Hamilton L, et al. Persistence and compliance with osteoporosis therapies among postmenopausal women in the UK Clinical Practice Research Datalink. *Osteoporos Int* 2020;31(3):533-45. PUBMED | CROSSREF
20. Kanis JA, Cooper C, Hiligsmann M, Rabenda V, Reginster JY, Rizzoli R. Partial adherence: a new perspective on health economic assessment in osteoporosis. *Osteoporos Int* 2011;22(10):2565-73. PUBMED | CROSSREF
21. Pedersen AB, Risbo N, Kafatos G, Neasham D, O'Kelly J, Ehrenstein V. Utilization patterns and factors associated with persistence of new users of anti-osteoporosis treatment in Denmark: a population-based cohort study. *Arch Osteoporos* 2023;18(1):19. PUBMED | CROSSREF
22. Lin SY, Chen YM, Chen WJ, Li CY, Ku CK, Chen CH, et al. Treatment patterns of long-dose-interval medication for persistent management of osteoporosis in Taiwan. *Arch Osteoporos* 2022;17(1):94. PUBMED | CROSSREF
23. Korean Society for Bone and Mineral Research. *Osteoporosis and Osteoporotic Fracture Fact Sheet 2023*. Seoul, Korea: Korean Society for Bone and Mineral Research; 2023.
24. Diab DL, Watts NB. Bisphosphonates in the treatment of osteoporosis. *Endocrinol Metab Clin North Am* 2012;41(3):487-506. PUBMED | CROSSREF
25. Bastounis A, Langley T, Davis S, Paskins Z, Gittoes N, Leonardi-Bee J, et al. Comparing medication adherence in patients receiving bisphosphonates for preventing fragility fractures: a comprehensive systematic review and network meta-analysis. *Osteoporos Int* 2022;33(6):1223-33. PUBMED | CROSSREF
26. Spångeus A, Johansson S, Woisetschläger M. Adherence to and persistence with zoledronic acid treatment for osteoporosis-reasons for early discontinuation. *Arch Osteoporos* 2020;15(1):58. PUBMED | CROSSREF
27. Landfeldt E, Ström O, Robbins S, Borgström F. Adherence to treatment of primary osteoporosis and its association to fractures--the Swedish Adherence Register Analysis (SARA). *Osteoporos Int* 2012;23(2):433-43. PUBMED | CROSSREF
28. Hansen C, Pedersen BD, Konradsen H, Abrahamsen B. Anti-osteoporotic therapy in Denmark--predictors and demographics of poor refill compliance and poor persistence. *Osteoporos Int* 2013;24(7):2079-97. PUBMED | CROSSREF
29. Yu TY, Cho H, Kim TY, Ha YC, Jang S, Kim HY. Utilization of osteoporosis-related health services: use of data from the Korean National Health Insurance Database 2008-2012. *J Korean Med Sci* 2018;33(3):e20. PUBMED | CROSSREF
30. HIRA Bigdata Open Portal. https://opendata.hira.or.kr/op/opc/olapMfrnIntrsDiagBhvInfoTab1.do. Updated 2024. Accessed January, 2024.
31. Chan DC, Chang CH, Lim LC, Brnabic AJ, Tsauo JY, Burge R, et al. Association between teriparatide treatment persistence and adherence, and fracture incidence in Taiwan: analysis using the National Health Insurance Research Database. *Osteoporos Int* 2016;27(9):2855-65. PUBMED | CROSSREF
32. Bonafede MM, Shi N, Bower AG, Barron RL, Grauer A, Chandler DB. Teriparatide treatment patterns in osteoporosis and subsequent fracture events: a US claims analysis. *Osteoporos Int* 2015;26(3):1203-12. PUBMED | CROSSREF
33. Silverman SL, Siris E, Kendler DL, Belazi D, Brown JP, Gold DT, et al. Persistence at 12 months with denosumab in postmenopausal women with osteoporosis: interim results from a prospective observational study. *Osteoporos Int* 2015;26(1):361-72. PUBMED | CROSSREF

34. McConnell M, Shieh A. Polypharmacy in osteoporosis treatment. *Clin Geriatr Med* 2022;38(4):715-26. PUBMED | CROSSREF

35. Rubæk M, Hitz MF, Holmberg T, Schønwandt BM, Andersen S. Effectiveness of patient education for patients with osteoporosis: a systematic review. *Osteoporos Int* 2022;33(5):959-77. PUBMED | CROSSREF

36. Nielsen D, Ryg J, Nielsen W, Knold B, Nissen N, Brixen K. Patient education in groups increases knowledge of osteoporosis and adherence to treatment: a two-year randomized controlled trial. *Patient Educ Couns* 2010;81(2):155-60. PUBMED | CROSSREF

37. Vuong T, Peters M, Merrifield A, Firipis M, Belcher J, Elgebaly Z. Investigating the impact of a national educational program on patient adherence to osteoporosis medications. *Arch Osteoporos* 2023;18(1):90. PUBMED | CROSSREF